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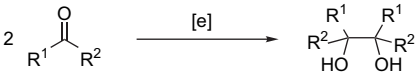
Tetrahedron

Tetrahedron Vol. 62, No. 52, 2006

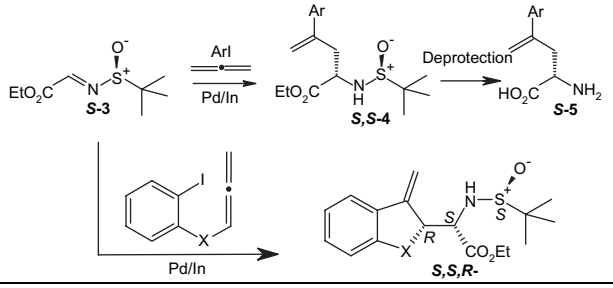
Contents

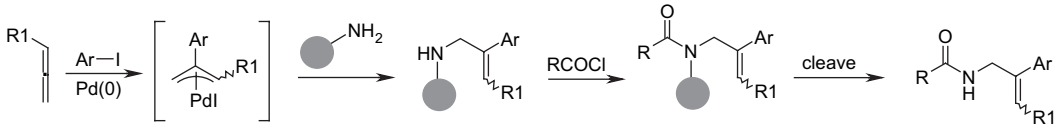
REPORT

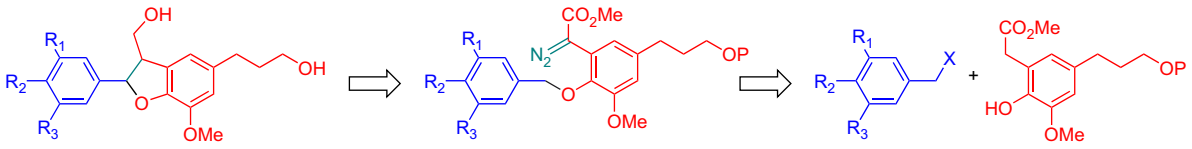


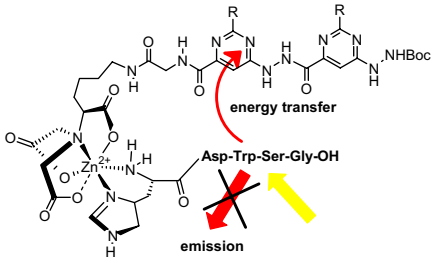
Pinacol coupling reaction, with particular emphasis on stereoselective protocols, is reviewed. The report contains 160 references.

ARTICLES

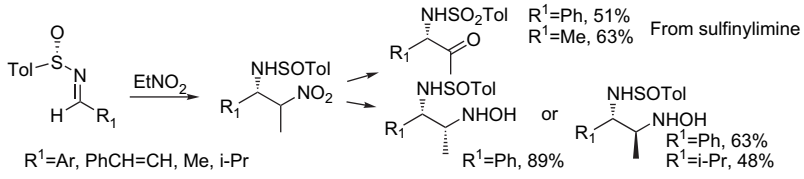


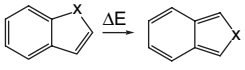


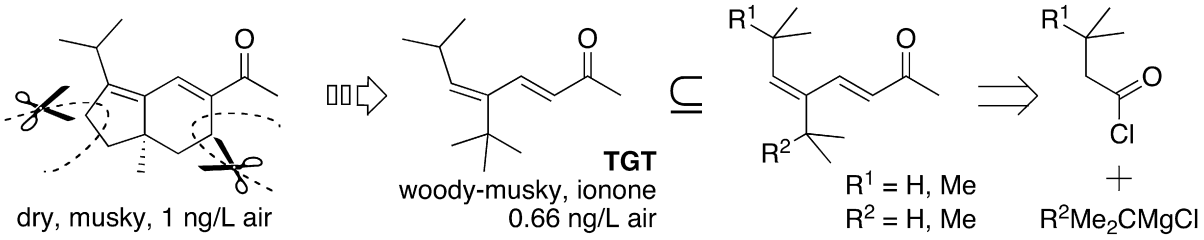


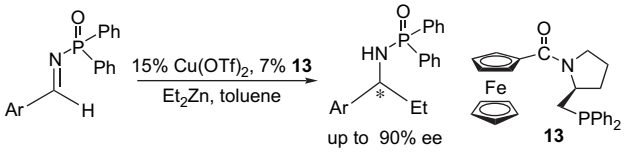


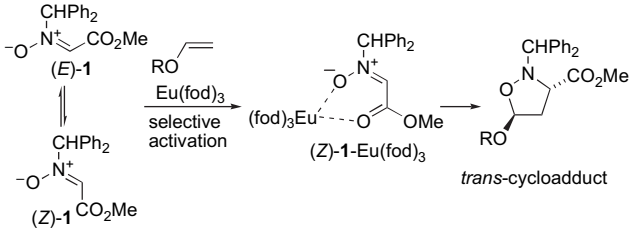
Merging reversible coordination, typically used for protein purification, with a heterocyclic luminescent probe leads to synthetic receptors for peptide structure investigations in aqueous buffer.

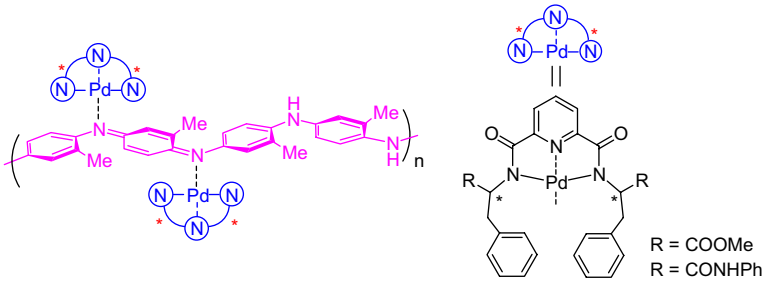


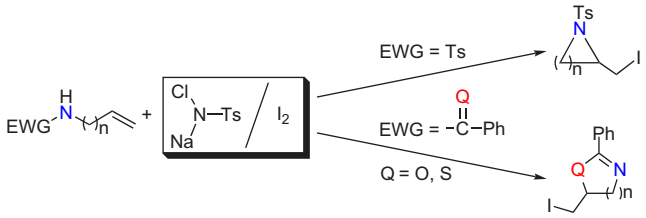


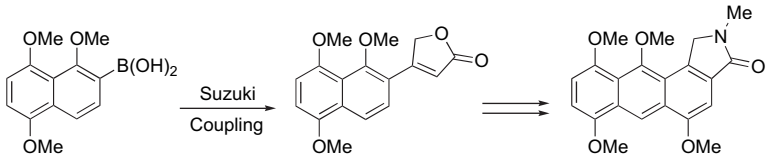


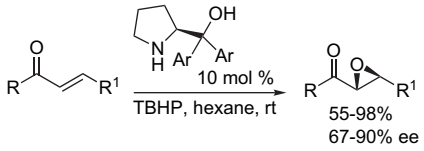


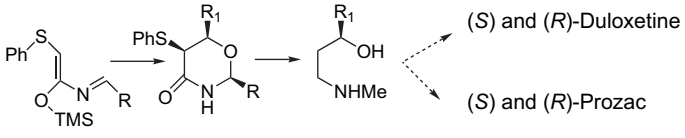


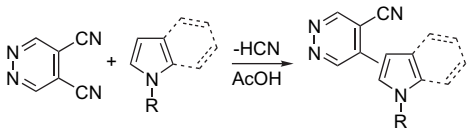


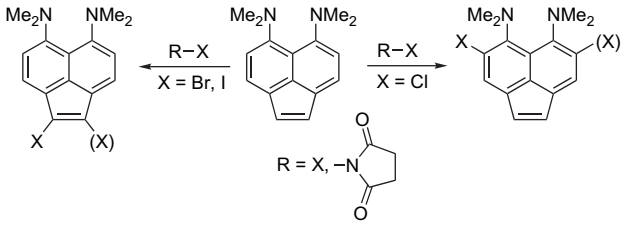


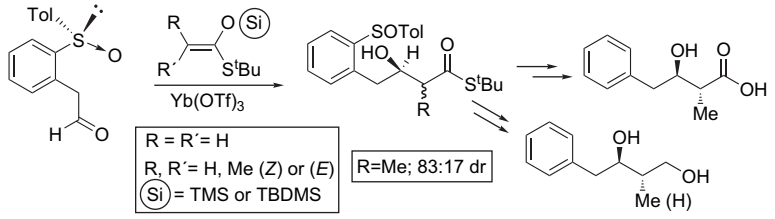


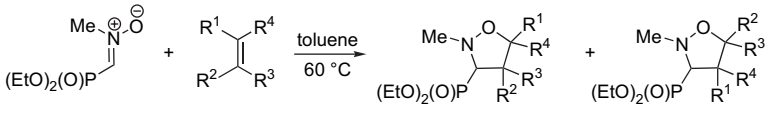


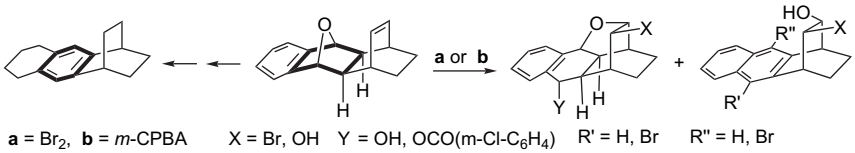


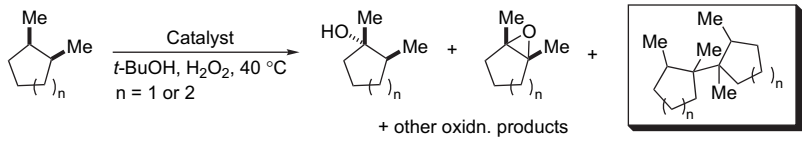


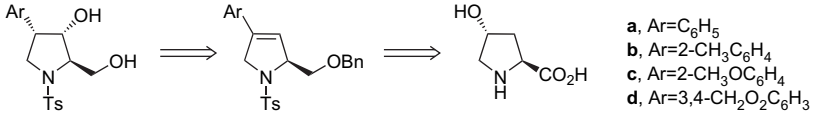




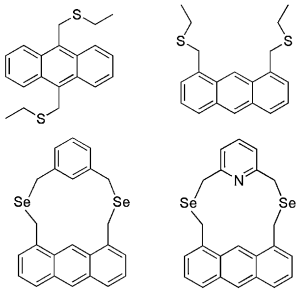


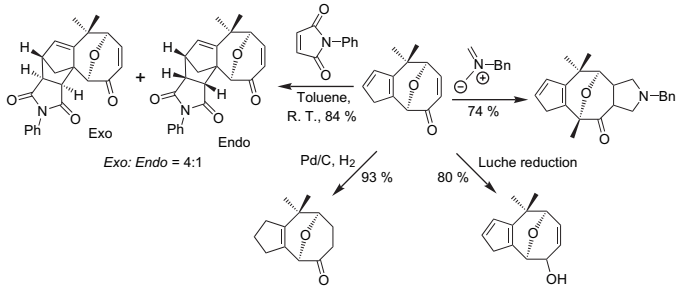


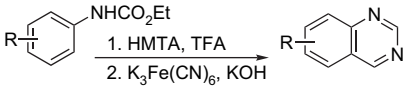


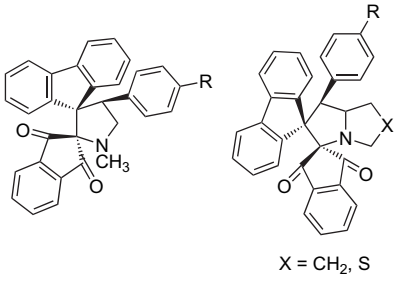


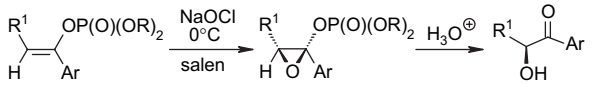
Two new selenium containing anthracene derivatives and two new sulfur containing anthracene derivatives were synthesized as fluorescent chemosensors for Hg^{2+} and Cu^{2+}.

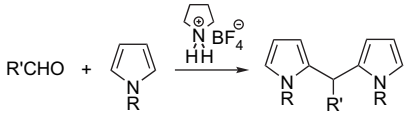


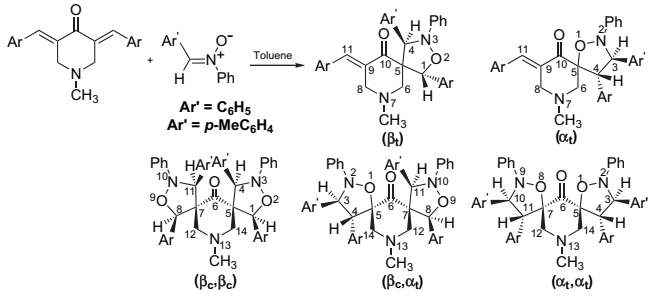


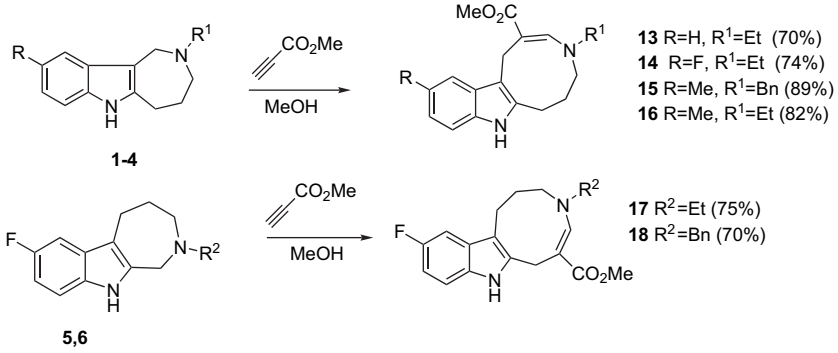


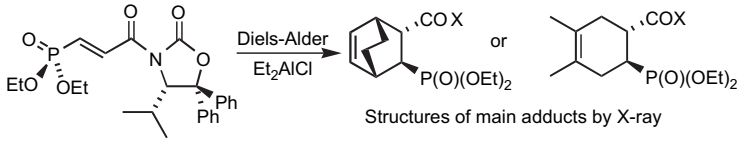


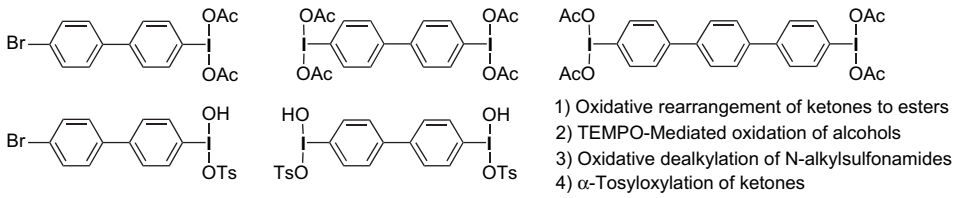


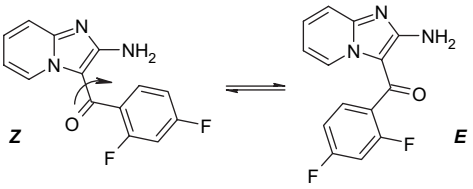


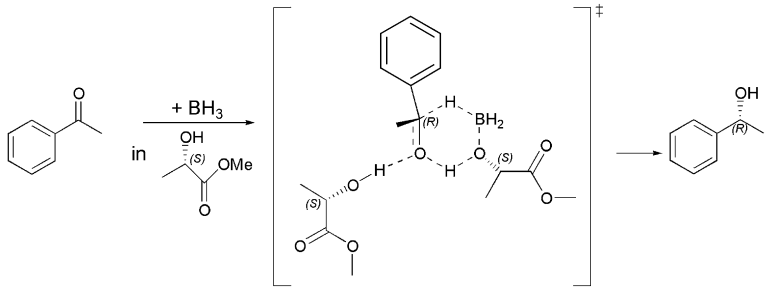


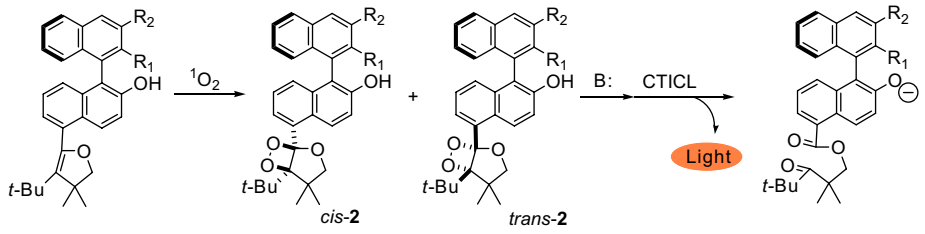












OTHER CONTENTS

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Musk or violet? The answer to this question asked in the title of the featured paper by Philip Kraft and Kasim Popaj is: both, musk and violet! The depicted target compound (*3E,5E*)-5-*tert*-butyl-7-methylocta-3,5-diene-2-one actually combines a typical musk odor with the characteristic ionone scent of violets, and this is illustrated also graphically by pictures of musk grains and violets (*Viola odorata* L., by courtesy of Roman Kaiser, Givaudan) that fade into a background, where green and violet tones run into one another. As shown on the right hand side, this as well as three other target molecules were designed as *seco*-structures to a musky carotol-derived lead structure. And indeed by this *seco*-design a whole new family of musk odorants with different shades of violet notes intertwined was discovered. The six-step synthetic route to these new, sterically highly demanding dienones consists of coupling branched alkyl magnesium with isovaleryl and 3,3-dimethylbutanoyl chloride, Grignard reaction of the resulting products with ethynyl magnesium bromide, dehydration and transformation into a Grignard reagent, subsequent reaction with acetaldehyde, (*E*)-selective hydrogenation, and concluding PCC oxidation. *Tetrahedron* **2006**, *62*, 12211–12219.

Abstracted/indexed in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts. Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

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ISSN 0040-4020

Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 62 (2006) 12137–12158
Tetrahedron

Tetrahedron report number 778

Evolution of the stereoselective pinacol coupling reaction

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Received 29 August 2006
Available online 28 September 2006

Contents

Keywords: Pinacol coupling; Reductive dimerization; Diastereoselective; Enantioselective.
Abbreviations: AIBN, 2,2-Azobisisobutyronitrile; BOC, *tert*-Butoxycarbonyl; Cbz, Benzyloxycarbonyl; COD, Cyclooctadiene; Cp, Cyclopentadienyl; DDB, 1,4-Bis(dimethylamino)-2,3-dimethoxybutane; DCM, Dichloromethane; DEPU, Diethyldiisopropylurea; DIPEA, Diisopropylethylamine; EBTHI, Ethylene-bis-tetrahydroindenyl; HMPA, Hexamethylphosphoric triamide; LAH, Lithium aluminium hydride; MOM, Methoxymethyl; PTSA, *para*-Toluenesulfonic acid; SET, Single electron transfer; TBAF, Tetrabutylammonium fluoride; TBAI, Tetrabutylammonium iodide; TBATFB, Tetrabutylammonium tetrafluoroborate; TBDMS, *tert*-Butyldimethylsilyl; TBDPS, *tert*-Butyldiphenylsilyl; TEA, Triethylamine; TESCl, Triethyl silylchloride; TfO, Trifluoromethylsulfonyl; THP, Tetrahydropyranyl; TIPS, Triisopropylsilyl; TMEDA, Tetramethylethylene diamine; TMSCl, Trimethylsilyl chloride.
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doi:10.1016/j.tet.2006.09.002

1. Introduction

Carbon–carbon bond-forming reactions are pivotal to organic synthesis. Chemists in many cases have succeeded in achieving good control over a number of such reactions and pinacol coupling can be placed in this category. Ever since the pioneering work by Fittig in 1859,[1] this reaction has remained as a challenging target for organic chemists, due to the need for dual control, diastereoselectivity and enantioselectivity in a single step. A slow and sustained evolution took place over about 150 years through a number of stages, an exponential growth being noticed in the last 10 years. The popularity of this reaction stems from its intrinsic ability to furnish 1,2-diols, which are a very important class of compounds. These can serve as the structural motif in total synthesis, and as chiral auxiliaries or chiral ligands. These diols can be even converted into a number of compounds such as aminoalcohols, epoxides, ketones etc. (Fig. 1).

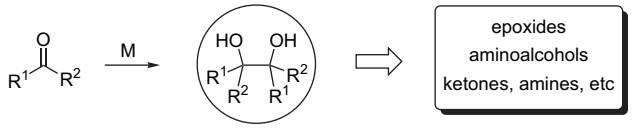


Figure 1. Pinacol coupling: a versatile reaction.

A variety of methods have been used to perform this reaction. Of these, the most reliable is the use of low-valent metals or metal complexes in stoichiometric or catalytic amount. Although the reaction path followed in pinacol coupling is described in the literature, the origin of the enantioselectivity is still not clear.[2] In the present report, we will describe different protocols adopted to pursue pinacol coupling in both a diastereoselective fashion and enantioselective fashion. A glimpse of the various compounds prepared using pinacol coupling as the key step will also be provided.

The most general method of presenting the mechanism of the pinacol coupling reaction is shown in Figure 2. The first step of this reaction is the generation of a ketyl radical, generally achieved through the homolytic cleavage of the carbonyl bond in the presence of a metal. A simultaneous electron transfer from the metal atom furnishes the metal bound ketyl radical, which can have several fates depending upon its stability. When the dimerization of two such radicals takes place through a pseudo-bridged metal atom, the *dl* selectivity in the product predominates, owing to steric reasons. On the other hand, when two such species couple through a non-bridged intermediate, the formation of the *meso* product is favoured. In the case of intramolecular

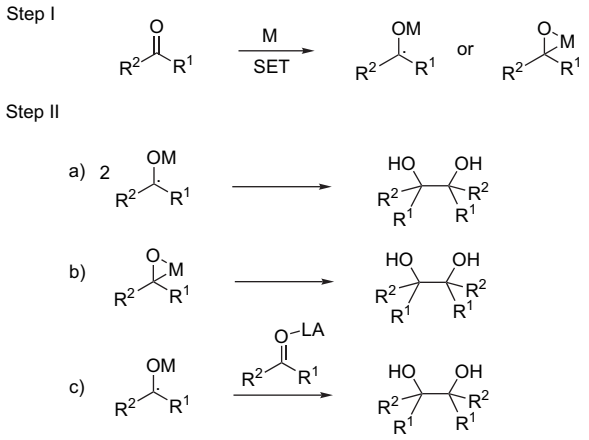


Figure 2. Mechanism of pinacol coupling.

pinacol coupling, the cis product is formed in a higher ratio through a metal-bridged intermediate. However, in the case of transition metals, the metal insertion into the carbonyl group generates an oxirane. Thus the carbonyl character is umpoled to initiate the attack by another molecule. The last possibility is the dimerization of a ketyl radical with an activated carbonyl group.

2. Reagents for pinacol coupling

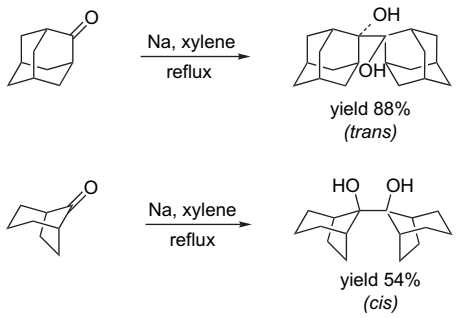
Earlier efforts on pinacol coupling utilized alkali or alkaline earth metals as the reagents, which provided poor diastereoselection. Later, several transition metals, lanthanides or p-block elements were used successfully to induce higher selectivity. More recently, high levels of diastereoselection and even enantioselection have been achieved using specifically designed metal complexes. The use of the reagents has therefore been subdivided into two classes. The stoichiometric use of metals or metal complexes for achieving stereoselectivity, is discussed in Section 2.1, whilst Section 2.2 deals with the catalytic protocols.

2.1. Stoichiometric protocols

2.1.1. Diastereoselective protocols.

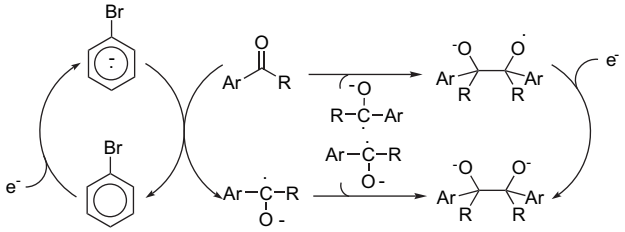
2.1.1.1. Alkali and alkaline earth metals. The use of sodium in the pinacol coupling reaction is an age-old process, frequently resulting in an unsatisfactory yield and selectivity or, sometimes, drastic conditions. In a few cases, a high selectivity was reported for hindered ketones (Scheme 1).[3,4]

Among other alkali metals, lithium in combination with a stoichiometric amount of TMSCl or liquid NH_3 provided



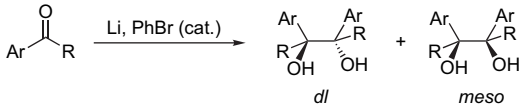
Scheme 1. Pinacol coupling of hindered ketones.

pinacols with low yield and selectivity.[5,6] Recently, Guo et al. reported a novel solvent-free system where a high diastereoselectivity was achieved using lithium and a catalytic amount of bromobenzene as the electron carrier (Scheme 2).[7] The selectivity in the case of aromatic aldehydes was very high (Table 1). Good diastereoselectivity was also achieved using amalgamated lithium.[8]



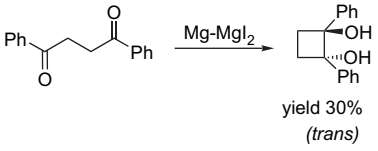
Scheme 2. Bromobenzene as electron carrier.

Table 1. Lithium mediated pinacol coupling



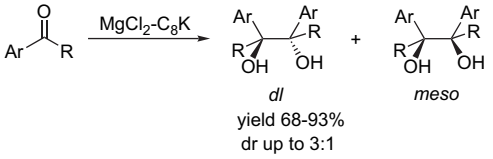
Entry	Substrate	Yield (%)	*dl*:*meso*
1	PhCHO	84	99:1
2	2-ClC_6H_4CHO	81	*dl* only
3	2,4-$Cl_2C_6H_3CHO$	90	*dl* only
4	PhCOMe	87	74:26
5	PhCH=CHCOMe	75	*dl* only

Magnesium is the only alkaline earth metal, which found early application in the pinacol coupling reaction in an amalgamated form. The selectivity, however, remained low in most cases. Even a combination of Mg/TMSCl was equally inefficient.[9] A equimolar mixture of Mg/MgI_2 proved little better in few cases (Scheme 3).[10]



Scheme 3. Preparation of a cyclobutanediol.

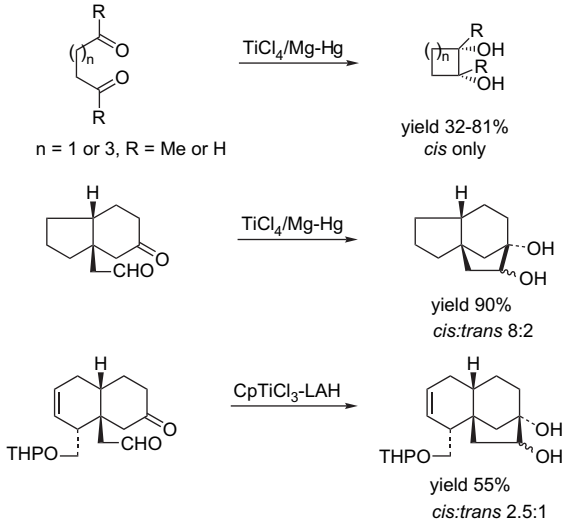
Magnesium as a fine dispersion on graphite can couple aldehydes or ketones with moderate selectivity.[11] A variety of aldehydes were coupled in high yields. The intramolecular cyclization also proceeded smoothly (Scheme 4).



Scheme 4. Magnesium-mediated pinacol coupling.

2.1.1.2. Transition metals. Titanium is the most popular reagent for pinacol coupling. The development of titanium chemistry proliferated in the early 1980s following three independent discoveries by Tyrlik et al.,[12] Mukaiyama et al.,[13] and McMurry and Fleming[14] that described low-valent titanium species for the reductive coupling of ketones/aldehydes. All these investigations unveiled the synthetic utility of low-valent titanium and opened new vistas in organometallic chemistry.

A number of reducing agents have been employed for the generation of low-valent titanium species, which are thought to be efficient reagents for the pinacol coupling reaction. Initially, Ti(II)-based coupling agents were used and these met with moderate success in terms of selectivity.[15] One of the most efficient precursor was developed by Corey et al. using $TiCl_4$ and magnesium amalgam.[16] This was further modified to $CpTiCl_3$–LAH for the cross-coupling of ketones with aldehydes (Scheme 5).

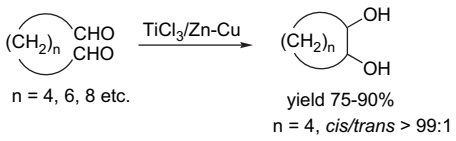


Scheme 5. Titanium(II)-mediated pinacol coupling.

A Ti(II)–porphyrin complex was also found to promote the pinacol coupling of aromatic ketones in moderate selectivity.[17]

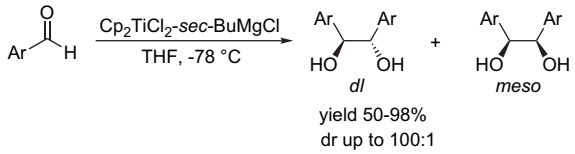
The combination of $TiCl_3$/Zn–Cu, introduced by McMurry and Rico, was used successfully for the intramolecular coupling of various aldehydes.[18] The cis isomer dominated in the smaller rings, whereas the trans isomer became prominent with rings containing 10 or more carbon atoms (Scheme 6).

Until the early 1980s there were hardly any reports of pinacol coupling using well-defined Ti^{3+} species.[19] Inanaga in



Scheme 6. Cyclization of dialdehydes using pinacol coupling.

1987 reported a cyclopentyl-bound Ti^{3+} reagent, generated by the reduction of Cp_2TiCl_2 with *sec*-BuMgCl, for the coupling of aromatic aldehydes.[20] Aldehydes containing an electron-donating group were coupled in excellent selectivity (Scheme 7).



Scheme 7. Titanium(III)-mediated pinacol coupling.

Aliphatic aldehydes showed poor selectivity. The stereochemical outcome was attributed to a dimeric structure (**1**), as shown in Figure 3.

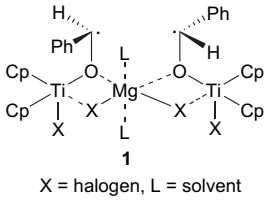
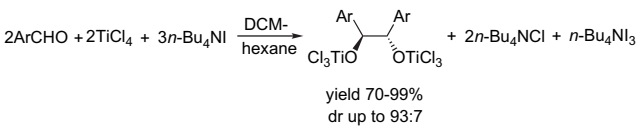


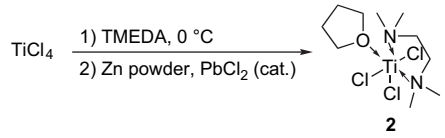
Figure 3. Trinuclear Ti(III)-complex responsible for high selectivity.

The high *dl* selectivity originated from repulsion of the aromatic groups. This assumption was reinforced by the experimental finding that the *dl* selectivity decreases with an electron-withdrawing substituent in the aromatic ring. Porta et al. showed that anhydrous $TiCl_3$ solutions in dichloromethane can provide pinacols with high selectivities.[21] Various other combinations, e.g., $Ti(O^iPr)_4$/EtMgBr,[22] $TiCl_4$/Zn,[23] Cp_2TiCl_2/SmI_2,[20] Cp_2TiCl_2/Zn,[20] or $Cp_2TiCl_2/^iPrMgI$,[20] were also used for pinacol coupling with a high degree of success. In most cases, a stoichiometric reductant was used to produce the low-valent titanium with a concomitant generation of a metal halide. This caused the undesired paths to operate simultaneously, resulting in a poor selectivity. To avoid such a possibility, Oshima et al. used tetrabutylammonium iodide as a stoichiometric reductant (Scheme 8).[24] Tetrabutylammonium triiodide, which was generated as the side product, did not interfere in the reaction. The newly generated Ti(III) was found to be very efficient for both aliphatic as well as aromatic aldehydes. The mechanism proposed was proved by further experimental studies.



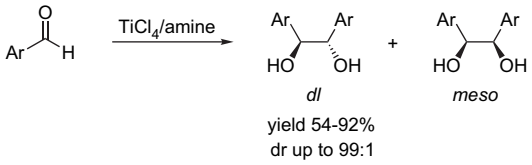
Scheme 8. Use of TBAI for the generation of titanium(III).

Addition of TMEDA and zinc to $TiCl_4$ in the presence of a catalytic amount of $PbCl_2$ provided [$TiCl_3$(TMEDA)(THF)] (**2**) in quantitative yield (Scheme 9). On employing the complex (**2**) with aromatic aldehydes, a high yield and excellent selectivity were observed in the pinacols.[25]



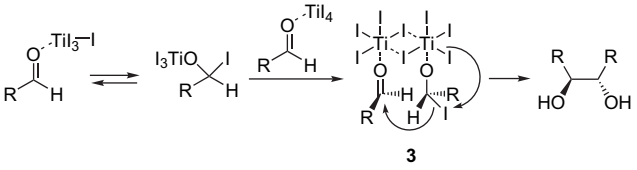
Scheme 9. Preparation of [$TiCl_3$(TMEDA)(THF)].

Addition of non-chelating amines, e.g., TEA,[26] or DIPEA,[27] to $TiCl_4$ proved to be equally effective in generating a Ti^{3+} species (Scheme 10).



Scheme 10. Use of amines for generation of titanium(III).

Pinacol coupling has also been achieved with Ti^{4+} species avoiding the use of any stoichiometric reductant. Titanium tetraiodide in propionitrile under an argon atmosphere provided hydrobenzoins in excellent yields and selectivities.[28] Aliphatic aldehydes were found to be inert in this reagent. To circumvent this problem, β-halogenated or α,β-unsaturated aliphatic aldehydes were employed.[29] The mechanism was believed to involve an iodination in the first step. The iodinated intermediate on reacting with another activated molecule formed (**3**) and, finally, the pinacol (Scheme 11).



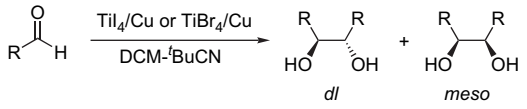
Scheme 11. Titanium(IV)-mediated pinacol coupling.

Other low-valent halogen derivatives were also employed for pinacol coupling reactions. Indeed, a low-valent titanium iodide generated by mixing TiI_4 and copper was found to provide better results than titanium dibromide or dichloride.[30] The superiority of the iodide derivative was explained by its monomeric nature, due to its larger size. Thus the inhibition of cluster formation resulted in a higher solubility and, in turn, a better selectivity.[31] The use of pivalonitrile as a co-solvent increased the solubility through coordination of the nitrogen lone pair (Table 2).

A number of other reagents, e.g., $TiCl_3$–K/I_2,[32] $TiCl_3$–Li/napthalene,[33] or $TiCl_2$–Zn,[34] to generate low-valent titanium were also employed for the pinacol coupling reaction.

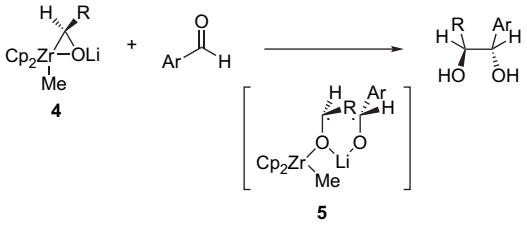
Pinacol coupling was also achieved through dimerization of anionic zirconaoxiranes (**4**) with aromatic aldehydes or

Table 2. Low-valent titanium halides for pinacol coupling



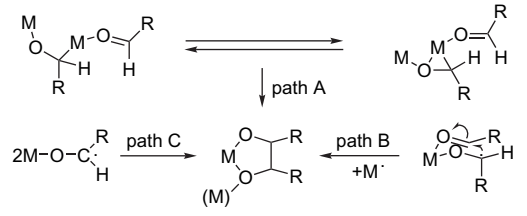
Entry	R	TiI_4/Cu		$TiBr_4$/Cu	
		Yield (%)	*dl*:*meso*	Yield (%)	*dl*:*meso*
1	Ph	94	>99:1	95	96:4
2	4-ClC_6H_4	93	>99:1	97	99:1
3	4-$MeOC_6H_4$	76	98:2	74	94:6
4	PhCH=CH	76	99:1	80	91:9
5	C_6H_{11}	98	85:15	75	75:25
6	Me_3C	92	85:15	—	—

ketones.[35] The cross-coupled products were produced in high yield with the selectivity up to 19:1 for *dl*:*meso* in the case of *p*-tolualdehyde. The higher selectivity was explained by a lithium-bound intermediate **5** (Scheme 12).



Scheme 12. Zirconium-mediated pinacol coupling.

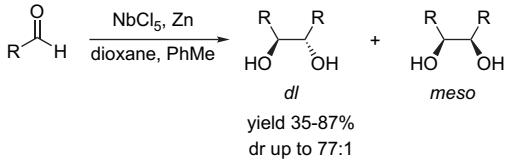
Among other early transition metals, vanadium has found widespread application in the stereoselective pinacol coupling reactions. In 1989 Pedersen et al. prepared a low-valent vanadium complex using $VCl_3(THF)_3$ and Zn. This complex showed a coupling ability towards aryl aldehydes with good yield and selectivity.[36] Aldehydes containing a chelating group in aromatic ring were found to be more suitable as a substrate. The reaction is believed to proceed via either path **A** or path **B** and not through path **C**, furnishing a cross-coupled product with two aldehydes of different reactivities in moderate yield, but poor selectivity (Scheme 13).



Scheme 13. Vanadium-mediated pinacol coupling.

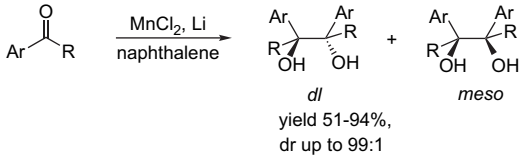
Aldehydes containing a sulfide or sulfone group were also coupled by employing this reagent. The effect of the size of the sulfur substituent was found to be optimum at a certain limit.[37]

Niobium proved to be effective for the coupling of aliphatic aldehydes in high selectivity. Even the intramolecular coupling proceeded with a high cis:trans ratio.[38] The in situ generation of Nb(III) by reducing $NbCl_5$ with Zn has been shown to be an excellent methodology for the pinacol coupling reaction (Scheme 14).[39] This reaction is believed to proceed through a niobiooxirane intermediate. Oshima et al. used Bu_4NI to reduce $NbCl_5$, which also provides a very high selectivity in the coupling of aromatic aldehydes.[24]



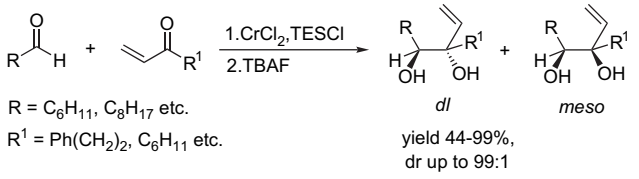
Scheme 14. Niobium-mediated pinacol coupling.

Reduction of manganese halides with lithium in the presence of an electron carrier generates active manganese species, which has been found to be an excellent promoter for the pinacol coupling reaction of a variety of aromatic aldehydes.[40] The ratio of manganese to aldehyde was found to be extremely important for a good yield. This protocol was equally effective for aromatic ketones, where a high selectivity was observed (Scheme 15).



Scheme 15. Manganese-mediated pinacol coupling.

A chromium-mediated cross-coupling between an α,β-unsaturated ketone and an aldehyde was reported by Takai et al. using an excess of $CrCl_2$ and TESCl.[41] The role of the silylating reagent was to trap the γ-siloxy-substituted allylic radical. This radical immediately reacts with Cr(II) to form γ-siloxy-substituted chromium complex, which couples with the aldehyde. A cyclopropane derivative was recovered in the absence of the silylating agent. The yield and selectivities were quite good (Scheme 16).



Scheme 16. Chromium-mediated pinacol coupling.

Zinc in the presence of trimethylsilyl chloride promoted the pinacol coupling of aromatic aldehydes.[42] Although the yields were moderate, the selectivities were very poor.

Inoue et al. used $FeCl_3$ and ^{n}BuLi to couple aromatic aldehydes and ketones. The yield and selectivity remained moderate.[43] The iron cluster **6** (Fig. 4) was also found to act as an efficient electron-transfer carrier in combination with ^{n}BuLi. The yield and the selectivity varied with the molar ratios of ^{n}BuLi employed.

2.1.1.3. p-Block elements. Very few p-block elements have been used in stoichiometric amounts to perform a stereoselective pinacol coupling reaction.

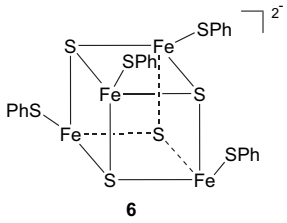


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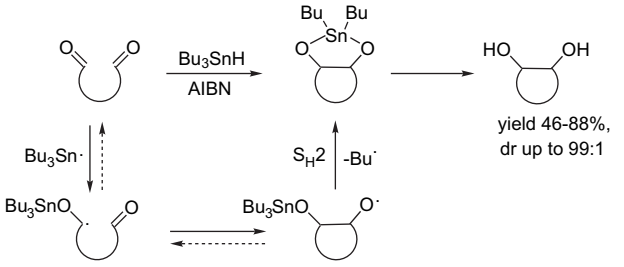
Figure 4. Iron complex used for pinacol coupling.

Schreibmann reported the pinacol coupling of acetophenone using aluminium amalgam in dichloromethane with a very high *dl* selectivity.[44]

Hexamethyldisilane in combination with a catalytic amount of CsF or TBAF afforded pinacols in moderate to good yield, but poor selectivity.[45]

Tributyltin hydride was found to promote intramolecular pinacol coupling in the presence of AIBN.[46] This reagent, with the ability to form five- or six-membered rings, showed an excellent selectivity for the cis isomer in very good yield. A thorough study of the reaction mechanism was conducted using isotope-labelling experiments. The key step was found to be an unprecedented addition of a tin ketyl radical to carbonyl. A subsequent intramolecular homolytic substitution (S_H2) provided the pinacol (Scheme 17).

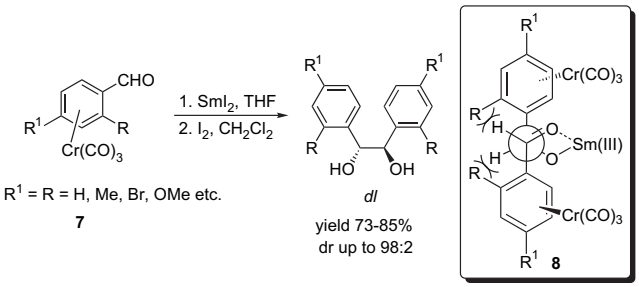


Scheme 17. Tin-mediated pinacol coupling.

2.1.1.4. Lanthanides. Among the lanthanides, samarium has been used most widely for both intra- and intermolecular pinacol coupling reactions. Hirao et al. showed however, that it is possible to promote pinacol coupling by using almost every lanthanide in the presence of TMSCl under sonication.[47] The selectivities varied, depending upon the lanthanide employed.

Kagan et al. introduced SmI_2 in 1983 for the pinacol coupling of aromatic or aliphatic aldehydes, which proceeded with very poor selectivity.[48] Although the addition of TMSCl accelerated the reaction considerably, there was no improvement in the diastereoselectivity of the product.[49] Yanada and Negoro later performed this reaction in protic solvents like MeOH without any improvement in the selectivity.[50] The story remained the same with other reagents, e.g., Sm/TMSCl/NaI[51] or Sm/Et_2AlI.[52]

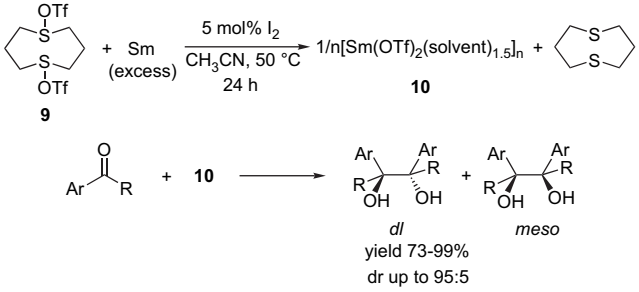
Uemura et al. reported *dl* selective pinacol coupling using a chromium-bound benzaldehyde complex (**7**).[53] A very high yield and selectivity were observed with various aldehydes (Scheme 18).



Scheme 18. Diastereoselective pinacol coupling using chromium-bound aldehydes.

Surprisingly, the addition of HMPA reversed the selectivity. The rationale for this high selectivity was explained through a Newman model (**8**), where both the oxygen atoms of the carbonyls were bound to the same samarium. This conformation was disrupted through coordination of a heteroatom or by an *o*-substituent, as a result of which, a reversal in the selectivity was observed in the case of the *o*-bromo derivative.

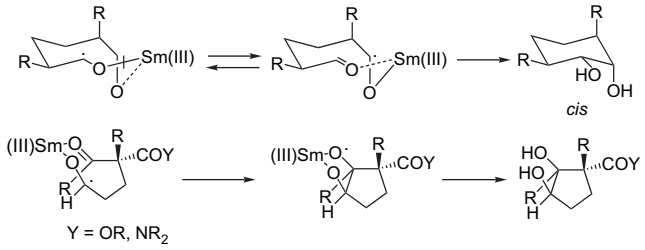
Besides samarium halides, divalent samarium triflate was found to be an excellent precursor. The in situ generation was achieved by reducing $Sm(OTf)_3$ with EtMgBr[54] or *sec*-BuLi.[55] The selectivity was very low in both cases. An excellent diastereoselectivity with aromatic ketones was reported by Tani et al. with a divalent samarium complex (**10**) prepared in situ from the hypervalent sulfur compound (**9**) (Scheme 19).[56]



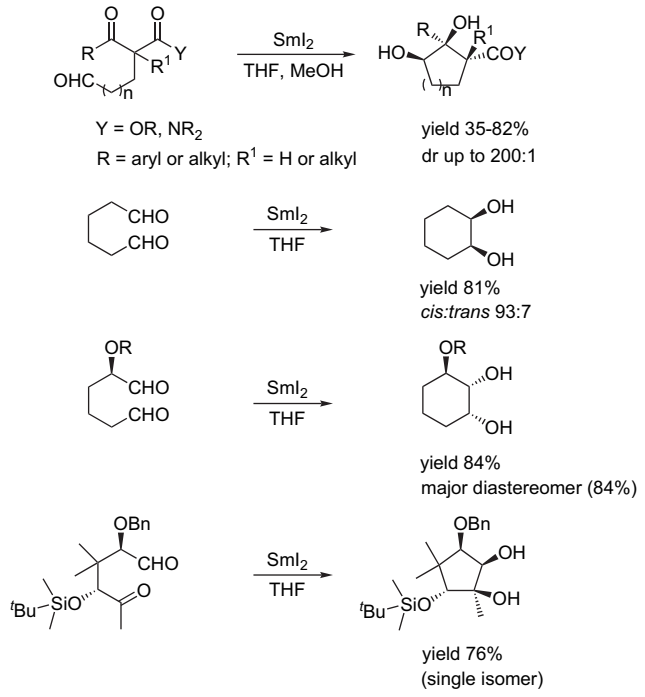
Scheme 19. Samarium triflate-mediated diastereoselective pinacol coupling.

The chemistry of samarium-mediated intramolecular pinacol coupling is rather rich and well established. The first example in this category was reported by Kagan et al. in the year 1983 during the synthesis of 1,2-diphenyl-1,2-cyclohexanediol.[57] Later, a number of publications appeared reporting that a definite stereocontrol was achieved with the help of a neighbouring coordinating group. Hanessian et al. prepared a number of cyclic diols from the corresponding dialdehydes or ketones with a high cis selectivity.[58] The stereochemical outcome was attributed to the inherent geometric preference for the coordination of the ketyl radical with the distal aldehyde carbonyl and the samarium(III) ion (Scheme 20). The most interesting feature of this coupling reaction is that the presence of an alkoxy,[58] ester,[59] amide[59] or siloxy[60] group in the neighbouring carbon on either or one of the carbonyl groups forces an *anti* orientation of the hydroxyl group with respect to the substituent (Scheme 21).

It is logical to assume that the dipolar repulsion (β-substituent effect) plays a key role in this reaction. To minimize the



Scheme 20. Origin of selectivity in samarium-mediated intramolecular pinacol coupling.

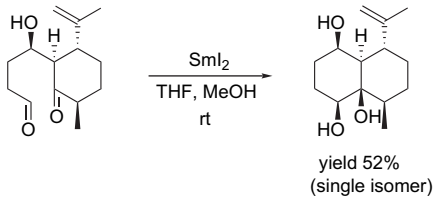


Scheme 21. Influence of neighbouring group in pinacol coupling.

electronic as well as steric repulsion with the α-substituent, a trans orientation of the hydroxyl group is favoured.

A free OH group was also found to effect the selectivity through coordination (Scheme 22).[61]

Fujiwara et al. proposed a detailed mechanism for the umpoled behaviour of the diaryl ketones during the synthesis of pinacols with a poor selectivity using ytterbium.[62] In the presence of trimethylsilyl bromide[63] or phenylthiotrimethylsilane,[64] metallic ytterbium was found to promote pinacol coupling efficiently. The former reagent was applied for



Scheme 22. Influence of hydroxyl group in pinacol coupling.

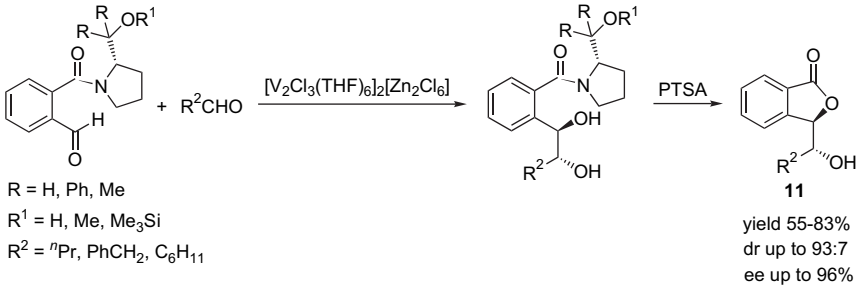
cyclic aliphatic ketones whereas the latter was effective for aromatic systems. The ratio of *dl*:*meso* went up to 4:1 in the case of the *p*-chloro derivative. The yields were all moderate.

2.1.2. Enantioselective protocols. There are very few examples of enantioselective pinacol coupling using stoichiometric protocols. Enantioselectivity in most cases has been achieved by either using a chiral auxiliary or by transferring the axial chirality to the central atom. The use of a stoichiometric amount of chiral complexes proved to be the most effective.

2.1.2.1. Alkali and alkaline earth metals. The enantioselectivity in a lithium-induced pinacol coupling of camphor originated from a selective coupling between two similar enantiomers. Pradhan et al. reported that, when optically active or racemic camphor was subjected to pinacol coupling under the same conditions, only a single pinacol or racemate was produced, respectively.[6] The stereochemistry of the single product formed was established to be *endo*:*endo*. The conclusion drawn was that the reaction took place only between a (+) and (+) or a (−) and (−) enantiomer. The single isomer was produced in moderate yield, but high selectivity.

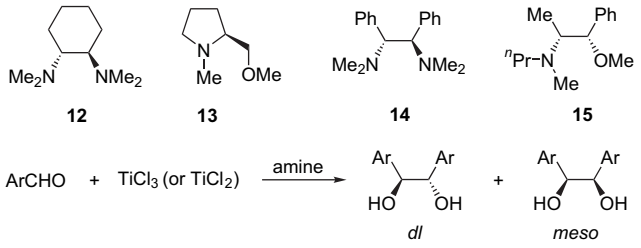
2.1.2.2. Transition metals. Using $[V_2Cl_3(THF)_6]_2$-$[Zn_2Cl_6]$ for the cross-coupling between an aliphatic and an aromatic aldehyde containing a chiral auxiliary, high enantioselectivity in the final product (**11**) was obtained (Scheme 23).[65]

Titanium is the most successful among all the metals in producing optically active pinacols from prochiral aldehydes. A preformed chiral titanium complex or titanium in combination with a chiral ligand is used as the most reliable tool to perform enantioselective pinacol coupling reactions. Matsubara et al. achieved a moderate enantioselectivity using a chiral amine with a low-valent titanium species.[66] Among the variety of chiral amines examined (**12**–**15**), *N*,*N*,*N*,*N*-tetramethylcyclohexylamine (**12**) proved to be the most effective in combination with $TiCl_3$, inducing 40% ee in hydrobenzoin. An insight into the reaction mechanism using various



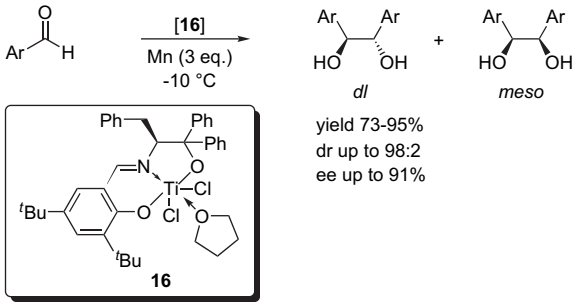
Scheme 23. Vanadium-mediated enantioselective pinacol coupling.

instrumental measurements revealed the presence of two types of particles in the solution. Cluster particles with the general formula $[(TiCl_3)_n(amine)_m]$ were inert and responsible for the drop of ee, whereas the monomeric particles $[TiCl_3(amine)_{1-2}(THF)_{1-2}]$ were responsible for the coupling. The addition of a co-solvent to break up the cluster resulted in an increased ee of 58%. In another report, Enders and Ullrich achieved 65% ee with a high *dl*:*meso* ratio using $TiCl_2$/amine **13** for the coupling of benzaldehyde.[67] No better selectivity was observed with other aldehydes (Scheme 24).



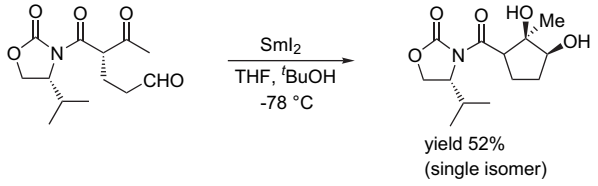
Scheme 24. Enantioselective pinacol coupling using optically active amines.

An enantioselectivity of up to 91% was reported by Riant et al. using a titanium hemi-SALEN complex **16** (Scheme 25).[68] A decrease in ee was observed with electron-withdrawing substituents at the *para* position.



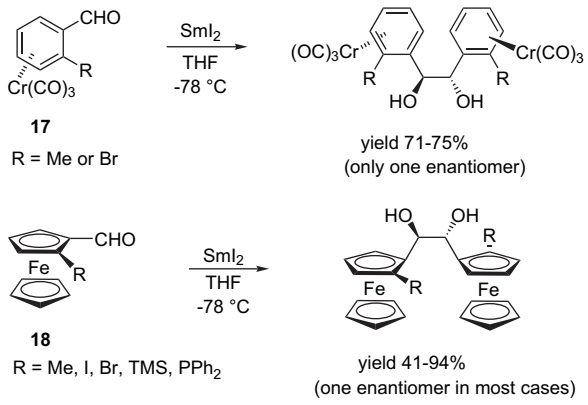
Scheme 25. Enantioselective pinacol coupling using a stoichiometric titanium complex.

2.1.2.3. Lanthanides. With a knowledge of the preferential cis selectivity of samarium-mediated intramolecular pinacol coupling reactions, a number of optically pure aldehydes were treated with SmI_2 to form the enantiomerically pure diols. One of the first examples was provided by Molander and Kenny through an intramolecular cross-coupling reaction (Scheme 26).[69]



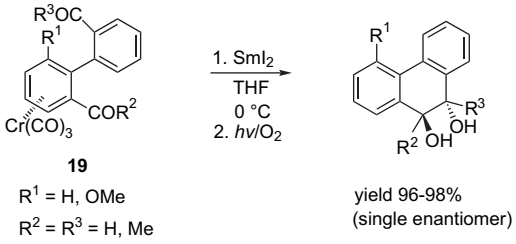
Scheme 26. Samarium-mediated enantioselective pinacol coupling.

Kagan et al. performed an intermolecular enantioselective pinacol coupling reaction between camphor and benzophenone using $SmBr_2$. As predicted, an optically pure diol was formed.[70] Uemura and Taniguchi showed that optically active chromium-bound *ortho*-substituted benzaldehydes (**17**) can be coupled in an enantioselective fashion using SmI_2.[71] The same methodology was further extended to optically active 2-substituted ferrocenecarboxaldehydes (**18**) (Scheme 27).



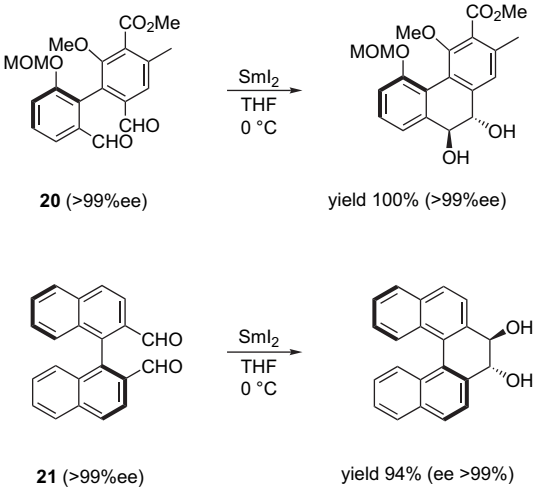
Scheme 27. Enantioselective pinacol coupling using optically active aldehydes.

Applying a similar methodology, chiral 1,2-diols were prepared from chiral mono $Cr(CO)_3$-complexed biphenyl derivatives **19** (Scheme 28).[72]



Scheme 28. Enantioselective pinacol coupling using chiral biaryls.

Suzuki et al. developed a new method for transferring the axial chirality of biphenyl derivatives to the central chirality through a pinacol coupling reaction.[73] After examining a variety of coupling agents, SmI_2 proved to be the most effective. The trans diols were obtained in a diastereomerically pure form starting from the aldehydes **20** and **21** (Scheme 29).



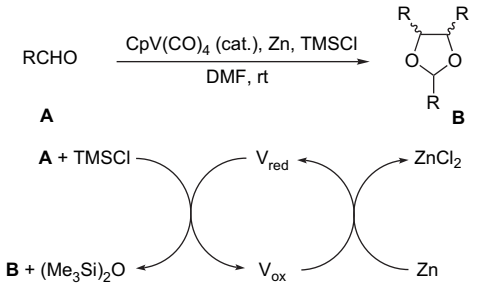
Scheme 29. Transfer of axial chirality.

2.2. Catalytic protocols

2.2.1. Diastereoselective protocols.

2.2.1.1. Transition metals. Although the introduction of catalytic protocols in the pinacol coupling reaction is not very old, it has developed exponentially in the last 10 years. Transition metals remained the most favoured reagents in this context.

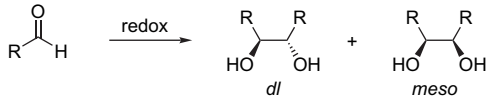
Hirao et al. in 1996 described the first catalytic cycle for a vanadium-mediated pinacol coupling reaction using Zn and TMSCl (Scheme 30).[74]



Scheme 30. First catalytic protocol for vanadium-mediated pinacol coupling.

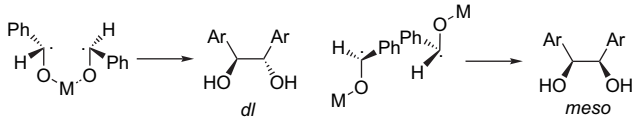
Soon after this report, various other methods were developed, based on similar reagents, e.g., $Cp_2VCl_2/Me_3SiCl/Zn$,[75] $VOCl_3/Me_3SiCl/Al$[76] etc. In most cases, a good selectivity was achieved (Table 3).

Table 3. Vanadium-mediated catalytic pinacol coupling



Entry	R	Redox	Yield (%)	*dl*:*meso*	Ref.
1	Ph	$VOCl_3$/Al/TMSCl	68	>95:5	76
2	4-ClC_6H_4	$VOCl_3$/Al/TMSCl	89	>95:5	76
3	4-MeC_6H_4	$VOCl_3$/Al/TMSCl	62	>95:5	76
4	C_6H_{11}	Cp_2VCl_2/Zn/TMSCl	66	90:10	75
5	Ph(Me)CH	Cp_2VCl_2/Zn/TMSCl	66	94:6	75
6	Me_2CH	Cp_2VCl_2/Zn/TMSCl	89	91:9	75

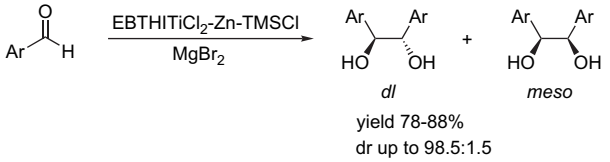
The higher *dl* selectivity was attributed to a metal-bridged intermediate. On the other hand, an acyclic intermediate was proposed for the *meso* product (Scheme 31).



Scheme 31. Origin of diastereoselectivity.

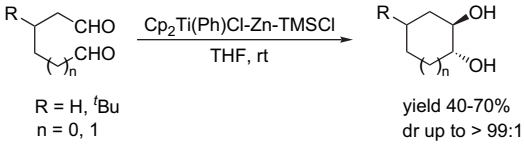
In addition to TMSCl, acetic anhydride was also found to regenerate the catalyst.[77] The pinacols were obtained in more than 80% yield with a variety of substituents at the *ortho*- or *para*-positions of the aromatic ring. The diastereoselectivity went up to 94:6 for *dl*:*meso* in the case of 2,6-$Me_2C_6H_3CHO$.

The immense potential of titanium to promote a high diastereoselection in the pinacol coupling reaction was realized through its stoichiometric protocols. A catalytic version is, however, highly desirable for expensive complexes. The first breakthrough came after the report by Fürstner and Hupperts on recycling titanium using TMSCl.[78] The well-documented Cp_2TiCl_2 prompted Gansäuer to pursue pinacol coupling with this reagent. As expected, a very good yield and diastereoselectivity were obtained with several aromatic aldehydes.[79] The preferential *syn* selectivity was attributed to a similar dimeric structure (**1**), as proposed by Inanaga and Handa.[20] The need to add 1 equiv of $MgBr_2$ was argued to contribute to a tighter trimeric species for better steric tuning. The slow addition of the mixture of TMSCl and aldehyde was the key to a higher selectivity and provided evidence for the silylation to be the rate-determining one. Hirao et al. applied the same protocol for the pinacol coupling of aliphatic aldehydes and ketones.[80] A high diastereoselectivity (96:4) for *dl*:*meso* was reported for cyclohexane carboxaldehyde, but it remained low for other acyclic aldehydes and ketones. A slightly higher selectivity for the aromatic aldehydes was achieved using *rac*-ethylenebis-(η^5-tetrahydroindenyl)titanium dichloride ($EBTHITiCl_2$) as a catalyst (Scheme 32).[81]



Scheme 32. Titanium-mediated catalytic pinacol coupling.

In most cases, the success of an organometallic complex depends upon the monomeric nature of the reagent in the solution state and, probably, this is the reason for the different behaviour of the newly generated titanium complexes from different sources. One of the easiest ways of prohibiting dimerization would be to increase the steric bulk of the ligand. With this logic in mind, Itoh et al. prepared the bulky $Cp_2TiPhCl$ for the coupling reaction.[82] Although the selectivity was lower with aliphatic or aromatic aldehydes, the intramolecular pinacol coupling of dialdehydes containing five to six carbon atoms proceeded with an excellent selectivity (Scheme 33).



Scheme 33. Catalytic pinacol coupling for cyclization of dialdehydes.

The high trans selectivity observed was contrary to the report of McMurry and Rico using $TiCl_3$/Zn–Cu.[18] This was explained by the restriction of the bulky titanium radical to coordinate with another aldehyde moiety, unlike McMurry's protocol, as a result of which, the repulsion of the two bulky titanium radicals favoured a trans orientation of the hydroxyl groups (Fig. 5).

Nelson et al. showed that instead of using complex ligands, it was possible to achieve high diastereoselection through a

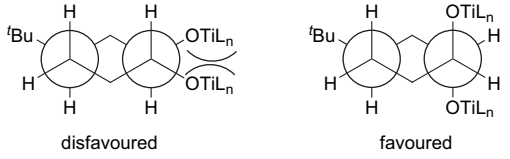
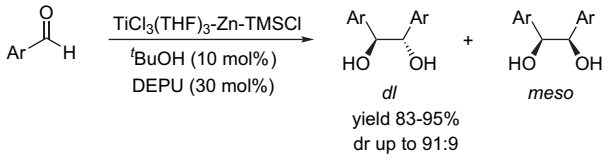


Figure 5. Origin of selectivity in cyclic diols.

proper tuning of the catalyst architecture.[83] $TiCl_3(THF)_3$–Zn–TMSCl redox in the presence of 10 mol % ^{t}BuOH and 30 mol % DEPU furnished a high *dl* selectivity for various aromatic aldehydes. In the optimized conditions, the 1,5-dialdehyde was also coupled with high selectivity (cis:trans=89:11) (Scheme 34).



Scheme 34. Diastereoselective pinacol coupling through ligand modification.

The catalytic cycle of titanium so far described was based on the stoichiometric use of TMSCl. Gansäuer and Bauer with 2,4,6-collidine hydrochloride salt also achieved a catalytic turnover through protonation of the metal–oxygen bond (Fig. 6).[84] This new protocol was found to be very effective for a variety of substituted aldehydes, furnishing an excellent selectivity (>95% for *dl*) and a high yield.

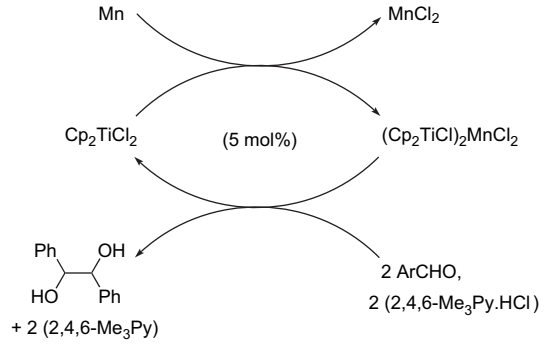
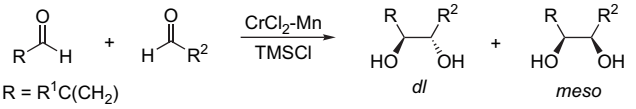


Figure 6. Development of a new catalytic cycle.

Hirao et al. established another catalytic cycle using acetyl chloride to cleave the metal–oxygen bond.[77] $TiCl_4$ in the presence of aluminium as a reductant and acetyl chloride as the catalyst regenerator provided a successful cycle for catalytic pinacol coupling of aromatic aldehydes. The yields were in the range 78–94% and the diastereomeric ratio for *dl*:*meso* was up to 91:9 for *p*-$CF_3C_6H_4CHO$.

Following the catalytic path established by Fürstner and Shi for the Nozaki–Hiyama–Kishi reaction,[85] a number of publications have appeared for the catalytic pinacol coupling of aldehydes or ketones using chromium.[86] A good yield and high selectivity have been achieved after optimizing the solvent polarity, steric properties of the silylating agent and the coreductant. Intramolecular pinacol coupling was also achieved in high cis selectivity. 2-Substituted acroleins were coupled with aldehydes in high selectivity using

Table 4. Catalytic, diastereoselective pinacol coupling using chromium salts



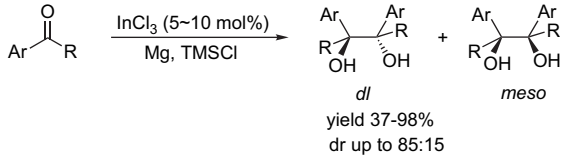
Entry	R^1	R^2	Yield (%)	*dl*:*meso*
1	^{t}Bu	^{t}Bu	61	>98:2
2	^{t}Bu	$Ph(CH_2)_2$	73	86:14
3	Me	^{t}Bu	54	28:72
4	H	^{t}Bu	52	22:78

$CrCl_2$/Mn/TMSCl (Table 4).[87] With decrease in the steric demand, a fall in the selectivity was noticed. The change of product conformation from *dl* to *meso* with changes in sterics was believed to be a consequence of the preferred conformation for the six-membered transition state for the cross-coupling reaction. It should be noted here that the reaction in this case does not proceed through a classical dimerization of two ketyl radicals. Instead, a chromium–allyl species attacks another aldehyde.[88]

Tu et al. proposed a similar catalytic method using nickel(II) chloride in combination with magnesium and TMSCl.[89] The catalytic cycle was believed to follow a similar path to that described for titanium. Although a variety of aromatic aldehydes were coupled in good yield, the diastereoselectivity remained low. Aromatic ketones and aliphatic aldehydes were also coupled with this protocol.

A cationic thiolate-bridged diruthenium complex [Cp*RuCl-($\mu_2S^iPr)_2$RuCp*][OTf] (Cp*=η^5–C_5Me_5) was used for the catalytic pinacol coupling reaction.[90] Unlike acetophenone, aromatic aldehydes were coupled in quantitative yield. The selectivity was low in all the cases.

2.2.1.2. p-Block elements. Among the p-block elements, only indium has been found to catalyze pinacol coupling reaction. $InCl_3$ in combination with Mg and TMSCl can couple aromatic aldehydes and ketones[91] (Scheme 35). An electron-withdrawing group in the aromatic ring was found to decrease both the yield and selectivity, whereas an electron-donating substituent seemed to have a favourable effect.

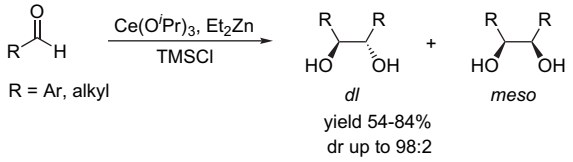


Scheme 35. Catalytic, diastereoselective pinacol coupling using indium.

2.2.1.3. Lanthanides. For the catalytic pinacol coupling reaction, cerium and samarium are the only successful candidates from the lanthanide group.

Groth and Jeske reported the first catalytic use of cerium in a method analogous to that described by Fürstner.[92] Diethylzinc was used in excess to generate the low-valent cerium, which was regenerated by TMSCl. The protocol proved to be effective even at a 3 mol % loading. Various aromatic

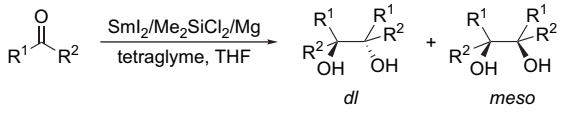
aldehydes were coupled in very high yield and excellent selectivity (Scheme 36). To overcome the need for demanding steric features for a higher selectivity, the reducing agents or the ligand framework were modified.[93] Long-chain aldehydes were also coupled for the first time with high selectivity using this modified procedure. The authors showed that, with an increase in the ligand sterics, the selectivity as well as the yield increased sharply.



Scheme 36. Catalytic, diastereoselective pinacol coupling using cerium.

Recently, Greeves et al. [94] have improved the selectivity through a slight modification of the original catalytic cycle proposed for samarium. Tetraglyme as an additive and Me_2SiCl_2 as the catalyst regenerator afforded a selectivity as high as 95:5 for the *dl*/*meso* for pivalaldehyde (Table 5).

Table 5. Catalytic, diastereoselective pinacol coupling using samarium



Entry	R^1	R^2	Yield (%)	*dl*:*meso*
1	Ph	H	83	20:80
2	Ph	Me	62	19:81
3	C_6H_{11}	H	63	81:19
4	Me_3C	H	76	95:5
5	C_6H_{11}	Me	74	94:6

For intramolecular pinacol coupling also protocol met with good success. The reversal of selectivity was attributed to the ease of reduction of aromatic aldehydes as compared to their aliphatic counterparts due to their low-energy LUMO electrons, as a result of which the concentration of these radicals becomes sufficiently high to allow dimerization between two such species resulting in *meso* products. On the other hand, the aliphatic ketyl radicals being less in population, prefer to attach to another aldehyde through a pseudo-bridged transition state (Fig. 7).

Namy and Hélion established a catalytic cycle using a new approach.[95] The reduction of trivalent samarium as well as cleavage of the Sm–O bond was achieved using mischmetall (a cheap alloy of light lanthanoids for industrial applications) (Fig. 8).

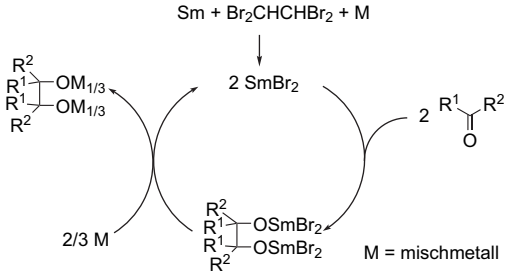
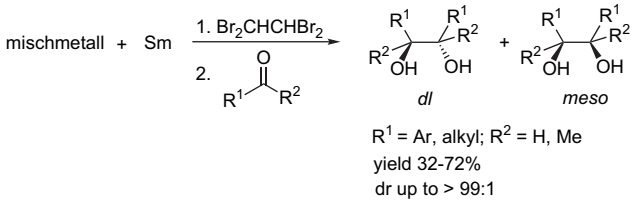


Figure 8. Development of catalytic cycle using mischmetall.

The *dl* selectivity went up to 100% in a highly demanding aldehyde.[96] The addition sequence and the addition time were found to be determining factors towards high selectivity. Following this protocol, under optimized conditions, a number of aldehydes and ketones were coupled with a high degree of success (Scheme 37).



Scheme 37. Catalytic, diastereoselective pinacol coupling using samarium.

2.2.2. Enantioselective protocols. Achieving enantioselectivity through the use of a chiral catalyst is considered to be the most modern way of synthesizing chiral compounds. For catalytic enantioselective pinacol coupling, titanium remains the most popular metal.

A variety of ligands (**22**–**28**) have been explored (Fig. 9). Cozzi and Umani-Ronchi were the first to notice a low chiral induction in the pinacols while using Ti–Schiff base complexes.[97] After examining various Schiff bases, they found that **22** induced 10% ee with high diastereoselectivity (*dl*:*meso*=90:10). Taking advantage of a high diastereoselectivity with *rac*-Brintzinger's catalyst (ethylenebis(tetrahydroindenyl)titanium dichloride), Nicholas and Dunlap tried to apply its chiral version to the catalytic pinacol coupling reaction.[98] They reported a moderate ee (60%) for the resulting pinacol in unoptimized conditions. To check the enantioselectivity of the pinacols using a similar ligand framework, the *ansa*-bis(indenyl) (Ti-**24**) and *ansa*-bis(tetrahydroindenyl)

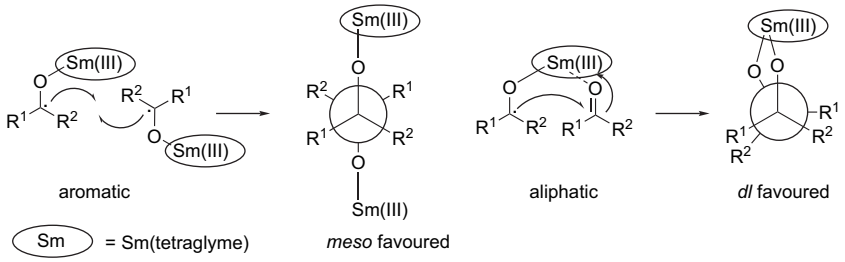


Figure 7. Rationale for reversal of selectivity.

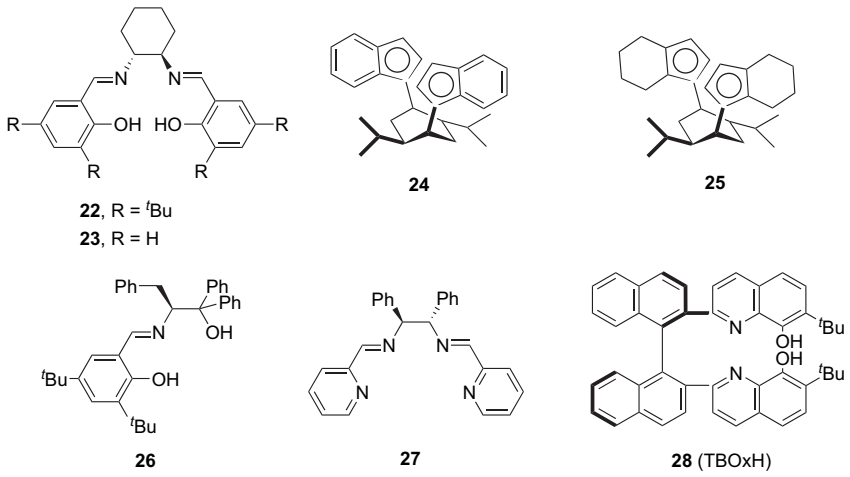


Figure 9. Chiral ligands used in catalytic, enantioselective pinacol coupling.

(Ti-**25**) metal complexes were employed.[99] A racemic product was, however, obtained using the bis(indenyl)complex (Ti-**24**), whereas a low ee resulted with the other complex (Ti-**25**). More recently, Riant et al. came up with a complex (**16**) using the hemi-SALEN ligand (**26**), which induced a moderate ee (64%) through a catalytic path.[68] This lower ee, as compared to its stoichiometric version, was rationalized through the inhibition of the proper catalytic path at a lower temperature. Later, our group reported a Ti-SALEN complex (Ti-**23**) as the first successful catalyst for this reaction.[100] Recently, You et al. reported an in situ generation of a Ti–Schiff base complex (Ti-**27**), which also showed a good enantioselectivity in most cases.[101]

The most effective catalyst for enantioselective pinacol coupling has been designed by Yamamoto et al. using a Cr complex of a tethered bis(8-quinolinolato) moiety (Cr-**28**).[102] The chromium complex was prepared in three steps in very high yield starting from the optically active 2,2-diiodo-1,1-binaphthyl. An X-ray crystallographic study of the racemic catalyst revealed a cis-β configuration of TBO*x*CrCl. This catalyst proved to be quite insensitive to steric as well as electronic changes in the aromatic ring. The enantioselectivity remained >95% in all cases. Indeed, the author also reported the first enantioselective coupling of aliphatic aldehydes.

A summary of various successful catalysts for pinacol coupling is provided in Table 6.

2.3. Other methods

2.3.1. Photochemical irradiation. The formation of benzopinacols upon irradiation was observed in 1900 by Ciamician[103] and, since then the photo-irradiation through sunlight has become a reliable method to prepare these compounds. The major drawback of this procedure, however, is the poor selectivity.[104] Recently, Li et al. reported the coupling of various aromatic aldehydes and ketones in excellent yields and, in some cases, very high selectivity.[105] The general mechanism involved in this reaction is excitation of the aldehyde group followed by extraction of hydrogen from the solvent to form the α-hydroxybenzyl radical. Finally, dimerization of this radical furnishes the product (Fig. 10).

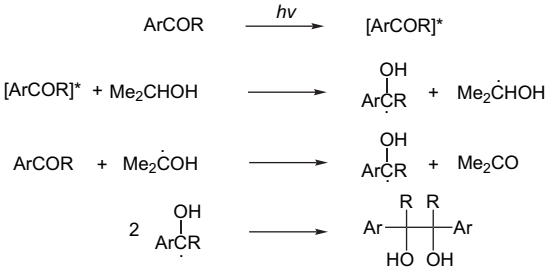
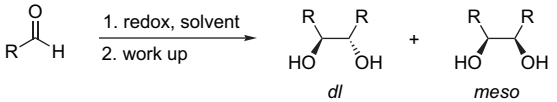


Figure 10. Mechanism of photo-induced pinacol coupling.

Table 6. Enantioselective pinacol coupling using various protocols

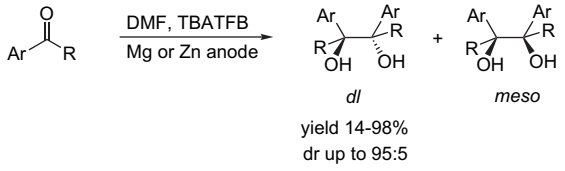


R	Redox	Cat. loading (mol %)	Temp (°C)	Yield (%)	*dl*:*meso*	ee (%)	Ref.
Ph	(Ti-**24**)–Zn–TMSCl	10	−10	94	98:2	95	100
4-MeC_6H_4	(Ti-**24**)–Zn–TMSCl	10	−10	84	91:9	96	100
2-MeC_6H_4	(Ti-**24**)–Zn–TMSCl	20	−10	75	96:4	82	100
2-Naphthyl	(Ti-**24**)–Zn–TMSCl	10	−10	82	94:6	91	100
Ph	(Cr-**28**)–Mn–TESCl	3	rt	94	98:2	97	102
3-MeOC_6H_4	(Cr-**28**)–Mn–TESCl	3	rt	92	98:2	97	102
4-$CF_3C_6H_4$	(Cr-**29**)–Mn–TESCl	3	rt	89	92:8	95	102
1-Naphthyl	(Cr-**28**)–Mn–TESCl	3	rt	92	96:4	98	102
–$(CH_2)_6$–	(Cr-**28**)–Mn–TMSCl	3	rt	44	93:7	84	102

Seebach and Daum showed that irradiation of a solution of acetophenone in the presence of a chiral amine at low temperature produced pinacol in 58% yield with 6% optical purity.[106]

2.3.2. Sonication. Ultrasonic irradiation has been used for quite some time as a tool to achieve pinacol coupling in a non-aqueous medium. Alkali metals such as Na or Li[107] or a combination of Sm/NH_4Cl[108] provided pinacols of various aromatic aldehydes and ketones in moderate to high yields, but with poor selectivity. Recently, Ranu et al. achieved high selectivity using Li in THF under sonication.[109] Aromatic aldehydes and ketones were coupled in moderate to high yields with the selectivity ranging from 75:25 to 98:2 for *dl*/*meso*.

2.3.3. Electrolysis. Electrochemical reductions have been used for a long time to prepare pinacols using a metal cathode (generally Hg) in an aqueous acidic or basic medium. Indeed, it is observed that the proportion of the *dl* isomer increases in aqueous alkaline solution over acidic conditions.[110] Using a Zn or Mg anode and a stainless steel cathode in the presence of TBATFB as a supporting electrolyte in DMF, a variety of aldehydes and ketones were coupled (Scheme 38).[111]



Scheme 38. Pinacol coupling using electrochemical methods.

Duñach et al. achieved a catalytic cycle of samarium in the presence of 5–10% of $SmCl_3$, based on the use of sacrificial anodes of Mg or Al.[112] A variety of aromatic aldehydes and ketones were coupled successfully in high yield, but with poor selectivity.

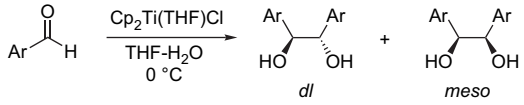
Seebach and Oei showed that it is possible to achieve some enantioselectivity using an achiral supporting electrolyte in a chiral medium.[113] The hydrodimerization of acetophenone in a solution containing (+)-DDB in combination with MeOH and LiBr, proceeded in 95% yield with a slight excess of one enantiomer. A maximum of 20% asymmetric induction was achieved in the electrochemical dimerization of acetophenone and its derivatives using chiral salts, e.g., (1*R*,2*S*)-$HOCHPhCHMeN^+Me_3I^-$.[114]

2.3.4. Reactions in aqueous media.

2.3.4.1. Alkali and alkaline earth metals. Magnesium is the only alkaline earth metal that can produce pinacol in a dilute aqueous solution of ammonium chloride, albeit with poor selectivity.[115]

2.3.4.2. Transition metals. Among the transition metals, titanium has remained the most successful in terms of selectivity. The reducing ability of titanium is very much dependant upon the pH of the medium and increases sharply with an increase in the pH value. In fact, aldehydes or ketones undergo coupling easily in a basic medium,[116] although with a low selectivity. A reagent-controlled highly selective pinacol coupling was reported by Schwartz and Barden using Cp_2TiCl in a mixed solvent of THF/H_2O for the α,β-unsaturated aldehydes (Table 7).[117] The selectivity was very high with $[(EBTHI)_2TiCl]$ for aromatic aldehydes.

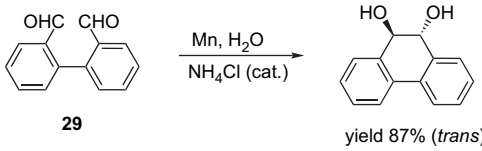
Table 7. Pinacol coupling in aqueous media



Entry	Ar	THF:H_2O	Yield (%)	*dl*:*meso*
1	Ph	20:80	82	95:5
2	4-FC_6H_4	80:20	85	94:6
3	4-$MeOC_6H_4$	80:20	88	94:6
4	Furfuraldehyde	80:20	75	95:5
5	Cinnamaldehyde	80:20	83	98:2

A variety of combinations such as Zn–Cu[118] or $Zn–ZnCl_2$[119] under ultrasonic irradiation were found to be effective. Zinc in the absence of any organic solvents, also afforded diols with a low selectivity.[120]

Aromatic aldehydes were found to react with manganese in an aqueous solution in the presence of a catalytic amount of acetic acid or in aqueous ammonium chloride. The yields were good but the selectivity was poor. [121] Surprisingly the intramolecular coupling of **29** afforded only the trans diastereomer in 87% yield (Scheme 39).

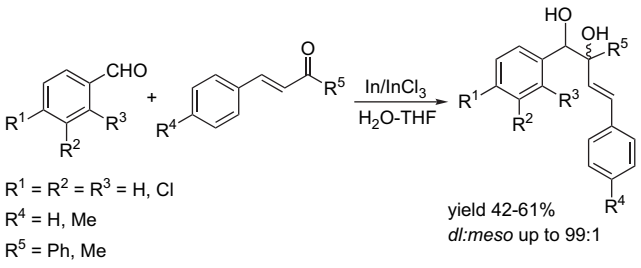


Scheme 39. Manganese-mediated pinacol coupling in aqueous media.

In situ generation of cadmium from $CdCl_2 \cdot H_2O$ in a DMF/H_2O medium by reduction with samarium metal enabled coupling of aromatic aldehydes in good yield with a *dl*:*meso* ratio of 89:11 for *o*-bromobenzaldehyde.[122]

2.3.4.3. p-Block elements. Among the p-block elements, aluminium has been widely used to promote pinacol coupling in an aqueous medium. In aqueous alkaline solution, aluminium powder was found to produce *vic* diols in moderate yield and selectivity under sonication.[123] An increase in the *meso* selectivity was noticed in the presence of metal fluorides.[124] Aluminium in an amalgamated form can also promote pinacol coupling of cycloalkanones in the mixed solvent THF/H_2O.[125]

Indium under prolonged sonication was found to promote pinacol coupling of substituted aromatic aldehydes in good yields, but with moderate selectivity.[126] Nair et al. showed that the cross-coupling between an aromatic aldehyde and a chalcone can be readily performed in aqueous THF in the presence of $In/InCl_3$.[127] The product yields were moderate and the *dl* selectivity was high (Scheme 40).



Scheme 40. Indium-mediated pinacol coupling in aqueous media.

2.3.4.4. Lanthanides. Samarium is the only lanthanide, which has been used for pinacol coupling in an aqueous medium. In aqueous acidic solution, samarium was found to couple aromatic aldehydes and diaryl ketones in high yield.[128] A binary combination of $SmCl_3$ with Sm or Mg was equally effective.[129] The selectivity was poor in all cases.

3. Synthetic applications of pinacol coupling

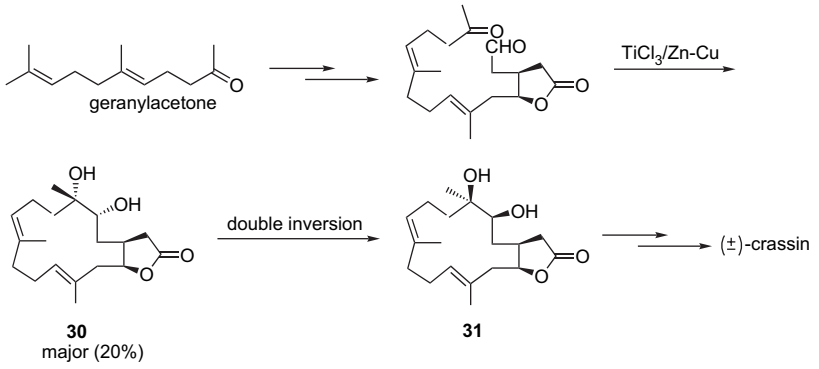
3.1. Terpenes

Pinacol coupling has been used successfully in many syntheses of di-, tri- or sesquiterpenes. McMurry and Dushin prepared racemic crassin, a diterpenoid, using $TiCl_3$/Zn–Cu to construct the 14-membered ring.[130] The keto–aldehyde coupling proceeded with 48% yield (including four isomers). As the yield of the desired isomer (**31**) was very low, the major isomer (**30**) was epimerized at the C_3, C_4 centre through double inversion (Scheme 41).

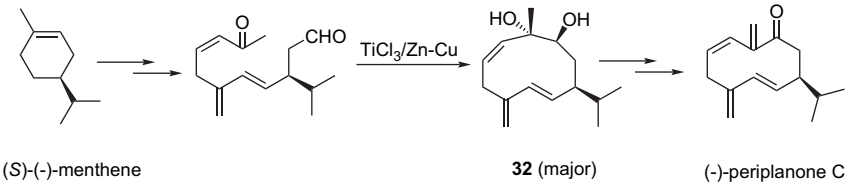
In another example, McMurry and Siemers reported the synthesis of (−)-periplanone C, a 10-membered sesquiterpene, which is an insect pheromone.[131] The 10-membered ring was constructed in a similar manner. Unlike the previous example and contrary to mechanistic calculations, the trans diol (**32**) was formed as the major product. Further transformations led to the final product (Scheme 42).

Corey and Kania prepared *rac* palominol and dolabellatrienone, a dolabellane class of marine diterpenoids, using pinacol coupling as the key step for the ring formation.[132] The coupling with low-valent titanium gave a mixture of two diastereomers (**33**) in a ratio of 2.1:1 as a separable mixture (53% yield) (Scheme 43).

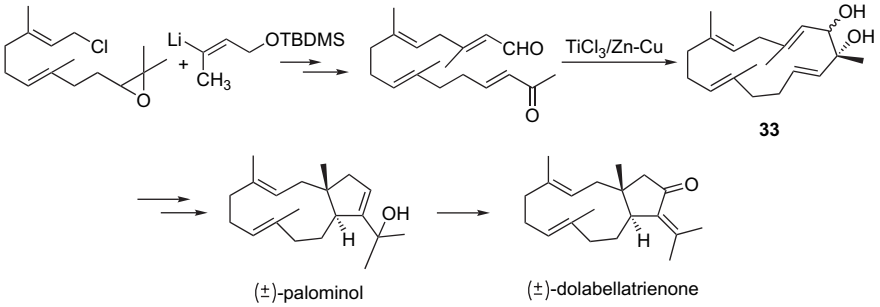
Li and Yue constructed the 14-membered ring of the macrocyclic diterpene, (+)-3,4-epoxycembrene-A, using $TiCl_4$/Zn.[133] The final product was obtained as a mixture of four



Scheme 41. Synthesis of (±)-crassin.

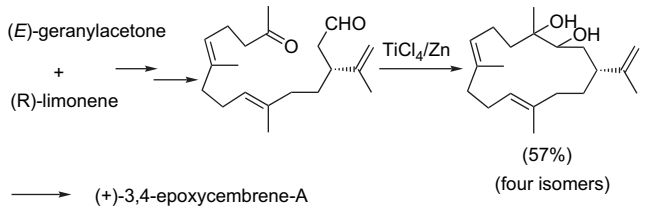


Scheme 42. Synthesis of (−)-periplanone C.



Scheme 43. Synthesis of (±)-dolabellatrienone.

stereoisomers (23:21:15:6), which were separated as epoxides through HPLC (Scheme 44).



Scheme 44. Synthesis of (+)-3,4-epoxycembrene-A.

During the synthesis of (+)-4,5-deoxyneodolabelline, a bicyclic diterpene, Williams and Heidebrecht showed that the low-valent titanium produced by $TiCl_3$/Zn–Cu, although less selective, is more efficient than the low-valent vanadium complex (Scheme 45).[134] The final product was separated after oxidation to obtain the desired isomer.

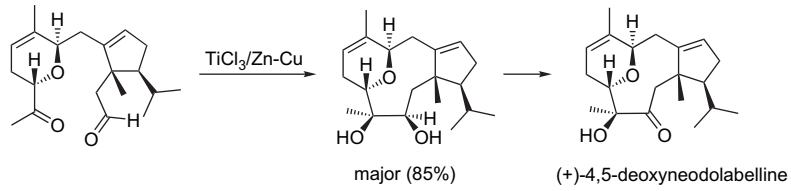
SmI_2 has proved to be equally effective for the preparation of various terpenes. Marcos et al. synthesized (+)-totarol, a tricyclic diterpene known to have pronounced biological activity, from zamoranic acid (**34**) using SmI_2 to form the C-ring. The major isomer (**35**) was shown to contain two α-OH groups (80%) (Scheme 46).[135]

Following a similar approach, another tetracyclic diterpene, 15-hibaen-14-one, was synthesized by the same group (Scheme 47).[136]

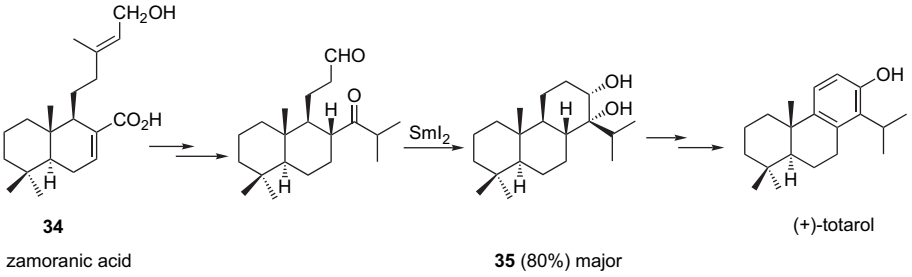
3.2. Sugars

The reaction of methyl trifluoropyruvate (**36**) and 2,3-di-*O*-isopropylidene-D-glyceraldehyde (**37**) in the presence of $TiCl_3$/Zn proceeded smoothly in moderate yield with a higher ratio of the trans isomer (**38**). This coupled product was further manipulated through a series of reactions to prepare D-ribose (Scheme 48).[137]

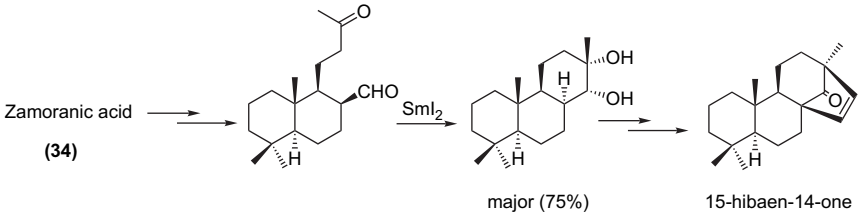
Schwartz and Barden have also prepared a mannitol derivative from 2,3-di-*O*-isopropylidene-D-glyceraldehyde (**37**) using acyclopentadienylzirconium complex (**39**) (Scheme 49). Although the yield was moderate, the selectivity was high (mannitol:iditol=88:12).[138]



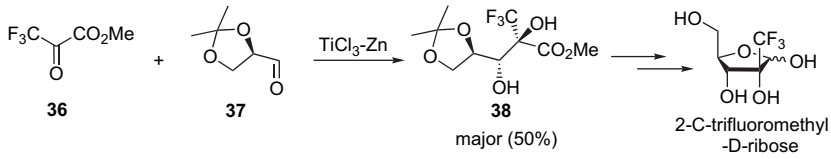
Scheme 45. Synthesis of (+)-4,5-deoxyneodolabelline.



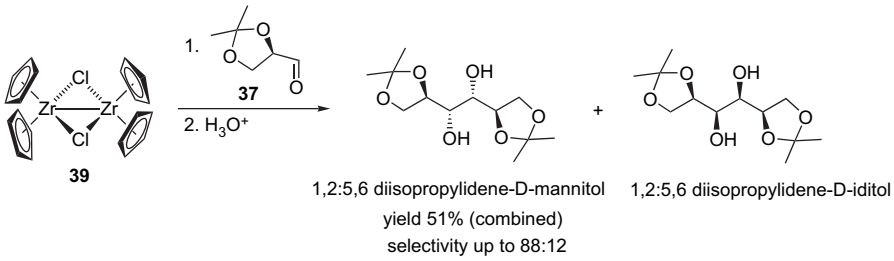
Scheme 46. Synthesis of (+)-totarol.



Scheme 47. Synthesis of 15-hibaen-14-one.



Scheme 48. Synthesis of D-ribose.



Scheme 49. Synthesis of protected sugars.

3.3. Inositols

Polyphosphoinositides play a significant role in the cellular signal transduction system. Among other derivatives, many *myo* and *chiro* inositols have been prepared from cheap chiral sources such as glucose isomers[139] or natural products, e.g., tartaric acid (Table 8).[140] SmI_2 has been used extensively for the intramolecular pinacol coupling, a key step for the preparation of these molecules. In all cases, a very high *syn* selectivity was observed.

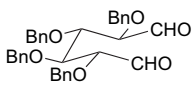
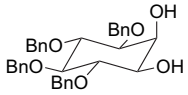
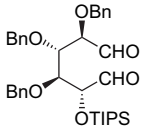
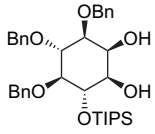
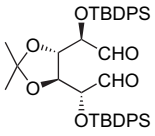
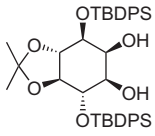
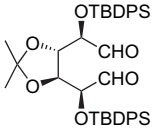
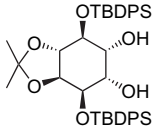
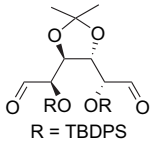
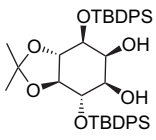
3.4. Taxol

Taxol, isolated from *Taxus brevifolia*, is a clinically very useful anticancer agent. There are many reports with different approaches for the synthesis of this molecule (Fig. 11). In many cases, intramolecular pinacol coupling has been used as the most reliable tool to synthesize this molecule or similar molecular structures (taxanes or taxadienes or hydroxytaxols) with the desired stereochemistry. Nicolaou et al. have used pinacol coupling as a key step to link the A- and C-ring by forming the C_9–C_{10} bond using $TiCl_3$/Zn–Cu with a predominant *syn* stereochemistry (**40**).[141] In a different approach, Swindell and Fan constructed the B-ring (**41**) by forming C_1–C_2 bond through pinacol coupling using $TiCl_4$/Zn, which was found to be more effective than SmI_2 in terms of selectivity.[142] In a few cases, SmI_2 has also proved to be a useful reagent for the construction of the C-ring with *syn* selectivity in a related molecular framework (**42**).[143] The keto-aldehyde coupling proceeded in 43% yield with the formation of the C_3–C_4 bond. Recently, Mukaiyama et al. have even constructed the A-ring of hydroxytaxol (**43**) using a $TiCl_2$/LAH combination with *syn* selectivity (64%).[144] Shirahama et al. constructed a similar molecular framework using SmI_2 to prepare the B-ring.[145] Although the yield was moderate, the selectivity was high.

3.5. Protease inhibitors

C_2-symmetric HIV protease inhibitor **44** was prepared using pinacol coupling as the key step. $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ or $NbCl_3$ proved to be equally effective, favouring a high

Table 8. Synthesis of inositols using pinacol coupling

Starting	Intermediate	Reagent	Product	Yield (%)/selectivity (Ref.)
L-Iditol		SmI_2, ^{t}BuOH–THF, −78 °C		56, *myo*, cis (139a)
D-Xylose		SmI_2, THF, −78 °C		70, *myo*, cis:trans>20:1 (139c)
D-Mannitol		SmI_2, ^{t}BuOH–THF, −50 °C		86, *myo*, cis:trans>92:8 (139b)
D-Sorbitol		SmI_2, ^{t}BuOH–THF, −70 °C		78, *chiro*, cis:trans 94:6 (139d)
2,3-*O*-Iso-propylidene-D-tartarate		SmI_2, ^{t}BuOH–THF, −78 °C		87, *myo*, cis (140)

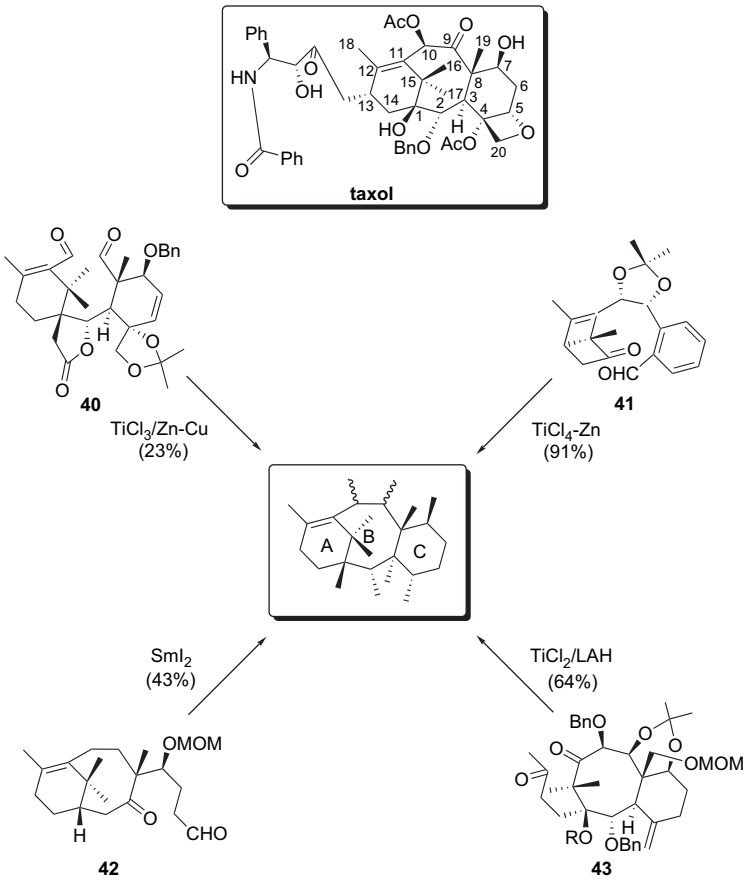
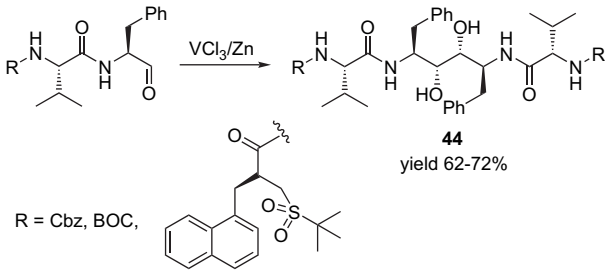


Figure 11. Construction of taxol and related frameworks using pinacol coupling.



Scheme 50. Synthesis of C_2-symmetric HIV protease inhibitors.

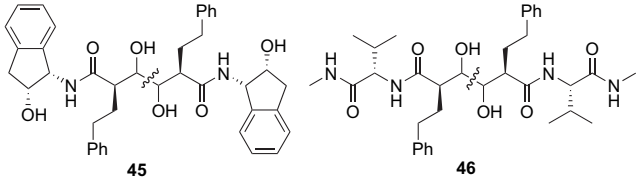


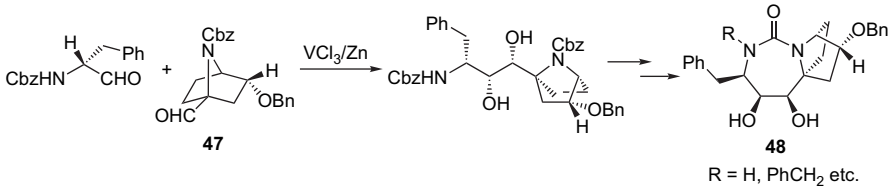
Figure 12. HIV protease inhibitors synthesized using pinacol coupling.

selectivity in the coupled product.[146] The yields were, however, high in the former case and this reagent was applicable, even on a multigram scale (Scheme 50).

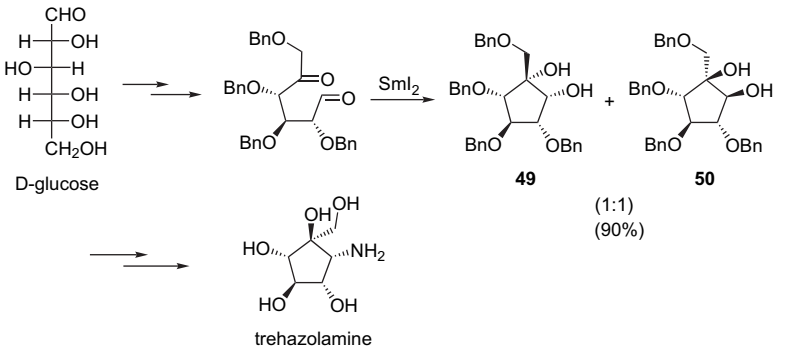
Samuelsson et al. prepared similar C_2-symmetric protease inhibitors (**45** and **46**) using vanadium to induce pinacol coupling as the key step (Fig. 12).[147] The selectivity in this case was not high.

Han et al. prepared a new class of HIV protease inhibitor, a tricyclic urease (**48**), through coupling of D-phenylalaninal and a hindered aldehyde (**47**) using VCl_3/Zn.[148] The selectivity of the cis isomer was found to be 85%. Further transformation of the diol led to the final product (Scheme 51).

Chiara et al. prepared the aglycon of the potent trehalase inhibitor, trehazolamine, from D-glucose using SmI_2-mediated pinacol coupling.[149] Although the relative stereochemistry of the newly generated stereocenters was cis, the two diastereomers (**49** and **50**) were produced in equal amounts



Scheme 51. Synthesis of tricyclic HIV protease inhibitors.



Scheme 52. Synthesis of trehazolamine.

(Scheme 52). They were separated either through crystallization or derivatization.

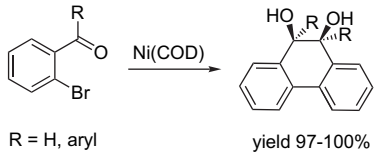
3.6. Antibiotics

Pedersen et al. synthesized the broad-spectrum antibiotics, fortimicins AM and AK, via successive inter- and intramolecular pinacol coupling.[150] Starting from an *N*-protected serine derivative (**51**), the first pinacol coupling using VCl_3/Zn determined the cis stereochemistry of the two hydroxyl groups in an intermolecular path (**52**). In another step, the intramolecular version with the same reagent provided the cyclic unit (**53**) with the desired orientation of the hydroxyl groups (Scheme 53).

3.7. Other compounds

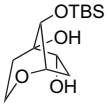
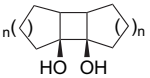
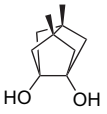
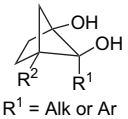
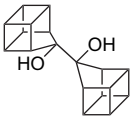
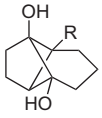
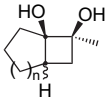
Besides the above complex molecules, pinacol coupling has been widely used for preparing various classes of compounds. Pedersen et al. prepared chiral [*N*-(alkoxycarbonyl)-amino]-1,2-diols[151] and γ-butyrolactones[152] using low-valent vanadium. They showed that hydroxymethylation of an aldehyde can also be effected via this reagent.[153] In all cases, a high yield and selectivity were observed. Banfi et al. prepared lactenediynes in high selectivity using low-valent vanadium.[154] 2-Bromobenzaldehyde was transformed into pinacols in one pot using an Ni(0)-mediated cascade reaction.[155] The pinacol coupling proceeded in excellent yield, resulting in only the cis isomer (Scheme 54).

Low-valent titanium has been used to prepare macrocyclic stilbenediol derivatives from bis-carbaldehydes.[156] High yields were realized, albeit with moderate selectivity. A variety of other molecular frameworks have been synthesized via the pinacol coupling reaction (Table 9).



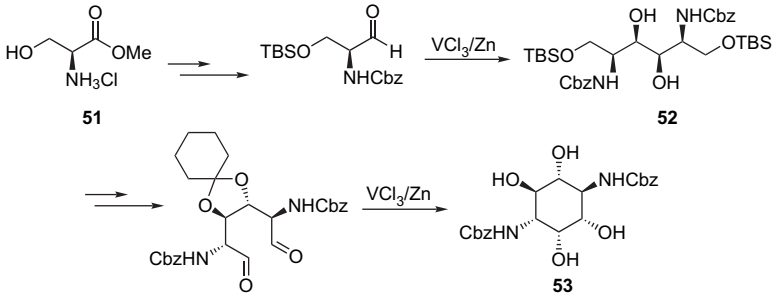
Scheme 54. Nickel-mediated cascade coupling.

Table 9. Miscellaneous frameworks prepared using pinacol coupling

Molecule	Reagent	Ref.	Molecule	Reagent	Ref.
	$TiCl_3$/Zn–Cu	157	 n = 1~4	SmI_2	159
	SmI_2	159	 R^1 = Alk or Ar R^2 = H	SmI_2	160
	$TiCl_4$/Zn	158	 R = H, Me	SmI_2	160
 R^1 = R^2 = Alk or Ar	SmI_2	159	 n = 1 - 3	SmI_2	159

4. Concluding remarks

It is evident from the above account that pinacol coupling, one of the earliest known carbon–carbon bond-forming



Scheme 53. Synthesis of fortimicins AM and AK.

reactions, has evolved as a versatile tool in synthetic organic chemistry. The initial bottleneck for the reaction was to obtain a preparatively useful yield. This was followed by efforts to improve the diastereoselectivity and more recently, the enantioselectivity. In these pursuits, a large number of metals from the periodic table have been examined. The reaction has now been frequently used during the synthesis of a variety of natural/unnatural products. The most recent success in this area has been the establishment of enantioselective protocols. Almost all kinds of aldehydes can now be coupled with high diastereoselectivity and enantioselectivity. The challenge, however, remains for the stereoselective coupling of ketones and imines. Equally interesting and useful will be the heterocoupling of carbonyl compounds and imines. This daunting task will require a deeper insight into the reaction mechanisms and fine tuning of metal complexes. The age-old reaction thus remains a fertile ground for exciting research in the future.

Acknowledgements

We are grateful to the Department of Science & Technology for financial support for our research, and the Council for Scientific & Industrial Research for a scholarship (to A.C.).

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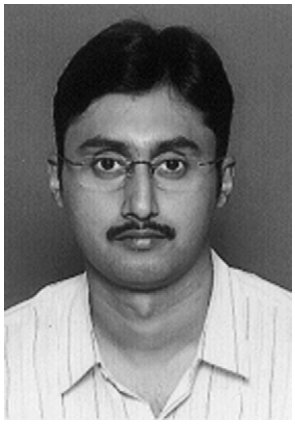
Biographical sketch



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Dr. N. N. Joshi received his Ph.D. degree from Mumbai University (in collaboration with B.A.R.C.). He then joined as Alexander von Humboldt fellow with Prof. H. M. R. Hoffmann, Germany. Later he moved to USA as postdoctoral Research Associate with Prof. H. C. Brown, with whom he enjoyed a long and productive tenure. His roots brought him back to India in 1991. He is currently a senior scientist in the National Chemical Laboratory, Pune. His research interests are in the area of enantioselective catalysis, organometallics chemistry and reaction mechanisms.

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Tetrahedron
Tetrahedron 62 (2006) 12159–12171

Enantioselective synthesis of non-proteinogenic 2-arylallyl-α-amino acids via Pd/In catalytic cascades

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Received 14 August 2006; revised 14 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—An efficient synthesis of both *R*- and *S*-enantiomers of 2-arylallyl-α-amino acids via a diastereoselective Pd/In mediated catalytic allylation of chiral *N*-sulfinyl-α-imino esters is described. The potential for further enhancement of molecular complexity and creating contiguous chiral centres by interfacing these processes with catalytic cyclisation–anion capture methodology is demonstrated.

1. Introduction

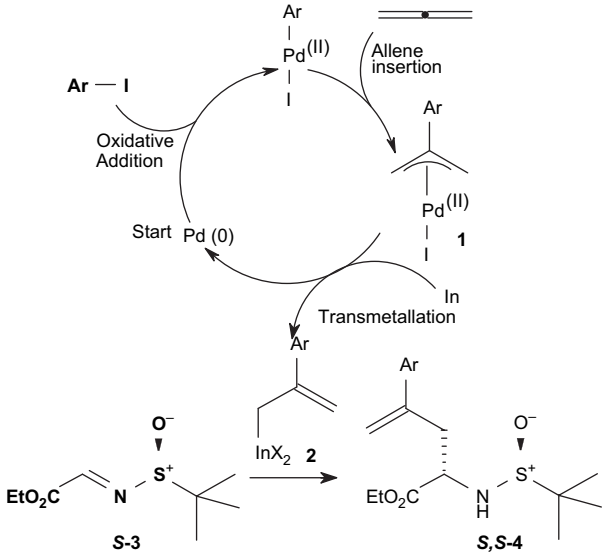
The synthesis of peptides and proteins containing non-natural α-amino acids vastly increases the structural and chemical diversity of polypeptides.

Novel α-amino acid side-chains and the availability of both *R*- and *S*-stereoisomers enable tuning of pharmacokinetics, formation of β-sheets and other peptide structural motifs that effect biological activity and structural properties.

The synthesis of 'designer' peptidomimetics, incorporating and/or modifying the beneficial aspects of the parent polypeptides whilst also possessing enhanced metabolic stability and/or improved pharmacokinetics, is an area of burgeoning interest.[1–3]

The asymmetric alkylation of glycine cation equivalents is a general, efficient route to non-proteinogenic α-amino acid derivatives. Previously, our group reported highly regio- and diastereoselective Pd/In mediated cascade allylations of carbonyl compounds including a highly stereoselective allylation of chiral *N*-sulfinyl aldimines.[4–10] We now report further applications of the *tert*-butyl sulfinyl chiral auxilliary, which has been widely used in the synthesis of chiral amines including 1,2-amino alcohols and α- and β-amino acids,[11–13] to a new approach to unusual α-amino acids.

The Pd/In bimetallic cascade process involves generation of an electrophilic π-allyl palladium species **1** that undergoes transmetallation in the presence of indium, furnishing nucleophilic η^1-allyl indium species **2**. Allylation of the enantiopure *N*-sulfinyl-α-imino ester **3**, affords *N*-sulfinyl-α-alkyl-α-amino esters **4** as single diastereoisomer (Scheme 1). Initial experiments employing iodobenzene and a catalyst system comprising of 10 mol % $Pd(OAc)_2$, 20 mol % tris-2-furyl phosphine and 20 mol % CuI in DMF at 40 °C confirmed these expectations (Table 1, entry 1).



Scheme 1. Reaction mechanism. Reagents and conditions: (i) ArI (0.75 mmol), allene (1 atm), In (0.75 mmol), $Pd(OAc)_2$ (10 mol %), tri-2-furyl phosphine (20 mol %), CuI (20 mol %), piperidine (0.5 mmol), DMF (20 ml/mmol), 40 °C, 24 h; (ii) 4 M HCl/dioxane (5 mol equiv), EtOH (10 ml/mmol), 30 min, rt, NaOH (2 mol equiv), 1:1 v/v EtOH/H_2O (10 ml/mmol) reflux, 2 h.

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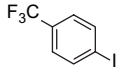
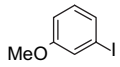
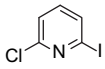
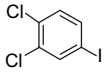
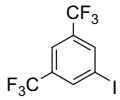
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.098

Table 1. Bimetallic cascade synthesis of chiral **4a–h** and **5a–h**[a]

Entry	ArI	Cascade product		Amino acid	
		Configuration	Yield (%)[b]	Configuration	Yield (%)[c]
1		*S,S*-**4a**	92	*S*-**5a**	100
		R,R-**4a**	80	*R*-**5a**	100
2		*S,S*-**4b**	69	*S*-**5b**	—
		R,R-**4b**	55	*R*-**5b**	100
3		*S,S*-**4c**	68	*S*-**5c**	50
		R,R-**4c**	68	*R*-**5c**	54
4		*S,S*-**4d**	54	*S*-**5d**	99
		R,R-**4d**	49	*R*-**5d**	99
5		*S,S*-**4e**	72	*S*-**5e**	97
		R,R-**4e**	67	*R*-**5e**	80
6		*S,S*-**4f**	52	*S*-**5f**	85
		R,R-**4f**	69	*R*-**5f**	79
7		*S,S*-**4g**	73	*S*-**5g**	73
		R,R-**4g**	74	*R*-**5g**	82
8		*S,S*-**4h**	69	*S*-**5h**	89
		R,R-**4h**	76	*R*-**5h**	68

[a] Conditions as for Scheme 1.
[b] Isolated yield.
[c] Isolated overall yield for the two-step deprotection.

The scope of the reaction was explored through a series of aryl iodides (Table 1). X-ray crystal structures of one such pair *S,S*-**6** and *R,R*-**6** (Fig. 1), derived by partial deprotection of *S,S*-**4g** and *R,R*-**4g**, established that the *S*-sulfinimine engenders *S* stereochemistry at the new chiral centre and the *R*-sulfinimine provides *R* stereochemistry at the new chiral centre.[14] Non-proteinogenic α-amino acids **5** are obtained in good to excellent yield (Table 1) from **4** via a two-step deprotection process (Scheme 2).

A rationale for the stereochemical outcome of the cascade **3**→**4** is summarised in Figure 2. The four possible Zimmerman–Traxler, chair-like transition states **7–10** have been modelled using semi-empirical calculations.[15] These correspond to additions of the allyl indium intermediate to either the *re* or *si* face of the *S*-sulfoximine, each of which can

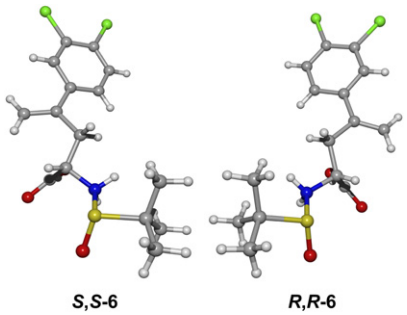
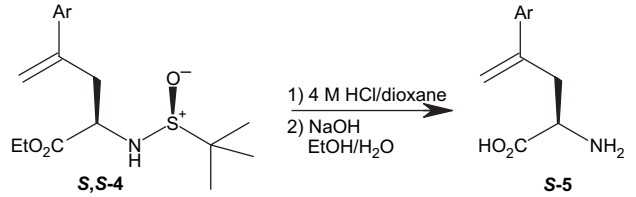


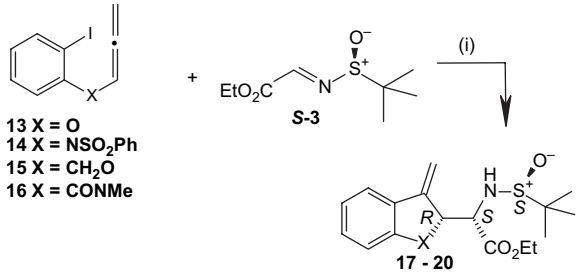
Figure 1. X-ray crystal structures of a matched pair of enantiomers.



Scheme 2. Deprotection of *N*-sulfinyl esters. Cleavage of the chiral sulfinyl auxilliary is carried out first by treatment with 4 M HCl in dioxane (5 mol equiv) for 30 min. Following the removal of the solvent the crude material is treated with 1 M aqueous NaOH solution (2 mol equiv) in a 1:1 v/v EtOH/H_2O under reflux for 2 h. The amino acids **5a–h** are isolated using an Amberlyst H^+ ion exchange resin (Table 1).

involve two possible chair-like arrangements. The heat of formation (ΔH_f) and imaginary vibrational frequencies (ν_i) for transition states corresponding to additions to the *S*-sulfoximine indicate a marked preference for transition state **10**, which locates the ester moiety axially. Closer inspection of this transition state reveals that the ester carbonyl oxygen is located near to the indium atom (O–In distance of 2.80 Å) indicating coordination to the indium atom. This transition state leads to the product possessing *S* stereochemistry at the newly created chiral centre. Interestingly, transition state **10** also locates the sulfoxide oxygen near to the metal centre (at a distance of 2.75 Å) and this, although now involves a four-membered ring, may also further stabilise the transition state. This type of chelation appears to be energetically important as the next most favourable transition state **8** locates the sulfoxide oxygen close to the metal centre at a distance of 2.75 Å. (Note: the calculations employed parameters for In(III) although the valence state of the In in this chemistry is not yet established.)

To further extend the scope of our chemistry, we have utilised bifunctional aryl iodide/allenes **13–16** (Scheme 3) allowing access to our catalytic cyclisation-anion capture methodology.[16] The cyclisation–allylation reaction is entirely regio- and diastereoselective generating two contiguous chiral centres with complete stereocontrol, affording **17–20** in moderate to good yield (Table 2).



Scheme 3. Tandem cyclisation–imine capture cascade. Reagents and conditions: (i) ArI (0.75 mmol), In (0.75 mmol), $Pd(OAc)_2$ (10 mol %), tri-2-furyl phosphine (20 mol %), CuI (20 mol %), piperidine (0.5 mmol), DMF (20 ml/mmol), 80 °C, 24 h.

A matched pair of X-ray crystal structures *S,S,R*-**18** and *R,R,S*-**18**[14] established that the *R*-sulfinimine engenders *R* stereochemistry at the 5-position and *S* stereochemistry at the 6-position (Table 2, entries 3 and 4, Fig. 3). Semi-empirical calculations reveal a similar trend to those described above. In this case, four chair-like transition states

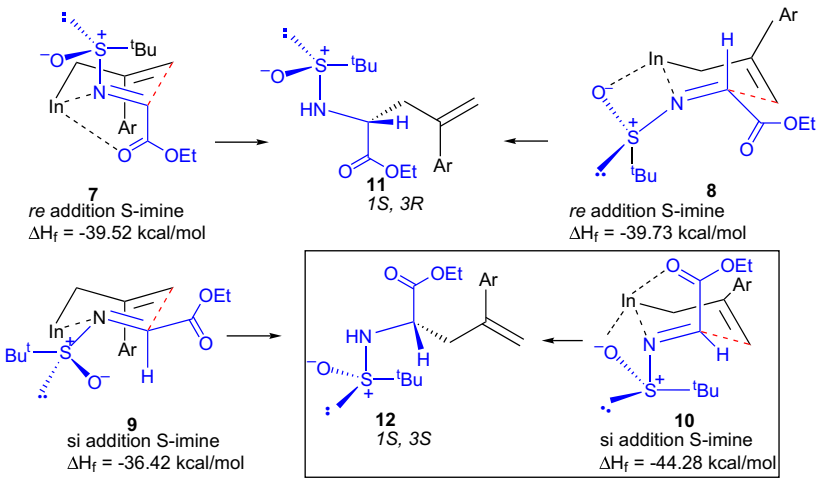
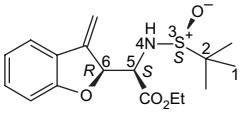
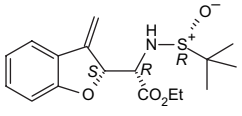
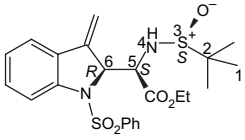
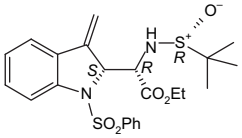
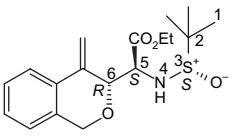
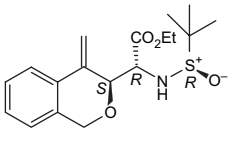


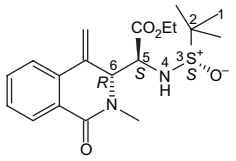
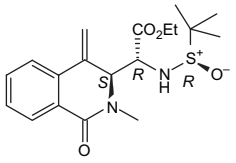
Figure 2. Stereochemical rationale for Scheme 2.

Table 2. Tandem cyclisation–allylation cascades[a]

Entry	Allene	Imine	Product	Yield (%)[b]
1	**13**	*S*-**3**	 ***S,S,R*-17**	64
2	**13**	*R*-**3**	 ***R,R,S*-17**	62
3	**14**	*S*-**3**	 ***S,S,R*-18**	44
4	**14**	*R*-**3**	 ***R,R,S*-18**	48
5	**15**	*S*-**3**	 ***S,S,R*-19**	62
6	**15**	*R*-**3**	 ***R,R,S*-19**	64

(*continued*)

Table 2. (*continued*)

Entry	Allene	Imine	Product	Yield (%)[b]
7	**16**	*S*-**3**	 ***S,S,R*-20**	28
8	**16**	*R*-**3**	 ***R,R,S*-20**	32

[a] General conditions as for Scheme 3.
[b] Isolated yield.

are possible giving rise to four possible diastereoisomeric products.

The most energetically favourable transition state **21** leads to the formation of **18**. As in the case of **10** (Fig. 2), this transition state appears to be stabilised by coordination to the indium involving both the sulfoxide and ester (Fig. 4). This transition state is calculated to be nearly 8 kcal/mol lower in energy than the next most energetically favoured transition state, thus accounting for the observed stereochemical preference in this reaction.

In conclusion, we have described a short, efficient, diastereoselective synthesis of 2-arylallyl-α-amino acids as single enantiomers with either *R* or *S* stereochemistry. Application of bifunctional allene/aryl iodides as substrates furnishes enantiopure *N*-sulfinyl-α-amino esters with two contiguous chiral centres via a regioselective process. The stereochemical outcome of both types of process has been modelled by semi-empirical calculations, which highlight the key transition state influence of chelation to indium by both the sulfoxide and carbonyl oxygen atoms.

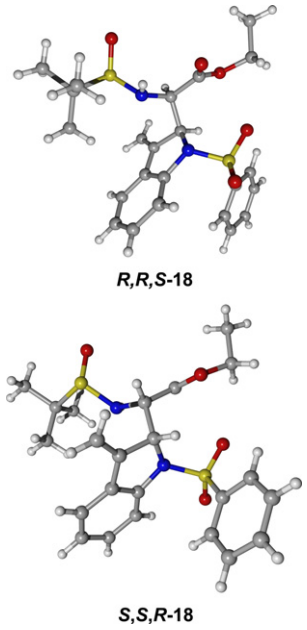


Figure 3. X-ray crystal structures of *R*,*R*,*S*-**18** and S,*S*,*R*-**18**.

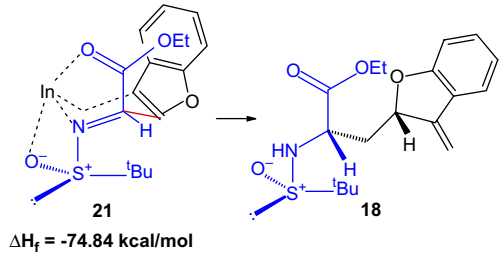


Figure 4. Stereochemical rationale for Scheme 3.

2. Experimental

2.1. General

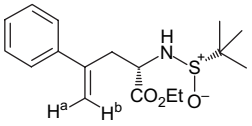
Unless otherwise noted all reagents were obtained from commercial suppliers and used without further purification. All solvents were dried or purified by literature procedures. Chromatography columns were prepared using Fisher chemicals 60A 35–70 μm silica gel. Nuclear magnetic resonance spectra were recorded using Bruker DPX300 and DRX500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) downfield relative to the internal reference tetramethylsilane. Unless otherwise specified NMR spectra were recorded in deuterochloroform at room temperature. Abbreviations used: Ar=aromatic, d=doublet, dd=doublet of doublets, dq=doublet of quartets, dt=doublet of triplets, m=multiplet, q=quartet, s=singlet, t=triplet. Mass spectra were recorded using a micromass ZMD 2000 spectrometer employing the electrospray (ES^+) ionisation technique. Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Infrared spectra were recorded using a Perkin–Elmer FTIR spectrometer. IR spectra of liquids were recorded as thin films on sodium chloride plates. IR spectra of solids were recorded using the 'golden gate' apparatus. Optical rotations were measured on an Optical Activity AA-1000 polarimeter.

Rotations are quoted in 10^{-1} deg cm^2/g and the concentration (c) is expressed in grams per 100 ml. Unless otherwise stated chloroform was the solvent. Microanalysis was performed using a Carlo-Erber 1108 elemental analyser and, for sulfur, by titration against barium perchlorate.

2.2. General procedure for the synthesis of *N*-sulfinylamino esters 4a–h

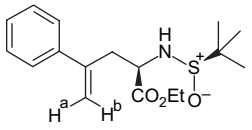
Aryl iodide (0.75 mmol) was added to a suspension of chiral α-imino ester **3** (0.5 mmol), indium metal powder (0.088 g, 0.75 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), tri-2-furyl phosphine (0.024 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol) and piperidine (0.05 ml, 0.5 mmol) in DMF (10 ml) in a Schlenk tube. The mixture was subjected to two freeze–pump–thaw cycles and then charged, using standard Schlenk techniques, with allene gas (0.5 bar). The mixture was stirred and heated to 40 °C (oil bath temperature) for 24 h, left to cool and vented. Ethyl acetate (20 ml) and 5% HCl aqueous solution (10 ml) was added and the mixture stirred for 20 min. The phases were separated and the aqueous layer extracted with ethyl acetate (20 ml). The organic extracts were combined and washed with water (3×40 ml), dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography to give the *N*-sulfinylamino esters.

2.2.1. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-phenyl-pent-4-enoate (*S*,*S*-4a).



Obtained as a pale yellow oil (0.149 g, 92%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.43 (diethyl ether); $[\alpha]_D^{20}$ +81.4 (c 1.2); Found: C, 62.90; H, 7.80; N, 4.35; S, 9.90, $C_{17}H_{25}NO_3S$ requires: C, 63.13; H, 7.79; N, 4.33; S, 9.91%; ν_{max}/cm^{-1}: 3294, 2983, 2253, 1794, 1732, 1630; δ_H (500 MHz, $CDCl_3$): 7.37–7.34 (3H, m, ArH), 7.29–7.27 (2H, m, ArH), 5.34 (1H, s, $=CH^a$), 5.12 (1H, s, $=CH^b$), 4.10–4.01 (4H, m, OCH_2CH_3, N*HCH*), 3.04 (1H, dd, NCHC*H*, J=1.0, 2.9 Hz), 2.85 (1H, dd, NCHC*H*, J=1.0, 3.2 Hz), 1.26 (3H, t, OCH_2CH_3, J=7.1 Hz), 1.16 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 173.3 (*C*O), 144.1 ($H_2C=$*C*), 140.5 (Ar), 128.9 (Ar), 128.2 (Ar), 126.6 (Ar), 117.0 ($=CH_2$), 62.1 (OC), 57.3 (NC), 56.5 (S*C*), 40.8 (NC*C*), 23.0 ($SC(CH_3)_3$), 14.5 (OC*C*); m/z (ES^+): 324 (MH^+).

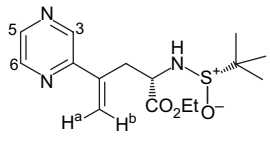
2.2.2. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-phenyl-pent-4-enoate (*R*,*R*-4a).



Obtained as a pale yellow oil (0.130 g, 80%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.43 (diethyl

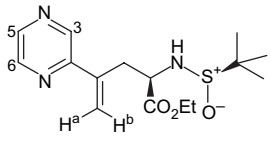
ether); $[\alpha]_D^{20}$ −79.9 (*c* 1.6); Found: C, 63.00; H, 7.80; N, 4.40; S, 9.90, $C_{17}H_{25}NO_3S$ requires: C, 63.13; H, 7.79; N, 4.33; S, 9.91%; ν_{max}/cm^{-1}: 3294, 2983, 2253, 1794, 1732, 1630; δ_H (500 MHz, $CDCl_3$): 7.37–7.34 (3H, m, ArH), 7.29–7.27 (2H, m, ArH), 5.34 (1H, s, =CH^a), 5.12 (1H, s, =CH^b), 4.10–4.01 (4H, m, OCH_2CH$_3$, NHC*H*), 3.04 (1H, dd, NCHC*H*, *J*=1.0, 2.9 Hz), 2.85 (1H, dd, NCHC*H*, *J*=1.0, 3.2 Hz), 1.26 (3H, t, OCH$_2$CH_3, *J*=7.1 Hz), 1.16 (9H, s, C(CH$_3$)$_3$); δ_c (75 MHz, $CDCl_3$): 173.3 (*C*O), 144.1 (H$_2$C=*C*), 140.5 (Ar), 128.9 (Ar), 128.2 (Ar), 126.6 (Ar), 117.0 (=*C*H$_2$), 62.1 (OC), 57.3 (NC), 56.5 (SC), 40.8 (NC*C*), 23.0 (SC(*C*H$_3$)$_3$), 14.5 (OC*C*); *m*/*z* (ES$^+$): 324 (MH$^+$).

2.2.3. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-pyrazin-2-yl-pent-4-enoate (*S*,*S*-4b).



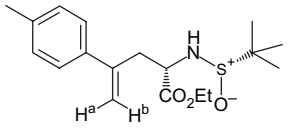
Obtained as a pale yellow oil (0.112 g, 69%) after flash chromatography (ethyl acetate); R_f 0.37 (ethyl acetate); $[\alpha]_D^{20}$ +63.5 (*c* 0.9); Found: C, 54.40; H, 6.90; N, 12.70, $C_{15}H_{23}N_3O_3S\cdot 0.25$ M H_2O requires: C, 54.61; H, 7.18; N, 12.74%; ν_{max}/cm^{-1}: 3584, 3436 (NH), 3289, 2982, 2963, 2240, 1734 (C=O), 1468, 1367, 1067; δ_H (500 MHz, $CDCl_3$): 8.74 (1H, s, pyrazinyl-3H), 8.47 (1H, d, pyrazinyl-6H, *J*=1.3 Hz), 8.39 (1H, d, pyrazinyl-5H, *J*=1.3 Hz), 5.81 (1H, s, =CH^a), 5.42 (1H, s, =CH^b), 4.14–4.04 (4H, br m, OCH_2, NHC*H*), 3.05 (1H, dd, NCHC*H*, *J*=5.3, 14.3 Hz), 2.93 (1H, dd, NHCHC*H*, *J*=8.2, 14.3 Hz), 1.18 (3H, t, OCH$_2$CH_3, *J*=7.2 Hz), 1.08 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 172.00 (CO), 152.02 (H$_2$C=*C*), 142.29 (Ar), 141.91 (Ar), 141.22 (Ar), 140.08 (Ar), 119.35 (=*C*H$_2$), 60.69 (O*C*), 55.82 (NC), 55.13 (SC), 37.13 (NC*C*), 21.54 (C(*C*H$_3$)$_3$), 13.08 (OC*C*); *m*/*z* (ES$^+$): 326 (MH$^+$).

2.2.4. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-pyrazin-2-yl-pent-4-enoate (*R*,*R*-4b).



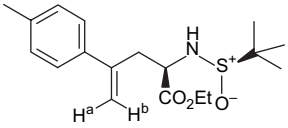
Obtained as a pale yellow oil (0.169 g, 35%) after flash chromatography (ethyl acetate); R_f 0.37 (ethyl acetate); $[\alpha]_D^{20}$ −63.6 (*c* 1.1); Found: C, 54.40; H, 6.85; N, 12.65, $C_{15}H_{23}N_3O_3S\cdot 0.25$ M H_2O requires: C, 54.61; H, 7.18; N, 12.74%; ν_{max}/cm^{-1}: 3447, 2981, 1734, 1633, 1519, 1469; δ_H (500 MHz, $CDCl_3$): 8.75 (1H, s, pyrazinyl-3H), 8.46 (1H, d, pyrazinyl-6H, *J*=1.3 Hz), 8.39 (1H, d, pyrazinyl-5H, *J*=1.3 Hz), 5.81 (1H, s, =CH^a), 5.42 (1H, s, =CH^b), 4.17–4.04 (4H, br m, OCH_2, NHC*H*), 3.05 (1H, dd, NCHC*H*, *J*=5.3 Hz, 14.3 Hz), 2.93 (1H, dd, NCHC*H*, *J*=8.2 Hz, 14.3 Hz), 1.18 (3H, t, OCH$_2$CH_3, *J*=7.2 Hz), 1.08 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 171.95 (CO), 152.02 (H$_2$C=*C*), 142.32 (Ar), 141.89 (Ar), 141.19 (Ar), 140.57 (Ar), 119.35 (=*C*H$_2$), 60.63 (O*C*), 55.85 (NC), 55.19 (SC), 37.09 (NC*C*), 21.76 (C(*C*H$_3$)$_3$), 13.08 (OC*C*); *m*/*z* (ES$^+$): 326 (MH$^+$).

2.2.5. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-*p*-tolyl-pent-4-enoate (*S*,*S*-4c).



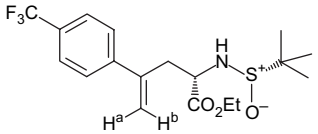
Obtained as a colourless oil (0.230 g, 68%) after flash chromatography (8:1 v/v Et_2O/hexane); R_f 0.53 (8:1 v/v Et_2O/hexane); $[\alpha]_D^{20}$ +87.2 (*c* 2.4); Found: C, 63.90; H, 8.40; N, 3.90; S, 9.40, $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50%; ν_{max}/cm^{-1}: 3456, 3280 (NH), 3082, 1733 (CO), 1626, 1563, 1511; δ_H (500 MHz, $CDCl_3$): 7.25 (2H, d, ArH, *J*=7.9 Hz), 7.14 (2H, d, ArH, *J*=7.9 Hz), 5.31 (1H, s, =CH^a), 5.07 (1H, s, =CH^b), 4.12 (2H, q, OCH_2, *J*=7.1 Hz), 4.03 (1H, d, NH, *J*=8.3 Hz), 4.02–3.91 (1H, m, NCH), 3.00 (1H, dd, NCHC*H*, *J*=5.4, 14.3 Hz), 2.80 (1H, dd, NCHC*H*, *J*=7.6, 14.3 Hz), 2.35 (3H, s, ArCH$_3$), 1.25 (3H, t, OCH$_2$CH_3, *J*=7.1 Hz), 1.17 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 171.29 (CO), 142.42 (H$_2$C=*C*), 136.50 (Ar), 136.05 (Ar), 128.11 (Ar), 125.21 (Ar), 114.65 (=*C*H$_2$), 60.54 (O*C*), 55.87 (NC), 55.08 (SC), 39.41 (NC*C*), 21.52 (C(*C*H$_3$)$_3$), 20.05 (OC*C*), 13.05 (Ar*C*H$_3$); *m*/*z* (ES$^+$): 338 (MH$^+$).

2.2.6. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-*p*-tolyl-pent-4-enoate (*R*,*R*-4c).



Obtained as a colourless oil (0.233 g, 68%) after flash chromatography (8:1 v/v Et_2O/hexane); R_f 0.53 (8:1 v/v Et_2O/hexane); $[\alpha]_D^{20}$ −88.6 (*c* 1.5); Found: C, 64.00; H, 8.40; N, 4.10; S, 9.40, $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50%; ν_{max}/cm^{-1}: 3276, 3085, 2980, 2958, 2926, 2869, 1737; δ_H (500 MHz, $CDCl_3$): 7.25 (2H, d, ArH, *J*=7.9 Hz), 7.14 (2H, d, ArH, *J*=7.9 Hz), 5.30 (1H, s, =CH^a), 5.07 (1H, s, =CH^b), 4.14–4.10 (2H, q, OCH$_2$, *J*=7.1 Hz), 4.03 (1H, d, NH, *J*=8.3 Hz), 4.0–3.9 (1H, m, NCH), 3.00 (1H, dd, NCHC*H*, *J*=5.4, 14.3 Hz), 2.80 (1H, dd, NCHC*H*, *J*=7.6, 14.3 Hz), 2.35 (3H, s, ArCH$_3$), 1.24 (3H, t, OCH$_2$CH_3, *J*=7.1 Hz), 1.16 (9H, s, C(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$): 173.34 (CO), 143.84 (H$_2$C=*C*), 137.96 (Ar), 137.48 (Ar), 129.54 (Ar), 126.63 (Ar), 116.09 (=*C*H$_2$), 61.99 (O*C*), 57.28 (NC), 56.52 (SC), 40.85 (NC*C*), 22.96 (C(*C*H$_3$)$_3$), 21.48 (OC*C*), 14.47 (Ar*C*H$_3$); *m*/*z* (ES$^+$): 338 (MH$^+$).

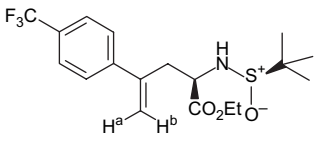
2.2.7. Ethyl 2*S*,4*S*-(2-methyl-propane-2-sulfinylamino)-4-(4-trifluoromethyl-phenyl)-pent-4-enoate (*S*,*S*-4d).



Obtained as a colourless oil (0.422 g, 54%) after flash chromatography (Et_2O); R_f 0.16 (Et_2O); $[\alpha]_D^{20}$ +82.2 (*c* 1.1);

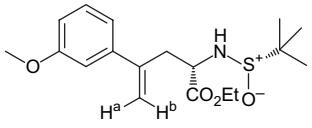
Found: C, 55.00; H, 6.30; N, 3.60; S, 8.10, $C_{18}H_{24}NSO_4F_3$ requires: C, 55.23; H, 6.18; N, 3.58; S, 8.19; F, 14.56%; ν_{max}/cm^{-1}: 3453, 3283 (NH), 3088, 2982, 2961, 2907, 2871, 1738 (CO), 1616; δ_H (500 MHz, $CDCl_3$): 7.60 (2H, ArH, d, J=8.2 Hz), 7.47 (2H, ArH, d, J=8.2 Hz), 5.41 (1H, s, =CH^a), 5.23 (1H, s, =CH^b), 4.12 (2H, m, OCH_2), 4.04 (1H, d, NH, 7.5 Hz), 3.97 (1H, dt, NCH, J=5.6, 7.5 Hz), 3.05 (1H, dd, NCHCH, J=5.6, 14.3 Hz), 2.86 (1H, dd, NCHCH, J=7.5, 14.3 Hz), 1.25 (3H, t, OCH_2CH_3, J=7.2 Hz), 1.16 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 172.99 (CO), 149.37 (Ar), 143.13 (H_2C=C), 130.17 (q, CF_3, J=32.39 Hz), 127.16 (Ar), 126.85 (Ar), 125.86 (q, F_3CC, 4.06 Hz), 118.89 (=CH_2), 62.20 (OC), 57.02 (NC), 56.52 (SC), 40.54 (NCC), 22.89 ($C(CH_3)_3$), 14.44 (OCC); m/z (ES$^+$): 392 (MH$^+$).

2.2.8. Ethyl 2*R*,4*R*-(2-methyl-propane-2-sulfinylamino)-4-(4-trifluoromethyl-phenyl)-pent-4-enoate (*R*,*R*-4d).



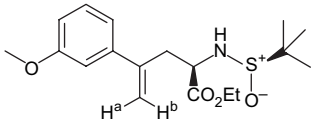
Obtained as a colourless oil (0.385 g, 49%) after flash chromatography (Et_2O); R_f 0.16 (Et_2O); $[\alpha]_D^{20}$ −80.4 (c 0.7); Found: C, 55.00; H, 6.20; N, 3.70; S, 8.30, $C_{18}H_{24}NSO_4F_3$ requires: C, 55.23; H, 6.18; N, 3.58; S, 8.19; F, 14.56%; ν_{max}/cm^{-1}: 3459, 3282 (NH), 2982, 3088, 2982, 2961, 2907, 2871, 1738 (CO), 1616, 1573; δ_H (500 MHz, $CDCl_3$): 7.60 (2H, ArH, d, J=8.2 Hz), 7.47 (2H, ArH, d, J=8.2 Hz), 5.41 (1H, s, =CH^a), 5.23 (1H, s, =CH^b), 4.19–4.06 (2H, m, OCH_2), 4.03 (1H, d, NH, J=7.5 Hz), 3.97 (1H, dt, NCH, J=5.6, 7.5 Hz), 3.04 (1H, dd, NCCH, J=5.6, 14.3 Hz), 2.87 (1H, dd, NCCH, J=7.5, 14.3 Hz); 1.25 (3H, t, OCH_2CH_3, J=7.19), 1.16 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 172.99 (CO), 149.37 (Ar), 143.13 (H_2C=C), 130.17 (q, CF_3, J=32.39 Hz), 127.16 (Ar), 126.85 (Ar), 125.86 (q, F_3CC, 4.06 Hz), 118.89 (=CH_2), 62.20 (OC), 57.02 (NC), 56.52 (SC), 40.54 (NCC), 22.89 ($C(CH_3)_3$), 14.44 (OCC); m/z (ES$^+$): 392 (MH$^+$).

2.2.9. Ethyl 2*S*,4*S*-(3-methoxy-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4e).



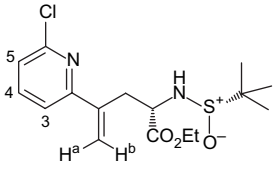
Obtained as a pale yellow oil (0.130 g, 72%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.47 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ +78.3 (c 2.1); Found: C, 60.40; H, 7.80; N, 3.70, $C_{18}H_{27}NO_4S\cdot0.25$ M H_2O requires: C, 60.39; H, 7.74; N, 3.91%; Found: 376.1552, $C_{18}H_{27}NO_4S\cdot Na$ requires: 376.1559; ν_{max}/cm^{-1}: 3583, 3453 (NH), 3283, 2978, 2836, 1736 (CO), 1628; δ_H (500 MHz, $CDCl_3$): 7.19 (1H, t, Ar-5H, J=7.7 Hz), 6.87 (1H, s, Ar-2H), 6.82 (1H, d, Ar-4H, J=7.7 Hz), 6.75 (1H, d, Ar-6H, J=7.7 Hz), 5.27 (1H, s, =CH^a), 5.04 (1H, s, =CH^b), 4.07–4.03 (2H, m, OCH_2), 3.97–3.92 (2H, m, NHCH), 3.74 (3H, s, OCH_3), 2.93 (1H, dd, NCCH, J=5.3, 14.0 Hz), 2.74 (1H, dd, NCCH, J=7.5, 14.0 Hz), 1.17 (3H, t, OCH_2CH_3, J=4.8 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.85 (CO), 158.60 (H_2C=C), 150.48 (Ar), 142.52 (Ar), 140.55 (Ar), 134.76 (Ar), 117.83 (Ar), 115.61 (=CH_2), 111.91 (Ar), 60.72 (NCC), 55.85 (ArOC), 55.09 (NC), 54.19 (SC), 21.61 ($C(CH_3)_3$), 13.15 (OCC); m/z (ES$^+$): 354 (MH$^+$).

2.2.10. Ethyl 2*R*,4*R*-(3-methoxy-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4e).



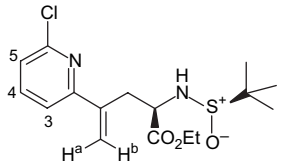
Obtained as a pale yellow oil (0.119 g, 67%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.47 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ −77.1 (c 1.2); Found: C, 61.30; H, 7.80; N, 4.00; S, 9.20, $C_{18}H_{27}NO_4S$ requires: C, 61.16; H, 7.70; N, 3.96; S, 9.07%; ν_{max}/cm^{-1}: 3282, 3082, 2980, 2958, 2907, 2869, 2836, 1737 (CO), 1627, 1598, 1577; δ_H (500 MHz, $CDCl_3$): 7.18 (1H, t, Ar-5H, J=7.9 Hz), 6.87 (1H, d, Ar-2H, 7.9 Hz), 6.82 (1H, s, Ar-4H), 6.76 (1H, d, Ar-6H, J=7.9 Hz), 5.27 (1H, s, =CH^a), 5.04 (1H, s, =CH^b), 4.07–4.03 (2H, m, OCH_2), 3.97–3.92 (2H, m, NHCH), 3.74 (3H, s, OCH_3), 2.93 (1H, dd, NCCH, J=5.3, 14.0 Hz), 2.74 (1H, dd, NCCH, J=7.5, 14.0 Hz), 1.17 (3H, t, OCH_2CH_3, J=7.1 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.85 (CO), 158.61 (H_2C=C), 142.22 (Ar), 140.55 (Ar), 128.44 (Ar), 117.43 (Ar), 115.61 (=CH_2), 111.92 (Ar), 111.42 (Ar), 60.62 (OC), 55.87 (OCH_3), 55.10 (SC), 54.19 (NC), (NCC), 21.55 ($C(CH_3)_3$), 13.05 (OCC); m/z (ES$^+$): 354 (MH$^+$).

2.2.11. Ethyl 2*S*,4*S*-(6-chloro-pyridin-2-yl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4f).



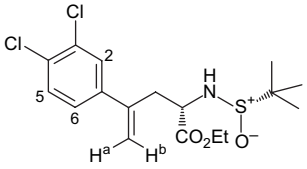
Obtained as a pale yellow oil (0.187 g, 52%) after flash chromatography (6:1 v/v ethyl acetate/hexane); R_f 0.41 (6:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ +86.7 (c 1.8); Found: C, 53.30; H, 6.60; N, 7.80; S, 9.00, $C_{16}H_{23}ClN_2O_3S$ requires: C, 53.55; H, 6.46; Cl, 9.88; N, 7.81; S, 8.93%; ν_{max}/cm^{-1}: 3417, 3209, 2981, 2961, 1737 (CO); δ_H (500 MHz, $CDCl_3$): 8.40 (1H, d, pyridyl-5H, J=2.3 Hz), 7.63 (1H, d, pyridyl-3H, J=8.4 Hz), 7.32 (1H, dd, pyridyl-4H, J=2.3, 8.4 Hz), 5.41 (1H, s, =CH^a), 5.27 (1H, s, =CH^b), 4.17–4.09 (3H, br m, NH, OCH_2), 3.96 (1H, m, NHCH), 3.00 (1H, dd, NCCH, 0.6, 5.0 Hz), 2.86 (1H, dd, H_2C=CCH, J=0.6, 7.7 Hz), 1.26 (3H, t, OCH_2CH_3, J=7.2 Hz), 1.18 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 172.82 (CO), 151.06 (H_2C=C), 147.96 (Ar), 140.11 (Ar), 136.86 (Ar), 135.10 (Ar), 124.36 (Ar), 119.32 (=CH_2), 62.36 (OC), 56.74 (NC), 56.61 (SC), 22.95 ($C(CH_3)_3$), 14.48 (O_2CC); m/z (ES$^+$): 359 (^{35}Cl MH$^+$), 361 (^{37}Cl MH$^+$).

2.2.12. Ethyl 2*R*,4*R*-(6-chloro-pyridin-2-yl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4f).



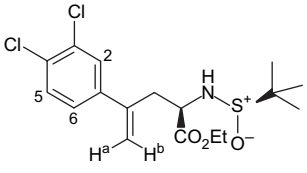
Obtained as a pale yellow oil (0.088 g, 49%) after flash chromatography (6:1 v/v ethyl acetate/hexane); R_f 0.41 (6:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ −84.9 (*c* 2.5); Found: C, 53.50; H, 7.00; Cl, 9.70; N, 7.70; S, 8.80, $C_{16}H_{23}ClN_2O_3S$ requires: C, 53.55; H, 6.46; Cl, 9.88; N, 7.81; S, 8.93%; ν_{max}/cm^{-1}: 3448, 3429, 2983, 1737 (CO), 1461, 1366; δ_H (500 MHz, $CDCl_3$): 8.32 (1H, d, pyridyl-5H, *J*=2.5 Hz), 7.57 (1H, dd, pyridyl-3H, *J*=2.5, 8.3 Hz), 7.25 (1H, d, pyridyl-4H, *J*=8.3 Hz), 5.34 (1H, s, =CH^a), 5.19 (1H, s, =CH^b), 4.06–4.01 (3H, br m, NH, OCH_2), 3.89 (1H, dd, NC*H*, *J*=5.0, 7.7 Hz), 2.92 (1H, dd, NCC*H*, *J*=0.6, 5.0 Hz), 2.78 (1H, dd, NCC*H*, *J*=0.6, 7.7 Hz), 1.19 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.10 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.39 (CO), 149.61 (H_2C=*C*), 146.53 (Ar), 138.68 (Ar), 135.47 (Ar), 133.69 (Ar), 117.92 (=*C*H_2), 60.72 (O*C*), 55.35 (N*C*), 54.94 (SC), 38.81 (NC*C*), 21.61 ($C(CH_3)_3$), 13.06 (OC*C*); *m*/*z* (ES$^+$): 359 (^{35}Cl MH$^+$), 361 (^{37}Cl MH$^+$).

2.2.13. Ethyl 2*S*,4*S*-(3,4-dichloro-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4g).



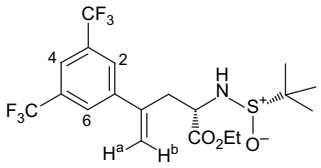
Obtained as a pale yellow oil (0.144 g, 73%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.22 (9:1 v/v diethyl ether/hexane); $[\alpha]_D^{20}$ +68.3 (*c* 1.1); Found: C, 52.20; H, 6.10; Cl, 17.80; N, 3.60; S, 7.90, $C_{17}H_{23}Cl_2NO_3S$ requires: C, 52.04; H, 5.91; Cl, 18.07; N, 3.57; S, 8.17%; ν_{max}/cm^{-1}: 3583, 3450 (NH), 3282, 2981, 2960, 1736 (CO), 1474, 1367, 1074; δ_H (500 MHz, $CDCl_3$): 7.37 (1H, s, Ar-2H), 7.33 (1H, d, Ar-5H, *J*=8.3 Hz), 7.12 (1H, d, Ar-6H, *J*=8.3 Hz), 5.29 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.06 (2H, dq, OCH_2, *J*=7.2, 13.1 Hz), 3.89 (1H, dd, NC*H*, *J*=7.7, 6.2 Hz), 2.90 (1H, dd, NCHC*H*, *J*=6.2, 14.5 Hz), 2.75 (1H, dd, NCHC*H*, *J*=7.7, 14.5 Hz), 1.18 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.10 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.51 (CO), 140.68 (*C*=CH_2), 131.57 (Ar), 130.73 (Ar), 129.87 (Ar), 128.87 (Ar), 127.77 (Ar), 124.67 (Ar), 117.79 (=*C*H_2), 60.58 (O*C*), 55.55 (N*C*), 55.14 (SC), 38.96 (NC*C*), 21.62 ($C(CH_3)_3$), 13.05 (OC*C*); *m*/*z* (ES$^+$): 393 ($^{35/35}$Cl MH$^+$), 395 ($^{35/37}$Cl MH$^+$), 397 ($^{37/37}$Cl MH$^+$).

2.2.14. Ethyl 2*R*,4*R*-(3,4-dichloro-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4g).



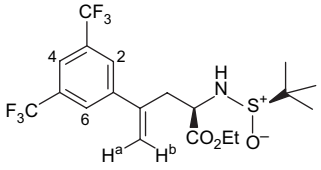
Obtained as a pale yellow oil (0.146 g, 74%) after flash chromatography (9:1 v/v diethyl ether/hexane); R_f 0.22 (9:1 v/v diethyl ether/hexane); $[\alpha]_D^{20}$ −70.8 (*c* 1.2); Found: C, 52.04; H, 5.91; Cl, 18.07; N, 3.57; S, 8.17, $C_{17}H_{23}Cl_2NO_3S$ requires: C, 52.00; H, 5.90; Cl, 18.10; N, 3.60; S, 8.20%; ν_{max}/cm^{-1}: 3583, 3450 (NH), 3274, 2978, 2956, 1736 (CO), 1473, 1366, 1070; δ_H (500 MHz, $CDCl_3$): 7.37 (1H, d, Ar-2H, *J*=2.0 Hz), 7.33 (1H, d, Ar-5H, *J*=8.3 Hz), 7.13 (1H, dd, Ar-6H, *J*=2, 8.3 Hz), 5.29 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.06 (2H, dq, OCH_2, *J*=7.6, 10.7 Hz), 3.89 (1H, dd, NC*H*, *J*=5.5, 7.4 Hz), 2.90 (1H, dd, NCHC*H*, *J*=5.5, 14.5 Hz), 2.73 (1H, dd, NCHC*H*, *J*=7.4, 14.5 Hz), 1.19 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.10 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.50 (CO), 140.68 (*C*=CH_2), 131.55 (Ar), 130.71 (Ar), 129.39 (Ar), 128.87 (Ar), 127.35 (Ar), 124.68 (Ar), 117.02 (=*C*H_2), 60.82 (O*C*), 55.55 (N*C*), 55.13 (SC), 38.95 (NC*C*), 21.51 ($C(CH_3)_3$), 13.05 (OC*C*); *m*/*z* (ES$^+$): 393 ($^{35/35}$Cl MH$^+$), 395 ($^{35/37}$Cl MH$^+$), 397 ($^{37/37}$Cl MH$^+$).

2.2.15. Ethyl 2*S*,4*S*-(3,5-bis-trifluoromethyl-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*S*,*S*-4h).



Obtained as a pale yellow oil (0.159 g, 69%) after flash chromatography (3:1–6:1 v/v ethyl acetate/hexane); R_f 0.58 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ +55.2 (*c* 3.2); Found: C, 49.50; H, 5.00; N, 3.00; S, 6.80, $C_{19}H_{23}F_6NO_3S$ requires: C, 49.67; H, 5.05; F, 24.81; N, 3.05; S, 6.98%; ν_{max}/cm^{-1}: 3583, 3454 (NH), 2983, 2963, 1739 (CO), 1632, 1378, 1279, 1180, 1136, 1078; δ_H (500 MHz, $CDCl_3$): 7.72 (3H, s, ArH), 5.41 (1H, s, =CH^a), 5.28 (1H, s, =CH^b), 4.13–4.01 (3H, br m, OCH_2, NH), 3.91–3.88 (1H, m, NCH), 3.07 (1H, dd, NCHC*H*, *J*=5.1, 14.5 Hz), 2.93 (1H, dd, NCHC*H*, *J*=7.3, 14.5 Hz), 1.18 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.07 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.35 (CO), 141.74 (H_2C=*C*), 140.72 (Ar), 130.90 (q, Ar, *J*=33.3 Hz), 125.86 (Ar), 122.2 (q, CF_3, *J*=272.8 Hz), 119.94 (Ar), 118.75 (=*C*H_2), 60.98 (O*C*), 55.93 (NC), 55.12 (SC), 38.76 (NC*C*), 21.43 ($C(CH_3)_3$), 12.93 (OC*C*); *m*/*z* (ES$^+$): 460 (MH$^+$).

2.2.16. Ethyl 2*R*,4*R*-(3,5-bis-trifluoromethyl-phenyl)-2-(2-methyl-propane-2-sulfinylamino)-pent-4-enoate (*R*,*R*-4h).



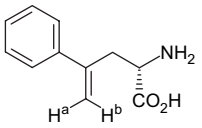
Obtained as a pale yellow oil (0.151 g, 66%) after flash chromatography (3:1–6:1 v/v ethyl acetate/hexane); R_f 0.58 (3:1 v/v ethyl acetate/hexane); $[\alpha]_D^{20}$ −53.0 (*c* 1.1); Found: C, 49.60; H, 5.10; N, 3.10; S, 6.80, $C_{19}H_{23}F_6NO_3S$ requires:

C, 49.67; H, 5.05; F, 24.81; N, 3.05; S, 6.98%; ν_{max}/cm^{-1}: 3450 (NH), 2978, 1739 (CO), 1629, 1374, 1278; δ_H (500 MHz, $CDCl_3$): 7.72 (3H, s, ArH), 5.41 (1H, s, =CH^a), 5.28 (1H, s, =CH^b), 4.13–4.02 (3H, br m, OCH_2, NH), 3.91–3.88 (1H, m, NC*H*), 3.07 (1H, dd, NCHC*H*, *J*=5.1, 14.5 Hz), 2.93 (1H, dd, NCHC*H*, *J*=7.3, 14.5 Hz), 1.18 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 1.07 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.34 (CO), 141.75 (H_2C=*C*), 140.72 (Ar), 130.90 (q, Ar, *J*=33.3 Hz), 125.54 (Ar), 122.23 (q, CF_3, *J*=272.8 Hz), 119.94 (Ar), 118.75 (=CH_2), 60.98 (O*C*), 55.93 (NC), 55.12 (SC), 38.76 (NC*C*), 21.43 ($C(CH_3)_3$), 12.93 (OC*C*); *m*/*z* (ES$^+$): 460 (MH^+).

2.3. General procedure for the synthesis of α-amino acids 5a–h

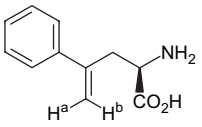
HCl (4 M) in dioxane (5 equiv) was added to a 0.1 M solution of the *N*-sulfinyl-α-amino ester in EtOH. The solution was stirred at room temperature for 2 h and the solvent removed in vacuo. NaOH solution (1 M, 2 equiv) was added to a 0.1 M solution of the ester in a 1:1 v/v H_2O/EtOH solvent system and the mixture stirred and heated to reflux (80 °C oil bath temperature) for 4 h. The solution was left to cool to room temperature and the solvent removed in vacuo. The residue was dissolved in deionised water and applied to the top of an Amberlyst 15H$^+$ form, 20–50 mesh ion exchange column and eluted with distilled water followed by a 1% NH_3 solution in deionised water. The ammonia fractions were visualised under UV light and the UV active fractions were collected and concentrated in vacuo to give the *amino acid products* as pale yellow to colourless solids.

2.3.1. 2-(*S*)-2-Amino-4-phenyl-pent-4-enoic acid (*S*-5a).



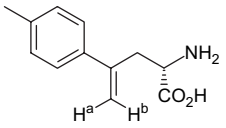
Obtained as colourless prisms (0.156 g, 100%) after ion exchange chromatography. Mp 130–132 °C; $[\alpha]_D^{20}$ +26.4 (*c* 0.3, MeOH); Found: 192.1021, $C_{11}H_{13}NO_2$ requires: 192.1019; ν_{max}/cm^{-1}: 3030 (br, OH), 2065, 1590 (CO), 1395, 1340; δ_H (500 MHz, D_2O): 6.90 (2H, d, ArH, 7.8 Hz), 6.85–6.75 (3H, m, ArH), 4.98 (1H, s, =CH^a), 4.73 (1H, s, =CH^b), 3.45 (1H, dd, NCH, *J*=5.1, 8.6 Hz), 2.76 (1H, dd, NCCH, *J*=5.1, 15.4 Hz), 2.47 (1H, dd, NCCH, *J*=8.6, 15.4 Hz); δ_C (75 MHz, D_2O): 171.00 (CO), 140.85 (H_2C=*C*), 137.72 (Ar), 128.62 (Ar), 128.36 (Ar), 126.12 (Ar), 118.04 (=CH_2), 51.23 (NC), 35.55 (NC*C*); *m*/*z* (ES$^+$): 192 (MH^+).

2.3.2. 2-(*R*)-2-Amino-4-phenyl-pent-4-enoic acid (*R*-5a).



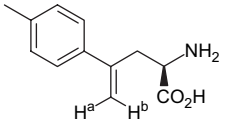
Obtained as colourless prisms (0.095 g, 100%) after ion exchange chromatography. Mp 138–140 °C; $[\alpha]_D^{20}$ −26.2 (*c* 0.6, MeOH); Found: C, 66.70; H, 6.65; N, 6.95, $C_{11}H_{13}NO_2 \cdot 0.33$ M H_2O requires: C, 66.99; H, 6.98; N, 7.10%; Found: 192.1022, $C_{11}H_{14}NO_2$ requires: 192.1025; ν_{max}/cm^{-1}: 3024 (br, OH), 2075, 1822, 1668, 1594 (CO), 1524, 1443, 1400, 1359; δ_H (500 MHz, D_2O): 7.15 (2H, d, ArH, 8.1 Hz), 7.09–6.98 (3H, m, ArH), 5.21 (1H, s, =CH^a), 4.95 (1H, s, =CH^b), 3.69 (1H, dd, NCH, *J*=5.1, 8.6 Hz), 2.98 (1H, dd, NCC*H*, *J*=5.1, 15.4 Hz), 2.71 (1H, dd, NCC*H*, *J*=8.6, 15.4 Hz); δ_C (75 MHz, D_2O): 171.31 (CO), 141.18 (H_2C=*C*), 138.08 (Ar), 128.93 (Ar), 128.67 (Ar), 126.47 (Ar), 118.40 (=CH_2), 51.44 (NCH), 35.80 (NC*C*); *m*/*z* (ES$^+$): 192 (MH^+).

2.3.3. 2-(*S*)-2-Amino-4-*p*-tolyl-pent-4-enoic acid (*S*-5c).



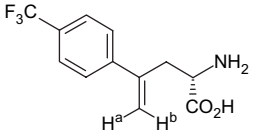
Obtained as colourless prisms (0.073 g, 61%) after ion exchange chromatography. Mp 165–167 °C; $[\alpha]_D^{20}$ +10.8 (*c* 0.2, MeOH); Found: C, 68.70; H, 7.20; N, 6.60, $C_{12}H_{15}NO_2 \cdot 0.25$ M H_2O requires: C, 68.71; H, 7.45; N, 6.68%; Found: 205.1097, $C_{12}H_{15}NO_2$ requires: 205.1097; ν_{max}/cm^{-1}: 3034 (br, OH), 2089, 1912, 1818, 1671 (CO), 1594, 1518, 1450, 1400, 1359; δ_H (300 MHz, D_2O): 7.24 (2H, ArH, d, *J*=8.0 Hz), 7.07 (2H, ArH, d, *J*=8.0 Hz), 5.37 (1H, s, =CH^a), 5.10 (1H, s, =CH^b), 3.88 (1H, dd, NCH, *J*=5.0, 8.7 Hz), 3.16 (1H, dd, NCCH, *J*=5.0, 14.9 Hz), 2.87 (1H, dd, NCCH, *J*=8.7, 14.9 Hz), 2.14 (3H, s, $ArCH_3$); δ_C (75 MHz, D_2O): 171.60 (CO), 141.2 (H_2C=*C*), 139.4 (Ar), 135.2 (Ar), 129.7 (Ar), 126.6 (Ar), 117.8 (=CH_2), 51.7 (ArCH_3), 36.0 (NC), 20.4 (NC*C*); *m*/*z* (ES): 206 (MH^+).

2.3.4. 2-(*R*)-2-Amino-4-*p*-tolyl-pent-4-enoic acid (*R*-5c).



Obtained as colourless prisms (0.084 g, 51%) after ion exchange chromatography. Mp 165–167 °C; $[\alpha]_D^{20}$ −10.6 (*c* 0.3, MeOH); Found: 205.1099, $C_{12}H_{15}NO_2$ requires: 205.1097; ν_{max}/cm^{-1}: 3030 (br, OH), 2087, 1818, 1670 (CO), 1594, 1518, 1450, 1401, 1359; δ_H (300 MHz, D_2O): 7.30 (2H, ArH, d, *J*=8.0 Hz), 7.13 (2H, ArH, d, *J*=8.0 Hz), 5.43 (1H, s, =CH^a), 5.16 (1H, s, =CH^b), 3.93 (1H, dd, NCH, *J*=5.0, 8.7 Hz), 3.22 (1H, dd, NCCH, *J*=5.0, 14.9 Hz), 2.92 (1H, dd, NCCH, *J*=8.7, 14.9 Hz), 2.20 (3H, s, $ArCH_3$); δ_C (75 MHz, D_2O): 171.66 (CO), 141.2 (H_2C=*C*), 139.4 (Ar), 135.3 (Ar), 129.8 (Ar), 126.6 (Ar), 117.8 (=CH_2), 51.7 (ArMe), 36.1 (NC), 20.5 (NC*C*); *m*/*z* (ES$^+$): 206 (MH^+).

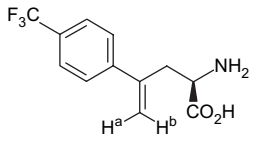
2.3.5. 2-(*S*)-2-Amino-4-(4-trifluoromethyl-phenyl)-pent-4-enoic acid (*S*-5d).



Obtained as colourless prisms (0.223 g, 99%) after ion exchange chromatography. Mp 141–143 °C; $[\alpha]_D^{20}$ +31.1

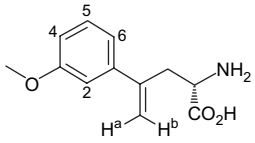
(*c* 0.6, MeOH), Found: C, 55.50; H, 4.80; N, 5.30, $C_{12}H_{13}NO_2F_3$ requires: C, 55.60; H, 4.67; N, 5.40%; ν_{max}/cm^{-1}: 3007 (br, OH), 2128, 1831, 1614 (CO), 1508, 1455, 1427, 1406, 1328; δ_H (500 MHz, CD_3OD): 7.95 (2H, d, ArH, *J*=8.3 Hz), 7.88 (2H, d, ArH, *J*=8.3 Hz), 5.86 (1H, s, =CH^a), 5.62 (1H, s, =CH^b), 3.73 (1H, dd, NC*H*, *J*=3.6, 10.5 Hz), 3.66 (1H, dd, NCC*H*, *J*=5.0, 15.1 Hz), 3.00 (1H, dd, NCC*H*, *J*=10.5, 15.1 Hz); δ_C (75 MHz, D_2O): 171.25 (CO), 162.45 (q, CF_3, *J*=36.8 Hz), 141.82 (H_2C=*C*), 129.32 (q, F_3C*C*, *J*=32.25 Hz), 126.83 (Ar), 125.64 (Ar), 121.95 (Ar), 114.26 (=CH_2), 51.44 (NC), 35.70 (NC*C*); *m*/*z* (ES$^+$): 260 (MH$^+$).

2.3.6. 2-(*R*)-2-Amino-4-(4-trifluoromethyl-phenyl)-pent-4-enoic acid (*R*-5d).



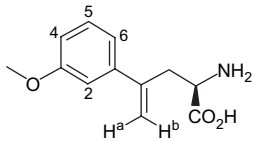
Obtained as colourless prisms (0.193 g, 99%) after ion exchange chromatography. Mp 141–143 °C; $[\alpha]_D^{20}$ −32.7 (*c* 0.5, MeOH); Found: C, 54.80; H, 4.80; N, 5.20, $C_{12}H_{13}NO_2F_3 \cdot 0.25$ M H_2O requires: C, 54.65; H, 4.78; F, 21.61; N, 5.31%; Found: 260.0887, $C_{12}H_{13}NO_2F_3$ requires: 260.0898; δ_H (500 MHz, CD_3OD): 6.84 (2H, d, ArH, *J*=8.3 Hz), 6.80 (2H, d, ArH, *J*=8.3 Hz), 4.86 (1H, s, =CH^a), 4.66 (1H, s, =CH^b), 3.26 (1H, dd, NC*H*, *J*=5.0, 9.1 Hz), 2.60 (1H, dd, NCC*H*, *J*=5.0, 15.1 Hz), 2.30 (1H, dd, NCC*H*, *J*=9.1, 15.1 Hz); δ_C (75 MHz, D_2O): 171.25 (CO), 162.45 (q, CF_3, *J*=36.8 Hz), 141.82 (H_2C=*C*), 129.32 (q, F_3C*C*, *J*=32.25 Hz), 126.83 (Ar), 125.64 (Ar), 121.95 (Ar), 114.26 (=CH_2), 51.44 (NC), 35.70 (NC*C*); *m*/*z* (ES$^+$): 260 (MH$^+$).

2.3.7. 2-(*S*)-2-Amino-4-(3-methoxy-phenyl)-pent-4-enoic acid (*S*-5e).



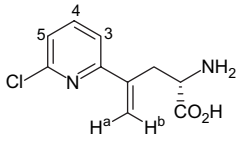
Obtained as colourless prisms (0.088 g, 97%) after ion exchange chromatography. Mp 144–147 °C; $[\alpha]_D^{20}$ +10.9 (*c* 0.2, MeOH); Found: 222.1126, $C_{12}H_{15}NO_3$ requires: 222.1125; ν_{max}/cm^{-1}: 3009 (br, OH), 2593, 2288, 2085, 1843, 1576 (CO), 1491, 1457, 1398; δ_H (500 MHz, D_2O): 7.22 (1H, dd, Ar-5H, *J*=7.7, 8.1 Hz), 6.99 (1H, d, Ar-4H, *J*=7.7 Hz), 6.94 (1H, s, Ar-2H), 6.84 (1H, d, Ar-6H, *J*=8.1 Hz), 5.45 (1H, s, =CH^a), 5.20 (1H, s, =CH^b), 3.93 (1H, dd, NCH, *J*=5.1, 8.1 Hz), 3.69 (3H, s, OCH_3), 3.18 (1H, dd, NCC*H*, *J*=5.1, 15.4 Hz), 2.96 (1H, dd, NCC*H*, *J*=8.1, 15.4 Hz); δ_C (75 MHz, D_2O): 171.57 (CO), 159.40 (H_2C=*C*), 141.21 (Ar), 140.10 (Ar), 130.41 (Ar), 119.67 (Ar), 119.05 (=CH_2), 114.96 (Ar), 112.57 (Ar), 55.70 (OCH_3), 51.70 (NC), 36.09 (NC*C*); *m*/*z* (ES$^+$): 222 (MH$^+$).

2.3.8. 2-(*R*)-2-Amino-4-(3-methoxy-phenyl)-pent-4-enoic acid (*R*-5e).



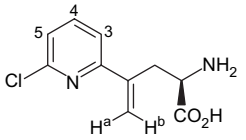
Obtained as colourless prisms (0.115 g, 80%) after ion exchange chromatography. Mp 147–149 °C; $[\alpha]_D^{20}$ −9.5 (*c* 0.3, MeOH); Found: C, 63.60; H, 6.80; N, 6.30, $C_{12}H_{15}NO_3 \cdot 0.25$ M H_2O requires: C, 63.84; H, 6.92; N, 6.20%; Found: 222.1130, $C_{12}H_{15}NO_3$ requires: 222.1120; ν_{max}/cm^{-1}: 3009 (br, OH), 2593, 2086, 1818, 1668, 1575 (CO), 1525, 1493; δ_H (500 MHz, CD_3OD): 7.18 (1H, t, Ar-5H, *J*=8.1 Hz), 7.01 (1H, d, Ar-4H, *J*=7.7 Hz), 6.99 (1H, d, Ar-2H, *J*=2.1 Hz), 6.77 (1H, dd, Ar-6H, *J*=8.1 Hz), 5.41 (1H, s, =CH^a), 5.17 (1H, s, =CH^b), 3.71 (3H, s, OCH_3), 3.44 (1H, dd, NCH, *J*=10.7, 11.1 Hz), 3.34 (1H, dd, NCCH, *J*=10.7, 15.2 Hz), 2.61 (1H, dd, NCCH, *J*=11.1, 15.2 Hz); δ_C (75 MHz, D_2O): 174.37 (CO), 159.51 (H_2C=*C*), 142.38 (Ar), 140.55 (Ar), 130.48 (Ar), 119.65 (Ar), 118.16 (=CH_2), 114.26 (Ar), 112.57 (Ar), 55.79 (OCH_3), 53.67 (NC), 36.96 (NC*C*); *m*/*z* (ES$^+$): 222 (MH$^+$).

2.3.9. 2-(*S*)-2-Amino-4-(6-chloro-pyridin-2-yl)-pent-4-enoic acid (*S*-5f).



Obtained as colourless prisms (0.066 g, 79%) after ion exchange chromatography. Mp 193–195 °C; $[\alpha]_D^{20}$ +31.7 (*c* 0.1, MeOH); Found: C, 52.00; H, 5.00; N, 11.70, $C_{10}H_{11}ClN_2O_2 \cdot 0.25$ M H_2O requires: C, 51.96; H, 5.01; N, 12.12%; Found: 227.0579, $C_{10}H_{11}ClN_2O_2$ requires: 227.0587; ν_{max}/cm^{-1}: 3456, (br, OH), 3049, 2929, 1854, 1630 (CO), 1523; δ_H (500 MHz, D_2O): 8.43 (1H, d, pyridyl-5H, *J*=2.1 Hz), 7.97 (1H, dd, pyridyl-4H, *J*=2.1, 8.3 Hz), 7.51 (1H, d, pyridyl-3H, *J*=8.3 Hz), 5.61 (1H, s, =CH^a), 5.43 (1H, s, =CH^b), 4.03 (1H, dd, NCH *J*=6.0, 7.7 Hz), 3.21 (1H, dd, NCC*H*, *J*=6.0, 15.4 Hz), 3.11 (1H, dd, NCC*H*, *J*=7.7, 15.4 Hz); δ_C (75 MHz, D_2O): 174.32 (CO), 142.57 (H_2C=*C*), 138.76 (Ar), 129.28 (Ar), 128.55 (Ar), 126.72 (Ar), 125.77 (Ar), 117.75 (=CH_2), 52.97 (NC), 36.87 (NC*C*); *m*/*z* (ES$^+$): 227 (^{35}Cl MH$^+$), 229 (^{37}Cl MH$^+$).

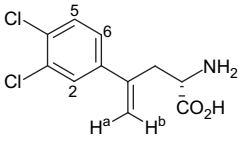
2.3.10. 2-(*R*)-2-Amino-4-(6-chloro-pyridin-2-yl)-pent-4-enoic acid (*R*-5f).



Obtained as colourless prisms (0.123 g, 79%) after ion exchange chromatography. Mp 196–198 °C; $[\alpha]_D^{20}$ −32.1

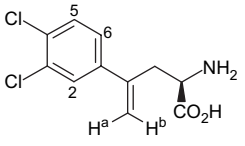
(*c* 0.3, MeOH); Found: 227.0583, $C_{10}H_{11}ClN_2O_2$ requires: 227.0587; ν_{max}/cm^{-1}: 3051 (br, OH), 2093, 1893, 1607 (CO), 1555, 1474, 1454, 1410; δ_H (500 MHz, D_2O): 8.17 (1H, d, pyridyl-5H, *J*=2.4 Hz), 7.89 (1H, dd, pyridyl-4H, *J*=2.4, 8.8 Hz), 7.89 (1H, d, pyridyl-3H, *J*=8.8 Hz), 5.23 (1H, s, =CH^a), 5.09 (1H, s, =CH^b), 3.54 (1H, dd, NCH, *J*=6.2, 7.7 Hz), 2.74 (1H, dd, NCC*H*, *J*=6.2, 15.5 Hz), 2.64 (1H, dd, NCC*H*, *J*=7.7, 15.5 Hz); δ_C (75 MHz, D_2O): 174.19 (CO), 150.06 (H_2C=*C*), 147.16 (Ar), 138.55 (Ar), 138.20 (Ar), 134.25 (Ar), 124.83 (Ar), 120.16 (=CH_2), 53.47 (NC), 36.45 (NC*C*); *m*/*z* (ES$^+$): 227 (^{35}Cl MH$^+$), 229 (^{37}Cl MH$^+$).

2.3.11. 2-(*S*)-2-Amino-4-(3,4-dichloro-phenyl)-pent-4-enoic acid (*S*-5g).



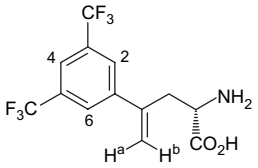
Obtained as colourless prisms (0.107 g, 82%) after ion exchange chromatography. Mp 147–148 °C; $[\alpha]_D^{20}$ +33.1 (*c* 0.4, MeOH); Found: C, 50.80; H, 4.50; Cl, 27.40; N, 5.30, $C_{11}H_{11}Cl_2NO_2$ requires: C, 50.79; H, 4.26; Cl, 27.26; N, 5.38%; ν_{max}/cm^{-1}: 3025 (br OH), 2064, 1899, 1840, 1761, 1670, 1579, 1517; δ_H (500 MHz, D_2O): 7.54 (1H, s, Ar-2H), 7.40 (1H, d, Ar-5H, *J*=8.4 Hz), 7.26 (1H, d, Ar-6H, *J*=8.4 Hz), 5.48 (1H, s, =CH^a), 5.26 (1H, s, =CH^b), 3.96 (1H, dd, NC*H*, *J*=5.1, 5.5 Hz), 3.15 (1H, dd, NCC*H*, *J*=5.5, 13.2 Hz), 2.98 (1H, dd, NCC*H*, *J*=5.1, 13.2 Hz); δ_C (75 MHz, D_2O): 165.14 (CO), 142.0 (H_2C=*C*), 141.14 (Ar), 134.78 (Ar), 134.39 (Ar), 133.30 (Ar), 131.07 (Ar), 128.91 (Ar), 120.84 (=CH_2), 54.02 (NC), 38.21 (NC*C*); *m*/*z* (ES$^+$): 260 ($^{35/35}$Cl MH$^+$), 262 ($^{35/37}$Cl MH$^+$), 264 ($^{37/37}$Cl MH$^+$).

2.3.12. 2-(*R*)-2-Amino-4-(3,4-dichloro-phenyl)-pent-4-enoic acid (*R*-5g).



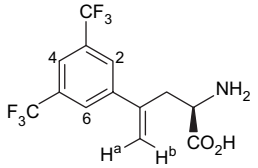
Obtained as colourless prisms (0.094 g, 73%) after ion exchange chromatography. Mp 146–148 °C $[\alpha]_D^{20}$ −31.4 (*c* 0.1, MeOH); Found: C, 49.30; H, 4.60; N, 4.70, $C_{11}H_{11}Cl_2NO_2 \cdot 0.5$ M H_2O requires: C, 49.09; H, 4.49; N, 5.20%; Found: 259.0164, $C_{11}H_{11}Cl_2NO_2$ requires: 259.0161; ν_{max}/cm^{-1}: 3033 (br, OH), 1669, 1576, 1516; δ_H (500 MHz, D_2O): 7.54 (1H, s, Ar-2H), 7.40 (1H, d, Ar-5H, *J*=8.4 Hz), 7.26 (1H, d, Ar-6H, *J*=8.4 Hz), 5.48 (1H, s, =CH^a), 5.26 (1H, s, =CH^b), 3.96 (1H, dd, NC*H*, *J*=5.1, 5.5 Hz), 3.15 (1H, dd, NCC*H*, *J*=5.5, 13.2 Hz), 2.98 (1H, dd, NCC*H*, *J*=5.1, 13.2 Hz); δ_C (75 MHz, D_2O): 171.48 (CO), 142.0 (H_2C=*C*), 141.14 (Ar), 134.78 (Ar), 134.39 (Ar), 133.30 (Ar), 131.07 (Ar), 128.91 (Ar), 120.84 (=CH_2), 54.02 (NC), 38.21 (NC*C*); *m*/*z* (ES$^+$): 260 ($^{35/35}$Cl MH$^+$), 262 ($^{35/37}$Cl MH$^+$), 264 ($^{37/37}$Cl MH$^+$).

2.3.13. 2-(*S*)-2-Amino-4-(3,5-bis-trifluoromethyl-phenyl)-pent-4-enoic acid (*S*-5h).



Obtained as colourless prisms (0.178 g, 89%) after ion exchange chromatography. Mp 152–155 °C; $[\alpha]_D^{20}$ +10.9 (*c* 0.5, MeOH); Found: C, 47.65; H, 3.30; N, 4.05, $C_{13}H_{11}F_6NO_2$ requires: C, 47.72; H, 3.39; N, 4.28%; Found: 328.0765, $C_{13}H_{11}F_6NO_2$ requires: 328.0767; ν_{max}/cm^{-1}: 3456 (NH), 3049 (br, OH), 2929, 1854, 1622 (CO), 1524, 1398, 1334, 1277; δ_H (500 MHz, CD_3OD): 8.01 (2H, s, Ar-2H, Ar-6H), 7.83 (1H, s, Ar-4H), 5.55 (1H, s, =CH^a), 5.40 (1H, s, =CH^b), 3.40 (1H, dd, NCH, *J*=4.1, 9.7 Hz), 3.33 (1H, dd, NCC*H*, *J*=4.1, 15.4 Hz), 2.79 (1H, dd, NCC*H*, *J*=9.7, 15.4 Hz); δ_C (75 MHz, CD_3OD): 173.70 (CO), 143.83 (H_2C=*C*), 143.11 (Ar), 133.42 (q, F_3CC, *J*=33.25 Hz), 128.64 (Ar), 125.14 (q, CF_3, *J*=271.82 Hz), 122.96 (Ar), 121.14 (=CH_2), 54.63 (NC), 38.29 (NC*C*); *m*/*z* (ES$^+$): 328 (MH$^+$).

2.3.14. 2-(*R*)-2-Amino-4-(3,5-bis-trifluoromethyl-phenyl)-pent-4-enoic acid (*R*-5h).



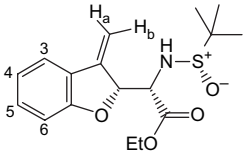
Obtained as colourless prisms (0.167 g, 68%) after ion exchange chromatography. Mp 153–156 °C; $[\alpha]_D^{20}$ −9.5 (*c* 0.6, MeOH); Found: C, 47.50; H, 3.30; N, 4.20, $C_{13}H_{11}F_6NO_2$ requires: C, 47.72; H, 3.39; N, 4.28%; ν_{max}/cm^{-1}: 3683, 2929 (br, OH), 2065, 1832, 1634 (CO), 1510, 1444; δ_H (500 MHz, D_2O): 7.40 (2H, s, Ar-2H, Ar-6H), 7.36 (1H, s, Ar-4H), 5.12 (1H, s, =CH^a), 4.95 (1H, s, =CH^b), 3.48 (1H, dd, NCH, *J*=5.5, 8.0 Hz), 2.78 (1H, dd, NCC*H*, *J*=5.5, 15.3 Hz), 2.79 (1H, dd, NCC*H*, *J*=8.0, 15.4 Hz); δ_C (75 MHz, CD_3OD): 173.65 (CO), 143.64 (H_2C=*C*), 142.96 (Ar), 133.22 (q, F_3CC, *J*=33.25 Hz), 128.56 (Ar), 125.14 (q, CF_3, *J*=271.82 Hz), 122.94 (Ar), 121.15 (=CH_2), 54.46 (NC), 38.17 (NC*C*); *m*/*z* (ES$^+$): 328 (MH$^+$).

2.4. General procedure for the synthesis of *N*-sulfinyl-α-amino esters 17–20

Bifunctional aryl iodide/allene (0.75 mmol) was added to a suspension of chiral α-imino ester (0.5 mmol), indium metal powder (0.088 g, 0.75 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), tri-2-furyl phosphine (0.024 g, 0.1 mmol), CuI (0.019 g, 0.1 mmol) and piperidine (0.05 ml, 0.5 mmol) in DMF (10 ml) in a Schlenk tube. The mixture was stirred and heated to 60 °C (oil bath temperature) for 24 h, left to cool and vented. Ethyl acetate (20 ml) and 5% HCl solution (10 ml) was added and the mixture

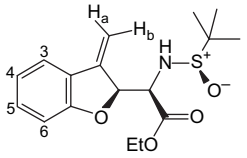
stirred for 20 min. The phases were separated and the aqueous layer extracted with ethyl acetate (20 ml). The organic extracts were combined and washed with water (3×100 ml), dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography to give the *N*-sulfinylamino esters.

2.4.1. Ethyl 2*S*,5*S*,6*R*-(3-methylene-2,3-dihydro-benzofuran-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-17).



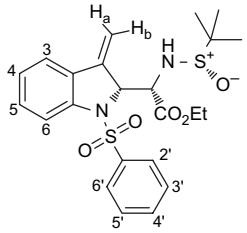
Obtained as a pale yellow oil (0.110 g, 64%) after flash chromatography (Et_2O); R_f 0.11 (Et_2O); $[\alpha]_D^{20}$ −42.2 (*c* 1.1); Found: C, 58.60; H, 7.20; N, 4.10, $C_{17}H_{23}NO_4S\cdot 0.5$ M H_2O requires: C, 58.94; H, 6.98; N, 4.04%; ν_{max}/cm^{-1}: 3286, 3078, 2984, 2968, 2869, 2836, 1739 (CO), 1634; δ_H (500 MHz, $CDCl_3$): 7.33 (1H, d, Ar-6H, *J*=7.6 Hz), 7.19 (1H, t, Ar-5H, *J*=7.6 Hz), 6.87 (1H, t, Ar-4H, *J*=7.6 Hz), 6.84 (1H, d, Ar-3H, *J*=7.6 Hz), 5.54 (2H, m, NCH, =CH^a), 5.09 (1H, s, =CH^b), 4.32 (2H, q, OCH_2, *J*=7.3 Hz), 4.21 (2H, m, NCH, OCH), 1.32 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.45 (CO), 163.13 (Ar), 144.48 (Ar), 131.14 (Ar), 126.52 (Ar), 124.27 (Ar), 121.39 (Ar), 121.11 (Ar), 110.67 (Ar), 102.69 (=CH_2), 85.78 (OCH), 62.99 (OCH_2), 62.65 (NC), 56.73 (S*C*), 22.57 ($C(CH_3)_3$), 14.50 (OCH_2CH_3); *m*/*z* (ES^+): 338 (MH^+).

2.4.2. Ethyl 2*R*,5*R*,6*S*-(3-methylene-2,3-dihydro-benzofuran-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-17).



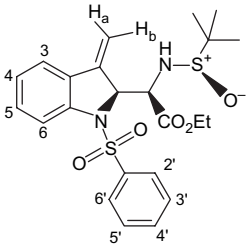
Obtained as a pale yellow oil (0.108 g, 64%) after flash chromatography (Et_2O); R_f 0.11 (Et_2O); $[\alpha]_D^{20}$ +39.7 (*c* 0.5); Found: C, 59.60; H, 6.85; N, 4.25, $C_{17}H_{23}NO_4S\cdot 0.25$ M H_2O requires: C, 59.71; H, 6.93; N, 4.10%; ν_{max}/cm^{-1}: 3281, 3077, 2959, 2869, 2836, 1737 (CO), 1634; δ_H (500 MHz, $CDCl_3$): 7.33 (1H, d, Ar-6H, *J*=7.6 Hz), 7.19 (1H, t, Ar-5H, *J*=7.6 Hz), 6.87 (1H, t, Ar-4H, *J*=7.6 Hz), 6.84 (1H, d, Ar-3H, *J*=7.6 Hz), 5.54 (2H, m, NCH, =CH^a), 5.09 (1H, s, =CH^b), 4.32 (2H, q, OCH_2, *J*=7.3 Hz), 4.21 (2H, m, NCH, OCH), 1.32 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.43 (CO), 163.12 (Ar*C*), 144.46 (Ar), 131.12 (Ar), 126.51 (Ar), 121.37 (Ar), 121.10 (Ar), 110.67 (Ar), 102.64 (=CH_2), 85.76 (OCH), 62.94 (OCH_2), 62.62 (NC), 56.68 (S*C*), 22.65 ($C(CH_3)_3$), 14.49 (OCH_2CH_3); *m*/*z* (ES^+): 338 (MH^+).

2.4.3. Ethyl 2*S*,5*S*,6*R*-(1-benzenesulfonyl-3-methylene-2,3-dihydro-1*H*-indol-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-18).



Obtained as colourless prisms (0.110 g, 46%) after flash chromatography (Et_2O). Mp 149–151 °C; R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ −16.3 (*c* 0.6); Found: C, 57.85; H, 5.65; N, 5.80; S, 13.35, $C_{23}H_{28}N_2O_5S_2$ requires: C, 57.96; H, 5.92; N, 5.88; S, 13.45%; ν_{max}/cm^{-1}: 3294 (NH), 3085, 3014, 2985, 1732 (CO), 1648, 1600, 1584; δ_H (500 MHz, $CDCl_3$): 7.71 (1H, d, Ar-6H, *J*=8.1 Hz), 7.55 (2H, d, Ar-2′H, Ar-6′H, *J*=7.7 Hz), 7.49 (1H, d, Ar-3H, *J*=7.5 Hz), 7.34 (2H, t, Ar-3′H, Ar-5′H, *J*=7.7 Hz), 7.27–7.23 (2H, m, Ar-4H, Ar-5H), 7.05 (1H, t, Ar-4′H, *J*=7.7 Hz), 5.44 (1H, s, =CH^a), 5.08 (1H, s, =CH^b), 4.97 (1H, d, NH, *J*=1.6 Hz), 4.37 (1H, d, $PhSO_2NCH$, *J*=7.6 Hz), 4.33 (2H, m, OCH_2), 4.15 (1H, dd, SNC*H*, *J*=1.6, 7.6 Hz), 1.32 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 0.91 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 170.09 (CO), 144.73 (H_2C=*C*), 143.14 (Ar), 136.75 (Ar), 133.91 (Ar), 131.61 (Ar), 130.57 (Ar), 129.44 (Ar), 127.61 (Ar), 121.19 (Ar), 118.02 (H_2C=C), 68.14 (SO_2NC), 64.46 (SC), 62.90 (SNC), 56.45 (OCH_2), 22.50 ($C(CH_3)_3$), 14.41 (OCH_2CH_3); *m*/*z* (ES^+): 477 (MH^+).

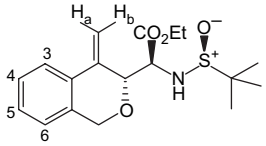
2.4.4. Ethyl 2*R*,5*R*,6*S*-(1-benzenesulfonyl-3-methylene-2,3-dihydro-1*H*-indol-2-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-18).



Obtained as colourless prisms (0.231 g, 48%) after flash chromatography (Et_2O). Mp 149–151 °C; R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ +15.7 (*c* 0.8); Found: C, 58.0; H, 5.90; N, 5.90; S, 13.60, $C_{23}H_{28}N_2O_5S_2$ requires: C, 57.96; H, 5.92; N, 5.88; S, 13.45%; ν_{max}/cm^{-1}: 3294 (NH), 3085, 3014, 2985, 1732 (CO), 1648, 1600, 1584; δ_H (500 MHz, $CDCl_3$): 7.71 (1H, d, Ar-6H, *J*=8.1 Hz), 7.55 (2H, d, Ar-2′H, Ar-6′H, *J*=8.2 Hz), 7.49 (1H, d, Ar-3H, *J*=7.5 Hz), 7.34 (2H, t, Ar-3′H, Ar-5′H, *J*=7.9 Hz), 7.27–7.23 (2H, m, Ar-4H, Ar-5H), 7.05 (1H, t, Ar-4′H, *J*=7.5 Hz), 5.44 (1H, s, =CH^a), 5.08 (1H, s, =CH^b), 4.97 (1H, d, NH, *J*=1.6 Hz), 4.37 (1H, d, SO_2NCH, *J*=7.6 Hz), 4.33 (2H, m, OCH_2), 4.15 (1H, dd, NC*H*, *J*=1.6, 7.6 Hz), 1.32 (3H, t, OCH_2CH_3, *J*=7.2 Hz), 0.91 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 170.09 (CO), 144.73 (H_2C=*C*), 143.14 (Ar), 136.75 (Ar), 133.91 (Ar), 131.61 (Ar), 130.57 (Ar), 129.44 (Ar), 127.61 (Ar), 121.19 (Ar), 118.02 (H_2C=C), 68.14 (SO_2NC),

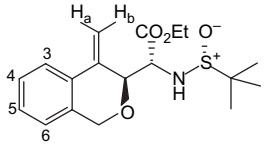
64.46 (SC), 62.90 (SNC), 56.45 (OC), 22.50 ($C(CH_3)_3$), 14.41 (OCH_2CH_3); *m*/*z* (ES^+): 477 (MH^+).

2.4.5. Ethyl 2*S*,5*S*,6*R*-(4-methylene-isochroman-3-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-19).



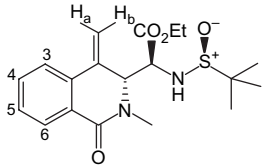
Obtained as a pale yellow oil (0.108 g, 62%) after flash chromatography (Et_2O); R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ −41.0 (*c* 0.7); Found: C, 61.80; H, 7.00; N, 3.70; S, 9.20, $C_{18}H_{25}NO_4S$ requires: C, 61.51; H, 7.17; N, 3.99; S, 9.12%; ν_{max}/cm^{-1}: 3296 (NH), 3126, 2980, 2960, 2905, 2868, 2841, 1738 (CO), 1628; δ_H (500 MHz, $CDCl_3$): 7.57 (1H, d, Ar-6H, *J*=2.5 Hz), 7.25–7.22 (2H, m, Ar-4H, Ar-5H), 7.03 (1H, m, Ar-3H), 5.72 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.89 (1H, dd, OCH, *J*=1.7, 3.8 Hz), 4.75 (1H, d, ArCH, *J*=14.5 Hz), 4.62 (1H, d, ArCH, *J*=14.5 Hz), 4.32 (1H, dd, NCH, *J*=3.8, 8.6 Hz), 4.27 (2H, dq, CO_2CH_2, *J*=1.3, 7.3 Hz), 1.29 (3H, t, OCH_2CH_3, *J*=7.1 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 171.49 (CO), 138.88 (=C), 134.58 (Ar), 132.32 (Ar), 128.33 (Ar), 127.83 (Ar), 124.89 (Ar), 124.14 (Ar), 110.09 (=CH_2), 79.17 (NC*C*), 66.91 (OCH_2), 62.40 (CO_2C), 62.06 (NC), 56.84 (SC), 22.96 ($C(CH_3)_3$), 14.51 (OCH_2CH_3); *m*/*z* (ES^+): 352 (MH^+).

2.4.6. Ethyl 2*R*,5*R*,6*S*-(4-methylene-isochroman-3-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-19).



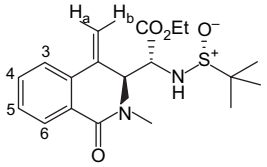
Obtained as a pale yellow oil (0.101 g, 58%) after flash chromatography (Et_2O); R_f 0.14 (Et_2O); $[\alpha]_D^{20}$ +41.5 (*c* 1.3); Found: 374.1402, $C_{18}H_{25}NO_4S{\cdot}Na$ requires: 374.1402; ν_{max}/cm^{-1}: 3450, 3297 (NH), 2959, 2868, 1738 (CO), 1628, 1576; δ_H (500 MHz, $CDCl_3$): 7.57 (1H, dd, Ar-6H, *J*=4.3, 9.0 Hz), 7.23 (2H, m, Ar-4H, Ar-5H), 7.03 (1H, dd, Ar-3H, *J*=4.3, 6.0 Hz), 5.72 (1H, s, =CH^a), 5.11 (1H, s, =CH^b), 4.89 (1H, m, NH), 4.75 (1H, d, OCH, *J*=14.5 Hz), 4.62 (1H, d, OCH, *J*=14.5 Hz), 4.32 (1H, dd, NCH, *J*=3.8, 8.6 Hz), 4.29–4.24 (3H, m, CO_2CH_2, OCH), 1.30 (3H, t, OCH_2CH_3, *J*=7.1 Hz), 1.09 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$): 170.08 (CO), 137.44 (=C), 133.15 (Ar), 130.89 (Ar), 126.90 (Ar), 126.40 (Ar), 123.46 (Ar), 122.71 (Ar), 108.66 (=CH_2), 77.74 (NC*C*), 65.48 (OCH_2), 60.98 (CO_2C), 60.92 (NC), 55.39 (SC), 21.53 ($C(CH_3)_3$), 13.09 (OCH_2CH_3); *m*/*z* (ES^+): 352 (MH^+).

2.4.7. Ethyl 2*S*,5*S*,6*R*-(2-methyl-4-methylene-1-oxo-1,2,3,4-tetrahydro-isoquinolin-3-yl)-(2-methyl-propane-2-sulfinylamino)acetate (*S*,*S*,*R*-20).



Obtained as a pale yellow oil (0.052 mg, 28%) after flash chromatography (EtOAc); R_f 0.10 (EtOAc); $[\alpha]_D^{20}$ −7.3 (*c* 0.4); Found: C, 60.20; H, 6.90; N, 7.10; S, 8.40, $C_{19}H_{26}N_2O_4S$ requires: C, 60.29; H, 6.92; N, 7.40; S, 8.47%; ν_{max}/cm^{-1}: 3459 (NH), 3274, 2961, 2239, 1739 (CO), 1648 (CO), 1602, 1573; δ_H (500 MHz, $CDCl_3$): 8.09 (1H, d, Ar-6H, *J*=7.7 Hz), 7.51 (1H, d, Ar-3H, *J*=7.7 Hz), 7.47 (1H, td, Ar-4H, *J*=0.9, 7.7 Hz), 7.40 (1H, td, Ar-5H, *J*=0.9, 7.7 Hz), 5.74 (1H, s, =CH^a), 5.31 (1H, s, =CH^b), 4.38 (1H, d, MeNC*H*, *J*=4.7 Hz), 4.27 (1H, d, NH, *J*=8.1 Hz), 4.11 (1H, dd, NCH, *J*=4.7, 8.1 Hz), 3.90 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.54 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.22 (3H, s, NCH_3), 1.15 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.53 (CO), 163.29 (NCO), 136.20 (=C), 134.46 (Ar), 132.19 (Ar), 128.10 (Ar), 127.83 (Ar), 127.27 (Ar), 123.68 (Ar), 115.76 (=CH_2), 68.33 (MeN*C*), 62.34 (OC), 59.54 (SNC), 56.22 (SC), 35.14 (NCH_3), 22.53 ($C(CH_3)_3$), 10.97 (OCH_2CH_3); *m*/*z* (ES^+): 379 (MH^+).

2.4.8. Ethyl (*R*)-((*S*)-2-methyl-4-methylene-1-oxo-1,2,3,4-tetrahydro-isoquinolin-3-yl)-((*R*)-2-methyl-propane-2-sulfinylamino)acetate (*R*,*R*,*S*-20).



Obtained as a pale yellow oil (0.130 g, 69%) after flash chromatography (EtOAc); R_f 0.10 (EtOAc); $[\alpha]_D^{20}$ +9.2 (*c* 0.6); Found: C, 60.50; H, 7.20; N, 7.40; S, 8.40, $C_{19}H_{26}N_2O_4S$ requires: C, 60.29; H, 6.92; N, 7.40; S, 8.47%; ν_{max}/cm^{-1}: 3459 (NH), 3274, 2964, 2239, 1744 (CO), 1658 (CO), 1602; δ_H (500 MHz, $CDCl_3$): 8.09 (1H, d, Ar-6H, *J*=7.8 Hz), 7.51 (1H, d, Ar-3H, *J*=7.7 Hz), 7.47 (1H, td, Ar-4H, *J*=0.9, 7.7 Hz), 7.40 (1H, td, Ar-4H, *J*=0.9, 7.7 Hz), 5.74 (1H, s, =CH^a), 5.31 (1H, s, =CH^b), 4.39 (1H, d, MeNC*H*, *J*=4.7 Hz), 4.27 (1H, d, NH, *J*=8.1 Hz), 4.14 (1H, dd, NCH, *J*=4.5, 8.1 Hz), 3.90 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.54 (1H, dq, OCH, *J*=7.3, 10.7 Hz), 3.23 (3H, s, NCH_3), 1.15 (9H, s, $C(CH_3)_3$), 1.13 (3H, t, OCH_2CH_3, *J*=7.3 Hz); δ_C (75 MHz, $CDCl_3$): 170.53 (CO), 163.29 (NCO), 136.20 (=C), 134.46 (Ar), 132.19 (Ar), 128.10 (Ar), 127.83 (Ar), 127.27 (Ar), 123.68 (Ar), 115.76 (=CH_2), 68.33 (MeN*C*), 62.34 (OC), 59.54 (SNC), 56.22 (SC), 35.14 (NCH_3), 22.53 ($C(CH_3)_3$), 10.97 (OCH_2CH_3); *m*/*z* (ES^+): 379 (MH^+).

Acknowledgements

We thank Leeds University, the EPSRC and Avecia for support.

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14. Supplementary crystallographic data for *S*,*S*-**6** (CCDC 277090), *R*,*R*-**6** (CCDC 277091) and *R*,*R*,*S*-**18** (CCDC 277092) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
15. Semi-empirical calculations were performed using MOPAC v7 by J. J. P. Stewart and the PM3 Hamiltonian. Approximate transition structures were located using the SADDLE routine within MOPAC following full conformational optimisation of the attached sub-structures (MM2). Transition structures were then fully optimised using the TS routine within MOPAC and these then characterised by observing them to have a single negative vibrational frequency following use of the FORCE calculation within MOPAC.
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Tetrahedron 62 (2006) 12172–12181
Tetrahedron

‘Catch and release’ cascades: a resin-mediated three-component cascade approach to small molecules

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Received 2 June 2006; revised 14 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—The application of a ‘catch and release’ approach to palladium-catalysed multi-component cascade reactions leads to diverse libraries of pharmacologically interesting small molecules in high yield and with excellent purity.

1. Introduction

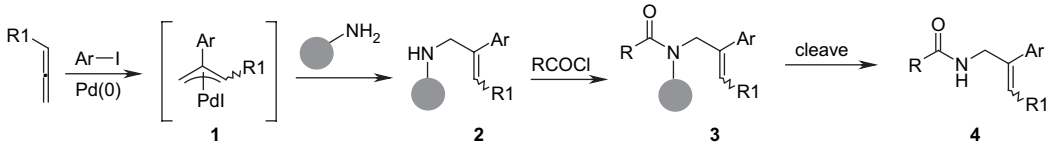
The development of high-throughput screening emphasised the need for new techniques to synthesise compound libraries with ‘drug-like’ properties. Classical multi-step solution-phase synthesis cannot generate large numbers of compounds in a parallel fashion, and thus new methods have been developed to enable rapid synthesis and separation of a desired compound from by-products and/or excess reagents. One way to approach this problem is to attach the desired compound to a solid support, and to separate it from by-products/reagents by filtration. The desired compound is then released from the resin and isolated in high purity.[1–3]

This resin-bound approach has become central to the drug discovery process in the pharmaceutical industry. Reactions can be driven to completion through the use of excess reagents; resin-washing is a very simple way of removing undesired reagents and by-products; physical losses are minimised since the product remains attached to the resin throughout the synthetic process; the process is highly amenable to automation. Nevertheless, there are limitations to undertaking synthetic processes with resin-bound products, in particular the diminished rate of some reactions compared to their solution-phase equivalent, and the often laborious development time for optimising solution-phase chemistry on a solid support.[4,5]

Recent developments in combinatorial synthesis have focused on these limitations. One method, known as ‘resin capture’ or ‘catch and release’, minimises these drawbacks by initiating the synthesis of a library in solution and subsequently transferring the product of the solution-phase synthesis onto solid support for further manipulation and isolation. First published by Armstrong and Brown to synthesise tetrasubstituted ethylenes,[6] the ‘catch and release’ approach enables the facile synthesis of quite complex products with exceptional purity and is now a commonly used combinatorial technique.[7–16]

2. Palladium-catalysed ‘catch and release’ cascade

The objective of the present study was to apply an extended ‘catch and release’ strategy to the palladium-catalysed three-component cascade reaction incorporating aryl iodides, allenes and nitrogen nucleophiles (Scheme 1). Previous work within our group had shown that the three-component catalytic cascade was amenable to solid-phase synthesis when the aryl iodide[17] or allene[18] was pre-attached to the resin. Our envisaged approach would extend this



1 2 3 4

Scheme 1.

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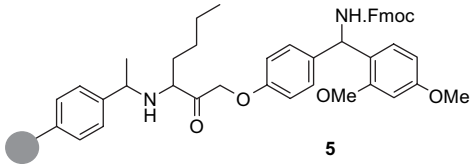
doi:10.1016/j.tet.2006.09.101

methodology in two ways: by utilising a resin-bound nucleophile to capture the product onto resin; by carrying out further manipulation of the resin-bound product prior to cleavage. It was hoped that this method would allow the rapid construction of diverse libraries of pharmacologically interesting small molecules.

Thus the π-allylpalladium species **1** (formed in solution from an allene and aryl iodide) would be captured by a resin-bound amino group to give resin-bound product **2**. Further manipulation of **2** by, for example, acylation with an acid chloride would provide resin-bound allylic amide **3**. This could be further functionalised or cleaved immediately to give **4**.

2.1. Development of methodology

A good resin for 'catch and release' strategies is Rink Amide MBHA resin **5**. Deprotection of the Fmoc group leaves a primary amino group, which is an ideal nucleophile for our cascade and the presence of the methoxy substituents facilitates cleavage via extended delocalisation of the carbocation via the oxygen lone pairs.

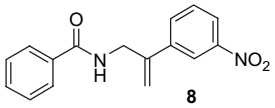
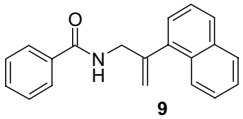
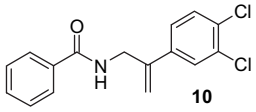
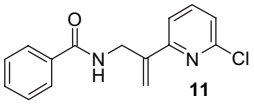
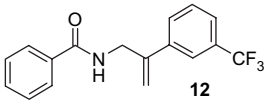
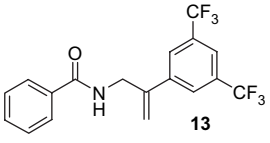
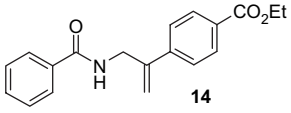
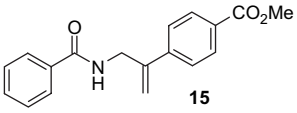


5

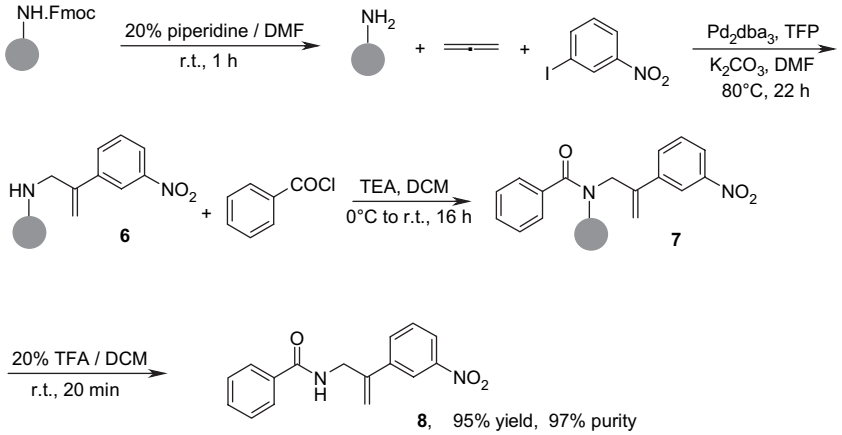
Having selected an appropriate resin, we decided to test the viability of the cascade using allene gas and a simple aryl iodide (Scheme 2).

The resin was deprotected using 20% piperidine in dimethylformamide and, after washing the resin, the three-component catalytic cascade was carried out using very similar reaction conditions to those employed in solution phase. Thus 1.1 equiv of the aryl iodide, 2.0 equiv of potassium carbonate, 2.5 mol % of tris (dibenzylideneacetone) dipalladium(0) and 10 mol % of tri-2-furylphosphine were reacted at 80 °C over 22 h. After washing, the resin-bound product **6** was acylated with excess benzoyl chloride (2 equiv) using triethylamine as base (3 equiv) in dichloromethane to give **7**, which after further washing was cleaved to give allylic amide **8**. The reaction was then repeated using different aryl iodides to provide a small library of allylic amides (Table 1).

Table 1. Cascade products using conditions shown in Scheme 2

Entry	Product	Yield (%)[a]	Purity (%)[b]
1	 **8**	95	97
2	 **9**	64	96
3	 **10**	55	96
4	 **11**	68	99
5	 **12**	75	98
6	 **13**	55	97
7	 **14**	76	98
8	 **15**	82	>99

[a] Isolated yield after column chromatography and/or crystallisation.
[b] HPLC analysis of crude product directly after cleavage.



Scheme 2.

The third column of Table 1 shows that the reaction yields varied from as low as 55% to as high as 95%. These yields represent the isolated yields of the final products after all four synthetic steps (deprotection, the three-component cascade, acylation and cleavage from the resin) and after any subsequent purification. Even the lowest overall yield of 55% represents an average yield exceeding 85% for each individual step. In the circumstances the yields were excellent, and it was pleasing to note that although we were using a primary amine as nucleophile in the cascade, no bis-adduct was formed as a by-product.

We were particularly encouraged by the purity exhibited by the products (the final column in Table 1). Purity was assessed by carrying out an HPLC analysis of the crude product directly after TFA cleavage (the only proviso being that some of the products were washed with ether before being left under high vacuum overnight to remove residual traces of TFA). For all the entries in Table 1, the purity of the compound is at least 95%. Indeed, for the methyl ester **15** the crude product was analytically pure by HPLC with no discernible trace of impurity. All HPLC analyses were recorded at 254 nm using a Luna 5μ (250×4.6 mm) phenyl–hexyl column.

Figure 1 shows the ^{1}H NMR spectrum of **13** recorded directly after cleavage and is typical of the spectra of crude products obtained from this solid-phase synthetic route.

It is noticeable from Table 1 that all of the products are derived from aryl iodides, which are rendered electron deficient by either the presence of an electron withdrawing substituent (entries 1, 3–8) or by extended conjugation (entry 2).

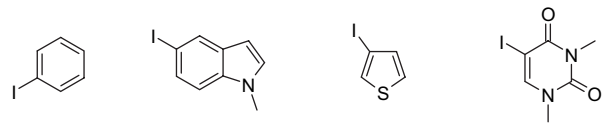


Figure 2.

Numerous attempts to incorporate the aryl/vinyl iodides shown in Figure 2 into the standard protocol proved unsuccessful. A complex mixture of products was obtained on cleavage from the resin, comprising at best 20–30% desired product and often significantly less. Using an excess of aryl iodide (up to 5 equiv), extending the reaction time up to 48 h, altering the solvent (acetonitrile and toluene) and varying the reaction temperature all failed to improve product yield and purity.

Electron withdrawing groups activate the carbon–iodine bond to oxidative addition by the nominally electron-rich palladium(0). However, this cannot alone explain the reaction failure as aryl iodides of the type shown in Figure 2 undergo the three-component cascade reaction using standard nitrogen nucleophiles in solution.[19]

Rather, a combination of both the nature of the nitrogen nucleophile and the nature of the π-allylpalladium intermediate is likely to be decisive here. The resin-bound amino group is sterically hindered, the polymer backbone hinders access of the amino group to the π-allylpalladium species, whilst the close proximity of the sp^2 carbons of the surrounding aryl groups inductively reduces the calculated pK_a, both of which impact adversely on the nucleophilicity of the amine. Therefore, in order for the cascade process to proceed satisfactorily, the π-allylpalladium species (which acts as

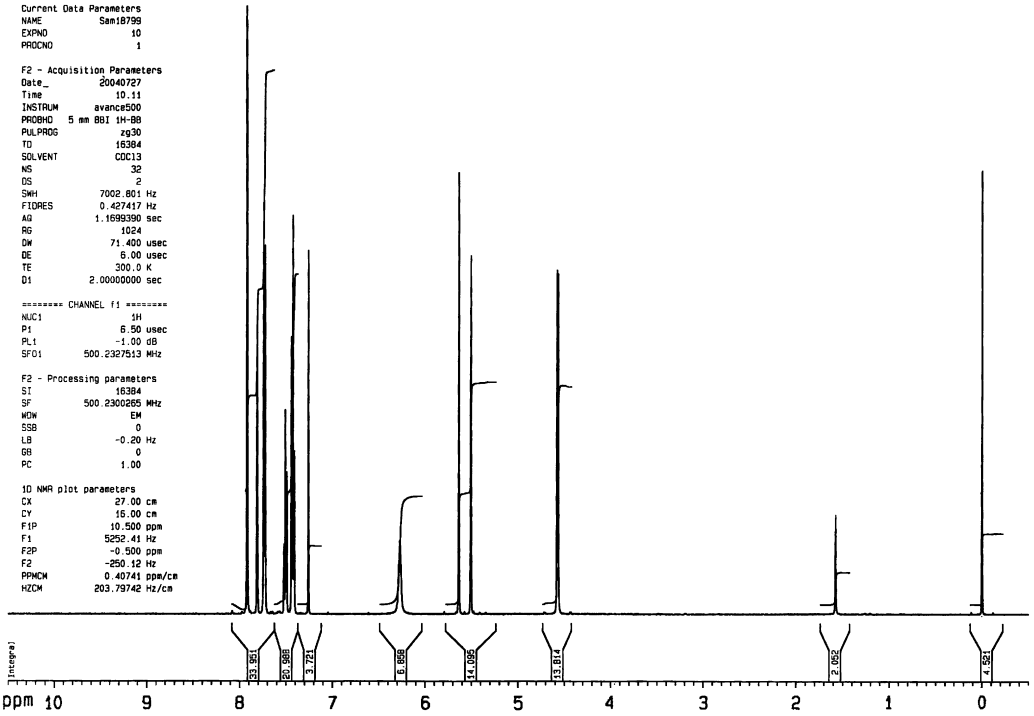


Figure 1. ^{1}H NMR ($CDCl_3$) of compound **13** directly after resin-cleavage.

the electrophile) is likely to require enhanced reactivity. The presence of an electron withdrawing group, which will render that species even more electrophilic, must tip the balance in favour of nucleophilic attack to give the desired cascade product. Thus a combination of steric and electronic factors prevents the cascade from proceeding unless an activated aryl iodide is employed.

2.2. Exploring diversity in the cascade

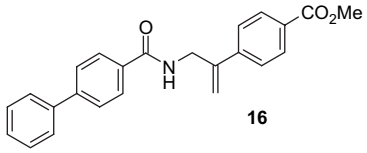
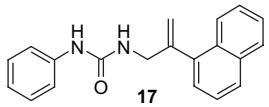
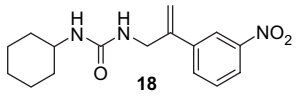
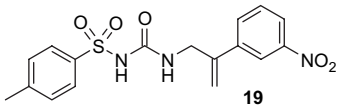
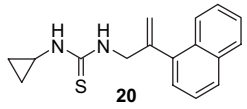
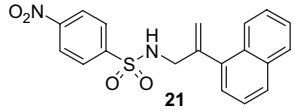
The compounds in Table 1 are derived using benzoyl chloride as the acylating agent. However, it is possible to use other reagents in order to introduce further diversity into the final products (Table 2).

Thus other acid chlorides are tolerated (entry 1) as are aryl and alkyl isocyanates (entries 2 and 3) and sulfonyl isocyanates (entry 4). As before, the products are obtained in high yields and excellent purity.

Attempts to extend the scope of the cascade using isothiocyanates and sulfonyl chlorides as reagents have, thus far, proved less successful (entries 5 and 6). Since both **20** and **21** fell below our purity cut-off they were not processed any further.

An explanation for the poor reactivity of isothiocyanates and sulfonyl chlorides again relates to the nucleophilicity of the resin-bound amino group. Following the three-component catalytic cascade, the resulting secondary amine will have both increased steric hindrance and an even lower pK_a (owing to the inductive effect of the sp^2 carbon of the *exo*-methylene double bond). Therefore, the nucleophilicity of that amino group will be relatively low, explaining why the product can attack the reactive acyl chloride and isocyanate reagents, but not the relatively less reactive isothiocyanate and sulfonyl chloride species. The order of reactivity suggested by these experiments is acyl chloride>isocyanate>isothiocyanate>sulfonyl chloride.

Table 2. Cascade products from alternative acylating agents

Entry	Product	Yield (%)[a]	Purity (%)[b]
1	 **16**	71	94
2	 **17**	90	92
3	 **18**	64	90
4	 **19**	68	>99
5	 **20**	ND	77
6	 **21**	ND	<20

ND=not done (conditions as per Table 1).
[a] Isolated yield after column chromatography and/or crystallisation.
[b] HPLC analysis of crude product directly after cleavage.

We have however managed to incorporate substituted allenes into the cascade (Scheme 3).

Thus cyclohexylallene **22** undergoes the cascade reaction under standard conditions to form resin-bound product **23**.

Acylation with benzoyl chloride proceeded smoothly to give **24**, which after cleavage gave compound **25** in 66% yield and very high purity (97%).

The product was obtained as an 11:1 mixture of *Z*:*E* geometric isomers (as measured by HPLC). NOE studies showed the *Z*-isomer to be the major product (Fig. 3).

The high selectivity for the *Z*-isomer arises from the preferential capture of the *anti*-π-allylpalladium species by the resin-bound nucleophile (Scheme 4).

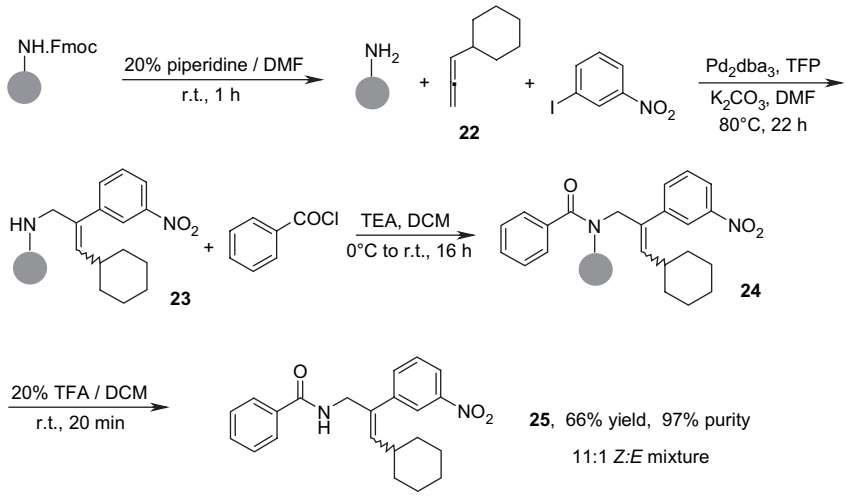
The π-allylpalladium intermediate can interconvert between the sterically congested *syn*-π-allyl **27**, where the cyclohexyl is in very close proximity with the aryl group, and *anti*-π-allyl **26**, where steric congestion is much reduced via η^1-allyl palladium(II) species. Our extensive work in this general area suggests that the *anti*-π-allyl **26** is formed initially and that *anti–syn* isomerisation reflects the rate of nucleophilic attack. Thus steric impediments to nucleophilic attack permit the isomerisation and lead to *Z*/*E* mixtures.

Thus, in the case in hand, steric bulk provided by the Rink amide linker surrounding the amino group is responsible.

Diversity can thus be incorporated into the cascade via the aryl iodide, allene and acylating agent. However, in order to maximise the potential synthetic applicability it was important to develop a strategy, which would allow the synthesis of acids via the cascade approach, thereby allowing further resin-bound coupling reactions.

Standard methods for hydrolysis of the resin-bound aryl esters proved unsatisfactory. Although heating to 65 °C with NaOH in 1:1 EtOH–water did lead to complete hydrolysis of resin-bound ethyl ester **14**, it proved difficult to reliably repeat these results; full conversion was not always achieved and there appeared to be a difficult compromise between solvents which suited the hydroxide base and solvents which allowed the resin to swell sufficiently to undergo hydrolysis.

An alternative literature strategy was to use the *tert*-butyl ester and to hydrolyse with zinc bromide in DCM.[20] Thus 4-iodobenzoic acid *tert*-butyl ester was utilised with allene gas and Rink amide resin in the three-component cascade and was thereafter acylated with benzoyl chloride to give



Scheme 3.

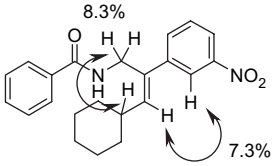
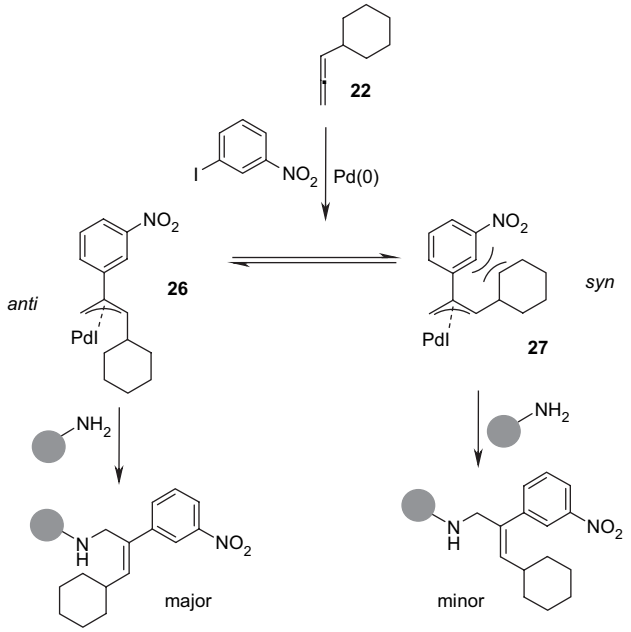


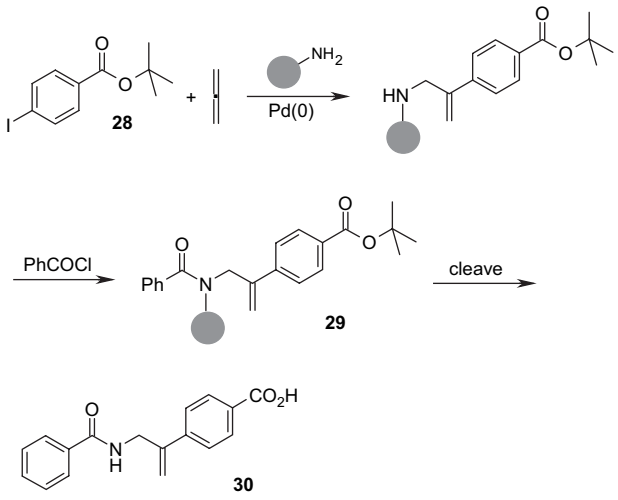
Figure 3.



Scheme 4.

29 (Scheme 5). In order to ascertain whether the cascade had been successful, the product was cleaved from the resin at this stage. Pleasingly, the mild conditions for resin-cleavage (20% TFA in dichloromethane at room temperature for 20 min) were also sufficient to cleave the *tert*-butyl ester, resulting in carboxylic acid **30** in 74% yield and 97% purity.

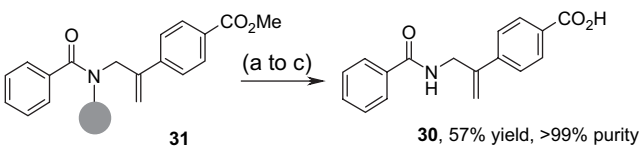
Although this provided a novel combinatorial route to carboxylic acids, our desire to carry out further resin-bound



Scheme 5.

manipulations of these acids for diversity screening, in the synthesis of pharmacologically interesting molecules, required a protocol whereby the esters were hydrolysed without cleaving from the resin.

Although attempts to cleave the ester using zinc bromide in DCM proved unsatisfactory we were able to solve the problem of hydrolysis by using potassium trimethylsilanolate to hydrolyse the methyl ester.[21,22] The cascade incorporating methyl-4-iodobenzoate proceeds very cleanly (Table 1, entry 8) affording resin-bound methyl ester **31**, which was stirred overnight at room temperature with 4 equiv of potassium trimethylsilanolate in dichloromethane (Scheme 6).



Scheme 6. Reagents and conditions: (a) TMSOK, DCM; (b) AcOH–THF (1:2); (c) 20% TFA–DCM.

The resin-bound acid was liberated on work-up using mildly acidic conditions (acetic acid and tetrahydrofuran (1:2 v/v)) to prevent cleavage from the resin. Subsequent resin-cleavage confirmed that the methyl ester had been hydrolysed in 57% yield with purity exceeding 99%.

3. Conclusion

A practical method for the synthesis of diverse libraries of pharmacologically interesting small molecules is described. This method utilises a 'catch and release' approach to resin-bound palladium-catalysed three-component cascade reactions to give products in high yield and with excellent purity.

In the ongoing work by the authors, this resin-mediated reaction has been used to develop potent, novel anti-cancer agents. This work will be outlined in more detail in the near future.

4. Experimental

4.1. General

Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were performed using a Carlo Erba MOD 1106 instrument. Electron ionisation (EI+), fast atom bombardment (FAB+) and accurate molecular weight mass spectra were recorded on a V.G.-AutoSpec instrument operating at 70 eV. Accurate molecular weights were determined using perfluorokerosine as an internal standard. Electrospray (ES+) mass spectra were recorded on a Micro Mass LCT time of flight 'KA111' instrument or a Micro Mass Lynx NT instrument. Chemical ionisation (CI+), EI+ and accurate mass measurements were also performed by the EPSRC National Service, Swansea on a Quattro instrument. Infra-red spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer using a diamond solid-phase transmission accessory unless otherwise specified. HPLC analyses were recorded at 254 nm on a Beckman 163 variable wavelength detector using a Luna 5μ (250×4.6 mm) phenyl–hexyl column unless otherwise stated. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker DRX500 instrument or at 300 MHz on a Bruker DPX300 instrument or at 250 MHz on a Bruker AC250 instrument. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument. Spectra were determined in $CDCl_3$ unless otherwise stated. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (δ 0.00). Coupling constants are given in hertz (Hz). ^{1}H NMR spectra are referenced to tetramethylsilane or residual protonated solvent. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dd=double doublet, dt=double triplet, td=triple doublet, ddd=double double doublet. Dichloromethane (DCM) was distilled from calcium hydride. All other commercially available reagents were used as received and where appropriate anhydrous quality material was purchased. The term ether refers to diethyl ether. All compounds are named according to the IUPAC system and were obtained using the ACD/i-Lab web service.

4.2. General procedure: solid-phase 'catch and release' three-component catalytic cascade

4.2.1. Step A. Removal of the Fmoc protecting group. Piperidine in DMF (20% v/v) was added to Rink Amide MBHA resin (loading 0.73 mmol/g). The solution was agitated at room temperature for 1 h, then filtered and the resin washed with DMF (3×) and DCM (3×). The resin was dried in vacuo at room temperature over 16 h and used directly in Step B.

4.2.2. Step B. Three-component catalytic cascade. A Schlenk tube was charged with the resin from Step A, the aryl iodide (1.1 mol equiv), potassium carbonate (2.0 mol equiv), tri-2-furylphosphine (10 mol %), tris (dibenzylideneacetone) dipalladium(0) (2.5 mol %) and DMF (10 ml) followed, after two freeze, pump, thaw cycles, by allene gas (1 atm, 25 °C). The mixture was allowed to warm to room temperature and then heated at 80–100 °C with gentle stirring for 16–24 h. The mixture was then allowed to cool, vented, filtered and the resin washed with DCM (1×), water (2×), methanol (3×) and DCM (3×). The resin was dried in vacuo at room temperature over 16 h and used directly in Step C.

4.2.3. Step C. Acylation of the cascade product. The acylating agent (2.0 mol equiv) in anhydrous DCM (2 ml) was added dropwise over 2 min to a stirred solution of the resin from Step B, triethylamine (3.0 mol equiv) and anhydrous DCM (10 ml) under nitrogen at 0 °C. The reaction mixture was allowed to warm to room temperature and was agitated for 16–24 h, then filtered and the resin washed with DCM (1×), water (1×), methanol (2×) and DCM (3×). The resin was dried in vacuo at room temperature over 16 h and used directly in Step D.

4.2.4. Step D. Cleavage from the resin. The resin from Step C was slurried in 20% v/v trifluoroacetic acid (TFA) in DCM. The mixture was allowed to stand at room temperature for 20 min, then filtered and the resin washed with DCM (2×). The combined filtrates were concentrated in vacuo to yield the product, which was immediately analysed for purity by HPLC and if necessary further purified by flash chromatography and/or crystallisation.

4.2.4.1. *N*-[2-(3-Nitrophenyl)-allyl]-benzamide (8). Prepared by the general procedure using the following:

Step A: Rink Amide MBHA resin (0.68 g, 0.50 mmol) agitated in 20% v/v piperidine in dimethylformamide (10 ml) for 1 h to give deprotected Rink Amide MBHA resin.
Step B: the product from step A (0.50 mmol), 1-iodo-3-nitrobenzene (137 mg, 1.1 mol equiv), potassium carbonate (138 mg, 2.0 mol equiv), tri-2-furylphosphine (12 mg, 10 mol %), tris (dibenzylideneacetone) dipalladium(0) (12 mg, 2.5 mol %) and allene gas (1 atm, 25 °C) in dimethylformamide (10 ml). The Schlenk tube was heated at 80 °C for 24 h to give **6**.
Step C: benzoyl chloride (0.116 ml, 2.0 mol equiv) in dichloromethane (2 ml) was added dropwise to a gently stirred solution of **6** (0.50 mmol) and triethylamine (0.199 ml, 3.0 mol equiv) in dichloromethane (10 ml) at

0 °C. The mixture was agitated at room temperature for 24 h to give **7**.
Step D: resin **7** (0.50 mmol) was slurried in 20% v/v trifluoroacetic acid in dichloromethane (10 ml) and allowed to stand for 20 min to give the product (purity 97% by HPLC). Crystallisation from ethyl acetate–hexane gave colourless plates (134 mg, 95% overall yield from Step A), mp 111–112 °C.

Found: C, 68.00; H, 5.25; N, 9.80. $C_{16}H_{14}N_2O_3$ requires: C, 68.10; H, 5.00; N, 9.90%.

δ_H (300 MHz): 8.35 (s, 1H, ArH), 8.16 (dd, 1H, *J* 8.2 Hz, ^4J 1.4 Hz, ArH), 7.80 (d, 1H, *J* 7.8 Hz, ArH), 7.71 (d, 2H, *J* 7.5 Hz, ArH), 7.56–7.51 (m, 2H, ArH), 7.42 (t, 2H, *J* 7.7 Hz, ArH), 6.37 (br s, 1H, NH), 5.66 (s, 1H, C=CH), 5.49 (s, 1H, C=CH), 4.60 (d, 2H, *J* 5.7 Hz, NCH_2).

δ_C (75 MHz): 168.4 (C=O), 148.5, 142.3, 140.0, 133.5, 132.1, 132.1, 129.7, 128.8, 126.9, 122.9, 121.1, 116.8, 43.5 (C–N).

m/*z* (ES+, %): 283 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1629 (C=C), 1520+1350 (NO_2).

HPLC: 97% purity; eluted with 1:1 v/v MeCN–H_2O at 0.7 ml/min.

4.2.4.2. *N*-(2-Naphthalen-1-yl-allyl)-benzamide (9). Prepared using the same method as for compound **8** but using 1-iodonaphthalene in step B (purity 96% by HPLC). Further purification by flash chromatography eluting with 3:1 v/v ether–hexane (R_f 0.40) gave a pale yellow oil (134 mg, 64% overall yield from Step A).

Found: C, 83.10; H, 6.10; N, 4.90. $C_{20}H_{17}NO$ requires: C, 83.50; H, 5.96; N, 4.90%.

δ_H (300 MHz): 8.15–8.09 (m, 1H, ArH), 7.87–7.77 (m, 2H, ArH), 7.72–7.67 (m, 2H, ArH), 7.49–7.31 (m, 7H, ArH), 6.58 (t, 1H, *J* 4.6 Hz, NH), 5.60 (d, 1H, ^2J 1.5 Hz, C=CH), 5.24 (d, 1H, ^2J 1.4 Hz, C=CH), 4.43 (d, 2H, *J* 4.7 Hz, NCH_2).

δ_C (75 MHz): 168.0 (C=O), 145.0, 138.9, 134.8, 134.1, 132.0, 131.9, 129.0, 128.8, 128.4, 127.4, 126.8, 126.4, 126.0, 125.9, 125.7, 116.4, 46.4 (C–N).

m/*z* (ES+, %): 310 (M+Na, 78), 288 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1651 (C=O), 1635 (C=C).

HPLC: 96% purity; eluted with 4:1 v/v MeCN–H_2O at 0.4 ml/min.

4.2.4.3. *N*-[2-(3,4-Dichloro-phenyl)-allyl]-benzamide (10). Prepared using the same method as for compound **8** but using 1,2-dichloro-4-iodobenzene in Step B (purity 96% by HPLC). Further purification by crystallisation from dichloromethane–hexane gave colourless prisms (122 mg, 55% overall yield from Step A), mp 105–106 °C.

Found: C, 62.40; H, 4.20; N, 4.40. $C_{16}H_{13}Cl_2NO$ requires: C, 62.70; H, 4.28; N, 4.60%.

δ_H (300 MHz): 7.72 (dd, 2H, *J* 6.9 Hz, ^4J 1.8 Hz, ArH), 7.56 (d, 1H, ^4J 2.0 Hz, ArH), 7.49 (d, 1H, *J* 7.3 Hz, ArH), 7.42–7.39 (m, 3H, ArH), 7.31–7.26 (m, 1H, ArH), 6.37 (br s, 1H, NH), 5.52 (s, 1H, C=CH), 5.36 (s, 1H, C=CH), 4.49 (d, 2H, *J* 5.3 Hz, NCH_2).

δ_C (75 MHz): 168.2 (C=O), 142.7, 138.7, 134.3, 133.2, 132.5, 132.3, 131.0, 129.1, 128.5, 127.3, 125.8, 116.0, 43.8 (C–N).

m/*z* (ES+, %): 306 ($^{35}Cl_2$, M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1629 (C=C).

HPLC: 96% purity; eluted with 4:1 v/v MeCN–H_2O at 0.5 ml/min.

4.2.4.4. *N*-[2-(6-Chloro-pyridin-3-yl)-allyl]-benzamide (11). Prepared using the same method as for compound **8** but using 2-chloro-5-iodopyridine in Step B (purity 99% by HPLC), colourless needles (136 mg, 68% overall yield from Step A), mp 88–89 °C.

Found: C, 65.80; H, 4.95; N, 10.30; Cl, 12.80. $C_{15}H_{13}ClN_2O$ requires: C, 66.10; H, 4.80; N, 10.40; Cl, 13.00%.

δ_H (300 MHz): 8.50 (d, 1H, ^4J 2.4 Hz, ArH), 7.79–7.71 (m, 3H, ArH), 7.54–7.40 (m, 3H, ArH), 7.31 (d, 1H, *J* 8.1 Hz, ArH), 6.27 (br s, 1H, NH), 5.57 (s, 1H, C=CH), 5.43 (s, 1H, C=CH), 4.54 (d, 2H, *J* 5.8 Hz, NCH_2).

δ_C (75 MHz): 167.4 (C=O), 151.0, 147.4, 140.7, 136.3, 133.9, 133.0, 131.8, 128.7, 126.9, 124.0, 116.2, 43.2 (C–N).

m/*z* (ES+, %): 273 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1629 (C=C).

HPLC: 99% purity; eluted with 7:3 v/v MeCN–H_2O at 0.5 ml/min.

4.2.4.5. *N*-[2-(3-Trifluoromethyl-phenyl)-allyl]-benzamide (12). Prepared using the same method as for compound **8** but using 3-iodobenzotrifluoride in Step B (purity 98% by HPLC). Trituration with ether gave a colourless amorphous solid (118 mg, 76% overall yield from Step A), mp 124–125 °C.

Found: C, 73.50; H, 6.05; N, 4.40. $C_{19}H_{19}NO_3$ requires: C, 73.80; H, 6.05; N, 4.50%.

δ_H (300 MHz): 8.03 (d, 2H, *J* 8.3 Hz, ArH), 7.70 (d, 2H, *J* 7.4 Hz, ArH), 7.55 (d, 2H, *J* 8.3 Hz, ArH), 7.49 (t, 1H, *J* 7.5 Hz, ArH), 7.41 (t, 2H, *J* 7.5 Hz, ArH), 6.20 (s, 1H, NH), 5.61 (s, 1H, C=CH), 5.42 (s, 1H, C=CH), 4.57 (d, 2H, *J* 5.6 Hz, NCH_2), 4.37 (q, 2H, *J* 7.1 Hz, OCH_2), 1.39 (t, 3H, *J* 7.1 Hz, CH_3).

δ_C (75 MHz): 167.4 (C=O), 166.3 (C=O), 143.6, 142.6, 134.2, 131.6, 130.0, 129.9, 128.6, 126.9, 126.0, 116.0, 61.0 (C–O), 43.5 (C–N), 14.3 (CH_3).

m/*z* (ES+, %): 310 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1723 (C=O), 1646 (C=O), 1632 (C=C).

HPLC: 98% purity; eluted with 7:3 v/v MeCN–H_2O at 0.6 ml/min.

4.2.4.6. Methyl 4-{1-[benzoylaminomethyl]vinyl} benzoate (15). Prepared using the same method as for compound **8** but using methyl 4-iodobenzoate in Step B (purity >99% by HPLC). Trituration with ether gave a colourless amorphous solid (120 mg, 82% overall yield from Step A), mp 136–137 °C.

Found: C, 71.80; H, 5.85; N, 4.50. $C_{18}H_{17}NO_3 \cdot 0.25H_2O$ requires: C, 72.00; H, 5.80; N, 4.70%.

δ_H (300 MHz): 8.02 (d, 2H, *J* 8.4 Hz, ArH), 7.70 (d, 2H, *J* 7.4 Hz, ArH), 7.55 (d, 2H, *J* 8.4 Hz, ArH), 7.49 (t, 1H, *J* 7.4 Hz, ArH), 7.41 (t, 2H, *J* 7.5 Hz, ArH), 6.20 (br s, 1H, NH), 5.62 (s, 1H, C=CH), 5.43 (s, 1H, C=CH), 4.57 (d, 2H, *J* 5.4 Hz, NCH_2), 3.91 (s, 3H, Me).

δ_C (75 MHz): 167.8 (C=O), 166.4 (C=O), 143.9, 143.2, 134.6, 132.1, 130.3, 130.1, 129.1, 127.3, 126.5, 116.4, 52.6 (C–N), 43.9 (C–O).

m/*z* (ES+, %): 295 (M+H, 100).

HRMS: found [M+H] 295.1199, [$C_{18}H_{17}NO_3$+H] requires 295.1203.

IR (ν_{max}/cm^{-1}): 1720 (C=O), 1643 (C=O), 1626 (C=C).

HPLC: 99.5% purity; eluted with 3:1 v/v MeCN–H_2O at 0.6 ml/min.

4.2.4.7. Methyl 4-(1-{[(biphenyl-4-ylcarbonyl)amino] methyl}vinyl) benzoate (16). Prepared using the same method as for compound **8** but using methyl 4-iodobenzoate in Step B and 4-biphenyl carbonyl chloride in Step C (purity 94% by HPLC). Trituration with ether gave colourless needles (131 mg, 71% overall yield from Step A), mp 198–199 °C.

Found: C, 76.80; H, 5.60; N, 3.70. $C_{24}H_{21}NO_3 \cdot 0.25H_2O$ requires: C, 76.70; H, 5.80; N, 3.70%.

δ_H (300 MHz): 8.03 (dd, 2H, *J* 8.3 Hz, ^4J 1.7 Hz, ArH), 7.70 (d, 2H, *J* 8.3 Hz, ArH), 7.64–7.55 (m, 6H, ArH), 7.46 (t, 2H, *J* 8.3 Hz, ArH), 7.41 (d, 1H, *J* 8.0 Hz, ArH), 6.24 (br s, 1H, NH), 5.64 (s, 1H, C=CH), 5.45 (s, 1H, C=CH), 4.59 (d, 2H, *J* 5.6 Hz, NCH_2), 3.91 (s, 3H, Me).

δ_C (75 MHz): 167.1 (C=O), 166.4 (C=O), 144.5, 143.6, 142.8, 139.9, 133.1, 129.9, 129.7, 128.9, 128.0, 127.4, 127.3, 127.2, 126.1, 116.1 (C=C), 52.26 (C–N), 43.5 (C–O).

m/*z* (EI+, %): 371 (M+H, 100).

HRMS: found [M+H] 371.1519, [$C_{24}H_{21}NO_3$+H] requires 371.1516.

IR (ν_{max}/cm^{-1}): 1715 (C=O), 1639 (C=O), 1607 (C=C).

HPLC: 94% purity; eluted with 3:1 v/v MeCN–H_2O at 0.3 ml/min.

4.2.4.8. *N*-[2-Naphthalen-1-yl-allyl]-3-phenyl-urea (17). Prepared using the same method as for compound **8** but using 1-iodonaphthalene in Step B and phenyl isocyanate in Step C (purity 92% by HPLC). Further purification by flash chromatography eluting with ether (R_f 0.42) gave colourless needles (136 mg, 90% overall yield from Step A), mp 98–99 °C.

Found: C, 79.40; H, 5.80; N, 9.30. $C_{20}H_{18}N_2O$ requires: C, 79.40; H, 6.00; N, 9.30%.

δ_H (300 MHz): 7.99 (dd, 1H, *J* 6.4 Hz, ^4J 3.1 Hz, ArH), 7.88–7.69 (m, 2H, ArH), 7.51–7.38 (m, 3H, ArH), 7.29–7.19 (m, 3H, ArH), 7.10 (t, 1H, *J* 7.4 Hz, ArH), 6.98 (d, 2H, *J* 7.4 Hz, ArH), 5.56 (d, 1H, ^2J 1.0 Hz, C=CH), 5.22 (s, 1H, C=CH), 4.22 (s, 2H, NCH_2).

δ_C (75 MHz): 157.9 (C=O), 145.0, 138.4, 137.2, 134.1, 131.8, 130.0, 128.8, 128.4, 126.8, 126.4, 126.0, 125.7, 125.6, 123.6, 116.7, 47.0 (C–N).

m/*z* (ES+, %): 303 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1683 (C=O), 1621 (C=C).

HPLC: 92% purity; eluted with 4:1 v/v MeCN–H_2O at 0.8 ml/min.

4.2.4.9. 1-Cyclohexyl-3-[2-(3-nitrophenyl)-allyl]-urea (18). Prepared using the same method as for compound **8** but using 3-iodonitrobenzene in Step B and cyclohexyl isocyanate in Step C (purity 90% by HPLC). Further purification by crystallisation from dichloromethane–hexane gave colourless needles (97 mg, 64% overall yield from Step A), mp 95–96 °C.

Found: C, 63.10; H, 7.00; N, 13.60. $C_{16}H_{21}N_3O_3$ requires: C, 63.30; H, 6.98; N, 13.80%.

δ_H (300 MHz): 8.29 (t, 1H, ^4J 2.0 Hz, ArH), 8.15 (dt, 1H, *J* 8.0 Hz, ^4J 2.0 Hz, ArH), 7.78 (dt, 1H, *J* 7.9 Hz, ^4J 1.9 Hz, ArH), 7.52 (t, 1H, *J* 8.0 Hz, ArH), 5.57 (s, 1H, C=CH), 5.41 (s, 1H, C=CH), 4.36 (br s, 1H, NH), 4.30 (d, 2H, *J* 5.4 Hz, NCH_2), 4.27 (br s, 1H, NH), 3.51 (m, 1H, CyH), 1.93–1.89 (m, 2H, CyH), 1.70–1.50 (m, 4H, CyH), 1.41–1.27 (m, 2H, CyH), 1.19–1.06 (m, 2H, CyH).

δ_C (75 MHz): 157.0 (C=O), 148.4, 143.8, 140.5, 132.2, 129.5, 122.7, 121.2, 115.8, 49.4 (C–N), 44.0 (C–N), 33.8 (C–C), 25.5 (C–C), 24.9 (C–C).

m/*z* (ES+, %): 305 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1640 (C=O), 1621 (C=C), 1532+1343 (NO_2).

HPLC: 90% purity; eluted with 4:1 v/v MeCN–H_2O at 0.8 ml/min.

4.2.4.10. 4-Methyl-*N*-({[2-(3-nitrophenyl)prop-2-en-1-yl]amino}carbonyl)benzene sulfonamide (19). Prepared using the same method as for compound **8** but using 3-iodonitrobenzene in Step B and *p*-toluenesulfonyl isocyanate in Step C (purity 99% by HPLC), colourless plates (128 mg, 68% overall yield from Step A), mp 136–137 °C.

Found: C, 54.50; H, 4.80; N, 11.0; S, 8.50. $C_{17}H_{17}N_3O_5S$ requires: C, 54.40; H, 4.56; N, 11.2; S, 8.50%.

δ_H (300 MHz): 8.20 (t, 1H, ^4J 1.9 Hz, ArH), 8.19 (dd, 1H, *J* 8.1 Hz, ^4J 1.7 Hz, ArH), 7.98 (br s, 1H, NH), 7.69 (d, 1H, *J* 7.8 Hz, ArH), 7.59 (d, 2H, *J* 8.3 Hz, ArH), 7.48 (t, 1H, *J* 8.0 Hz, ArH), 7.19 (d, 2H, *J* 8.1 Hz, ArH), 6.80 (t, 1H, *J* 5.4 Hz, NH), 5.57 (s, 1H, C=CH), 5.35 (s, 1H, C=CH), 4.34 (d, 2H, *J* 5.6 Hz, NCH_2), 2.41 (s, 3H, CH_3).

δ_C (75 MHz): 158.0 (C=O), 151.6, 145.5, 142.4, 140.2, 136.6, 132.4, 130.3, 129.9, 127.1, 123.2, 121.5, 117.2, 44.0 (C–N), 22.0 (CH_3).

m/*z* (ES+, %): 398 (M+Na, 91), 376.3 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1695 (C=O), 1631 (C=C), 1549+1344 (NO_2).

HPLC: 99% purity; eluted with 7:3 v/v MeCN–H_2O: 70/30 at 0.5 ml/min.

4.2.4.11. *N*-[(2*Z*)-3-Cyclohexyl-2-(3-nitrophenyl)-prop-2-en-1-yl] benzamide (25). Prepared using the same method as for compound **8** but with the following change to Step B.

Step B: to the resin from Step A was added 3-iodonitrobenzene (137 mg, 1.1 mol equiv), cyclohexylallene (122 mg, 2.0 mol equiv), tris (dibenzylideneacetone) dipalladium (12 mg, 2.5 mol %), tri-2-furylphosphine (12 mg, 10 mol %) and potassium carbonate (138 mg, 2.0 mol equiv). The mixture was agitated under nitrogen for 24 h, filtered and the resin washed with methanol (10 ml), water (10 ml), methanol (2×10 ml), dichloromethane (3×10 ml) and dried in vacuo at room temperature over 16 h.

The combined filtrates following cleavage in Step D were concentrated in vacuo to give an 11:1 mixture of *Z* and *E* stereoisomers (overall purity 97% by HPLC). Crystallisation from acetonitrile yielded the major *Z*-isomer **25** as colourless prisms (120 mg, 66% overall yield from Step A), mp 97–98 °C. Attempted isolation of the minor isomer by flash chromatography proved unsuccessful.

Found: C, 72.30; H, 6.60; N, 7.70. $C_{22}H_{24}N_2O_3$ requires: C, 72.50; H, 6.64; N, 7.70%.

δ_H (300 MHz): 8.28 (t, 1H, ^4J 1.9 Hz, ArH), 8.08 (dd, 1H, *J* 8.1 Hz, ^4J 1.8 Hz, ArH), 7.74 (dd, 1H, *J* 7.9 Hz, ^4J 1.8 Hz, ArH), 7.63 (dd, 2H, *J* 7.6 Hz, ^4J 2.0 Hz, ArH), 7.50–7.45 (m, 2H, ArH), 7.40–7.36 (m, 2H, ArH), 5.95 (d, 1H, *J* 9.5 Hz, C=CH), 5.89 (s, 1H, NH), 4.62 (d, 2H, *J* 5.2 Hz, NCH_2), 2.59–2.53 (m, 1H, CyH), 1.80–1.70 (m, 5H, CyH), 1.42–1.33 (m, 2H, CyH), 1.28–1.21 (m, 3H, CyH).

δ_C (75 MHz): 168.9 (C=O), 148.9, 142.6, 142.1, 134.6, 132.6, 132.0, 129.9, 129.0, 127.2, 122.4, 121.5, 38.8 (C–N), 38.3 (C–C), 33.7 (C–C), 26.2 (C–C), 26.0 (C–C).

m/*z* (ES+, %): 365 (M+H, 100).

IR (ν_{max}/cm^{-1}): 1643 (C=O), 1633 (C=C).

HPLC: 97% purity; eluted with 7:3 v/v MeCN–H_2O at 0.5 ml/min.

4.2.5. 4-[1-(Benzoylamino-methyl)-vinyl] benzoic acid (30).

a. Via hydrolysis of resin-bound *tert*-butyl ester

Prepared using the same method as for compound **8** but using 4-iodobenzoic acid *tert*-butyl ester in Step B (purity 97% by HPLC), colourless amorphous solid (103 mg, 74% overall yield from Step A), mp 194–195 °C.

Found: C, 70.60; H, 5.30; N, 4.70. $C_{17}H_{15}NO_3 \cdot 0.5H_2O$ requires: C, 70.30; H, 5.38; N, 4.80%.

δ_H (DMSO-d_6, 500 MHz): 8.86 (t, 1H, *J* 5.6 Hz, NH), 7.94 (d, 2H, *J* 8.3 Hz, ArH), 7.86 (d, 2H, *J* 7.3 Hz, ArH), 7.67 (d, 2H, *J* 8.3 Hz, ArH), 7.53 (t, 1H, *J* 7.3 Hz, ArH), 7.47 (t, 2H, *J* 7.4 Hz, ArH), 5.64 (s, 1H, C=CH), 5.34 (s, 1H, C=CH), 4.37 (d, 2H, *J* 5.6 Hz, NCH_2).

δ_C (DMSO-d_6, 75 MHz): 167.4 (C=O), 166.6 (C=O), 144.1, 143.2, 134.6, 131.6, 130.3, 129.8, 128.7, 127.6, 126.3, 114.6, 42.5 (C–N).

m/*z* (ES+, %): 282.3 (M+H, 100).

HRMS: found [M+H] 281.1046, [$C_{17}H_{15}NO_3$+H] requires 281.1046.

IR (ν_{max}/cm^{-1}): 3300–2300 (O–H), 1673 (C=O), 1642 (C=O), 1607 (C=C).

HPLC: 98% purity; eluted with 7:3 v/v MeCN–H_2O at 0.3 ml/min.

b. Via hydrolysis of resin-bound methyl ester

Resin-bound methyl ester **31** (0.50 mmol) was prepared by following Steps A, B and C of the procedure for compound **15**.

*Silanolate conversion of methyl ester **31***: resin-bound methyl ester **31** (0.50 mmol) was added to an agitated slurry of potassium trimethylsilanolate (257 mg, 4.0 mol equiv) in dry dichloromethane (10 ml) at room temperature under nitrogen. The reaction mixture was agitated for 16 h and the resin filtered and washed with methanol (10 ml), water (10 ml) and methanol (10 ml). The resin was then acidified with 1:2 v/v acetic acid in tetrahydrofuran, filtered and washed with methanol (10 ml), water (10 ml), methanol

(10 ml) and dichloromethane (2×10 ml). The resin was dried in vacuo at room temperature over 16 h and used directly in the next step.

*Cleavage from the resin to give acid **30***: the resin from the hydrolysis step (0.50 mmol) was slurried in 20% v/v trifluoroacetic acid in dichloromethane (10 ml) and allowed to stand for 20 min to give **30** (purity >99% by HPLC) as a colourless amorphous solid (80 mg, 57% overall yield from Step A).

HPLC: >99% purity; eluted with 7:3 MeCN–H_2O at 0.4 ml/min.

Acknowledgements

We would like to thank the Mary and Alice Smith Scholarship Fund, University of Leeds for funding. We also thank GlaxoSmithKline, Harlow for the kind provision of Rink Amide MBHA resin.

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Tetrahedron 62 (2006) 12182–12190
Tetrahedron

Synthesis of dihydrodehydrodiconiferyl alcohol and derivatives through intramolecular C–H insertion

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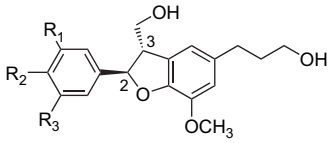
Received 25 September 2006; revised 9 October 2006; accepted 10 October 2006
Available online 27 October 2006

Abstract—The natural dihydrobenzofuran neolignan **1** and its derivative **3** have been prepared through intramolecular C–H insertion catalyzed by a Rh(II) chiral complex. Moderate diastereo and enantioselectivities were observed. The *cis* and *trans* diastereomers were separated and unambiguously identified. The absolute configurations of the major isomers were established through chiral HPLC analysis and study of the Cotton effects in their circular dichroism curves.

1. Introduction

Dihydrobenzofuran neolignans are a subtype of natural products of great interest regarding to their biological activities. Thus, they have been proved to have antioxidant,[1] antitumoral,[2] neuritogenic[3] and antimicrobial[4] activities, to be useful in the treatment of liver fibrosis,[5] and to be able to act as adenosine antagonist agents.[6] They possess a core skeleton of 2,3-dihydrobenzofuran with an aryl substituent on C-2 and a methyl, hydroxymethyl or methoxycarbonyl group on C-3. Most of them have been assigned a *trans* 2,3 relative stereochemistry, and some of which have been described as *cis* had to be reassigned.[7] The main synthetic approaches to these neolignans are biomimetic oxidative coupling of phenylpropenes,[8] pericyclic reactions[8] or intramolecular C–H coupling of aryl tosylhydrazones with Ru(II) salts.[9] We have reported the preparation of this kind of compounds through the reaction of benzoxasilepins with benzaldehydes in the presence of Lewis acids,[10] a modification of the Sakurai–Hosomi reaction.[11] Now we present a different way of synthesis based on the intramolecular C–H insertion of the products resulting from treatment of diazo compounds with Rh(II) salts.[12] Here we advance the synthesis of the natural bioactive neolignans dihydrodehydrodiconiferyl alcohol (**1**)[13], 3-*O*-demethyldihydrodehydrodiconiferyl alcohol (**2**)[14] and the synthetic derivative **3**, which incorporates a phenyl ring with three methoxy groups, a common pattern in this class of compounds.



1: R_1=H, R_2=OH, R_3=OMe
2: R_1=H, R_2=R_3=OH
3: R_1=R_2=R_3=OMe

2. Results and discussion

2.1. Strategy

Scheme 1 shows the retrosynthetic analysis for these compounds. After decomposition of the diazo compounds and C–H insertion, the dihydrobenzofurans would be formed. Simple transformations would lead to the desired products. Diazoesters can be prepared from the condensation products of appropriate aromatic precursors. This strategy allows the presence of different substitution patterns on the rings, which could afford, not only the desired structures, but other neolignans with this skeleton.

2.2. Synthetic approach

Eugenol was transformed into alcohol **4**,[10] and then the hydroxy group protected as pivaloate to give **5** (see Scheme 2). Claisen rearrangement by heating in *N*,*N*′-dimethylaniline yielded **6**. Its coupling with several benzyl iodides[15] in the presence of potassium carbonate in acetone allowed the isolation of the esters **7**, **8** and **9**. Ozonization of these compounds in DCM in the presence of NaOH, MeOH[16] and

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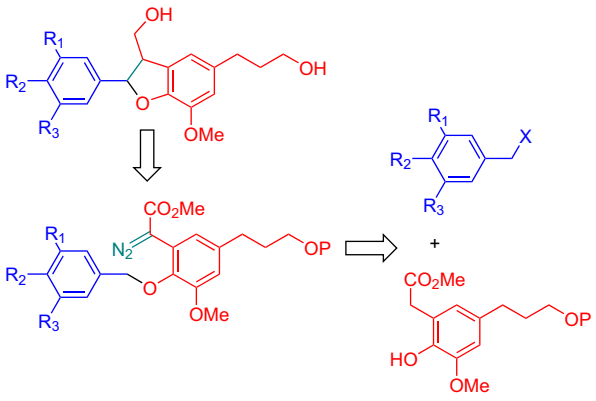
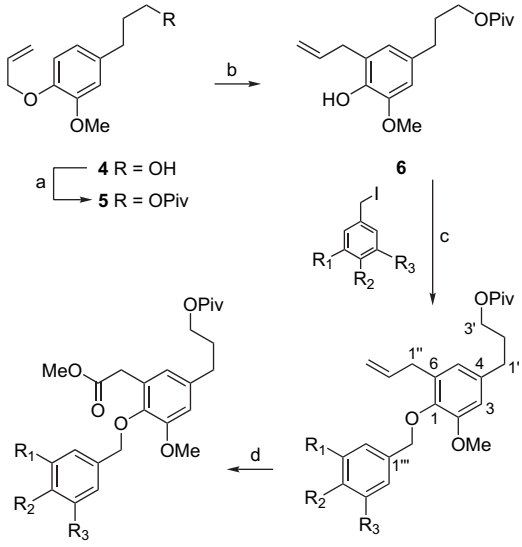
doi:10.1016/j.tet.2006.10.018



Scheme 1. Retrosynthetic analysis for preparation of compounds **1**–**3**.

pyridine resulted in the double bond degradation into the corresponding methyl esters,[17] thus allowing good isolated yields of **10**, **11** and **12**.

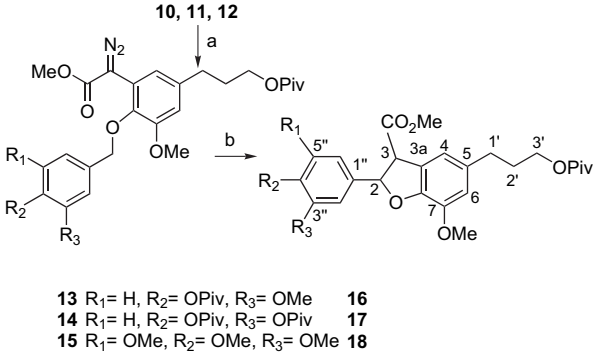


Scheme 2. *Reagents and conditions*: (a) pivaloyl chloride, DMAP, Py, Δ, 79%; (b) DMA, Δ, 91%; (c) K_2CO_3, acetone, Δ, 74, 61 and 82% to yield **7**, **8** and **9**, respectively and (d) O_3, NaOH, CH_2Cl_2, MeOH, Py, −78 °C; 90, 61 and 74% (**10**, **11** and **12**, respectively).

The presence of a benzylic methylene α to ester position in **10**, **11** and **12**, allowed the introduction of a diazo group by reaction of these compounds with azides in basic media. Several organic azides, different bases and reaction conditions were tested, and in all cases low yields were obtained. Alternative activation procedures also failed. The best results were obtained by direct treatment with *p*-ABSA (*p*-acetamidobenzenesulfonylazide) and DBU in CH_3CN (around 30% yield). In this way, diazo derivatives **13**, **14** and **15** were obtained. The low yields in our substrates when compared with those reported for model systems[12d] could be attributed to undesired reactions due to the presence of the oxygenated aliphatic side chains.

2.3. Stereoselectivity in the C–H insertion

The insertion step was performed using the rhodium chiral complex Rh_2[(*S*)-DOSP]$_4$ (tetrakis[(*S*)-(−)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]dirhodium (II)) as catalyst,[18] which had previously been reported to give the best results on similar substrates.[12d,19] In order to get the reaction to proceed, strict anhydrous conditions were needed, as very small traces of water react with the intermediate carbenoids to yield α-hydroxy esters. In all three cases the insertion proceeds instantly with quantitative yields (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) *p*-ABSA, DBU, CH_3CN, from 0 °C to rt 27, 30 and 29% (**13**, **14** and **15**, respectively) and (b) Rh_2[(*S*)-DOSP]$_4$, toluene, 0 °C, quantitative.

However, the reaction always afforded *cis*/*trans* mixtures (Table 1); a 3:1 diastereoselectivity in favour of the *cis* isomer was observed with **16** and **17**, while **18** gave no diastereoselectivity. The observed enantioselectivities were also low (Table 1), and all the efforts to improve them were unsuccessful as the reaction did not proceed below 0 °C. It was highly surprising to see these poor stereoselectivities on the basis of the published results for the simple 2-phenyl-2,3-dihydrobenzofuran core skeleton.[12d] Fortunately, the diastereomers could be separated by column chromatography, and the mixture of enantiomers analyzed by HPLC (provided with a chiral column and a circular dichroism detector), which allowed us to assign their absolute configuration.

2D-NOESY spectra allowed us to differentiate between *cis* and *trans* isomers, although not in a definitive manner. H-2

Table 1. Stereoselectivity in the intramolecular C–H insertions[a]

	16 (R_1=OMe, R_2=OPiv, R_3=H)	**17** (R_1=R_2=OPiv, R_3=H)	**18** (R_1=R_2=R_3=OMe)
cis:*trans*	75:25	77:23	50:50
trans	ee=34%, t_{R1}=12.8 (−) major, t_{R2}=14.8 (+) minor	[b]	ee=6%, t_{R1}=14.3 (+) minor, t_{R2}=17.8 (−) major
cis	ee=29%, t_{R1}=15.5 (−) minor, t_{R2}=26.5 (+) major	ee=28%, t_{R1}=19.7 (−) minor, t_{R2}=22.5 (+) major	ee=20%, t_{R1}=24.3 (+) major, t_{R2}=27.5 (−) minor

[a] Retention times (t_R) in minutes. Signs in parenthesis are due to the Cotton effect observed for the circular dichroism spectrum.

[b] Reliable HPLC analysis could not be performed with the available sample of the minor *trans* isomer.

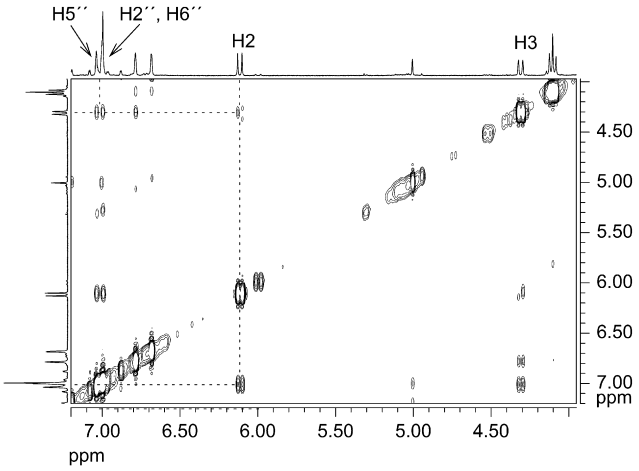


Figure 1. 2D-NOESY spectrum of **16**-*trans*.

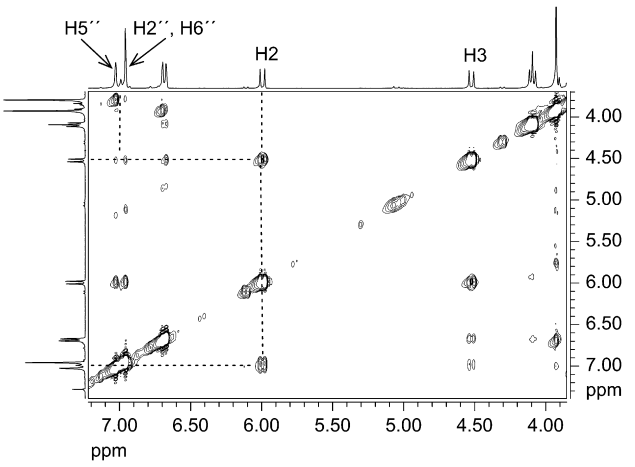


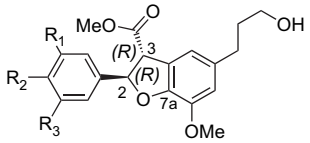
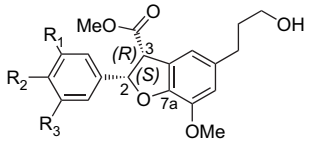
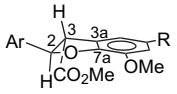
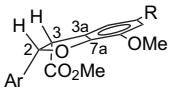
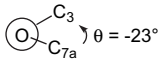
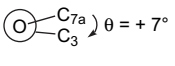
Figure 2. 2D-NOESY spectrum of **16**-*cis*.

and H-3 show cross peaks in both compounds, but much stronger in the *cis* compounds, as it can be observed for **16**-*cis* and **16**-*trans* (Figs. 1 and 2). It can also be observed that the coupling constants between H-2 and H-3 are very similar: 8.4 Hz for **16**-*cis* and 9.5 Hz for **16**-*trans*. Therefore, *J* values are not useful to distinguish *cis*/*trans* diastereomers. However, as we had previously observed for similar compounds,[10] there is a significant difference in chemical shifts between the methoxycarbonyl groups, appearing at 3.81 ppm in the *trans* isomer and at 3.27 ppm in the *cis* one; this effect is due to the fact that in the *cis* isomer this methyl is located in the shielding zone of the phenyl group on C-2. Similar results were obtained for **17**[20] and **18** (Table 1).

The analysis of the circular dichroism spectra allowed to establish the absolute configurations of the prepared *trans*-2-phenyl-2,3-dihydrobenzofurans, as their observed Cotton effect can be connected with the configuration through the well established rules given by Antus.[21] The five-membered ring in the dihydrobenzofuran should adopt an envelope conformation, with a characteristic torsion angle (C7a–O–C2–C3), in which the phenyl ring on C-2 is in an equatorial disposition. Therefore, it can establish a correlation between the sign of the band ^1L_b (α) in the dichroism spectrum, which appears around 280 nm, and the helicity (P or M) of the five-membered ring in the dihydrobenzofuran. The sign of the Cotton effect is highly influenced by the nature of the substituents on the aromatic rings, especially if there is a methoxy group on the position 7. As the products we prepared, **16** and **18**, have that methoxy group, the P helicity is connected with a positive Cotton effect, and M with a negative. Following these criteria, the absolute configurations of **16** and **18**-*trans* have been assigned (Table 2).

However, the application of the same rules to the *cis* diastereomers was somewhat obscured because the ^1L_b band is hardly perceptible. This phenomenon could be due to the fact that, in these compounds, the five-membered ring is almost in a planar conformation, and therefore there is no helicity. X-ray structures previously described by us[22] confirm

Table 2. Absolute configuration of the major enantiomer from the insertion reaction

	trans isomers	*cis* isomers
	 **16**-*trans*: R_1= H, R_2= OPiv, R_3= OMe **18**-*trans*: R_1= OMe, R_2= OMe, R_3= OMe	 **16**-*cis*: R_1= H, R_2= OPiv, R_3= OMe **17**-*cis*: R_1= H, R_2= OPiv, R_3= OPiv **18**-*cis*: R_1= OMe, R_2= OMe, R_3= OMe
Projection of the dihydrobenzofuran ring		
Newman projection through O–C2 bond[a]		
Helicity Cotton effect	*M* Negative (^1L_b band)	*P* Positive (^1L_a band)

[a] Calculated dihedral θ values (MOPAC, AM1).

this point. However, as the strong ^1L_a band (which appears around 250 nm) has the same sign as the ^1L_b band, it could be used to establish the absolute configuration[23] for the *cis* isomers (Table 2). As a result, we can propose that the absolute configuration for the major enantiomer of the *trans* compounds is (2*R*,3*R*), while for the *cis* is (2*S*,3*R*), in all the studied cases.

2.4. Preparation of the target molecules

To conclude the synthesis, **16** and **18** (*cis* and *trans*) were treated with $LiAlH_4$, with excellent results, in order to reduce the methyl ester and to remove the pivaloyl protecting group in a single step. Strict anhydrous conditions had to be used to avoid epimerization of the *cis* isomers into the *trans*, and for the same reason, the *cis* isomers had to be reduced at low temperature. In this way we obtained **1**-*trans* and **1**-*cis* (81, 100% yield). Their spectroscopic data are in agreement with those described for the natural products (*trans*)[13] and its isomer.[10] The same conditions were used to prepare **3**-*trans* and **3**-*cis* (81, 80% yield, respectively). No loss of stereochemical integrity was observed under those conditions. Again NOE effects between H-2 and H-3 were observed in both diastereomers of **3**, although the comparison of chemical shifts of the signals in ^1H NMR due to H-2 proved to be a better tool to distinguish both diastereomers, 5.84 ppm (8.4 Hz) for *trans* and 5.57 ppm (7.4 Hz) for the *cis*.

3. Conclusion

Two dihydrobenzofuran neolignans have been prepared through a convergent strategy in which the key step is an intramolecular C–H insertion in the presence of a chiral rhodium catalyst. The process can be extended to the preparation of other natural products with different substitution patterns on the aromatic rings. Although the stereoselectivity of the reaction was moderate to low, both *cis* and *trans* isomers could be isolated and identified thoroughly using several NMR techniques. Additionally, the circular dichroism data allowed to establish the absolute configuration of all the chiral compounds.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 or Avance DRX 500 spectrometer. Chemical shifts are given in parts per million relative to TMS. Carbon substitution degrees were established by DEPT multipulse sequence, and ^{13}C NMR peak assignments were made with the aid of 2D NMR (HMBC, HMQC, COSY and NOESY). Infrared spectra were recorded in liquid film between NaCl plates on a FT-IR Mattson Genesis II spectrometer, and mass spectra were performed on a AutoSpec-Q VG-Analytical (Fisons) (HRMS) instrument, using the Fast Atom Bomb technique (FAB) with a 1% NaI doped matrix of thioglycerol or glycerol.

The reactions were monitored by TLC (unless other technique is specified), using Macherey Nagel Alugram Sil G/UV_{254} plates. UV light and 5% phosphomolibdic or sulfuric acid solutions in methanol were employed for revealing. SDS 60 A CC 35–70 μm silica was used for column chromatography. All solvents were purified and dried following standard procedures.[24] Enantiomeric excesses were calculated from chiral HPLC performed in a Jasco HPLC chromatograph equipped with a circular dichroism detector and a Daicel Chiracel OD-H 150×4.6 mm column and eluting with mixtures of hexane and isopropanol.

4.2. Synthesis of dihydrobenzofuran neolignans 1 and 3

4.2.1. Allyl 2-methoxy-4-(3-pivaloyloxypropyl)phenyl ether (5). A solution of **4** (0.535 g, 2.4 mmol) in anhyd CH_2Cl_2 (2.4 mL) was added to a mixture of dimethylaminopyridine (30 mg, 0.24 mmol) and pyridine (0.6 mL, 7.2 mmol) under an argon atmosphere. Pivaloyl chloride (0.3 mL, 2.4 mmol) was added and the solution was refluxed for 14 h. The reaction crude mixture was washed with 5% HCl (3×40 mL) and brine (40 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography yielding **5** (0.594 g, 1.9 mmol, 79%). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.82 (1H, d, J=7.9 Hz, H6); 6.72 (1H, d, J=2.1 Hz, H3); 6.70 (1H, dd, J=7.9 Hz, J=2.1 Hz, H5); 6.09 (1H, ddt, J=17.3 Hz, J=10.8 Hz, J=5.4 Hz, H2″); 5.40 (1H, ddd, J=17.3 Hz, J=3.0 Hz, J=1.5 Hz, H3″); 5.28 (1H, ddd, J=10.4 Hz, J=3.0 Hz, J=1.5 Hz, H3″); 4.60 (2H, dt, J=5.4 Hz, J=1.5 Hz, H1″); 4.09 (2H, t, J=6.5 Hz, H3′); 3.88 (3H, s, OMe); 2.65 (2H, t, J=7.6 Hz, H1′); 1.95 (2H, m, H2′); 1.23 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.50 (C, CO); 149.34 (C, C2); 146.23 (C, C1); 134.25 (C, C4); 133.514 (CH, C2″); 120.13 (CH, C5); 117.75 (CH_2, C3″); 113.62 (CH, C6); 112.10 (CH, C3); 69.98 (CH_2, C1″); 63.48 (CH_2, C3′); 55.84 (CH_3, OMe); 38.72 (C, OCO*C*(CH_3)$_3$); 31.67 (CH_2, C1′); 30.35 (CH_2, C2′); 27.18 (CH_3, OCOC(*C*H_3)$_3$). IR (film) ν_{max}: 2959, 2936, 2871, 1726, 1514, 1463, 1283, 1263, 1230, 1159, 1034, 997, 926, 804 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{18}H_{26}O_4Na$): 329.1723, found: 329.1725 $[M+Na]^+$.

4.2.2. 2-Methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenol (6). A solution of **5** (9.792 g, 32 mmol) in *N*,*N*′-dimethylaniline (82 mL, 640 mmol) was refluxed under an inert atmosphere for 24 h. The reaction crude mixture was diluted with CH_2Cl_2 (80 mL), washed with 5% HCl (9×50 mL) and brine (100 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography yielding **6** (8.743 g, 29 mmol, 91%). Yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.58 (2H, s, H3, H5); 6.02 (ddt, 1H, J=16.6 Hz, J=10.0 Hz, J=6.6 Hz, H2″); 5.58 (1H, s, OH); 5.10 (1H, ddd, J=17.1 Hz, J=3.4 Hz, J=1.4 Hz, H3″); 5.06 (1H, ddd, J=10.4 Hz, J=3.4 Hz, J=1.4 Hz, H3″); 4.09 (2H, t, J=6.5 Hz, H3′); 3.89 (3H, s, OMe); 3.40 (2H, dt, J=6.5 Hz, J=1.4 Hz, H1″); 2.62 (2H, t, J=7.7 Hz, H1′); 1.94 (2H, m, H2′); 1.24 (9H, s, OCOC(*C*H_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, CO); 146.20 (C, C2); 141.48 (C, C1); 136.64 (CH, C2″); 132.29 (C, C4); 125.52 (C, C6); 121.83 (CH, C5); 115.35 (CH_2, C3″); 108.82 (CH, C3); 63.53 (CH_2, C3′); 55.95 (CH_3, OMe); 38.73 (C, OCO*C*(CH_3)$_3$); 33.82 (CH_2, C1″); 31.81 (CH_2, C1′); 30.52 (CH_2, C2′); 27.18

(CH_3, $OCOC(CH_3)_3$). IR (film) ν_{max}: 3453, 2971, 2936, 2871, 1724, 1604, 1499, 1462, 1435, 1286, 1156, 1075, 909 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{18}H_{26}O_4Na$): 323.1723, found: 329.1728 $[M+Na]^+$.

4.3. General procedure for the reaction between 6 and several benzyl iodides

K_2CO_3 (1.5 equiv) was added to a solution of **6** (1.0 equiv) and benzyl iodide (1.0–1.5 equiv) in acetone (7 mL) under an inert atmosphere. The mixture was refluxed until the reaction was completed (TLC monitoring). The reaction crude mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic extracts dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography.

4.3.1. (3-Methoxy-4-pivaloyloxybenzyl) [2-methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenyl] ether (7). Starting from 4-methoxy-3-pivaloyloxybenzyl iodide (1.5 g, 4.3 mmol) and 0.88 g (2.9 mmol) of **6**, and following the general procedure during 6 h, **7** was obtained as a colourless oil (74%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.14 (1H, br s, H2‴); 7.00 (2H, br s, H5‴, H6‴); 6.65 (1H, d, *J*=1.9 Hz, H3); 6.61 (1H, d, *J*=1.9 Hz, H5); 5.94 (1H, ddt, *J*=17.5 Hz, *J*=9.7 Hz, *J*=6.4 Hz, H2″); 5.04 (2H, m, H3″); 4.97 (2H, s, $ArCH_2O$); 4.10 (2H, t, *J*=6.5 Hz, H3′); 3.88 (3H, s, CH_3O–C2); 3.84 (3H, s, CH_3O–C3‴); 3.37 (2H, dt, *J*=6.5 Hz, *J*=1.5 Hz, H1″); 2.66 (2H, t, *J*=7.7 Hz, H1′); 1.97 (2H, m, H2′); 1.40 (9H, s, $ArOCOC(CH_3)_3$); 1.25 (9H, s, $ROCOC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.49 (C, RO*C*O); 176.64 (C, ArO*C*O); 152.56 (C, C2); 151.08 (C, C3‴); 143.89 (C, C1); 139.70 (C, C4‴); 137.20 (CH, C2″); 137.10 (C, C4); 136.74 (C, C1‴); 133.84 (C, C6); 122.34 (CH, C5‴); 121.74 (CH, C5); 119.97 (CH, C6‴); 115.58 (CH_2, C3″); 112.08 (CH, C2‴); 110.65 (CH, C3); 74.27 (CH_2, $ArCH_2O$); 63.53 (CH_2, C3′); 55.88 (CH_3, OCH_3); 55.75 (CH_3, OCH_3); 39.03 (C, $ArOCOC(CH_3)_3$); 38.75 (C, $ROCOC(CH_3)_3$); 34.24 (CH_2, C1″); 32.01 (CH_2, C1′); 30.28 (CH_2, C2′); 27.22 (CH_3, $OCOC(CH_3)_3$). IR (film) ν_{max}: 2970, 2934, 2870, 1753, 1725, 1588, 1509, 1480, 1462, 1282, 1154, 1117, 1034 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{31}H_{42}O_7Na$): 549.2823, found: 549.2818 $[M+Na]^+$.

4.3.2. [2-Methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenyl] (3,4-dipivaloyloxybenzyl) ether (8). Starting from 3,4-dipivaloyloxybenzyl iodide (1.43 g, 3.4 mmol) and 1.04 g (3.4 mmol) of **6**, and following the general procedure for 15 h, **8** was obtained as a colourless oil (65%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.32 (1H, dd, *J*=8.3 Hz, *J*=2.0 Hz, H6‴); 7.27 (1H, d, *J*=2.0 Hz, H2‴); 7.13 (1H, d, *J*=8.3 Hz, H5‴); 6.64 (1H, d, *J*=2.0 Hz, H3); 6.61 (1H, d, *J*=2.0 Hz, H5); 5.94 (1H, ddt, *J*=17.7 Hz, *J*=9.4 Hz, *J*=6.5 Hz, H2″); 5.03 (2H, m, H3″); 4.96 (2H, s, $ArCH_2O$); 4.10 (2H, t, *J*=6.5 Hz, H3′); 3.86 (3H, s, OCH_3); 3.37 (2H, dt, *J*=6.5 Hz, *J*=1.4 Hz, H1″); 2.65 (2H, t, *J*=7.7 Hz, H1′); 1.97 (2H, m, H2′); 1.37 (18H, s, $ArOCOC(CH_3)_3$); 1.24 (9H, s, $ROCOC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.50 (C, RO*C*O); 175.85 (C, ArO*C*O); 175.76 (C, ArO*C*O); 152.51 (C, C2); 143.83 (C, C1); 142.38 (C, C3‴)*; 141.96 (C, C4‴)*; 137.19 (CH, C2″); 137.16 (C, C4); 136.73 (C, C1‴); 133.77 (C, C6); 125.36 (CH, C6‴); 123.07 (CH, C5‴); 122.58 (CH, C2‴); 121.74 (CH, C5); 115.58 (CH_2, C3″); 110.63 (CH, C3); 73.46 (CH_2, $ArCH_2O$); 63.53 (CH_2, C3′); 55.68 (CH_3, OCH_3); 39.09 (C, $ArOCOC(CH_3)_3$); 38.73 (C, $ROCOC(CH_3)_3$); 34.18 (CH_2, C1″); 31.99 (CH_2, C1′); 30.26 (CH_2, C2′); 27.20 (CH_3, $OCOC(CH_3)_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2964, 2926, 2900, 2862, 1750, 1716, 1578, 1472, 1272, 1248, 1144, 1107 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{35}H_{48}O_8Na$): 619.3241, found: 619.3239 $[M+Na]^+$.

4.3.3. [2-Methoxy-4-(3-pivaloyloxypropyl)-6-(2-propenyl)phenyl] (3,4,5-trimethoxybenzyl) ether (9). Starting from 3,4,5-trimethoxybenzyl iodide (1.04 g, 3.3 mmol) and 1.0 g (3.3 mmol) of **6**, and following the general procedure for 15 h, **9** was obtained as a colourless oil (82%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.72 (2H, s, H2‴, H6‴); 6.65 (1H, d, *J*=1.9 Hz, H3); 6.61 (1H, d, *J*=1.9 Hz, H5); 5.94 (1H, ddt, *J*=17.5 Hz, *J*=9.5 Hz, *J*=6.5 Hz, H2″); 5.04 (2H, m, H3″); 4.91 (2H, s, $ArCH_2O$); 4.10 (2H, t, *J*=6.5 Hz, H3′); 3.89 (9H, s, CH_3O); 3.87 (3H, s, CH_3O–$C_{4‴}$); 3.38 (2H, dt, *J*=6.5 Hz, *J*=1.5 Hz, H1″); 2.66 (2H, t, *J*=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.24 (9H, s, $OCOC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.48 (C, RO*C*O); 153.13 (C, C3‴, C5‴)*; 152.6 (C, C2)*; 143.93 (C, C1); 137.52 (C, C4‴); 137.24 (CH, C2″); 137.12 (C, C4); 133.81 (C, C1‴); 133.72 (C, C6); 121.73 (CH, C5); 115.56 (CH_2, C3″); 110.66 (CH, C3); 104.93 (CH, C2‴, C6‴); 74.77 (CH_2, $ArCH_2O$); 63.50 (CH_2, C3′); 60.81 (CH_3, $C_{4‴}$–OCH_3); 56.04 (CH_3, $C_{3‴}$–OCH_3 y $C_{5‴}$–OCH_3)#; 55.75 (CH_3, C_2–OCH_3)#; 38.74 (C, $ROCOC(CH_3)_3$); 34.21 (CH_2, C1″); 31.99 (CH_2, C1′); 30.28 (CH_2, C2′); 27.21 (CH_3, $ROCOC(CH_3)_3$). * and # Assignments may be interchanged. IR (film) ν_{max}: 2957, 2936, 2835, 1721, 1587, 1457, 1420, 1282, 1234, 1152, 1125, 1004 cm^{-1}. HRFABMS (*m/z*): calcd ($C_{28}H_{38}O_7Na$): 509.2510, found: 509.2509 $[M+Na]^+$.

4.4. General procedure for ozonolysis of 7, 8 and 9

A solution of NaOH (5 equiv) in MeOH (5 mL) was added to a solution of allyl derivatives in CH_2Cl_2 (25 mL) and the mixture cooled to −80 °C. A stream of O_3 was bubbled through the stirred solution (20 min, TLC monitoring). The reaction crude mixture was diluted with water (30 mL) and 5% HCl (10 mL), and then extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with 5% HCl (2×10 mL) and brine (2×10 mL), dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography.

When required, the isolated aldehydes were oxidized as follows. A solution of $NaClO_2$ (6 mmol) and $Na_2HPO_4 \cdot H_2O$ (6 mmol) in water (7 mL) was added dropwise to a solution of the aldehyde (2 mmol) and 2-methyl-2-butene (4 mL) in ^tBuOH (20 mL). After 18 h the mixture was diluted with H_2O (60 mL) and extracted with Et_2O (3×60 mL). The combined organic extracts were washed with 1 M aq NaOH (2×10 mL), brine (2×10 mL) and dried over anhyd $MgSO_4$. The filtrate was cooled to 0 °C and treated with a saturated solution of CH_2N_2 in Et_2O (4 mL). The solution was concentrated in vacuo and the residue was purified by flash chromatography.

4.4.1. [2-Methoxy-6-(methoxycarbonylmethyl)-4-(3-pivaloyloxypropyl)phenyl] (3-methoxy-4-pivaloyloxybenzyl) ether (10). Starting from 0.52 g (2 mmol) of **7** and following the general procedure, **10** was obtained as a colourless oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.12 (1H, br s, H2‴); 6.98 (2H, br s, H5‴, H6‴); 6.71 (1H, d, J=1.8 Hz, H3); 6.65 (1H, d, J=1.8 Hz, H5); 4.99 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.4 Hz, H3′); 3.88 (3H, s, C_2–OCH_3); 3.84 (3H, s, $C_{3‴}$–OCH_3); 3.62 (3H, s, COOCH_3); 3.59 (2H, s, H1″); 2.66 (2H, t, J=7.7 Hz, H1′); 1.97 (2H, m, H2′); 1.39 (9H, s, ArOCOC(CH_3)$_3$); 1.24 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*OC(CH$_3$)$_3$); 176.64 (C, ArO*C*OC(CH$_3$)$_3$); 172.12 (C, *C*OOMe); 152.45 (C, C2); 151.07 (C, C3‴); 144.23 (C, C1); 139.72 (C, C4‴); 137.14 (C, C4); 136.54 (C, C1‴); 128.25 (C, C6); 122.37 (CH, C5); 122.31 (CH, C5‴); 119.10 (CH, C6‴); 112.12 (CH, C3); 111.86 (CH, C2‴); 74.10 (CH$_2$, Ar*C*H$_2$O); 63.52 (CH$_2$, C3′); 55.87 (CH$_3$, O*C*H$_3$); 55.74 (CH$_3$, O*C*H$_3$); 51.86 (CH$_3$, COO*C*H$_3$); 39.01 (C, ArOCO*C*(CH$_3$)$_3$); 38.74 (C, ROCO*C*(CH$_3$)$_3$); 35.74 (CH$_2$, C1″); 31.93 (CH$_2$, C1′); 30.19 (CH$_2$, C2′); 27.18 (CH$_3$, ArOCOC(*C*H$_3$)$_3$, ROCOC(*C*H$_3$)$_3$). IR (film) ν_{max}: 2968, 2935, 2870, 1752, 1725, 1509, 1478, 1462, 1282, 1154, 1118, 1033, 888 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{42}O_9Na$): 581.2721, found: 581.2724 [M+Na]$^+$.

4.4.2. [2-Methoxy-6-(methoxycarbonylmethyl)-4-(3-pivaloyloxypropyl)phenyl] (3,4-dipivaloyloxybenzyl) ether (11). Starting from 1.83 g (3.1 mmol) of **8** and following the general procedure, **11** was obtained as a colourless oil (61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30 (1H, dd, J=8.3 Hz, J=2.0 Hz, H6‴); 7.25 (1H, d, J=1.9 Hz, H2‴); 7.12 (1H, d, J=8.3 Hz, H5‴); 6.69 (1H, d, J=1.9 Hz, H3); 6.65 (1H, d, J=1.9 Hz, H5); 4.99 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.4 Hz, H3′); 3.85 (3H, s, OCH_3); 3.62 (3H, s, COOCH_3); 3.60 (2H, s, H1″); 2.65 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.36 (9H, s, ArOCOC(CH_3)$_3$); 1.36 (9H, s, ArOCOC(CH_3)$_3$); 1.23 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.46 (C, RO*C*O); 175.82 (C, ArO*C*O); 175.73 (C, ArO*C*O); 172.14 (C, *C*OOMe); 152.41 (C, C2); 144.15 (C, C1); 142.37 (C, C4‴); 141.98 (C, C3‴); 137.21 (C, C4); 136.59 (C, C1‴); 128.20 (C, C6); 125.42 (CH, C6‴); 123.07 (CH, C5‴); 122.62 (CH, C2‴); 122.34 (CH, C5); 111.84 (CH, C3); 73.27 (CH$_2$, Ar*C*H$_2$O); 63.52 (CH$_2$, C3′); 55.68 (CH$_3$, O*C*H$_3$); 51.88 (CH$_3$, COO*C*H$_3$); 39.09 (C, ArOCO*C*(CH$_3$)$_3$); 39.07 (C, ArOCO*C*(CH$_3$)$_3$); 38.74 (C, ROCO*C*(CH$_3$)$_3$); 35.73 (CH$_2$, C1″); 31.93 (CH$_2$, C1′); 30.20 (CH$_2$, C2′); 27.21 (CH$_3$, ArOCOC(*C*H$_3$)$_3$, ROCOC(*C*H$_3$)$_3$). IR (film) ν_{max}: 2971, 2873, 1758, 1726, 1590, 1480, 1278, 1258, 1156, 1026, 1116 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{35}H_{48}O_{10}Na$): 651.3140, found: 651.3139 [M+Na]$^+$.

4.4.3. [2-Methoxy-6-(methoxycarbonylmethyl)-4-(3-pivaloyloxypropyl)phenyl] (3,4,5-trimethoxybenzyl) ether (12). Starting from 0.89 g (1.8 mmol) of **9** and following the general procedure, **12** was obtained as a colourless oil (74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.71 (2H, s, H2‴, H6‴); 6.70 (1H, d, J=2.4 Hz, H3); 6.66 (1H, d, J=2.4 Hz, H5); 4.94 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.4 Hz, H3′); 3.89 (9H, s, OCH_3); 3.86 (3H, s, C_2–OCH_3); 3.64 (3H, s, COOCH_3); 3.62 (2H, s, H1″); 2.66 (2H, t, J=7.6 Hz, H1′); 1.97 (2H, m, H2′); 1.23 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.54 (C, RO*C*O); 172.12 (C, *C*OOCH$_3$); 153.10 (C, C3‴, C5‴); 152.46 (C, C2); 144.25 (C, C1); 137.45 (C, C4‴); 137.19 (C, C4); 133.52 (C, C1‴); 128.22 (C, C6); 122.36 (CH, C5); 111.82 (CH, C3); 104.93 (CH, C2‴, C6‴); 74.64 (CH$_2$, Ar*C*H$_2$O); 63.51 (CH$_2$, C3′); 60.81 (CH$_3$, C_2–O*C*H$_3$); 56.03 (CH$_3$, O*C*H$_3$); 55.75 (CH$_3$, O*C*H$_3$); 51.89 (CH$_3$, COO*C*H$_3$); 38.74 (C, OCO*C*(CH$_3$)$_3$); 35.72 (CH$_2$, C1″); 31.92 (CH$_2$, C1′); 30.18 (CH$_2$, C2′); 27.19 (CH$_3$, OCOC(*C*H$_3$)$_3$). IR (film) ν_{max}: 2957, 2839, 1723, 1589, 1460, 1154, 1125, 1006 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{38}O_9Na$): 541.2408, found: 541.2408 [M+Na]$^+$.

4.5. General procedure for the diazo transfer to 10, 11 and 12

DBU was added to a solution of the diazo derivatives and *p*-ABSA in CH_3CN (5 mL, freshly distilled) at 0 °C under an argon atmosphere. The mixture was allowed to reach room temperature and stirred for 18–24 h (TLC monitoring). The reaction crude mixture was diluted with CH_2Cl_2 (30 mL), washed with NH_4Cl aq saturated solution (3×10 mL) and brine (10 mL), dried over anhyd $MgSO_4$, concentrated in vacuo, and the residue was purified by flash chromatography.

4.5.1. [6-(Diazo(methoxycarbonyl)methyl)-2-methoxy-4-(3-pivaloyloxypropyl)phenyl] (3-methoxy-4-pivaloyloxybenzyl) ether (13). Compound **10** (0.555 g, 1 mmol), *p*-ABSA (1.486 g, 6 mmol) and DBU (1.2 mL) were reacted as described previously to yield **13** (0.159 g, 0.27 mmol, 27%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.04 (1H, d, J=1.7 Hz, H2″); 7.01 (1H, d, J=1.9 Hz, H5); 6.96 (1H, d, J=8.0 Hz, H5″); 6.89 (1H, dd, J=8.0 Hz, J=1.8 Hz, H6″); 6.69 (1H, d, J=1.9 Hz, H3); 4.95 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.5 Hz, H3′); 3.89 (3H, s, C_2–OCH_3); 3.81 (3H, s, $C_{3″}$–OCH_3); 3.79 (3H, s, COOCH_3); 2.68 (2H, t, J=7.7 Hz, H1′); 1.98 (2H, m, H2′); 1.38 (9H, s, ArOCOC(CH_3)$_3$); 1.23 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.46 (C, RO*C*O); 176.49 (C, ArO*C*O); 166.10 (C, *C*OOCH$_3$); 152.42 (C, C2); 151.06 (C, C3″); 142.08 (C, C1); 140.04 (C, C1″); 137.71 (C, C4); 135.41 (C, C4″); 122.34 (CH, C5″); 121.12 (CH, C5); 120.52 (CH, C6″); 120.06 (C, C6); 112.38 (CH, C2″); 111.71 (CH, C3); 74.92 (CH$_2$, Ar*C*H$_2$O); 74.71 (C, *C*N$_2$); 63.45 (CH$_2$, C3′); 55.86 (CH$_3$, C_2–O*C*H$_3$); 55.76 (CH$_3$, $C_{3″}$–O*C*H$_3$); 51.81 (CH$_3$, COO*C*H$_3$); 38.99 (C, *C*(CH$_3$)$_3$); 38.72 (C, *C*(CH$_3$)$_3$); 32.12 (CH$_2$, C1′); 30.18 (CH$_2$, C2′); 27.17 (CH$_3$, C(*C*H$_3$)$_3$). IR (film) ν_{max}: 2967, 2934, 2870, 2102, 1751, 1725, 1605, 1499, 1479, 1461, 1282, 1154, 1113, 1034 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{40}N_2O_9Na$): 607.2626, found: 607.2631 [M+Na]$^+$.

4.5.2. [6-(Diazo(methoxycarbonyl)methyl)-2-methoxy-4-(3-pivaloyloxypropyl)phenyl] (3,4-dipivaloyloxybenzyl) ether (14). Compound **11** (0.497 g, 0.79 mmol), *p*-ABSA (1.1646 g, 4.7 mmol) and DBU (2.4 mL) were reacted as described previously to yield **14** (0.162 g, 0.25 mmol, 30%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.25 (1H, dd, J=7.8 Hz, J=2.1 Hz, H6″); 7.23 (1H, br s, H2″); 7.12 (1H, d, J=7.8 Hz, H5″); 7.04 (1H, d, J=1.6 Hz, H5); 6.68 (1H, d, J=1.7 Hz, H3); 4.96 (2H, s, ArCH_2O); 4.10 (2H, t, J=6.1 Hz, H3′); 3.85 (3H, s, OCH_3); 3.82 (3H, s,

COOCH_3); 2.68 (2H, t, J=7.7 Hz, H1′); 1.98 (2H, m, H2′); 1.36 (18H, s, ArOCOC(CH_3)$_3$); 1.23 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*O); 175.75 (C, ArO*C*O); 175.70 (C, ArO*C*O); 166.20 (C, *C*OOCH$_3$); 152.39 (C, C2); 142.38 (C, C3″)*; 142.21 (C, C4″)*; 142.08 (C, C1); 137.80 (C, C4); 135.57 (C, C1″); 125.74 (CH, C6″); 123.12 (CH, C2″); 122.93 (CH, C5″); 121.01 (CH, C5); 119.83 (C, C6); 111.68 (CH, C3); 73.90 (CH$_2$, Ar*C*H$_2$O); 71.09 (C, *C*N$_2$); 63.50 (CH$_2$, C3′); 55.81 (CH$_3$, OCH_3); 51.92 (CH$_3$, COO*C*H$_3$); 39.10 (C, ArOCO*C*(CH$_3$)$_3$); 38.75 (C, ROCO*C*(CH$_3$)$_3$); 32.16 (CH$_2$, C1′); 30.20 (CH$_2$, C2′); 27.20 (CH$_3$, OCOC(*C*H$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2971, 2872, 2105, 1758, 1725, 1590, 1480, 1279, 1154, 1116 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{35}H_{46}N_2O_{10}Na$): 677.3045, found: 677.3041 [M+Na]$^+$.

4.5.3. 2-[Diazo(methoxycarbonyl)methyl)-6-methoxy-4-(3-pivaloyloxypropyl)phenyl] (3,4,5-trimethoxybenzyl) ether (15). Compound **13** (0.443 g, 1 mmol), *p*-ABSA (1.337 g, 5.4 mmol) and DBU (1.1 mL) were reacted as described previously to yield **15** (0.144 g, 0.26 mmol, 29%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.99 (1H, d, J=1.8 Hz, H5); 6.69 (1H, d, J=1.9 Hz, H3); 6.60 (2H, s, H2″, H6″); 4.90 (2H, s, ArCH_2O); 4.09 (2H, t, J=6.5 Hz, H3′); 3.90 (3H, s, C$_2$–OCH_3); 3.84 (9H, s, OCH_3); 3.78 (3H, s, COOCH_3); 2.67 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.22 (9H, s, ROCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.47 (C, RO*C*O); 166.08 (C, *C*OOCH$_3$); 153.02 (C, C3″, C4″); 152.39 (C, C2); 142.08 (C, C1); 137.70 (C, C4); 132.32 (C, C1″); 121.12 (CH, C5); 120.10 (C, C6); 111.65 (CH, C3); 105.37 (CH, C2″, C6″); 75.48 (CH$_2$, Ar*C*H$_2$O); 60.15 (C, *C*N$_2$); 63.41 (CH$_2$, C3′); 60.77 (CH$_3$, C$_{4''}$–OCH_3); 55.95 (CH$_3$, C$_2$–OCH_3)*; 55.86 (CH$_3$, C$_{3''}$–OCH_3)*; 51.85 (CH$_3$, COO*C*H$_3$); 38.71 (C, OCO*C*(CH$_3$)$_3$); 32.10 (CH$_2$, C1′); 30.19 (CH$_2$, C2'); 27.16 (CH$_3$, OCOC(*C*H$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2955, 2840, 2099, 1723, 1590, 1492, 1459, 1426, 1279, 1234, 1154, 1126, 1006, 735 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{36}N_2O_9Na$): 567.2313, found: 567.2316 [M+Na]$^+$.

4.6. General procedure for the C–H insertion of 13, 14 and 15

A Schlenk flask with 4 Å molecular sieves was purged with argon. A solution of the diazocompound in freshly distilled (sodium) toluene (2 mL) was introduced and the mixture cooled to 0 °C. A solution of tetrakis[(*S*)-(−)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]dirhodium (0.01 equiv) in anhydrous toluene (1 mL) was cannulated into the flask. Nitrogen bubbled immediately and the yellow colour disappeared instantly. The mixture was concentrated in vacuo and the residue purified by flash chromatography.

4.6.1. 7-Methoxy-3-(methoxycarbonyl)-2-(3-methoxy-4-pivaloyloxy)phenyl-5-(3-pivaloyloxy-propyl)-2,3-dihydrobenzo[*b*]furan (16). Starting from **13** (0.12 g, 0.21 mmol) and following the general procedure, **16** was obtained (0.10 g, 0.19 mmol, 90%) as a *cis*:*trans* mixture (3:1), which could be separated by flash chromatography. Enantiomeric excesses were determined by chiral HPLC, being 34% for **16**-*trans* and 29% for **16**-*cis*.

16*-*trans. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.04 (1H, br s, H5″); 7.00 (2H, br s, H2″, H6″); 6.79 (1H, d, J=1.0 Hz, H4); 6.69 (1H, d, J=1.0 Hz, H6); 6.12 (1H, d, J=8.4 Hz, H2); 4.31 (1H, d, J=8.3 Hz, H3); 4.10 (2H, t, J=6.4 Hz, H3′); 3.91 (3H, s, C$_7$–OCH_3); 3.85 (3H, s, COOCH_3); 3.81 (3H, s, C$_{3''}$–OCH_3); 2.67 (2H, t, J=6.9 Hz, H1′); 1.96 (2H, m, H2′); 1.37 (9H, s, OCOC(CH_3)$_3$); 1.24 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*O); 176.61 (C, ArO*C*O); 171.09 (C, *C*OOCH$_3$); 151.32 (C, C3″); 146.02 (C, C7a); 144.22 (C, C7); 140.15 (C, C4″); 138.68 (C, C1″); 135.08 (C, C5); 124.86 (C, C3a); 122.80 (CH, C2″)*; 118.25 (CH, C6″)*; 116.54 (CH, C4); 112.96 (CH, C6); 110.14 (CH, C5″); 86.21 (CH, C2); 63.44 (CH$_2$, C3′); 56.16 (CH, C3); 56.12 (CH$_3$, C$_7$–OCH_3)$^{\#}$; 55.98 (CH$_3$, C$_{3''}$–OCH_3)$^{\#}$; 52.69 (CH$_3$, COO*C*H$_3$); 39.04 (C, OCO*C*(CH$_3$)$_3$); 38.76 (C, OCO*C*(CH$_3$)$_3$); 31.97 (CH$_2$, C1′); 30.59 (CH$_2$, C2′); 27.21 (CH$_3$, OCOC(*C*H$_3$)$_3$); 27.17 (CH$_3$, OCOC(*C*H$_3$)$_3$). * and $^{\#}$ Assignments may be interchanged. IR (film) ν_{max}: 2966, 2935, 2870, 1750, 1725, 1606, 1499, 1460, 1281, 1201, 1154, 1112, 1032, 731 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{40}O_9Na$): 579.2565, found: 579.2560 [M+Na]$^+$.

16*-*cis. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.03 (1H, br s, H5″)*; 6.96 (2H, br s, H2″, H6″)*; 6.70 (1H, d, J=1.6 Hz, H4); 6.68 (1H, d, J=1.6 Hz, H6); 6.00 (1H, d, J=9.7 Hz, H2); 4.52 (1H, d, J=9.7 Hz, H3); 4.09 (2H, t, J=6.4 Hz, H3′); 3.93 (3H, s, C$_7$–OCH_3); 3.80 (6H, s, C$_{3''}$–OCH_3); 3.27 (3H, s, COOCH_3); 2.67 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.37 (9H, s, OCOC(CH_3)$_3$); 1.24 (9H, s, OCOC(CH_3)$_3$). * Assignments may be interchanged. ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, RO*C*O); 176.59 (C, ArO*C*O); 170.43 (C, *C*OOCH$_3$); 151.00 (C, C3″); 147.10 (C, C7a); 144.31 (C, C7); 140.11 (C, C4″); 135.32 (C, C5); 125.80 (C, C3a); 122.23 (CH, C2″)*; 118.68 (CH, C6″)*; 117.19 (CH, C6); 112.96 (CH, C4); 110.53 (CH, C5″); 86.20 (CH, C2); 63.49 (CH$_2$, C3′); 56.03 (CH$_3$, C$_7$–OCH_3, C$_{3''}$–OCH_3); 54.55 (CH, C3); 51.93 (CH$_3$, COO*C*H$_3$); 39.02 (C, OCO*C*(CH$_3$)$_3$); 38.75 (C, OCO*C*(CH$_3$)$_3$); 31.97 (CH$_2$, C1′); 30.54 (CH$_2$, C2′); 27.21 (CH$_3$, OCOC(*C*H$_3$)$_3$); 27.17 (CH$_3$, OCOC(*C*H$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2966, 2935, 2870, 1750, 1725, 1605, 1500, 1478, 1461, 1281, 1153, 1111, 1032, 731 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{31}H_{40}O_9Na$): 579.2565, found: 579.2561 [M$^+$Na]$^+$.

4.6.2. 7-Methoxy-3-(methoxycarbonyl)-2-(3,4-dipivaloyloxy)phenyl-5-(3-pivaloyloxypropyl)-2,3-dihydrobenzo[*b*]furan (17). Starting from **14** (0.042 g, 0.06 mmol) and following the general procedure, **17** was obtained (17 mg, 0.03 mmol, 50%) as a *cis*:*trans* mixture (77:23). The enantiomeric excess of **17**-*cis* was determined by chiral HPLC as 28%.

4.6.3. 7-Methoxy-3-(methoxycarbonyl)-5-(3-pivaloyloxypropyl)-2-(3,4,5-trimethoxy)phenyl-2,3-dihydrobenzo[*b*]furan (18). Starting from **15** (0.17 g, 0.31 mmol) and following the general procedure, **18** was obtained (0.16 g, 0.31 mmol, 99.8%) as a *cis*:*trans* mixture (1:1), which could be separated by flash chromatography. Enantiomeric excesses were determined by chiral HPLC, being 6.0% for **18**-*trans* and 20% for **18**-*cis*.

18*-*trans. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.79 (1H, d, J=1.0 Hz, H4); 6.69 (1H, d, J=1.0 Hz, H6); 6.66 (2H, s, H2″, H6″); 6.05 (1H, d, J=8.6 Hz, H2); 4.33 (1H, d, J=8.6 Hz, H3); 4.10 (2H, t, J=6.5 Hz, H3′); 3.91 (3H, s, C_7–OCH_3); 3.86 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.85 (3H, s, $C_{4''}$–OCH_3); 3.84 (3H, s, COOCH_3); 2.67 (2H, t, J=6.8 Hz, H1′); 1.96 (2H, m, H2′); 1.24 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, ROCO); 171.14 (C, COOCH$_3$); 153.38 (C, C3″, C5″); 146.02 (C, C7a); 144.25 (C, C7); 137.94 (C, C4″); 135.60 (C, C1″); 135.02 (C, C5); 124.89 (C, C3a); 116.48 (CH, C4); 112.94 (CH, C6); 103.11 (CH, C2″); 86.69 (CH, C2); 63.39 (CH$_2$, C3′); 60.78 (CH$_3$, $C_{4''}$–OCH$_3$); 56.14 (CH$_3$, $C_{3''}$–OCH$_3$); 56.09 (CH$_3$, C_7–OCH$_3$)*; 56.08 (CH, C3)*; 52.68 (CH$_3$, COOCH$_3$); 38.73 (C, OCOC(CH$_3$)$_3$); 31.93 (CH$_2$, C1′); 30.54 (CH$_2$, C2′); 27.18 (CH$_3$, OCOC(CH$_3$)$_3$). * Assignments may be interchanged. IR (film) ν_{max}: 2955, 2837, 1722, 1587, 1458, 1282, 1153, 1123, 1005 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{36}O_9Na$): 539.2252, found: 539.2248 [M+Na]$^+$.

18*-*cis. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.70 (1H, d, J=1.3 Hz, H6); 6.68 (1H, d, J=1.3 Hz, H4); 6.64 (2H, s, H2″, H6″); 5.94 (1H, d, J=9.6 Hz, H2); 4.51 (1H, d, J=9.6 Hz, H3); 4.10 (2H, t, J=6.5 Hz, H3′); 3.93 (3H, s, C_7–OCH_3); 3.86 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.84 (3H, s, $C_{4''}$–OCH_3); 3.31 (3H, s, COOCH_3); 2.67 (2H, t, J=7.7 Hz, H1′); 1.96 (2H, m, H2′); 1.24 (9H, s, OCOC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.51 (C, ROCO); 170.48 (C, COOCH$_3$); 152.93 (C, C3″, C5″); 147.06 (C, C7a); 144.34 (C, C7); 137.74 (C, C4″); 135.30 (C, C5); 132.26 (C, C1″); 125.91 (C, C3a); 117.12 (CH, C4); 112.94 (CH, C6); 103.54 (CH, C2″, C6″); 86.63 (CH, C2); 63.46 (CH$_2$, C3′); 60.82 (CH$_3$, $C_{4''}$–OCH$_3$); 56.13 (CH$_3$, $C_{3''}$–OCH_3, $C_{5''}$–OCH$_3$); 55.98 (CH$_3$, C_7–OCH$_3$); 54.43 (CH, C3); 51.85 (CH$_3$, COOCH$_3$); 38.74 (C, OCOC(CH$_3$)$_3$); 31.95 (CH$_2$, C1′); 30.52 (CH$_2$, C2′); 27.19 (CH$_3$, OCOC(CH$_3$)$_3$). IR (film) ν_{max}: 2955, 2837, 1722, 1588, 1459, 1233, 1153, 1124, 1005 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{28}H_{36}O_9Na$): 539.2252, found: 539.2250 [M+Na]$^+$.

4.7. General procedure for the reduction and deprotection of 16 and 18 (*cis* and *trans*)

A solution of esters in THF (1.5 mL) was added dropwise to a cooled suspension (−20 °C for *cis* isomers and 0 °C for *trans*) of $LiAlH_4$ (20 equiv) in THF (1.5 mL). The mixture was stirred for 1 h and quenched by dropwise addition of water at the same temperature until the bubbling stopped. Then 5% aq HCl (20 mL) was added and the mixture was allowed to reach room temperature and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhyd $MgSO_4$, concentrated in vacuo, and the residue purified by flash chromatography.

4.7.1. *trans*-Dihydrodehydrodiconiferyl alcohol (1-*trans*). Starting from 23 mg (0.04 mmol) of **16**-*trans*, and following the general procedure, **1**-*trans*[13] was obtained as a colourless oil (12 mg, 0.033 mmol, 81%).

4.7.2. *cis*-Dihydrodehydrodiconiferyl alcohol (1-*cis*). Starting from 35 mg (0.06 mmol) of **16**-*cis*, and following the general procedure, **1**-*cis*[10] was obtained as a colourless oil (21 g, 0.06 mmol, 100%).

4.7.3. *trans*-3-(Hydroxymethyl)-5-(3-hydroxypropyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrobenzo-[*b*]furan (3-*trans*). Starting from 72 mg (0.14 mmol) of **18**-*trans*, and following the general procedure, **3**-*trans* was obtained as a colourless oil (46 mg, 0.11 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.69 (2H, br s, H4, H6); 6.66 (2H, s, H2″); 5.57 (1H, d, J=7.4 Hz, H2); 4.00 (1H, dd, J=10.9 Hz, J=6.0 Hz, CH_2OH); 3.93 (1H, dd, J=11.0 Hz, J=4.7 Hz, CH_2OH); 3.90 (3H, s, C_7–OCH_3); 3.85 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.84 (3H, s, $C_{4''}$–OCH_3); 3.70 (2H, t, J=6.3 Hz, H3′); 3.63 (1H, m, H3); 2.68 (2H, t, J=7.7 Hz, H1′); 1.90 (2H, m, H2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 153.31 (C, C3″, C5″); 146.46 (C, C7a); 144.18 (C, C7); 137.67 (C, C4″); 136.85 (C, C1″); 135.53 (C, C5); 127.50 (C, C3a); 115.90 (CH, C4)*; 112.45 (CH, C6)*; 103.10 (CH, C2″, C6″); 87.80 (CH, C2); 63.84 (CH$_2$, CH$_2$OH); 62.24 (CH$_2$, C3′); 60.81 (CH$_3$, $C_{4''}$–OCH$_3$); 56.13 (CH$_3$, $C_{3''}$–OCH$_3$, $C_{5''}$–OCH$_3$); 55.99 (CH$_3$, C_7–OCH$_3$); 53.84 (CH, C3); 34.58 (CH$_2$, C2′); 31.98 (CH$_2$, C1′). * Assignments may be interchanged. IR (film) ν_{max}: 3379, 2934, 2876, 2837, 1592, 1494, 1458, 1420, 1324, 1123, 909, 729 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{22}H_{30}O_8Na$): 445.1833, found: 445.1830 [M+Na]$^+$.

4.7.4. *cis*-3-(Hydroxymethyl)-5-(3-hydroxypropyl)-7-methoxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrobenzo[*b*]-furan (3-*cis*). Starting from 24 mg (0.05 mmol) of **18**-*cis*, and following the general procedure, **3**-*cis* was obtained as a colourless oil (15 mg, 0.04 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.77 (1H, d, J=1.3 Hz, H4); 6.72 (1H, d, J=1.3 Hz, H6); 6.71 (2H, s, H2″); 5.85 (1H, d, J=8.4 Hz, H2); 3.94 (3H, s, C_7–OCH_3); 3.91 (1H, dd, J=8.7 Hz, J=5.0 Hz, CH_2OH); 3.87 (1H, dd, J=8.7 Hz, J=6.7 Hz, CH_2OH); 3.89 (6H, s, $C_{3''}$–OCH_3, $C_{5''}$–OCH_3); 3.88 (3H, s, $C_{4''}$–OCH_3); 3.73 (2H, t, J=6.3 Hz, H3′); 3.69 (1H, m, H3); 2.71 (2H, t, J=7.7 Hz, H1′); 1.92 (2H, m, H2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 153.40 (C, C3″, C5″); 145.95 (C, C7a); 144.21 (C, C7); 135.73 (C, C5, C4″); 132.23 (C, C1″); 129.20 (C, C3a); 116.88 (CH, C4); 112.45 (CH, C6); 103.14 (CH, C2″, C6″); 87.07 (CH, C2); 63.00 (CH$_2$, CH$_2$OH); 62.27 (CH$_2$, C3′); 60.90 (CH$_3$, $C_{4''}$–OCH$_3$); 56.16 (CH$_3$, $C_{3''}$–OCH$_3$, $C_{5''}$–OCH$_3$); 55.99 (CH$_3$, C_7–OCH$_3$); 49.50 (CH, C3); 34.60 (CH$_2$, C2′); 31.99 (CH$_2$, C1′). IR (film) ν_{max}: 3379, 2936, 2835, 2998, 1591, 1494, 1459, 1421, 1123, 1324, 1233, 1208 cm^{-1}. HRFABMS (*m*/*z*): calcd ($C_{22}H_{30}O_8Na$): 445.1833, found: 445.1834 [M+Na]$^+$.

Acknowledgements

We wish to acknowledge the Spanish Ministerio de Educación y Ciencia for financial support (Project BQU2002-03254) and for scholarships to L.J.-G. and S.G.-M.

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Synthesis and peptide-binding properties of a luminescent pyrimidine zinc(II) complex

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Received 12 September 2006; revised 7 October 2006; accepted 10 October 2006
Available online 27 October 2006

Abstract—The synthesis and peptide-binding properties of a Zn(II)nitrilotriacetate complex substituted with pyrimidine hydrazine amides are reported. The metal complex provides millimolar binding affinity in aqueous buffer to peptides bearing N-terminal His. The pyrimidine heterocycles intermolecularly interact with the bound peptide and quench the emission of nearby Trp residues by energy transfer.

1. Introduction

Reversible interactions of ions or molecules by hydrogen bonds, electrostatic or van der Waals interactions are the foundation of molecular recognition processes.[1] However, the strength of hydrogen bonds and electrostatic interactions decreases rapidly as the polarity of the surrounding solvent increases.[2] This hampers the binding of substrates such as peptides, hormones, or carbohydrates under physiological conditions, which is of interest for medicinal applications and the design of biosensors. The use of reversibly coordinating metal complexes as binding sites is a suitable alternative, which may provide high affinity in competitive solvents.[3] Recent examples showed the ability of suitable metal complexes for selective binding to peptides[3c] and protein surface epitopes[4,5] under physiological conditions. Such synthetic receptors find use as bioanalytical probes[6] or markers[7] or can interfere with protein function, e.g., inhibiting enzyme activity[8] or protein–protein interactions.[9] We report here the use of a functionalized zinc(II) nitrilotriacetato (NTA) complex to label small peptides with pyrimidine hydrazino amides. Fluorescence resonance energy transfer (FRET)[10] from nearby Trp residues sensitizes an emission of the heteroaromatic pyrimidine ring.

2. Results and discussion

2.1. Synthesis

Various transition metal ion (e.g., Cu^{2+}, Ni^{2+}, and Zn^{2+}) complexes of NTA or IDA[11] bind to the imidazole side chains of surface exposed histidines of proteins.[12] This coordinative interaction is widely used for protein purification by immobilized metal affinity chromatography (IMAC)[13,14] and two-dimensional protein crystallization.[15] The dependence of the NTA binding constant on the divalent metal in $[M(NTA)]^-$ ($M=Mn^{2+}$, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}) has been intensively studied.[16] Although Ni^{2+} or Cu^{2+} NTA complexes show higher affinities to N-terminal His,[12] a Zn^{2+} complex[17,18] was chosen for peptide binding to obtain a diamagnetic compound, which allows NMR investigations. The synthesis of the peptide-binding Zn(II)–pyrimidine complex **6** is shown in Figure 1. As spacer between the complex and the heteroarene we choose a Gly unit to assist the possible formation of a hydrogen bond to a coordinated peptide. Compound **1**,[19] obtained from lysine methyl ester, is coupled to Boc-Gly-OH. After Boc deprotection, heterocycle **3**, which was reported recently,[3b] was introduced by standard peptide coupling procedures. Cleavage of the methyl ester under basic conditions generates the NTA ligand and complexation with Zn^{2+} leads to the desired functionalized complex **5**. To improve water solubility, the analogous complex **9**, extended by one pyrimidine hydrazine unit, was prepared (Fig. 2).

2.2. Structure

To derive structural information about the binding motif of **5** to the pentapeptide NH_2-His-Leu-Leu-Val-Phe-OMe

Keywords: Metal complex; Peptide binding; Histidine; Luminescence; Pyrimidine.
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doi:10.1016/j.tet.2006.10.019

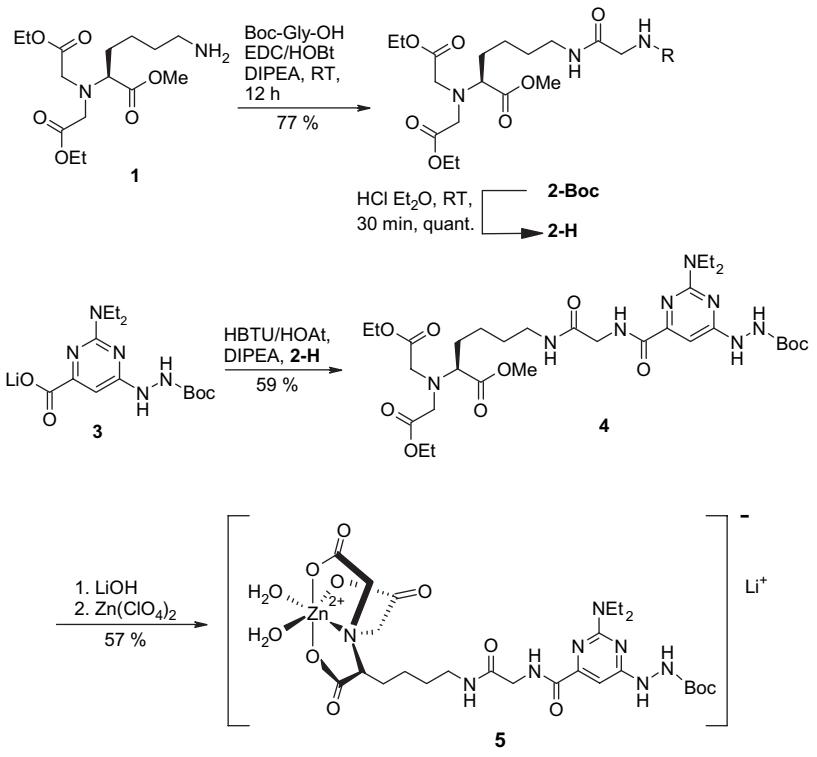

Figure 1. Synthesis of zinc(II)-NTA pyrimidine complex **5**.

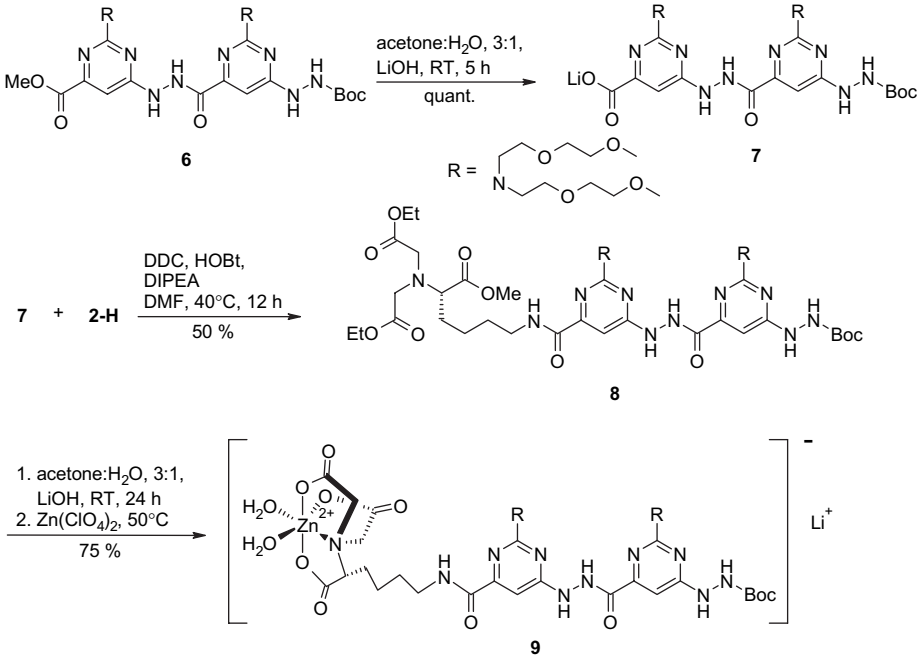

Figure 2. Synthesis of water-soluble zinc(II)-NTA pyrimidine complex **9**.

(Fig. 3) NMR experiments in DMSO-d_6 were performed.[20] Resonance signals of the NMR spectra of **5**—H-His-Leu-Leu-Val-Phe-OMe (c=3.3×10^{-2} M) were assigned (see Supplementary data, Fig. S-1 for details) and temperature-induced shift was used to identify hydrogen bonding of NH groups (see Supplementary data, Tables S-1, S-2 and Fig. S-2).[21] Shifts larger than −2 ppb/K typically indicate a strong interaction, while values smaller than −4 ppb/K show solvent exposed atoms.[22] The smallest ppb/K value (−2.57 ppb/K) in the aggregates spectrum was obtained for NH-**C**. This proton is most likely hydrogen bound to both the lone pair of the oxygen atom of the amide bond and the lone pair of the nitrogen atom in the pyrimidine ring. The temperature dependent shift of −2.95 ppb/K of NH-**G** indicates a hydrogen bond between peptide and complex. All other temperature dependent shifts of

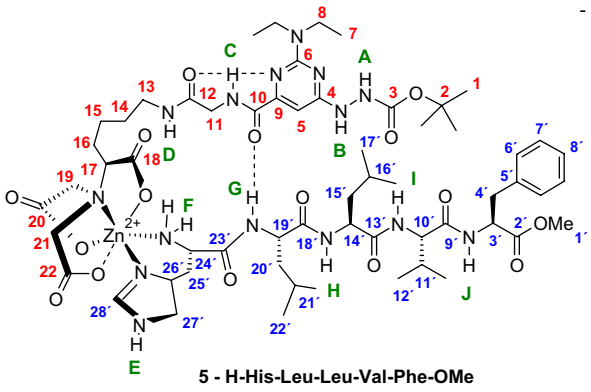

Figure 3. Structure and numbering of the proposed aggregate formed in an equimolar mixture of **5** and H-His-Leu-Leu-Val-Phe-OMe (c=3.3×10^{-2} M) in DMSO-d_6.

5—H-His-Leu-Leu-Val-Phe-OMe show values of 3 ppb/K or higher suggesting no strong hydrogen bonds.

2D-NOESY and ROESY[23] experiments (see Supplementary data, Figs. S-3 and S-4 for details) showed 10 contacts between functionalized complex **5** and the coordinated pentapeptide. The data support the depicted aggregate structure[24] (Fig. 3) with interactions of NH-**C** and protons at C-11 to NH-**G**, NH-**H** and protons at C-19′ to C22′, and contacts of imidazole and parts of the NTA ligand. A similar aggregate analysis was attempted using complex **9** and H-His-Asp-Trp-Ser-Gly-OH in buffered water. Resonance signals of the individual compounds were assigned and their chemically induced shift in the mixture indicates interactions of complex and peptide (see Supplementary data, Figs. S-5 and S-6). However, substantial signal broadening in the spectrum of the mixture did not allow a more detailed analysis.

2.3. Peptide binding

The Trp emission of peptides is quenched upon their coordination to complex **9**. A perfect overlap of the pyrimidine absorption spectrum with the Trp emission allows intramolecular energy transfer (Fig. 4). The FRET emission of the pyrimidine chromophore is visible in aprotic solvents, such as acetonitrile, but weak in aqueous media. Therefore, Trp emission quenching (Fig. 5) was used to monitor the binding of complex **9** to pentapeptides H-His-Asp-Trp-Ser-Gly-OH and H-His-Thr-Trp-Asp-Asp-OH.

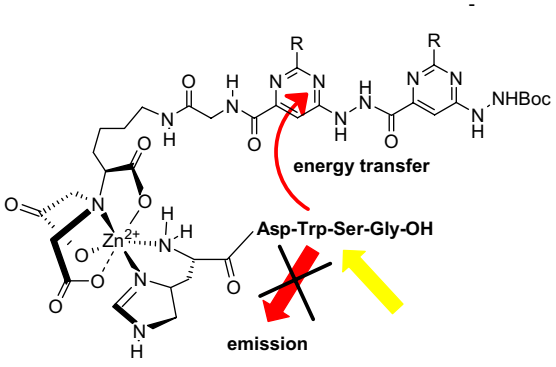

Figure 4. Intramolecular energy transfer within the peptide–metal complex aggregate leading to Trp emission quenching.

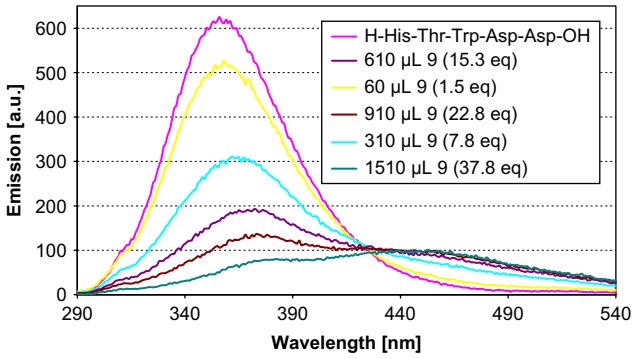

Figure 5. Fluorescence titration of H-His-Thr-Trp-Asp-Asp-OH (1.0×10^{-5} mol/L) with compound **9** in TRIS buffered aqueous solution at pH 7.2; λ_{ex}=280 nm.

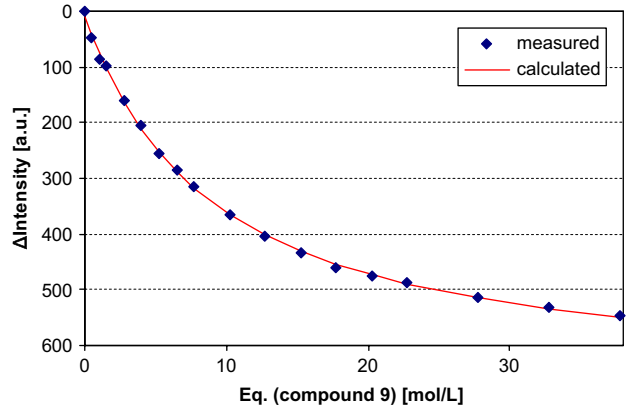

Figure 6. Fluorescence titration of H-His-Thr-Trp-Asp-Asp-OH (1.0×10^{-5} mol/L) with compound **9** in Tris buffered aqueous solution at pH 7.2; λ_{ex}=280 nm.

A binding stoichiometry of 1:1 for complex **9** and the peptides was confirmed by Job's plot analysis (see Supplementary data, Figs. S-7 and S-9 for data). Emission titration data were used to derive binding affinities, which are, as expected for the complexation of N-terminal histidine to a Zn(II)-NTA, in the millimolar range. The binding affinity of **9** to H-His-Asp-Trp-Ser-Gly-OH (log K=4.6±0.3 L/mol; Fig. S-8) is slightly higher than the value for H-His-Thr-Trp-Asp-Asp-OH (log K=4.0±0.3 L/mol; Fig. 6).[25] Ligand **8** or Trp-containing peptides missing N-terminal histidine show no affinity under the experimental conditions, confirming the importance of the Zn(II)-NTA to His complexation for the binding. The addition of a non-substituted Zn(II)-NTA complex or pyrimidine amino acids does not affect the Trp emission.

3. Conclusion

The combination of an imidazole-coordinating metal complex, which binds to N-terminal His, with luminescent pyrimidine hydrazine acids (PHA) leads to a luminescent non-covalent peptide label. The proposed binding process occurs in two steps. Initially, the Zn(II)-NTA complex strongly coordinates to the imidiazole of an N-terminal His, followed by weaker intramolecular interaction of the PHA moiety to the backbone of the peptide. Within the aggregate, quenching of Trp peptide emission by energy transfer to the PHA moieties signals the binding process. Zn(II)-NTA–PHA

complexes like **9** may find use as molecular probes to explore peptidic structures in physiological solution.

4. Experimental

4.1. 2-(Bis-ethoxycarbonylmethyl-amino)-6-(2-*tert*-butoxycarbonylamino-acetylamino)-hexanoic acid methyl ester (2-Boc)

To a solution of 131 mg (0.75 mmol) Boc-Gly-OH, 122 mg (0.9 mmol) HOBt, 158 μL (140 mg, 0.9 mmol) NEt_3, and 447 μL (339 mg, 2.63 mmol) Huenig's base in 2 mL of DMF was added a solution of 302 mg (0.75 mmol) amine **1** in 1 mL of DMF at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 18 h. The solution was diluted with H_2O (4 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic phase was dried over Na_2SO_4, evaporated, and then concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc, R_f=0.36) to afford 280 mg of **2-Boc** as a colorless oil in 76% yield. IR (KBr disk) cm^{-1}: 3362, 2981, 2938, 2251, 1740, 1670, 1166. ^1H NMR ($CDCl_3$, 400 MHz): δ=1.28 (t, ^3J=7.1 Hz, 6H), 1.47 (s, 9H), 1.48–1.67 (m, 4H), 1.70–1.74 (m, 2H), 3.28–3.31 (m, 2H), 3.45 (t, ^3J=7.6 Hz, 1H), 3.61 (s, 2H), 3.62 (s, 2H), 3.71 (s, 3H), 3.81–3.85 (m, 2H), 4.17 (q, ^3J=7.1 Hz, 4H), 5.42 (br s, 1H), 6.51 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ=14.2 (+), 22.5 (−), 28.2 (−), 28.3 (+), 29.3 (−), 39.1 (−), 44.2 (−), 51.4 (+), 52.7 (−), 60.7 (−), 64.1 (+), 79.9 (C_{quat}), 156.0 (C_{quat}), 169.5 (C_{quat}), 171.5 (C_{quat}), 173.3 (C_{quat}). MS (ESI, DCM/MeOH+10 mmol/L NH_4Ac): *m/z* (%)=490.3 [M+H^+] (100). HRMS calcd for $C_{22}H_{39}N_3O_9$: 489.2686; found: 489.2680±0.0004.

4.2. 6-(2-Amino-acetylamino)-2-(bis-ethoxycarbonyl-methyl-amino)-hexanoic acid methyl ester dihydrochloride (2-H)

Compound **2-Boc** (259 mg, 0.53 mmol) was dissolved in 3 mL of ether saturated with HCl. The solution was stirred for 15 h. The precipitate was filtered off, washed with cold ether, and dried in vacuum to afford the deprotected amine **2-H** as a colorless, hygroscopic salt in quantitative yield (242 mg). The salt was used for subsequent reactions without further purification. Mp: >200 °C (decomp.). IR (KBr disk) cm^{-1}: 3423, 2955, 1747, 1656, 1558, 1378, 1224, 1019, 914, 706. ^1H NMR (DMSO-d_6, 300 MHz): δ=1.17 (t, ^3J=7.0 Hz), 1.30–1.48 (m, 4H), 1.51–1.63 (m, 2H), 3.01–3.14 (m, 2H), 3.32–3.42 (m, 1H), 3.34–3.54 (m, 4H), 3.55–3.61 (m, 5H), 4.04 (q, ^3J=7.0 Hz, 4H), 8.16–8.34 (m, 3H), 8.48–8.52 (m, 1H), 9.94 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 150 MHz): δ=15.1 (+), 22.6 (−), 28.4 (−), 29.2 (−), 38.4 (−), 39.9 (−), 51.0 (+), 52.1 (−), 59.0 (−), 63.7 (+), 165.5 (C_{quat}), 170.7 (C_{quat}), 172.3 (C_{quat}). MS (ESI, DCM/MeOH+10 mmol/L NH_4Ac): *m/z* (%)=390.2 [M+H^+] (100).

4.3. 2-(Bis-ethoxycarbonylmethyl-amino)-6-(2-{[6-(*N′*-*tert*-butoxycarbonyl-hydrazino)-2-diethylamino-pyrimidine-4-carbonyl]-amino}-acetylamino)-hexanoic acid methyl ester (4)

A solution of 120 mg (0.26 mmol) of the deprotected amine **2-H**, 86 mg (0.26 mmol) of **3**, 70 mg (0.52 mmol) HOBt, 197 mg (0.52 mmol) HBTU and 224 μL (168 mg, 1.3 mmol) of Huenig's base in 4 mL of DMF was stirred for 24 h at rt. The solution was cooled to 0 °C, diluted with cold H_2O (5 mL), and extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried over $MgSO_4$, evaporated, and then concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc, R_f=0.3) to afford **4** as a white solid in 59% (106 mg) yield. Mp: 144 °C; IR (KBr disk) cm^{-1}: 3325, 2989, 1735, 1649, 1532, 1380, 1187, 1093. ^1H NMR ($CDCl_3$, 600 MHz): δ=1.17 (t, ^3J=6.9 Hz, 6H), 1.22–1.28 (m, 6H), 1.35–1.45 (m, 2H), 1.47 (s, 9H), 1.55–1.60 (m, 2H), 1.66–1.72 (m, 2H), 3.23–3.33 (m, 2H), 3.40 (t, ^3J=7.6 Hz, 1H), 3.58–3.62 (m, 8H), 3.67 (s, 3H), 4.07–4.16 (m, 6H), 6.45–6.75 (m, 2H), 6.65 (br s, 1H), 6.69 (br s, 1H), 8.51 (t, ^3J=5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=13.2 (+), 14.2 (+), 22.9 (−), 28.2 (+), 28.4 (−), 29.6 (−), 39.1 (−), 41.9 (−), 43.2 (−), 51.4 (+), 52.7 (−), 60.6 (−), 64.6 (+), 81.7 (C_{quat}), 115.4 (+), 155.7 (C_{quat}), 155.8 (C_{quat}), 156.9 (C_{quat}), 160.1 (C_{quat}), 164.8 (C_{quat}), 168.7 (C_{quat}), 171.5 (C_{quat}), 173.2 (C_{quat}). MS (ESI, MeOH+10 mmol/L NH_4Ac): *m/z* (%)=719.4 [M+Na^+] (22), 697.4 [MH^+] (100).

4.4. Zn-NTA-complex 5

Seventy-three milligrams (0.1 mmol) of ester **4** and 3 mg (0.30 mmol) of LiOH were dissolved in a 4:1 acetone/water mixture and stirred for 1 day at 40 °C. The solvents were removed under reduced pressure to afford the hygroscopic 2-(bis-carboxymethyl-amino)-6-(2-{[6-(*N′*-*tert*-butoxycarbonyl-hydrazino)-2-diethylamino-pyrimidine-4-carbonyl]-amino}-acetylamino)-hexanoic acid Li salt (61 mg, 95%) in almost quantitative yield. The salt was used for complexation without further purification. Mp: >250 °C (decomp.). ^1H NMR (D_2O, 300 MHz): δ=0.52–0.73 (m, 6H), 0.86–1.69 (m, 15H), 2.78–3.22 (m, 5H), 3.34–3.63 (m, 4H), 3.84–4.06 (m, 4H), 6.34 (s, 1H), 7.12–7.24 (m, 1H), 7.34–7.45 (m, 1H). MS (ESI, H_2O/MeCN/MeOH+10 mmol/L NH_4Ac): *m/z* (%)=391.3 [M+H^+] (100), 408.2 [M+NH_4^+] (22), 798.7 [2M+NH_4^+] (37), 803.6 [2M+Na^+] (23).

Sixty-four milligrams (0.10 mmol) of the lithium salt were suspended in 10 mL of H_2O and 13.6 mg (0.10 mmol) of $ZnCl_2$ was added. The reaction mixture was stirred for 45 min at 40 °C, filtered and the solvent was removed under reduced pressure. The solid was dissolved in EtOH and treated with hexane precipitating **5** in 65% (47 mg) yield. IR (KBr disk) cm^{-1}: 3412, 2987, 2944, 2880, 1931, 1605, 1537, 1418, 1264, 965, 820. ^1H NMR (MeOH-d_4, 600 MHz): δ=1.15 (t, ^3J=7.0 Hz, 6H), 1.29–1.68 (m, 15H), 3.03–3.21 (m, 3H), 3.31–3.34 (m, 4H), 3.63 (q, ^3J=7.0 Hz, 4H), 4.05–4.10 (m, 2H), 6.52 (s, 1H). ^{13}C NMR (MeOH-d_4, 150 MHz): δ=13.8 (+), 26.8 (−), 28.3 (−), 28.7 (+), 30.3 (−), 42.8 (−), 43.6 (−), 55.7 (−), 60.3 (−), 69.1 (+), 81.7 (C_{quat}), 91.8 (+), 157.7 (C_{quat}), 158.7 (C_{quat}), 161.9 (C_{quat}), 167.3 (C_{quat}), 171.1 (C_{quat}), 178.1 (C_{quat}), 178.3 (C_{quat}), 179.5 (C_{quat}), 180.5 (C_{quat}). MS (ESI, H_2O/MeOH+10 mmol/L NH_4Ac): *m/z* (%)=687.4 [M−H^+]$^-$ (100).

4.5. Dipyrimidine 7

To a solution of **6** (200 mg, 0.24 mmol) in 4 mL of water/acetone (v/v, 3:1) was added $LiOH\cdot H_2O$ (11.5 mg,

0.27 mmol). The reaction mixture was stirred for 6 h at rt. Acetone was removed in vacuum and the remaining solvent was lyophilized. Compound **7** (200 mg) was obtained quantitatively. IR ($CHCl_3$) cm^{-1}: 3423, 1668, 1618, 1529, 1374, 1084, 668. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.34 (s, 9H), 3.19 (m, 12H), 3.40–3.44 (m, 8H), 3.52–3.58 (m, 8H), 3.62–3.67 (m, 8H), 3.69–3.72 (m, 8H), 6.36 (s, 1H), 6.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=27.5, 46.7, 46.9, 58.0, 68.6, 69.3, 69.4, 70.9, 71.0, 82.4, 158.2, 161.5. UV (MeCN) λ_{max} (log ε): 336 (6.76).

4.6. Compound 8

A mixture of **7** (200 mg, 0.24 mmol), **2-H** (94 mg, 0.28 mmol), HOBt (96 mg, 0.71 mmol), EDC (110 mg, 0.71 mmol), and DIPEA (153 mg, 1.18 mmol) in 8 mL of DMF was stirred for 12 h at 40 °C. The solution was allowed to cool to rt, solvents were removed in vacuum and the crude product was purified by column chromatography (CH_2Cl_2/MeOH 1:40, R_f=0.30) to afford compound **8** as a yellow oil (135 mg, 50%). IR ($CHCl_3$) cm^{-1}: 3295, 1639, 1583, 1506, 1406, 1091. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.23 (t, J=7.2 Hz, 6H), 1.32–1.40 (m, 2H), 1.44 (s, 9H), 1.59–1.71 (m, 4H), 3.29–3.39 (m, 13H), 3.48–3.51 (m, 10H), 3.57–3.60 (m, 10H), 3.65–3.68 (m, 8H), 3.78–3.80 (m, 10H), 4.07–4.14 (m, 4H), 6.98 (s, 1H), 7.29 (s, 1H), 7.46 (s, 1H, NH), 8.73 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.2, 23.3, 28.2, 28.7, 30.3, 40.1, 51.4, 52.6, 58.8, 60.6, 64.7, 69.4, 70.4, 71.7, 71.8, 81.6, 155.5, 171.5, 173.1. UV (MeCN): λ_{max} (log ε): 332 (6.05). MS (ESI, MeOH+10 mmol/L NH_4Ac): m/z (%)=1143.8 [MH^+] (26), 572.5 [M+2H^+] (100). HRMS calcd: 1143.6261 [M^+]; found: 1143.6289.

4.7. Complex 9

To a solution of **8** (130 mg, 0.12 mmol) in 3 mL of water/acetone (v/v, 3:1) was added $LiOH \cdot H_2O$ (15.2 mg, 0.36 mmol). The reaction mixture was stirred for 24 h at rt. Acetone was removed in vacuum and the remaining solution was lyophilized. The residue and zinc carbonate (29 mg, 0.05 mmol) were dissolved in H_2O (20 mL). After stirring for 1 h the suspension was heated to 55 °C for 24 h. Insoluble particles were filtered off and the filtrate was lyophilized. The raw product was dissolved in ethanol and ether was added. The precipitated material was separated from solution by centrifugation to give **9** (97 mg, 75%). IR ($CHCl_3$) cm^{-1}: 3282, 2930, 1722, 1585, 1511, 1431, 1369, 1249, 1161, 1096, 847, 782. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.35 (s, 9H), 1.43–1.52 (m, 4H), 1.72–1.80 (m, 2H), 3.07–3.19 (m, 16H), 3.26–3.44 (m, 16H), 3.55–3.56 (m, 8H), 3.64–3.73 (m, 10H), 6.45 (s, 1H), 6.54 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=28.1, 47.3, 56.8, 68.3, 69.3, 69.4, 71.0, 160.8, 176.2. UV (MeCN) λ_{max} (log ε): 338 (6.06). MS (ESI, MeOH+10 mmol/L NH_4Ac): m/z (%)=1133.7 [MH^+] (80), 566.4 [M+2H^+] (100). HRMS calcd: 1135.4614 [M^-+2H]$^+$; found: 1135.4586.

Acknowledgements

X.L. thanks the European Union (Asia Link Medicinal Chemistry Program) for a research training scholarship. V.M. thanks the German Academic Exchange Service (DAAD, IQN-MC Program) for a postdoctoral fellowship. We thank the Fonds der Chemischen Industrie for support of the work.

Supplementary data

Spectroscopic investigations of the aggregate of **5**—H-His-Leu-Leu-Val-Phe-OMe and **9**—H-His-Asp-Trp-Ser-Gly-OH. Analysis of the binding of compound **9** with H-His-Asp-Trp-Ser-Gly-OH and H-His-Thr-Trp-Asp-Asp-OH in aqueous buffer. Copies of proton NMR spectra of compounds **7–9**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.019.

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17. Binding affinity of Ni(II)- and Zn(II)-NTA complexes to peptides in organic solvents and buffered water were derived from ITC binding experiments. A Li[Ni(NTA)-Gly-Boc] complex shows a binding affinity of $5\pm0.3\times10^5$ L/mol to NH_2-His-Leu-Leu-Val-Phe-OMe in DMSO. The binding of Ni(II)-NTA complexes to N-terminal His is typically 500-fold tighter if compared to the affinity of the corresponding Zn-NTA complex.
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23. The ROESY spectrum was recorded on a Bruker Avance 600 NMR spectrometer at 300 K with a mixing time of 500 ms.
24. Signal overlap prohibits the observation of additional cross-peaks and contacts.
25. The second pentapeptide has an overall negative charge, which may lead to repulsion with the negatively charged NTA complex, thus reducing the binding affinity. However, the difference between the affinities compared to error margins is small.

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Preparation of α-amino ketones, β-amino hydroxylamines using asymmetric aza-Henry reactions of *N*-*p*-tolylsulfinylimines with nitroethane

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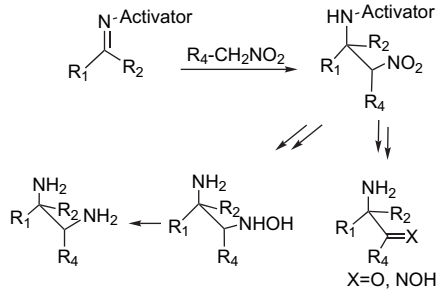
Received 31 August 2006; revised 3 October 2006; accepted 10 October 2006
Available online 30 October 2006

Abstract—*N*-Sulfinylimines derived from aromatic and aliphatic aldehydes react with nitroethane and NaOH, yielding mainly two diastereoisomeric β-nitroamines as the result of a highly diastereoselective reaction and further epimerization of the carbon linked to the nitro group. The resulting β-nitroamines are used as precursors of *N*-sulfonyl α-amino methyl ketones and β-amino hydroxylamines.

1. Introduction

Diastereoselective and enantioselective versions of the aza-Henry (or nitro-Mannich) reaction are recently attracting a great deal of attention.[1–3] This interest is due to the formation of optically pure β-nitroamines, which are attractive targets in asymmetric synthesis mainly due to their possible but not always easy conversion to diamines.[4] Additionally, the nitro moiety can be transformed into other interesting functional groups like carbonyl groups,[5] hydroxylamines,[6] and oximes or nitriles[7] (Scheme 1).



Scheme 1. Aza-Henry reaction and some interesting transformations.

We have recently reported the asymmetric diastereoselective aza-Henry reaction of nitromethane with a wide variety of *N*-*p*-tolylsulfinylimines from aliphatic and aromatic aldehydes as well as from ketones, even when they have enolizable protons.[8] Depending on the reaction conditions employed (NaOH or TBAF) we were able to obtain as the major product one of the two possible diastereoisomers.

As a part of our ongoing investigations on the asymmetric aza-Henry reaction, we present herein the results obtained when these *N*-*p*-tolylsulfinylimines are treated with nitroethane under the conditions previously optimized with nitromethane, and the transformation of the resulting β-nitro sulfinylamines into other compounds of interest such as α-amino methyl ketones and β-amino hydroxylamines.

2. Results and discussion

N-Sulfinylimines **1a–i** have been obtained by condensation of the corresponding aldehydes and ketones with (*S*)-*N*-*p*-tolylsulfinylamide following the $Ti(OEt)_4$ Davis' protocol[9] with slight modifications in the work-up.[10]

Aza-Henry reactions of *N*-sulfinylimines **1** with $EtNO_2$, under the same reaction conditions optimized when $MeNO_2$ was used as nucleophile,[8] led to a mixture of diastereoisomers (Table 1). The four possible ones were obtained with very low diastereoselectivity with the aromatic *N*-sulfinylaldimine **1a** using TBAF as the base (entry 1) with no improvement by lowering the reaction temperature. Nevertheless, when this reaction was carried out in the presence of NaOH, diastereoisomers **2a** and **3a** were clearly predominant and can be easily separated from **4a** and **5a** by simple crystallization in ether (entry 2). A similar result was

Keywords: Asymmetric synthesis; Diastereoselectivity; Imines; Amines; Sulfoxides.
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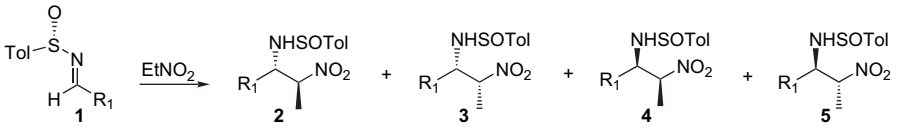
doi:10.1016/j.tet.2006.10.021

Table 1. Aza-Henry reaction of nitroethane with *N*-sulfinylaldimines (*Ss*)-**1a–g**



Entry	Substrate's R_1	s.m./prod	Conditions	Conv [%][a]	*t* [h]	Ratio of products **2/3/4/5**[a]	Yield[b] (**2/3**) [%]
1	C_6H_5	**a**	Method B	95	0.5	28:13:38:21	92 (**2–5**)
2	C_6H_5	**a**	Method A	81	36	50:44:3:3	75 [43 (**2a**)/32 (**3a**)] 70[d] (58:42)
3	*p*-CNC_6H_4	**b**	Method A	100	26	51:41:3:5	82 [45 (**2b**)/37 (**3b**)]
4	*p*-$MeOC_6H_4$	**c**	Method A	74	66	55:41:2:2	68 [40 (**2c**)/28 (**3c**)]
5	PhCH=CH	**d**	Method A	93	72	51:40:6:3[c]	70 [36 (**2d**)/34 (**3d**)]
6	Me	**e**	Method A	94	17	91 (**2+3**):5:4	80[e]
7	Me	**e**	Method A, Yb(O*i*-Pr)$_3$ (1 equiv)	93	24	42:40:9:9	Not determined
8	*i*-Pr	**f**	Method A	62	138	83:17	48[f] (83:17) 42[d] (93:7)
9	*i*-Pr	**f**	NaOH (5 equiv), 40 °C	73	168	81:19	34[g]

Method A: $EtNO_2$ (solvent), NaOH (5 equiv), 4 Å MS, 40 °C. Method B: $EtNO_2$ (solvent), TBAF.
[a] Determined by ^1H NMR.
[b] After flash chromatography.
[c] Determined after isolation of products by flash chromatography.
[d] After crystallization in ether.
[e] After chromatography the ratio **2e/3e** was 55.2:44.8 (determined by HPLC).
[f] Recovered starting material: 17%.
[g] Recovered starting material: 15%.

obtained with other aromatic imines **1b**,**c**, α,β-unsaturated **1d**, and the aliphatic *N*-sulfinylimine **1e**, derived from acetaldehyde (entries 3–6). In the later case, the addition of Yb(O*i*-Pr)$_3$ produced a deleterious effect on the stereoselectivity of the reaction (entry 7).[11] The bulkier aliphatic *i*-Pr substituent required longer reaction times to afford the β-nitroamines with higher stereoselectivity (entry 8). The results in entries 8 and 9 clearly illustrate that the isolated yields decreased when the reactions were carried out in the absence of molecular sieves, which could suggest that they have some role in preventing the hydrolysis of the *N*-sulfinylimine, by absorbing the water generated by the HO^-.

The bulky *tert*-butyl *N*-sulfinylimine reacts with nitroethane under both catalyzed (Yb(O*i*-Pr)$_3$) and uncatalyzed conditions affording the corresponding β-nitroamines in very low yields.[12] Finally, *N*-sulfinylketimines failed to undergo aza-Henry reaction with nitroethane under the same reaction conditions.

The absolute configurations of compounds **2f** and **3a** were respectively established as (*Ss*, 1*S*,2*S*) and (*Ss*, 1*S*,2*R*) by X-ray crystallography (Fig. 1). The major diastereoisomers **2** obtained in the reactions carried out in the presence of NaOH have been assigned the same configurations as **2f** by assuming that all imines should evolve through the same stereochemical course.[13]

When compounds **2a** and **3a** were treated independently with nitromethane using NaOH as well as TBAF, a mixture

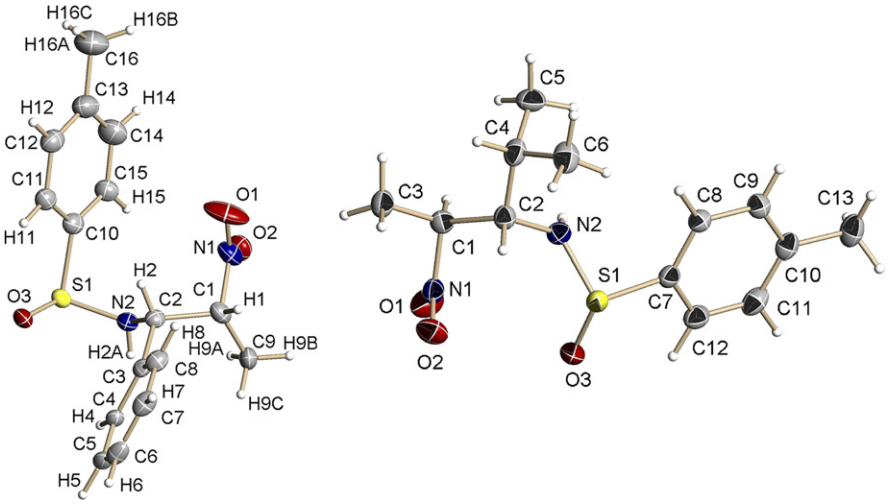
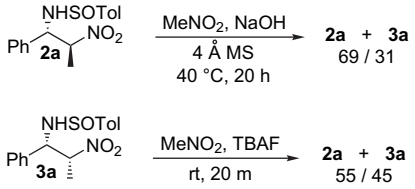


Figure 1. X-ray structure of **2f** and **3a**.

of **2a** and **3a** was obtained in both cases (Scheme 2). It indicates that the carbon bearing the nitro group is easily epimerizable under both reaction conditions. The fact that no traces of the compounds resulting from the aza-Henry reaction with nitromethane were detected in the latter experience, despite the presence of nitromethane as solvent, also indicates that retro aza-Henry reaction is not taking place under these conditions. The above results suggest that the lack of stereoselectivity observed in these reactions could be due to the epimerization under the reaction conditions, and therefore it is not easily avoidable. The use of only 1 equiv of NaOH after 40 h affords the same mixture of diastereoisomers, but the conversion decreases to 64%.



Scheme 2. Isomerization of **2a** into **3a**.

The high selectivity observed at the new chiral center bearing the sulfinamide moiety when NaOH was used as the base is in agreement with the proposed model for the reactions with nitromethane[8] and could be attributed to a rigid transition state in which both reacting partners were coordinated to the metal, as outlined in Figure 2. The *S* configuration of the sulfoxide favors the TS leading the (*S*s, *S*) diastereoisomer (**I** in Fig. 2), since the TS affording the (*S*s, *R*) diastereoisomer (**II** in Fig. 2) would be destabilized by the steric interactions of the bulky *p*-tolyl group.

Several synthetic manipulations of the β-nitroamines **2** and **3** can be envisioned (Schemes 3 and 4). All the attempts carried out to transform the nitro group in the sulfinyl β-nitroamines **2** and **3** into a carbonyl one were unsuccessful. However, this transformation could be easily achieved from the corresponding sulfonyl β-nitroamines **6** and **7** (easily prepared from **2** and **3** by oxidation with *m*-CPBA). Thus, the reaction of a mixture of **6a** and **7a** with *t*-BuOK/*t*-BuOH and subsequent addition of $KMnO_4$ afforded the corresponding ketone **8a** in 73% yield and 80% ee.[14] This loss of optical purity can be explained through epimerization of the stereogenic center once the ketone is formed, due to the acidity at the α position.[15] This acidity is lower when R is an aliphatic chain and thus ketone **8e** is obtained optically pure (ee>99%) from β-nitroamines **2e** and **3e** following the same procedure.[16] Therefore, ketones **8a** and **8e** are obtained in 51 and 63% yields, respectively, from the corresponding sulfinylimines **1a** and **1e** employing only one final chromatographic purification.[17]

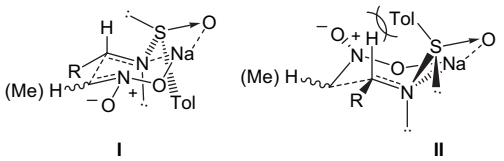
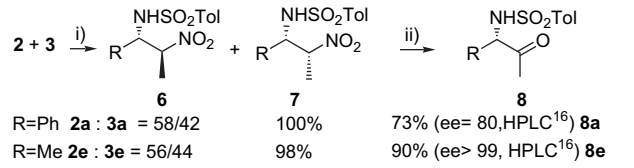
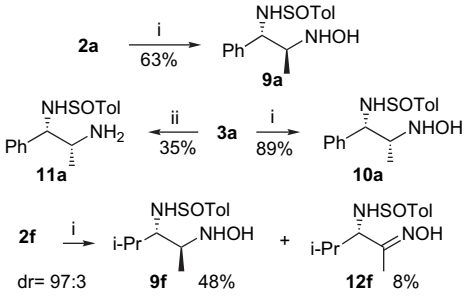


Figure 2. Transition states involved in aza-Henry reactions of nitromethane and nitroethane with *N*-sulfinylaldimines in the presence of NaOH.



Scheme 3. Preparation of α-amino ketones **8a** and **8e**. (i) *m*-CPBA, CH_2Cl_2, rt–0 °C, 30 min, 90%; (ii) (a) *t*-BuOK/*t*-BuOH, rt, 10 min; (b) EtOAc, $KMnO_4$, 0 °C, 2 h 30 min.



Scheme 4. Preparation of β-amino hydroxylamines. (i) Al/Hg (3 equiv), 40 min; (ii) Al/Hg (10 equiv), 65 h.

When compounds **2a** and **3a**, which can be obtained by flash chromatography in 43 and 32% yields, respectively, were independently treated for 40 min with aluminum amalgam[18] (3 equiv) in THF/H_2O at rt, the corresponding hydroxylamines **9a** and **10a** could be isolated in 63 and 89% yields, respectively, after flash chromatography. Prolonging the reaction times of **3a** and using 10 equiv of aluminum amalgam the 1,2-diamine **11a** was obtained in 35% yield. When the β-nitroamine **2f**, with aliphatic substituents, was submitted to the same reaction conditions hydroxylamine **9f** could be isolated in 48% yield along with 8% of the oxime **12f**.

3. Conclusions

In summary, the aza-Henry reaction of *N*-sulfinylimines derived from aromatic and aliphatic aldehydes with nitroethane and NaOH takes place to afford the corresponding β-nitroamines as a mixture of two major diastereoisomers (**2** and **3**) as a consequence of the easy epimerization at the carbon linked to the nitro group. The synthetic interest of these compounds is illustrated with several transformations. After separation of the minor isomers (**4** and **5**) by crystallization of the crude, β-nitroamines **2** and **3** are transformed into *N*-sulfonyl α-amino methyl ketones **8** in good yields. Reduction of the nitro group using aluminum amalgam provides β-amino hydroxylamines in moderate to good yields.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were acquired in a Bruker spectrometer at 200 or 300 MHz and 75 MHz, respectively. THF and CH_2Cl_2 were distilled from sodium-benzophenone and P_2O_5, respectively. Melting points were measured using a *Gallemkamp* apparatus in open capillary tubes. Optical

rotations were recorded in cells with 10 cm path length on a Perkin–Elmer 241 MC polarimeter. Flash column chromatography was performed using silica gel Merk-60 (230–400 mesh) or Redisep™ normal phase columns in an Isco CombiFlash instrument. All reagents were purchased from Aldrich. All the *N*-sulfinylimines and ketimines were synthesized using Davis' methodology[9] with slight modifications in the work-up.[10]

4.2. General procedure for the aza-Henry reaction of (*S*)-*N*-sulfinylimines by using NaOH. (Method A)

Powdered NaOH (2 mmol) was added to a slurry of the corresponding *N*-sulfinylimine (0.4 mmol) and the same weight of 4 Å MS in $EtNO_2$ (5.7 mL) at rt. The reaction mixture was stirred at the indicated temperature and reaction time specified in each case (Table 1). All reactions were monitored by TLC (hex/EtOAc 2:1), the mixture was filtrated through a short pad of silica gel, and the crude purified by flash chromatography.

4.2.1. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-nitro-1-phenyl-propylamine (2a) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-2-nitro-1-phenyl-propylamine (3a). These compounds were obtained following the general method A and method B. *Method A*: at 40 °C after 36 h as a mixture **2a/3a/others**=50:44:3:3. After flash chromatography **2a** and **3a** were obtained in 43 and 32% yields, respectively. Crystallization from ether of the crude provides a mixture of **2a** and **3a** in 70% combined yield (**2a/3a**=58:42). *Method B*: a 1 M solution of TBAF (66 μL) was added to a solution of the corresponding *N*-sulfinylimine (0.328 mmol) in $EtNO_2$ (4.7 mL) at rt. The reaction mixture was stirred for 0.5 h. The reaction was monitored by TLC (hex/EtOAc 2:1), the mixture (**2a/3a/4a/5a**=28:13:38:21) was filtrated through a short pad of silica gel, the solvent evaporated, and the crude purified by flash chromatography. Data of the major diastereoisomer **2a**: white solid; mp: 123–125 °C; $[\alpha]_D^{20}$ +153 (*c* 0.2, $CHCl_3$); IR: 3184, 1554, 1455, 1389, 1360, 1089, 1057 cm^{-1}; ^1H NMR (300 MHz): δ 7.53 (d, *J*=8.3 Hz, 2H), 7.42–7.30 (m, 7H), 4.94 (br d, *J*=6.4 Hz, 1H), 4.80 (dq, *J*=8.1, 6.6 Hz, 1H), 4.69 (dd, *J*=8.1, 6.6 Hz, 1H), 2.43 (s, 3H), 1.33 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 141.8, 140.9, 136.6, 129.7, 129.2, 129.0, 127.7, 125.4, 87.3, 60.6, 21.4, 17.0; MS (FAB) *m/z* 319.1 (M+1, 81), 154 (32), 139 (100); HRMS [M+1]: calcd for $C_{16}H_{19}N_2O_3S$: 319.1116; found: 319.1124. Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80; S, 10.07. Found: C, 60.56; H, 5.84; N, 8.40; S, 9.62. Data of the minor diastereoisomer **3a**: mp: 120 °C; $[\alpha]_D^{20}$ +160 (*c* 0.2, $CHCl_3$); IR: 3196, 2924, 1554, 1389, 1361, 1088, 1051 cm^{-1}; ^1H NMR (300 MHz): δ 7.57 (d, *J*=8.1 Hz, 2H), 7.40–7.31 (m, 7H), 4.95–4.86 (m, 2H), 4.79 (dq, *J*=6.8, 5.0 Hz, 1H), 2.43 (s, 3H), 1.46 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.0, 141.3, 136.3, 129.8, 129.0, 128.9, 127.6, 125.4, 86.6, 60.0, 21.4, 14.9; MS (FAB) *m/z* 319.1 (M+1, 45), 154 (28), 139 (100); HRMS [M+1]: calcd for $C_{16}H_{19}N_2O_3S$: 319.1116; found: 319.1115.

4.2.2. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-nitro-1-(4-nitrilephenyl)-propylamine (2b) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-2-nitro-1-(4-nitrilephenyl)-propylamine (3b). These compounds were obtained following the general method A at 40 °C after 26 h in 45 and 37% yields, respectively, after flash chromatography (hex/EtOAc 2:1). Data of **2b** as a mixture **2b/3b**=85:15; white solid, mp: 78 °C; $[\alpha]_D^{20}$ +236 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz): δ 7.70 (d, *J*=7.7 Hz, 2H), 7.52–7.34 (m, 6H), 5.13 (d, *J*=7.67 Hz, 1H), 4.80–4.78 (m, 1H), 4.66–4.61 (m, 1H), 2.45 (s, 3H), 1.37 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.1, 141.9, 139.5, 132.4, 129.7, 127.8, 125.2, 117.8, 112.1, 86.2, 59.6, 21.2, 17.2. Data of **3b**: ^1H NMR (300 MHz): δ 7.70 (d, *J*=8.3 Hz, 2H), 7.56–7.34 (m, 6H), 4.94–4.75 (m, 3H), 2.45 (s, 3H), 1.49 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.8, 142.3, 132.7, 129.4, 127.7, 125.5, 125.4, 117.0, 113.0, 87.0, 59.5, 21.4, 14.2.

4.2.3. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-nitro-1-(4-methoxyphenyl)-propylamine (2c) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-2-nitro-1-(4-methoxyphenyl)-propylamine (3c). These compounds were obtained following the general method A at 40 °C after 66 h in 40 and 28% yields, respectively, after flash chromatography (hex/EtOAc 2:1). Data of **2c**: yellow oil; $[\alpha]_D^{20}$ +89 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz): δ 7.52 (d, *J*=8.2 Hz, 2H), 7.32–7.25 (m, 4H), 6.94 (d, *J*=8.8 Hz, 2H), 4.80–4.65 (m, 3H), 3.82 (s, 3H), 2.43 (s, 3H), 1.33 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 160.0, 142.0, 141.5, 129.8, 129.0, 128.0, 125.4, 114.3, 86.7, 59.6, 55.3, 21.4, 15.0. Data of **3c**: colorless oil; $[\alpha]_D^{20}$ +135 (mixture **3c/2c/4c** or **5c**=86:10:4, *c* 2, $CHCl_3$); ^1H NMR (300 MHz): δ 7.57 (d, *J*=8.5 Hz, 2H), 7.34–7.24 (m, 4H), 6.92 (d, *J*=8.7 Hz, 2H), 4.84–4.75 (m, 3H), 3.65 (s, 3H), 2.43 (s, 3H), 1.46 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 160.0, 141.8, 141.1, 129.4, 129.0, 128.2, 125.4, 114.6, 87.5, 60.2, 55.3, 21.4, 16.9.

4.2.4. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-1-nitro-2-methyl-4-phenylbut-3-en-2-amine (2d) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-1-nitro-2-methyl-4-phenylbut-3-en-2-amine (3d). These compounds were obtained following the general method A at 40 °C after 72 h in 36 and 34% yields, respectively, after flash chromatography (hex/EtOAc 2:1). Data of **2d**: yellow oil; $[\alpha]_D^{20}$ +134 (*c* 0.8, $CHCl_3$); IR (film): 3196, 2924, 1545, 1088, 1056 cm^{-1}; ^1H NMR (300 MHz): δ 7.60 (d, *J*=8.2 Hz, 2H), 7.42–7.20 (m, 7H), 6.73 (d, *J*=15.8 Hz, 1H), 6.13 (dd, *J*=15.8, 7.8 Hz, 1H), 4.77–4.58 (m, 2H), 4.46–4.32 (qd, *J*=6.8, 1.0 Hz, 1H), 2.42 (s, 3H), 1.51 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.0, 141.1, 135.8, 135.5, 129.7, 128.7, 128.6, 126.8, 125.5, 123.9, 85.9, 58.8, 21.4, 16.2; MS (FAB) *m/z* 345 (M+1, 55), 139 (100), 154 (10); [M+1]: calcd for $C_{18}H_{21}N_2O_3S$: 345.1272; found: 345.1282. Data of **3d**: colorless oil; $[\alpha]_D^{20}$ +143 (*c* 0.81, $CHCl_3$); ^1H NMR (300 MHz): δ 7.61 (d, *J*=8.3 Hz, 2H), 7.43–7.29 (m, 7H), 6.75 (d, *J*=15.8 Hz, 1H), 6.16 (dd, *J*=15.8, 8.1 Hz, 1H), 4.69–4.57 (m, 2H), 4.43–4.34 (ddd, *J*=6.5, 4.1, 1.1 Hz, 1H), 2.43 (s, 3H), 1.51 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.0, 141.3, 136.4, 135.6, 129.8, 128.7, 128.6, 126.9, 125.5, 122.6, 86.0, 58.2, 21.4, 15.4; MS (FAB) *m/z* 345 (M+1, 9), 139 (100), 154 (24); [M+1]: calcd for $C_{18}H_{21}N_2O_3S$: 345.1272; found: 345.1279.

4.2.5. (2*S*,3*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-3-nitrobutan-2-amine (2e) and (2*S*,3*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-3-nitrobutan-2-amine (3e). These compounds were obtained

following the general method A at 40 °C after 17 h as a **2e/3e/others**=91:5:4 mixture in an 80% combined yield of **2e** and **3e** after flash chromatography (CombiFlash) as a **2e/3e**=55.2:44.8 mixture (determined by HPLC with a Chiralpak® AD, hex/*i*-PrOH=93:7, 0.7 mL/min, *T*=25 °C, major diastereomer t_R=27.3 min, minor diastereomer t_R=32.9 min). Data of the mixture: IR (film): 3196, 1550, 1389, 1452, 1391, 1363, 1088, 1058 cm^{-1}; ^1H NMR (300 MHz): δ 7.55 (d, *J*=7.9 Hz, 2H **2e**), 7.51 (d, *J*=7.9 Hz, 2H **3e**), 7.28 (br d, 2H **2e** and 2H **3e**), 4.73 (br d, *J*=8.9 Hz, 1H **2e** and 1H **3e**), 4.45–4.36 (m, 1H **2e** and 1H **3e**), 3.77–3.58 (m, 1H **2e** and 1H **3e**), 2.40 (s, 3H **2e** and 3H **3e**), 1.37–1.31 (4d, 6H **2e** and 6H **3e**); MS (FAB) *m/z* 257.1 (M+1, 59), 139 (100), 55 (16); HRMS [M+1]: calcd for $C_{11}H_{17}N_2O_3S$: 257.0960; found: 257.0973. Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93; S, 12.51. Found: C, 51.76; H, 6.32; N, 10.65; S, 12.27. Data of the major diastereoisomer **2e**: ^{13}C NMR (75 MHz): δ 141.8, 140.7, 129.7, 125.7, 86.7, 51.3, 21.4, 18.4, 14.9. Data of the minor diastereoisomer **3e**: ^{13}C NMR (75 MHz): δ 141.7, 140.3, 129.6, 125.8, 87.0, 51.1, 20.0, 15.6, 14.2.

4.2.6. (3*S*,4*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-methyl-4-nitropentan-3-amine (2f). This compound was obtained following the general method A at 40 °C after 138 h as a **2f/3f**=83:17 mixture in 48% yield after flash chromatography (CombiFlash) recovering 17% of starting material **1f**. Compound **2f** was obtained as a 93:7 mixture after crystallization in ether. Data of the diastereoisomer **2f**: white solid; mp: 115–116 °C; $[\alpha]_D^{20}$ +33 (*c* 1, $CHCl_3$); IR (film): 3197, 1549, 1454, 1389, 1362, 1089, 1061 cm^{-1}; ^1H NMR (300 MHz): δ 7.62 (d, *J*=8.1 Hz, 2H), 7.31 (d, *J*=7.9 Hz, 2H), 4.90–4.80 (m, 1H), 4.72 (d, *J*=9.4 Hz, 1H), 3.27 (ddd, *J*=9.3, 7.3, 4.5 Hz, 1H), 2.41 (s, 3H), 1.83 (sept, *J*=6.9 Hz, 1H), 1.61 (d, *J*=6.9 Hz, 3H), 1.06 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.5, 141.9, 129.7, 125.3, 83.7, 64.4, 31.8, 21.4, 20.1, 19.2, 17.9; MS (FAB) *m/z* 285 (M+1, 55), 139 (100), 55 (21); HRMS [M+1]: calcd for $C_{13}H_{21}N_2O_3S$: 285.1273; found: 285.1281. Anal. Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.91; H, 7.09; N, 9.85; S, 11.28. Found: C, 55.0; H, 6.94; N, 9.56; S, 11.00.

4.3. Typical procedure for the oxidation of *p*-tolylsulfinylamines to *p*-tolylsulfonylamines

m-CPBA (0.12 mmol) was added to a solution of the corresponding sulfinylamine (0.1 mmol) in CH_2Cl_2 (0.5 mL) at rt. The reaction mixture was stirred at 0 °C for 30–50 min. The reactions were monitored by TLC (hex/EtOAc 3:1) and when the reaction was completed, CH_2Cl_2 (1 mL) was added, the organic phase was washed with $NaHSO_3$ (2×1 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×1 mL). The organic extracts were washed with a saturated solution of $NaHCO_3$ (2×1 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent evaporated, obtaining the corresponding pure sulfonylamines without further purification.

4.3.1. (1*S*,2*S*)-*N*-(*p*-Tolylsulfonyl)-2-nitro-1-phenylpropylamine (6a). This compound was obtained following the general method for oxidation starting from **2a** at 0 °C after 30 min in 100% yield. Data of **6a**: white solid; mp: 171 °C; $[\alpha]_D^{20}$ +68 (*c* 0.375, $CHCl_3$); IR (film): 3255, 1598, 1458, 1388, 1359, 1165, 1092, 1068 cm^{-1}; ^1H NMR (300 MHz): δ 7.54 (d, *J*=8.4 Hz, 2H), 7.22–7.01 (m, 7H), 5.8 (br d, *J*=9.3 Hz, 1H), 4.89–4.75 (m, 2H), 2.35 (s, 3H), 1.51 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 143.7, 136.7, 135.1, 128.7, 128.8, 127.1, 127.2, 86.2, 60.3, 21.4, 15.56.

4.3.2. (1*S*,2*R*)-*N*-(*p*-Tolylsulfonyl)-2-nitro-1-phenylpropylamine (7a). This compound was obtained following the general method for oxidation starting from **3a** at 0 °C after 30 min in 100% yield. Data of **7a**: white solid; mp: 156–157 °C; $[\alpha]_D^{20}$ +55 (*c* 0.10, $CHCl_3$); IR (film): 3419, 1551, 1458, 1389, 1321, 1162, 1089 cm^{-1}; ^1H NMR (300 MHz): δ 7.54 (d, *J*=8.2 Hz, 2H), 7.30–6.95 (m, 7H), 5.50 (br d, *J*=9 Hz, 1H), 4.78 (m, 2H), 2.38 (s, 3H), 1.62 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz): δ 143.7, 136.7, 134.9, 129.5, 128.8, 128.7, 127.41, 126.8, 86.0, 60.2, 21.4, 15.7.

4.3.3. (1*S*,2*S*)-*N*-(*p*-Tolylsulfonyl)-2-nitrobutylamine (6e) and (1*S*,2*R*)-*N*-(*p*-tolylsulfonyl)-2-nitrobutylamine (7e). These compounds were obtained following the general method at 0 °C after 45 min in 98% yield. Data of the mixture **6e** and **7e**: IR (film): 3277, 1552, 1439, 1394, 1334, 1093, 1034 cm^{-1}; ^1H NMR (300 MHz): δ 7.76–7.73 (m, 4H), 7.31 (br d, *J*=8.1 Hz, 4H), 5.42–5.37 (m, 2H), 4.59 (qd, *J*=6.8, 1.7 Hz, 1H), 4.49 (qd, *J*=1.9, 1.6 Hz, 1H), 3.80–3.69 (m, 2H), 2.42 (s, 6H), 1.50 (d, *J*=6.8 Hz, 3H), 1.49 (d, *J*=6.9 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 150.0, 143.9, 137.4, 130.0, 127.0, 127.0, 86.2, 86.2, 53.5, 52.1, 51.6, 21.5, 17.5, 16.7, 15.4, 15.3.

4.4. Procedure for preparing *N*-sulfonyl α-amino methyl ketones (8)

The corresponding nitro sulfone (0.075 mmol), obtained by oxidation of *p*-tolylsulfinylnitroamines with *m*-CPBA (1.2 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C, was dissolved in 3 mL of *t*-BuOH at 60 °C and added to a solution of *t*-BuOK (0.26 mmol) in 1 mL of *t*-BuOH at rt. The mixture was stirred under argon atmosphere for 10 min while cooling to rt and then 18 mL of ethyl acetate was added and the reaction mixture was cooled to 0 °C. Immediately, a solution of $KMnO_4$ (0.11 mmol) in 5.4 mL of water at 0 °C was added to the mixture and stirred vigorously for 2 h 30 min at 0 °C, whereupon 0.3 mL of 1 M solution of H_2SO_4 was added at once and stirred for 5 min, then 0.15 mL of 1 M solution of sodium bisulfite ($NaHSO_3$) was added until the solution turns colorless. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2× 4 mL). The combined organic layers were washed with ice-cold water (2×4 mL) and brine and then dried over $MgSO_4$ anhydride. The crude was purified by flash chromatography (hex/EtOAc=90:10–70:30).

4.4.1. (*S*)-(+)-*N*-(*p*-Tolylsulfonyl)-3-amino-3-phenyl-2-propanone (8a).[15] Yield: 73%; mp: 157 °C (Ref. 15 136–137 ° C); ee=80%; $[\alpha]_D^{20}$ +202 (*c* 0.8, $CHCl_3$) [Ref. 15 $[\alpha]_D^{20}$ +287 (*c* 0.8, $CHCl_3$)]. The enantiomeric excess of ketone **8a** has been determined by HPLC with a Chiralpak®

AD column (hex/*i*-PrOH=90:10, 1 mL/min, T=25 °C), minor enantiomer t_R=37.1 min (10%), major enantiomer t_R=41.8 min (90%).

4.4.2. (*S*)-(+)-*N*-(*p*-Tolylsulfonyl)-amino-2-butanone (8e). Yield: 90%; mp: 93–94 °C; $[\alpha]_D^{20}$ +57 (*c* 0.6, $CHCl_3$); IR (film): 3269, 1721, 1428, 1420, 1050, 1088, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 5.6 (br d, J=6.3 Hz, 1H), 3.93 (quin, J=7.2 Hz, 1H), 2.43 (s, 3H), 2.11 (s, 3H), 1.35 (d, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6, 143.6, 136.9, 129.7, 127.1, 57.7, 26.2, 21.5, 18.8; MS (FAB^+) *m*/*z*: 242.0 (M+1, 100), 198.0 (42), 155.0 (38), 136.0 (37), 91.0 (47); HRMS [M+1]: calcd for $C_{11}H_{15}NO_3S$: 242.0851; found: 242.0852. The enantiomeric excess of ketone **8e** (>99%) has been determined by HPLC with a Chiralpak® AD column (hex/*i*-PrOH=90:10, 1 mL/min, T=25 °C), t_R=21.8 min.

4.5. Procedure for preparing β-amino hydroxylamines

Aluminum amalgam (48 mg) was added to a solution of the corresponding sulfinylnitroamine (0.12 mmol) in THF/H_2O (9:1) (11.7 mL). The reaction mixture was stirred at rt for 40 min whereupon it was filtrated through a short pad of Celite and the crude purified by flash chromatography (hex/EtOAc=1:2).

4.5.1. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-hydroxylamine-1-phenylpropylamine (9a). Yield: 63%; $[\alpha]_D^{20}$ +74 (*c* 1.7, $CHCl_3$); IR (film): 3251, 2100, 1650, 1492, 1455, 1087, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J=8.2 Hz, 2H), 7.42–7.32 (m, 7H), 5.49 (br d, J=2.8 Hz, 1H), 4.44 (dd, J=9.4 and 2.8 Hz, 1H), 2.97 (dq, J=9.4 and 6.5 Hz, 1H), 2.40 (s, 3H), 1.05 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 141.4, 140.3, 129.5, 128.6, 128.2, 128.0, 125.5, 61.5, 61.4, 21.3, 15.4; MS (FAB^+) *m*/*z*: 305.0 (M+1, 33), 106 (100), 57 (49); HRMS [M+1]: calcd for $C_{16}H_{20}N_2O_2S$: 305.1327; found: 305.1330.

4.5.2. (1*S*,2*R*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-hydroxylamine-1-phenylpropylamine (10a). Yield: 89%; $[\alpha]_D^{20}$ +78 (*c* 0.2, $CHCl_3$); IR (film): 3251, 1632, 1492, 1453, 1089, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J=8.2 Hz, 2H), 7.42–7.32 (m, 7H), 5.07 (br t, J=3.5 Hz, 1H), 4.95 (br d, J=3.1 Hz, 1H), 3.40 (dq, J=6.7 and 4.0 Hz, 1H), 2.43 (s, 3H), 0.69 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 141.7, 139.3, 129.7, 128.5, 127.6, 127.5, 125.4, 61.2, 57.4, 21.4, 10.8; MS (FAB^+) *m*/*z*: 305.0 (M+1, 39), 289 (55), 219 (26); HRMS [M+1]: calcd for $C_{16}H_{20}N_2O_2S$: 305.1323; found: 305.1322.

4.5.3. (3*S*,4*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-methyl-4-hydroxylamine-pentan-3-amine (9f). Yield: 48%; $[\alpha]_D^{20}$ +83 (*c* 0.9, $CHCl_3$); IR (film): 3352, 2089, 1645, 1492, 1464, 1087, 1045, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.30 (br d, J=6.9 Hz, 1H), 3.32–3.26 (m, 1H), 2.79 (dq, J=9.7 and 6.4 Hz, 1H), 2.41 (s, 3H), 1.89 (quind, J=6.8 and 2.5 Hz, 1H), 1.24 (d, J=6.4 Hz, 3H), 1.11 (d, J=6.81 Hz, 3H), 0.79 (d, J=6.7 Hz, 3H); MS (FAB^+) *m*/*z*: 271.2 (M+1, 46), 194 (100), 109 (17), 139 (21), 83 (43); HRMS [M+1]: calcd for $C_{13}H_{22}N_2O_2S$: 271.1486; found: 271.1495.

Acknowledgements

We thank the Spanish Government for financial support (Grants BQU2003-04012 and CTQ2005-07328).

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Local aromaticity study of heterocycles using *n*-center delocalization indices: the role of aromaticity on the relative stability of position isomers

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Received 15 August 2006; revised 23 September 2006; accepted 10 October 2006
Available online 30 October 2006

Abstract—A quantitative study on local aromaticity based on *n*-center electron delocalization indices, *n* being the number of atoms in the ring, is performed on a series of heterocycles containing N, O or S. The results indicate that the order of stability within a series of position isomers is not controlled by aromaticity but by other structural factors. Thus, for a certain series of monocycles position isomers (diazoles, triazoles, tetrazoles, diazines, triazines, and tetrazines) the most stable compound is the least aromatic one and vice versa. However, aromaticity controls the stability for series of isomers where these structural factors are similar. For the case of isocompounds, like isobenzopyrrole, isobenzofuran or isobenzothiophene, the large decrease in the aromaticity of the benzene ring with regard to their isomers makes them less stable.

1. Introduction

The concept of aromaticity was first introduced by Kekulé in 1865,[1] who related the 'extra stabilization' displayed by certain cyclic unsaturated compounds to a cyclic π electron delocalization. The most significant example of aromatic compound is benzene, the cyclic π electron delocalization of this compound, as it is well known, was represented by Kekulé as the coexistence of two equivalent valence structures, called since then Kekulé valence structures or Kekulé resonance structures.

Clar's rule, also known as π-sextets rule,[2,3] and Chemical Graph Theory (CGT) indices[4–18] are qualitative measures of the local aromaticity based on the Kekulé valence structures for polycyclic aromatic hydrocarbons (PAH's). Clar's rule states that the Kekulé valence structure with the largest number of disjoint aromatic π-sextets is the most important for the characterization of the properties of PAH's. Aromatic π-sextets are defined as six π-electrons localized in a single benzene-like ring separated from adjacent rings by formal C–C single bonds. The Clar's structure for a given PAH is the valence structure having the maximum number of isolated and localized aromatic π-sextets, with a minimum number of localized double bonds. It also indicates that the most aromatic rings are those displaying π-sextets at the Clar's structure. According to CGT, the local aromaticity is given by the quotient of the number of times a ring appears in all Kekulé valence structures as a benzene Kekulé ring and the number of Kekulé valence structures. Aromaticity indices so obtained were demonstrated to be a more quantitative description of Clar's rule.[18] For instance, Scheme 1 shows the Kekulé structures for phenanthrene, the Clar's structure (the π-sextets are indicated with a circle) and the values of the CGT indices, reflecting larger aromaticity for the outer rings.

The partitioning of the π electrons into individual rings using the 'numerical Kekulé valence structures', NKVS, has also been employed as an aromaticity index.[18,19] For a certain Kekulé structure the corresponding NKVS represents the number of π electrons within each individual ring (6, 3, and 5 according to the first Kekulé valence structure in Scheme 1). The number of π electrons of a certain ring is calculated by adding all the NKVS and dividing by the total number of Kekulé structures (26/5 and 18/5 for, respectively, outer and inner rings of phenanthrene). The larger the number of π electrons in the ring the larger is the local aromaticity.

Other indices of local aromaticity are based on quantitative measures. Most of them belong to two groups: structure based indices and magnetic-based indices. All of them were completely reviewed in two recent special issues of Chemical Reviews.[20] The most widely used magnetic-based index is the NICS (nucleus-independent chemical shift) index,[21] which is defined as the negative value of the shielding, computed at a ring center (NICS(0)) or at some other

Keywords: Aromaticity; Heterocycles; *n*-Center delocalization indices; Atoms in molecules.
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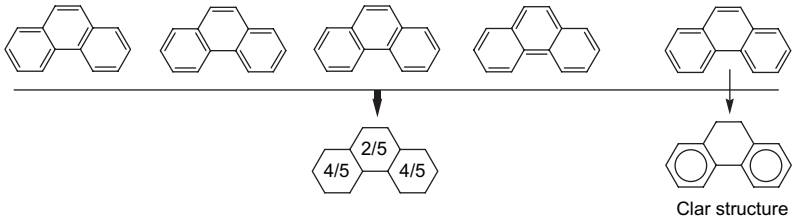
doi:10.1016/j.tet.2006.10.022



Scheme 1. Kekulé structure, the Clar's structure and the values of the CGT indices for phenanthrene.

interesting point of the system. For instance, the NICS(1) is computed at the distance of 1 Å above the ring center, where the π orbitals have their maximum density. For planar or nearly planar molecules, the influences of other magnetic shielding contributions different from the π system are reduced using NICS(1).[21]

The use of multicenter bond indices or *n*-center delocalization indices, *n*-DI's, as a measure of aromaticity in 5 and 6-center rings was initially proposed by Giambiagi et al.[22–25] They interpreted all the possible valence structures of benzene, including those of Kekulé, in terms of 6-center electron delocalization.[24,25] Since the *n*-DI measures the extension of the electron delocalization to *n* atoms, aromatic molecules are expected to display larger *n*-DI's than those of non-aromatic when they are computed for all atoms of the ring. *n*-DI's have been recently applied to study the total and local aromaticity of a large number of aromatic and antiaromatic systems.[26–32] In our previous work[32] we have compared indices derived from the *n*-DI's with the CGT indices, and the total and ring resonance energies, RE, calculated by the Conjugated Ring Circuits Model,[18,33–36] obtaining a very good agreement between qualitative and quantitative indices for polybenzenoid hydrocarbons. Overall, *n*-DI's are a quantitative representation of electron delocalization not influenced by other factors, contrary to what happens to magnetic indices (like NICS) and measure local aromaticity due to a certain ring current.[30,32] Moreover, they can be applied on any system, contrary to structural based indices, like HOMA's, or aromatic stabilization energies, which require a reference system that, for instance, make them not useful for transition states.

In this work, we study heterocyclic aromatic compounds, containing four-, five-, or six-membered rings with N, O, and S atoms. Our aim is to discuss the contribution of aromaticity to the relative stability for some series of positional isomers, showing that the small differences of aromaticity are less important than other structural factors, but in the absence of these factors aromaticity controls stability. These results are also in line with NICS(0) and NICS(1) values. However, one should be careful when using NICS, especially when studying systems that contain a different number of rings because they are not always straightforwardly related to local aromaticity.[30,37–39] We also show that *n*-DI's provide a quantitative interpretation of the qualitative predictions on local aromaticity based on CGT. To reach this conclusion, the values of the *n*-DI's are compared to the CGT indices and the ring π electron populations obtained from the NKVS.

Successful comparison of *n*-DI's with resonance energies of some of the molecules studied here has already been presented in our previous work.[31] We are not comparing *n*-DI's with isodesmic and homodesmotic aromatic stabilization energies as most of the molecules studied here contain heteroatoms. Recent studies[40,41] have evidenced some shortcomings in the calculation of strain energies employing these processes that are also expected to hold for the calculation of aromatic stabilization energies.

1.1. Calculation of *n*-DI's and computational details

Since the mathematical derivation of the *n*-center delocalization index via Generalized Population Analysis, GPA, in the context of Mulliken analysis[42] and QTAIM,[31] has been presented in previous papers, we are only showing the relevant expressions employed for its calculation. Thus, expanding the number of electrons of a molecule, *N*, in terms of the *n*-order spin free density matrix, the expressions 1 and 2 for the *n*-center electron delocalization are obtained within the framework of the QTAIM. $\Delta_n(A,B,\ldots,M)$ represents the electron population correlated along the *n*-centers, in other words, the delocalized-electron population among those *n* atoms. Thus, it is defined as the summation running over those permutations (denoted by *P*) of the *n* atoms *A*, *B*, …, *M* that provide different values of $\delta_n(A,B,\ldots,M)$, as defined by Eq. 2. The summation in $\delta_n(A,B,\ldots,M)$ is the '*n*-center electron delocalization term' assigned to every specific permutation. Permutations of the atoms in Eq. 2 provide different values when $n>3$ unless symmetry makes some of them equivalent.

The expressions 1 and 2 are strictly valid for mono-determinant wave functions, the MO's employed can be HF or Kohn–Sham (KS). Nevertheless, it has to be noticed that, for KS formalism, the mono-determinant wave function is an approximation to the real one. So that Eq. 2 is an approximation to the correct DFT delocalization index, which does not include electron correlation explicitly and corresponds to some effective independent particle model.[43]

$$\Delta_n(A,B,\ldots,M) = \sum_P \delta_n(A,B,\ldots,M) \tag{1}$$

$$\delta_n(A,B,\ldots,M) = 4n \sum_{i,j,k,\ldots,m}^{N/2} \langle i|j\rangle_A \langle j|k\rangle_B \cdots \langle m|i\rangle_M \tag{2}$$

We have studied a series of polycyclic aromatic molecules containing 1–3 rings (Fig. 1). In particular, 29 monocyclic, 23 bicyclic and 4 tricyclic compounds. All the bicycles and tricycles considered are formed by benzenoid rings fused to one of the monocycles studied. The nomenclature employed is an acronym where the first letter indicates whether the

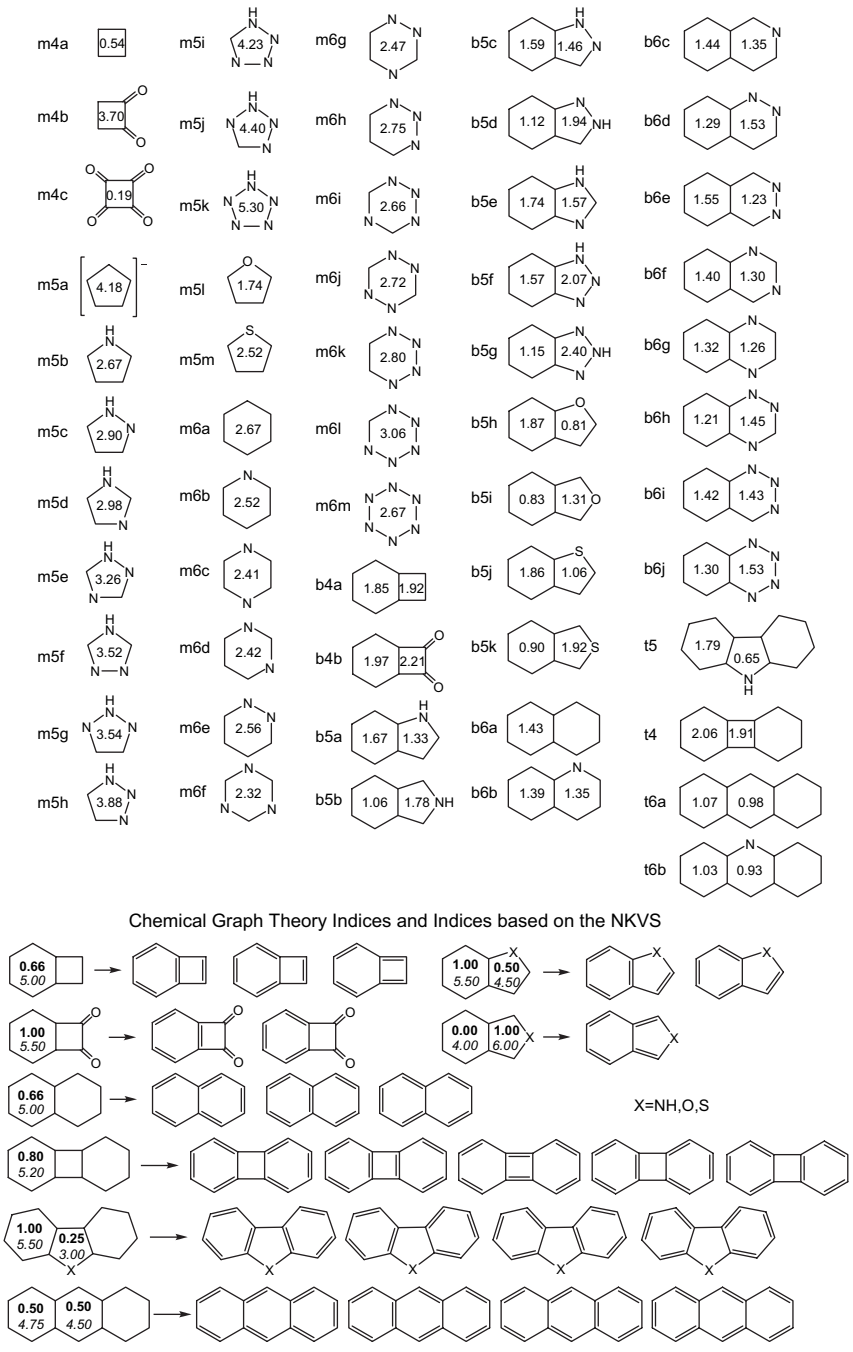


Figure 1. Molecular nomenclature and values of *n*-DI's (in au), CGT indices (in boldface) and ring π electron populations obtained from NKVS's (in italics).

molecule is monocyclic (m), bicyclic (b) or tricyclic (t); it is followed by a number indicating the number of centers in the non-benzenoid ring (except for benzene, naphthalene, and anthracene where all the rings are benzenoids), finally another letter is added to differentiate compounds.

The calculations were carried out on Kohn–Shan MO's computed at the B3LYP/6-311++G(d,p) level of calculation. The Gaussian 03 program[44] was employed to obtain the molecular geometries, energies and the MO's. The AIMPAC package of programs developed by Bader and co-workers[45] was used to integrate the Atomic Overlap Matrix (AOM) within the atomic domains. Our own program, NDELOC,[46] was used to compute the *n*-DI's according to Eqs. 1 and 2.

n-DI's can be rigorously split into σ and π contributions for planar molecules bearing always in mind that the zero-flux surfaces must be determined using the total electron density. We have found in previous studies on polycyclic aromatic hydrocarbons that the π contribution, π *n*-DI's, correspond to 95% of the total *n*-DI's for highly delocalized systems with $n \geq 5$.[31] Because of computational reasons, we have only calculated the π *n*-DI's but not the total *n*-DI's. The non-planar **m6m** molecule is an exception where the 6-DI value was calculated using all the occupied MO's. The accuracy of the QTAIM numerical integration was checked by comparing the summation of the AOM terms for a pair of MO's *i*,*j*, $\sum_A \langle i|j\rangle_A$, with the value of the overlap integral over the whole space, $\langle i|j\rangle$, which is expected to be 0. We

found that the differences between $\langle i|j\rangle$ and $\sum_A \langle i|j\rangle_A$ is less than 2×10^{-5} for all cases.

Several position isomers are included within the series of molecules studied, we have computed the relative energies of these isomers with regard to the most stable one, ΔE, and compared the results with their relative aromaticities. The structures were confirmed as energy minima, but the zero point vibrational energy correction (ZPVE) was not included in the calculation of ΔE since only electronic effects are going to be compared.

2. Results and discussion

2.1. Monoheterocycles

Figure 1 shows the molecules studied and the values of 4, 5, and 6-DI's computed for them. It has to be noticed that the direct comparison of *n*-DI's computed for rings with a different number of centers does not provide a picture of relative aromatic stabilization. In fact, aromatic stabilization does not only depend on the extension of the electron delocalization over the *n* centers, but also on the number of centers (see Ref. 31 for a detailed discussion). The fact that **m5a**–**m5k** molecules display much larger 5-DI's than the 6-DI of benzene cannot be interpreted as an indication as these five-membered rings are more aromatic than benzene. This is not a shortcoming affecting to this work as our goal is to compare the aromaticity and stability of isomers.

The monocyclic compounds **m4a**, **m4b**, and **m4c** display 4-DI values that can be justified by the well-known Hückel rule. Hence, the 4*n*-electron systems (**m4a** and **m4c**) are antiaromatic and therefore show very small 4-DI values, on the contrary the 4*n*+2-system (**m4b**) is aromatic and therefore shows a large 4-DI.

All the five centers and six electrons ([5c–6e]) monocycles studied here are aromatic and display large 5-DI's. The order of aromaticity indicated by 5-DI's follows some trends: (i) inclusion of heteroatoms decreases the aromaticity with regard to the cyclopentadienyl anion (**m5a**) in the order O>S≈N; (ii) in contrast, the inclusion of more and more N's in the pyrrole ring (**m5b**) increases the aromaticity up to reach values larger than that of **m5a** for systems with four (**m5i** and **m5j**) and five N's (**m5k**); (iii) for 5-center rings with the same number of N's the most aromatic ring is that having the largest number of N–N bonds, in the case of two compounds with the same number of N–N bonds the most aromatic is that having the smallest number of –N–N–H units.

[6c–6e] monocyclic polyazoles (**m6b**–**m6m**) are all planar but **m6m**, which presents a twisted-boat geometry due to the important electron–electron repulsion between N-lone pairs. 6-DI's calculated for this series indicate that insertion of N atoms decreases the aromaticity unless they form N–N bonds. Thus, we observe Δ_6(**m6a**)>Δ_6(**m6b**)>Δ_6(**m6c**)≈Δ_6(**m6d**)>Δ_6(**m6f**) for compounds with increasing number of nitrogens with no N–N bond. The same trend holds for series where N atoms are inserted in rings with one N–N bond: Δ_6(**m6e**)>Δ_6(**m6g**), and two N–N bonds: Δ_6(**m6h**)>Δ_6(**m6i**) (Fig. 1). On the contrary, progressive formation of N–N bonds increases Δ_6 values, thus: Δ_6(**m6b**)<Δ_6(**m6e**)<Δ_6(**m6h**)<Δ_6(**m6k**)<Δ_6(**m6l**). This series breaks for **m6m**, whose Δ_6 is equivalent to that of benzene. Nevertheless, this can be expected from its non-planar geometry, which decreases the effective π overlapping.

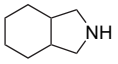
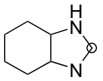
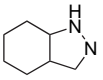
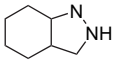
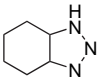
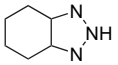
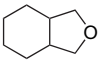
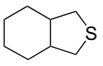
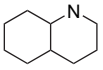
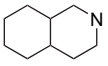
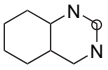
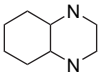
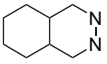
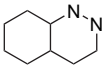
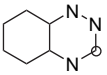
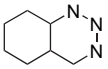
Table 1 also collects the values of the B3LYP/6-311++G(d,p) relative energies of position isomers in the series. It shows that the order of stability is reversed with regard to the order of aromaticity. Thus, in the series of diazoles (**m5c** and **m5d**), triazoles (**m5e**–**m5h**), tetrazoles (**m5i** and **m5j**), diazines (**m6c**–**m6e**), triazines (**m6f**–**m6h**), and tetrazines (**m6i**–**m6k**) the most stable compound is the least aromatic one and vice versa. The fact that the most stable isomer is not necessarily the most aromatic was already discussed by Havenith et al.[47] This trend is supported by values of NICS(0) and NICS(1) calculated by Schleyer et al.[21] for the same compounds, if we exclude diazoles and diazines. Thus, NICS(0) and NICS(1) indicate that the most aromatic isomer is the most stable for diazoles, whereas for diazines the most stable isomer is the most aromatic using NICS(0) but the contrary is found using NICS(1).[21] Also, particular cases are observed for NICS(0) values in the series of triazines and tetrazines; i.e., according to NICS(0) the least stable is the most aromatic but the most stable does not correspond to the least aromatic isomer. Summarizing, the order of stability seems not to be controlled by the aromaticity but other structural factors. Thus, aromaticity is just a small stabilizing factor compared to other destabilizing factors.

The relative energies of isomers shown in Table 1 point out that three structural factors are of main importance for the stability: (i) N–N bonds destabilize the energy of diazines and diazoles, thus the most stable isomer is that showing the smallest number of N–N bonds; (ii) N–N bonds where none of the nitrogens is attached to a hydrogen destabilize more than –N–N–H units for azoles, as can be seen from the relative energies of the following pairs of isomers: **m5e/m5f**, **m5g/m5h**, and **m5j/m5i**; (iii) the –N–C–N–C– structure is more stabilizing than the –N–C–C–N– one and the –N–N–N– unit is less destabilizing than the presence of two N–N bonds for azines, look for instance at the pairs **m6c/m6d** and **m6i/m6j**. A simple qualitative rule that summarizes the relative stability of the isomers of azoles and azines can be derived from (i), (ii), and (iii). The larger the number of –N–C–N– units (marked in Table 1 with an open circle on the C atom) the larger is the stability of the compound. When two isomers present the same number of –N–C–N– units, the most stable is that showing the largest number of –N–N–H units for azoles and –N–N–N– units for azines.

2.2. Polyheterocycles

The *n*-DI's computed for this series agree perfectly with aromaticity indices based on CGT (Fig. 1). Thus, CGT indices and the ring π electron populations obtained from the NKVS (also included in Fig. 1) suggest that the local aromaticity of the benzene ring is larger in **b4b** than in **b4a**. Moreover, CGT indices and NKVS's suggest a large decrease on the local aromaticity of benzene rings fused to five-membered

Table 1. Relative energies (in kcal mol^{-1}) for the series of isomers drawn in Figure 1

m5d		0.0	**b5a**		0.0
m5c		10.6	**b5b**		9.1
m5e		0.0	**b5e**		0.0
m5f		6.8	**b5c**		14.6
m5g		12.7	**b5d**		19.5
m5h		17.4	**b5g**		0.0
m5j		0.0	**b5f**		0.2
m5i		2.9	**b5h**		0.0
m6d		0.0	**b5i**		14.4
m6c		4.1	**b5j**		0.0
m6e		23.0	**b5k**		11.0
m6f		0.0	**b6b**		0.0
m6g		27.3	**b6c**		1.2
m6h		44.0	**b6f**		0.0
m6i		0.0	**b6g**		3.1
m6j		7.1	**b6e**		23.0
m6k		20.9	**b6d**		24.1
			b6h		0.0
			b6i		16.3

Open circles indicate –N–C–N– units (see text for details).

rings in isocompounds, like isobenzopyrrole (**b5b**), isobenzofuran (**b5i**), and isobenzothiophene (**b5k**) (Fig. 1), with regard to the corresponding non-isocompounds. In contrast, the local aromaticity of the corresponding five-membered ring increases from non-iso to isocompounds. This qualitative expectation is confirmed by the values of the 6-DI's and 5-DI's of the series comprising from **b5a** to **b5k**. Also, the values of the NICS(0) and NICS(1) for benzopyrrole, benzofuran, benzothiophene, and the corresponding isocompounds confirm this trend.[21] However, Martínez et al.[48] reported NICS values that showed the opposite trend for the same molecules. It seems that they mistook the values of the six-membered rings for the five-membered rings.

The qualitative character of CGT indices and NKVS's does not allow distinguishing the local aromaticity of the two six-membered rings fused in the **b6a–b6j** series. This trend is not changed by the presence of N atoms. On the contrary, 6-DI's show small differences among the rings (Fig. 1). These differences can be explained considering the different weight of Kekulé valence structures; the one with the smallest number of N=N formal double bonds being the most important. Thus, when this structure does not display a π-sextet on the benzene ring, the aromaticity of the benzene ring decreases and that of the nitrogenated ring increases (**b6d**, **b6h**, and **b6j**). The contrary is found for **b6e**, where the benzene ring shows the largest local aromaticity of the series. As for the remaining molecules of the series, there is no favored Kekulé valence structure on the basis of the number of N=N formal double bonds. The same trend is followed by NICS(0) and NICS(1) values calculated by Schleyer et al.[21] For instance, NICS(0) for the benzene ring of **b6d** and **b6e** are, respectively, −8.76 and −9.93, and NICS(1) are −10.85 and −11.28. Moreover, the opposite trend is displayed by the nitrogenated rings, the NICS(0) values are, respectively, −6.81 and −5.61 for **b6d** and **b6e**, and the NICS(1) are −11.50 and −10.13.

6-DI's and 5-DI's are also in good agreement with CGT indices and NKVS's for tricyclic compounds. Thus, the most aromatic benzenoid rings correspond to **t4** and **t5**, where all the Kekulé valence structures display π-sextets on these rings. The valence structure of **t4** where the benzenoid and cyclobutadiene rings display 4π electrons is the only exception. However, this valence structure is expected to have a very small weight for obvious reasons. As CGT Indices do not consider different weights for valence structures, the local aromaticity they reflect for the benzenoid rings of **t4** is smaller than those of **t5**. On the other hand, the 5-DI of pyrrole ring in **t5** shows an important decrease in aromaticity as expected from CGT indices. **t6a** and **t6b** are other examples of good agreement between qualitative and quantitative indices. Thus, 6-DI's are quite similar between outer and inner rings but slightly larger for the former. The ring π electron populations obtained from NKVS's display the same trend. However, NICS(0) and NICS(1) values show larger aromaticity for the inner rings in **t6a** and **t6b**.[49] The reasons for discrepancies displayed by different indices (like PDI, HOMA, ring critical points, ring currents, circuit resonance energies, etc.) about the local aromaticity in linear polyacenes have been extensively discussed in a series of recent articles.[30–32,50]

Finally, the relative energies of series of bicyclic isomers are also collected in Table 1. Contrary to that found for monocyclic compounds, the effect of aromaticity on the stability of different isomers can be noticed in the absence of other significant structural factors. Thus, the pairs **b5a/b5b**, **b5j/b5k**, and **b5h/b5i** display energies that are 9.1, 11.0, and 14.4 kcal mol^{-1} higher for the iso-compounds. These relative energies follow the same trend as the differences on the

6-DI's of the benzene ring, the most aromatic ring of both. Moreover, the relative energy increases as the aromaticity of the five-membered ring decreases (see values of 5-DI's for pyrrole, furan, and thiophene). The pair **b5c/b5d** is another example for the influence of aromaticity. In this case, the energy of the iso-compound is 4.9 kcal mol^{-1} higher. The relative energies of the remaining isomers can be explained by the same rules as stated above for monocyclic compounds.

3. Conclusions

n-DI's have been employed to study the local aromaticity of heterocycles containing –N, –O, and –S quantitatively, as well as the corresponding polyheterocycles formed by fusing benzene rings to one of them. The values of the *n*-DI's are in agreement with the qualitative interpretation of the local aromaticity provided by the Chemical Graph Theory. In addition, *n*-DI's provide information about the aromaticity changes arising from the substitution of C's by N's in benzene rings. According to the *n*-DI's we can get the following conclusions:

(i) The aromaticity of five-membered rings is reduced by the inclusion of a heteroatom (O>S≈N). However, the inclusion of more and more N atoms in the pyrrole ring increases the aromaticity reaching values larger than that of cyclopentadienyl anion for 4- and 5-nitrogen systems.
(ii) For 5- and 6-center rings with the same number of nitrogens the most aromatic ring is that having the largest number of N–N bonds.
(iii) The order of stability within a series of position isomers is not controlled by aromaticity but by other important structural factors as the increase of intramolecular electrostatic repulsions. Thus, for certain series of monocycles position isomers (diazoles, triazoles, tetrazoles, diazines, triazines, and tetrazines) the most stable compound is the least aromatic one and vice versa. However, aromaticity controls the stability for series of isomers where these structural factors are constant. For the case of isocompounds, like isobenzopyrrole, isobenzofuran or isobenzothiophene, the large decrease of the aromaticity of the benzene ring with regard to their isomers makes them less stable. NICS(0) and NICS(1) indices are in line with these results.

Acknowledgements

We thank 'Centro de Supercomputación de Galicia' (CESGA) for access to its computational facilities. N.O. thanks 'Universidade de Vigo' for a post graduated fellowship. Helpful discussion with Dr. M. J. González Moa is deeply acknowledged.

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Tetrahedron
Tetrahedron 62 (2006) 12211–12219

Musk or violet? Design, synthesis and odor of *seco*-derivates of a musky carotol lead

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Received 14 August 2006; revised 8 October 2006; accepted 10 October 2006
Available online 3 November 2006

Dedicated with best wishes to Professor Georg Fráter on the occasion of his 65th birthday

Abstract—By a six-step synthetic route consisting of a Li_2MnCl_4-catalyzed coupling of branched alkyl magnesium chlorides with isovaleryl and 3,3-dimethylbutanoyl chloride, Grignard reaction of the product with ethynyl magnesium bromide, dehydration and transformation into a Grignard reagent, subsequent reaction with acetaldehyde, (*E*)-selective hydrogenation of the alkynol triple bond with lithium aluminum hydride, and finally pyridinium chlorochromate oxidation, four sterically highly demanding target structures were synthesized diastereoselectively. These four molecular targets were designed as *seco*-structures to a musky carotol lead, and their olfactory profiles that merge violet like with musky notes to different extents, provide interesting insight into structure–odor correlation.

1. Introduction

In the course of work for his master thesis on carotol derivatives in the late 1960s in the laboratory of Professor Janusz Kulesza in Lodz, Józef Kula discovered an interesting new musk odorant. Ozonolysis of carotol with subsequent intramolecular aldol condensation and dehydration of the resulting intermediate dihydroxy ketone afforded a product mixture imparting a pleasant musky scent.[1,2] They believed this scent to originate from its main compound to which they assigned structure **1** and named 'mageritone' (Fig. 1).[1] Over 30 years later however, Józef Kula, having become a professor at the University of Lodz, revisited this chemistry with his group and found mageritone **1** to have only a weak and uncharacteristic smell.[2,3] The actual cause of the musk odor of that mageritone-containing product mixture was the isomeric dienone **2**, which was present at a concentration of less than 5%. The odor and structure of this tetrahydroindene **2** was proven by a directed partial synthesis with isomerization of the double bond catalyzed by Pd/C in refluxing cyclohexene.[3] It was characterized as emanating a dry musky odor with a threshold of around 1 ng/L air.[2]

Already in the early 1960s, Kazimir Sestanj[4] discovered that the *seco*-structure **3**, in which the two carbon atoms C-2 and C-3 were cut out of the β-ionone ring,[5] retained all important odor characteristics of β-ionone. He reported two synthetic routes to **3**, the first one of which commenced with a Reformatsky reaction of ethyl 2-bromo-3-methylbutanoate with triethyl *ortho*-formiate, followed by Grignard reaction with methyl magnesium iodide, hydrolysis, and aldol condensation of the intermediate aldehyde with acetone.[4] The second approach started from 3-isopropyl-4-methylpent-1-yn-3-ol that was transformed into its acetate by reaction with ketene, which was then rearranged by silver-catalyzed Saucy–Marbet reaction[6] to the corresponding aldehyde. Grignard reaction with acetylene magnesium bromide and Rupe rearrangement of the resulting 5-isopropyl-6-methylhept-4-en-1-yn-3-ol at 50 °C in formic acid concluded his second synthesis of **3**.

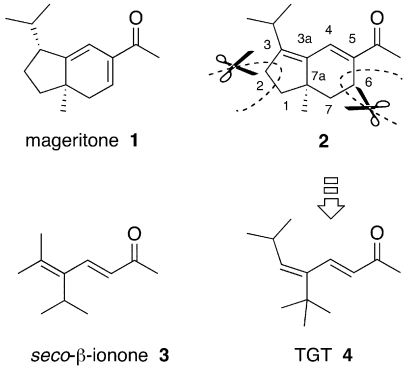

Figure 1. Mageritone (**1**), the *seco*-β-ionone of Sestanj (**3**), and the first target structure **4**, devised as a *seco*-structure to the musk odorant **2**.

Keywords: Alkynols; Carotol; Chemoselective hydrogenation; Ionone odorants; Odor–structure correlation; *seco*-Derivatives.
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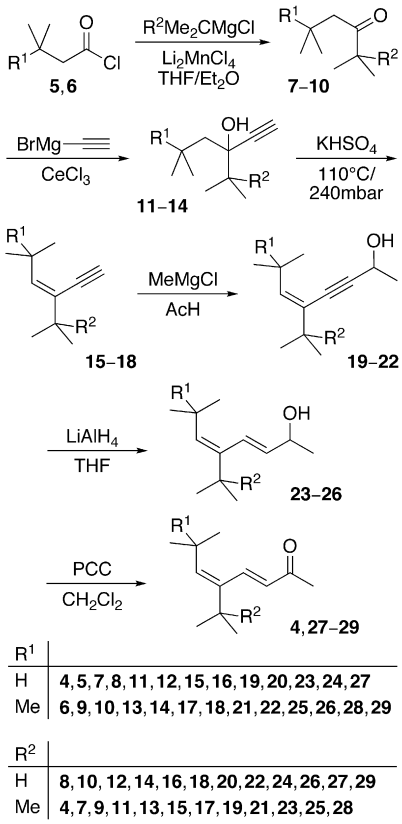
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.020

With the structural features and the odor characteristics of Sestanj's *seco*-β-ionone **3** in mind, the question arises as to what would be the odor of a *seco*-structure of the carotol derivative **2**, in which C-2 and C-6 were cut out from the 2,6,7,7a-tetrahydro-1*H*-inden-5-yl system. This target compound **4** (Fig. 1) should sterically mimic the musk odorant **2**, but would at the same time structurally resemble the truncated ionone **3**: Would the target molecule **4** thus smell musky or violet like? Or better still, can one construct in this way an odorant that would combine aspects of both primary odor notes? And finally, how would the exchange of a *tert*-butyl by an isopropyl group and vice versa or, in other words, how would the bulkiness of the substituents affect the odor character and intensity? In the following, these questions are addressed with the synthesis of **4** as well as of three additional derivatives **27–29** (Scheme 1), in which *tert*-butyl and isopropyl groups are permuted.



R^1	
H	**4,5,7,8,11,12,15,16,19,20,23,24,27**
Me	**6,9,10,13,14,17,18,21,22,25,26,28,29**

R^2	
H	**8,10,12,14,16,18,20,22,24,26,27,29**
Me	**4,7,9,11,13,15,17,19,21,23,25,28**

Scheme 1. Synthesis of the target structures **4** and **27–29** from isovaleryl and *tert*-butylacetyl chloride.

2. Results and discussion

Due to the severe steric hindrance of the *tert*-butyl and isopropyl groups, the synthesis of target compound **4** turned out to be far more difficult than anticipated. Attempts to introduce the *tert*-butyl group by reacting the Wittig–Horner reagent of Lee and Wiemer[7] with isopropyl methyl ketone failed utterly, and the aldol condensation of the lithium enolate of ethyl 3,3-dimethylbutanoate with isopropyl methyl ketone also proved unsuccessful. Even all attempts to prepare aldol adducts by treatment of ethyl 2-acetyl-3,3-dimethylbutanoate with isopropyl lithium, and ethyl 2-*tert*-butyl-4-methyl-3-oxopentanoate with methyl lithium were to no avail. Thus, we finally decided to employ acetylene chemistry, just as Sestanj[4] had with his symmetric system. We decided, however, against a Rupe rearrangement in the final step, as yields are often low and Sestanj[4] did not report one for this step. Most importantly, however, we wanted to control the geometry of both double bonds of the target structure **4** and its derivatives **27–29** throughout the entire synthetic sequence.

To ensure the (3*E*)-configuration of the double bond in conjugation with the carbonyl group in the target structures **4** and **27–29**, the partial reduction of 2-alkynols[8] with lithium aluminum hydride was envisaged, followed by subsequent oxidation of the resulting allylic alcohols. This partial hydrogenation was discovered by Chanley and Sobotka in 1949,[8a] and it proceeds in a completely *trans*-selective manner as was rationalized by mechanistic studies.[9] More recently, this method had also been employed in a muscone synthesis of Thies and Daruwala[10] by siloxy-Cope ring expansion. The oct-5-en-3-yn-2-ols required as substrates for the partial hydrogenation with lithium aluminum hydride were projected to be prepared following the route recently reported by us in the synthesis of *seco*-theaspiranes.[11] The entire synthetic sequence is delineated in Scheme 1, and starts from isovaleryl (**5**) and *tert*-butylacetyl chloride (**6**), respectively, which are both commercially available.

In the synthesis of our first and principal target molecule **4**, isovaleryl chloride (**5**) was coupled with *tert*-butyl magnesium chloride applying the manganese-catalyzed acylation reaction developed by Cahiez and Laboue.[12] In the presence of the soluble ate complex Li_2MnCl_4, prepared by mixing manganese(II) chloride with 2 equiv of lithium chloride at room temperature,[13] 2,2,5-trimethylhexan-3-one (**7**) was obtained in 53% yield after 4.5 h of reaction at 0 °C and room temperature, standard workup, and purification by distillation in vacuo.

The construction of the but-3-yn-2-ol side chain was next on the agenda, and to avoid protecting groups to selectively eliminate one hydroxy group only, it was decided to carry this out stepwise by a procedure developed by us in the synthesis of *seco*-theaspiranes:[11] Instead of employing the Grignard reagent prepared from but-3-yn-2-ol and 2 equiv of ethyl magnesium bromide, ketone **7** was to be reacted with acetylene magnesium bromide, then transformed to a Grignard reagent itself and reacted with acetaldehyde. The intermediary tertiary carbinol **11** could then be dehydrated without any selectivity issue. In addition, we had observed[11] that the reaction with acetylene magnesium bromide was far less prone to sterical hindrance than the analogous one with the Grignard reagent of but-3-yn-2-ol. Thus, we were rather astonished to find that the sterically crowded ketone **7** did not react with acetylene magnesium bromide at room temperature or in refluxing THF. However, in the presence of stoichiometric amounts of cerium chloride as introduced for sterically hindered ketones by Imamoto et al.,[14] the Grignard reaction with ethynyl magnesium bromide went smoothly, even at room temperature albeit not exothermic. After quenching with aqueous ammonium chloride, extraction and chromatographic purification furnished the desired *tert*-butyl ethynyl carbinol **11** in excellent 68% yield.

Tertiary alcohols could dehydrate following an E1 or E2 mechanism, and only the latter leads to a well-defined double-bond geometry. As the bulky *tert*-butyl and the isopropyl groups tend to adopt *anti*-periplanar conformations with respect to one another, an *anti*-selective E2 dehydration should provide the desired *Z*-configured enyne product **15**, and these reactive conformations should also favor an E2 mechanism over the E1 alternative. A quick conformational search (MMFF/PM3) indicated the first conformer of **11** to lead to *E*-geometry by *anti*-selective E2 elimination to be disfavored by 2.47 kcal/mol, so we were confident of a good selectivity. Heating the *tert*-butyl ethynyl carbinol **11** in a Kugelrohr apparatus to 110 °C/240 mbar in the presence of potassium hydrogen sulfate with trapping of the evaporating product in a cold trap at −78 °C indeed provided exclusively the desired *Z*-configured product **15** as was established by a NOESY experiment on the first target structure **4** (vide infra). Therefore, no special *anti*-selective dehydration reagents, such as Martin's sulfurane,[15] were required.

The isomerically pure (*Z*)-3-*tert*-butyl-5-methylhex-3-en-1-yne (**15**) thus obtained in 54% yield after flash chromatography was then transformed into the corresponding Grignard reagent by reaction with methyl magnesium chloride. Addition of acetaldehyde, refluxing the resulting reaction mixture overnight, quenching with aqueous ammonium chloride, and the usual workup with chromatographic purification furnished the first alk-5-en-3-yn-2-ol intermediate **19** in 85% yield. The stage was thus set for the crucial (*E*)-selective partial reduction of the triple bond according to the method of Chanley and Sobotka.[8] Carrying out this reaction proved as easy as analogous hydride reductions of ketones, and (*Z*)-5-*tert*-butyl-7-methyloct-5-en-3-yn-2-ol (**19**) was simply added dropwise into a stirred suspension of 1 equiv of lithium aluminum hydride in THF. After heating to reflux for 3 h, the reaction was quenched with water and aqueous sodium hydroxide. The standard workup procedure then afforded alka-3,5-dien-2-ol **23** in an excellent 80% yield as one single diastereoisomer, which was deduced from the assignment of the target structure **4** to be also (3*E*,5*E*)-configured.

All that was missing for the completion of the first target molecule **4** was the oxidation of the allylic hydroxy function to a carbonyl group, for which a full panoply of oxidation reagents is available, including activated manganese dioxide, first employed by Ball et al.[16] for the oxidation of vitamin A, also a polyunsaturated allylic alcohol. Yet manganese dioxide oxidations are generally slow, and we decided to employ pyridinium chlorochromate on Celite®,[17] instead, which we found most versatile and convenient to use.[11,17b] And once more this reagent system worked very well, and the corresponding ketone **4** was obtained as a colorless odoriferous liquid in 73% yield after simply filtering off the insoluble materials and chromatography of the resulting residue on silica gel. Strong and distinct crosspeaks between 6-H and the protons of the *tert*-butyl group, as well as between 4-H and all seven protons of the isopropyl moiety in the ^{1}H–^{1}H NOESY experiment unequivocally proved the intended (3*E*,5*E*)-configuration of our first target structure **4**. Most gratifyingly, however, the scent of ketodienone **4** also met our high expectations in that it combined characteristics of violet and musk odorants, two independent families of primary odorants with no known olfactory overlap. The intense woody-musky odor of the first target structure **4** was reminiscent of the violet-woody odor of β-ionone as much as of the woody-musky odor of Cashmeran® [6,7-dihydro-1,1,2,3,3-pentamethyl-4(5*H*)-indanone],[2,18] with fruity facets in the direction of raspberries. Impressive was also the odor threshold of 0.66 ng/L air that was measured by us for the new odorant **4**. Hence, it is only slightly weaker than the best benchmarks of both the musk,[2] ionone,[19] and irone[20] family, and better than many commercial odorants.

Incited by the interesting olfactory properties of the ketodienone **4** as well as by the short synthetic route to these sterically crowded structures, it was desired to study the scope of the synthetic sequence and the importance of the bulky groups on the odor characteristics. The *tert*-butyl and isopropyl groups should therefore be systematically permuted, which amounted to the synthesis of the three additional structures **27**–**29**.

Employing the manganese-catalyzed acylation detailed above, isovaleryl (**5**) and 3,3-dimethylbutanoyl chloride (**6**) were coupled with isopropyl (for **8** and **10**, respectively) and *tert*-butyl magnesium chloride (in case of **9**), and the corresponding methylhexan-3-ones **8**–**10** were obtained in 51–52% yield. These were all submitted in the next step to the cerium chloride-mediated Grignard reaction with ethynyl magnesium bromide at room temperature, which yielded after workup and chromatographic purification the acetylene alcohols **12**–**14** in 71–76% yield. Dehydration of these alcohols **12**–**14** with potassium hydrogen sulfate at 110 °C/240 mbar followed in all cases an *anti*-selective E2 mechanism as was proven by NOESY experiments on the final products **27**–**29**, and the hex-3-en-1-ynes **16**–**18** were isolated in 37–52% yield after chromatography. Transfer Grignard reaction with methyl magnesium chloride, followed by reaction of the resulting Grignard reagent with acetaldehyde, then provided in 76–83% yield the sterically demanding alkynols **20**–**22**. The subsequent partial reduction of these oct-5-en-3-yn-2-ols **20**–**22** with lithium aluminum hydride went smoothly, and the exclusively (3*E*)-configured products **24**–**26** were isolated in excellent 80–83% yield. The synthesis of the three additional target structures was completed with the pyridinium chlorochromomate oxidation of the allylic alcohols **24**–**26** that provided the highly methyl-substituted octa-3,5-dien-2-ones **27**–**29** in 70–75% yield as colorless odoriferous liquids. In all cases, the geometry of both double bonds was unambiguously determined by distinct NOE crosspeaks between the hydrogen atoms of the methyl groups and 4-H and 6-H, respectively (see Section 4 for details).

3. Olfactory evaluation and conclusions

Interestingly, the odor of the octa-3,5-dien-2-one target structures **4** and **27**–**29** critically depends on the steric bulk of the substituents. The smallest representative **27** with a diisopropyl substituted Δ^5 double bond was the weakest odorant of the series, with an odor threshold as high as 251 ng/L air (Fig. 2). Its odor does not resemble musks or ionones; instead it emanates a vague woody-fruity odor

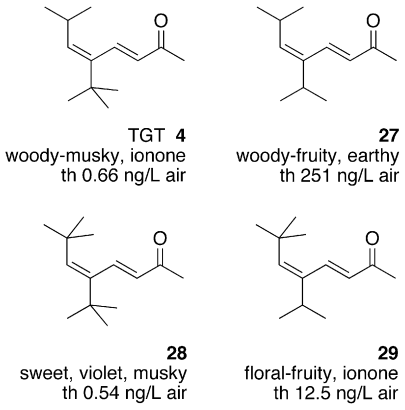


Figure 2. Comparison of the target structures **4** and **27**–**29** concerning the odor character and threshold.

with earthy and rooty nuances. Replacement of the 5-isopropyl group by a *tert*-butyl substituent gives the original target structure **4**, with its well-balanced woody-musky Cashmeran® and typical violet-raspberry β-ionone characters. And this striking shift in the odor character from **27**→**4** coincides with an almost 400-fold intensity gain in odor threshold. Upon replacement of the second isopropyl group of compound **4** by a *tert*-butyl moiety the good odor threshold of 0.66 ng/L air even improved further slightly to 0.54 ng/L air, measured for the di-*tert*-butyl derivative **28**. Both the musk and the violet notes of the original target structure **4** were retained in odorant **28**. In comparison, the violet note of **28** was described as sweeter but less fruity as that of **4**, devoid of a pronounced raspberry tonality, while the musky side of **28** had also a woody character as in Cashmeran®, but different from **4** exhibited also slightly camphoraceous and agrestic facets. If the 5-*tert*-butyl moiety of this musk odorant **28** is replaced by an isopropyl group, the musk character disappears completely, while the fruity, raspberry side reappears. So, target structure **29** can be considered entirely an ionone odorant. Its floral-fruity odor of violets and raspberries resembles those of α-irone and β-ionone; yet, with 12.5 ng/L air, the *seco*-structure **29** is about 100 times weaker than β-ionone (0.12 ng/L air)[19] in terms of odor threshold.

These data impressively demonstrate the importance of hydrophobic volumes on both odor character and intensity, and show how one can fine-tune olfactory properties with only slight structural changes. With perhaps the exception of **27**, our design concept of new *seco*-structures devised from the carotol musk odorant **2** and the truncated β-ionone structure **3** worked out well. In terms of overall olfactory performance, the original target structure **4**, however, remained the best, which highlights once again the significance of the shape similarity in odorant design.

The synthetic hurdle in the preparation of these highly branched systems was tackled by simple and industrially applicable Grignard reactions from the ketones **7**–**10**, which are themselves easily accessible by Li_2MnCl_4-catalyzed Grignard reactions on the acid chlorides **5** and **6**. The chemoselective hydrogenation of **19**–**22** employing lithium aluminum hydride was however crucial for the success of this efficient strategy, which opens up a general and stereodefined access to numerous polyene systems.

4. Experimental

4.1. General methods

All reactions were performed under nitrogen atmosphere, unless otherwise stated. Starting materials, reagents, and solvents were purchased from SAFC, Acros or Alfa Aesar, and used without further purification. Anhyd cerium(III) chloride was prepared by heating the heptahydrate for 3 h at 140 °C/0.2 mbar. Merck silica gel 60 (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical TLC was performed on precoated Merck silica gel 60 F_{254} plates on glass, and the products were visualized with phosphomolybdic acid. Attenuated-total-reflection IR spectra were recorded on a Bruker VECTOR 22 with Harrick SplitPea micro ATR unit. ^{1}H and ^{13}C NMR spectra were measured either with a Bruker AVANCE DPX-400 or an AVANCE 500 TCI spectrometer. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra were recorded with a Finnigan MAT 95 or on a HP Chemstation 6890 GC/5973 with mass sensitive detector. The Mikroanalytisches Laboratorium Ilse Beetz in 96301 Kronach, Germany, performed the elemental analyses. The odor thresholds are geometrical means of individual thresholds that were determined by GC-olfactometry injecting different dilutions of sample substance into a gas chromatograph in descending order of concentration until the panelists failed to detect an odor at the correct retention time.

4.2. Preparation of compounds 4 and 7–29

4.2.1. 2,2,5-Trimethylhexan-3-one (7). Between 0 and 2 °C, a *tert*-butyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol) was added within 3 h to a stirred mixture of isovaleryl chloride (**5**, 121 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL, prepared according to Ref. 13) in THF (1 L). The resulting reaction mixture was stirred for additional 30 min at 0 °C, and then for 1 h at room temperature. Water (700 mL) was added dropwise with stirring, and the aqueous layer was extracted with Et_2O (2×500 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator at 42 °C/100 mbar. The resulting residue was purified by distillation in a 10-cm Vigreux assembly to afford the title compound **7** at 46–48 °C/6 mbar. Yield 53% (75.4 g); colorless liquid; IR (neat, cm^{-1}) 1704 (ν C=O), 1467 (δ_{as} CH_3), 1365 (δ_s CH_3); ^{1}H NMR ($CDCl_3$, ppm) δ 0.89 (d, J=7.0 Hz, 6H, 5-Me_2), 1.12 (s, 9H, 2-Me_3), 2.16 (sept, J=7.0 Hz, 1H, 5-H), 2.35 (d, J=7.0 Hz, 2H, 4-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 22.5 (q, 5-Me_2), 23.9 (d, C-5), 26.2 (q, 2-Me_3), 44.0 (s, C-2), 45.4 (t, C-4), 215.3 (s, C-3); MS (EI, %) *m*/*z* 142 (6) [M^+], 85 (38) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$], 43 (8) [$C_3H_7^+$].

4.2.2. 3-*tert*-Butyl-5-methylhex-1-yn-3-ol (11). In one dash, a soln of **7** (48.4 g, 340 mmol) in THF (400 mL) was added at 0 °C to anhyd cerium(III) chloride (83.3 g, 340 mmol), and the suspension was stirred at room temperature for 5 h. The resulting viscous slurry was added at ambient temperature dropwise with stirring over a period of 30 min to a soln of ethynyl magnesium bromide in THF (0.5 M, 1020 mL, 510 mmol), upon which no temperature rise was observed. The reaction mixture was stirred at room temperature overnight, quenched with satd aq NH_4Cl (800 mL) and

extracted with Et_2O (3×400 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography on silica gel furnished the title compound **11**. Yield 68% (38.9 g); yellowish oil; R_f 0.30 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3489 (ν O–H), 3308 (ν C≡C–H), 1467 (δ_{as} CH_3), 1366 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.02 (s, 9H, 1′-Me_3), 1.02–1.04 (2d, J=7.0 Hz, 6H, 5-Me_2), 1.42 (dd, J=14.0 and 7.5 Hz, 1H, 4-H_a), 1.58 (dd, J=14.0 and 5.0 Hz, 1H, 4-H_b), 1.83 (br s, 1H, OH), 2.07 (dseptd, J=7.5, 7.0 and 5.0 Hz, 1H, 5-H), 2.45 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.1/24.7 (2q, 5-Me_2), 24.9 (q, 1′-Me_3), 25.5 (d, C-5), 38.8 (s, C-1′), 43.4 (t, C-4), 73.6 (d, C-1), 77.1 (s, C-3), 85.9 (s, C-2); MS (EI, %) m/z 153 (4) [M^+-CH_3], 111 (70) [$M^+-C_4H_9$], 70 (49) [$C_5H_{10}^+$], 57 (93) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.3. (*Z*)-3-*tert*-Butyl-5-methylhex-3-en-1-yne (15). In a Kugelrohr apparatus, the alkynol **11** (34.2 g, 203 mmol) was heated to 110 °C/240 mbar in the presence of $KHSO_4$ (5.53 g, 40.6 mmol) for 3 h, with the evaporating product mixture being trapped in a bulb cooled to −78 °C. This crude product was purified by flash chromatography on silica gel to provide the title compound **15**. Yield 54% (16.5 g); colorless liquid; R_f 0.57 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3312 (ν C≡C–H), 1461 (δ_{as} CH_3), 1362 (δ_s CH_3), 955 (δ C≡C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.98 (d, J=7.0 Hz, 6H, 5-Me_2), 1.08 (s, 9H, 1′-Me_3), 2.87 (dsept, J=9.5 and 7.0 Hz, 1H, 5-H), 3.11 (s, 1H, 1-H), 5.57 (d, J=9.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.4 (q, 5-Me_2), 29.1 (q, 1′-Me_3), 29.8 (d, C-5), 34.9 (s, C-1′), 81.4 (s, C-2), 81.8 (d, C-1), 129.7 (s, C-3), 142.3 (d, C-4); MS (EI, %) m/z 150 (20) [M^+], 107 (36) [M^+-CH_3], 93 (42) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$], 43 (16) [$C_3H_7^+$].

4.2.4. (*Z*)-5-*tert*-Butyl-7-methyloct-5-en-3-yn-2-ol (19). At room temperature, a soln of **15** (790 mg, 5.26 mmol) in THF (15 mL) was added dropwise to a stirred methyl magnesium chloride soln in THF (3 M, 2.10 mL, 6.30 mmol), and the resulting reaction mixture was refluxed for 2 h. A soln of acetaldehyde (278 mg, 6.31 mmol) in THF (6 mL) was then added within 5 min, and the reaction mixture was again heated to reflux overnight. The reaction mixture was allowed to cool to room temperature, quenched with satd aq NH_4Cl (100 mL), and extracted with Et_2O (3×150 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel to furnish the title compound **19**. Yield 85% (868 mg); colorless oil; R_f 0.13 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3354 (ν O–H), 1460 (δ_{as} CH_3), 1361 (δ_s CH_3), 1073 (ν C–O), 861 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J=6.5 Hz, 6H, 7-Me_2), 1.08 (s, 9H, 1′-Me_3), 1.51 (d, J=6.5 Hz, 3H, 1-H_3), 2.07 (br s, 1H, OH), 2.80 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 4.71 (q, J=6.5 Hz, 1H, 2-H), 5.49 (d, J=9.5 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.5 (q, 7-Me_2), 24.6 (q, C-1), 29.2 (q, 1′-Me_3), 29.8 (d, C-7), 35.0 (s, C-1′), 59.8 (d, C-2), 81.7 (s, C-3), 95.9 (s, C-4), 129.9 (s, C-5), 140.9 (d, C-6); MS (EI, %) m/z 194 (14) [M^+], 179 (3) [M^+-CH_3], 123 (36) [$M^+-C_4H_7O$], 93 (42) [$C_7H_9^+$], 57 (100) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.5. (3*E*,5*E*)-5-*tert*-Butyl-7-methylocta-3,5-dien-2-ol (23). To a stirred suspension of lithium aluminum hydride (139 mg, 3.65 mmol) in THF (2.0 mL), a soln of **19** (716 mg, 3.68 mmol) in THF (15 mL) was added dropwise at room temperature, and the reaction mixture was refluxed for 3 h. At 2–4 °C water (0.15 mL) was added dropwise, followed by 15% aq NaOH (0.15 mL) and again water (0.45 mL). After stirring for a further 30 min at room temperature, the formed precipitate was filtered off by suction with the aid of a sintered funnel and washed with Et_2O (20 mL). The combined filtrates were evaporated under reduced pressure and the resulting residue was purified by flash chromatography on silica gel to provide the title compound **23**. Yield 80% (579 mg); colorless oil; R_f 0.11 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3331 (ν O–H), 1461 (δ_{as} CH_3), 1360 (δ_s CH_3), 1060 (ν C–O), 969 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.92 (d, J=6.5 Hz, 6H, 7-Me_2), 1.02 (s, 9H, 1′-Me_3), 1.31 (d, J=6.5 Hz, 3H, 1-H_3), 1.58 (d, J=1.0 Hz, 1H, OH), 2.58 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 4.37 (quintd, J=6.5 and 1.0 Hz, 1H, 2-H), 5.09 (d, J=9.5 Hz, 1H, 6-H), 5.53 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.06 (d, J=16.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 23.5 (q, C-1), 23.6/23.7 (2q, 7-Me_2), 27.7 (d, C-7), 29.6 (q, 1′-Me_3), 35.1 (s, C-1′), 69.2 (d, C-2), 128.6 (d, C-6), 131.2 (d, C-3), 136.9 (s, C-4), 143.5 (s, C-5); MS (EI, %) m/z 196 (5) [M^+], 181 (3) [M^+-CH_3], 139 (16) [$M^+-C_4H_9$], 123 (24) [$M^+-C_4H_9O$], 57 (100) [$C_4H_9^+$], 43 (88) [$C_3H_7^+$].

4.2.6. (3*E*,5*E*)-5-*tert*-Butyl-7-methylocta-3,5-dien-2-one (4). At room temperature, pyridinium chlorochromate (795 mg, 3.68 mmol) was added portionwise to a suspension of dienol **23** (481 mg, 2.45 mmol) and Celite® (5.00 g) in CH_2Cl_2 (25 mL). After stirring for 5 h at ambient temperature, the reaction mixture was diluted with Et_2O (15 mL), the insoluble materials filtered off over a pad of Celite® and washed with Et_2O (10 mL). The combined filtrates were evaporated on a rotary evaporator, and the resulting residue was purified by chromatography on silica gel to furnish the target compound **4**. Yield 73% (348 mg); colorless odoriferous liquid; odor description: very pleasant woody-musky odor reminiscent of β-ionone and Cashmeran® with fruity facets in the direction of raspberries; odor threshold: 0.66 ng/L air; R_f 0.10 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1696 (ν C=O conj), 1463 (δ_{as} CH_3), 1360 (δ_s CH_3), 1247 (ν_{as} C=C–C=O), 980 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.95 (d, J=6.5 Hz, 6H, 7-Me_2), 1.08 (s, 9H, 1′-Me_3), 2.31 (s, 3H, 1-H_3), 2.59 (dsept, J=10.0 and 6.5 Hz, 1H, 7-H), 5.33 (d, J=10.0 Hz, 1H, 6-H), 6.11 (d, J=16.5 Hz, 1H, 3-H), 7.22 (d, J=16.5 Hz, 1H, 4-H); ^1H–^1H NOESY ($CDCl_3$) 1′-Me_3×6-H, 7-Me_2×4-H, 7-H×4-H; ^{13}C NMR ($CDCl_3$, ppm) δ 23.4 (q, 7-Me_2), 27.2 (q, C-1), 27.9 (d, C-7), 29.7 (q, 1′-Me_3), 35.4 (s, C-1′), 131.8 (d, C-6), 135.5 (d, C-3), 142.2 (s, C-5), 142.7 (d, C-4), 198.5 (s, C-2); MS (EI, %) m/z 194 (3) [M^+], 151 (100) [$M-C_2H_3O^+$], 123 (26) [$M-C_4H_7O^+$], 57 (74) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.38; H, 11.46.

4.2.7. 2,5-Dimethylhexan-3-one (8). As described for the preparation of **7**, from isopropyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol), isovaleryl chloride (**5**, 121 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL), the title compound **8** was obtained after standard workup and purification by distillation in a 10-cm Vigreux assembly at 45–47 °C/8 mbar. Yield 52% (66.7 g); colorless

liquid; IR (neat, cm^{-1}) 1708 (ν C=O), 1466 (δ_{as} CH_3), 1365 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.90 (d, J=7.0 Hz, 6H, 5-Me_2), 1.08 (d, J=7.0 Hz, 6H, 2-Me_2), 2.16 (sept, J=7.0 Hz, 1H, 5-H), 2.32 (d, J=7.0 Hz, 2H, 4-H_2), 2.57 (sept, J=7.0 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ 18.1 (q, 2-Me_2), 22.5 (q, 5-Me_2), 24.2 (d, C-5), 41.0 (d, C-2), 49.4 (t, C-4), 215.1 (s, C-3); MS (EI, %) m/z 128 (12) [M^+], 85 (41) [$M^+-C_3H_7$], 57 (100) [$M^+-C_4H_7O$], 43 (39) [$C_3H_7^+$].

4.2.8. 3-Isopropyl-5-methylhex-1-yn-3-ol (12). As described for the preparation of **11**, from **8** (19.2 g, 150 mmol) and anhyd cerium(III) chloride (37.0 g, 150 mmol) in THF (200 mL), and a soln of ethynyl magnesium bromide in THF (0.5 M, 450 mL, 225 mmol), the title compound **12** was obtained after standard workup and purification by chromatography on silica gel. Yield 71% (16.5 g); colorless oil; R_f 0.31 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3467 (ν O–H), 3309 (ν C≡C–H), 1468 (δ_{as} CH_3), 1368 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.00 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.02 (d, J=6.5 Hz, 6H, 5-Me_2), 1.48 (dd, J=14.0 and 6.5 Hz, 1H, 4-H_a), 1.62 (dd, J=14.0 and 6.0 Hz, 1H, 4-H_b), 1.81 (sept, J=7.0 Hz, 2H, 1′-H, 1-H), 1.89 (br s, 1H, OH), 2.02 (sept, J=6.5 Hz, 1H, 5-H), 2.44 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 16.8–17.7 (2q, 1′-Me_2), 24.2–24.3 (2q, 5-Me_2), 24.8 (d, C-5), 38.3 (d, C-1′), 47.1 (t, C-4), 73.1 (d, C-1), 74.4 (s, C-3), 86.0 (s, C-2); MS (EI, %) m/z 139 (2) [M^+-CH_3], 111 (62) [$M^+-C_3H_7$], 97 (32) [$M^+-C_4H_9$], 43 (100) [$C_3H_7^+$].

4.2.9. (*Z*)-3-Isopropyl-5-methylhex-3-en-1-yne (16). As described for the preparation of **15**, from **12** (6.63 g, 43.0 mol) and $KHSO_4$ (1.17 g, 8.60 mmol), the title compound **16** was obtained after standard workup and purification by chromatography on silica gel. Yield 52% (3.05 g); colorless liquid; R_f 0.58 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3312 (ν C≡C–H), 1465 (δ_{as} CH_3), 1362 (δ_s CH_3), 923 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.98 (d, J=6.5 Hz, 6H, 5-Me_2), 1.07 (d, J=7.0 Hz, 6H, 1′-Me_2), 2.32 (sept, J=7.0 Hz, 1H, 1′-H), 2.83 (dsept, J=9.5 and 6.5 Hz, 1H, 5-H), 3.07 (s, 1H, 1-H), 5.56 (d, J=9.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.6 (q, 1′-Me_2), 22.3 (q, 5-Me_2), 29.6 (d, C-5), 34.8 (d, C-1′), 81.0 (s, C-2), 81.4 (d, C-1), 126.3 (s, C-3), 144.0 (d, C-4); MS (EI, %) m/z 136 (25) [M^+], 121 (29) [M^+-CH_3], 93 (100) [$M^+-C_3H_7$], 79 (100) [$C_6H_8^+$], 43 (17) [$C_3H_7^+$].

4.2.10. (*Z*)-5-Isopropyl-7-methyloct-5-en-3-yn-2-ol (20). As described for the preparation of **19**, from **16** (1.50 g, 11.0 mol), methyl magnesium chloride soln in THF (3 M, 4.40 mL, 13.2 mmol) and acetaldehyde (582 mg, 13.2 mmol) in THF (30 mL), the title compound **20** was obtained after standard workup and purification by chromatography on silica gel. Yield 83% (1.65 g); colorless oil; R_f 0.14 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3317 (ν O–H), 1464 (δ_{as} CH_3), 1361 (δ_s CH_3), 1070 (ν C–O), 854 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J=6.5 Hz, 6H, 5-Me_2), 1.05 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.50 (d, J=6.5 Hz, 3H, 1-H_3), 2.00 (br s, 1H, OH), 2.30 (sept, J=7.0 Hz, 1H, 1′-H), 2.77 (dsept, J=9.5 and 6.5 Hz, 1H, 5-H), 4.70 (q, J=6.5 Hz, 1H, 2-H), 5.48 (d, J=9.5 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.7 (q, 1′-Me_2), 22.4 (q, 5-Me_2), 24.6 (q, C-1), 29.5 (d, C-7), 34.9 (s, C-1′), 58.9 (d, C-2), 81.3 (s, C-3), 95.6 (s, C-4), 126.6 (s, C-5), 142.7 (d, C-6); MS (EI, %) m/z 180 (13) [M^+], 165 (4) [M^+-CH_3], 137 (26) [$M^+-C_3H_7$], 95 (24) [$M^+-C_6H_{12}$], 43 (100) [$C_3H_7^+$].

4.2.11. (3*E*,5*Z*)-5-Isopropyl-7-methylocta-3,5-dien-2-ol (24). As described for the preparation of **23**, from **20** (1.38 g, 7.66 mmol) and lithium aluminum hydride (291 mg, 7.66 mmol) in THF (25 mL), the title compound **24** was obtained after standard workup and purification by chromatography on silica gel. Yield 81% (1.13 g); colorless oil; R_f 0.13 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3328 (ν O–H), 1461 (δ_{as} CH_3), 1361 (δ_s CH_3), 1055 (ν C–O), 963 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J=6.5 Hz, 6H, 7-Me_2), 1.04 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.31 (d, J=6.5 Hz, 3H, 1-H_3), 1.73 (d, J=1.0 Hz, 1H, OH), 2.56 (sept, J=7.0 Hz, 1H, 1′-H), 2.73 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 4.38 (quintd, J=6.5 and 1.0 Hz, 1H, 2-H), 5.16 (d, J=9.5 Hz, 1H, 6-H), 5.72 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.47 (d, J=16.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.4 (q, 1′-Me_2), 23.3 (q, 7-Me_2), 23.5 (q, C-1), 26.3 (d, C-7), 29.4 (d, C-1′), 69.6 (d, C-2), 126.0 (d, C-6), 132.2 (d, C-3), 134.6 (d, C-4), 139.2 (s, C-5); MS (EI, %) m/z 182 (3) [M^+], 164 (6) [M^+-H_2O], 137 (18) [$M^+-C_2H_5O$], 109 (41) [$M^+-C_4H_9O$], 43 (100) [$C_3H_7^+$].

4.2.12. (3*E*,5*Z*)-5-Isopropyl-7-methylocta-3,5-dien-2-one (27). As described for the preparation of **4**, from **24** (910 mg, 5.00 mmol), pyridinium chlorochromate (1.62 g, 7.51 mmol) and Celite® (10.0 g) in CH_2Cl_2 (50 mL), the title compound **27** was obtained after standard workup and purification by chromatography on silica gel. Yield 70% (631 mg); colorless odoriferous liquid; odor description: vague woody-fruity odor with earthy and rooty undertones; odor threshold: 251 ng/L air; R_f 0.13 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1669 (ν C=O), 1463 (δ_{as} CH_3), 1358 (δ_s CH_3), 1253 (ν_{as} C=C–C=O), 971 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.00 (d, J=6.5 Hz, 6H, 7-Me_2), 1.07 (d, J=7.0 Hz, 6H, 1′-Me_2), 2.31 (s, 3H, 1-H_3), 2.62 (sept, J=7.0 Hz, 1H, 1′-H), 2.92 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 5.60 (d, J=9.5 Hz, 1H, 6-H), 6.22 (d, J=16.0 Hz, 1H, 3-H), 7.56 (d, J=16.0 Hz, 1H, 4-H); ^1H–^1H NOESY (C_6D_6) 7-Me_2×6-H, 1′-Me_2×6-H, 7-Me_2×4-H, 7-H×4-H; ^{13}C NMR ($CDCl_3$, ppm) δ 22.3 (q, 1′-Me_2), 23.2 (q, 7-Me_2), 26.9 (q, C-1), 27.5 (d, C-1′), 28.9 (d, C-7), 126.2 (d, C-6), 139.0 (s, C-5), 139.6 (d, C-3), 143.4 (d, C-4), 198.9 (s, C-2); MS (EI, %) m/z 180 (2) [M^+], 165 (3) [M^+-CH_3], 137 (100) [$M^+-C_3H_7$], 109 (50) [$M^+-C_4H_7O$], 43 (76) [$C_3H_7^+$]. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.00; H, 11.10.

4.2.13. 2,2,5,5-Tetramethylhexan-3-one (9). As described for the preparation of **7**, from *tert*-butyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol), 3,3-dimethylbutanoyl chloride (**6**, 135 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL), the title compound **9** was obtained after standard workup and purification by distillation in a 10-cm Vigreux assembly at 47–49 °C/3 mbar. Yield 52% (81.3 g); colorless liquid; IR (neat, cm^{-1}) 1707 (ν C=O), 1464 (δ_{as} CH_3), 1364 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.02 (s, 9H, 5-Me_3), 1.11 (s, 9H, 2-Me_3), 2.37 (s, 2H, 4-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 26.2 (q, 2-Me_3), 29.6 (q, 5-Me_3), 30.4 (s, C-5), 44.6 (s, C-2), 47.8 (t, C-4), 215.4 (s, C-3);

MS (EI, %) *m/z* 156 (4) [M^+], 99 (22) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$].

4.2.14. 3-*tert*-Butyl-5,5-dimethylhex-1-yn-3-ol (13). As described for the preparation of **11**, from **9** (18.8 g, 120 mmol) and anhyd cerium(III) chloride (29.6 g, 120 mmol) in THF (200 mL), and a soln of ethynyl magnesium bromide in THF (0.5 M, 360 mL, 180 mmol), the title compound **13** was obtained after standard workup and purification by chromatography on silica gel. Yield 74% (16.2 g); colorless oil; R_f 0.28 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3486 (ν O–H), 3308 (ν C≡C–H), 1466 (δ_{as} CH_3), 1365 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.02 (s, 9H, 1′-Me_3), 1.12 (s, 9H, 5-Me_3), 1.58 (d, J=14.5 Hz, 1H, 4-H_a), 1.62 (d, J=14.5 Hz, 1H, 4-H_b), 1.84 (br s, 1H, OH), 2.49 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.9 (q, 1′-Me_3), 29.5 (s, C-5), 31.0 (q, 5-Me_3), 39.7 (s, C-1′), 46.7 (t, C-4), 74.7 (d, C-1), 75.6 (s, C-3), 86.8 (s, C-2); MS (EI, %) *m/z* 167 (2) [M^+-CH_3], 125 (6) [$M^+-C_4H_9$], 111 (26) [$M^+-C_5H_{11}$], 57 (100) [$C_4H_9^+$].

4.2.15. (*Z*)-3-*tert*-Butyl-5,5-dimethylhex-3-en-1-yne (17). As described for the preparation of **15**, from **13** (5.02 g, 2.75 mmol) and $KHSO_4$ (749 mg, 5.50 mmol), the title compound **17** was obtained after standard workup and purification by chromatography on silica gel. Yield 37% (1.68 g); colorless liquid; R_f 0.56 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3311 (ν C≡C–H), 1462 (δ_{as} CH_3), 1361 (δ_s CH_3), 936 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.10 (s, 9H, 1′-Me_3), 1.19 (s, 9H, 5-Me_3), 3.24 (s, 1H, 1-H), 5.76 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 29.2 (q, 1′-Me_3), 29.9 (q, 5-Me_3), 32.4 (s, C-5), 35.9 (s, C-1′), 81.9 (s, C-2), 85.0 (d, C-1), 129.5 (s, C-3), 144.7 (d, C-4); MS (EI, %) *m/z* 164 (26) [M^+], 149 (58) [M^+-CH_3], 107 (80) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$].

4.2.16. (*Z*)-5-*tert*-Butyl-7,7-dimethyloct-5-en-3-yn-2-ol (21). As described for the preparation of **19**, from **17** (1.43 g, 8.70 mol), methyl magnesium chloride soln in THF (3 M, 3.50 mL, 10.5 mmol) and acetaldehyde (463 mg, 10.5 mmol) in THF (25 mL), the title compound **21** was obtained after standard workup and purification by chromatography on silica gel. Yield 76% (1.38 g); colorless oil; R_f 0.12 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3320 (ν O–H), 1460 (δ_{as} CH_3), 1360 (δ_s CH_3), 1087 (ν C–O), 931 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.08 (s, 9H, 1′-Me_3), 1.17 (s, 9H, 7-Me_3), 1.50 (d, J=6.5 Hz, 3H, 1-H_3), 1.95 (br s, 1H, OH), 4.72 (q, J=6.5 Hz, 1H, 2-H), 5.69 (s, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.2 (q, C-1), 29.3 (q, 1′-Me_3), 30.1 (q, 7-Me_3), 32.5 (s, C-7), 36.0 (s, C-1′), 59.0 (d, C-2), 82.6 (s, C-3), 98.3 (s, C-4), 129.7 (s, C-5), 143.3 (d, C-6); MS (EI, %) *m/z* 208 (16) [M^+], 193 (6) [M^+-CH_3], 165 (17) [$M^+-C_2H_5O$], 151 (18) [$M^+-C_4H_9$], 57 (78) [$C_4H_9^+$].

4.2.17. (3*E*,5*E*)-5-*tert*-Butyl-7,7-dimethylocta-3,5-dien-2-ol (25). As described for the preparation of **23**, from **21** (1.17 g, 5.62 mmol) and lithium aluminum hydride (213 mg, 5.62 mmol) in THF (25 mL), the title compound **25** was obtained after standard workup and purification by chromatography on silica gel. Yield 80% (947 mg); colorless oil; R_f 0.10 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3335 (ν O–H), 1460 (δ_{as} CH_3), 1359 (δ_s CH_3), 1057 (ν C–O), 973 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.00 (s, 9H, 1′-Me_3), 1.04 (s, 9H, 7-Me_3), 1.31 (d, J=6.5 Hz, 3H, 1-H_3), 1.63 (d, J=1.5 Hz, 1H, OH), 4.37 (quintd, J=6.5 and 1.5 Hz, 1H, 2-H), 5.27 (d, J=1.5 Hz, 1H, 6-H), 5.38 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.12 (dd, J=16.0 and 1.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 23.0 (q, C-1), 29.6 (q, 1′-Me_3), 31.7 (q, 7-Me_3), 32.6 (s, C-7), 36.2 (s, C-1′), 69.2 (d, C-2), 128.2 (d, C-6), 133.1 (d, C-3), 136.7 (d, C-4), 144.0 (s, C-5); MS (EI, %) *m/z* 210 (2) [M^+], 153 (6) [$M^+-C_4H_9$], 109 (58) [$M^+-C_6H_{13}O$], 57 (100) [$C_4H_9^+$].

4.2.18. (3*E*,5*E*)-5-*tert*-Butyl-7,7-dimethylocta-3,5-dien-2-one (28). As described for the preparation of **4**, from **25** (762 mg, 3.62 mmol), pyridinium chlorochromate (1.17 g, 5.43 mmol) and Celite® (5.0 g) in CH_2Cl_2 (40 mL), the title compound **28** was obtained after standard workup and purification by chromatography on silica gel. Yield 75% (567 mg); colorless odoriferous liquid; odor description: floral, sweet, violet, musky, with woody, slightly camphoraceous and agrestic facets; odor threshold: 0.54 ng/L air; R_f 0.10 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1675 (ν C=O conj), 1462 (δ_{as} CH_3), 1359 (δ_s CH_3), 1249 (ν_{as} C=C–C=O), 983 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.05 (s, 9H, 1′-Me_3), 1.06 (s, 9H, 7-Me_3), 2.30 (s, 3H, 1-H_3), 5.42 (d, J=1.5 Hz, 1H, 6-H), 6.02 (d, J=16.5 Hz, 1H, 3-H), 7.37 (dd, J=16.5 and 1.5 Hz, 1H, 4-H); ^1H–^1H NOESY (C_6D_6) 1′-Me_3×6-H, 7-Me_3×6-H, 7-Me_3×4-H; ^{13}C NMR ($CDCl_3$, ppm) δ 27.1 (q, C-1), 29.7 (q, 1′-Me_3), 31.6 (q, 7-Me_3), 32.8 (s, C-7), 36.4 (s, C-1′), 132.6 (d, C-6), 135.8 (d, C-3), 142.5 (s, C-5), 145.2 (d, C-4), 197.9 (s, C-2); MS (EI, %) *m/z* 193 (5) [M^+-CH_3], 165 (73) [$M^+-C_2H_3O$], 151 (38) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$]. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.75; H, 11.63.

4.2.19. 2,5-Dimethylhexan-3-one (10). As described for the preparation of **7**, from isopropyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol), 3,3-dimethylbutanoyl chloride (**6**, 135 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL), the title compound **10** was obtained after standard workup and purification by distillation in a 10-cm Vigreux assembly at 46–48 °C/6 mbar. Yield 51% (72.6 g); colorless liquid; IR (neat, cm^{-1}) 1709 (ν C=O), 1465 (δ_{as} CH_3), 1364 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.01 (s, 9H, 5-Me_3), 1.05 (d, J=7.0 Hz, 6H, 2-Me_2), 2.34 (s, 2H, 4-H_2), 2.56 (sept, J=7.0 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ 17.9 (q, 2-Me_2), 29.6 (q, 5-Me_3), 30.8 (s, C-5), 42.0 (d, C-2), 52.6 (t, C-4), 214.4 (s, C-3); MS (EI, %) *m/z* 142 (10) [M^+], 99 (26) [$M^+-C_3H_7$], 71 (34) [$M^+-C_4H_7O$], 57 (100) [$C_4H_9^+$], 43 (39) [$C_3H_7^+$].

4.2.20. 3-Isopropyl-5,5-dimethylhex-1-yn-3-ol (14). As described for the preparation of **11**, from **10** (17.1 g, 120 mmol) and anhyd cerium(III) chloride (29.6 g, 120 mmol) in THF (180 mL), and a soln of ethynyl magnesium bromide in THF (0.5 M, 360 mL, 180 mmol), the title compound **14** was obtained after standard workup and purification by chromatography on silica gel. Yield 76% (15.4 g); colorless oil; R_f 0.30 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3486 (ν O–H), 3308 (ν C≡C–H), 1468 (δ_{as} CH_3), 1365 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.96–1.01 (2d, J=7.0 Hz, 6H, 1′-Me_2), 1.11 (s, 9H, 5-Me_3), 1.52 (d, J=14.5 Hz, 1H, 4-H_b), 1.68 (d, J=14.5 Hz, 1H, 4-H_a),

1.78 (sept, J=7.0 Hz, 1H, 1′-H), 1.89 (br s, 1H, OH), 2.48 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 16.7/17.7 (2q, 1′-Me_2), 31.1 (q, 5-Me_3), 31.2 (s, C-5), 40.1 (d, C-1′), 50.0 (t, C-4), 73.7 (s, C-3), 74.3 (d, C-1), 86.3 (s, C-2); MS (EI, %) *m/z* 153 (2) [M^+-CH_3], 125 (14) [$M^+-C_3H_7$], 97 (18) [$M^+-C_5H_{11}$], 57 (100) [$C_4H_9^+$], 43 (33) [$C_3H_7^+$].

4.2.21. (*Z*)-3-Isopropyl-5,5-dimethylhex-3-en-1-yne (18). As described for the preparation of **15**, from **14** (8.75 g, 52.0 mol) and $KHSO_4$ (1.42 g, 10.4 mmol), the title compound **18** was obtained after standard workup and purification by chromatography on silica gel. Yield 50% (3.91 g); colorless liquid; R_f 0.59 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3311 (ν C≡C–H), 1461 (δ_{as} CH_3), 1362 (δ_s CH_3), 927 (δ C≡C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.06 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.18 (s, 9H, 5-Me_3), 2.31 (sept, J=7.0 Hz, 1H, 1′-H), 3.19 (s, 1H, 1-H), 5.74 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.7 (q, 1′-Me_2), 30.0 (q, 5-Me_3), 32.7 (s, C-5), 36.9 (d, C-1′), 81.3 (s, C-2), 84.2 (d, C-1), 126.0 (s, C-3), 146.6 (d, C-4); MS (EI, %) *m/z* 150 (30) [M^+], 135 (24) [M^+-CH_3], 107 (100) [$M^+-C_3H_7$], 33 (42) [$M^+-C_4H_9$], 57 (7) [$C_4H_9^+$], 43 (23) [$C_3H_7^+$].

4.2.22. (*Z*)-5-Isopropyl-7,7-dimethyloct-5-en-3-yn-2-ol (22). As described for the preparation of **19**, from **18** (2.11 g, 14.0 mol), methyl magnesium chloride soln in THF (3 M, 5.60 mL, 16.8 mmol) and acetaldehyde (741 mg, 16.8 mmol) in THF (40 mL), the title compound **22** was obtained after standard workup and purification by chromatography on silica gel. Yield 80% (2.18 g); colorless oil; R_f 0.13 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3317 (ν O–H), 1460 (δ_{as} CH_3), 1361 (δ_s CH_3), 1070 (ν C–O), 875 (δ C=C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.04 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.16 (s, 9H, 7-Me_3), 1.50 (d, J=6.5 Hz, 3H, 1-H_3), 1.97 (br s, 1H, OH), 2.29 (sept, J=7.0 Hz, 1H, 1′-H), 4.70 (q, J=6.5 Hz, 1H, 2-H), 5.66 (s, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.8 (q, 1′-Me_2), 24.2 (q, C-1), 30.1 (q, 5-Me_3), 32.8 (s, C-7), 36.8 (d, C-1′), 59.0 (d, C-2), 81.8 (s, C-3), 97.7 (s, C-4), 126.1 (s, C-5), 145.2 (d, C-6); MS (EI, %) *m/z* 194 (25) [M^+], 179 (4) [M^+-CH_3], 151 (43) [$M^+-C_3H_7$], 137 (17) [$M^+-C_4H_9$], 57 (15) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.23. (3*E*,5*Z*)-5-Isopropyl-7,7-dimethylocta-3,5-dien-2-ol (26). As described for the preparation of **23**, from **22** (1.91 g, 9.83 mmol) and lithium aluminum hydride (373 mg, 9.83 mmol) in THF (40 mL), the title compound **26** was obtained after standard workup and purification by chromatography on silica gel. Yield 83% (1.61 g); colorless oil; R_f 0.11 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3330 (ν O–H), 1461 (δ_{as} CH_3), 1362 (δ_s CH_3), 1056 (ν C–O), 970 (δ C=C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.03 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.13 (s, 9H, 7-Me_3), 1.51 (d, J=6.5 Hz, 3H, 1-H_3), 1.71 (d, J=1.0 Hz, 1H, OH), 2.55 (sept, J=7.0 Hz, 1H, 1′-H), 4.38 (quintd, J=6.5 and 1.0 Hz, 1H, 2-H), 5.34 (s, 1H, 6-H); 5.66 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.68 (d, J=16.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.6/22.7 (2q, 1′-Me_2), 23.4 (q, C-1), 31.0 (d, C-1′), 31.8 (q, 7-Me_3), 32.2 (s, C-7), 69.5 (d, C-2), 127.2 (d, C-6), 132.1 (d, C-3), 136.5 (d, C-4), 140.6 (s, C-5); MS (EI, %) *m/z* 196 (3) [M^+], 178 (5) [M^+-H_2O], 153 (6) [$M^+-C_3H_7$], 139 (3) [$M^+-C_4H_9$], 123 (21) [$M^+-C_4H_9O$], 57 (46) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.24. (3*E*,5*Z*)-5-Isopropyl-7,7-dimethylocta-3,5-dien-2-one (29). As described for the preparation of **4**, from **26** (1.32 g, 6.72 mmol), pyridinium chlorochromate (2.17 g, 10.0 mmol) and Celite® (10.0 g) in CH_2Cl_2 (70 mL), the title compound **29** was obtained after standard workup and purification by chromatography on silica gel. Yield 71% (928 mg); colorless odoriferous liquid; odor description: floral-fruity, violet, raspberries, reminiscent to α-irone and β-ionone; odor threshold: 12.5 ng/L air; R_f 0.11 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1669 (ν C=O conj), 1460 (δ_{as} CH_3), 1360 (δ_s CH_3), 1254 (ν_{as} C=C–C=O), 976 (δ C=C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.05 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.22 (s, 9H, 7-Me_3), 2.31 (s, 3H, 1-H_3), 2.60 (sept, J=7.0 Hz, 1H, 1′-H), 5.77 (s, 1H, 6-H), 6.16 (d, J=16.5 Hz, 1H, 3-H), 7.82 (d, J=16.5 Hz, 1H, 4-H); ^{1}H–^{1}H NOESY ($CDCl_3$) 7-Me_3×4-H, 1′-Me_2×6-H; ^{13}C NMR ($CDCl_3$, ppm) δ 22.6 (d, 1′-Me_2), 27.2 (q, C-1), 30.0 (d, C-1′), 32.0 (q, 7-Me_3), 33.1 (s, C-7), 126.1 (d, C-6), 140.2 (s, C-5), 141.0 (d, C-3), 145.3 (d, C-4), 198.9 (s, C-2); MS (EI, %) *m/z* 194 (2) [M^+], 179 (4) [M^+-CH_3], 151 (100) [$M^+-C_2H_3O$], 137 (19) [$M^+-C_4H_9$], 57 (12) [$C_4H_9^+$], 43 (74) [$C_3H_7^+$]. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.34; H, 11.41.

Acknowledgements

Thanks are due to Dr. Gerhard Brunner for the NMR experiments, to Dr. Fabian Kuhn for the mass spectrometry data, to Katarina Grman for the determination of odor thresholds, and to Alain E. Alchenberger and Anne-Sylvie Selezneff for the olfactory evaluations presented here. Careful proofreading of the manuscript by Dr. Markus Gautschi, Dr. Samuel Derrer, and Tony M^{c}Stea is also acknowledged with gratitude.

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Chiral ferrocenyl amidophosphine ligand for highly enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines

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Received 15 August 2006; revised 1 October 2006; accepted 8 October 2006
Available online 30 October 2006

Abstract—The asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines afforded *N*-diphenylphosphinoylamides with enantioselectivity of up to 90% ee in the presence of a catalytic amount of chiral ligand (*S*)-*N*-ferrocenoyl-2-[(diphenylphosphino)methyl]-pyrrolidine **13** (7 mol %) and $Cu(OTf)_2$ (15 mol %). The remarkable improvement of enantioselectivities, as compared with the same type of chiral ligand **6**, could be explained by the unique structure of ferrocenyl amidophosphine ligand combining with the reactive intermediate of this addition reaction.

1. Introduction

The efficient and enantioselective synthesis of chiral amines is of primary importance due to their extensive utilization in organic synthesis as resolving agents,[1] raw materials or intermediates in the production of some biologically active substances[2] and chiral auxiliaries for asymmetric synthesis.[2,3] The catalytic asymmetric addition of organometallic reagents to imines is one of the most efficient approaches to chiral amines.[3,4] Due to the good tolerance of various functionalities with respect to organolithiums and Grignard reagents, the enantioselective addition of dialkylzinc reagents to C=N double bonds has attracted much attention,[5] although stoichiometric amounts of ligands were usually required to obtain high yields and enantioselectivities. Recently, catalytic systems[6–12] were developed for highly enantioselective addition of diorganozincs to activated *N*-arylimines **1**,[6] *N*-acylimines **2**,[7,8] *N*-sulfonylimines **3**[9,10,11a] and *N*-phosphinoylimines **4**,[11b,12] in the presence of *a small number* of catalytic amounts of chiral catalysts or ligands (Fig. 1). More recently, we reported the enantioselective addition of diethylzinc to the *N*-diphenylphosphinoylimines **4** with up to 97% ee in the presence of 6 mol % of *N*,*P*-ferrocenyl ligands.[13] This is in great contrast to the catalytic asymmetric alkylation of carbonyl compounds with dialkyzinc reagents, which has become a very effective and general method.[14] Not surprisingly, the asymmetric addition of dialkyzincs to C=N bond in the presence of a catalytic amount of chiral ligands is at the infant stage in spite of its great potential in organic synthesis.

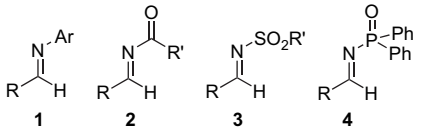

Figure 1. The structure of activated imines.

In transition-metal-mediated asymmetric catalytic additions, the nature of the starting imines plays a critical role for the success of these reactions. That is, strong substrate dependence is very obvious, especially in transition-metal-mediated catalytic asymmetric alkylation of imines either by means of stoichiometric or catalytic amounts of chiral ligands. For instance, the asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines **4** afforded the corresponding addition product with up to 94% ee in the presence of a stoichiometric amount of chiral ligand **5**,[5b] while the addition of diethylzinc to imine **3** with a different electron-withdrawing group on the nitrogen led to a racemic product under the same conditions and identical ligand **5** (Fig. 2). Similar phenomena were also observed in the asymmetric addition of diethylzinc to *N*-sulfonylimines **3** and *N*-phosphinoylimines **4** in the presence of a catalytic amount of chiral ligands **6**,[9b,12a] **7**,[11a,b] or **8**,[11a,b] respectively (Fig. 2). To the best of our knowledge, there has been no report on highly enantioselective addition of diorganozincs to the C=N bond of different types of imines, such as *N*-sulfonylimines and *N*-phosphinoylimines, by means of the same chiral ligand.

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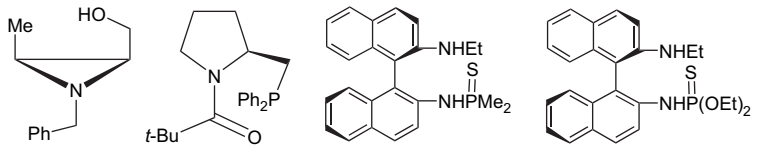
doi:10.1016/j.tet.2006.10.015



N-sulfonylimines **3**	0% ee[5b]	63% ee[9b]	90% ee[11a]	34% ee[11a]
N-phosphinoylimines **4**	94% ee[5b]	23% ee[12a]	13% ee[11b]	85% ee[11b]

Figure 2.

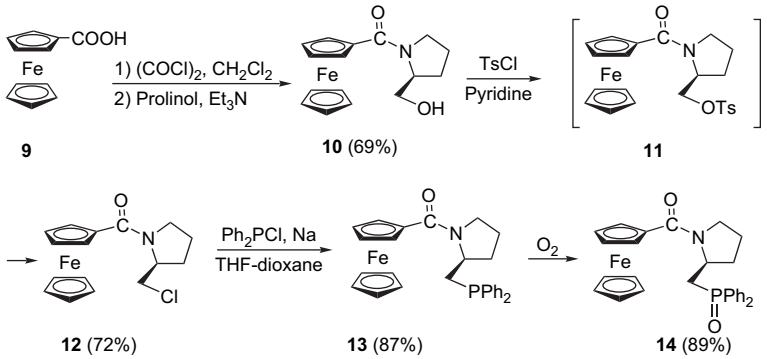
The development of new chiral ligands plays a key role for overcoming this substrate limitation because subtle changes in conformational, steric and/or electronic properties of the chiral ligands can often result in dramatic variation of the enantioselectivity and reactivity. In a previous article, we reported the synthesis of chiral ferrocenyl amidophosphine ligand **13** and its application in the copper-catalyzed enantioselective addition of diethylzinc to the C═N bond of *N*-sulfonylimines **3**.[15] In order to examine the generality of chiral ferrocenyl amidophosphine ligand towards other imine substrates, herein we report the chiral ferrocenyl amidophosphine–$Cu(OTf)_2$-catalyzed enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines **4** with enantioselectivity of up to 90% ee.

2. Results and discussion

The chiral ferrocenyl amidophosphine ligand **13** was easily synthesized from the reaction of ferrocenecarboxylic acid with L-proline. The preparation of **13** is outlined in Scheme 1. The reaction of ferrocenecarboxylic acid **9** with oxalyl chloride in CH_2Cl_2 gave ferrocenoyl chloride, which was combined with (*S*)-prolinol in the presence of Et_3N to produce (*S*)-*N*-ferrocenoyl prolinol **10** in 69% yield.[16] We planned to prepare (*S*)-*N*-ferrocenoyl prolinol tosylate **11** by the reaction of (*S*)-*N*-ferrocenoyl prolinol **10** with TsCl in the presence of pyridine, but after work-up, an unexpected chlorine-substituted product **12** was obtained in 72% yield and confirmed by HRMS, ^1H NMR, ^{13}C NMR and IR analyses. Treatment of **12** with $NaPPh_2$ in the presence of THF/dioxane afforded the chiral ferrocenyl amidophosphine ligand **13** in 84% yield according to the reported procedure.[17]

The chiral ferrocenyl amidophosphine ligand **13** was easily oxidized, due to its instability in air, to afford the corresponding (*S*)-*N*-ferrocenoyl diphenylphosphinoylmethylpyrroline **14** after being exposed to air for some hours (Scheme 1). The single crystal growth of **14** was performed in EtOAc at room temperature, and orange red crystals were obtained. The absolute configuration of chiral compound **14** was confirmed by X-ray diffraction (Fig. 3).[18] X-ray structural analysis revealed that the nitrogen atom on pyrrolidine ring has a planar structure with the sum of the three bond angles being 359.9°. This is not a trigonal-pyramidal structure because the nitrogen atom (sp^2) on pyrrolidine ring forms a conjugated system with carbonyl (CO) group and Cp ring moiety (Fig. 3). The C(11)–N(1)–C(15), C(11)–N(1)–C(12) and C(15)–N(1)–C(12) bond angles in **14** are 119.6°, 128.4° and 111.9°, respectively.[18]

At the outset of our study, we examined the effects of the ratio of $Cu(OTf)_2$ to ligand **13** on yields and enantioselectivities of the reaction of diethylzinc with *N*-diphenylphosphinoylimines derived from benzaldehyde at −5 to 0 °C, and the results are summarized in Table 1 (entries 1–8). When 4 mol % of ligand **13** equivalent to imine **15** was used, yields and enantioselectivities of the reaction increased with increase in the amounts of $Cu(OTf)_2$ (Table 1 entries 1–4). The use of 15 mol % of $Cu(OTf)_2$ gave the best yield (53%) and enantioselectivity (70% ee, Table 1 entry 4). When 7 mol % of ligand **13** was used in the presence of 15 mol % of $Cu(OTf)_2$, the enantioselectivity increased to 78% (entry 7). Increasing the amount of the catalyst did not result in higher asymmetric induction (Table 1 entries 7 and 8). So, the combination of 7 mol % of chiral ligand **13** and 15 mol % of $Cu(OTf)_2$ seemed the most suitable catalyst for the alkylation of imines. Raising the reaction



Scheme 1. Synthesis of ligand **13**.

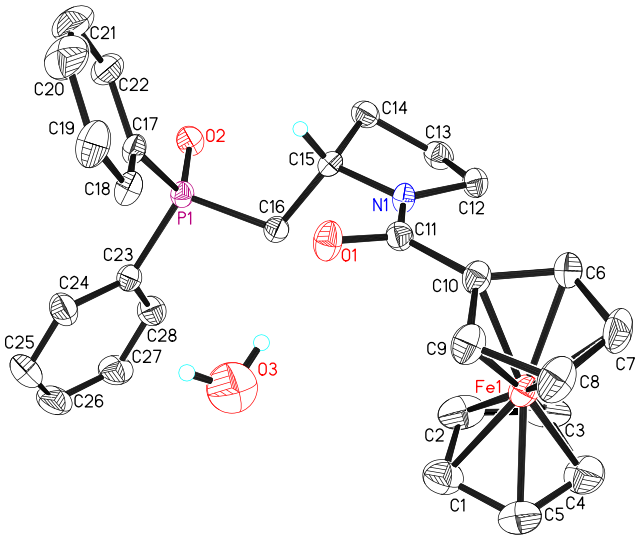


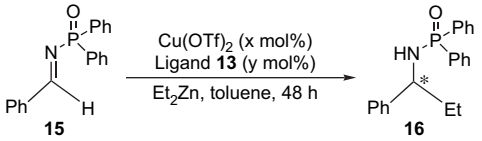
Figure 3. X-ray crystal structure of compound **14** including one H_2O molecule. Selected bond distances (Å) and angles (°) are: O(1)–C(11), 1.248(4); N(1)–C(11), 1.343(4); C(10)–C(11), 1.480(5); N(1)–C(15), 1.478(4); C(15)–C(16), 1.527(4); P(1)–C(16), 1.813(3); P(1)–O(2), 1.488(2); P(1)–C(17), 1.798(3); P(1)–C(23), 1.804(4); N(1)–C(15)–C(16), 111.1(3); O(1)–C(11)–N(1), 119.1(3); N(1)–C(11)–C(10), 122.2(3); O(1)–C(11)–C(10), 118.7(3); C(11)–N(1)–C(15), 119.6(3); C(11)–N(1)–C(12), 128.4(3); C(15)–N(1)–C(12), 111.9(3); C(15)–C(16)–P(1), 113.4(2); O(2)–P(1)–C(16), 112.79(14); O(2)–P(1)–C(17), 112.60(15); C(17)–P(1)–C(23), 108.76(16).

temperature from −5 to 0 °C to room temperature (20–25 °C) resulted in a drop in the addition selectivity from 78% to 73% (Table 1 entries 9 and 6). Addition of 4 Å molecular sieves (MS) to the reaction system did not benefit the enantioselectivities and the yields of the products (Table 1, entries 10 vs 6). In contrast, Gong and other groups have reported that the use of 4 Å MS very obviously affects the reaction product both in terms of yields and enantiomeric excesses.[19] Addition of CuI (4 mg) did not affect the chemical yield and enantioselectivity of the reaction (Table 1, entry 11).

Recently, Charette and Boezio reported the same type of chiral ligands **6** for the addition of diethylzinc to *N*-diphenylphosphinoylimine **15** with low enantioselectivity of 23% ee.[12a] Comparison of our results (up to 78% ee) with those of Boezio and Charette demonstrates that the replacement of the pivaloyl group on the pyrrolidine nitrogen atom by a ferrocenoyl unit results in a remarkable improvement in the enantioselectivity. These results also suggest that the hindrance of rigid, bulky ferrocenyl unit and the electron-donating conjugated effect of the Cp ring possessing a partial negative charge play an important role in the enantioselection in the addition of diethylzinc to *N*-diphenylphosphinoylimine. The high enantioselectivity by **13** is understandable: (a) because the nitrogen atom (sp^2) on pyrrolidine ring forms an extended conjugated system with carbonyl (CO) group and Cp ring moiety (Fig. 3), the rotation about the N–CO and Cp–CO sigma bonds is retarded and the structure of ligand **13** is also made more rigid; (b) steric repulsion between the rigid, bulky ferrocenyl unit and Ph_2P group makes the carbonyl oxygen atom point towards Ph_2P group (Fig. 3), which is helpful to form a chelate with copper or zinc; (c) the electron-donating conjugated effect of the Cp ring with a partial negative charge strengthens further the coordinating ability of carbonyl oxygen atom and increases the possibility of formation of a zinc cuprate–oxygen phosphine complex,[9b] which is the reactive intermediate of 1,4-conjugate addition;[20] (d) the rigid, bulky ferrocenyl substituent effectively shields one face of the chelate, which may prohibit the approach of *N*-diphenylphosphinoylimine **15** from this face and is responsible for the high enantioselectivity.

Chartte et al.[12d] reported that the level of asymmetric induction was greatly dependent upon the order of addition of reagents in the Cu(II)–Me-DuPHOS-catalyzed asymmetric ethylation of *N*-diphenylphosphinoylimine **15**. We also investigated the effect of the order of addition of reagents on enantioselectivity (Table 2). A slight improvement in product ee was observed when $Cu(OTf)_2$ was mixed with

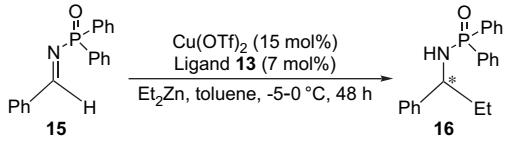
Table 1. Optimization of the reaction conditions of the enantioselective ethylation of imines[a]



Entry	Ligand (%)	$Cu(OTf)_2$ (%)	Temp (°C)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	4	3	−5 to 0	30	60	*R*
2	4	6	−5 to 0	45	67	*R*
3	4	10	−5 to 0	52	69	*R*
4	4	15	−5 to 0	53	70	*R*
5	4	20	−5 to 0	51	70	*R*
6	7	15	−5 to 0	60	78	*R*
7	10	15	−5 to 0	60	78	*R*
8	15	15	−5 to 0	60	78	*R*
9	7	15	20 to 25	54	73	*R*
10[e]	7	15	−5 to 0	55	76	*R*
11	7	15	−5 to 0	61	78	*R*

[a] All reactions were carried out in toluene with the 0.3 mmol of imine and the order of addition of the reagents was $Cu(OTf)_2$–L-imine–Et_2Zn.
[b] The isolated yield.
[c] The ee was determined by HPLC with Daicel Chiralcel OD: 2-propanol/hexane (10/90), 0.5 mL/min: t_R=12.9 min, t_S=16.6 min.
[d] The absolute configuration was assigned as *R* by comparing retention time of HPLC with the literature value.[12,13]
[e] MS (4 Å) was added.

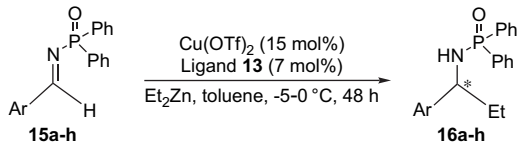
Table 2. The effect of the order of addition

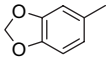


Entry	Method[a]	Yield (%)[b]	ee (%)[c]	Config.[d]
1	A	60	78	*R*
2	B	35	79	*R*

[a] Method A: the order of addition of the reagents was $Cu(OTf)_2$–L-imine–Et_2Zn. The mole ratio of imine/Et_2Zn was 1/3. Method B: the order of addition of the reagents was $Cu(OTf)_2$-Et_2Zn-L-imine. The mole ratio of imine/Et_2Zn was 1/3.
[b] The isolated yield.
[c] The ee was determined by HPLC with Daicel Chiralcel OD: 2-propanol/hexane (10/90), 0.5 mL/min: t_R=12.9 min, t_S=16.6 min.
[d] The absolute configuration was assigned as *R* by comparing retention time of HPLC with the literature value.[12,13]

Table 3. The enantioselective addition of diethylzinc to various *N*-diphenylphosphinoylimines **15**[a]



Entry	Ar	Imine	Yield (%)[b]	ee (%)[c]	Config.[d]
1	C_6H_5	**15a**	60	78	*R*
2	2-$MeOC_6H_4$	**15b**	64	78	*R*
3	4-$MeOC_6H_4$	**15c**	67	84	*R*
4		**15d**	72	78	*R*
5	4-MeC_6H_4	**15e**	78	83	*R*
6	2-ClC_6H_4	**15f**	69	90	*R*
7	4-ClC_6H_4	**15g**	65	73	*R*
8	2-Furyl	**15h**	76	85	*R*

[a] All reactions were carried out in toluene with 0.3 mmol and the order of addition of the reagents was $Cu(OTf)_2$–L-imine–Et_2Zn.
[b] The isolated yield.
[c] Determined by chiral HPLC with a Chiralcel OD or a Chiralpak AD column.[12,13]
[d] Absolute configuration assigned by comparison with known elution order from a Chiralcel OD column and a Chiralpak AD column according to the literature.[12,13]

Et_2Zn prior to the addition of ligand **13**, however, this resulted in a great decrease in chemical yield (Table 2, entry 2).

These reaction conditions were then tested on a variety of other *N*-phosphinoylimines derived from different arylaldehydes in this catalytic system, the results are presented in Table 3. As can be seen from Table 3, good to excellent enantioselectivities (73–90% ee) could be achieved for various aromatic *N*-diphenylphosphinoylimines containing *ortho*-, *para*- or *meta*-substituents on the benzene ring (Table 3, entries 2–7). The presence of electron-donating or electron-withdrawing substituents on the aromatic ring is also compatible with these reaction conditions. The best asymmetric induction (as high as 90% ee) was found by using an imine bearing a 2-ClC_6H_4 group as the substrate in the presence of chiral ligand **13** (Table 3, entry 6). It is advantageous that imine derived from furfural can be converted to an adduct in 76% yield and 85% ee (Table 3, entry 8), because the product is a useful intermediate for the synthesis of biologically active compounds. Until now, chiral ligand **13** is only one example that can afford highly enantioselective addition of diethylzinc to the C=N bond of the different types of imines such as *N*-sulfonylimines[15] and *N*-phosphinoylimines.

3. Conclusion

In conclusion, we have reported copper-catalyzed highly enantioselective addition of diethylzinc to *N*-phosphinoylimines in the presence of catalytic amount of chiral ferrocenyl O,P-ligand **13**. The X-ray structure analysis of derivative **14** of **13** reveals that the nitrogen atom on pyrrolidine ring forms an extended conjugated system with carbonyl (CO) group and Cp ring moiety. The X-ray structure of **14** in combination with proposed reactive intermediate during addition reaction explained that the introduction of a ferrocenyl group into the chiral amidophosphine ligands results in a remarkable improvement in the enantioselectivity, as compared with the same type of chiral ligand **6**. To the best of our knowledge, this is the first case of the highly enantioselective addition of diorganozincs to the C=N bond of the different types of imines such as *N*-sulfonylimines and *N*-phosphinoylimines by means of the identical chiral ligand. Further application of chiral O,P-ligand **13** for asymmetric synthesis is under investigation in our laboratory.

4. Experimental

4.1. General

Melting points were determined using YRT-3 melting point apparatus, and were uncorrected. Optical rotations were measured with Perkin Elmer, model 341 Polarimeter at 20 °C in $CHCl_3$. The ee value was determined by HPLC using a chiral column with hexane/2-propanol (ratio as indicated) as the eluent. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. The chromatographic system consisted of a JASCO model PU-1580 intelligent HPLC pump and a JASCO model UV-1575 intelligent UV–vis detector (254 nm). The injection loop had a 20 μL capacity. The column used was a Chiralcel OD or a Chiralpak AD (250×4.6 mm) from Daicel Chemical Ind., Ltd (Japan). The column was operated at ambient temperature. NMR spectra (^1H and ^{13}C) were performed on a Bruker DPX 400 (400 MHz) spectrometer using solutions in $CDCl_3$ (referenced internally to Me_4Si); *J* values are given in hertz. IR spectra were determined on a Therme Nicolet IR 200 spectrophotometer. TLC was performed on dry silica gel plates developed with hexane/ethyl acetate. Mass spectra were obtained using a Waters a-Tof micro™ instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent.

4.2. Reagents and solvents

Except for diethylzinc purchased from Aldrich and $Cu(OTf)_2$ from Alfa Aesar, all other reagents were purchased in China. Toluene was pre-dried over calcium chloride, and then distilled from sodium before use. Ether was distilled from sodium benzophenone ketyl. All other reagents are commercially available and were used as received. The imines **15a**,[21] **15b**,[22] **15c**,[23] **15d**,[21] **15e**,[12] **15f**,[21] **15g**[12] and **15h**[12] are known compounds and prepared according to the reported procedure.[12,19–21]

4.3. Synthesis of (*S*)-ferrocenoyl prolinol 10

To a solution of ferrocenecarboxylic acid **9** (2.3 g, 10 mmol) in 30 mL of freshly distilled dichloromethane under nitrogen, oxylyl chloride (1.76 mL, 20 mmol) was slowly added via syringe. Gas evolution was accompanied by the formation of a dark red homogeneous solution after 30 min. The reaction mixture was stirred for an additional 30 min, followed by removal of the solvent in vacuo. The resultant crude ferrocenoyl chloride was dissolved in dichloromethane (20 mL) and added slowly to a solution of pyrrolidinol (1.2 g, 12 mmol) and triethylamine (2.7 mL, 20 mmol) in

30 mL of dried dichloromethane at 0 °C under nitrogen. The resulting mixture was allowed to stir at room temperature overnight and then quenched with 40 mL of distilled water. The organic phase was separated, and the aqueous phase was extracted three times with dichloromethane (3×20 mL). After the combined organic phases were dried over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by column chromatography on a silica gel column (eluted with dichloromethane/methanol (93/7)) to afford **10** (2.16 g, 69%) as an orange red solid. Mp 169.1–170.5 °C; $[\alpha]_D^{20}$ 48.6 (*c* 0.4, in CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.59 (m, 1H, $CH_2CH\mathit{H}$), 1.80–1.87 (m, 1H, $CH_2C\mathit{H}H$), 1.95–2.01 (m, 1H, $C\mathit{H}HCH_2$), 2.10–2.14 (m, 1H, $CH\mathit{H}CH_2$), 3.57–3.59 (m, 1H, NC*H*H), 3.61–3.63 (m, 1H, NCH*H*), 3.75–3.80 (m, 1H, NCH), 3.97–4.02 (m, 1H, HO*CH*H), 4.42–4.44 (m, 1H, HO*C*H*H*), 4.23–5.40 (m, 9H, FcH), 5.40 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 28.2, 29.7, 49.7, 62.3, 68.3, 69.4, 69.8, 70.2, 70.5, 71.8, 172.8; IR (KBr pellets): 3335, 2876, 1583, 1464, 1410, 1226, 1099, 1058, 1032, 1006, 819 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{20}FeNO_2$: 314.0843 (M^++H), found: 314.0844.

4.4. Synthesis of (*S*)-2-(chloromethyl)pyrrolidinocarbonylferrocene 12

To a solution of **10** (666 mg, 2.12 mmol), dry pyridine (2.5 mL) and dimethylaminopyridine (26 mg, 0.21 mmol) in a mixture of dichloromethane (15 mL), TsCl (478 mg, 2.5 mmol) was added slowly at −5 to 0 °C under nitrogen. After stirring for 10 h at the same temperature and 14 h at room temperature, 1 N HCl (10 mL) was added and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (ethyl acetate/petroleum ether (1/2) as developing solvent) to yield the product **12** as an orange red solid (539 mg, 72%). Mp 95.2–96.2 °C; $[\alpha]_D^{20}$ −76.6 (*c* 0.4, in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.85 (m, 1H, $CH\mathit{H}CH_2$), 2.04–2.09 (m, 3H, $C\mathit{H}HCH_2$, $CH_2C\mathit{H}_2$), 3.59–3.65 (m, 1H, NC*H*H), 3.77–3.80 (m, 1H, ClC*H*H), 3.87–3.89 (m, 1H, ClCH*H*), 3.96–4.01 (m, 1H, NCH*H*), 4.49–4.50 (m, 1H, NCH), 4.21–4.80 (m, 9H, FcH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.21, 27.67, 45.61, 49.61, 58.48, 69.29, 69.77, 70.11, 70.25, 71.70, 169.86; IR (KBr pellets): 3101, 2978, 1607, 1461, 1394, 1160, 1102, 1052, 1000, 816 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}ClFeNO$: 354.0504 (M^++H), found: 354.0505.

4.5. Synthesis of (*S*)-[2-(diphenylphosphino)methyl]-pyrrolidinocarbonylferrocene 13

In a dried Schlenk tube, small pieces of sodium (184 mg, 8.0 mmol) were added at 0 °C to a solution of Ph_2PCl (0.36 mL, 1.9 mmol, 95% purity) in dried 1,4-dioxane (2 mL) and stirred under reflux for 6 h under a nitrogen atmosphere. The mixture was cooled to 0 °C and a solution of the compound **12** (353 mg, 1.0 mmol) in THF (2 mL) was then added at 0 °C. After stirring for 40 min, the mixture was filtered through Celite and the Celite was washed by THF four times to afford a red filtrate. Concentration and silica gel column chromatography (eluted with ethyl acetate/petroleum ether, (1/4)) gave **13** (418 mg, 87%) as an orange red solid. Mp 114.8–116.0 °C; $[\alpha]_D^{20}$ −38.6 (*c* 0.8, in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.82–1.84 (m, 1H, $CH_2CH\mathit{H}$), 1.85–2.10 (m, 4H, $CH_2C\mathit{H}H$, $C\mathit{H}_2CH_2$, NC*H*), 3.22–3.24 (m, 1H, PC*H*H), 3.56–3.61 (m, 1H, PCH*H*), 3.95–3.97 (m, 1H, NC*H*H), 4.31–4.33 (m, 1H, NCH*H*), 4.18–4.72 (m, 9H, FcH), 7.26–7.57 (m, 10H, 2×PhH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.51, 29.7, 30.7, 32.5, 48.8, 56.3, 56.5, 65.9, 69.5, 69.9, 70.1, 71.1, 128.4, 128.5, 128.7, 128.8, 129.0, 132.6, 132.8, 133.0, 133.2, 136.4, 138.6, 169.4; IR (KBr pellets): 3098, 3053, 2921, 1601, 1462, 1404, 1159, 1099, 823, 747 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{28}FeNOP$: 481.1258 (M^++H), found: 481.1286.

4.6. Synthesis of (*S*)-(−)-*N*-ferrocenoyl-2-[(diphenylphosphinyl)methyl]-pyrrolidine 14

Powdered compound **13** (100 mg, 0.21 mmol) was placed in a glass vessel, and then exposed to air at room temperature, and often stirred with a glass stick. After about 48 h (monitored by thin layer chromatography), purification of the resulting solid by preparative silica gel TLC plate (CH_2Cl_2/acetone=3/1) afforded compound **14** (92 mg) in 89% yield. Compound **14** was recrystallized with EtOAc to afford orange red crystal. Mp 129.4–130.2 °C; $[\alpha]_D^{20}$ +6 (*c* 0.3 in CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.8–2.32 (m, 6H, $C\mathit{H}_2C\mathit{H}_2$, $PC\mathit{H}_2$), 3.51–3.60 (m, 1H, NC*H*H), 3.85–3.91 (m, 1H, NCH*H*), 4.30–4.37 (m, 1H, NCH), 4.19–4.74 (m, 9H, FcH), 7.26–8.08 (m, 10H, 2×PhH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.46, 30.42, 33.30, 48.52, 54.83, 69.53, 69.88, 70.06, 70.35, 70.82, 128.51, 128.63, 128.95, 130.29, 130.38, 131.21, 131.31, 131.50, 132.35, 169.75; IR (KBr pellets): 3098, 3053, 2921, 1601, 1462, 1404, 1159, 1115, 1099, 1028, 823 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{29}FeNO_2P$: 498.1285 (M^++H), found: 498.1264.

4.7. General procedure for the asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines

A solution of $Cu(OTf)_2$ (16.3 mg, 0.045 mmol) and ligand **13** (10.1 mg, 0.021 mmol) in dry toluene (3 mL) was stirred for 1 h at room temperature under a nitrogen atmosphere. *N*-(Diphenylphosphinoyl)imine **15** (0.3 mmol) was added, and the solution was stirred for an additional 10 min; then diethylzinc (1 mol/L in *n*-hexane, 0.9 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 48 h at −5 to 0 °C, and then saturated aqueous NH_4Cl (10 mL) was added. After extraction with CH_2Cl_2 (3×15 mL), the combined organic layers were dried over anhydrous Na_2SO_4. The residue obtained upon removal of volatiles under reduced pressure was purified by the preparative silica gel TLC plate (ethyl acetate) to afford the addition product *N*-(1-arylpropyl)-*P*,*P*-diphenylphosphinic amide **16**.

4.7.1. (*R*)-*N*-(1-Phenylpropyl)-*P*,*P*-diphenylphosphinoylamide 16a (entry 1 in Table 3). White solid. Mp 117.5–118.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, 3H, *J*=7.4 Hz, $CH_2C\mathit{H}_3$), 1.80–1.89 (m, 1H, $C\mathit{H}HCH_3$), 1.98–2.10 (m, 1H, $CH\mathit{H}CH_3$), 3.23–3.27 (m, 1H, NH), 4.06–4.14 (m, 1H, C*H*NH), 7.14–7.43 (m, 11H, ArH), 7.76–7.87 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (CH_3), 32.5 (CH_2), 57.2 (CHNH), 126.6, 127.1, 128.2,

128.4, 128.4 (Ar), 128.5, 128.5, 131.7, 131.7, 131.8, 131.9, 132.6, 132.7, 143.5 (Ar); IR (KBr pellets): 3141, 1457, 1435, 1190, 1105, 905, 752 cm^{-1}. Enantiomeric excess: 78%, Chiralcel OD, hexane/*i*-PrOH=90/10, 0.5 mL/min, t_R=12.9 min, t_S=16.6 min.

4.7.2. (*R*)-*N*-[1-(2-Methoxylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 16b (entry 2 in Table 3). White solid. Mp 118–119.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (t, 3H, J=7.4 Hz, CH_3CH$_2$), 1.87–2.03 (m, 2H, CH$_2$CH$_3$), 3.73 (s, 3H, CH_3O), 3.95–4.00 (m, 1H, NH), 4.13–4.17 (m, CHN), 6.83–6.94 (m, 3H, ArH), 7.21–7.44 (m, 7H, ArH), 7.71–7.84 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2 (CH_3), 31.1 (CH_2), 55.2 (CH_3O), 55.4 (CHNH), 111.0, 120.6, 128.1, 128.2, 128.3, 128.4, 128.6, 131.3, 131.5, 131.6, 131.8, 131.9, 132.6, 132.7, 157.0 (Ar); IR (KBr pellets): 3185, 3058, 1602, 1494, 1463, 1243, 1192, 1125, 910, 752 cm^{-1}. Enantiomeric excess: 78%, Chiralpak AD, hexane/*i*-PrOH=90/10, 1.0 mL/min, t_R=22.2 min, t_S=27.7 min.

4.7.3. (*R*)-*N*-[1-(4-Methoxylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 16c (entry 3 in Table 3). White solid. Mp 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J=7.3 Hz, 3H, CH$_2$CH_3) 1.86–1.74 (m, 1H, CHHCH$_3$), 2.06–1.94 (m, 1H, CHHCH$_3$), 3.20–3.21 (m, 1H, NH), 3.79 (s, 3H, OCH_3), 4.04–4.06 (m, 1H, CHN), 6.82–7.08 (m, 4H, ArH), 7.33–7.50 (m, 6H, ArH), 7.76–7.86 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (CH_3), 32.3 (CH_2), 55.1 (CH_3O), 56.5 (CHN), 113.6, 127.5, 128.1, 128.3, 131.5, 131.6, 132.0, 132.0, 132.1, 133.2, 135.5, 158.4 (Ar); IR (KBr pellets): 3146, 1513, 1452, 1438, 1247, 1194, 1175, 752 cm^{-1}. Enantiomeric excess: 84%, Chiralpak AD, hexane/*i*-PrOH=80/20, 1.0 mL/min, t_R=11.0 min, t_S=13.5 min.

4.7.4. (*R*)-*N*-[1-Benzo[1,3]dioxol-5-yl-propyl]-*P*,*P*-diphenylphosphinoylamide 16d (entry 4 in Table 3). White solid. Mp 115.2–116.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, 3H, J=7.2 Hz, CH_3CH$_2$), 1.74–1.79 (m, 1H, CHHCH$_3$), 1.95–1.99 (m, 1H, CHHCH$_3$), 3.24 (br s, 1H, NH), 4.00–4.03 (m, 1H, CHN), 5.93 (s, 2H, OCH_2O), 6.56–6.70 (m, 3H, ArH), 7.27–7.50 (m, 6H, ArH); 7.74–7.88 (m, 4H ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (CH_3), 32.5 (CH_2), 57.1 (CHNH), 100.9, 106.8, 108.0, 120.1, 128.3, 128.4, 131.7, 131.8, 131.9, 132.5, 132.6, 137.6, 146.5, 147.8 (Ar); IR (KBr pellets): 3148, 1437, 1244, 1178, 1107, 1041, 931, 723 cm^{-1}. Enantiomeric excess: 78%, Chiralpak AD, hexane/*i*-PrOH=80/20, 1.0 mL/min, t_R=9.7 min, t_S=15.0 min.

4.7.5. (*R*)-*N*-[1-(4-Methylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 16e (entry 5 in Table 3). White solid. Mp 124.5–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, J=7.6 Hz, 3H, CH$_2$CH_3) 1.78–1.85 (m, 1H, CHHCH$_3$), 1.96–2.32 (m, 1H, CHHCH$_3$), 2.33 (s, 3H, CH_3), 3.26 (br s, 1H, NH), 4.01–4.05 (m, 1H, CHN), 7.04–7.11 (m, 4H, ArH), 7.32–7.45 (m, 6H, ArH), 7.74–7.86 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (CH_3), 32.3 (CH_2), 55.1 (CH_3Ar), 56.5 (CHNH), 126.5, 128.3, 129.1, 131.6, 131.7, 131.9, 132.6, 133.2, 136.6, 140.6 (Ar); IR (KBr pellets): 3135, 1452, 1435, 1178, 1089, 1060, 931, 722 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}NOP$: 348.1517 (M^++H), found: 348.1519. Enantiomeric excess: 83%, Chiralpak AD, hexane/*i*-PrOH=80/20, 1.0 mL/min, t_R=8.7 min, t_S=10.2 min.

4.7.6. (*R*)-*N*-[1-(2-Chlorophenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 16f (entry 6 in Table 3). White solid. Mp 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J=7.3 Hz, 3H, CH$_2$CH_3) 1.80–2.01 (m, 2H, CH_2CH$_3$), 3.59–3.61 (m, 1H, NH), 4.48–4.50 (m, 1H, CHN), 7.11–7.34 (m, 6H, ArH), 7.36–7.53 (m, 4H, ArH), 7.67–7.76 (m, 2H, ArH), 7.80–7.90 (m, 2H, ArH); IR (KBr pellets): 3059, 1437, 1185, 1124, 1111, 908, 750 cm^{-1}. Enantiomeric excess: 90%, Chiralpak AD, hexane/*i*-PrOH=80/20, 0.7 mL/min, t_R=14.3 min, t_S=19.1 min.

4.7.7. (*R*)-*N*-[1-(4-Chlorophenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 16g (entry 7 in Table 3). White solid. Mp 154.5–155.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, J=7.3 Hz, 3H, CH$_2$CH_3) 1.73–1.86 (m, 1H, CHHCH$_3$), 1.92–2.04 (m, 1H, CHHCH$_3$), 3.31 (br s, 1H, NH), 4.05–4.10 (m, 1H, CHN), 7.08 (d, J=8.4 Hz, 2H, ArH), 7.23–7.44 (m, 8H, ArH), 7.70–7.73 (m, 2H, ArH), 7.83–7.86 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (CH_3), 32.4 (CH_2), 56.6 (CHNH), 128.0 (Ar), 128.3, 128.4, 128.5, 128.6, 131.8, 131.9, 132.5, 132.6, 132.8, 142.1 (Ar); HRMS (ESI) calcd for $C_{21}H_{21}ClNOP$: 368.0971 (M^+−H), found: 368.0974. Enantiomeric excess: 73%, Chiralpak AD, hexane/*i*-PrOH=80/20, 1.0 mL/min, t_R=7.2 min, t_S=10.9 min.

4.7.8. (*R*)-*N*-[1-(2-Furyl)propyl]-*P*,*P*-diphenylphosphinoylamide 16h (entry 8 in Table 3). White solid. Mp 96–97.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J=7.4 Hz, 3H, CH$_2$CH_3), 1.83–2.05 (m, 2H, CH_2CH$_3$), 3.30 (br s, 1H, NH), 4.15–4.17 (m, 1H, CHN), 6.04 (d, J=3.2 Hz, 1H), 6.23 (dd, J=3.2, 1.8 Hz, 1H), 7.31 (dd, J=1.8, 0.8 Hz, 1H), 7.34–7.48 (m, 6H, ArH), 7.88 (m, 4H, ArH); IR (KBr pellets): 3182, 1437, 1176, 1124, 1009, 893, 724 cm^{-1}. Enantiomeric excess: 85%, Chiralpak AD, hexane/*i*-PrOH=95/5, 1.0 mL/min, t_R=37.8 min, t_S=41.8 min.

4.8. X-ray crystallographic study

An orange red crystal of approximate dimensions 0.20×0.18×0.18 mm was mounted on a glass fibre. Crystallographic data for **14** were measured on a Rigaku RAXIS-IV imaging plate area detector. The data were collected at 291(2) K using graphite monochromated Mo Kα (λ=0.71073 Å), 2.05°<θ<27.52°. The structures were solved by a direct method and expanded by using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan crystallographic software package. Crystal data for **14**: monoclinic C_2: a=23.329 [5] Å, α=90°, b=8.1310 [16] Å, β=120.96 [3]°, c=14.925 [3] Å, γ=90°; V=2427.8 (8) Å^3; formula unit $C_{28}H_{29}FeNO_2P$ with Z=4; D_{calcd}=1.385 g cm^{-3}; F (000)=1060; μ(Mo Kα)=0.715 mm^{-1}. Full-matrix least-squares refinement on F^2 based on 3858 independent reflections (R_{int}=0.0233) converged with 303 parameters. Final R indices [I>2 sigma (I)]: R_1=0.0385, wR_2=0.0821; R indices (all data): R_1=0.0385, wR_2=0.0821; GoF=1.052.

Acknowledgements

We are grateful to the National Natural Sciences Foundation of China (NNSFC: 20172047), the Ministry of Education of China, and the Education commission of Henan Province for the financial supports.

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1,3-Dipolar cycloaddition of α-alkoxycarbonylnitrones with vinyl ethers and allyl alcohols in the presence of Eu(fod)$_3$: selective activation of (*Z*)-isomers of the nitrones

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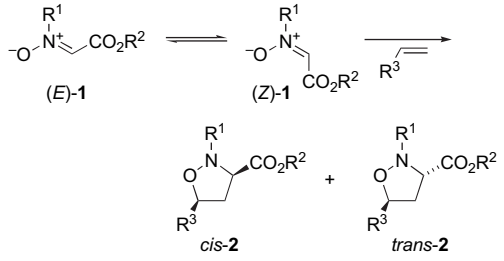
Received 11 September 2006; revised 5 October 2006; accepted 6 October 2006
Available online 3 November 2006

Abstract—Uncatalyzed cycloaddition of α-alkoxycarbonylnitrones **1** with vinyl ethers **7** gave mixtures of *cis*- and *trans*-cycloadducts **8**, whereas Eu(fod)$_3$-catalyzed cycloaddition of **1** with **7** gave the *trans*-cycloadducts *trans*-**8** in a highly stereoselective manner. NMR studies indicated that Eu(fod)$_3$ selectively activated (*Z*)-nitrones (*Z*)-**1** in *E*,*Z*-equilibrium mixtures of nitrones **1**. In contrast, the reaction of **1** with allyl alcohols **12** in the presence of Eu(fod)$_3$ resulted in sequential transesterification and intramolecular cycloaddition to give intramolecular cycloadducts **13**.

1. Introduction

Intermolecular 1,3-dipolar cycloadditions of nitrones are fundamental and very useful for synthesizing various biologically useful compounds, including alkaloids, antibiotics, and amino acids.[1] Cycloaddition of α-alkoxycarbonylnitrone **1** is particularly attractive because of its high reactivity. However, the cycloaddition of **1** with olefins often gives mixtures of *cis*- and *trans*-isoxazolidines *cis*-**2** and *trans*-**2**,[2] probably due to *E*,*Z*-equilibration of **1** in solution even at room temperature (Scheme 1). Although, the geometrical equilibration of **1** was reported in early 1980s,[3] there was little attempt to control the equilibration in the cycloaddition until the middle of the 1990s.

In the course of studies to achieve cycloaddition with controlling the equilibrium, the reaction of **1** with allyl alcohols in the presence of magnesium bromide,[4] salt effects on 1,3-dipolar cycloaddition of α-carboxylnitrone with olefins,[5] and asymmetric reaction of nitrone **1** with vinyl ethers using a chiral copper catalyst[6] and cyclic nitrones as (*E*)-geometry-fixed equivalents of **1**[7–10] have been reported. Recently, we found that Eu(fod)$_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanatedionate) europium(III)] can selectively activate (*Z*)-**1** by forming (*Z*)-**1**–Eu(fod)$_3$ complex, which reacts with vinyl ethers to give the *trans*-isoxazolidine with excellent stereoselectivity.[11] It was also reported that treatment of **1** with allyl alcohols in the presence of Eu(fod)$_3$ induces tandem transesterification and intramolecular cycloaddition, affording bicyclic compounds. We now present a full account of this work, including a consideration of the electronic properties of **1**, NMR studies of **1** in the presence of Eu(fod)$_3$, and cycloaddition of a related cyclic nitrone with vinyl ethers in the presence of Eu(fod)$_3$.



Scheme 1.

Keywords: 1,3-Dipolar cycloaddition; α-Alkoxycarbonylnitrones; Vinyl ethers; Europium; Stereoselective.
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doi:10.1016/j.tet.2006.10.014

2. Results and discussion

2.1. Electronic properties of α-alkoxycarbonylnitrone 1

We considered that the resonance effect between the nitrone moiety and α-carbonyl group may be the reason for the facile *E*,*Z*-equilibration of **1**; if this is so, the nitrone **1** can be regarded as an isoelectronic structure of a β-diketone anion since both have six π-electrons in a five-membered conjugated system (Fig. 1).

To test this working hypothesis, the bond distances between atoms were calculated at the HF/6-31G* level for the nitrone **3** bearing a ketone group as an electron-withdrawing group, the nitrone **4** without a conjugated system, acetone **5**, and the anion of the β-diketone **6** (Fig. 2).[12] The nitrogen–oxygen single bonds of (*E*)-**3** and (*Z*)-**3** are shorter than that of **4**, and the nitrogen–carbon double bonds of (*E*)-**3** and (*Z*)-**3** are longer than that of **4**. These findings can be interpreted by assuming that the nitrogen–oxygen single bond of **3** has the partial nature of a double bond, and the nitrogen–carbon double bond of **3** has the partial nature of a single bond. In addition, the length of the carbon–oxygen double bond of (*E*)-**3** and (*Z*)-**3** was estimated to be between those in acetone **5** and the anion **6**. All these data strongly suggest that the nitrone **3** exhibits a resonance effect between the nitrone moiety and the α-carbonyl group similar to that of the anion **6**; in other words, the nitrone **3** is isoelectronic with the β-diketone anion.

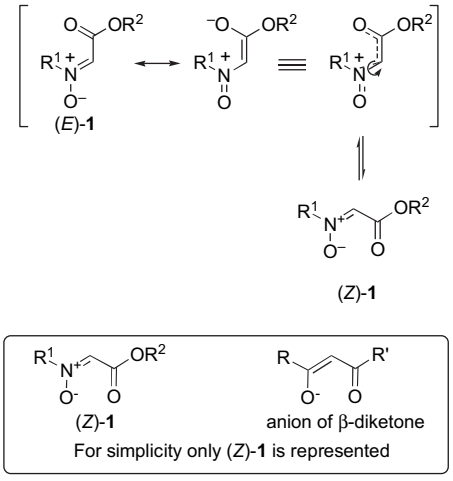


Figure 1.

2.2. Cycloaddition of 1 with vinyl ethers in the presence of Eu(fod)$_3$

A shift reagent for NMR spectra, Eu(fod)$_3$, bears β-diketone anions (fod; 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) as ligands (Fig. 3). Therefore, we expected that Eu(fod)$_3$ would selectively activate (*Z*)-**1** in an equilibrium mixture of (*Z*)-**1** and (*E*)-**1** by forming (*Z*)-**1**–Eu(fod)$_3$ complex, which, in turn, could stereoselectively undergo 1,3-dipolar cycloaddition (Scheme 2). Since the Lewis acid should lower the LUMO energy of (*Z*)-**1**,[13] use of dipolarophiles having a high HOMO energy, for example, vinyl ethers, is reasonable.[14–16]

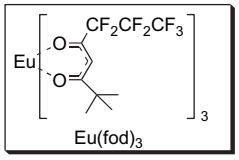
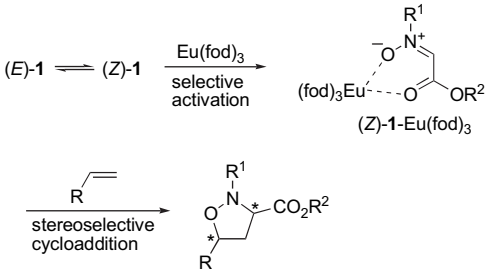


Figure 3.



Scheme 2.

Thus, the reactions of nitrones **1a** and **1b** with several vinyl ethers **7a–d** were first examined as shown in Scheme 3 and Table 1. Reactions of **1** with **7** in the absence of Eu(fod)$_3$ gave mixtures of cycloadducts *trans*-**8** and *cis*-**8** (entries 1, 3, 5, 8, and 10), whereas the reactions of **1** with **7** in the presence of a stoichiometric amount of Eu(fod)$_3$ afforded *trans*-**8** with high selectivity (entries 2, 4, 6, 9, and 11). The effect of Eu(fod)$_3$ in the reactions of **1b** with **7a–d** was remarkably compared with that in the reaction of **1a** with **7a** (entry 2 vs entry 4). Equilibration of **1b** is known to be much faster than that of **1a**,[3a] and hence **1b** would more efficiently form the (*Z*)-**1**–Eu(fod)$_3$ complex. Although, the use of a reduced amount of Eu(fod)$_3$ required a prolonged reaction time, satisfactory *trans*-selectivity was still obtained (entry 7).

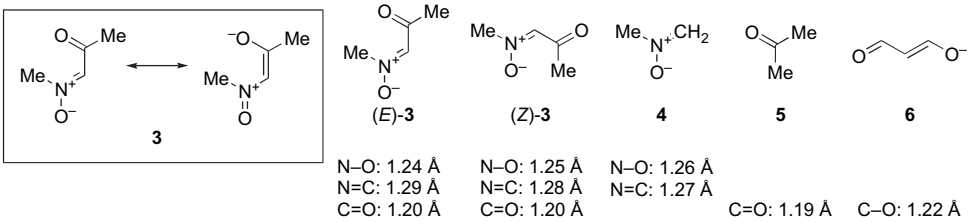
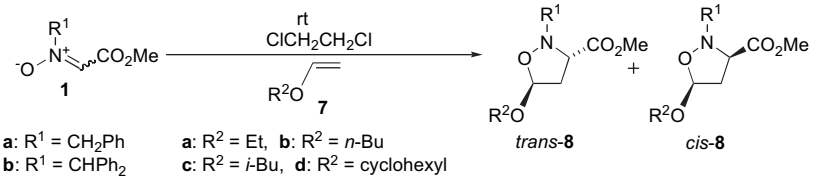


Figure 2. Results of HF/6-31G* calculations for **3**–**6**.

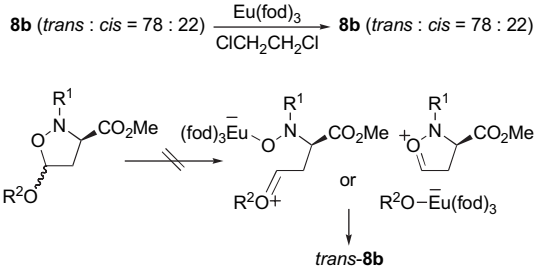


Scheme 3.

Table 1. Reaction of nitrones **1a**,**b** with vinyl ethers **7a–d**

Entry	Nitrone	Eu(fod)$_3$	Conditions	Product	Yield (%)	Ratio (*trans*-**8**/*cis*-**8**)
1	**1a**	None	**7a** (20 equiv), 36 h	**8a**	86	78:22
2		1 equiv	**7a** (20 equiv), 7 h		87	85:15
3	**1b**	None	**7a** (20 equiv), 36 h	**8b**	89	72:28
4		1 equiv	**7a** (20 equiv), 7 h		Quant.	>98:2
5	**1b**	None	**7b** (20 equiv), 36 h	**8c**	73	75:25
6		1 equiv	**7b** (20 equiv), 6 h		Quant.	>98:2
7		0.3 equiv	**7b** (3 equiv), 48 h		85	>98:2
8	**1b**	None	**7c** (20 equiv), 36 h	**8d**	76	74:26
9		1 equiv	**7c** (20 equiv), 7 h		89	95:5
10	**1b**	None	**7d** (20 equiv), 36 h	**8e**	82	71:29
11		1 equiv	**7d** (20 equiv), 7 h		92	>98:2

As shown in Scheme 4, the treatment of **8b** (*trans*:*cis*=72:28) with Eu(fod)$_3$ resulted in complete recovery of the starting mixture without any change in the ratio.[17] This result strongly suggests that the product *trans*-**8b** obtained by the reaction of **1b** with **7a** in the presence of Eu(fod)$_3$ is a kinetically controlled product. The stereochemical assignments of cycloadducts **8a** and **8b** were made on the basis of comparison of their ^{1}H NMRs with those of known compounds *trans*-**8a**′[6a] and *cis*-**8a**′,[6a] as depicted in Figure 4. Furthermore, the structure of *trans*-**8b** was confirmed by the NOE difference spectra. The stereochemistries of the other products, *trans*-**8c**,**d**, were assigned by comparing their ^{1}H NMR spectra with that of *trans*-**8b**.



Scheme 4.

To examine the coordinating abilities of the nitrones and vinyl ethers, NMR studies of the nitrones **1b** and **9**, and the vinyl ether **7a** in the presence or absence of Eu(fod)$_3$ were conducted (Table 2). In the ^{1}H NMR spectrum ($CDCl_3$) of **1b** in the presence of 0.15 equiv of Eu(fod)$_3$, the signals of the methoxy protons (Ha) and methyne proton (Hb) of the *Z*-isomer were shifted downfield by 1.23 and 0.46 ppm, respectively, whereas the signal of the methoxy protons (Ha) of the *E*-isomer was shifted by only 0.09 ppm. In the case of **9**, the signals of both Ha and Hb were more strongly shifted than that of Ha′. However, in the ^{1}H NMR spectrum

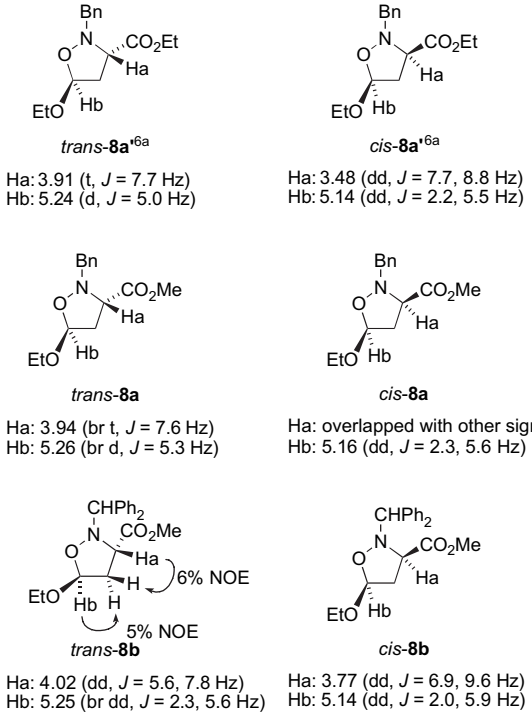
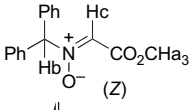
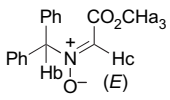
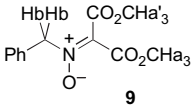
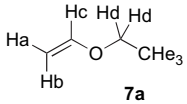


Figure 4.

of **7a**, none of the protons showed a large down-field shift (<0.07 ppm). These results suggested that the nitrones **1b** and **9** formed (*Z*)-**1b**–Eu(fod)$_3$ and **9**–Eu(fod)$_3$ complexes, respectively, and that Eu(fod)$_3$ did not readily coordinate with the vinyl ether **7a** (Fig. 5).

All these results are consistent with the reaction mechanism as shown in Scheme 5. Thus, Eu(fod)$_3$ selectively activates (*Z*)-**1** by forming (*Z*)-**1**–Eu(fod)$_3$ complex, which reacts

Table 2. Chemical shifts of **1b**, **9**, and **7a** in the presence of $Eu(fod)_3$

Compound	No. additive (A) δ (ppm)	+0.15 equiv of $Eu(fod)_3$ (B) δ (ppm)	(B)–(A) $\Delta\delta$ (ppm)
 (*Z*)	Ha: 3.71 Hb: 6.28 Hc: —[a]	Ha: 4.94 Hb: 6.74 Hc: —[a]	Ha: 1.23 Hb: 0.46 Hc: —[a]
 (*E*) **1b**	Ha: 3.71 Hb: —[a] Hc: 8.24	Ha: 3.80 Hb: —[a] Hc: 8.28	Ha: 0.09 Hb: —[a] Hc: 0.04
 **9**	Ha: 3.88 Ha′: 3.84 Hb: 5.73	Ha: 4.31 Ha′: 3.97 Hb: 5.98	Ha: 0.43 Ha′: 0.13 Hb: 0.25
 **7a**	Ha: 3.98 Hb: 4.18 Hc: 6.46 Hd: 3.75 He: 1.29	Ha: 4.02 Hb: 4.23 Hc: 6.53 Hd: 3.81 He: 1.34	Ha: 0.04 Hb: 0.05 Hc: 0.07 Hd: 0.06 He: 0.05

[a] The signal was overlapped with those of aromatic protons.

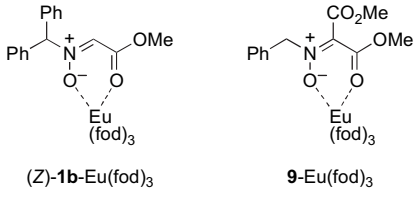
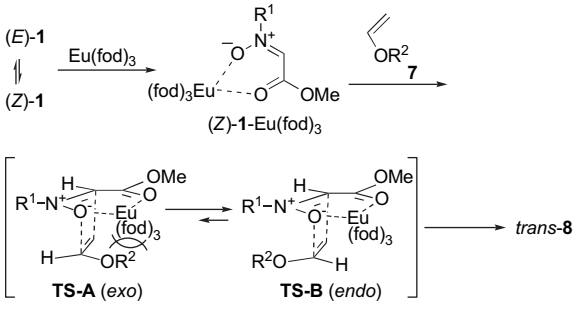


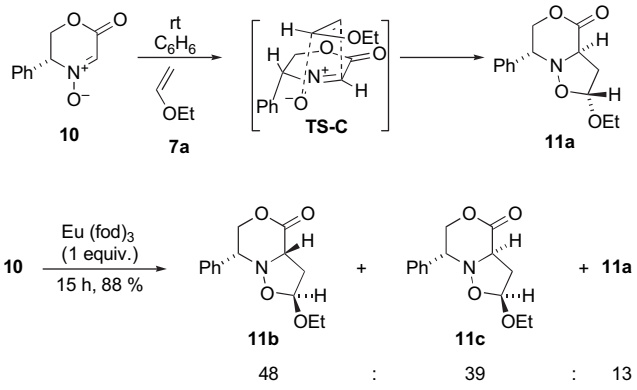
Figure 5.

with the vinyl ether **7** via *endo* transition state **TS-B** to give the cycloadduct *trans*-**8**, because the *exo* transition state **TS-A** would have severe steric interaction between the substituent (R^2O) and the bulky $Eu(fod)_3$.



Scheme 5.

For comparison with the reaction of the *E*,*Z*-equilibrating nitrone **1**, we examined the reaction of the cyclic nitrone **10**[7a–h] with vinyl ether **7a** in the presence of $Eu(fod)_3$ (Scheme 6). Because the nitrone **10** is fixed in *E*-geometry, it cannot act as a bidentate ligand of $Eu(fod)_3$. In the absence of $Eu(fod)_3$, the reaction of **10** with vinyl ether is known to give **11a** as the major cycloadduct via the β-*exo* transition state **TS-C** having the least steric hindrance.[7a,c] In contrast, the reaction of **10** with **7a** in the presence of $Eu(fod)_3$, surprisingly, afforded **11b** as the major isomer. The stereo structure of **11b** was established by X-ray diffraction analysis (Fig. 6)[18] and that of **11c** was tentatively assigned as shown



Scheme 6.

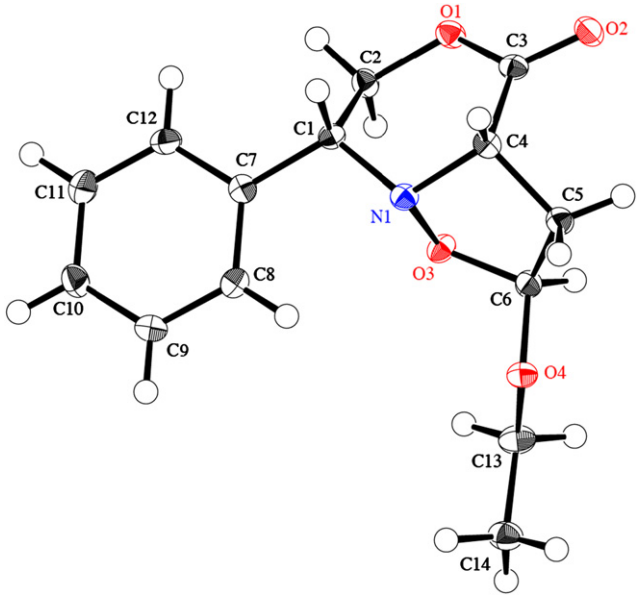
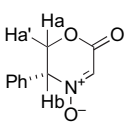
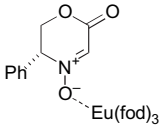
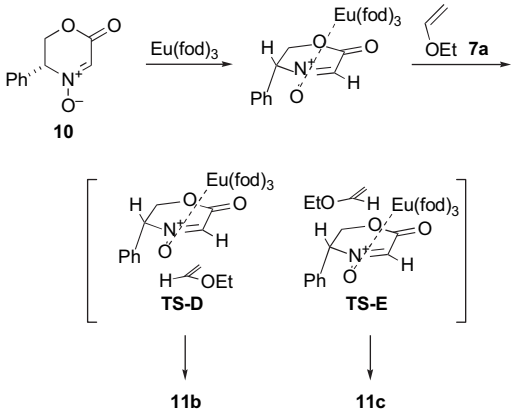


Figure 6. ORTEP drawing of **11b**.

Table 3. Chemical shifts of **10** in the presence of $Eu(fod)_3$

Compound	No. additive (A) δ (ppm)	+0.05 equiv of $Eu(fod)_3$ (B) δ (ppm)	(B)−(A) $\Delta\delta$ (ppm)	
 **10**	Ha: 4.74 Ha′: 4.84 Hb: 5.10	Ha: 4.85 Ha′: 4.94 Hb: 5.40	Ha: 0.11 Ha′: 0.10 Hb: 0.30	 **10**-$Eu(fod)_3$

in Scheme 6. To clarify the reason for the difference, the coordination mode of **10** with $Eu(fod)_3$ was verified again by means of NMR experiments (Table 3). The ^1H NMR spectrum of **10** with 0.05 equiv of $Eu(fod)_3$ showed that the signal of proton Hb was shifted more than those of Ha and Ha′. This suggested that $Eu(fod)_3$ coordinated with the oxygen atom of the nitrone moiety instead of the carbonyl-oxygen atom, forming **10**–$Eu(fod)_3$ complex. The stereochemical course of the reaction of **10** with **7a** in the presence of $Eu(fod)_3$ can be explained by considering the transition states **TS-D** and **TS-E**, as shown in Scheme 7. Thus,



Scheme 7.

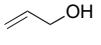
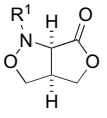
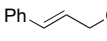
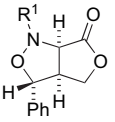
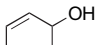
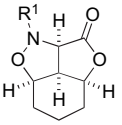
$Eu(fod)_3$ coordinating with the oxygen atom is located on the opposite side of the phenyl group, thereby avoiding steric interaction. As a result, the vinyl ether **7a** approaches from the vacant sites to react via α-*exo* **TS-D** and **TS-E**, affording **11b** and **11c**, respectively.

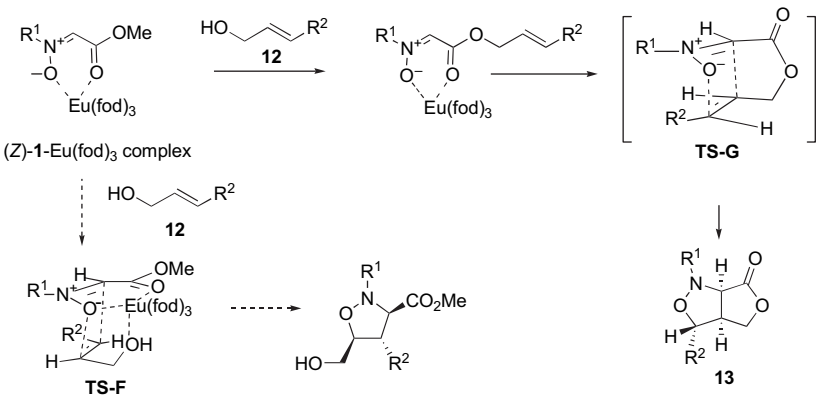
2.3. Reaction of 1 with allyl alcohols in the presence of $Eu(fod)_3$

Next, we turned our attention to the use of allyl alcohols **12** as the dipolarophiles, which might coordinate with the Lewis acid as in the case of the reaction using $MgBr_2$.[4] However, the reaction of allyl alcohols **12** in the presence of $Eu(fod)_3$ gave intramolecular-type bicyclic products **13** (Table 4). Thus, treatment of the nitrone **1b** with large excess of allyl alcohol **12a** and a stoichiometric amount of $Eu(fod)_3$ caused transesterification and intramolecular cycloaddition to give **13a** (entry 1). Use of other allyl alcohols **12b** and **12c** also gave the corresponding intramolecular cycloadducts **13b** and **13c** in moderate yields (entries 2 and 3). As observed in the titanium tetrachloride-catalyzed reaction, the amounts of **12** and $Eu(fod)_3$ could be reduced in the presence of molecular sieves 4 Å (entry 3).[19b]

These results are similar to those of the reactions employing titanium catalyst,[19] and different from those of the reactions using magnesium bromide.[4] In the case of allyl alcohols, transesterification was promoted by $Eu(fod)_3$, and the cycloaddition proceeded not via **TS-F** but via **TS-G** to afford the intramolecular cycloadducts **13** (Scheme 8).

Table 4. Reaction of nitrone **1b** with allyl alcohols **12a–c** in the presence of $Eu(fod)_3$

Entry	Allyl alcohol	Conditions	Yield (%)	Product
1	 **12a** (10 eq.)	1 equiv $Eu(fod)_3$, 4 Å MS, $ClCH_2CH_2Cl$, rt, 14 h	68	 **13a**
2	 **12b** (5 eq.)	1 equiv $Eu(fod)_3$, 4 Å MS, $ClCH_2CH_2Cl$, rt, 5 days	92	 **13b**
3	 **12c** (3 eq.)	0.1 equiv $Eu(fod)_3$, 4 Å MS, $ClCH_2CH_2Cl$, rt then 60 °C, 10 h	71	 **13c**



Scheme 8.

3. Conclusion

We investigated the activation mode of α-alkoxycarbonylnitrone derivatives with $Eu(fod)_3$. $Eu(fod)_3$ selectively activated the *Z*-isomer of nitrones (**1**) existing as *E*,*Z*-equilibrium mixtures by forming the (*Z*)-**1**–$Eu(fod)_3$ complex, which reacts with vinyl ethers to give the *trans*-adducts stereoselectively. In the reaction of *E*-geometry-fixed cyclic nitrone, the major product is different from that of the reaction without $Eu(fod)_3$. In the case of allyl alcohols **12**, $Eu(fod)_3$ promoted the transesterification between the nitrones **1** and allyl alcohols.

4. Experimental

4.1. General

All melting points were determined with a Yanagimoto MP-21 melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on Hitachi 270-30 and Shimadzu FTIR-8100 spectrometers. ^{1}H NMR spectra were measured with a JEOL JNM-EX270 (270 MHz) or a JEOL-JNM-AL300 (300 MHz) spectrometer. The chemical shifts are expressed in parts per million downfield from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual chloroform (δ=7.25) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Mass spectra were taken with a JEOL JMS-DX302 mass spectrometer. Unless otherwise noted, all experiments were carried out under an atmosphere of dry argon using anhydrous solvents. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used.

4.2. Methyl [(phenylmethyl)imino]acetate *N*-oxide (1a)

This was prepared from *N*-benzylhydroxylamine and methyl glyoxylate hemiacetal in refluxing benzene employing a Dean–Stark trap; mp 89–92 °C (hexane–AcOEt) (lit.,[3a] mp 90–92 °C).

4.3. Methyl [(diphenylmethyl)imino]acetate *N*-oxide (1b)

This was prepared from *N*-diphenylmethylhydroxylamine[20] and methyl glyoxylate by the same procedure as that described for **1a**; mp 133.5–134 °C (hexane–AcOEt) (lit.,[3a] mp 131.5–132.5 °C).

4.4. General procedure A: cycloaddition of α-methoxycarbonylnitrones (1a,b) with vinyl ethers (7a–d) in the absence of $Eu(fod)_3$ (Table 1, entries 1, 3, 5, 8, and 10)

To a stirred solution of **1** (1 equiv) in $ClCH_2CH_2Cl$ was added **7** (20 equiv) at room temperature. After completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel (hexane/AcOEt=4:1) to afford the cycloadduct **8** as an inseparable mixture of *trans*-**8** and *cis*-**8**.

4.5. General procedure B: cycloaddition of α-methoxycarbonylnitrones (1a,b) with vinyl ethers (7a–d) in the presence of $Eu(fod)_3$ (Table 1, entries 2, 4, 6, 7, 9, and 11)

To a stirred mixture of **1** (1 equiv) and $Eu(fod)_3$ (1 equiv) in $ClCH_2CH_2Cl$ was added **7** (20 equiv) at room temperature. After completion of the reaction, the mixture was diluted with $CHCl_3$ and washed successively with a 10% aqueous solution of tartaric acid and brine. The organic phase was subjected to column chromatography on Al_2O_3 to remove fod. Further purification by column chromatography on silica gel (hexane/AcOEt=4:1) afforded mainly *trans*-**8**.

4.6. Methyl (5-ethoxy-2-phenylmethylisoxazolidine-3-yl)carboxylate (8a) (Table 1, entries 1 and 2)

Following general procedure A, a 78:22 mixture (21.9 mg, 96%) of *trans*-**8a** and *cis*-**8a** was obtained from **1a** (16.7 mg, 87 μmol), **7a** (160 μl, 1.7 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 1). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H×22/100, *J*=7.3 Hz), 1.23 (t, 3H×78/100, *J*=7.3 Hz), 2.59 (ddd, 1H×78/100, *J*=1.7, 7.6, 12.9 Hz), 2.5–2.8 (m, 2H×22/100), 2.76 (ddd, 1H×78/100, *J*=5.3, 7.3, 12.9 Hz), 3.35–3.85 (m, 3H×22/100), 3.48 (qd, 1H×78/100, *J*=7.3, 9.6 Hz), 3.67 (s, 3H×78/100), 3.69 (s, 3H×22/100), 3.80 (qd, 1H×78/100, *J*=7.3, 9.6 Hz), 3.94 (br t, 1H×78/100, *J*=7.6 Hz), 4.05 (d, 1H×22/100, *J*=13.9 Hz), 4.17 (d, 1H×78/100, *J*=12.9 Hz), 4.19 (d, 1H×22/100, *J*=13.9 Hz), 4.35 (d, 1H×78/100, *J*=12.9 Hz), 5.16 (dd, 1H×22/100, *J*=2.3, 5.6 Hz), 5.26 (br d, 1H×78/100, *J*=5.3 Hz), 7.24–7.42 (m, 5H).

Following general procedure B, an 85:15 mixture (18.7 mg, 87%) of *trans*-**8a** and *cis*-**8a** was obtained from **1a** (15.7 mg, 87 μmol), **7a** (160 μl, 1.7 mmol), $Eu(fod)_3$ (90 mg, 87 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 2). IR ($CHCl_3$) 1742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H×15/100, J=7.3 Hz), 1.23 (t, 3H×85/100, J=7.3 Hz), 2.59 (ddd, 1H×85/100, J=1.7, 7.6, 12.9 Hz), 2.5–2.8 (m, 2H×15/100), 2.76 (ddd, 1H×85/100, J=5.3, 7.3, 12.9 Hz), 3.35–3.85 (m, 3H×15/100), 3.48 (qd, 1H×85/100, J=7.3, 9.6 Hz), 3.67 (s, 3H×85/100), 3.69 (s, 3H×15/100), 3.80 (qd, 1H×85/100, J=7.3, 9.6 Hz), 3.94 (br t, 1H×85/100, J=7.6 Hz), 4.05 (d, 1H×15/100, J=13.9 Hz), 4.17 (d, 1H×85/100, J=12.9 Hz), 4.19 (d, 1H×15/100, J=13.9 Hz), 4.35 (d, 1H×85/100, J=12.9 Hz), 5.16 (dd, 1H×15/100, J=2.3, 5.6 Hz), 5.26 (br d, 1H×85/100, J=5.3 Hz), 7.24–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.9, 15.0, 39.7, 52.4, 63.3, 65.0, 65.4, 103.5, 127.4, 128.3, 129.0, 137.0, 171.5; MS (*m*/*z*) 265 (0.3), 220 (28), 175 (10), 143 (13), 116 (43), 105 (100); HRMS calcd for $C_{14}H_{19}NO_4$: 265.1314, found: 265.1309.

4.7. Methyl (2-diphenylmethyl-5-ethoxyisoxazolidine-3-yl)carboxylate (8b) (Table 1, entries 3 and 4)

Following general procedure A, a 72:28 mixture (31.4 mg, 89%) of *trans*-**8b** and *cis*-**8b** was obtained from **1b** (23.2 mg, 86 μmol), **7a** (160 μl, 1.7 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 3). ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (t, 3H×72/100, J=7.3 Hz), 1.23 (t, 3H×28/100, J=7.3 Hz), 2.45–2.72 (m, 2H×28/100), 2.60 (ddd, 1H×72/100, J=2.3, 7.9, 13.2 Hz), 2.80 (td, 1H×72/100, J=5.6, 13.2 Hz), 3.25 (qd, 1H×72/100, J=7.3, 9.6 Hz), 3.31–3.44 (m, 2H×28/100), 3.42 (s, 3H×28/100), 3.38 (qd, 1H×72/100, J=7.3, 9.6 Hz), 3.59 (s, 3H×72/100), 3.77 (dd, 1H×28/100, J=6.9, 9.6 Hz), 4.02 (dd, 1H×72/100, J=5.6, 7.8 Hz), 4.91 (br s, 1H×28/100), 5.14 (dd, 1H×28/100, J=2.0, 5.9 Hz), 5.25 (br dd, 1H×72/100, J=2.3, 5.6 Hz), 5.28 (br s, 1H×72/100), 7.10–7.60 (m, 10H).

Following general procedure B, *trans*-**8b** (29.5 mg, quant) was obtained from **1b** (23.3 mg, 87 μmol), **7a** (160 μl, 1.7 mmol), $Eu(fod)_3$ (89.8 mg, 87 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 4). Mp 64–65 °C (MeOH–H_2O); IR ($CHCl_3$) 1743 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (t, 3H, J=7.3 Hz), 2.60 (ddd, 1H, J=2.3, 7.9, 13.2 Hz, spin saturation at δ=4.02 → NOE 6%), 2.80 (td, 1H, J=5.6, 13.2 Hz, spin saturation at δ=5.25 → NOE 6%), 3.25 (qd, 1H, J=7.3, 9.6 Hz), 3.38 (qd, 1H, J=7.3, 9.6 Hz), 3.59 (s, 3H), 4.02 (dd, 1H, J=5.6, 7.8 Hz), 5.25 (br dd, 1H, J=2.3, 5.6 Hz), 5.28 (br s, 1H), 7.10–7.35 (m, 6H), 7.48 (br d, 2H, J=7.9 Hz), 7.57 (br d, 2H, J=7.9 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 14.8, 39.6, 52.2, 63.7, 64.3, 77.1, 104.3, 126.9, 127.2, 127.8, 128.0, 128.2, 128.7, 141.4, 142.7, 172.2; HRMS calcd for $C_{20}H_{23}NO_4$: 341.1627, found: 341.1616.

4.8. Methyl [5-(*n*-butyloxy)-2-diphenylmethylisoxazolidine-3-yl]carboxylate (8c) (Table 1, entries 5–7)

Following general procedure A, a 75:25 mixture (17.4 mg, 73%) of *trans*-**8c** and *cis*-**8c** was obtained from **1b** (17.2 mg, 64 μmol), **7b** (164 μl, 1.3 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 5). ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7.3 Hz), 1.2–1.7 (m, 4H), 2.4–2.9 (m, 2H), 3.1–3.8 (m, 2H+25/100H), 3.43 (s, 3H×25/100), 3.57 (s, 3H×75/100), 4.00 (dd, 1H×75/100, J=6.0, 7.3 Hz), 4.91 (s, 1H×25/100), 5.13 (br dd, 1H×25/100, J=2.0, 5.9 Hz), 5.25 (br dd, 1H×75/100, J=2.0, 6.0 Hz), 5.25 (s, 1H×75/100), 7.1–7.6 (m, 10H).

Following general procedure B, compound *trans*-**8c** (26.0 mg, quant) was obtained from **1b** (17.9 mg, 67 μmol), **7a** (160 μl, 1.3 mmol), $Eu(fod)_3$ (66.4 mg, 64 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 6). Furthermore, *trans*-**8c** (19.5 mg, 85%) was also obtained from **1b** (16.7 mg, 60 μmol), **7a** (23 μl, 0.18 mmol), $Eu(fod)_3$ (18.6 mg, 18 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 7). Mp 49–50 °C (MeOH–H_2O); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7.3 Hz), 1.32 (br sext, 2H, J=7.3 Hz), 1.42–1.58 (m, 2H), 2.59 (ddd, 1H, J=2.0, 7.6, 12.9 Hz), 2.77 (br td, 1H, J=6.0, 12.9 Hz), 3.18 (td, 1H, J=6.9, 9.2 Hz), 3.36 (td, 1H, J=6.9, 9.2 Hz), 3.57 (s, 3H), 4.00 (dd, 1H, J=6.0, 7.3 Hz), 5.23 (dd, 1H, J=2.0, 6.0 Hz), 5.25 (s, 1H), 7.14–7.31 (m, 6H), 7.46 (br d, 2H, J=6.9 Hz), 7.57 (br d, 2H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.0, 19.3, 31.6, 39.9, 52.3, 64.5, 68.2, 77.2, 104.5, 126.8, 12.2, 127.8, 128.1, 128.2, 128.6, 141.3, 142.7, 172.3; HRMS calcd for $C_{22}H_{27}NO_4$: 369.1940, found: 369.1925.

4.9. Methyl [5-(*iso*-butyloxy)-2-diphenylmethylisoxazolidine-3-yl]carboxylate (8d) (Table 1, entries 8 and 9)

Following general procedure A, a 74:26 mixture (17.5 mg, 76%) of *trans*-**8d** and *cis*-**8d** was obtained from **1b** (16.7 mg, 62 μmol), **7c** (160 μl, 1.2 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 8). ^1H NMR (270 MHz, $CHCl_3$) δ 0.90 (d, 6H×74/100, J=6.6 Hz), 0.92 (d, 6H×26/100, J=6.6 Hz), 1.26 (m, 1H×26/100), 1.82 (sept, 1H×74/100, J=6.6 Hz), 2.4–2.8 (m, 2H), 2.94 (dd, 1H×74/100, J=6.6, 9.2 Hz), 3.08 (dd, 1H×26/100, J=6.9, 9.6 Hz), 3.19 (dd, 1H×74/100, J=6.6, 9.2 Hz), 3.44 (s, 3H×26/100), 3.4–3.7 (m, 2H×26/100), 3.56 (s, 3H×74/100), 4.00 (br t, 1H×74/100, J=7.3 Hz), 4.91 (s, 1H×26/100), 5.11 (dd, 1H×26/100, J=2.3, 5.3 Hz), 5.21 (br dd, 1H×74/100, J=2.0, 5.3 Hz), 5.24 (s, 1H×74/100), 7.1–7.7 (m, 10H).

Following general procedure B, *trans*-**8d** (18.5 mg, 89%) was obtained from **1b** (15.2 mg, 57 μmol), **7c** (160 μl, 1.2 mmol), $Eu(fod)_3$ (59.0 mg, 57 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 9). Mp 53–54 °C; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$) δ 0.90 (d, 6H, J=6.6 Hz), 1.82 (sept, 1H, J=6.6 Hz), 2.58 (ddd, 1H, J=2.0, 7.9, 12.9 Hz), 2.24 (ddd, 1H, J=5.3, 6.6, 12.9 Hz), 2.94 (dd, 1H, J=6.6, 9.2 Hz), 3.19 (dd, 1H, J=6.6, 9.2 Hz), 3.56 (s, 3H), 4.00 (br t, 1H, J=7.3 Hz), 5.21 (br dd, 1H, J=2.0, 5.3 Hz), 5.24 (s, 1H), 7.14–7.34 (m, 6H), 7.45 (br d, 2H, J=8.6 Hz), 7.57 (br d, 2H, J=8.6 Hz); MS (*m*/*z*) 369 (11), 296 (4), 167 (100%); HRMS calcd for $C_{22}H_{27}NO_4$: 369.1940, found: 369.1940.

4.10. Methyl [5-cyclohexyloxy-2-diphenylmethylisoxazolidine-3-yl]carboxylate (8e) (Table 1, entries 10 and 11)

Following general procedure A, a 71:29 mixture (25.1 mg, 83%) of *trans*-**8e** and *cis*-**8e** was obtained from **1b**

(17.6 mg, 65 μmol), **7d** (170 μl, 1.2 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 10). ^1H NMR (270 MHz, $CDCl_3$) 1.1–2.0 (m, 10H), 2.4–2.8 (m, 2H), 3.33 (m, 1H×71/100), 3.4–3.9 (m, 2H×29/100), 3.45 (s, 3H×29/100), 3.55 (s, 3H×71/100), 3.99 (dd, 1H×71/100, J=6.6, 7.6 Hz), 4.95 (s, 1H×29/100), 5.26 (s, 1H×71/100), 5.29 (dd, 1H×29/100, J=2.3, 5.6 Hz), 5.42 (dd, 1H×71/100, J=2.0, 5.6 Hz), 7.1–7.6 (m, 10H).

Following general procedure B, *trans*-**8e** (22.2 mg, 92%) was obtained from **1b** (16.5 mg, 61 μmol), **7d** (170 μl, 1.2 mmol), $Eu(fod)_3$ (61.3 mg, 590 μmol) and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 11). IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 1.1–1.9 (m, 10H), 2.55 (ddd, 1H, J=2.0, 7.6, 12.9 Hz), 2.73 (ddd, 1H, J=5.6, 6.6, 12.9 Hz), 3.33 (m, 1H), 3.55 (s, 3H), 3.99 (dd, 1H, J=6.6, 7.6 Hz), 5.26 (s, 1H), 5.42 (dd, 1H, J=2.0, 5.6 Hz), 7.1–7.3 (m, 6H), 7.45 (br d, 2H, J=8.3 Hz), 7.57 (br d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 23.8, 24.1, 25.6, 30.9, 33.3, 40.3, 52.1, 64.6, 74.9, 77.2, 101.2, 126.8, 127.1, 127.8, 128.2, 128.6, 141.2, 142.7, 172.4; MS (m/z) 395 (12), 182 (6), 167 (100); HRMS calcd for $C_{24}H_{29}NO_4$: 395.2097, found: 395.2093.

4.11. (1*R*,5*R*,8*R*)-6-Aza-8-ethoxy-3,7-dioxa-5-phenylbicyclo[4.3.0]nonan-2-one (11a), (1*S*,5*R*,8*S*)-isomer (11b), and (1*R*,5*R*,8*S*)-isomer (11c)

A solution of the nitrone **10** (57.3 mg, 0.30 mmol), **7a** (0.08 ml, 0.86 mmol), and $Eu(fod)_3$ (311 mg, 0.30 mmol) in benzene (5 ml) was stirred at room temperature for 15 h. The mixture was diluted with benzene, washed successively with a 10% aqueous solution of tartaric acid and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (4:1) to give a 48:39:13 mixture of **11b**, **11c**, and **11a** (68.7 mg, 87%). The ratio was estimated on the basis of integrations of the triplets (OCH_2CH_3) in the ^1H NMR spectrum of the mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H×39/100, J=7.1 Hz, **11c**), 1.19 (t, 3H×13/100, J=7.1 Hz, **11a**), 1.21 (t, 3H×48/100, J=7.1 Hz, **11b**). The mixture was subjected to column chromatography on silica gel with hexane–AcOEt (4:1). The first fraction gave a mixture of **11a** and **11b**, and the second fraction gave **11c**. Further chromatography of the mixture of **11a** and **11b** on silica gel with toluene–ether (20:1) gave **11a** and **11b**. Compound **11a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, J=7.1 Hz), 2.68 (ddd, 1H, J=1.0, 8.2, 13.2 Hz), 2.79 (ddd, 1H, J=5.0, 8.9, 13.2 Hz), 3.42 (qd, 1H, J=7.1, 9.6 Hz), 3.72 (qd, 1H, J=7.1, 9.6 Hz), 4.12 (dd, 1H, J=3.6, 9.9 Hz), 4.27 (dd, 1H, J=9.9, 11.9 Hz), 4.36 (dd, 1H, J=3.6, 11.9 Hz), 4.49 (br t, 1H, J=8.2 Hz), 5.19 (br d, 1H, J=5.0 Hz), 7.32–7.50 (m, 5H). This spectrum was identical with that of an authentic sample.[7c] Compound **11b**: mp 144–145 °C (hexane–CH_2Cl_2); $[\alpha]_D^{23}$ 2.24 (c 0.151, $CHCl_3$); IR (KBr) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J=7.2 Hz), 2.70 (ddd, 1H, J=2.7, 9.0, 14.0 Hz), 2.99 (ddd, 1H, J=1.5, 6.3, 14.0 Hz), 3.51 (ddd, 1H, J=7.2, 9.6, 14.3 Hz), 3.75 (ddd, 1H, J=7.2, 9.6, 14.3 Hz), 4.33 (dd, 1H, J=1.5, 9.0 Hz), 4.57 (dd, 1H, J=4.5, 11.0 Hz), 4.65 (br dd, 1H, J=4.5, 11.0 Hz), 5.11 (t, 1H, J=11.1 Hz), 5.27 (br d, 1H, J=6.3 Hz), 7.31–7.49 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.0, 41.1, 59.6, 62.0, 64.2, 67.3, 100.6, 127.4, 128.2, 128.6, 134.9, 170.4; HRMS calcd for $C_{14}H_{17}NO_4$: 263.1158, found: 263.1166.

Compound **11c**: mp 133.5–136.5 °C (hexane–CH_2Cl_2); $[\alpha]_D^{23}$ +38.9 (c 0.196, $CHCl_3$); IR (KBr) 1753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, J=7.1 Hz), 2.82 (ddd, 1H, J=2.3, 7.3, 13.5 Hz), 3.01 (ddd, 1H, J=5.9, 10.2, 13.5 Hz), 3.32 (qd, 1H, J=7.1, 9.3 Hz), 3.48 (qd, 1H, J=7.1, 9.3 Hz), 4.20 (dd, 1H, J=9.9, 11.5 Hz), 4.26 (dd, 1H, J=3.9, 11.5 Hz), 4.43 (dd, 1H, J=7.5, 10.5 Hz), 4.64 (dd, 1H, J=4.3, 9.9 Hz), 5.19 (dd, 1H, J=2.3, 5.6 Hz), 7.32–7.48 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8, 41.3, 61.7, 63.9, 64.3, 70.5, 103.2, 127.6, 128.6, 128.8, 135.9, 169.3; HRMS calcd for $C_{14}H_{17}NO_4$: 263.1167, found: 263.1179.

4.12. General procedure C: transesterification and intramolecular cycloaddition of the nitrone 1a with allyl alcohols 12

A suspension of the nitrone **1b**, allyl alcohol **12**, $Eu(fod)_3$, and 4 Å MS in $ClCH_2CH_2Cl$ was stirred at the temperature indicated in Table 4 for a period. After filtration, the filtrate was diluted with CH_2Cl_2, washed successively with 10% aqueous solution of tartaric acid and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on Al_2O_3 with CH_2Cl_2 to give the crude cycloadduct **13**, which was further chromatographed on silica gel with *n*-hexane–AcOEt to afford **13**.

4.13. (3a*R**,6a*R**)-Tetrahydro-1-diphenylmethyl-1*H*,6*H*-furo[3,4-*c*]isoxazole-6-one (13a)

A crude product was obtained from **1b** (28.9 mg, 0.11 mmol), **12a** (56 μl, 0.82 mmol), $Eu(fod)_3$ (112 mg, 0.11 mmol), and 4 Å MS (300 mg). Purification by preparative TLC on silica gel with CH_2Cl_2 gave **13a** (21.5 mg, 68%). ^1H NMR (270 MHz, $CDCl_3$) δ 3.52 (m, 1H), 3.89 (dd, 1H, J=2.3, 9.2 Hz), 4.13 (d, 1H, J=8.3 Hz), 4.26 (dd, 1H, J=2.6, 9.6 Hz), 4.33 (dd, 1H, J=7.5, 9.0 Hz), 4.43 (dd, 1H, J=7.3, 9.6 Hz), 4.96 (br s, 1H), 7.17–7.37 (m, 6H), 7.5–7.58 (m, 4H). This spectrum was identical with that of an authentic sample.[19a]

4.14. (3*R**,3a*R**,6a*R**)-Tetrahydro-3-phenyl-1-diphenylmethyl-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (13b)

A crude product was obtained from **1b** (30.0 mg, 0.112 mmol), **12b** (114 mg, 0.56 mmol), $Eu(fod)_3$ (116 mg, 0.112 mmol), and 4 Å MS (300 mg). Purification by preparative TLC on silica gel with CH_2Cl_2 gave **13a** (37.7 mg, 92%). ^1H NMR (270 MHz, $CDCl_3$) δ 3.37 (dddd, 1H, J=3.0, 5.6, 6.3, 8.6 Hz), 4.16 (d, 1H, J=8.6 Hz), 4.41 (dd, 1H, J=9.9, 5.6 Hz), 4.45 (dd, 1H, J=9.9, 3.0 Hz), 4.97 (d, 1H, J=6.3 Hz), 5.29 (s, 1H), 7.15–7.38 (m, 11H), 7.42–7.60 (m, 4H). This spectrum was identical with that of an authentic sample.[19a]

4.15. (3*R**,3a*S**,4*S**,6a*R**)-Tetrahydro-1-diphenylmethyl-3,4-propano-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (13c)

A crude product was obtained from **1b** (30.0 mg, 0.111 mmol), **12c** (34 μl, 0.33 mmol), $Eu(fod)_3$ (11.6 mg,

0.011 mmol), and 4 Å MS (300 mg). Purification by preparative TLC on silica gel with CH_2Cl_2 gave **13c** (26.4 mg, 71%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31–1.70 (m, 4H), 1.90–2.05 (m, 1H), 2.15–2.27 (m, 1H), 3.25 (q, 1H, J=7.6 Hz), 4.28 (d, 1H, J=8.6 Hz), 4.45 (br, 1H), 4.62 (dt, 1H, J=2.6, 6.9 Hz), 5.05 (br s, 1H), 7.17–7.35 (m, 6H), 7.52–7.58 (m, 4H). This spectrum was identical with that of an authentic sample.[19a]

Acknowledgements

Financial support of this study by a Grant-in-Aid for Scientific Research on Priority Area 'Creation of Biologically Functional Molecules' from the Ministry of Education, Culture, Sports, Science, and Technology of Japan is gratefully acknowledged.

Supplementary data

Calculated geometries of compounds (*E*)-**3**, (*Z*)-**3**, and **4**–**6**; ^{1}H NMR spectra of diastereomeric mixtures of **8a**–**d**; ^{1}H NMR spectra of *trans*-**8a**–**d**; ^{1}H NMR spectra of **1b**, **9**, **7a**, and **10**; ^{1}H NMR spectra of **1b**, **9**, **7a**, and **10** with Eu(fod)$_3$; ^{1}H NMR spectra of **13a**–**c**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.014.

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17. For Eu(fod)$_3$-induced epimerization of an acetal, see Ref. 16c.
18. Crystal data for **11c**: $C_{14}H_{17}NO_4$, M_w=263.29, orthorhombic, $P2_12_12_1$, a=7.28050(10) Å, b=12.9039(2) Å, c=13.6564(3) Å, V=1282.98(4) Å^3, Z=4, Dc=1.363 g/cm^3, F(000)=560, colorless block crystal, dimensions of 0.20×0.18×0.13 mm. The data collection was performed at a temperature of 93(1) K to $2\theta_{max}$=136.5° ($-8\leq h\leq 8$, $-15\leq k\leq 15$, $-15\leq l\leq 16$) using a Rigaku RAXIS RAPID with graphite monochromated Cu Kα radiation. The structure was solved with direct methods 1. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 1379 observed reflections and 174 variable parameters. $R[F^2>2\sigma(F^2)]$=0.0249, $wR(F^2)$=0.0644. Crystallographic data (excluding structural factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 618991. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).
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Chirality induction of π-conjugated chains through chiral complexation

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Received 5 August 2006; revised 5 October 2006; accepted 6 October 2006
Available online 30 October 2006

Abstract—Chirality induction of π-conjugated polyanilines through chiral complexation with the chiral palladium(II) complexes was demonstrated to afford the chiral conjugated polymer complexes. Complexation of the emeraldine base of poly(*o*-toluidine) (POT) with the chiral palladium(II) complex bearing one labile coordination site led to the formation of the chiral conjugated polymer complex, which exhibited an induced circular dichroism (ICD) based on the chirality induction into a π-conjugated backbone. The mirror image of the CD signal was observed with the chiral conjugated polymer complex, which was obtained from the chiral palladium(II) complex possessing the opposite configuration. The chirality of the podand ligand moieties of the palladium complex is considered to induce a propeller twist of the π-conjugated molecular backbone. The crystal structure of the chiral conjugated complex of *N*-bis(4′-dimethylaminophenyl)-1,4-benzoquinonediimine (L^3) as a model compound of the polyaniline revealed a chiral propeller twist conformation of the π-conjugated backbone. Furthermore, chiral complexation with the cationic palladium(II) complexes provided the ionic chiral conjugated complexes.

1. Introduction

π-Conjugated polymers have received extensive interest because of the potential application to electronic materials depending on their electrical properties.[1] Much progress has been made in understanding the chemistry and physics of the π-conjugated polymers. One of the most important π-conjugated polymers, polyaniline, is redox-active and exists in various redox states from leucoemeraldine in a high reduction state to pernigraniline in a high oxidation state. The redox properties have been demonstrated to be controlled by the introduction of an acceptor unit.[2] The structural and chiral control is to be investigated for further functionalization. Chiral polyaniline has been focused on due to their potential applications in molecular recognition and chiral separation.[3] Chiral polyaniline and its derivatives were synthesized only by doping with a chiral acid,[4] polymerization of aniline in the presence of a chiral acid dopant,[5] or template polymerization of aniline in the presence of a chiral molecular template.[6] Another interesting function of polyanilines is coordination properties of two nitrogen atoms of the quinonediimine moiety. In a previous paper, the emeraldine base form of polyanilines, which contains the quinonediimine unit, has been revealed to coordinate to transition metals, affording the conjugated polymer complex systems.[7] The polymer complex can effectively serve as an oxidation catalyst.[7a,b,d] Furthermore, we have already demonstrated that the controlled complexation of polyanilines with palladium(II) compounds by changing the coordination mode is achieved to afford the single-strand or cross-linked network conjugated complexes, in which the quinonediimine moieties serve as bridging coordination sites.[7f] Also, controlled complexation with the redox-active quinonediimine derivative has been achieved to afford the conjugated polymeric complex, the conjugated trimetallic macrocycle, or the conjugated bimetallic complex, depending on the coordination mode.[7g,h,8] The introduction of chiral complexes is considered to be a strategy to induce chirality into a π-conjugated backbone of polyanilines, giving the chiral conjugated complexes.[7h] We herein describe a full scope of chirality induction of polyaniline derivatives through complexation with chiral palladium(II) compounds.

2. Results and discussion

Chiral palladium(II) complexes, ((*S*,*S*)-L^1)Pd(MeCN) ((*S*,*S*)-**1**) and ((*R*,*R*)-L^1)Pd(MeCN) ((*R*,*R*)-**1**), were designed and prepared by the treatment of the *N*-heterocyclic tridentate podand ligands, *N*,*N*′-bis[(*S*)-1-methoxycarbonyl-2-phenylethyl]-2,6-pyridinedicarboxamide ((*S*,*S*)-L^1H_2) and *N*,*N*′-bis[(*R*)-1-methoxycarbonyl-2-phenylethyl]-2,6-pyridinedicarboxamide ((*R*,*R*)-L^1H_2), respectively, with $Pd(OAc)_2$ in acetonitrile as shown in Scheme 1. This similar synthetic method was also used for the synthesis of chiral

Keywords: Polyaniline; Quinonediimine; Palladium complex; Chiral conjugated complex; Chirality induction.
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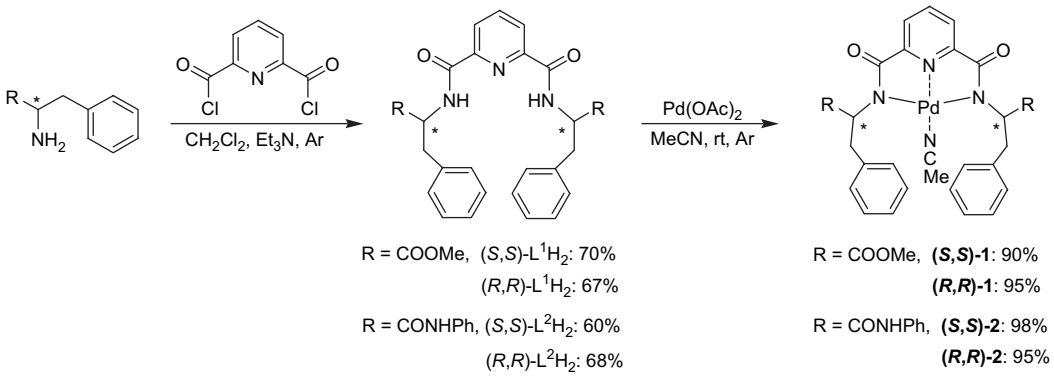
doi:10.1016/j.tet.2006.10.016



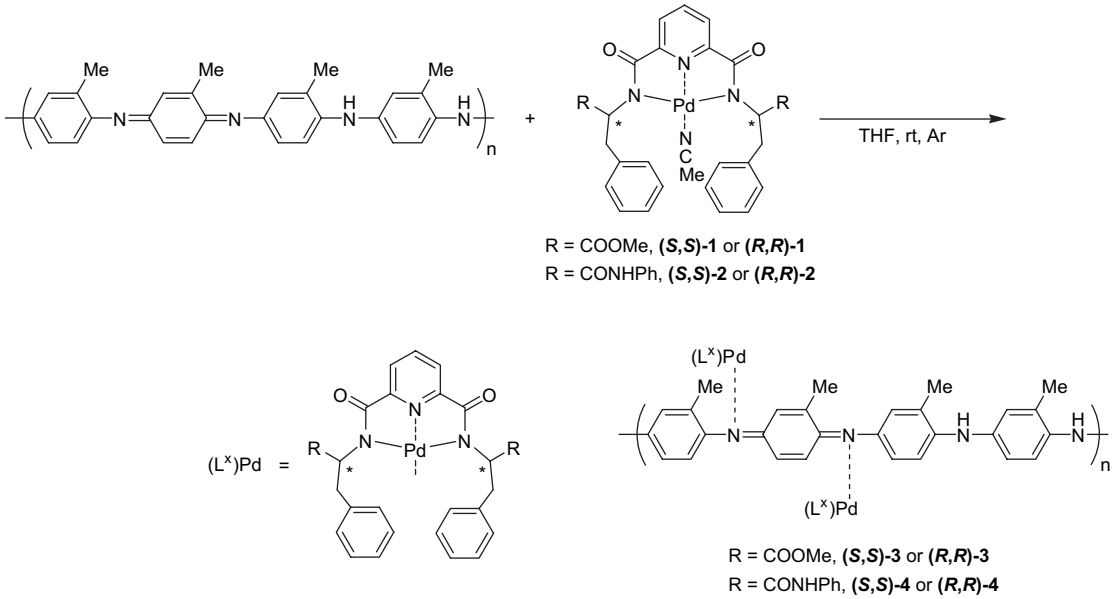
Scheme 1.

palladium complexes, ((*S*,*S*)-L^2)Pd(MeCN) ((*S*,*S*)-**2**) and ((*R*,*R*)-L^2)Pd(MeCN) ((*R*,*R*)-**2**), bearing the amide moieties instead of the ester ones. These palladium(II) complexes have one interchangeable coordination site through exchange of acetonitrile. π-Conjugated polymers with potential metal-coordination sites are expected to coordinate to the palladium center by displacement of this labile ligand.

Treatment of the emeraldine base form of poly(*o*-toluidine) (POT)[7g] with the chiral palladium(II) complex (*S*,*S*)-**1** or (*S*,*S*)-**2** in THF led to the formation of the conjugated polymer complex, POT–((*S*,*S*)-L^1Pd) ((*S*,*S*)-**3**) or POT–((*S*,*S*)-L^2Pd) (*S*,*S*)-**4**, respectively, as shown in Scheme 2. The electronic spectrum of (*S*,*S*)-**3** in THF exhibited broad absorption at around 500–800 nm, which is probably due to a low-energy charge-transfer transition with significant contribution from palladium (Fig. 1). This result indicates the coordination of the quinonediimine nitrogen atoms to the palladium centers. It should be noted that the complex (*S*,*S*)-**3** exhibits an induced circular dichroism (ICD) at around 500–800 nm. Furthermore, the mirror image of the CD signal was observed with (*R*,*R*)-**3**, which was obtained from the complexation of POT with (*R*,*R*)-**1** (Fig. 1). These findings suggest that the chirality induction of a π-conjugated backbone of POT is achieved by the chiral complexation. A similar absorption spectrum was observed in the case of the amide (*S*,*S*)-**4** as shown in Figure 1.

To gain further insight into chirality induction, the chiral complexation with a model unit of polyaniline, *N*,*N*′-bis(4′-dimethylaminophenyl)-1,4-benzoquinonediimine (L^3),[9] was investigated. The complexation of L^3 with 2 molar equiv of (*S*,*S*)-**1** or (*R*,*R*)-**1** afforded the chiral conjugated 1:2 complex, ((*S*,*S*)-L^1)Pd(L^3)Pd((*S*,*S*)-L^1) ((*S*,*S*)-**5**) or ((*R*,*R*)-L^1)Pd(L^3)Pd((*R*,*R*)-L^1) ((*R*,*R*)-**5**), respectively (Scheme 3). The chiral conjugated complexes, ((*S*,*S*)-L^2)Pd(L^3)Pd((*S*,*S*)-L^2) ((*S*,*S*)-**6**) and ((*R*,*R*)-L^2)Pd(L^3)Pd((*R*,*R*)-L^2) ((*R*,*R*)-**6**), were also prepared from (*S*,*S*)-**2** or (*R*,*R*)-**2**, respectively, by the same complexation route. The electronic spectra of (*S*,*S*)-**5** and (*S*,*S*)-**6** in dichloromethane exhibited a broad absorption at around 600–900 nm based on the similar chiral complexation as mentioned above (Fig. 2).

Variable temperature ^{1}H NMR studies of the conjugated complex (*S*,*S*)-**5** indicated interesting molecular dynamics in solution (Fig. 3). The protons of the quinonediimine moiety of the *syn*-isomer at 233 K were observed at 9.14 and 7.14 ppm as singlet peaks, whereas the *anti* isomer



Scheme 2.

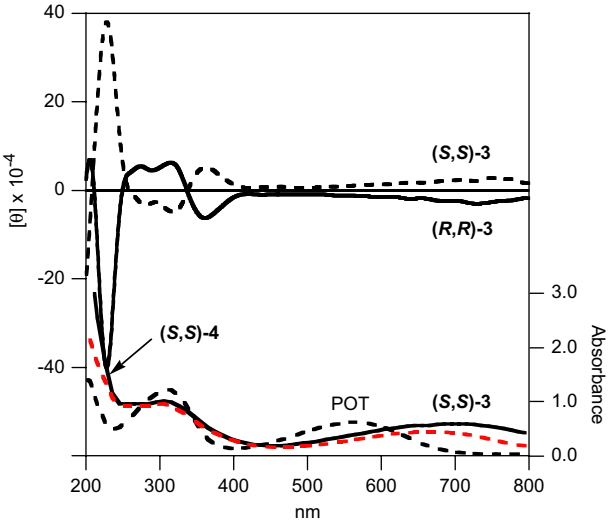


Figure 1. CD spectra (top) of (*S*,*S*)-**3** and (*R*,*R*)-**3** in THF (1.3×10^{-3} M of the monomer unit), and UV–vis spectra (bottom) of (*S*,*S*)-**3**, (*S*,*S*)-**4**, and POT in THF (1.3×10^{-3} M of the monomer unit).

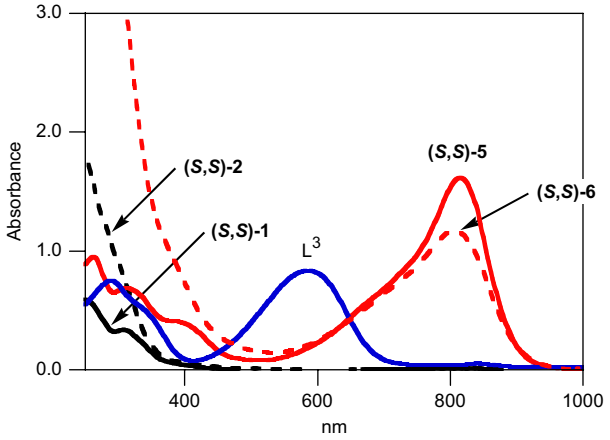
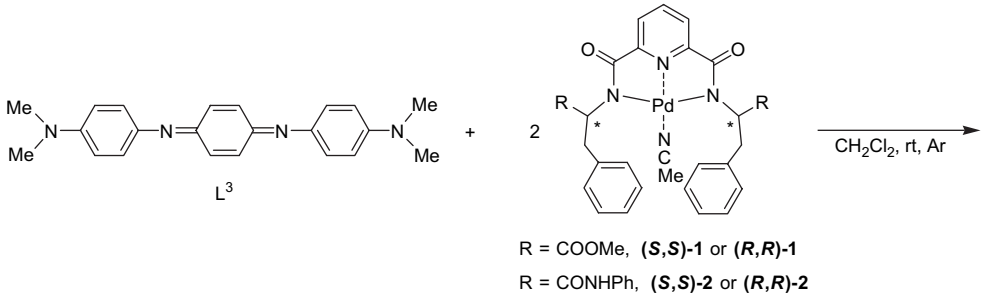


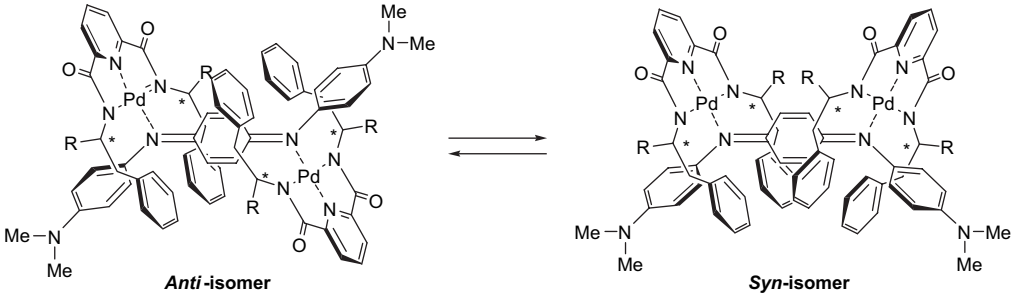
Figure 2. UV–vis spectra of L^3, (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**5**, and (*S*,*S*)-**6** in dichloromethane (5.0×10^{-5} M).

exhibited doublet peaks of those protons at 7.84 and 6.92 ppm. As the temperature was lowered, the peaks of (*S*,*S*)-**5***syn* increased gradually. The equilibrium constant K_{eq} between (*S*,*S*)-**5***syn* and (*S*,*S*)-**5***anti* was calculated from variable temperature ^{1}H NMR spectra shown in Figure 3. The temperature dependence of K_{eq} is used to construct the van't Hoff plot of ln K_{eq} versus T^{-1} (Fig. 4). The *syn* configuration is enthalpically more favorable than the *anti* one in CD_2Cl_2 by 2.3 kcal mol^{-1}, but entropically less favorable by 11.0 cal mol^{-1} K^{-1}.

The mirror image relationship of the CD signals around the CT band of the quinonediimine moiety in dichloromethane was observed between (*S*,*S*)-**5** and (*R*,*R*)-**5** as shown in Figure 5. The ICD at around 600–800 nm appears to be reflected by the chirality of the palladium(II) complexes. Such ICD was not observed in the case of **1**. Similar chiral complexation was also observed in the case of the chiral complexes **6** (Fig. 6). These results indicate the chirality induction into the quinonediimine moiety through the chiral complexation.

Further structural information was obtained by the single-crystal X-ray structure determination. The crystal structure of (*R*,*R*)-**5** indicates that the two (L^1)Pd units are bridged by the quinonediimine moiety of L^3 to form the C_2-symmetrical 2:1 complex (*R*,*R*)-**5***syn* with the Pd–Pd separation 7.59 Å, as depicted in Figure 7. Each phenylene ring of L^3 has an opposite dihedral angle of 47.3° with respect to the quinonediimine plane, resulting in a propeller twist of 75.6° between the planes of the two phenylene rings. Schematic





Scheme 3.

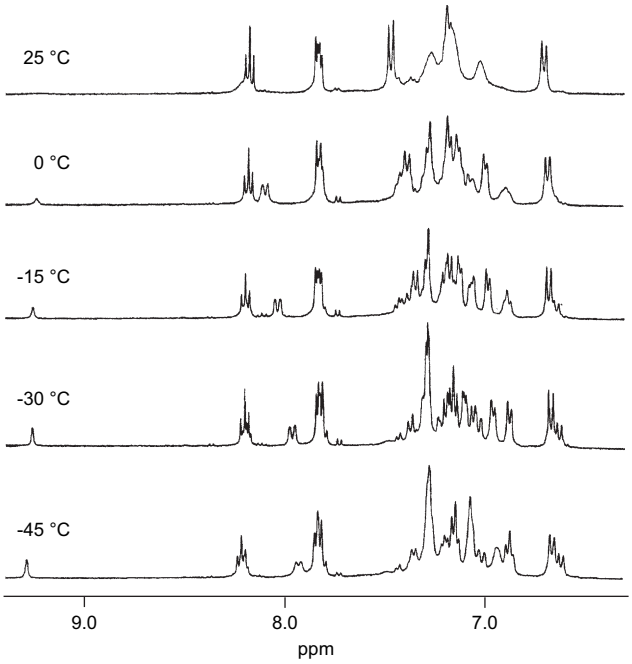


Figure 3. Variable temperature ^{1}H NMR spectrum of (*S*,*S*)-**5** in CD_2Cl_2.

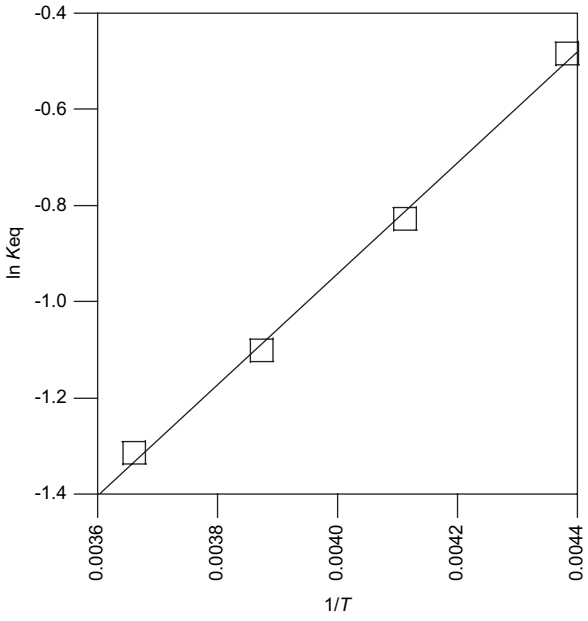


Figure 4. Plot of ln K_{eq} versus T^{-1} for (*S*,*S*)-**5** in CD_2Cl_2.

representation of the crystal structure of (*R*,*R*)-**5***syn* is shown in Figure 8. The chirality of the podand moieties of (L^1)Pd is considered to induce a propeller twist in the π-conjugated chain. Similar complexation behavior is considered to be the case with the polymer complexation. Therefore, the random twist conformation of POT might be transformed into the helical conformation with a predominant screw sense through the chiral complexation. Furthermore, these findings strongly indicate that the chiral structure of quinonediimines is controlled by chiral complexation.

Chirality induction was realized by the complexation of polyanilines and oligoanilines with the chiral palladium

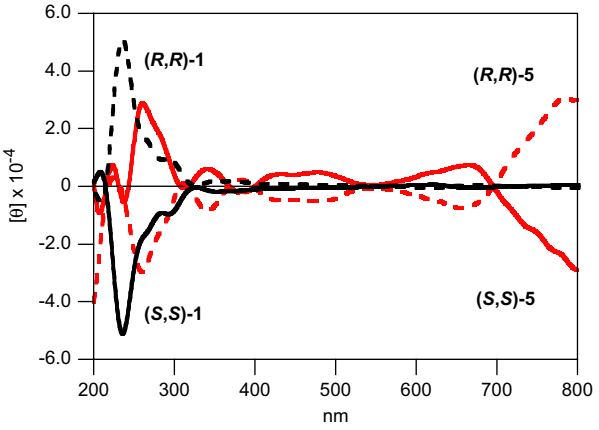


Figure 5. CD spectra of **1** (1.0×10^{-4} M) and **5** (5.0×10^{-5} M) in dichloromethane.

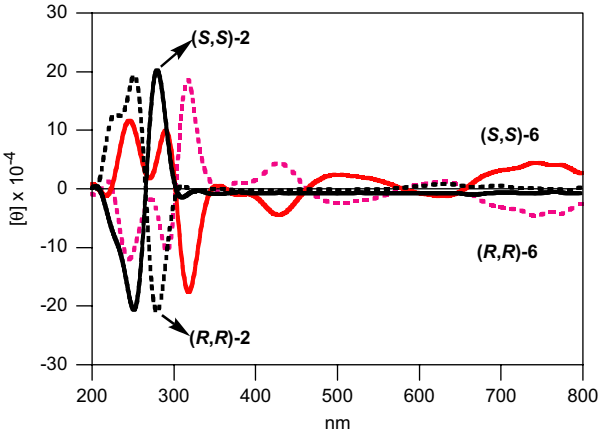


Figure 6. CD spectra of **2** (4.0×10^{-5} M) and **6** (2.0×10^{-5} M) in dichloromethane.

complexes. In order to obtain further insight, the complexation with the cationic palladium complexes **7**[10] possessing weak Pd–N coordination bonds instead of Pd–N covalent bonds in the complexes **1** and **2** was investigated (Fig. 9). The cationic palladium complexes, ((*S*,*S*)-L^4)Pd(MeCN) ((*S*,*S*)-**7**) and ((*R*,*R*)-L^4)Pd(MeCN) ((*R*,*R*)-**7**), were prepared, respectively, by the treatment of the *N*-heterocyclic tridentate podand ligand, 2,6-bis[(*S*)-4′-isopropyloxazolin-2′-yl]-pyridine ((*S*,*S*)-L^4H_2) and 2,6-bis[(*R*)-4′-isopropyloxazolin-2′yl]pyridine ((*R*,*R*)-L^4H_2), with $Pd(MeCN)_4(BF_4)_2$ in acetonitrile (Scheme 4).

The complexation of L^3 with 2 molar equiv of (*S*,*S*)-**7** or (*R*,*R*)-**7** led to the formation of the chiral conjugated 1:2 complex, ((*S*,*S*)-L^4)Pd(L^3)Pd((*S*,*S*)-L^4) ((*S*,*S*)-**8**) or ((*R*,*R*)-L^4)Pd(L^3)Pd((*R*,*R*)-L^4) ((*R*,*R*)-**8**), respectively, as shown in Scheme 5. The complexes **8** are more stable in the coordination solvent, acetonitrile. In the ^{1}H NMR spectrum of the conjugated complex (*S*,*S*)-**8**, two sets of peaks based on *syn* and *anti* isomers were observed at 298 K in CD_3CN. The electronic spectra of **8** in acetonitrile exhibited a broad absorption at around 600–900 nm (Fig. 10), probably due to the chiral complexation of the quinonediimine moiety as observed in the conjugated complexes **5** and **6**.

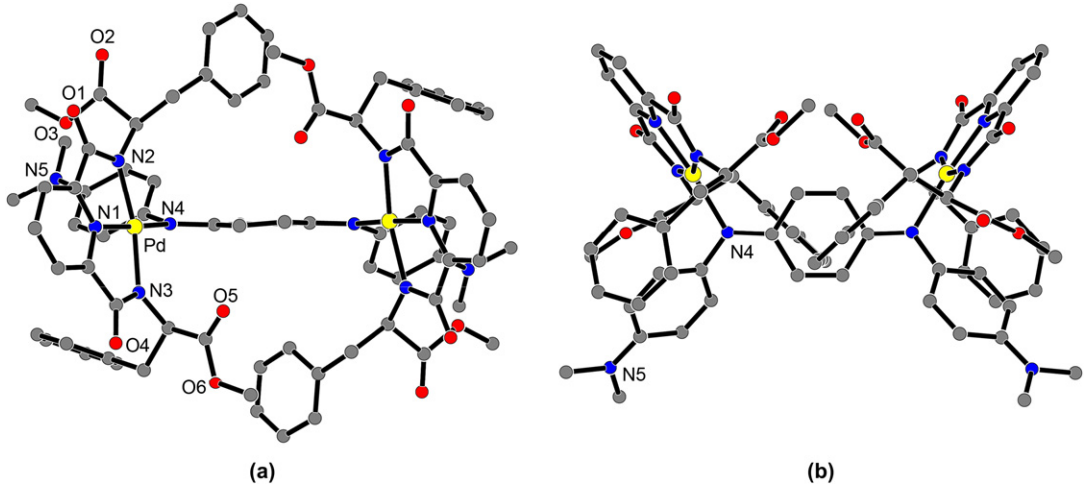


Figure 7. (a) Top view and (b) side view of the X-ray crystal structure of (*R*,*R*)-**5***syn* (hydrogen atoms are omitted for clarity).

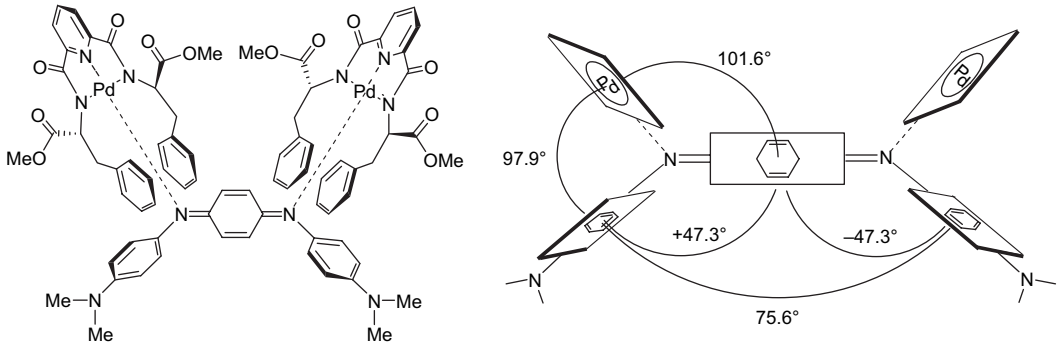


Figure 8. Schematic representation of (*R*,*R*)-**5***syn*.

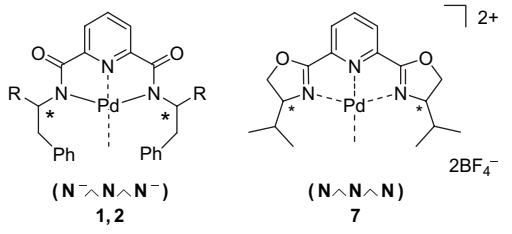
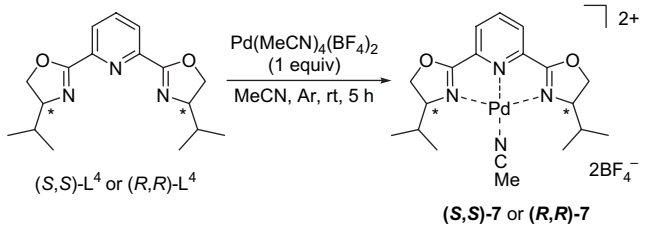


Figure 9. Structure of palladium(II) complexes **1**, **2**, and cationic palladium(II) complex **7**.

The CD spectra of (*S*,*S*)-**8** and (*R*,*R*)-**8** exhibited ICD at around 600–800 nm based on the CT band of the quinonediimine moiety, and these are in a good mirror image relationship (Fig. 11). Such ICD was not observed in the case of **7**. These findings indicate the similar complexation behavior as observed with the chiral conjugated complexes **5** and **6**.



Scheme 4.

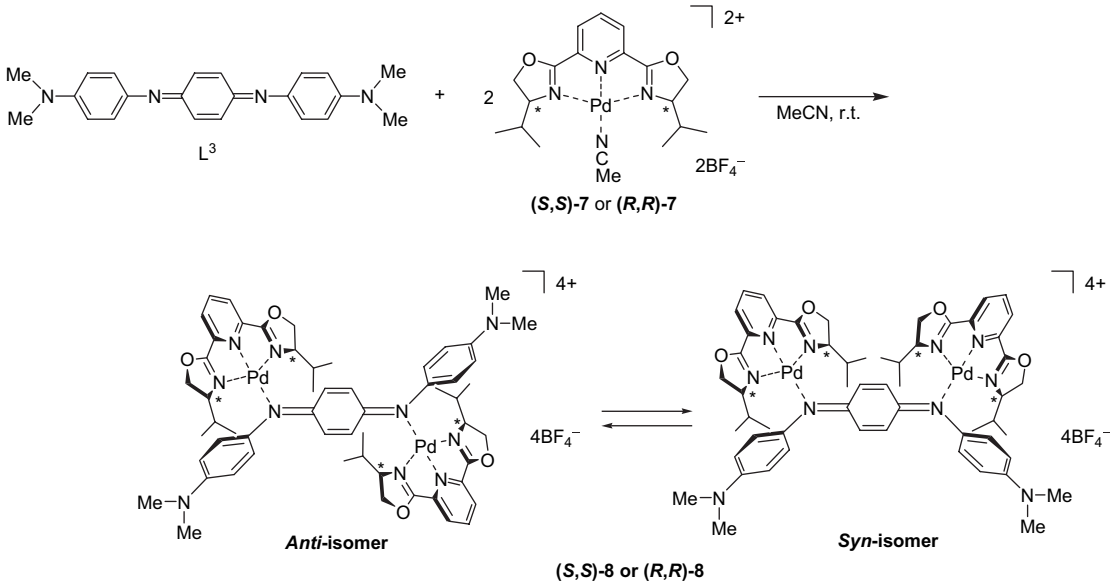
3. Conclusion

Chirality induction of a π-conjugated backbone of the emeraldine base of poly(*o*-toluidine) and the quinonediimine derivative through chiral complexation with the chiral palladium(II) complexes bearing one interchangeable coordination site was achieved to afford the chiral conjugated complexes. The crystal structure of the chiral conjugated complex **5** with the quinonediimine derivative revealed a chiral propeller twist conformation of the π-conjugated moiety. The chirality of the podand ligand is considered to regulate a propeller twist of the π-conjugated backbone. Our strategy for chirality induction through chiral complexation provides an efficient and feasible route to chiral d,π-conjugated complexes, in which the introduced metals are envisioned to play an important role as a metallic dopant and interact with each other through π-conjugation. These chiral conjugated complexes are considered to be potent as promising functionalized materials and asymmetric redox catalysts.

4. Experimental

4.1. General comments

All reagents and solvents were purchased from commercial sources and were further purified with the standard methods,



Scheme 5.

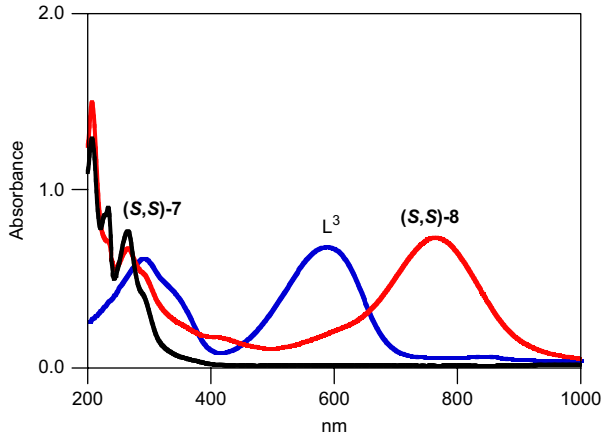


Figure 10. UV–vis spectra of L^3 (4.0×10^{-5} M), (*S*,*S*)-**7** (4.0×10^{-5} M), and (*S*,*S*)-**8** (4.0×10^{-5} M) in MeCN.

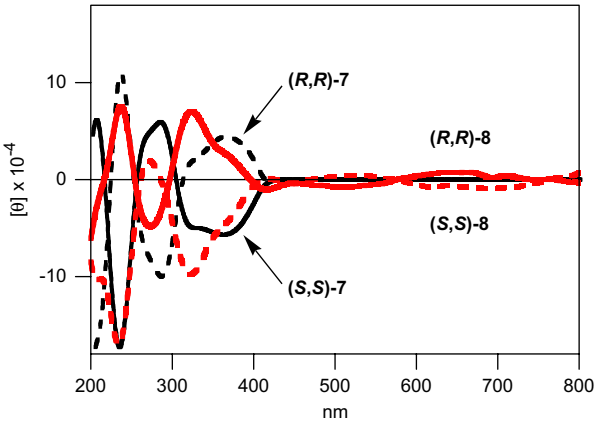


Figure 11. CD spectra of **7** (8.0×10^{-5} M) and **8** (4.0×10^{-5} M) in MeCN.

if necessary. Melting points were determined on a Yanagimoto Micromelting Point Apparatus and were uncorrected. Infrared spectra were obtained with a JASCO FT/IR-480plus. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-400 spectrometer (400 and 100 MHz, respectively). Mass spectra were run on a JEOL JMS-700 mass spectrometer. Electronic spectra were obtained by using a Hitachi U-3500 spectrophotometer. CD spectra were recorded using JASCO J-720 and J-725 spectropolarimeters.

4.2. Synthesis of poly(*o*-toluidine)

Poly(*o*-toluidine) was prepared according to our previous procedure.[7g] The molecular weight of poly(*o*-toluidine) was estimated to be 4191 as determined by gel permeation chromatography (GPC) (polystyrene standard with THF as an eluent). Elemental analysis ($C_{7.00}H_{6.75}N_{1.00}$) indicated the emeraldine base structure consisting of the amine and imine moieties at ca. 1:1 ratio.

4.3. Synthesis of 1

To a stirred mixture of phenylalanine methyl ester hydrochloride (129.4 mg, 0.6 mmol) and triethylamine (0.21 mL, 1.5 mmol) was added drop-wise 2,6-pyridyldicarbonyl dichloride (61.2 mg, 0.3 mmol) in dichloromethane (8 mL) under argon at 0 °C for 7 h and then at room temperature for 18 h. The resulting mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo. The chiral ligands, *N*,*N*′-bis[(*S*)-1-methoxycarbonyl-2-phenylethyl]-2,6-pyridinedicarboxamide ((*S*,*S*)-L^1H_2) and *N*,*N*′-bis[(*R*)-1-methoxycarbonyl-2-phenylethyl]-2,6-pyridinedicarboxamide ((*R*,*R*)-L^1H_2), were isolated by recrystallization from acetonitrile.

4.3.1. (*S*,*S*)-L^1H_2. Yield 70%; mp 124–126 °C (uncorrected); IR (KBr, cm^{-1}): 3335, 1754, 1679, 1656, 1548, 1516; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ 8.36 (d, 2H, J=8.4 Hz, H_{NH}), 8.19 (d, 2H, J=7.6 Hz, H_{py}), 8.03 (t, 1H, J=7.6 Hz, H_{py}), 7.29–7.18 (m, 10H, H_{ph}), 4.95–4.89 (m,

2H, H_{ethyl}), 3.72 (s, 6H, H_{OMe}), 3.34 (dd, 2H, J=14.0, 5.6 Hz, H_{ethyl}), 3.19 (dd, 2H, J=14.0, 8.8 Hz, H_{ethyl}); MS (EI): m/z=489 (M^+). Anal. Calcd for $C_{27}H_{27}N_3O_6$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.37; H, 5.41; N, 8.55.

4.3.2. (*R*,*R*)-L^{1}H$_2$. Yield 67%; mp 124–126 °C (uncorrected); IR (KBr, cm^{-1}): 3335, 1754, 1679, 1656, 1548, 1516; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ 8.36 (d, 2H, J=8.4 Hz, H_{NH}), 8.19 (d, 2H, J=7.6 Hz, H_{py}), 8.03 (t, 1H, J=7.6 Hz, H_{py}), 7.29–7.18 (m, 10H, H_{ph}), 4.95–4.89 (m, 2H, H_{ethyl}), 3.72 (s, 6H, H_{OMe}), 3.34 (dd, 2H, J=14.0, 5.6 Hz, H_{ethyl}), 3.19 (dd, 2H, J=14.0, 8.8 Hz, H_{ethyl}); MS (EI): m/z=489 (M^+). Anal. Calcd for $C_{27}H_{27}N_3O_6$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.42; H, 5.29; N, 8.43.

A mixture of (*S*,*S*)-L^{1}H$_2$ or (*R*,*R*)-L^{1}H$_2$ (24.5 mg, 0.05 mmol) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) in acetonitrile (5.0 mL) was stirred under argon at room temperature for 2 h. After evaporation of the solvent, the palladium complex (*S*,*S*)-**1** or (*R*,*R*)-**1** was isolated as yellow crystal by recrystallization from benzene and hexane.

4.3.3. (*S*,*S*)-1. Yield 90%; mp 200–201 °C (decomp.); IR (KBr, cm^{-1}): 1730, 1594; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ 8.07 (t, 1H, J=8.0 Hz, H_{py}), 7.53 (d, 2H, J=8.0 Hz, H_{py}), 7.34 (d, 4H, J=8.1 Hz, H_{ph}), 7.26 (dd, 4H, J=8.1, 7.5 Hz, H_{ph}), 7.16 (t, 2H, J=7.5 Hz, H_{ph}), 4.70 (dd, 2H, J=10.0, 4.2 Hz, H_{ethyl}), 3.69 (s, 6H, H_{OMe}), 3.27 (dd, 2H, J=13.6, 4.2 Hz, H_{ethyl}), 2.85 (dd, 2H, J=13.6, 10.0 Hz, H_{ethyl}); MS (FAB): m/z=594 ((M−MeCN)$^+$+1). Anal. Calcd for $C_{29}H_{28}N_4O_6Pd$: C, 54.85; H, 4.44; N, 8.82. Found: C, 54.85; H, 4.21; N, 8.60.

4.3.4. (*R*,*R*)-1. Yield 95%; mp 200–201 °C (decomp.); IR (KBr, cm^{-1}): 1730, 1594; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ 8.07 (t, 1H, J=8.0 Hz, H_{py}), 7.53 (d, 2H, J=8.0 Hz, H_{py}), 7.34 (d, 4H, J=8.1 Hz, H_{ph}), 7.26 (dd, 4H, J=8.1, 7.5 Hz, H_{ph}), 7.16 (t, 2H, J=7.5 Hz, H_{ph}), 4.70 (dd, 2H, J=10.0, 4.2 Hz, H_{ethyl}), 3.69 (s, 6H, H_{OMe}), 3.27 (dd, 2H, J=13.6, 4.2 Hz, H_{ethyl}), 2.85 (dd, 2H, J=13.6, 10.0 Hz, H_{ethyl}); MS (FAB): m/z=594 ((M−MeCN)$^+$+1). Anal. Calcd for $C_{29}H_{28}N_4O_6Pd$: C, 54.85; H, 4.44; N, 8.82. Found: C, 54.79; H, 4.11; N, 8.56.

4.4. Synthesis of 2

To a stirred mixture of phenylalanine–phenylamide hydrochloride (144.2 mg, 0.6 mmol) and triethylamine (0.42 mL, 1.5 mmol) was added drop-wise 2,6-pyridyldicarbonyl dichloride (61.2 mg, 0.3 mmol) in dichloromethane (8 mL) under argon at 0 °C for 7 h and then at room temperature for 18 h. The resulting mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo. The chiral ligands, *N*,*N*′bis[(*S*)-1-phenylcarbamoyl-2-phenylethyl]-2,6-pyridinedicarboxamide ((*S*,*S*)-L^{2}H$_2$) and *N*,*N*′-bis[(*R*)-1-phenylcarbamoyl-2-phenylethyl]-2,6-pyridinedicarboxamide ((*R*,*R*)-L^{2}H$_2$), were isolated by recrystallization from acetonitrile.

4.4.1. (*S*,*S*)-L^{2}H$_2$. Yield 60%; mp 250–252 °C (uncorrected); IR (KBr, cm^{-1}): 3292, 1695, 1675, 1646, 1599, 1559, 1539; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.55 (d, 2H, J=7.7 Hz, H_{NH}), 8.32 (d, 2H, J=7.7 Hz, H_{py}), 8.01 (t, 1H, J=7.7 Hz, H_{py}), 7.89 (br s, 2H, H_{NH}), 7.42 (d, 4H, J=8.0 Hz, H_{ph}), 7.35–7.26 (m, 12H, ph), 7.23 (t, 2H, J=7.3 Hz, H_{ph}), 7.10 (t, 2H, J=7.7 Hz, H_{ph}), 4.96 (dd, 2H, J=7.7, 7.5 Hz, H_{ethyl}), 3.40–3.31 (m, 4H, H_{ethyl}); MS (EI): m/z=611 (M^+). Anal. Calcd for $C_{37}H_{33}N_5O_4$: C, 72.65; H, 5.44; N, 11.45. Found: C, 72.37; H, 5.41; N, 11.35.

4.4.2. (*R*,*R*)-L^{2}H$_2$. Yield 68%; mp 250–252 °C (uncorrected); IR (KBr, cm^{-1}): 3292, 1695, 1675, 1646, 1599, 1559, 1539; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.55 (d, 2H, J=7.7 Hz, H_{NH}), 8.32 (d, 2H, J=7.7 Hz, H_{py}), 8.01 (t, 1H, J=7.7 Hz, H_{py}), 7.89 (br s, 2H, H_{NH}), 7.42 (d, 4H, J=8.0 Hz, H_{ph}), 7.35–7.26 (m, 12H, ph), 7.23 (t, 2H, J=7.3 Hz, H_{ph}), 7.10 (t, 2H, J=7.7 Hz, H_{ph}), 4.96 (dd, 2H, J=7.7, 7.5 Hz, H_{ethyl}), 3.40–3.31 (m, 4H, H_{ethyl}); MS (EI): m/z=611 (M^+). Anal. Calcd for $C_{37}H_{33}N_5O_4$: C, 72.65; H, 5.44; N, 11.45. Found: C, 72.26; H, 5.51; N, 11.34.

A mixture of (*S*,*S*)-L^{2}H$_2$ or (*R*,*R*)-L^{2}H$_2$ (30.6 mg, 0.05 mmol) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) in acetonitrile (5.0 mL) was stirred under argon at room temperature for 2 h. After evaporation of the solvent, the palladium complex (*S*,*S*)-**2** or (*R*,*R*)-**2** was isolated as yellow crystal by recrystallization from benzene and hexane.

4.4.3. (*S*,*S*)-2. Yield 98%; mp 202–203 °C (decomp.); IR (KBr, cm^{-1}): 3280, 1596, 1495; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ 9.07 (s, 2H, H_{NH}), 7.73 (dd, 4H, J=7.7, 1.0 Hz, H_{ph}), 7.53 (t, 1H, J=7.7 Hz, H_{py}), 7.36–7.30 (m, 8H, H_{ph} and H_{ph}), 7.23 (d, 2H, J=7.7 Hz, H_{py}), 7.10 (t, 6H, J=7.3 Hz, H_{ph} and H_{ph}), 7.02 (t, 2H, J=7.3 Hz, H_{ph}), 5.18 (dd, 2H, J=9.9, 4.4 Hz, H_{ethyl}), 3.42 (dd, 2H, J=14.1, 4.4 Hz, H_{ethyl}), 2.68 (dd, 2H, J=14.1, 9.9 Hz, H_{ethyl}); MS (FAB): m/z=716 ((M−MeCN)$^+$+1). Anal. Calcd for $C_{39}H_{34}N_6O_4Pd$: C, 61.87; H, 4.53; N, 11.10. Found: C, 61.77; H, 4.52; N, 11.09.

4.4.4. (*R*,*R*)-2. Yield 95%; mp 202–203 °C (decomp.); IR (KBr, cm^{-1}): 3280, 1596, 1495; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ 9.07 (s, 2H, H_{NH}), 7.73 (dd, 4H, J=7.7, 1.0 Hz, H_{ph}), 7.53 (t, 1H, J=7.7 Hz, H_{py}), 7.36–7.30 (m, 8H, H_{ph} and H_{ph}), 7.23 (d, 2H, J=7.7 Hz, H_{py}), 7.10 (t, 6H, J=7.3 Hz, H_{ph} and H_{ph}), 7.02 (t, 2H, J=7.3 Hz, H_{ph}), 5.18 (dd, 2H, J=9.9, 4.4 Hz, H_{ethyl}), 3.42 (dd, 2H, J=14.1, 4.4 Hz, H_{ethyl}), 2.68 (dd, 2H, J=14.1, 9.9 Hz, H_{ethyl}); MS (FAB): m/z=716 ((M−MeCN)$^+$+1). Anal. Calcd for $C_{39}H_{34}N_6O_4Pd$: C, 61.87; H, 4.53; N, 11.10. Found: C, 61.80; H, 4.50; N, 10.88.

4.5. Synthesis of 3

To POT (2.73 mg, 26 mmol) in THF solution (20 mL) was added **1** (0.5 molar equiv to the monomer unit of POT, 8.25 mg, 13 mmol) in THF solution. The mixture was stirred at room temperature for 30 min and filtered through a membrane under argon. The electronic and CD spectra of the filtrate **3** in THF were measured. The electronic and CD spectra were measured in a 0.10 cm quartz cell at room temperature with 1.3×10^{-3} M concentration of the monomer unit of POT under argon.

4.6. Synthesis of 4

To POT (2.73 mg, 26 mmol) in THF solution (20 mL) was added **2** (0.5 molar equiv to the monomer unit of POT, 9.84 mg, 13 mmol) in THF solution. The mixture was stirred at room temperature for 30 min and filtered through a membrane under argon. The electronic spectrum of the filtrate **4** in THF was measured. The electronic spectrum was measured in a 0.10 cm quartz cell at room temperature with 1.3×10^{-3} M concentration of the monomer unit of POT under argon.

4.7. Synthesis of 5

N,*N*′-Bis(4′-dimethylaminophenyl)-1,4-benzoquinonediimine (L^3) was prepared according to the literature procedure.[9] A mixture of L^3 (13.8 mg, 0.04 mmol) and (*S*,*S*)-**1** or (*R*,*R*)-**1** (50.8 mg, 0.08 mmol) was stirred in dichloromethane (10 mL) under argon at room temperature for 4 h. After evaporation of the solution, the chiral complex (*S*,*S*)-**5** or (*R*,*R*)-**5** was isolated by recrystallization from chloroform and ethyl ether.

4.7.1. (*S*,*S*)-5. Yield 90%; mp 180–181 °C (decomp.); IR (KBr, cm^{-1}): 1731, 1591, 1362, 1162; ^1H NMR (600 MHz, CD_2Cl_2, 233 K, *syn*:*anti*=1:2): δ 9.14 (s, 2H, phenylene$_{syn}$), 8.09 (t, 2H, J=7.2 Hz, py$_{anti}$), 8.08 (t, 2H, J=7.2 Hz), 7.84 (d, 2H, J=9.6 Hz, phenylene$_{anti}$), 7.73–7.69 (m, 8H, py$_{syn}$ and py$_{anti}$), 7.26 (d, 4H, J=9.3 Hz, ph$_{syn}$), 7.18 (d, 4H, J=9.3 Hz, ph$_{anti}$), 7.14 (s, 2H, phenylene$_{syn}$), 7.11–6.95 (m, 24H, ph$_{syn}$ and ph$_{anti}$), 6.92 (d, 2H, J=9.6 Hz, phenylene$_{anti}$), 6.86–6.83 (m, 8H, ph$_{syn}$), 6.78–6.76 (m, 8H, ph$_{anti}$), 6.56 (d, 4H, J=9.3 Hz, ph$_{anti}$), 6.52 (d, 4H, J=9.3 Hz, ph$_{syn}$), 3.52–3.48 (m, 2H, ethylene$_{syn}$), 3.40 (s, 6H, OMe), 3.38 (s, 6H, OMe), 3.33 (s, 6H, OMe), 3.32 (s, 6H, OMe), 3.24–3.20 (m, 4H, ethylene$_{anti}$), 3.15–3.13 (m, 2H, ethylene$_{syn}$), 3.12 (br s, 24H, CH$_{3(amine)}$), 3.05–3.00 (m, 4H, ethylene$_{anti}$), 2.94–2.87 (m, 8H, ethylene$_{syn}$, ethylene$_{syn}$ and ethylene$_{anti}$), 2.71–2.69 (m, 2H, ethylene$_{syn}$), 2.38–2.36 (m, 2H, ethylene$_{syn}$); MS (FAB): m/z=1532 (M^+). Anal. Calcd for $C_{76}H_{74}N_{10}O_{12}Pd_2\cdot0.5CHCl_3$: C, 57.72; H, 4.72; N, 8.80. Found: C, 57.86; H, 4.67; N, 9.11.

4.7.2. (*R*,*R*)-5. Yield 95%; mp 180–181 °C (decomp.); IR (KBr, cm^{-1}): 1731, 1591, 1362, 1162; ^1H NMR (600 MHz, CD_2Cl_2, 233 K, *syn*:*anti*=1:2): δ 9.14 (s, 2H, phenylene$_{syn}$), 8.09 (t, 2H, J=7.2 Hz, py$_{anti}$), 8.08 (t, 2H, J=7.2 Hz), 7.84 (d, 2H, J=9.6 Hz, phenylene$_{anti}$), 7.73–7.69 (m, 8H, py$_{syn}$ and py$_{anti}$), 7.26 (d, 4H, J=9.3 Hz, ph$_{syn}$), 7.18 (d, 4H, J=9.3 Hz, ph$_{anti}$), 7.14 (s, 2H, phenylene$_{syn}$), 7.11–6.95 (m, 24H, ph$_{syn}$ and ph$_{anti}$), 6.92 (d, 2H, J=9.6 Hz, phenylene$_{anti}$), 6.86–6.83 (m, 8H, ph$_{syn}$), 6.78–6.76 (m, 8H, ph$_{anti}$), 6.56 (d, 4H, J=9.3 Hz, ph$_{anti}$), 6.52 (d, 4H, J=9.3 Hz, ph$_{syn}$), 3.52–3.48 (m, 2H, ethylene$_{syn}$), 3.40 (s, 6H, OMe), 3.38 (s, 6H, OMe), 3.33 (s, 6H, OMe), 3.32 (s, 6H, OMe), 3.24–3.20 (m, 4H, ethylene$_{anti}$), 3.15–3.13 (m, 2H, ethylene$_{syn}$), 3.12 (br s, 24H, CH$_{3(amine)}$), 3.05–3.00 (m, 4H, ethylene$_{anti}$), 2.94–2.87 (m, 8H, ethylene$_{syn}$, ethylene$_{syn}$, and ethylene$_{anti}$), 2.71–2.69 (m, 2H ethylene$_{syn}$), 2.38–2.36 (m, 2H, ethylene$_{syn}$); MS (FAB): m/z=1532 (M^+). Anal. Calcd for $C_{76}H_{74}N_{10}O_{12}Pd_2\cdot0.5CHCl_3$: C, 57.72; H, 4.72; N, 8.80. Found: C, 57.62; H, 4.75; N, 8.95.

4.8. Equilibrium measurement of 5

Measurement of the equilibrium constants at various temperatures was carried out by the integration of the appropriate peaks during ^1H NMR spectroscopy. Spectra were taken in CD_2Cl_2 from 228 to 298 K. The thermodynamic parameters were determined from the van't Hoff plot of $\ln K_{eq}$ versus T^{-1}.

4.9. X-ray structure analysis of (*R*,*R*)-5*syn*

All measurements for (*R*,*R*)-**5** were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo Kα radiation. The structure of (*R*,*R*)-**5** was solved by heavy-atom Patterson Methods and expanded by using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 6478 observed reflections ($I>2\sigma(I)$) and 451 variable parameters.

4.9.1. Crystal data for (*R*,*R*)-5*syn*. $C_{76}H_{74}O_{12}N_{10}Pd_2$, Fw=1532.28, monoclinic, space group $C2$ (#5), a=33.1760(1), b=15.3324(4), c=18.1523 Å, β=155.9623(8)°, V=3761.1(1) Å^3, Z=2, T=4.0 °C, D_{calcd}=1.353 g cm^{-3}, μ (Mo Kα)=5.44 cm^{-1}, Mo Kα radiation (λ=0.71069 Å), $R1$=0.066, $wR2$=0.177. Crystallographic data (excluding structure factors) for the structure reported in this paper were deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 223573. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

4.10. Synthesis of 6

A mixture of L^3 (13.8 mg, 0.04 mmol) and (*S*,*S*)-**2** or (*R*,*R*)-**2** (60.4 mg, 0.08 mmol) was stirred in acetonitrile (10 mL) under argon at room temperature for 4 h. After evaporation of the solution, the chiral complex (*S*,*S*)-**6** or (*R*,*R*)-**6** was isolated by recrystallization from chloroform and ethyl ether.

4.10.1. (*S*,*S*)-6. Yield 85%; mp 207–208 °C (decomp.); IR (KBr, cm^{-1}): 3387, 1677, 1594, 1518; ^1H NMR (400 MHz, CD_2Cl_2, 273 K, *syn*:*anti*=1.6:1): δ 10.01 (s, 4H, NH$_{anti}$), 9.77 (s, 4H, NH$_{syn}$), 8.32 (s, 2H, phenylene$_{syn}$), 8.14 (t, 4H, J=7.7 Hz, py$_{syn}$ and py$_{anti}$), 8.00 (d, 1H, J=9.5 Hz, phenylene$_{anti}$), 7.87 (d, 4H, J=7.7 Hz, py$_{anti}$), 7.79 (d, 4H, J=7.7 Hz, py$_{syn}$), 7.71 (d, 1H, J=9.5 Hz, phenylene$_{anti}$), 7.45 (d, 4H, J=7.9 Hz, NHph$_{anti}$), 7.39 (d, 4H, J=7.9 Hz, NHph$_{syn}$), 7.29–7.15 (m, 26H, NHph$_{anti}$, NHph$_{syn}$ and ph$_{anti}$), 7.08–6.95 (m, 44H, ethylene-ph$_{anti}$, ethylene-ph$_{syn}$, and ph$_{syn}$), 6.84 (d, 1H, J=9.5 Hz, phenylene$_{anti}$), 6.79 (d, 1H, J=9.5 Hz, phenylene$_{anti}$), 6.72 (s, 2H, phenylene$_{syn}$), 6.57 (d, 4H, J=8.4 Hz, ph$_{anti}$), 6.44 (d, 4H, J=8.4 Hz, ph$_{syn}$), 3.76–3.20 (m, 24H, ethylene), 3.09 (s, 6H, Me$_{anti}$), 3.05 (s, 6H, Me$_{anti}$), 2.80 (s, 6H, Me$_{syn}$), 2.76 (s, 6H, Me$_{syn}$); MS (FAB): m/z=1777 (M^++1). Anal. Calcd for $C_{96}H_{86}N_{14}O_8Pd_2\cdot0.5CHCl_3$: C, 64.32; H, 4.89; N, 10.88. Found: C, 64.12; H, 4.67; N, 10.92.

4.10.2. (*R*,*R*)-6. Yield 87%; mp 207–208 °C (decomp.); IR (KBr, cm^{-1}): 3387, 1677, 1594, 1518; ^1H NMR

(400 MHz, CD_2Cl_2, 273 K, *syn*:*anti*=1.6:1): δ 10.01 (s, 4H, NH_{anti}), 9.77 (s, 4H, NH_{syn}), 8.32 (s, 2H, $phenylene_{syn}$), 8.14 (t, 4H, J=7.7 Hz, py_{syn} and py_{anti}), 8.00 (d, 1H, J=9.5 Hz, $phenylene_{anti}$), 7.87 (d, 4H, J=7.7 Hz, py_{anti}), 7.79 (d, 4H, J=7.7 Hz, py_{syn}), 7.71 (d, 1H, J=9.5 Hz, $phenylene_{anti}$), 7.45 (d, 4H, J=7.9 Hz, $NHph_{anti}$), 7.39 (d, 4H, J=7.9 Hz, $NHph_{syn}$), 7.29–7.15 (m, 26H, $NHph_{anti}$, $NHph_{syn}$, and ph_{anti}), 7.08–6.95 (m, 44H, ethylene-ph_{anti}, ethylene-ph_{syn}, and ph_{syn}), 6.84 (d, 1H, J=9.5 Hz, $phenylene_{anti}$), 6.79 (d, 1H, J=9.5 Hz, $phenylene_{anti}$), 6.72 (s, 2H, $phenylene_{syn}$), 6.57 (d, 4H, J=8.4 Hz, ph_{anti}), 6.44 (d, 4H, J=8.4 Hz, ph_{syn}), 3.76–3.20 (m, 24H, ethylene), 3.09 (s, 6H, Me_{anti}), 3.05 (s, 6H, Me_{anti}), 2.80 (s, 6H, Me_{syn}), 2.76 (s, 6H, Me_{syn}); MS (FAB): m/z=1777 (M^++1). Anal. Calcd for $C_{96}H_{86}N_{14}O_8Pd_2\cdot 0.5CHCl_3$: C, 64.32; H, 4.89; N, 10.88. Found: C, 64.03; H, 4.75; N, 10.95.

4.11. Synthesis of 7

A mixture of 2,6-bis[(*S*)-4′-isopropyloxazolin-2′-yl]pyridine ((*S*,*S*)-L^4H_2) or 2,6-bis[(*R*)-4′-isopropyloxazolin-2′-yl]pyridine ((*R*,*R*)-L^4H_2) (45.2 mg, 0.15 mmol) and $Pd(MeCN)_4(BF_4)_2$ (66.6 mg, 0.15 mmol) in acetonitrile (5.0 mL) was stirred under argon at room temperature for 5 h. After evaporation of the solution, the palladium complex ((*S*,*S*)-L^4)$Pd(MeCN)(BF_4)_2$ ((*S*,*S*)-**7**) or ((*R*,*R*)-L^4)$Pd(MeCN)(BF_4)_2$ ((*R*,*R*)-**7**) was isolated as pale-yellow crystal by recrystallization from acetonitrile and ethyl ether.

4.11.1. (*S*,*S*)-7. Yield 98%; mp 204–206 °C (decomp.); IR (KBr, cm^{-1}): 2964, 1641, 1608, 1578; ^1H NMR (400 MHz, CD_3CN): δ 8.56 (t, 1H, J=8.04 Hz, H_{py}), 8.08 (d, 2H, J=8.04 Hz, H_{py}), 5.05–4.94 (m, 4H, H_{ox}), 4.44–4.39 (m, 2H, H_{ox}), 2.12–2.07 (m, 2H, H_{ox}), 1.95 (s, 3H, H_{NH}), 0.98 (d, 6H, J=6.6 Hz, H_{Me}), 0.97 (d, 6H, J=6.6 Hz, H_{Me}). Anal. Calcd for $C_{19}H_{26}N_4O_2Pd(BF_4)_2$: C, 36.66; H, 4.21; N, 9.00. Found: C, 36.49; H, 4.19; N, 9.01.

4.11.2. (*R*,*R*)-7. Yield 95%; mp 204–206 °C (decomp.); IR (KBr, cm^{-1}): 2964, 1641, 1608, 1578; ^1H NMR (400 MHz, CD_3CN): δ 8.56 (t, 1H, J=8.04 Hz, H_{py}), 8.08 (d, 2H, J=8.04 Hz, H_{py}), 5.05–4.94 (m, 4H, H_{ox}), 4.44–4.39 (m, 2H, H_{ox}), 2.12–2.07 (m, 2H, H_{ox}), 1.95 (s, 3H, H_{NH}), 0.98 (d, 6H, J=6.6 Hz, H_{Me}), 0.97 (d, 6H, J=6.6 Hz, H_{Me}). Anal. Calcd for $C_{19}H_{26}N_4O_2Pd(BF_4)_2$: C, 36.66; H, 4.21; N, 9.00. Found: C, 36.77; H, 4.28; N, 8.82.

4.12. Synthesis of 8

A mixture of L^3 (17.2 mg, 0.05 mmol) and (*S*,*S*)-**7** or (*R*,*R*)-**7** (62.3 mg, 0.10 mmol) was stirred in acetonitrile (5 mL) under argon at room temperature for 5 h. After evaporation of the solution, the chiral complex (*S*,*S*)-**8** or (*R*,*R*)-**8** was isolated by recrystallization from acetonitrile and diethyl ether.

4.12.1. (*S*,*S*)-8. Yield 80%; mp 198–199 °C (decomp.); IR (KBr, cm^{-1}): 2961, 1591, 1502; ^1H NMR (400 MHz, CD_3CN, 233 K, *syn*:*anti*=1:2.2): δ 8.63 (s, 2H, $phenylene_{syn}$), 8.542 (t, 2H, J=8.0 Hz, py_{anti}), 8.538 (t, 2H, J=8.0 Hz, py_{syn}), 8.46 (d, 2H, J=8.7 Hz, $phenylene_{anti}$), 8.12 (d, 4H, J=8.0 Hz, py_{anti}), 8.11 (d, 4H, J=8.0 Hz, py_{syn}), 7.90 (d, 8H, J=8.6 Hz, ph_{syn} and ph_{anti}), 7.43 (d, 2H, J=8.7 Hz, $phenylene_{anti}$), 7.24 (s, 2H, $phenylene_{syn}$), 6.94 (d, 8H, J=8.6 Hz, ph_{syn} and ph_{anti}), 4.87–4.79 (m, 16H, Ox_{syn} and Ox_{anti}), 3.95–3.88 (m, 2H, Ox_{syn}), 3.80–3.73 (m, 2H, Ox_{anti}), 3.58–3.50 (m, 2H, Ox_{syn}), 3.32–3.24 (m, 2H, Ox_{anti}), 3.18 (br s, 24H, NCH_3), 1.49–1.42 (m, 8H, CH), 0.84–0.75 (m, 24H, CH_3), 0.67–0.58 (m, 24H, CH_3); MS (FAB): m/z=1420 (($M-BF_4$)$^+$). Anal. Calcd for $C_{56}H_{70}N_{10}O_4Pd_2(BF_4)_4$: C, 44.62; H, 4.68; N, 9.29. Found: C, 44.64; H, 4.41; N, 9.18.

4.12.2. (*R*,*R*)-8. Yield 71%; mp 198–199 °C (decomp.); IR (KBr, cm^{-1}): 2961, 1591, 1502; ^1H NMR (400 MHz, CD_3CN, 233 K, *syn*:*anti*=1:2.2): δ 8.63 (s, 2H, $phenylene_{syn}$), 8.542 (t, 2H, J=8.0 Hz, py_{anti}), 8.538 (t, 2H, J=8.0 Hz, py_{syn}), 8.46 (d, 2H, J=8.7 Hz, $phenylene_{anti}$), 8.12 (d, 4H, J=8.0 Hz, py_{anti}), 8.11 (d, 4H, J=8.0 Hz, py_{syn}), 7.90 (d, 8H, J=8.6 Hz, ph_{syn} and ph_{anti}), 7.43 (d, 2H, J=8.7 Hz, $phenylene_{anti}$), 7.24 (s, 2H, $phenylene_{syn}$), 6.94 (d, 8H, J=8.6 Hz, ph_{syn} and ph_{anti}), 4.87–4.79 (m, 16H, Ox_{syn} and Ox_{anti}), 3.95–3.88 (m, 2H, Ox_{syn}), 3.80–3.73 (m, 2H, Ox_{anti}), 3.58–3.50 (m, 2H, Ox_{syn}), 3.32–3.24 (m, 2H, Ox_{anti}), 3.18 (br s, 24H, NCH_3), 1.49–1.42 (m, 8H, CH), 0.84–0.75 (m, 24H, CH_3), 0.67–0.58 (m, 24H, CH_3); MS (FAB): m/z=1420 (($M-BF_4$)$^+$). Anal. Calcd for $C_{56}H_{70}N_{10}O_4Pd_2(BF_4)_4$: C, 44.62; H, 4.68; N, 9.29. Found: C, 44.44; H, 4.74; N, 9.61.

Acknowledgements

This work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, Murata Scientific Foundation, and Iketani Science Technology Foundation. Thanks are also due to the Analytical Center, Graduate School of Engineering, Osaka University, for the use of the NMR and MS instruments.

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Electrophilic cyclization of *N*-alkenylamides using a chloramine-T/I_2 system

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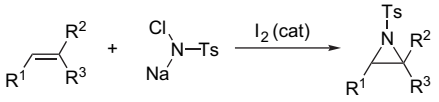
Received 28 August 2006; revised 4 October 2006; accepted 5 October 2006
Available online 27 October 2006

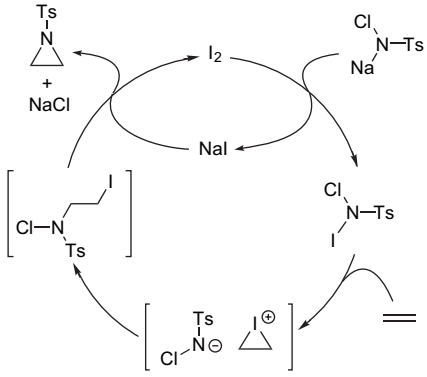
Abstract—A new protocol for the cyclization of *N*-alkenylamides using chloramine-T and iodine is described. When *N*-alkenylsulfonamides are treated with chloramine-T and iodine, three- to six-membered *N*-heterocycles are obtained with complete stereoselectivity. The method is compatible with the cyclization of the allylbenzamide or allylbenzthioamide to afford an oxazoline or thiazoline derivative, respectively. Mechanistic studies indicate that the chloramine-T/I_2 system functions as an effective iodonium species.

1. Introduction

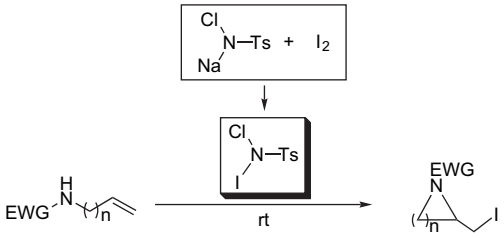
The functionalization of a double bond activated by an electrophile is one of the most useful reactions in organic synthesis. Ring formation through the reaction of a heteroatom and a cyclic onium ion is a versatile method for the stereocontrolled synthesis of heterocycles.[1] The electrophilic cyclization of nonconjugated olefinic carboxylic acids was initially exploited by Bougault.[2] Electrophiles, such as halogens, halo reagents, selenium derivatives, and certain metallic salts, for the activation of the olefinic moiety have been developed for use in this type of cyclization. Barluenga and González reported on a versatile reagent, bis(pyridine)iodine tetrafluoroborate (IPy_2BF_4), not only for the cyclization[3] but also for many other useful and unique transformations.[4] Quite recently, we reported that *tert*-butyl hypoiodite (*t*-BuOI)[5] is a powerful reagent for the cyclization of *N*-alkenylamides[6] and the aziridination of olefins with sulfonamides.[7] Since the polarity of the O–I of the reagent should be an important factor in such reactions, an N–I bond having electron-withdrawing groups on the nitrogen would be expected to act in a similar fashion. Our group (Eq. 1)[8] and the Sharpless group[9] simultaneously reported on the iodine- or bromine-catalyzed aziridination of olefins using chloramine-T. In our study, we proposed that a reactive species having N–I bond, generated from chloramine-T and iodine, is involved in the reaction path and functions as a key intermediate (Scheme 1). From these points of view, we report here on the use of inexpensive chloramine-T and I_2 as reagents for the cyclization of *N*-alkenylamides (Scheme 2).



(1)



Scheme 1. Proposed path for the I_2-catalyzed aziridination of olefins using chloramine-T.



Scheme 2. A reactive species having an N–I bond for the cyclization of *N*-alkenylamides.

Keywords: Alkenylamides; Chloramine-T; Iodine; Heterocycles.
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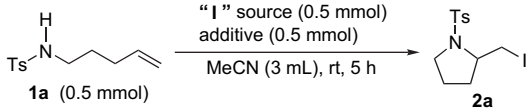
doi:10.1016/j.tet.2006.10.003

2. Results and discussion

To evaluate the ability of the chloramine-T/I_2 system in the electrophilic cyclization of *N*-(4-pentenyl)-*p*-toluenesulfonamide (**1a**), some related reagents were employed in the reaction (Table 1). Although the desired cyclization in the presence of the only iodine proceeded, the yield of iodomethylated *N*-tosylpyrrolidine **2a** was moderate, under the reaction conditions used. The addition of *t*-BuONa to the above conditions was ineffective. As expected, the use of a combination of iodine and chloramine-T successfully caused efficient cyclization, giving **2a** in 98% yield. The use of sodium iodide as an 'I' source instead of iodine vastly decreased the efficiency. The presence of species acting as an iodonium ion should be important to induce this cyclization.

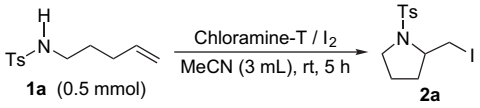
Table 1. Evaluation of iodinating reagents in the cyclization of *N*-(4-pentenyl)-*p*-toluenesulfonamide



'I' source	Additive	Yield (%)	Recovery (%)
I_2	—	61	25
I_2	*t*-BuONa	63	37
I_2	Chloramine-T	98	0
NaI	Chloramine-T	52	46

The effect of the amounts of the two reagents, iodine and chloramine-T, on cyclization was examined as shown in Table 2. Even if a half amount of either chloramine-T or iodine against **1a** was employed in the reaction, almost the same efficiency was observed, compared with the use of stoichiometric amounts of the two reagents. Interestingly, it was found that a half amount of chloramine-T and iodine is sufficient for the reaction to reach completion in almost quantitative yield (entry 4). These results indicate that both I atoms are able to serve as iodonium species.

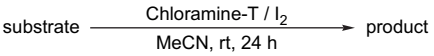
Table 2. Optimization of the amount of the reagents

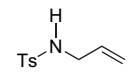
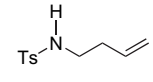
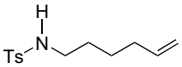
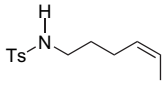
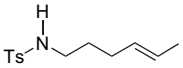


Entry	Chloramine-T (mmol)	I_2 (mmol)	Yield (%)
1	0.50	0.50	98
2	0.25	0.50	97
3	0.50	0.25	95
4	0.25	0.25	97

A variety of *N*-alkenylsulfonamides were examined using the chloramine-T/I_2 system under selected conditions (method A and B) as shown in Table 3. In method A, stoichiometric amounts of chloramine-T and I_2 were used against the *N*-alkenylsulfonamides and in method B a half amount of the reagents were used. Method A gave good results for the formation of aziridine **2b** by the cyclization of *N*-allyl-*p*-toluenesulfonamide (**1b**). The aziridination of **1b** also proceeded by method B, a rather low yield was

Table 3. Cyclization of a variety of alkenylsulfonamides using the chloramine-T/I_2 system



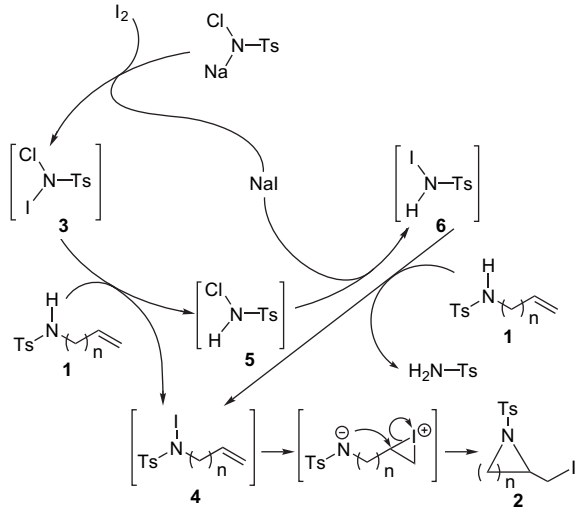
Substrate	Product	Yield (%) A[a]	Yield (%) B[b]
 (1b)	 (2b)	81	54
 (1c)	 (2c)	8	8
 (1d)	 (2d)	45	40
 (1e)	 (2e)	78[c]	37[c]
 (1f)	 (2f)	80[c]	62[c]

[a] Method A: substrate (0.50 mmol)/chloramine-T (0.50 mmol)/I_2 (0.50 mmol).
[b] Method B: substrate (0.50 mmol)/chloramine-T (0.25 mmol)/I_2 (0.25 mmol).
[c] Reaction time: 5 h.

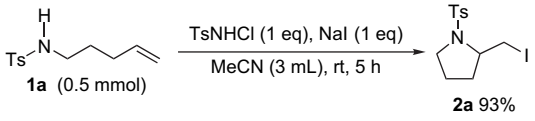
obtained, under the conditions used. Although the efficiency of cyclization of **1c** was unsatisfactory, a four-membered nitrogen heterocycle, an azetidine was obtained using these methods. In the reaction, 3-iodo-*N*-tosylpyrrolidine via 5-*endo* cyclization and ICl adduct to the C–C double bond were obtained. When *N*-(5-hexenyl)-*p*-toluenesulfonamide (**1d**) was employed in the reaction using both method A and B, moderate yields of the corresponding piperidine were obtained, in which ICl adduct was also observed. Both *trans*- and *cis*-(4-hexenyl)-*p*-toluenesulfonamides, **1e** and **1f**, were converted into the corresponding pyrrolidines in good yields with complete stereoselectivities, indicating that the present reaction proceeds through a three-membered iodonium ion intermediate.

Although the precise mechanism and the nature of the active species are unclear at present, the following findings provide support for the reaction pathway depicted in Scheme 3. As proposed in our previous work,[8] the reaction of chloramine-T with iodine is very rapid, affording *N*-chloro-*N*-iodo-*p*-toluenesulfonamide (**3**). If the active species having an N–I bond reacts with *N*-alkenylsulfonamides **1** in a manner similar to *t*-BuOI,[6] the species **3** might iodinate the nitrogen of the sulfonamides, not an olefinic moiety. In fact, when a solution of *N*-methyl-*p*-toluenesulfonamide (methyl, δ 2.41 ppm) in CD_3CN was treated with chloramine-T and I_2, a new methyl singlet at δ 3.14 ppm, identical to the peak produced in the reaction of *N*-methyl-*p*-toluenesulfonamide and *t*-BuOI,[6] appeared. The NMR study supports the formation of *N*-iodo-*N*-alkenylsulfonamides **4** by the reaction of sulfonamides with species **3** generated from chloramine-T and iodine. Cyclization of *N*-iodinated alkenylsulfonamides would be expected to proceed via a

three-membered iodonium ion, the generation of which would be confirmed by the complete stereoselectivity shown in Table 3. In order to investigate the fact that even a half amount of chloramine-T and I_2 against *N*-alkenylsulfonamides, especially **1a**, is sufficient for the cyclization, the following experiment was performed. Since it is likely that *N*-chlorinated sulfonamide **5** and NaI would be formed after the reaction of **1** and **3**, sulfonamide **1a** was treated with **5**, which was prepared separately,[10] in the presence of NaI under the reaction conditions, leading to efficient cyclization (Scheme 4). These results suggest that compound **5** might be converted into the active species **6** with NaI, after which the species would function as a source of iodonium ions for the cyclization.



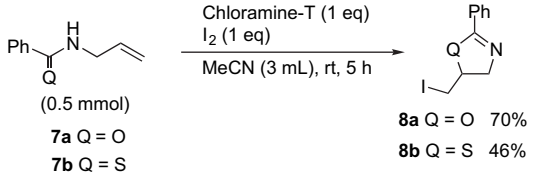
Scheme 3. Plausible reaction pathway to *N*-heterocycles.



Scheme 4. Cyclization of *N*-alkenylamide in the presence of TsNHCl and NaI.

Although the cyclization of *N*-(4-pentenyl)amides having benzoyl and Boc groups instead of tosyl group were carried out to investigate the scope and limitation of the reagents, the corresponding *N*-heterocycles were not obtained. From these results, the acidity of the tosylamide moiety would be important to perform the iodination with species **3**.

However, *N*-allylbenzamide or *N*-allylbenzthioamide derivatives were found to be employed in the cyclization (Scheme 5). The reaction of *N*-(2-propenyl)benzamide (**7a**) with stoichiometric amounts of chloramine-T and iodine in acetonitrile at room temperature gave the iodomethylated oxazoline **8a** in 70% yield. The thioamide derivative **7b** was allowed to react under the reaction conditions, affording the corresponding thiazoline **8b** in moderate yield.



Scheme 5. Cyclization of *N*-allylbenz(thio)amides.

3. Conclusions

A simple and efficient method for the cyclization of various alkenylamides using chloramine-T and I_2 was developed. The precise mechanism of this reaction is presently unclear, but auxiliary experiments suggest that *N*-iodo-*N*-alkenylamides are generated as intermediates. Since the cyclization pathway involves a cyclic iodonium ion, the stereochemistry could be completely controlled. Chloramine-T and iodine are both readily available, inexpensive and easily handled, and the combination of these reagents enabled both I atoms of iodine to function as iodonium species. Applications of the system to other organic synthesis are currently in progress.

4. Experimental

4.1. General experimental method

All reactions were carried out under an atmosphere of nitrogen. Acetonitrile was freshly distilled over CaH_2. ^1H and ^{13}C NMR spectra were recorded at 270 and 68 MHz or 400 and 100 MHz, respectively. Flash column chromatography (FCC) was performed using silica gel FL60D (Fuji Silysia Chemical Co.). Analytical thin layer chromatography was performed using EM reagent and 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and spraying with an ethanolic phosphomolybdic acid solution followed by heating.

4.2. General procedure for the preparation of *N*-alkenylamides

Following the general procedure of Ing's method,[11] a mixture of an alkenyl halide (50 mmol), potassium phthalimide (100 mmol), and dimethylformamide (50 mL) was heated at 85 °C for 3 h. After cooling to room temperature, Et_2O (100 mL) and H_2O (100 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (50 mL×2). The combined organic layer was washed successively with water (100 mL×2) and brine (100 mL) and dried over K_2CO_3, and the solvent was removed under reduced pressure to give the white solid. A slurry of the given phthalimide derivative (50 mmol), EtOH (50 mL) and hydrazine hydrate (100 mmol) was heated to reflux for 30 min. After cooling to room temperature, the reaction mixture was filtered through a paper filter, and the solid was washed with dichloromethane (250 mL) to give an alkenylamine. Triethylamine (20 mL) and an acid chloride (50 mmol) was added to the solution of the amine obtained at 0 °C. The solution was allowed to warm to room temperature over the course of 12 h. After washing with 1 N hydrochloric acid (100 mL), 1 N aqueous K_2CO_3 (100 mL), water (100 mL×2), and brine (100 mL) and dried over K_2CO_3, and the solvent was removed under reduced pressure to give the yellow oil.

Purification by flash chromatography (hexane/ethyl acetate, 9:1) led to isolation of desired *N*-alkenylamide as a colorless oil.

4.3. General procedure for cyclization of *N*-alkenylamides

Method A: chloramine-T (0.5 mmol) and iodine (0.5 mmol) were added to a solution of *N*-alkenylamides (0.5 mmol) in acetonitrile (3 mL). The mixture was allowed to stir in the dark at room temperature for the indicated times under an atmosphere of nitrogen, quenched with 0.3 M aqueous $Na_2S_2O_3$ (3 mL), extracted with CH_2Cl_2, dried over $MgSO_4$, and the extract was then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate).

Method B: chloramine-T (0.5 mmol) and iodine (0.5 mmol) of method A was changed to chloramine-T (0.25 mmol) and iodine (0.25 mmol).

4.3.1. 2-Iodomethyl-1-(*p*-toluenesulfonyl)pyrrolidine (2a). Spectroscopic data were in agreement with those of previously published material.[12] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.55 (m, 1H), 1.76–1.90 (m, 3H), 2.44 (s, 3H), 3.14–3.26 (m, 2H), 3.46–3.51 (m, 1H), 3.61 (dd, 1H, J=2.8, 9.6 Hz), 3.70–3.76 (m, 1H), 7.34 (d, 2H, J=8.0 Hz), 7.72 (d, 2H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 11.5, 21.5, 23.8, 32.0, 50.1, 60.7, 127.5, 129.8, 134.2, 143.7.

4.3.2. 2-Iodomethyl-1-(*p*-toluenesulfonyl)aziridine (2b). Spectroscopic data were in agreement with those of previously published material.[13] Colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.18 (d, 1H, J=3.2 Hz), 2.45 (s, 3H), 2.83 (d, 1H, J=6.8 Hz), 3.01–3.12 (m, 3H), 7.36 (d, 2H, J=8.2 Hz), 7.84 (d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 2.5, 21.8, 36.3, 41.1, 128.1, 129.5, 134.3, 144.7.

4.3.3. 2-Iodomethyl-1-(*p*-toluenesulfonyl)azetidine (2c). Spectroscopic data were in agreement with those of previously published material.[6] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.85–1.99 (m, 1H), 2.03–2.15 (m, 1H), 2.47 (s, 3H), 3.28 (dd, 1H, J=9.9, 10.0 Hz), 3.42 (dt, 1H, J=8.3, 8.3 Hz), 3.54 (dd, 1H, J=3.8, 9.9 Hz), 3.65 (dt, 1H, J=3.7, 8.3 Hz), 3.89–4.00 (m, 1H), 7.38 (d, 2H, J=8.2 Hz), 7.72 (d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 9.8, 21.7, 24.1, 45.9, 62.9, 128.2, 129.8, 131.7, 144.2.

4.3.4. 2-Iodomethyl-1-(*p*-toluenesulfonyl)piperidine (2d). Spectroscopic data were in agreement with those of previously published material.[12] Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.25–1.58 (m, 5H), 2.03–2.12 (m, 1H), 2.43 (s, 3H), 2.94 (dt, 1H, J=2.3, 14.2 Hz), 3.22 (dd, 1H, J=5.0, 10.0 Hz), 3.36 (dd, 1H, J=10.0, 10.0 Hz), 3.71 (dd, 1H, J=3.5, 14.2 Hz), 4.24–4.28 (m, 1H), 7.30 (d, 2H, J=8.1 Hz), 7.72 (d, 2H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 4.0, 17.7, 21.5, 24.3, 26.2, 40.6, 53.8, 127.0, 129.8, 137.9, 143.3.

4.3.5. *erythro*-2-(1-Iodoethyl)-1-(*p*-toluenesulfonyl)pyrrolidine (2e). Spectroscopic data were in agreement with those of previously published material.[12] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.31–1.44 (m, 1H), 1.68–2.06 (m, 3H), 1.83 (d, 3H, J=7.0 Hz), 2.45 (s, 3H), 3.27–3.36 (m, 1H), 3.44–3.53 (m, 1H), 3.96–4.02 (m, 1H), 4.75 (dq, 1H, J=3.8, 7.0 Hz), 7.34 (d, 2H, J=8.1 Hz), 7.72 (d, 2H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 21.5, 24.4, 25.1, 30.4, 36.8, 49.3, 65.5, 127.5, 129.7, 135.1, 143.6.

4.3.6. *threo*-2-(1-Iodoethyl)-1-(*p*-toluenesulfonyl)pyrrolidine (2f). Spectroscopic data were in agreement with those of previously published material.[12] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.33–1.43 (m, 1H), 1.78–1.93 (m, 3H), 1.87 (d, 3H, J=7.0 Hz), 2.44 (s, 3H), 3.10–3.17 (m, 1H), 3.34–3.39 (m, 2H), 4.71–4.81 (m, 1H), 7.32 (d, 2H, J=8.3 Hz), 7.74 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 20.4, 21.6, 24.4, 28.5, 30.2, 51.4, 65.4, 127.6, 129.8, 133.7, 143.8.

4.3.7. 5-Iodomethyl-2-phenyl-2-oxazoline (8a). Spectroscopic data were in agreement with those of previously published material.[6] Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.28–3.42 (m, 2H), 3.80 (dd, 1H, J=6.6, 15.1 Hz), 4.17 (dd, 1H, J=8.1, 15.1 Hz), 4.75–4.86 (m, 1H), 7.38–7.51 (m, 3H), 7.92–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 7.8, 60.7, 78.2, 127.3, 128.0, 128.2, 131.3, 163.2.

4.3.8. 5-Iodomethyl-2-phenyl-2-thiazoline (8b). Spectroscopic data were in agreement with those of previously published material.[6] Yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.23 (dd, 1H, J=10.0, 10.1 Hz), 3.38 (dd, 1H, J=5.3, 10.0 Hz), 4.17–4.25 (m, 1H), 4.26 (dd, 1H, J=8.1, 19.5 Hz), 4.62 (dd, 1H, J=1.5, 19.5 Hz), 7.38–7.50 (m, 3H), 7.79–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 9.9, 51.5, 69.8, 128.4, 128.8, 131.4, 132.8, 166.3.

4.3.9. 3-Iodo-1-(*p*-toluenesulfonyl)pyrrolidine. Colorless crystalline solid; mp 99–103 °C; TLC R_f 0.17 (hexane/EtOAc, 4:1); IR (KBr): 1345, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.07–2.33 (m, 2H, –NCH_2CHCH_2–), 2.44 (s, 3H, ArCH_3), 3.44 (t, 2H, J=6.8 Hz, –$CHCH_2CH_2N$–), 3.56 (dd, 1H, J=4.7, 11.5 Hz, –NC*H*HCH–), 3.90 (dd, 1H, J=5.8, 11.5 Hz, –NCH*H*CH–), 4.13–4.21 (m, 1H, –NCH_2CHCH_2–), 7.34 (d, 2H, J=8.0 Hz, Ar*H*), 7.73 (d, 2H, J=8.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 17.3, 21.5, 38.1, 46.9, 58.6, 127.5, 129.8, 133.8, 143.8; MS (CI, methane): 352 ([M+1]$^+$, 100), 224 ([M−I]$^+$, 14), 196 ([M−Ts]$^+$, 10), 184 (18), 155 (13); Anal. Calcd for $C_{11}H_{14}INO_2S$: C, 37.62; H, 4.02; N, 3.99. Found: C, 37.84; H, 3.90; N, 3.92.

4.3.10. *N*-(3-Chloro-4-iodobutyl)-*p*-toluenesulfonamide (A) and *N*-(4-chloro-3-iodobutyl)-*p*-toluenesulfonamide (B). Compounds **A** and **B** obtained as an inseparable mixture, 79:21 in 23% yield. Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) (**A**+**B**): δ 1.76–1.93 (m, 2H, –C*H*HCH_2NHTs, **A**+**B**), 2.14–2.30 (m, 2H, –CH*H*CH_2NHTs, **A**+**B**), 3.01–3.26 (m, 4H, –CH_2CH_2NHTs, **A**+**B**), 3.36 (dd, 1H, J=8.2, 10.3 Hz, **B**),[†] 3.55 (dd, 1H, J=4.6, 10.3 Hz, **B**),[†] 3.76 (dd, 1H, J=9.9, 11.1 Hz, **A**),[†] 3.95–4.06 (m, 1H,

[†] Identification of the chemical shifts was determined by the comparison of those of the similar compounds.[14]

$ClCH_2CHICH_2$–, **B**),[†] 4.00 (dd, 1H, J=4.3, 11.1 Hz, **A**),[†] 4.16–4.26 (m, 1H, $ICH_2CHClCH_2$–, **A**),[†] 7.37 (d, 4H, Ar*H*, J=8.2 Hz, **A+B**), 7.76 (d, 4H, Ar*H*, J=8.2 Hz, **A+B**); MS (CI, isobutane): *m*/*z* (relative intensity, %) (**A** and **B**): 388 ($[M+1]^+$, 13), 352 ($[M-Cl]^+$, 19), 260 ($[M-I]^+$, 44), 184 ($[CH_2NHTs]^+$, 100), 155 ($[ArSO_2]$, 27).

4.3.11. *N*-(5-Chloro-6-iodobutyl)-*p*-toluenesulfonamide (C) and *N*-(6-chloro-5-iodobutyl)-*p*-toluenesulfonamide (D). Compounds **C** and **D** obtained as an inseparable mixture, 47:53 in 32% yield. Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) (**C+D**): δ 1.25–1.60 (m, 8H, $-CH_2CH_2CH_2NHTs$, **C+D**), 1.60–1.80 (m, 2H, $-CHHCH_2NHTs$, **C+D**), 1.80–2.05 (m, 2H, $-CHHCH_2NHTs$, **C+D**), 2.86–3.02 (m, 4H, $-CH_2CH_2NHTs$, **C+D**), 3.35 (dd, 1H, J=8.4, 9.9 Hz, **D**),[†] 3.52 (dd, 1H, J=4.9, 9.9 Hz, **D**),[†] 3.74 (dd, 1H, J=10.1, 11.0 Hz, **C**),[†] 3.81–3.94 (m, 1H, $ClCH_2CHICH_2$–, **D**),[†] 3.99 (dd, 1H, J=4.6, 11.0 Hz, **C**),[†] 4.04–4.17 (m, 1H, $ICH_2CHClCH_2$–, **C**),[†] 7.32 (d, 4H, Ar*H*, J=8.2 Hz, **C+D**), 7.76 (d, 4H, Ar*H*, J=8.2 Hz, **C+D**); MS (CI, isobutane): *m*/*z* (relative intensity, %) (**C** and **D**): 416 ($[M+1]^+$, 13), 380 ($[M-Cl]^+$, 74), 288 ($[M-I]^+$, 7), 254 (100).

4.4. The NMR study of the iodination of *N*-methyl-*p*-toluenesulfonamide

Chloramine-T (0.02 mmol) and iodine (0.02 mmol) were added to a solution of *N*-methyl-*p*-toluenesulfonamide (0.02 mmol) in CD_3CN (0.5 mL). After 10 min, ^{1}H NMR of the mixture was measured. The conversion of 13% of *N*-methyl-*p*-toluenesulfonamide to *N*-iodo-*N*-methyl-*p*-toluenesulfonamide was observed.[6]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Japan. Y.M. expresses his special thanks for the 21st century center of excellence (21COE) program, 'Creation of Integrated EcoChemistry of Osaka University'. We also wish to acknowledge the Instrumental Analysis Center, Faculty of Engineering, Osaka University.

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Synthetic studies on the CDEF ring system of lactonamycin

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Received 4 August 2006; revised 26 September 2006; accepted 5 October 2006
Available online 30 October 2006

Abstract—Both (1) furan–maleimide Diels–Alder cycloaddition reaction and (2) furan–benzyne cycloaddition, Suzuki cross-coupling, boron-mediated aldol, and electrophilic aromatic substitution reactions were examined for the construction of the CDEF ring system of lactonamycin (**1**).

1. Introduction

Lactonamycin (**1**) and lactonamycin-Z (**2**) have intriguing structural features, which include a naphtho[*e*]isoindole ring system (DEF-rings) and a densely oxygenated fused perhydrofuran-furanone ring system (AB-rings) (Fig. 1).[1] Lactonamycin (**1**) shows significant levels of antimicrobial activity against Gram-positive bacteria being especially active against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) with minimum inhibitory concentration levels of 0.39 and 0.20 μg/mL, respectively. In addition, it shows significant levels of cytotoxicity against various tumor cell lines with IC_{50} ranging from 0.06 to 3.30 μg/mL. Whilst there has been no total synthesis of **1** yet published, synthetic studies toward lactonamycin **1** have been reported by four groups. Cox and Danishefsky have described two routes to model systems of the densely oxygenated ABCD portion,[2] while Kelly's group more recently reported an asymmetric synthesis of the AB ring system.[3] Of particular relevance to the work presented here, two syntheses of model systems related to the aromatic CDEF core of lactonamycin have also been reported. Behar's approach was based on the construction of ring E by an elegant tandem conjugate cyanide addition–Dieckmann condensation.[4] Shortly thereafter, Kelly published a second approach toward the same lactonamycin segment by the assemblage of the D and E rings using Diels–Alder cycloaddition reactions.[5] Danishefsky and co-workers recently completed a diastereoselective synthesis of the entire lactonamycin aglycon, with the CDEF fragment assembled using successive Diels–Alder reactions.[6] Finally, we have reported the synthesis of the ABCD tetracyclic ring system of lactonamycin using an iterative sequence of Michael addition and oxidation reactions.[7] Herein, we report our own studies on the approaches to the CDEF ring system using notably benzyne–furan and maleimide–furan cycloaddition reactions, Suzuki coupling reaction, and electrophilic aromatic substitutions.

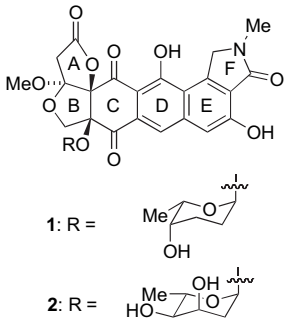

Figure 1. Structures of lactonamycin (**1**) and lactonamycin-Z (**2**).

2. Results and discussion

2.1. The benzyne cycloaddition strategy

Initially, we sought to synthesize the lactonamycin CDEF ring system **3** by formation of the hydroquinone ring C using a double Friedel–Crafts acylation of naphthol **5** using succinic anhydride **4** (Scheme 1). In turn, naphthalene **5** should be available using a [4+2] cycloaddition reaction of the aryne derived from iodo-triflate **7** and the diene **6**,[8] and subsequent aromatization.[9] Whilst the regioselectivity of the cycloaddition reaction could be problematical, the use of symmetrical dienes to replace **6** and ring D manipulation was considered as a fall back option. Finally, iodo-triflate

Keywords: Lactonamycin; Diels–Alder reaction; Benzyne; Suzuki coupling; Butenolide; Friedel–Crafts reaction.
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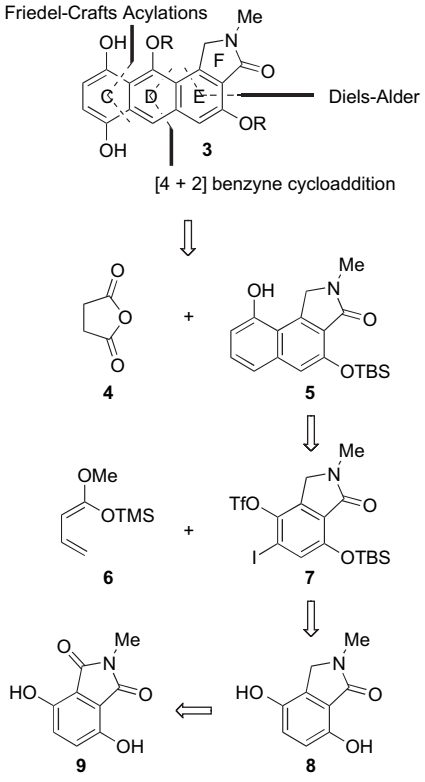
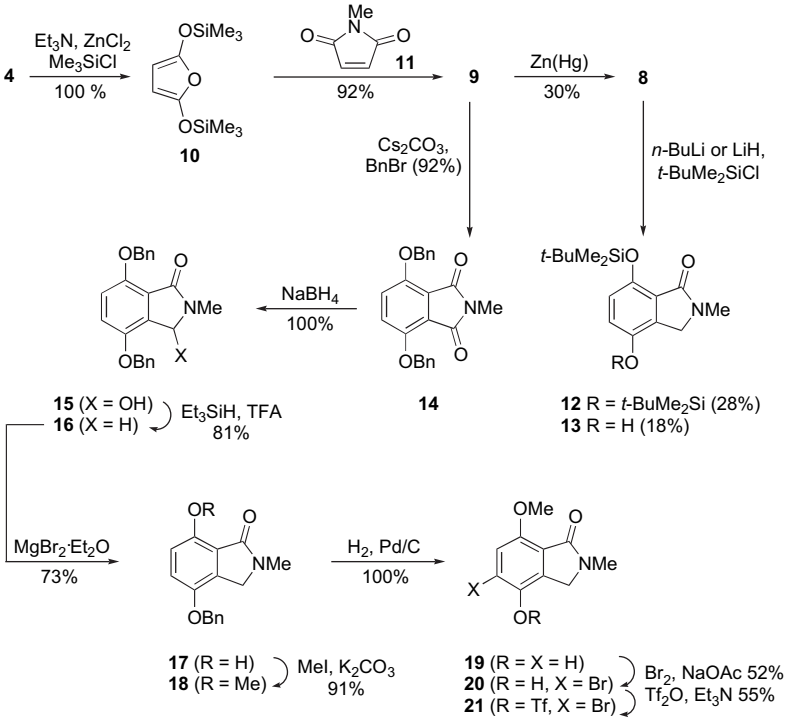
doi:10.1016/j.tet.2006.10.004

7 should be available from imide **9** via reduction, iodination, and triflation.



Scheme 1. Initial retrosynthetic analysis.

Diels–Alder reaction of diene **10**[10] with *N*-methylmaleimide **11** and in situ aromatization gave imide **9**[11] in excellent overall yield (92%) (Scheme 2).[12] In contrast, the synthesis of imide **9** from the hydrolysis of commercial 3,6-dihydroxyphthalonitrile[13] and subsequent coupling with $MeNH_2$ was less efficient (25%) due to the poor solubility of the intermediate phthalic acid and partial decarboxylation.[14] Subsequent conversion to the benzyne precursor **7** proved troublesome. Clemmensen reduction[15] of imide **9** to lactam **8** proceeded in poor yield and the product was difficult to purify. Attempted selective mono-*tert*-butyldimethylsilylation of hydroquinone **8** using excess lithium carbonate[16] gave an intractable mixture, whereas silylation using *n*-butyllithium or lithium hydride (1 equiv) gave the desired mono-protected hydroquinone **13** (18%), diether **12** (28%), and recovered hydroquinone **8** (30%). Finally, both iodination[17] and bromination of phenol **13** were unsuccessful giving mixtures of products. In the light of these difficulties the approach was modified with a two-step imide reduction[12b,18] and substrate benzylation to overcome the poor reactivity and low solubility of hydroquinone **9**. Sequential sodium borohydride and triethylsilane–TFA[18b,c] reduction of diether **14** gave lactam **16** (81%). We next sought to convert the diether **16** into the corresponding phenol **19** for regioselective ring halogenation. Selective mono-debenzylation using magnesium bromide[19] gave phenol **17** (73%) as the only isomer, the structure of which was established by NOE analysis and X-ray crystal structure determination. Methylation of phenol **17** and debenzylation by hydrogenolysis gave the methyl ether **19** (91% overall). Attempted iodination or bromination of phenol **19** largely proved unsatisfactory under diverse reaction conditions. However, reaction with bromine in the presence of sodium acetate in acetic acid[20] gave the bromide **20** (52%), the structure of which was established by X-ray crystal structure determination. Attempted conversion of the derived bromo-triflate **21** into the corresponding benzyne and trapping with 2-methoxyfuran[9b,21] via bromine–lithium exchange using



Scheme 2. Synthesis of imide **9** and derivatization to benzyne precursor **21**.

n- or *tert*-butyllithium in THF, diethyl ether, or hexane at −78 or −100 °C gave only intractable mixtures of products. Consequently, the benzyne strategy in Scheme 1 is abandoned.

2.2. The palladium coupling and Friedel–Crafts cyclization strategies

Our attention was next directed toward an approach whereby the carbon framework of the lactonamycin tetracyclic CDEF ring system would be assembled using either a sequential Michael addition or a palladium coupling reaction and subsequent Friedel–Crafts hydroxyalkylation (Fig. 2). The naphthalene partners **27** and **28** were prepared by the methods in Scheme 3 using a benzyne–furan cycloaddition reaction to provide naphthalene **25**[22] and regioselective *ortho*-bromination.[23,24] The substitution pattern of bromide **26** was defined by NMR experiments, and confirmed by X-ray crystal structure determination. Boronic acid **28** was readily prepared from bromide **27** by sequential bromine–lithium exchange at −78 °C to furnish the corresponding insoluble lithio-derivative, condensation with $B(O^iPr)_3$, and subsequent hydrolysis.

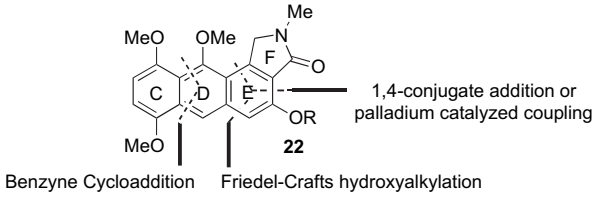
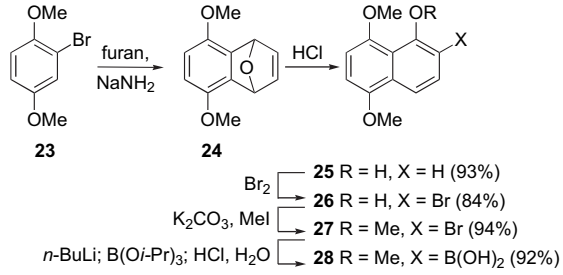
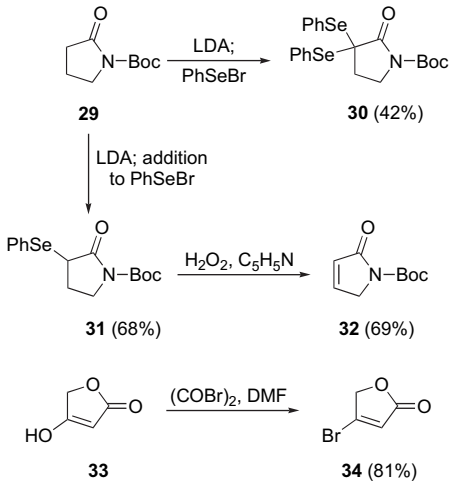


Figure 2. Summary of the conjugate addition and Friedel–Crafts reaction approach.



Scheme 3. Synthesis of naphthalene **28**.

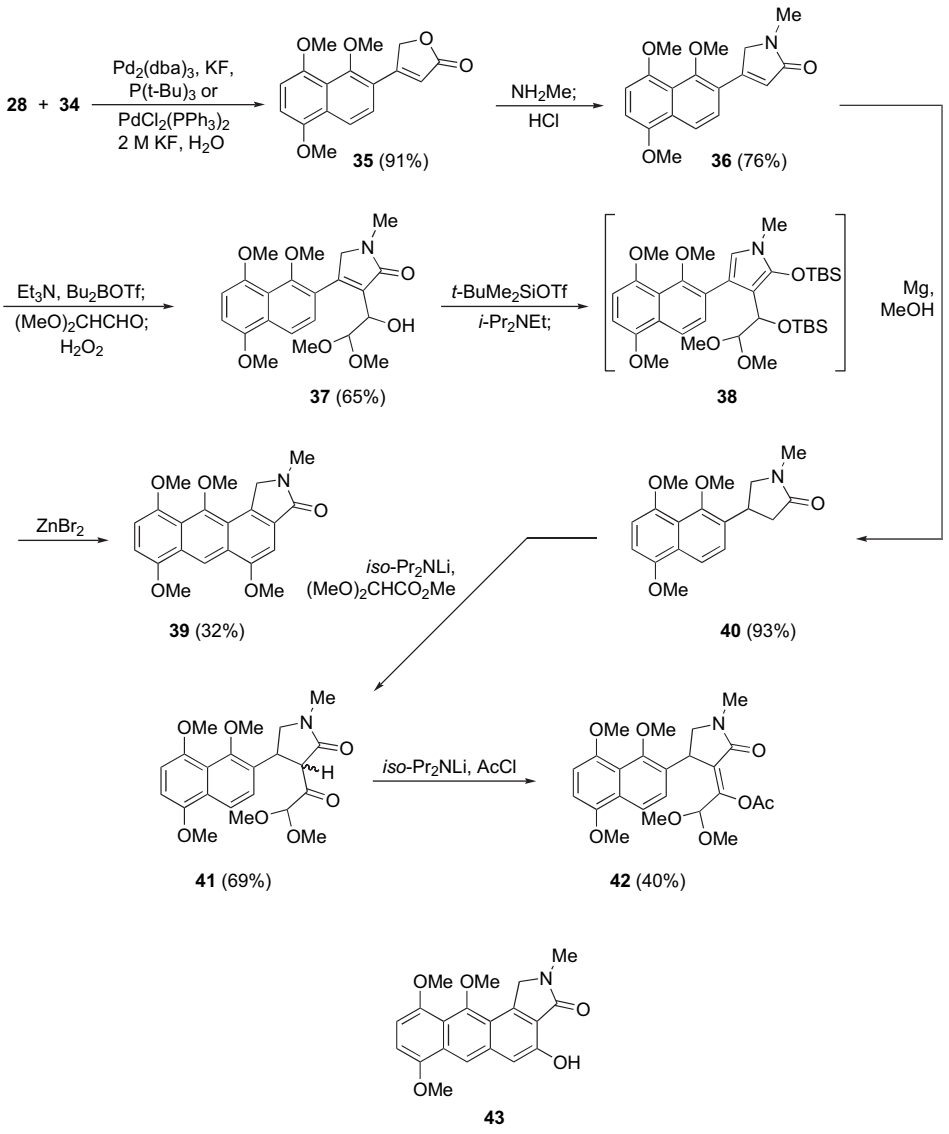
We planned to introduce the pyrrolinone unit 1) by Michael addition of organometallic reagents derived from bromide **27** to a 2-pyrrolinone derivative 2) or by palladium-catalyzed coupling of **28** with a related 4-bromo-2-pyrrolinone or a synthetic equivalent. Although such Michael addition reactions have indirect literature precedent, attempted additions to *N*-alkyl-2-pyrrolinones have been reported to be fruitless.[25] Not surprisingly, the presence of an electron-withdrawing group on the nitrogen appears to substantially increase the potency of the Michael acceptor.[25,26] Thus, carbamate **32** (Scheme 4) was selected as the Michael acceptor to be prepared by a selenoxide elimination reaction[27] and furanone **34** to explore the complimentary palladium coupling reaction. In contrast to the Zoretic and Soja results,[28] the conversion of lactam **29** into the selenide **31** was most conveniently carried out using only 1 equiv of lithium di-*iso*-propylamide and with inverse addition to suppress the formation of the diselenide **30**. Selenide oxidation with hydrogen peroxide in the presence of pyridine gave the unsaturated γ-lactam **32** in good overall yield. Bromobutenolide **34** was readily prepared from tetronic acid **33** using oxalyl bromide (81%).[29]



Scheme 4. Synthesis of the pyrrolinone and furanone coupling partners.

Unfortunately, attempted conversion of the bromide **27**, via the corresponding Grignard reagent or aryllithium, to a cuprate, and addition to the simple Michael acceptor 2-cyclohexenone or to lactam **32** proved to be unsuccessful, probably on account of proton transfer to the naphthyl carbanion.[30] In contrast, the Suzuki coupling reaction[31] of the boronic acid **28** and the bromide **34** smoothly provided the adduct **35** (Scheme 5). Reaction of the butenolide **35** with methylamine followed by reaction with hydrogen chloride in dioxane readily provided lactam **36**, which was presumably formed via reversible ring opening and an imine–enamine tautomerization.[32] In order to introduce the last carbon fragment α to the carbonyl of lactam **36**, an enol boration and aldol reaction sequence were examined. Thus, lactam **36** was converted into the aldol adduct **37** (65%) by sequential reaction with dibutylboron triflate, triethylamine, and dimethoxyacetaldehyde. Such a process, which presumably proceeds via the 2-(dibutylboryloxy)-pyrrole, has indirect precedent in aldol reactions of esters and enoates,[33] or with amides using dicyclohexylboron iodide,[34] although has not been applied to functionalize the unsaturated amides before.

Attempted cyclizations of the acetal **37** to produce the corresponding anthracene **43** or an equivalent system using diverse Brønsted and Lewis acid catalysts at −78 to 120 °C gave only intractable mixtures of products. We reasoned that these failures resulted from deactivation of the nucleophilicity of the naphthalene unit by the electron-withdrawing pyrrolinone carbonyl. The conversion of pyrrolinone **37** to a silyloxypyrrole was expected to not only alleviate this deactivation, but also incorporates an additional electron-donating substituent onto the naphthalene ring, *ortho* to the site of cyclization. Thus, the pyrrolinone **37** was converted into the pyrrole **38** by reaction with *tert*-butyldimethylsilyl triflate and Hünig's base.[35] Subsequent



Scheme 5. Synthesis and cyclization of lactam **36**.

reaction with zinc bromide gave an unstable adduct tentatively assigned as the anthracene **39**,[36] which presumably arose via the desired Friedel–Crafts methoxy alkylation and loss of water or silanol by an E_1 process via the pyrrole-stabilized carbenium ion. As an alternative possible route to the desired anthracene, pyrrolinone **36** was reduced using magnesium in methanol (93%)[37] and the resulting γ-lactam **40** was converted into the keto-lactam **41** (69%) by a crossed Claisen condensation reaction.[38] Acetal **41** was converted into the *Z*-enol acetate **42** (40%) by deprotonation with lithium di-*iso*-propylamide and O-acylation with acetyl chloride.[39] The geometry of the enol acetate **42** was confirmed as *Z* by an NOESY experiment. Frustratingly, attempted cyclization of either keto-ester **41** or the enol acetate **42** under acidic or Lewis acid condition gave complex mixtures of products.

3. Conclusion

The Suzuki coupling of boronic acid **28** with the bromobutenolide **34** and subsequent reaction with methylamine gave the naphthyl lactam **36**. Attempted conversion into the CDEF unit of the antibacterial natural product lactonamycin using an aldol reaction with dimethoxyacetaldehyde and Friedel–Crafts hydroxy alkylation gave the isomeric anthracene lactam **39** rather than the required tetracycle **43**.

4. Experimental[†]

4.1. 4,7-Dihydroxy-2-methyl-2,3-dihydro-1,3-isoindoledione (9)

(a) 3,6-Dihydroxyphthalonitrile (3.00 g, 18.7 mmol) and KOH (19.0 g, 339 mmol) in H_2O (19 mL) were heated at reflux for 3 h (Ar). After cooling to 0 °C, the mixture was acidified with 30% H_2SO_4 and extracted with EtOAc (15×75 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and rotary evaporated. The residue was

[†] General experimental conditions and additional experiments are available in Supplementary data.

dried over large quantities of P_4O_{10} under *vacuum* to yield 3,6-dihydroxyphthalic acid (3.59 g) as an off-white solid, which was used directly without further purification: ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.01 (s, 1H), 14.43 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 156.5, 124.7, 113.9; *m/z* (EI) 198 ($M^{+\bullet}$); *m/z* (HRMS) (EI) calcd for $C_8H_6O_6$ ($M^{+\bullet}$): 198.0164; found: 198.0159. The crude dihydroxyphthalic acid (3.59 g) and $MeNH_2$ (2.0 M in THF; 18.7 mL, 37.5 mmol) in THF (45 mL) were stirred at room temperature for 1.5 h, heated at reflux for 1.5 h, after which time DCC (3.87 g, 18.7 mmol) was added at room temperature. The mixture was stirred overnight, heated at reflux for 10 h, and cooled. Dicyclohexylurea was filtered off and the filtrate was dried ($MgSO_4$), filtered, and rotary evaporated. The yellow solid was recrystallized from MeOH to give imide **9** as yellow needles (905 mg, 25%).

(b) Diene **10**[10] (85.0 g, 350 mmol) and *N*-methylmaleimide **11** (43.0 g, 385 mmol) were stirred at 40 °C for 72 h (Ar), with small aliquots of CH_2Cl_2 added to enable stirring. After cooling to 0 °C, TFA (10 mL) was added dropwise and the mixture was stirred for 45 min. The resultant solid was filtered off and washed with cold EtOAc and Et_2O to yield imide **9** (61.7 g, 92%) as a yellow solid. Recrystallization from MeOH gave imide **9** as yellow needles: R_f=0.36 (EtOAc/hexanes, 1:1); mp >230 °C (MeOH); IR (KBr disc) 3440, 3334, 1741, 1680, 1643, 1450, 1383, 1302, 1002, 928 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 2.91 (s, 3H), 7.04 (s, 2H), 10.15 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 148.3, 126.1, 114.7, 23.6; *m/z* (CI, NH_3) 211 $(M+NH_4)^+$, 194 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_9H_8NO_4$ $(M+H)^+$: 194.0453; found: 194.0450. Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.10; H, 3.48; N, 7.26%.

4.2. 4,7-Dihydroxy-2-methyl-2,3-dihydro-1-isoindolone (8)

Concd HCl (4.8 mL) was added to Zn powder (33.8 g, 518 mmol) and $HgCl_2$ (2.81 g, 10.4 mmol) at 0 °C. The mixture was stirred for 5 min at room temperature before being allowed to stand for 15 min. Concd HCl (52 mL), glacial AcOH (35 mL), and phthalimide **9** (5.00 g, 25.9 mmol) were successively added to the amalgam at 0 °C. The mixture was heated at reflux overnight, cooled to room temperature, and filtered. After the addition of H_2O (60 mL), the mixture was extracted with EtOAc (6×100 mL) and the combined organic extracts were rotary evaporated. The residue was dissolved in saturated aqueous sodium EDTA (50 mL) and the mixture was extracted with EtOAc (8×80 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 5:1) to give lactam **8** (1.4 g, 30%) as a white solid: R_f=0.35 (EtOAc/hexanes, 7:3); mp 220 °C (dec) (MeOH); IR (KBr disc) 3458, 3409, 3141, 1658, 1614, 1477, 1456, 1296 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.00 (s, 3H), 4.26 (s, 2H), 6.63 (d, 1H, J=8.5 Hz), 6.79 (d, 1H, J=8.5 Hz), 8.68 (br s, 1H), 9.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.4, 147.9, 145.1, 127.9, 119.9, 118.5, 115.9, 49.9, 29.1; *m/z* (CI, NH_3) 197 $(M+NH_4)^+$, 180 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_9H_{10}NO_3$ $(M+H)^+$: 180.0661; found: 180.0651. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.19; H, 4.83; N, 7.68%.

4.3. 7-*tert*-(Butyldimethylsilyloxy)-4-hydroxy-2-methyl-2,3-dihydro-1-isoindolone (13)

(a) A suspension of hydroquinone **8** (303 mg, 1.69 mmol) in THF (12 mL) was heated at reflux for 10 min. After cooling to −78 °C, *n*-BuLi (2.5 M in hexanes; 744 μL, 1.86 mmol) was added dropwise and the solution was allowed to warm to room temperature over 1 h. *t*-BuMe_2SiCl (280 mg, 1.86 mmol) was added at −78 °C and the solution was allowed to warm to room temperature overnight. After rotary evaporation, the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (4×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated. Chromatography (EtOAc/hexanes, 3:7) gave the disilylated hydroquinone **12** (193 mg, 28%) and the desired monosilylated hydroquinone **13** (89 mg, 18%) as white solids.

(b) LiH (18 mg, 2.23 mmol) was added portionwise to a suspension of hydroquinone **8** (400 mg, 2.23 mmol) in DMF (8 mL) at −78 °C and the solution was allowed to warm to room temperature over 1 h. *t*-BuMe_2SiCl (336 mg, 2.23 mmol) was added at −78 °C and the solution was allowed to warm to room temperature overnight. After rotary evaporation, the residue was partitioned between H_2O (15 mL) and EtOAc (20 mL), the layers were separated and the aqueous phase was further extracted with EtOAc (4×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 3:7) to give the disilylated hydroquinone **12** (245 mg, 27%) and the desired mono-silylated hydroquinone **13** (98 mg, 15%) as white solids. Ether **13**: R_f=0.21 (EtOAc/hexanes, 4:1); mp >230 °C (MeOH/hexanes); IR (KBr disc) 3139, 1660, 1600, 1500, 1459, 1271 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d_6) δ 0.14 (s, 6H), 0.97 (s, 9H), 2.98 (s, 3H), 4.21 (s, 2H), 6.67 (d, 1H, J=8.5 Hz), 6.83 (d, 1H, J=8.5 Hz), 9.51 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 146.7, 145.1, 129.2, 123.3, 121.0, 119.1, 49.0, 29.3, 26.2, 18.6, −4.2; *m/z* (CI, NH_3) 294 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{15}H_{24}NO_3Si$ $(M+H)^+$: 294.1525; found: 294.1518. Anal. Calcd for $C_{15}H_{23}NO_3Si$: C, 61.40; H, 7.90; N, 4.77. Found: C, 61.40; H, 7.88; N, 4.68%. Diether **12**: R_f=0.29 (EtOAc/hexanes, 1:9); mp 106–108 °C (Et_2O/hexanes); IR (film) 1700, 1493, 1274, 1251, 1004, 836 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.21 (s, 6H), 0.99 (s, 9H), 1.03 (s, 9H), 3.11 (s, 3H), 4.16 (s, 2H), 6.67 (d, 1H, J=9.0 Hz), 6.76 (d, 1H, J=9.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 167.4, 147.4, 144.3, 132.9, 123.6, 122.1, 120.9, 49.4, 29.3, 25.9, 25.7, 18.5, 18.1, −4.2, −4.5; *m/z* (CI, NH_3) 408 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{21}H_{38}NO_3Si_2$ $(M+H)^+$: 408.2390; found: 408.2383. Anal. Calcd for $C_{21}H_{37}NO_3Si_2$: C, 61.88; H, 9.16; N, 3.44. Found: C, 62.08; H, 9.26; N, 3.51%.

4.4. 4,7-Di-(benzyloxy)-2-methyl-2,3-dihydro-1,3-isoindoledione (14)

Cs_2CO_3 (20.2 g, 62.1 mmol) was added to hydroquinone **9** (3.00 g, 15.5 mmol), $PhCH_2Br$ (9.3 mL, 77.7 mmol), and KI (258 mg, 1.55 mmol) in DMF (25 mL). The mixture was stirred at room temperature for 8 h, quenched with

iced H_2O (50 mL), and extracted with EtOAc (5×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/hexanes, 3:1 to CH_2Cl_2) to give isoindolinedione **14** (5.35 g, 92%) as a pale yellow solid. Recrystallization from MeOH yielded imide **14** as pale yellow needles: R_f=0.15 (CH_2Cl_2); mp 155 °C (MeOH); IR (film) 1689, 1500, 1453, 1265, 1058 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.09 (s, 3H), 5.20 (s, 4H), 7.03 (s, 2H), 7.24–7.46 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.5, 149.8, 136.3, 128.8, 128.1, 126.9, 122.3, 119.6, 71.4, 23.8; *m/z* (EI) 373 ($M^{+\bullet}$); *m/z* (HRMS) (EI) calcd for $C_{23}H_{19}NO_4$ ($M^{+\bullet}$): 373.1314; found: 373.1313. Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 74.01; H, 4.99; N, 3.63%.

4.5. 4,7-Di-(benzyloxy)-3-hydroxy-2-methyl-2,3-dihydro-1-isoindolone (15)

$NaBH_4$ (172 mg, 4.54 mmol) was added portionwise to imide **14** (113 mg, 0.30 mmol) in MeOH (2 mL) and $CHCl_3$ (3 mL) at 0 °C. After 1 h and rotary evaporation, the residue was partitioned between H_2O (15 mL) and CH_2Cl_2 (15 mL). The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2×10 mL) and EtOAc (10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/CH_2Cl_2, 1:9 to 1:4) to give hydroxylactam **15** (114 mg, 100%) as a white solid. Recrystallization from EtOAc gave lactam **15** as colorless prisms: R_f=0.26 (EtOAc/CH_2Cl_2, 1:4); mp 136–137 °C (EtOAc); IR (film) 3344, 1687, 1501, 1453, 1274, 1027 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.41 (d, 1H, *J*=9.0 Hz), 5.03 (s, 2H), 5.10 (s, 2H), 5.71 (d, 1H, *J*=9.0 Hz), 6.74 (d, 1H, *J*=9.0 Hz), 6.87 (d, 1H, *J*=9.0 Hz), 7.21–7.48 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 165.8, 149.8, 148.5, 136.9, 136.6, 133.3, 128.7, 128.6, 128.1, 127.8, 127.3, 127.0, 120.1, 117.6, 116.8, 81.3, 71.5, 70.9, 26.2; *m/z* (CI, NH_3) 393 $(M+NH_4)^+$, 376 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{23}H_{22}NO_4$ $(M+H)^+$: 376.1549; found: 376.1552. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.67; H, 5.70; N, 3.70%.

4.6. 4,7-Di-(benzyloxy)-2-methyl-2,3-dihydro-1-isoindolone (16)

TFA (70 mL) and Et_3SiH (17.2 mL, 108 mmol) were added with stirring sequentially to hydroxylactam **15** (27.0 g, 71.9 mmol) in CH_2Cl_2 (70 mL) at 0 °C. After stirring for 15 min, the resulting colorless solution was rotary evaporated and the residue was partitioned between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (200 mL), and the aqueous layer was further extracted with EtOAc (3×200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2 to Et_2O/CH_2Cl_2, 7:3) to give lactam **16** (20.9 g, 81%) as a white solid. Recrystallization from MeOH and Et_2O gave lactam **16** as colorless crystals: R_f=0.32 (Et_2O/CH_2Cl_2, 1:9); mp 116 °C (MeOH/Et_2O); IR (film) 1690, 1500, 1453, 1265, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 3H), 4.31 (s, 2H), 5.09 (s, 2H), 5.23 (s, 2H), 6.83 (d, 1H, *J*=9.0 Hz), 6.92 (d, 1H, *J*=9.0 Hz), 7.28–7.41 (m, 8H), 7.54 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 150.3, 147.7, 137.4, 136.7, 131.9, 128.7, 128.5, 128.2, 127.6, 127.4, 127.0, 122.7, 115.2, 114.8, 71.7, 70.5, 49.5, 29.4; *m/z* (CI, NH_3) 736 $(2M+NH_4)^+$, 719 $(2M+H)^+$, 360 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{23}H_{22}NO_3$ $(M+H)^+$: 360.1600; found: 360.1596. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.96; H, 5.97; N, 3.80%.

4.7. 4-Benzyloxy-7-hydroxy-2-methyl-2,3-dihydro-1-isoindolone (17)

$MgBr_2 \cdot OEt_2$ (10.4 g, 40.1 mmol) was added portionwise to diether **16** (13.1 g, 36.4 mmol) in PhMe (650 mL) and Et_2O (100 mL) at 75 °C (Ar). The mixture was heated to reflux overnight, cooled to 0 °C, quenched with ice-cold HCl (2 M, 250 mL), and diluted with EtOAc (400 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (3×350 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and rotary evaporated to yield a white solid, which was washed with hot hexanes and recrystallized from MeOH to give phenol **17** (7.16 g, 73%) as white needles: R_f=0.29 (Et_2O/hexanes, 1:1); mp 127–129 °C (MeOH); IR (film) 3400, 1678, 1503, 1453, 1283, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 4.32 (s, 2H), 5.09 (s, 2H), 6.80 (d, 1H, *J*=8.5 Hz), 6.97 (d, 1H, *J*=8.5 Hz), 7.35–7.41 (m, 5H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 149.5, 146.6, 136.8, 128.8, 128.6, 128.2, 127.5, 118.1, 117.5, 115.0, 71.0, 50.6, 28.9; *m/z* (CI, NH_3) 270 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{16}H_{16}NO_3$ $(M+H)^+$: 270.1130; found: 270.1130. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.46; H, 5.66; N, 5.13%. Crystal data for phenol **19**: $C_{16}H_{15}NO_3$, M=269.3, monoclinic, $P2_1$ (no. 14), a=13.727(11), b=6.873(4), c=15.329(8) Å, β=108.97(5)°, V=1367.8(15) $Å^3$, Z=4, D_c=1.308 g cm^{-3}, μ(Cu Kα)=0.74 mm^{-1}, T=293 K, colorless platy needles; 2121 independent measured reflections, F^2 refinement, R_1=0.051, wR_2=0.141, 1530 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 120°$], 175 parameters; for additional crystal data and structure refinement, see Supplementary data.

4.8. 4-Benzyloxy-7-methoxy-2-methyl-2,3-dihydro-1-isoindolone (18)

Phenol **17** (11.3 g, 42.0 mmol), MeI (3.9 mL, 62.9 mmol), and K_2CO_3 (8.70 g, 62.9 mmol) in Me_2CO (210 mL) were heated at reflux for 8 h. The mixture was rotary evaporated and the residue was partitioned between H_2O (250 mL) and CH_2Cl_2 (250 mL). The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (3×250 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 4:1) to give methyl ether **18** (10.8 g, 91%) as a white solid: R_f=0.24 (EtOAc/hexanes, 4:1); mp 142–145 °C (CH_2Cl_2); IR (film) 1688, 1502, 1263, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.93 (s, 3H), 4.29 (s, 2H), 5.11 (s, 2H), 6.82 (d, 1H, *J*=9.0 Hz), 6.99 (d, 1H, *J*=9.0 Hz), 7.33–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 151.4, 147.2, 136.8, 132.0, 128.6, 128.1, 127.3, 121.5, 115.3, 111.2, 70.6, 56.3, 49.4, 29.4; *m/z* (CI, NH_3) 284 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{17}H_{18}NO_3$ $(M+H)^+$: 284.1287; found: 284.1288.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.97; H, 5.91; N, 4.82%.

4.9. 4-Hydroxy-7-methoxy-2-methyl-2,3-dihydro-1-isoindolone (19)

Benzyl ether **18** (9.70 g, 34.2 mmol) and 10% Pd/C (0.97 g, 10% w/w) in MeOH (50 mL) and EtOAc (50 mL) were stirred overnight under H_2 (atmospheric pressure), filtered through a pad of Celite®, and rotary evaporated. The residue was chromatographed (CH_2Cl_2 to MeOH/CH_2Cl_2, 1:19) to give phenol **19** (6.59 g, 100%) as a white solid. Recrystallization from MeOH yielded phenol **19** as white crystals: R_f=0.14 (EtOAc); mp >230 °C (MeOH); IR (KBr disc) 3172, 1662, 1612, 1502, 1427, 1267, 1061 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.98 (s, 3H), 3.75 (s, 3H), 4.23 (s, 2H), 6.83 (d, 1H, J=8.5 Hz), 6.89 (d, 1H, J=8.5 Hz), 9.47 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 150.1, 146.2, 130.0, 121.1, 118.9, 113.0, 56.6, 49.1, 29.3; *m/z* (CI, NH_3) 194 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{10}H_{12}NO_3$ $(M+H)^+$: 194.0817; found: 194.0817. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.28; H, 5.64; N, 7.14%.

4.10. 5-Bromo-4-hydroxy-7-methoxy-2-methyl-2,3-dihydro-1-isoindolone (20)

Br_2 (117 μL, 2.28 mmol) in glacial AcOH (0.5 mL) was added dropwise to phenol **19** (400 mg, 2.07 mmol) and NaOAc·$3H_2O$ (620 mg, 4.55 mmol) in glacial AcOH (2.4 mL). After stirring at room temperature for 30 min, saturated aqueous $Na_2S_2O_5$ (15 mL) was added and the mixture was extracted successively with CH_2Cl_2 (15 mL) and EtOAc (4×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (MeOH/CH_2Cl_2, 3:97) to give bromide **20** (295 mg, 52%) as a white solid. Recrystallization from MeOH yielded bromide **20** as white needles: R_f=0.18 (EtOAc); mp >230 °C (MeOH); IR (KBr disc) 3467, 1662, 1591, 1500, 1456, 1404, 1365, 1298, 1219, 1101, 1068 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.98 (s, 3H), 3.78 (s, 3H), 4.30 (s, 2H), 7.15 (s, 1H), 9.63 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 150.4, 142.9, 131.9, 120.7, 116.3, 114.6, 56.8, 49.7, 29.3; *m/z* (CI, NH_3) 274, 272 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{10}H_{11}{}^{81}BrNO_3$ $(M+H)^+$: 273.9902; found: 273.9903; calcd for $C_{10}H_{11}{}^{79}BrNO_3$ $(M+H)^+$: 271.9922; found: 271.9921. Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; N, 5.15. Found: C, 44.26; H, 3.78; N, 5.06%. Crystal data for bromide **27**: $C_{10}H_{10}BrNO_3$, M=272.1, monoclinic, $P2_1$ (no. 15), a=12.273(16), b=10.084(17), c=17.528(4) Å, β=102.95(13)°, V=2114.1(7) $Å^3$, Z=8, D_c=1.710 g cm^{-3}, μ(Cu Kα)=5.22 mm^{-1}, T=293 K, colorless platy needles; 1514 independent measured reflections, F^2 refinement, R_1=0.064, wR_2=0.167, 1034 independent observed absorption corrected reflections $[|F_o| > 4\sigma(|F_o|),\ 2\theta \leq 120°]$, 147 parameters; for additional crystal data and structure refinement, see Supplementary data.

4.11. 5-Bromo-7-methoxy-2-methyl-1-oxo-2,3-dihydro-1*H*-4-isoindolyl trifluoromethanesulfonate (21)

$(CF_3SO_2)_2O$ (96 μL, 0.57 mmol) was added dropwise to phenol **20** (103 mg, 0.38 mmol) and freshly distilled Et_3N (105 μL, 0.76 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The mixture was allowed to warm to room temperature overnight and rotary evaporated. The residue was partitioned between saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (8 mL), the layers were separated and the aqueous phase was further extracted with EtOAc (2×8 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 4:1) to give triflate **21** (84 mg, 55%) as a white solid: R_f=0.41 (EtOAc); mp 156–159 °C (MeOH); IR (film) 1700, 1476, 1424, 1214, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.99 (s, 3H), 4.45 (s, 2H), 7.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 156.4, 137.4, 134.2, 121.8, 120.6, 118.5 (q, J_{C-F}=321 Hz), 116.8, 56.8, 49.4, 29.4; *m/z* (CI, NH_3) 406, 404 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{11}H_{10}{}^{81}BrF_3NO_5S$ $(M+H)^+$: 405.9395; found: 405.9392; calcd for $C_{11}H_{10}{}^{79}BrF_3NO_5S$ $(M+H)^+$: 403.9415; found: 403.9419.

4.12. 2-Bromo-5,8-dimethoxy-1-naphthol (26)[24]

(a) A freshly prepared solution of Br_2 in CH_2Cl_2 (1.0 M, 18.4 mL, 18.4 mmol) was added dropwise to naphthol **25**[22,41] (3.60 g, 17.5 mmol) in CH_2Cl_2 (170 mL) at −78 °C. After stirring for 30 min, the mixture was allowed to warm to room temperature, stirred for a further 30 min, and poured into ice-cold saturated aqueous $NaHCO_3$ (250 mL). The phases were separated, the aqueous portion was further extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:9 to 3:7) to give bromonaphthol **26** (4.21 g, 84%) as a white solid.

(b) NBS (6.72 g, 37.7 mmol) in MeCN (75 mL) was added dropwise to naphthol **25**[22,40] (7.00 g, 34.3 mmol) in MeCN (100 mL) at −20 °C. After stirring at −20 °C for 1 h, the mixture was rotary evaporated and the residual solid was dissolved in CH_2Cl_2. The solution was washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:9 to 3:7) to give bromonaphthol **26** (6.33 g, 65%) as a white solid. Recrystallization from Et_2O and hexanes yielded bromide **26** as transparent plates: R_f=0.28 (EtOAc/hexanes, 1:4); mp 135 °C (Et_2O/hexanes); IR (film) 3332, 1610, 1390, 1253, 1126, 1088, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.02 (s, 3H), 6.66 (d, 1H, J=8.5 Hz), 6.72 (d, 1H, J=8.5 Hz), 7.55 (d, 1H, J=9.0 Hz), 7.60 (d, 1H, J=9.0 Hz), 10.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 150.3, 149.1, 130.8, 127.2, 116.1, 114.2, 105.5, 104.7, 103.4, 56.6, 55.7; *m/z* (CI, NH_3) 302, 300 $(M+NH_4)^+$, 285, 283 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{12}H_{12}{}^{81}BrO_3$ $(M+H)^+$: 284.9949; found: 284.9939; calcd for $C_{12}H_{12}{}^{79}BrO_3$ $(M+H)^+$: 282.9970; found: 282.9963. Anal. Calcd for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92. Found: C, 51.19; H, 4.03%. Crystal data for bromide **26**: $C_{12}H_{11}BrO_3$, M=283.1, orthorhombic, $P2_12_12_1$ (no. 61), a=6.032(13), b=15.959(4), c=23.569(3) Å, V=2268.8(8) $Å^3$, Z=8, D_c=1.658 g cm^{-3}, μ(Cu Kα)=4.86 mm^{-1}, T=293 K, colorless plates; 1673 independent measured reflections, F^2 refinement, R_1=0.075, wR_2=0.200, 1214 independent observed absorption corrected reflections $[|F_o| > 4\sigma(|F_o|),\ 2\theta \leq 126°]$, 150 parameters; for additional crystal data and structure refinement, see Supplementary data.

4.13. 2-Bromo-1,5,8-trimethoxynaphthalene (27)

Naphthol **26** (5.50 g, 19.4 mmol), Cs_2CO_3 (12.7 g, 38.9 mmol), and MeI (3.6 mL, 58.3 mmol) in Me_2CO (25 mL) were heated at reflux overnight. The mixture was rotary evaporated, the residual solid was partitioned between EtOAc (100 mL) and H_2O (100 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (2×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/hexanes, 3:7) to give trimethoxynaphthalene **27** (5.43 g, 94%) as a white solid: R_f=0.44 (EtOAc/hexanes, 1:4); mp 67–69 °C (CH_2Cl_2/hexanes); IR (film) 1617, 1578, 1456, 1406, 1343, 1259, 1094, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.96 (s, 6H), 6.75 (d, 1H, J=8.5 Hz), 6.84 (d, 1H, J=8.5 Hz), 7.62 (d, 1H, J=9.0 Hz), 7.93 (d, 1H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 149.8, 149.3, 130.0, 128.0, 122.3, 119.6, 116.3, 107.6, 104.3, 61.8, 57.2, 55.8; m/z (CI, NH_3) 316, 314 $(M+NH_4)^+$, 299, 297 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{13}H_{17}{}^{81}BrNO_3$ $(M+NH_4)^+$: 316.0371; found: 316.0372; calcd for $C_{13}H_{17}{}^{79}BrNO_3$ $(M+NH_4)^+$: 314.0392; found: 314.0397. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.62; H, 4.35%.

4.14. 1,5,8-Trimethoxy-2-naphthaleneboronic acid (28)

n-BuLi (2.5 M in hexanes; 1.75 mL, 4.38 mmol) was added dropwise to bromonaphthalene **27** (1.00 g, 3.37 mmol) in THF (25 mL) at −78 °C. After 5 min, triisopropyl borate (1.01 mL, 4.38 mmol) was added dropwise with stirring. After 30 min at −78 °C, the solution was allowed to warm to room temperature and after 1 h, 10% aqueous HCl (20 mL) was added and the mixture was vigorously stirred for 45 min. The layers were separated and the aqueous phase was further extracted with EtOAc (4×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes, 1:4 to 2:3) to give boronic acid **28** (811 mg, 92%) as a white solid: R_f=0.41 (EtOAc/hexanes, 1:1); mp 128–132 °C (EtOAc/hexanes); IR (film) 3430, 1620, 1575, 1503, 1462, 1380, 1358, 1259, 1100, 1060, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 6.68 (br s, 2H), 6.82 (s, 2H), 7.91 (d, 1H, J=8.5 Hz), 8.10 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 149.8, 149.6, 131.5, 131.1, 119.7, 118.4, 106.0, 105.3, 64.0, 56.6, 55.9; m/z (CI, NH_3) 280 $(M+NH_4)^+$, 263 $(M+H)^+$. Anal. Calcd for $C_{13}H_{15}BO_5$: C, 59.58; H, 5.77. Found: C, 59.60; H, 5.79%. It was found to be essential to add the triisopropyl borate only 5 min after the addition of *n*-BuLi. Failure to do so gave the reduced 1,4,8-trimethoxynaphthalene[30a,41] as by-product, the amount of which increased on extending the metalation period.

4.15. *tert*-Butyl 2-oxo-3-phenylselenenyl-1-pyrrolidinecarboxylate (31)

n-BuLi (2.5 M in hexanes; 648 μL, 1.62 mmol) was added dropwise to freshly distilled *i*-Pr_2NH (250 μL, 1.78 mmol) in THF (5 mL) at 0 °C (Ar). After stirring for 45 min at 0 °C, the solution was cooled to −78 °C and transferred dropwise to pyrrolidinone **29**[42] (300 mg, 1.62 mmol) in THF (5 mL) at −78 °C (Ar). The resulting solution was stirred at −78 °C for 1.5 h before being transferred dropwise to PhSeBr (402 mg, 1.70 mmol) in THF (4 mL) at −78 °C (Ar). After stirring at −78 °C for 15 min, saturated aqueous NH_4Cl (10 mL) was added, the layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:9) to give the selenide **31** (375 mg, 68%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.98–2.08 (m, 1H), 2.37–2.50 (m, 1H), 3.32–3.41 (m, 1H), 3.55–3.62 (m, 1H), 3.89–3.93 (m, 1H), 7.24–7.33 (m, 3H), 7.64 (d, 2H, J=7.0 Hz); m/z (CI, NH_3) 700 $(2M[^{80}Se^{78}Se]+NH_4)^+$, 359, 357 $(M+NH_4)^+$, 342, 340 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{15}H_{23}N_2O_3{}^{80}Se$ $(M+NH_4)^+$: 359.0874; found: 359.0877; calcd for $C_{15}H_{23}N_2O_3{}^{78}Se$ $(M+NH_4)^+$: 357.0882; found: 357.0890. Direct addition of PhSeBr to the lactam enolate gave an adduct that was tentatively assigned as the corresponding diselenide **30**. *n*-BuLi (2.5 M in hexanes; 7.3 mL, 18.3 mmol) was added dropwise with stirring to freshly distilled *i*-Pr_2NH (2.6 mL, 18.3 mmol) in THF (40 mL) at 0 °C (Ar). After 30 min, the solution was cooled to −78 °C and transferred dropwise with stirring via cannula to pyrrolidinone **29** (3.22 g, 17.4 mmol) in THF (40 mL) at −78 °C (Ar). After 1.5 h, PhSeBr (4.31 g, 18.3 mmol) in THF (40 mL) was added dropwise with stirring via cannula at −78 °C. After 3 h, saturated aqueous NH_4Cl (120 mL) was added, the layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (hexanes) to give an adduct that was tentatively assigned as the pyrrolidinone **30** (3.6 g, 42%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.24 (t, 2H, J=7.0 Hz), 3.29 (t, 2H, J=7.0 Hz), 7.31–7.43 (m, 6H), 7.73 (d, 4H, J=7.5 Hz).

4.16. *tert*-Butyl 2-oxo-2,5-dihydro-1*H*-1-pyrrolecarboxylate (32)

Pyridine (108 μL, 1.33 mmol) and aqueous H_2O_2 (35% w/w, 329 μL, 3.99 mmol) were successively added to selenide **31** (227 mg, 0.67 mmol) in CH_2Cl_2 (7.4 mL) at −78 °C and the mixture was allowed to warm to room temperature over 2 h. Saturated aqueous NH_4Cl (5 mL) was added, the layers were separated, and the organic phase was washed with aqueous HCl (1 M, 5 mL) and brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:3) to give lactam **32** (84 mg, 69%) as a white solid: R_f=0.29 (EtOAc/hexanes, 1:1); IR (film) 1774, 1739, 1718, 1359, 1321, 1296, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 4.37 (d, 2H, J=2.0 Hz), 6.17–6.20 (m, 1H), 7.19–7.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 149.6, 145.1, 128.0, 83.0, 51.6, 28.1; m/z (CI, NH_3) 201 $(M+NH_4)^+$, 184 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_9H_{14}NO_3$ $(M+H)^+$: 184.0974; found: 184.0974.

4.17. 4-Bromo-5*H*-2-furanone (34)[29]

Oxalyl bromide (10.0 mL, 108 mmol) was added dropwise over 1 h to a suspension of tetronic acid (**33**) (9.00 g, 89.9 mmol) in CH_2Cl_2 (200 mL) and DMF (9 mL), while carefully maintaining the reaction temperature at 0 °C. The yellow solution turned green and was stirred successively at 0 °C for 1 h and at room temperature for 2 h. H_2O

(250 mL) was added, the layers were separated, and the aqueous phase was further extracted with Et_2O (4×100 mL). The combined organic extracts were washed successively with H_2O, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and rotary evaporated. Recrystallization of the residual solid from Et_2O gave bromofuranone **34** (11.9 g, 81%) as white needles: R_f=0.41 (EtOAc/hexanes, 7:3); mp 76–77 °C (Et_2O); IR (film) 1776, 1748, 1600, 1264, 1154, 1014, 867 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, 2H, J=1.5 Hz), 6.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 146.3, 121.7, 74.9; m/z (CI, NH_3) 182, 180 $(M+NH_4)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_4H_7{}^{81}BrNO_2$ $(M+NH_4)^+$: 181.9640; found: 181.9635; calcd for $C_4H_7{}^{79}BrNO_2$ $(M+NH_4)^+$: 179.9660; found: 179.9665.

4.18. 4-(1,5,8-Trimethoxy-2-naphthyl)-5*H*-2-furanone (35)

(a) P(*t*-Bu)$_3$ (3.6 mg, 0.018 mmol) was added to boronic acid **28** (135 mg, 0.52 mmol), bromofuranone **34** (80 mg, 0.49 mmol), $Pd_2(dba)_3$ (6.7 mg, 0.0074 mmol), and KF (86 mg, 1.47 mmol) in Ar sparged THF (2 mL) (Ar). The mixture was heated at 60 °C for 6 h, after which time a further amount of bromolactone **34** (80 mg, 0.49 mmol) was added (80 mg, 0.49 mmol). The mixture was heated at 60 °C for an additional 12 h, cooled to room temperature, diluted with EtOAc (5 mL), and filtered through a pad of Celite®. The filtered residue was washed repeatedly with EtOAc and the filtrate was rotary evaporated and chromatographed (Et_2O/hexanes, 1:1) to give furanone **35** (99 mg, 64%) as a yellow solid. Recrystallized from EtOAc and hexanes yielded furanone **35** as bright yellow needles.

(b) Boronic acid **28** (1.45 g, 5.53 mmol), bromofuranone **34** (1.17 g, 7.19 mmol), and $PdCl_2(PPh_3)_2$ (78 mg, 0.11 mmol) in aqueous KF (2 M, 15 mL) and THF (15 mL) were heated at reflux for 5 h. After cooling to room temperature, the layers were separated and the aqueous phase was further extracted with EtOAc (4×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (Et_2O/hexanes, 1:1) to give furanone **35** (1.52 g, 91%) as a yellow solid. Recrystallization from EtOAc and hexanes yielded furanone **35** as bright yellow needles: R_f=0.18 (Et_2O/hexanes, 1:1); mp 139–141 °C (EtOAc/hexanes); IR (film) 1746, 1603, 1572, 1455, 1417, 1369, 1347, 1260, 1159, 1077, 1050, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 5.42 (d, 2H, J=1.5 Hz), 6.60 (s, 1H), 6.87 (s, 2H), 7.46 (d, 1H, J=9.0 Hz), 8.07 (d, 1H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 162.1, 156.6, 150.2, 149.5, 130.0, 124.4, 120.7, 120.6, 119.3, 115.6, 107.0, 106.4, 73.4, 62.9, 56.6, 56.0; m/z (CI, NH_3) 318 $(M+NH_4)^+$, 301 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{17}H_{20}NO_5$ $(M+NH_4)^+$: 318.1341; found: 318.1352. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.98; H, 5.22%.

4.19. 1-Methyl-4-(1,5,8-trimethoxy-2-naphthyl)-1,5-dihydro-2-pyrrolone (36)

Furanone **35** (3.1 g, 10.3 mmol) and $MeNH_2$ (2.0 M in MeOH; 31 mL, 61.9 mmol) were heated at 65 °C for 3 h, and the mixture was rotary evaporated and the residue was dissolved in anhydrous dioxane (100 mL). HCl (4.0 M in dioxane; 7.7 mL, 31.0 mmol) was added and the mixture was heated at reflux for 6 h. After cooling to room temperature, the mixture was diluted with EtOAc (100 mL), carefully washed with saturated aqueous $NaHCO_3$ (2×150 mL) and brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc to MeOH/EtOAc, 1:19) to give pyrrolinone **36** (2.47 g, 76%) as a yellow solid. Recrystallization from EtOAc yielded pyrrolinone **36** as yellow crystals: R_f=0.16 (EtOAc); mp 165–167 °C (EtOAc); IR (film) 1678, 1452, 1414, 1367, 1350, 1260, 1111, 1074, 1035, 820, 800, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 3.79 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.54 (s, 2H), 6.71 (s, 1H), 6.79 (d, 1H, J=8.5 Hz), 6.83 (d, 1H, J=8.5 Hz), 7.46 (d, 1H, J=9.0 Hz), 8.04 (d, 1H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.4, 151.8, 150.2, 149.6, 129.3, 124.9, 124.2, 122.9, 120.9, 118.9, 106.7, 105.4, 62.3, 56.6 (2C), 55.9, 29.0; m/z (CI, NH_3) 627 $(2M+H)^+$, 331 $(M+NH_4)^+$, 314 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{18}H_{20}NO_4$ $(M+H)^+$: 314.1392; found: 314.1396. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.06; H, 6.13; N, 4.45%.

4.20. 3-(1-Hydroxy-2,2-dimethoxyethyl)-1-methyl-4-(1,5,8-trimethoxy-2-naphthyl)-1,5-dihydro-2-pyrrolone (37)

$Bu_2BOSO_2CF_3$ (1.0 M in CH_2Cl_2; 1.76 mL, 1.76 mmol) was added dropwise to pyrrolinone **36** (500 mg, 1.60 mmol) in anhydrous CH_2Cl_2 (8.5 mL) at −78 °C. The mixture was stirred for 5 min and freshly distilled Et_3N (267 μL, 1.91 mmol) was added dropwise. After stirring for 1.5 h at −78 °C, the solution was treated with freshly distilled anhydrous dimethoxyacetaldehyde[43,44] (664 mg, 6.38 mmol) in one portion. The mixture was stirred for 2 h at −78 °C, diluted with EtOAc (25 mL), and washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was further extracted with EtOAc (4×20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2 then EtOAc) to give acetal **37** as an oil. Et_2O was added to the oil and evaporated in vacuo at 40 °C. The procedure was repeated three times to give acetal **37** (434 mg, 65%) as an off-white foam: R_f=0.11 (EtOAc); mp 105–108 °C (EtOAc); IR (film) 3404, 2935, 1671, 1452, 1414, 1261, 1072, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.34 (s, 3H), 3.42 (s, 3H), 3.77 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 4.34 (d, 1H, J=20.0 Hz), 4.47–4.54 (m, 2H), 4.91 (d, 1H, J=7.0 Hz), 6.79 (d, 1H, J=8.5 Hz), 6.83 (d, 1H, J=8.5 Hz), 7.53 (d, 1H, J=8.5 Hz), 8.09 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 154.2, 150.4, 150.0, 149.6, 132.0, 129.2, 127.6, 124.3, 120.9, 118.7, 106.2, 105.1, 104.8, 67.9, 62.6, 56.6, 55.9, 55.7 (2C), 54.1, 28.9; m/z (CI, NH_3) 418 $(M+H)^+$; m/z (HRMS) (CI, NH_3) calcd for $C_{22}H_{28}NO_7$ $(M+H)^+$: 418.1866; found: 418.1847. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.12; H, 6.32; N, 3.23%.

4.21. 5,7,10,11-Tetramethoxy-2-methyl-1,2-dihydronaphtho[2,3-*e*]isoindol-3-one (39)

i-Pr_2NEt (55 μL, 0.32 mmol) and TMSOTf (82 μL, 0.36 mmol) were successively added dropwise to acetal **37** (60 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (6 mL) at −78 °C (Ar). The mixture was allowed to warm to room temperature over 1 h, after which *i*-Pr_2NEt (28 μL,

0.22 mmol) and *t*-$BuMe_2OSO_2CF_3$ (49 μL, 0.22 mmol) were successively added dropwise at 0 °C. After stirring for further 2 h at room temperature, anhydrous $ZnBr_2$ (32 mg, 0.14 mmol) was added in one portion. The mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (6 mL) and H_2O (8 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (3×8 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and rotary evaporated. Preparative thin layer chromatography (EtOAc) gave an unstable yellow solid, tentatively assigned as the tetramethoxyanthracene **39** (17 mg, 32%), which decomposed within 36 h: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.99 (s, 3H), 4.07 (s, 6H), 4.15 (s, 3H), 4.95 (s, 2H), 6.72 (d, 1H, *J*=8.0 Hz), 6.79 (d, 1H, *J*=8.0 Hz), 7.28 (s, 1H), 9.13 (s, 1H); *m/z* (ES^+) 368 $(M+H)^+$; *m/z* (ES^-) 366 (M−H).

4.22. 1-Methyl-4-(1,5,8-trimethoxy-2-naphthyl)-2-pyrrolidinone (40)

Mg turnings (419 mg, 17.2 mmol) were added to pyrrolinone **36** (270 mg, 0.86 mmol) in MeOH (24 mL) at 0 °C. After stirring for 30 min at 0 °C, a vigorous exothermic reaction occurred. The mixture was successively stirred at room temperature for 20 min and diluted with CH_2Cl_2 (25 mL) and saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2/EtOAc gradient) to give pyrrolidinone **40** (253 mg, 93%) as a yellow oil, which crystallized upon standing: R_f=0.17 (EtOAc); mp 87–89 °C (EtOAc); IR (film) 1691, 1601, 1581, 1504, 1452, 1414, 1349, 1261, 1105, 1065, 1003, 802, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (dd, 1H, *J*=8.0, 17.0 Hz), 2.85 (dd, 1H, *J*=9.5, 17.0 Hz), 2.92 (s, 3H), 3.42 (dd, 1H, *J*=7.0, 10.0 Hz), 3.79 (dd, 1H, *J*=8.5, 10.0 Hz), 3.80 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.24–4.33 (m, 1H), 6.72 (d, 1H, *J*=8.5 Hz), 6.80 (d, 1H, *J*=8.5 Hz), 7.36 (d, 1H, *J*=9.0 Hz), 8.05 (d, 1H, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 153.4, 149.6, 149.5, 132.7, 127.8, 123.9, 120.6, 119.1, 106.3, 103.8, 63.0, 56.7, 56.6, 55.8, 38.7, 29.6, 29.4; *m/z* (CI, NH_3) 631 $(2M+H)^+$, 333 $(M+NH_4)^+$, 316 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{18}H_{22}NO_4$ $(M+H)^+$: 316.1549; found: 316.1550. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.73; H, 6.84; N, 4.52%.

4.23. 3-(2,2-Dimethoxyacetyl)-1-methyl-4-(1,5,8-trimethoxy-2-naphthyl)-2-pyrrolidinone (41)

n-BuLi (2.5 M in hexanes; 232 μL, 0.58 mmol) was added dropwise to freshly distilled *i*-Pr_2NH (76 μL, 0.58 mmol) in anhydrous THF (2 mL) at 0 °C. After stirring for 45 min at 0 °C and cooling to −78 °C, pyrrolidinone **40** (166 mg, 0.53 mmol) in anhydrous THF (3 mL) was added dropwise and the solution was stirred for further 1.5 h. The mixture was added dropwise to methyl dimethoxyacetate (258 μL, 2.11 mmol) in anhydrous THF (1.5 mL) at −78 °C. Stirring was continued for 5 min at −78 °C and 5 min at room temperature, after which saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL) were successively added. The layers were separated and the aqueous phase was further extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (CH_2Cl_2 then EtOAc/hexanes, 1:1 to 7:3) to give ketoacetal **41** (151 mg, 69%) as an orange solid containing both diastereoisomers (1:9): R_f=0.30 (EtOAc/hexanes, 4:1); mp 125–127 °C (EtOAc/hexanes); IR (film) 2935, 1737, 1691, 1601, 1581, 1450, 1413, 1350, 1259, 1105, 1066, 1001, 800, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) selected peaks for major isomer δ 2.88 (s, 3H), 3.26–3.30 (m, 1H), 3.27 (s, 3H), 3.34 (s, 3H), 3.79–3.84 (m, 1H), 3.81 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.45 (d, 1H, *J*=8.5 Hz), 4.69–4.75 (m, 1H), 5.11 (s, 1H), 6.70 (d, 1H, *J*=8.5 Hz), 6.77 (d, 1H, *J*=8.5 Hz), 7.30 (d, 1H, *J*=9.0 Hz), 8.03 (d, 1H, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) selected peaks for major isomer δ 200.7, 169.0, 153.8, 149.4, 149.3, 130.5, 127.9, 123.9, 120.5, 119.0, 106.2, 103.9, 102.3, 63.0, 57.1, 56.4, 55.6, 55.0, 54.25, 54.20, 32.3, 29.7; *m/z* (CI, NH_3) 418 $(M+H)^+$; *m/z* (HRMS) (CI, NH_3) calcd for $C_{22}H_{28}NO_7$ $(M+H)^+$: 418.1866; found: 418.1855. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.38; H, 6.67; N, 3.35%.

4.24. (3-(*Z*)-1-Acetoxy-2,2-dimethoxyethylidene)-1-methyl-4-(1,5,8-trimethoxy-2-naphthyl)-2-pyrrolidinone (42)

LDA (1.8 M in heptane, THF, and PhEt; 114 μL, 0.21 mmol) was added dropwise to ketone **41** (78 mg, 0.19 mmol) in anhydrous THF (2 mL) at −78 °C. After stirring at this temperature for 1.5 h, freshly distilled AcCl (53 μL, 0.75 mmol) was added dropwise and the mixture was allowed to warm to room temperature overnight. EtOAc (8 mL) and H_2O (8 mL) were added, the layers were separated, and the aqueous phase was further extracted with EtOAc (3×8 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (EtOAc) to give enol acetate **42** (34 mg, 40%) as a light amber oil: R_f=0.18 (EtOAc/hexanes, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.89 (s, 3H), 2.94 (s, 3H), 3.20–3.23 (m, 1H), 3.21 (s, 3H), 3.90 (s, 3H), 3.94–3.99 (m, 1H), 3.95 (s, 3H), 3.99 (s, 3H), 4.62 (d, 1H, *J*=0.5 Hz), 4.98 (dd, 1H, *J*=2.5, 8.5 Hz), 6.70 (d, 1H, *J*=8.5 Hz), 6.77 (d, 1H, *J*=8.5 Hz), 7.30 (d, 1H, *J*=9.0 Hz), 8.03 (d, 1H, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 165.7, 152.7, 149.7, 149.3, 146.5, 134.2, 128.1, 125.3, 125.1, 120.6, 119.1, 106.1, 103.6, 100.2, 62.6, 56.6, 55.79, 55.76, 54.6, 54.2, 33.2, 29.9, 20.9; *m/z* (EI) 459 ($M^{+\bullet}$); *m/z* (HRMS) (EI) calcd for $C_{24}H_{29}NO_8$ ($M^{+\bullet}$): 459.1893; found: 459.1888.

Acknowledgements

We thank GlaxoSmithKline for the generous endowment (to A.G.M.B.), the Royal Society and the Wolfson Foundation for a Royal Society Wolfson Research Merit Award (to A.G.M.B.), the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Sciences at Imperial College, the Engineering and Physical Sciences Research Council and AstraZeneca for generous support of our studies. We additionally thank Peter R. Haycock and Richard N. Sheppard for high-resolution NMR spectroscopy.

Supplementary data

Additional experimental procedures and structural data for all new compounds and crystallographic data (including ORTEPs and CIFs) for compounds **17**, **20**, and **26** (CCDC 613463, 613464 and 613465, respectively). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.004.

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Diaryl-2-pyrrolidinemethanols catalyzed enantioselective epoxidation of α,β-enones: new insight into the effect of structural modification of the catalyst on reaction efficiency

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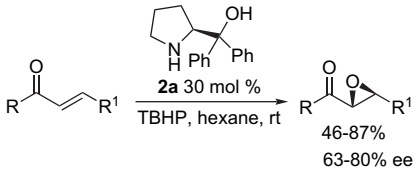
Received 28 July 2006; revised 18 September 2006; accepted 5 October 2006
Available online 27 October 2006

Abstract—Catalytic enantioselective epoxidation of α,β-unsaturated ketones promoted by diaryl-2-pyrrolidinemethanols and *tert*-butyl hydroperoxide (TBHP) is described. Investigation on structural modifications of the diaryl-2-pyrrolidinemethanols showed that fine tuning of the stereoelectronics of the substituents on the aryl moiety is important to achieve high efficiency. By employing a structurally optimized organocatalyst, significantly reduced loading (10 mol %) can be used to produce the epoxides in high yield and up to 90% ee at room temperature.

1. Introduction

Enantiomerically enriched α,β-epoxy ketones are versatile intermediates in organic synthesis and important synthetic pharmaceuticals.[1] Efficient asymmetric epoxidation reactions of α,β-unsaturated ketones, mainly chalcones, have been reported using chiral metal alkyl hydroperoxide systems.[2] Moreover, polyaminoacids[3] and cinchona alkaloids[4] have been used in the presence of hydrogen peroxide as an oxygen source under basic conditions. The development of simple, catalytic and environmentally benign methodologies to access optically pure compounds is a fundamental goal of current organic synthesis. Asymmetric organocatalysis[5] satisfies most of these requirements; low cost and easily accessible chiral organic molecules are able to catalyze an ever-increasing number of reactions under operational simplicity and mild conditions. In order to achieve good yields of products and satisfactory level of enantioselectivity, in most of the reactions, e.g., those promoted by proline-based compounds, 20–30 mol % of catalyst loading is generally employed. Thus, one of the most challenging goals in organocatalysis is to reduce catalyst loading to the level used in metal-catalyzed asymmetric synthesis (≤10 mol %).

Chiral diaryl-2-pyrrolidinemethanol ethers have been successfully employed as organocatalysts in different transformations such as C–C bond forming reactions,[6] functionalizations of carbonyl compounds[7] and epoxidation of α,β-unsaturated aldehydes.[8] On the other hand, the OH-free prolinols have met with poor success as promoters because of the formation of unreactive cyclic *N*,*O*-acetals with carbonyl compounds.[9] Very recently, the asymmetric vinylogous Michael addition reaction has been promoted by diaryl-2-pyrrolidinemethanols through the formation of iminium intermediates.[10] We have recently discovered that commercially available (*S*)-diphenyl-2-pyrrolidinemethanol **2a** and TBHP oxidize unsaturated α,β-ketones into the corresponding epoxides in good yield and enantioselectivity (up to 80% ee), using 30 mol % catalyst loading at room temperature (Scheme 1).[11]



Scheme 1.

In exploring the effects of structural modification on catalyst activity, investigation on stereoelectronic substitution on the phenyl moiety gave improved understanding of mechanism and more importantly a remarkable enhancement of the reaction efficiency.[12] Indeed, bis(3,5-dimethylphenyl)-((*S*)-pyrrolidin-2-yl)methanol **2b**, when employed at 20 mol % loading and 4 °C, afforded the epoxides in higher yield and ee (up to 92% ee). Nonlinear effects (NLE)[13] investigation using (*S*)-diphenyl-2-pyrrolidinemethanol **2a**, at different degrees of optical purity, afforded a linear relationship, suggesting the involvement of a single molecule of the catalyst in the enantiodifferentiating step. The postulated

Keywords: Epoxidation; α,β-Enones; Asymmetric organocatalysis; Epoxides.
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doi:10.1016/j.tet.2006.10.005

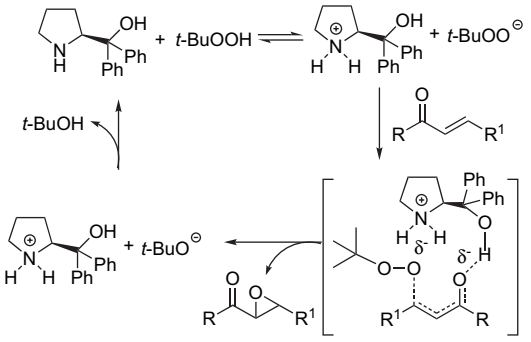


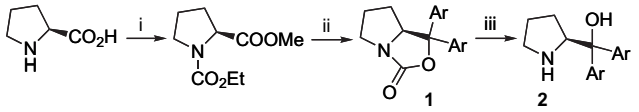
Figure 1. Proposed catalytic cycle for the epoxidation.

catalytic cycle for the epoxidation involves the formation of a ionic pair, made of *tert*-butyl hydroperoxide anion and ammonium cation, as the active species (Fig. 1).[11]

Further understanding of the catalyst activity, through fine-tuned stereoelectronic modifications on the phenyl ring, is important for the development of a more efficient and practical epoxidation reaction. Hence, in this study, novel modified diaryl-2-pyrrolidinemethanols were synthesized and tested as promoters for the epoxidation, which was successfully improved by using a more active organocatalyst at significantly reduced loading.

2. Results and discussion

Our preliminary investigation[12] on the effect of substituents on the phenyl ring showed that (i) electron-donating substituents at *para* and *meta* positions enhanced catalyst activity; (ii) substitution at *meta* positions was found to be beneficial for the enantioselectivity. These results reinforced the mechanistic hypothesis involving the ionic pair as active species (Fig. 1). In fact, the equilibrium for its formation would be favoured for those catalysts having electron-donating groups, which through inductive or mesomeric effects can increase amine basicity. In order to further improve our oxidative system, a more detailed analysis of the stereoelectronic effects on catalyst activity was undertaken. In the light of previous results,[12] *ortho*-substituted and *meta*-disubstituted catalysts with electron-donating groups were thought to be the most suitable compounds to prepare and check in the epoxidation. (*S*)-Diaryl-2-pyrrolidinemethanols are readily accessible starting from L-proline according to the general established procedures[14] (Scheme 2).



Ar=*o*-methyl-*p*-methoxyphenyl (**c**)
Ar=*o*,*p*-dimethoxyphenyl (**d**) 12%
Ar=*m*,*m*′-dimethoxy-p-methoxyphenyl (**e**) 49%
Ar=*m*,*m*′-di-*t*-butylphenyl (**f**) 31%
Ar=*m*,*m*′-dimethyl-*p*-methoxyphenyl (**g**) 68%

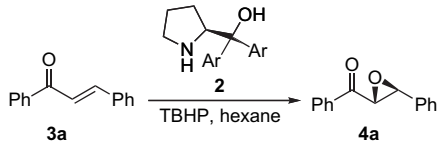
Scheme 2. Reagents and conditions: (i) ethyl chloroformate, K_2CO_3, MeOH, 0 °C to rt, 97%; (ii) ArMgBr, THF, 0–60 °C; (iii) KOH, EtOH/H_2O, reflux.

Grignard addition to (*S*)-proline-*N*-ethyl carbamate methyl ester did not furnish compound **1c**, while the *o*,*p*-dimethoxy substituted compound **1d** was obtained in 48% yield. This was probably due to the bigger steric congestion of the *o*-methyl substituent with respect to *o*-methoxy group at the reactive site of the organometallic reagent, which prevented the addition. Catalyst **2d** was isolated in 25% yield after hydrolysis. Next, sterically more encumbered groups were introduced at the *meta* positions and the corresponding compounds **2e**,**f** were obtained in 49% and 31% yield for the two steps, respectively. Finally, compound **2g** was obtained in good overall 68% yield.

Catalysts **2d**–**g** were then checked under the optimal conditions (TBHP 1.2 equiv, +4 °C, 20 mol % catalyst loading)[12] previously found for catalyst **2b** on *trans*-chalcone **3a** (Table 1, entry 1).

The epoxidation of **3a**, using the *o*,*p*-dimethoxy substituted catalyst **2d**, afforded **4a** in very low yield and low enantioselectivity (entry 2). Although we expected the trisubstituted catalyst **2e** to be less reactive than **2b**, because of electron-withdrawing inductive effect of the methoxy groups at *meta* positions, the slightly bigger *m*-methoxy substituents were not beneficial for the enantioselectivity (entry 3). Interestingly, the activity of catalyst **2f**, bearing sterically encumbered *m*-*tert*-butyl groups, was completely inhibited (entry 4). These results showed that *ortho*-type substitution is detrimental in all respects, probably because of steric effect on the OH group, which prevented activation via hydrogen bonding with the enone carbonyl moiety. Substitution at the *meta* positions proved to be crucial for catalyst performance. Small or major modifications of the substituent nature, with respect to the methyl group of **2b**, were deleterious (entries 3 and 4). Thus, methyl substitution at the *meta* positions would seem optimal to achieve high enantioselectivity. We then studied the epoxidation with the trisubstituted promoter **2g**. This compound should have had improved activity with respect to **2b** due to the introduction of additional electron-donating *p*-methoxy groups and had a comparable impact on enantioselectivity. The epoxidation was carried

Table 1. Asymmetric epoxidation of **3a** by **2**/TBHP system



Entry	**2** (mol %)	*T* (°C)	*t* (h)	Yield **4a** (%)[a]	ee **4a** (%)[b]
1[c]	**b** (20)	+4	112	90	91 (α*R*,β*S*)
2	**d** (20)	+4	112	9	43 (α*R*,β*S*)
3	**e** (20)	+4	86	37	86 (α*R*,β*S*)
4	**f** (20)	+4	90	<5	—
5	**g** (15)	+4	106	70	92 (α*R*,β*S*)
6	**g** (10)	rt	110	93	89 (α*R*,β*S*)
7[c]	**b** (10)	rt	95	61	88 (α*R*,β*S*)
8[d]	**a** (30)	rt	94	72	75 (α*R*,β*S*)
9	**g** (5)	rt	120	77	88 (α*R*,β*S*)
10	**g** (2)	rt	120	47	83 (α*R*,β*S*)

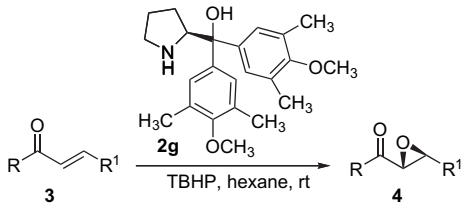
[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC on chiral column. Absolute configuration (α*R*,β*S*) was determined by comparison of the HPLC retention times with those in the literature.
[c] Yield and ee are reported in Ref. 12.
[d] Yield and ee are reported in Ref. 11.

out at lower catalyst loading (15 mol %) under the same conditions and the epoxide was isolated in good yield and high ee (entry 5). A better comparison on catalysts activity can be gained by comparing the results obtained at 10 mol % loading, working at room temperature (entries 6 and 7). After similar reaction times, the epoxide was isolated in comparable ee, but a higher yield was achieved when using catalyst **2g**. The relevance of the substitution pattern on catalyst efficiency can be clearly observed when comparing the results with those obtained using the original promoter **2a** at 30 mol % (entry 8). It is worth noting that the amount of catalyst **2g** could be further reduced to 2 mol % (entries 9 and 10) without particularly affecting the enantioselectivity, although the yield of **4a** decreased.

Having established that **2g** proved about equal to **2b** (compare entries 1 and 6), but at half the catalyst loading (10 mol %) we next screened a series of α,β-enones under the conditions reported in entry 6 of Table 1 (Table 2).

Epoxides of chalcones bearing electron-donating or withdrawing groups on the phenyl rings were obtained in good to high yield and high ee (entries 1–8). Predictably, the conversion was somewhat decreased for chalcones having electron-donating substituent on the β-phenyl ring (entries 4 and 5). Although the epoxide of the *o*-substituted β-phenyl ring **4i** was obtained with decreased ee (entry 9), it is worth noting that the same reaction when carried out by 30 mol % of the commercial promoter **2a** was considerably slower and the product was obtained in modest yield and significantly reduced ee (entry 10). Finally, the epoxidation of more challenging alkyl substituted α,β-unsaturated ketones led to the formation of the epoxides in good ee (entries 11–13).

Table 2. Catalytic asymmetric epoxidation of **3** by **2g**/TBHP system[a]



Entry	R, R^1	**3**	*t* (h)	Yield **4** (%)[b]	ee **4** (%)[c]
1	Ph, Ph	**a**	110	93	89
2	*p*-BrC_6H_4, Ph	**b**	172	98	86
3	*m*-$CH_3C_6H_4$, Ph	**c**	137	87	89
4	Ph, *p*-CH_3	**d**	153	80	86
5[d]	Ph, *p*-OCH_3	**e**	120	61	87
6	Ph, *p*-CN	**f**	170	65	86
7	2-Furyl, Ph	**g**	179	78	90
8	Ph, *p*-Cl	**h**	167	88	87
9[e]	Ph, *o*-Cl	**i**	76	70	69
10[f]	Ph, *o*-Cl	**i**	143	45	34
11[d]	CH_3, Ph	**j**	216	55	83
12	Ph, CH_3	**k**	119	95	67
13	Ph, $(CH_2)_2$Ph	**l**	162	80	71

[a] Molar ratios: **3**/**2g**/TBHP 1:0.10:1.2.
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC on chiral columns. Absolute configuration (α*R*,β*S*) was determined by comparison of the HPLC retention times with those in the literature.
[d] 20 mol % was used in this reaction.
[e] 15 mol % was used in this reaction.
[f] The reaction was carried out with 30 mol % of **2a**.

3. Conclusion

In summary, careful choice of stereoelectronic phenyl substitution is necessary in order to improve the activity of diaryl-2-pyrrolidinemethanols as promoters in asymmetric epoxidation of α,β-enones. Electron-rich derivative **2g**, easily obtained in good overall yield from L-proline, proved to be a more active catalyst than previously reported analogues and it could be employed at 10 mol % level, which is considerably lower than firstly reported (30 mol % loading). The optimized catalytic epoxidation reaction afforded epoxides in good to high yield and high ee at room temperature.

4. Experimental

4.1. General

All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of argon. THF was freshly distilled before use from $LiAlH_4$. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 400 spectrometer at room temperature in $CDCl_3$ as solvent. Optical rotations were performed on a Jasco Dip-1000 digital polarimeter using the Na lamp. FTIR spectra were recorded as a thin film on NaCl plates using Bruker Vector 22 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. All commercially available reagents were purchased from Aldrich. Petrol ether (PE) refers to light petroleum ether (bp 40–60 °C). α,β-Enones which were not commercially available were prepared via aldol condensation using standard conditions.[15] Hexane of HPLC grade was used as solvent for the epoxidation. The absolute configuration of the predominant enantiomer of epoxides was determined by comparison with the HPLC retention times, using Daicel Chiralcel OD and Daicel Chiralpak AD columns, as reported in the literature. (*S*)-Proline-*N*-ethyl carbamate ethyl ester was prepared according to the literature.[16]

4.2. General procedure for the preparation of carbamates 1 from (*S*)-proline-*N*-ethyl carbamate methyl ester

Magnesium turnings (251 mg, 10.3 mmol) were placed in a dried two-necked round-bottom flask attached with a reflux condenser under argon atmosphere. After adding dry THF (3 mL) and few iodine crystals to the reaction vessel, the turnings were left under stirring for 2 h. Aryl bromide (9.4 mmol) in dry THF (8 mL) was added dropwise in 15 min. The mixture was then refluxed under stirring for 45 min. After cooling the reaction mixture at 0 °C, a solution of (*S*)-proline-*N*-ethyl carbamate methyl ester (805 mg, 4 mmol) in THF (18 mL) was cannulated into the reaction vessel. The resulting mixture was warmed up to room temperature gradually and then heated up to 60 °C. After stirring

overnight, the reaction was quenched with saturated ammonium chloride solution (50 mL) extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography typically eluting with mixtures of PE/ethyl acetate 90/10 to 50/50 afforded the corresponding carbamate **1**.

4.2.1. Carbamate 1d. Compound **1d** was obtained in 48% yield as white gum; $[\alpha]_D^{24}$ −118.1 (*c* 1.25, $CHCl_3$); ν_{max}/cm^{-1} 2945, 1743, 1463, 1209, 798, 750; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, d, *J*=8.5 Hz), 6.94 (1H, d, *J*=8.5 Hz), 6.51–6.43 (3H, m), 6.39–6.34 (1H, m), 4.53 (1H, dd, *J*=9.6, 6.6 Hz), 3.82 (3H, s), 3.78 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.67–3.59 (1H, m), 3.30–3.22 (1H, m), 2.09–2.00 (1H, m), 1.98–1.89 (1H, m), 1.75–1.68 (1H, m), 1.50–1.42 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.6, 159.8, 157.6, 129.7, 128.3, 124.1, 120.6, 103.9, 103.5, 99.1, 99.0, 86.7, 69.4, 55.4, 55.2, 55.1, 44.9, 28.0, 25.9; MS (ESI$^+$, *m*/*z*): 422 [(M+Na$^+$), 28%], 438 [(M+K$^+$), 35%], 400 [(M+H$^+$), 20%]; Anal. Calcd (%) for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.29; H, 6.20; N, 3.42.

4.2.2. Carbamate 1e. Compound **1e** was obtained in 59% yield as dark yellow gum; $[\alpha]_D^{24}$ −134.3 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} 2940, 1749, 1418, 1128, 756; δ_H (400 MHz, $CDCl_3$) 6.73 (2H, s), 6.58 (2H, s), 4.47 (1H, dd, *J*=10.5, 5.4 Hz), 3.84 (12H, s), 3.83 (6H, s), 3.80–3.71 (1H, m), 3.30–3.25 (1H, m), 2.06–1.98 (1H, m), 1.93–1.86 (1H, m), 1.79–1.73 (1H, m), 1.25–1.15 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.3, 153.2, 153.0, 138.7, 138.1, 137.3, 135.6, 103.6, 102.8, 85.8, 77.3, 69.3, 60.8, 56.3, 56.2, 46.1, 29.0, 24.8; MS (ESI$^+$, *m*/*z*): 498 [(M+K$^+$), 12%], 460 [(M+H$^+$), 35%]; Anal. Calcd (%) for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.60; H, 6.49; N, 3.14.

4.2.3. Carbamate 1f. Compound **1f** was obtained in 65% yield as yellow gum; $[\alpha]_D^{25}$ −82.2 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2963, 1749, 1476, 1248, 754; δ_H (400 MHz, $CDCl_3$) 7.38 (2H, d, *J*=1.4 Hz), 7.35–7.33 (1H, m), 7.30–7.28 (1H, m), 7.24 (2H, d, *J*=1.4 Hz), 4.48 (1H, dd, *J*=10.5, 5.3 Hz), 3.77–3.70 (1H, m), 3.26–3.20 (1H, m), 2.01–1.95 (1H, m), 1.94–1.85 (1H, m), 1.84–1.74 (1H, m), 1.29 (36H, s), 1.16–1.10 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.9, 150.7, 150.4, 143.4, 139.6, 122.1, 122.0, 121.0, 119.7, 119.6, 86.8, 70.7, 45.9, 34.9, 31.4, 29.3, 24.8; MS (ESI$^+$, *m*/*z*): 526 [(M+Na$^+$), 12%], 504 [(M+H$^+$), 35%]; Anal. Calcd (%) for $C_{34}H_{49}NO_2$: C, 81.06; H, 9.80; N, 2.78. Found: C, 81.18; H, 9.68; N, 2.66.

4.2.4. Carbamate 1g. Compound **1g** was obtained in 84% yield as yellow gum; $[\alpha]_D^{24}$ −168.8 (*c* 1.54, $CHCl_3$); ν_{max}/cm^{-1} 2947, 1752, 1484, 1227, 1012, 756; δ_H (400 MHz, $CDCl_3$) 7.14 (2H, s), 6.98 (2H, s), 4.50 (1H, dd, *J*=10.5, 5.5 Hz), 3.75–3.68 (1H, m), 3.69 (6H, s), 3.26–3.20 (1H, m), 2.27 (6H, s), 2.25 (6H, s), 2.01–1.94 (1H, m), 1.93–1.82 (1H, m), 1.70–1.55 (1H, m), 1.14–1.07 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.7, 156.7, 156.1, 138.6, 135.6, 130.8, 130.6, 126.2, 125.7, 85.5, 59.6, 46.0, 28.9, 24.7, 16.3; MS (ESI$^+$, *m*/*z*): 434 [(M+K$^+$), 15%], 396 [(M+H$^+$), 100%]; Anal. Calcd (%) for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.73; H, 7.27; N, 3.44.

4.3. General procedure for the hydrolysis of carbamates to (*S*)-diaryl-2-pyrrolidinemethanols 2

A solution of **1** (2.2 mmol), KOH (2.4 g, 43 mmol), EtOH (10 mL) and H_2O (2.0 mL) was heated overnight at 80 °C (in some examples up to two days time was necessary to complete conversion of starting material as assessed by TLC analysis). After cooling to room temperature, EtOH was removed under reduced pressure, and the aqueous layer was extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography typically eluting with mixtures of PE/ethyl acetate 80/20 to pure ethyl acetate afforded compounds **2**.

4.3.1. Bis(2,4-dimethoxyphenyl)((*S*)-pyrrolidin-2-yl)methanol 2d. Compound **2d** was obtained in 25% yield as yellow gum; $[\alpha]_D^{24}$ −83.5 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} 3463, 2938, 1462, 1209, 1031, 833, 754; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, d, *J*=8.7 Hz), 7.54 (1H, d, *J*=8.7 Hz), 6.56–6.51 (1H, m), 6.49–6.45 (1H, m), 6.36–6.25 (2H, m), 5.13 (1H, t, *J*=8.4 Hz), 3.75 (3H, s), 3.73 (3H, s), 3.63 (3H, s), 3.51 (3H, s), 3.09–3.00 (2H, m), 1.91–1.76 (3H, m), 1.58–1.55 (1H, m); δ_C (100 MHz, $CDCl_3$) 160.1, 157.6, 156.5, 131.4, 129.6, 127.8, 127.6, 124.4, 123.1, 104.3, 103.7, 99.8, 99.1, 76.9, 62.0, 55.7, 55.4, 55.2, 47.4, 26.8, 25.2; MS (ESI$^+$, *m*/*z*): 374 [(M+H$^+$), 18%], 356 [(M−17), 100%]; Anal. Calcd (%) for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.68; H, 7.20; N, 3.61.

4.3.2. Bis(3,4,5-trimethoxyphenyl)((*S*)-pyrrolidin-2-yl)methanol 2e. Compound **2e** was obtained in 83% yield as yellow gum; $[\alpha]_D^{23}$ −60.3 (*c* 1.17, $CHCl_3$); ν_{max}/cm^{-1} 3450, 2940, 1458, 1128, 756; δ_H (400 MHz, $CDCl_3$) 6.81 (2H, s), 6.73 (2H, s), 4.14 (1H, t, *J*=7.8 Hz), 3.85 (6H, s), 3.84 (6H, s), 3.80 (6H, s), 3.04–2.90 (2H, m), 1.77–1.53 (4H, m); δ_C (100 MHz, $CDCl_3$) 152.9, 152.7, 143.5, 140.7, 136.7, 136.5, 103.7, 103.2, 102.8, 72.9, 64.8, 60.7, 56.2, 56.1, 46.6, 26.4, 25.3; MS (ESI$^+$, *m*/*z*): 434 [(M+H$^+$), 10%], 416 [(M−17), 100%]; Anal. Calcd (%) for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.62, H, 7.30; N, 3.15.

4.3.3. Bis(3,5-di-*tert*-butylphenyl)((*S*)-pyrrolidin-2-yl)methanol 2f. Compound **2f** was obtained in 48% yield as yellow gum; $[\alpha]_D^{22}$ −58.2 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} 3417, 2963, 1392, 1248, 757; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J*=1.4 Hz), 7.35 (2H, d, *J*=1.4 Hz), 7.26 (1H, s), 7.18 (1H, s), 4.73 (1H, t, *J*=7.8 Hz), 2.33–2.27 (1H, m), 2.25–2.15 (1H, m), 1.94–1.88 (1H, m), 1.75–1.55 (3H, m), 1.32 (18H, s), 1.24 (18H, s); δ_C (100 MHz, $CDCl_3$) 150.7, 150.4, 143.1, 142.4, 122.1, 120.5, 119.9, 119.2, 78.2, 66.2, 46.2, 35.0, 34.9, 31.6, 26.6, 24.7; MS (ESI$^+$, *m*/*z*): 478 [(M+H$^+$), 100%], 460 [(M−17), 60%]; Anal. Calcd (%) for $C_{33}H_{51}NO$: C, 82.96; H, 10.76; N, 2.93. Found: C, 82.85; H, 10.66; N, 2.85.

4.3.4. Bis(3,5-dimethyl-4-methoxyphenyl)((*S*)-pyrrolidin-2-yl)methanol 2g. Compound **2g** was obtained in 81% yield as pale yellow gum; $[\alpha]_D^{25}$ −48.1 (*c* 1.15, $CHCl_3$); ν_{max}/cm^{-1} 3446, 2946, 1484, 1224, 1136, 756; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, s), 7.09 (2H, s), 4.18 (1H, t,

J=7.6 Hz), 3.66 (6H, s), 3.00–2.89 (2H, m), 2.25 (6H, s), 2.24 (6H, s), 1.75–1.67 (2H, m), 1.62–1.53 (2H, m); δ_C (100 MHz, $CDCl_3$) 155.3, 155.2, 143.3, 140.6, 130.1, 129.8, 126.8, 126.7, 126.0, 125.7, 76.4, 64.5, 59.4, 46.6, 26.2, 25.4, 16.3; MS (ESI$^+$, m/z): 370 [(M+H$^+$), 10%], 352 [(M−17), 100%]; Anal. Calcd (%) for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.65; H, 8.53; N, 3.70.

4.4. General procedure for the asymmetric epoxidation of α,β-enones

To a stirred solution of catalyst **2g** (5.5 mg, 0.015 mmol) and α,β-enone **3** (0.150 mmol) in hexane (300 μL) at room temperature was added TBHP (5–6 M decane solution, 33 μL, 0.18 mmol). Stirring was maintained for the time indicated in Table 2. The crude reaction mixture was directly purified by flash chromatography on silica gel (PE/diethyl ether 99/1) to provide the epoxy ketone **4**. Epoxides data were as described previously.[2c,11,12,17–23]

4.5. Determination of enantiomeric excess for epoxy ketones 4

4.5.1. *trans*-(2*R*,3*S*)-Epoxy-1,3-diphenylpropan-1-one 4a.[2c] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 98/2, flow rate 1.0 mL/min, t_R(2*S*,3*R*)=17.3 min, t_R(2*R*,3*S*)=18.5 min.

4.5.2. *trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(4-bromophenyl)-propan-1-one 4b.[17] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min, t_R(2*R*,3*S*)=20.2 min, t_R(2*S*,3*R*)=22.6 min.

4.5.3. *trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(3-methylphenyl)-propan-1-one 4c.[4f] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 30/1, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=17.8 min, t_R(2*R*,3*S*)=18.8 min.

4.5.4. *trans*-(2*R*,3*S*)-Epoxy-3-(4-methylphenyl)-1-phenyl-1-propan-1-one 4d.[18] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=17.1 min, t_R(2*R*,3*S*)=19.6 min.

4.5.5. *trans*-(2*R*,3*S*)-Epoxy-3-(4-methoxyphenyl)-1-phenyl-1-propan-1-one 4e.[17] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=21.7 min, t_R(2*R*,3*S*)=23.1 min.

4.5.6. *trans*-(2*R*,3*S*)-Epoxy-3-(4-cyanophenyl)-1-phenyl-1-propan-1-one 4f.[19] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 90/10, flow rate 0.9 mL/min, t_R(2*S*,3*R*)=35.0 min, t_R(2*R*,3*S*)=38.3 min.

4.5.7. *trans*-(2*R*,3*S*)-Epoxy-3-phenyl-1-(2-furyl)-1-propan-1-one 4g.[20] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min, t_R(2*S*,3*R*)=15.3 min, t_R(2*R*,3*S*)=16.8 min.

4.5.8. *trans*-(2*R*,3*S*)-Epoxy-3-(4-chlorophenyl)-1-phenyl-1-propan-1-one 2h.[21] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 55/1, flow rate 0.5 mL/min, t_R(2*S*,3*R*)=54.5 min, t_R(2*R*,3*S*)=57.0 min.

4.5.9. *trans*-(2*R*,3*S*)-Epoxy-3-(2-chlorophenyl)-1-phenyl-1-propan-1-one 2i.[4f] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 96/4, flow rate 1.0 mL/min, t_R(2*R*,3*S*)=10.1 min, t_R(2*S*,3*R*)=11.5 min.

4.5.10. *trans*-(3*R*,4*S*)-Epoxy-4-phenylbutan-2-one 4j.[2c] HPLC (Chiralpak AD): λ 254 nm, hexane/*i*-PrOH 98/2, flow rate 1.0 mL/min, t_R(3*R*,4*S*)=10.9 min, t_R(3*S*,4*R*)=13.7 min.

4.5.11. *trans*-(2*R*,3*S*)-Epoxy-1-phenylbutan-1-one 4k.[22] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 94/6, flow rate 0.8 mL/min, t_R(2*S*,3*R*)=10.7 min, t_R(2*R*,3*S*)=11.6 min.

4.5.12. *trans*-(2*R*,3*S*)-Epoxy-5-phenylpentanophenone 4l.[23] HPLC (Chiralcel OD): λ 254 nm, hexane/*i*-PrOH 20/1, flow rate 1.0 mL/min, t_R(2*R*,3*S*)=16.6 min, t_R(2*S*,3*R*)=18.3 min.

Acknowledgements

Ministero Italiano dell'Università e Ricerca Scientifica e Tecnologica (MIUR) is gratefully acknowledged for financial support.

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5-Phenylthio-1,3-oxazinan-4-ones via hetero Diels–Alder reactions: synthesis of (*R*)- and (*S*)-Duloxetines and Fluoxetines

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Received 22 July 2006; revised 21 September 2006; accepted 5 October 2006
Available online 27 October 2006

Abstract—The synthesis of 5-phenylthio-1,3-oxazinan-4-ones, through a hetero Diels–Alder strategy, is described. The cycloadducts thus prepared have been shown to be useful intermediates for the synthesis of 1,3-aminoalcohols, valuable intermediates in the preparation of biologically significant molecules, e.g., optically active Duloxetines and Fluoxetines. In the course of this elaboration a novel microwave assisted desulfurization reaction is reported.

1. Introduction

Hetero Diels–Alder cycloaddition is a versatile strategy for the synthesis of natural compounds containing six-membered heterocyclic rings.[1–9] Moreover, this strategy has found important applications through the elaboration of the cyclic adducts thus obtained to acyclic compounds with a well-defined stereo- and regio-control of the present functionalities. Reported herein is the application of hetero Diels–Alder methodology to the synthesis of open-chain compounds containing the 1,3-hydroxy-amino moiety, which is present in a large class of pharmaceutically important compounds such as Duloxetine (Cymbalta®)[10–12] and Fluoxetine (Prozac®).[13,14] Prozac and Cymbalta have been chosen as target compounds being potent and highly selective inhibitors of neutral serotonin-reuptake and among the most important drugs for the treatment of psychiatric disorders and metabolic problems. Last but not the least, their market is very interesting from an industrial point of view.[15] As a matter of fact the establishment of new synthetic protocols, which allow the building-up of small libraries, with an easily obtainable different substitution pattern on the scaffold, is of primary importance for researchers involved in the preparation and the study of this class of compounds. Recent disclosure from these laboratories[16] have demonstrated that 5-unsubstituted perhydrooxazinan-4-ones, obtained via a hetero Diels–Alder strategy, may be adopted as useful intermediates for the preparation of 1,3-aminoalcohols. In continuation of our studies on the use of hetero Diels–Alder strategy in the synthesis of heterocyclic compounds with different substitution pattern and their use for the preparation of acyclic derivatives we would like to present here our recent results on the synthesis and use of the 5-phenylthio-perhydrooxazinan-4-ones in the preparation of racemic and optically active 1,3-aminoalcohols. Compared to the previously reported studies in the same field, we anticipated that the synthesis of the 5-phenylthio-substituted oxazinan-4-ones may have its importance if the position five of the heterocyclic adduct is substituted by an easily removable group, as the thiophenyl one. Moreover, the intrinsic important reactivity of this functionality would allow further elaborations, e.g., introduction of an extra group and/or functionalities. As an example, the parent acyclic β-hydroxy-α-phenylthiocarboxy derivatives[17–20] have been shown to be useful intermediates for the synthesis of 1,3-aminoalcohols.[21,22]

2. Results and discussion

2.1. Synthesis of racemic 5-thiophenyl-1,3-oxazinan-4-ones

5-Phenylthio-1,3-oxazinan-4-ones have been obtained from the easily available 1,3-azadienes,[23–28] prepared from silylimines and ketenes, and using aldehydes as dienophiles. In the present study, the starting azadiene is a neutral

Keywords: Hetero Diels–Alder; 1,3-Amino-alcohols; Prozac; Duloxetine.
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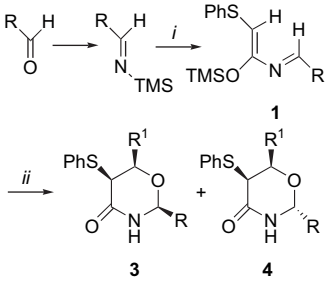
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.006

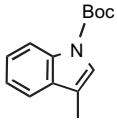
3-trimethylsilyloxy-4-thioaryl-2-aza-1,3-diene, already used in a previous study for the preparation of a β-lactam ring by a 4π-conrotatory electrocyclization.[29]

In detail, reaction of the neutral azadiene **1** with an aldehyde R^1CHO **2**, in the presence of a stoichiometric amount of boron trifluoride etherate in dichloromethane (DCM) at −78 °C, gives rise to the formation of the expected 5-phenylthio-1,3-oxazinan-4-ones **3** and **4** with various substitution patterns at the C_2 and the C_6 carbon atoms (Scheme 1 and Table 1).[30–35] The results shown in Scheme 1 and Table 1 warrant some comments. (1) No traces of azedinones, arising from a 4π-conrotatory electrocyclization, have been detected in the crude reaction mixtures.[29,36] (2) All the reactions are completely regioselective. (3) The use of an excess of Lewis acid does not influence the reaction course since the value of the diastereomeric ratio as well as that of the yield remains substantially untouched (Table 1 entry 2). (4) In all the experiments performed, irrespective of the starting azadiene and the dienophilic aldehyde used, a cis-relationship between the C_5H and C_6H is established, shown by the relative coupling constants (J_{cis}=2–4 Hz) and NOE experiments. Careful analysis of the results reported in Table 1 clearly allows to allocate, from the stereochemical relationship of C_2H–C_5H–C_6H, two groups of cycloadducts: one (compounds **3a**–**3f**) presenting the three ring-protons in a basket conformation and an other group (compounds **4a**–**4f**) presenting the same cis-configuration between the C_5H and C_6H but a trans-relationship between C_2H and C_5H as pointed out by the combined analysis of coupling constants and NOEs. In order to ascertain if this stereo-difference originates from a different cyclization mechanism (hetero Diels–Alder vs a competitive open-chain Mukaiyama mechanism[37]) and taking into account that, as already known,[38–40] an equilibrium between the cyclic perhydrooxazinan-4-ones and the open-chain derivatives may exist (Scheme 2), extra experiments were performed. Treatment of pure **3a** with an excess of BF_3 etherate in methylene chloride for 4 h at room temperature gives rise to a mixture of **3a** and **4a** in 90/10 diastereomeric ratio as evaluated by ^1H NMR spectroscopic analysis. This is, in our opinion, a clear evidence that some degree of isomerization could take place *after* the formation of the Diels–Alder adduct thus suggesting the exclusion of a different reaction mechanism (e.g., a competitive Mukaiyama type addition–cyclization two-step mechanism). A further confirmation of this working hypothesis comes out from the results obtained when a hydroxyalkyl group, which should not favor the formation of a positive charge, is present on the C_2 stereocenter (heterocyclic numbering). As a matter of fact in this case only two products were obtained (vide infra): they have the same basket conformation for the C_2, C_5, and C_6 hydrogen atoms and differ for opposite absolute configuration of these centers. Nevertheless, it must be pointed out that these speculations are interesting from a mechanistic point of view but useless from a practical one since this isomerization is immaterial in our strategic plan because of the loss of the C_2 stereogenic center in the final products (see Schemes 3 and 4). For this reason no more investigations, so far, have been undertaken.

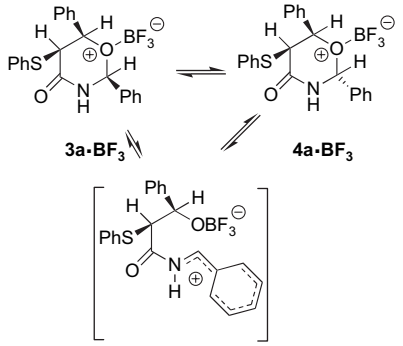


Scheme 1. Reagents and conditions: (i) Ref. 29; (ii) R^1CHO (**2**), DCM, $BF_3 \cdot Et_2O$.

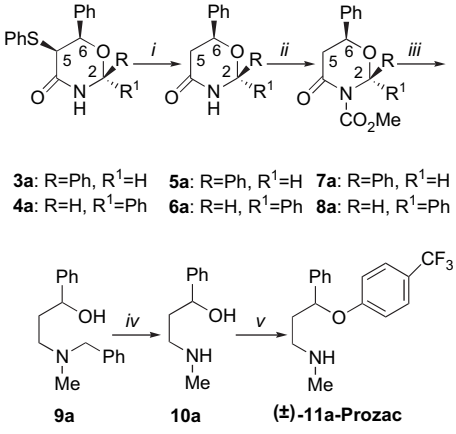
Table 1. Synthesis of perhydrooxazinan-2-ones **3** and **4**

Exps.	R	R^1	Azadiene	Products	Ratio	Ys, %[a]
1	Ph	Ph	**1a**	**3a/4a**	90/10	35
2	Ph	Ph	**1a**	**3a/4a**	74/26	33[b]
3	Ph		**1a**	**3b/4b**	40/60	38
4	*p*-MeO–Ph	Ph	**1b**	**3c/4c**	80/20	55
5	*o*-TIPSO–Ph	Ph	**1c**	**3d/4d**	85/15	48
6	Ph	Me	**1a**	**3e/4e**	50/50	51
7	Ph		**1a**	**3f/4f**	40/60	41

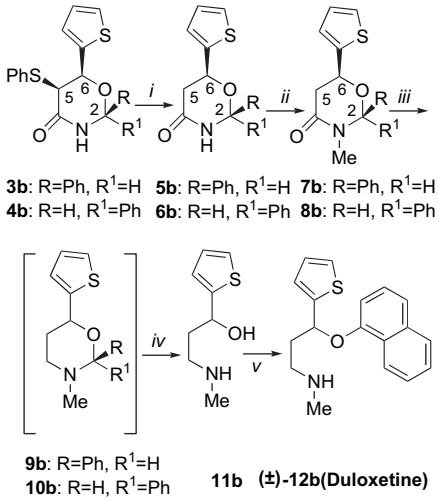
[a] The yields have been calculated on the dienophilic aldehyde.
[b] $BF_3 \cdot Et_2O$ (5 equiv) has been used.



Scheme 2.



Scheme 3. Reagents and conditions: (i) MW, Nickel-Raney/EtOH; (ii) LiHMDS, ClCOOMe, THF; (iii) $LiAlH_4$/THF; (iv) Ref. 40; (v) Ref. 41.



Scheme 4. Reagents and conditions. (i) aluminum amalgam, *i*-PrOH; (ii) LiHMDS, MeI, THF; (iii) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$, THF; (iv) HCl_{aq}; (v) Ref. 49.

2.2. Synthesis of racemic (±)-Prozac and (±)-Duloxetine

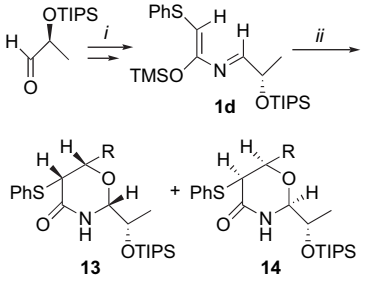
Having the desired perhydrooxazinones in hand, we followed our strategic plan by elaboration of the diastereomeric mixture of compounds **3a/4a** and **3b/4b** to the racemic (±)-Prozac and (±)-Duloxetine, respectively.

The synthetic protocols are outlined in Schemes 3 and 4.

Compounds **3a** and **4a** were easily desulfurated by the use of Nickel-Raney in a novel microwave-mediated[41–45] desulfurization reaction.[18,46–49] Thus treatment of adducts **3a** and **4a** with Raney-Nickel in a microwave oven allows to obtain, in a very short time (2 min) and high yields (80% and 92%, respectively), the corresponding desulfurated derivatives **5a** and **6a**. *N*-Carboxymethyl derivatives **7a** and **8a** were obtained in quantitative yields by treatment of **5a** and **6a** with methyl chloroformate and LiHMDS in THF. Reduction of the amide and carboxymethyl functionalities with lithium aluminum hydride gave rise to open-chain *N*-benzyl derivative **9a**. Following already known procedures, this intermediate was easily converted to the racemic Prozac via hydrogenolysis of the benzyl group and arylation of the hydroxy functionality.[50] It must be stressed that the same synthetic protocol, applied to the diastereomeric mixture of **3a** and **4a**, gave the same results in terms of yields of the overall process. By the same strategy, with slight modifications, (±)-Duloxetine was prepared. Desulfuration of oxazinan-4-ones **3b** and **4b** by the above reported microwave-mediated Nickel-Raney methodology partially failed when applied to these compounds giving rise to low yields of the desired 5-unsubstituted derivatives **5b** and **6b**, probably due to side reactions on the thienyl ring. Different procedures, known in the literature to give good results, failed partially or completely. Finally we have found that desulfuration with aluminum amalgam[51] was the method of choice. Once we prepared the derivatives **5b** and **6b**, their elaboration to the final (±)-Duloxetine was a straightforward task. Methylation by LiHMDS and methyl iodide gave rise, in quantitative yields, to the *N*-methyl intermediates **7b** and **8b**. Reduction of the amide functionality by means of Ph_2SiH_2, in the presence of 1 mol % $RhH(CO)(PPh_3)_3$ in THF,[52] resulted in the production of the partially unstable intermediates **9b** and **10b**. Ring opening by aqueous hydrochloric acid furnished the corresponding aminol **11b**. (±)-Duloxetine was obtained by means arylation of **11b** according to a literature procedure (Scheme 4).[50]

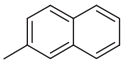
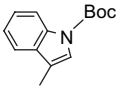
2.3. Synthesis of optically active 5-thiophenyl-substituted oxazinan-4-ones

Owing to the different biological activity exhibited by individual enantiomers of Prozac and Duloxetine, a number of enantioselective syntheses of these important compounds have been developed in recent years.[53–55,50,56] In this section we report the results obtained by our group in the synthesis of optically active aminoalcohols **10a** and **11b** and, therefore, of optically active (*R*)- and (*S*)-Fluoxetines and Duloxetines [(*R*)-**11a**, (*S*)-**11a** and (*R*)-**12b**, (*S*)-**12b**, respectively]. To reach this task and taking advantage of our experience on the synthesis of optically active perhydrooxazinan-4-ones by hetero Diels–Alder strategy, we prepared optically active azadiene **1d** using, in its preparation, the trimethylsilylimine derived from optically active (*S*)-lactic aldehyde and the 2-phenylthioacetylchloride as source of the ketene (Scheme 5). Reaction of the optically active azadiene **1d** with a range of aldehydes furnished two oxazinan-4-ones **13** and **14** in diastereomeric ratios and yields reported in Table 2. The two diastereoisomers presented the same basket conformation for the protons on the heterocyclic ring *but* an opposite absolute configuration of the C_2, C_5, and C_6 stereocenters.



Scheme 5. Reagents and conditions: (i) Ref. 29; (ii) RCHO (**2**), DCM, $BF_3 \cdot Et_2O$.

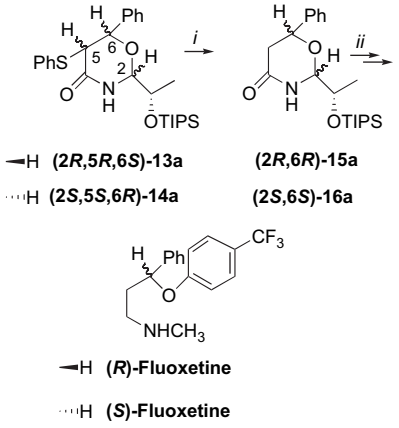
Table 2. Synthesis of oxazinan-4-ones **13** and **14**

Exps.	R	Products	Ratio[a]	Ys, %[b]
1	Ph	**13a/14a**	50/50	81
2		**13b/14b**	60/40	90
3	Me	**13c/14c**	50/50	32
4		**13d/14d**	50/50	41
5		**13e/14e**	63/37	55

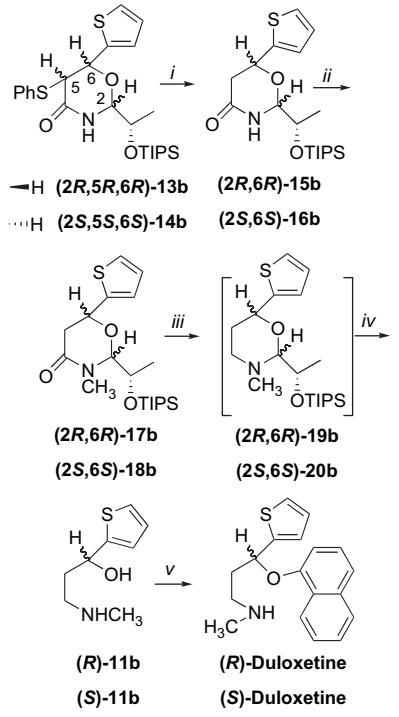
[a] Diastereomeric ratios have been determined on the crude reaction mixtures to avoid enrichments in the course of purification processes.
[b] The yields have been calculated on the dienophilic aldehyde.

2.4. Synthesis of (*R*)- and (*S*)-Fluoxetines and (*R*)- and (*S*)-Duloxetines

Once again, having in hand the desired heterocyclic compounds, we followed our strategic plan, aimed to obtain enantiomerically pure (*S*)- and (*R*)-Fluoxetines and (*S*)- and (*R*)-Duloxetines by elaboration of compounds **13a** and **14a** and compounds **13b** and **14b** to optically active aminoalcohols (1*S*)-**10a**, (1*R*)-**10a** and (1*S*)-**11b**, (1*R*)-**11b**, respectively. Conversion of compounds **13a** and **14a** to the (*S*)- and (*R*)-Fluoxetines proved to be an easy task. Accordingly, compounds **15a** and **16a** were easily obtained in quantitative yields by desulfuration of **13a** and **14a** as already described for the racemic derivatives by means of microwave assisted Raney-Nickel delsufuration. Elaboration of **15a** and **16a** to the target (*S*)- and (*R*)-Fluoxetines has been already described in a previous paper (Scheme 6).[16] On the other hand elaboration of compounds **13b** and **14b** to the (*S*)- and (*R*)-Duloxetines was performed according to the protocol described for the racemic compound. Thus, desulfuration by means of aluminum amalgam followed by N-methylation (LiHMDS, CH_3I), amide functionality reduction, and final arylation with fluoronaphthalene furnished the (*S*)- and (*R*)-Duloxetines (Scheme 7).



Scheme 6. Reagents and conditions: (i) MW, Nickel-Raney/EtOH; (ii) Ref. 16.



Scheme 7. Reagents and conditions. (i) aluminum amalgam, *i*-PrOH; (ii) LiHMDS, MeI, THF; (iii) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$, THF; (iv) HCl_{aq}; (v) Ref. 50.

3. Conclusions

In conclusion we have reported an extra contribution to the applications of azadienes of type **1** in the synthesis of valuable intermediates for the preparation of biologically significant molecules. Moreover, the 5-thio-substituted cyclic adducts thus obtained may be considered as cyclic form of α-thio-carboxylic acid derivatives and, accordingly, may undergo further elaborations. Studies in this vein are currently in progress. Finally, the novel microwave assisted desulfuration herein described, represents a valuable method, alternative to those available for this task (e.g., use of expensive and toxic tributyltin hydride). Its application to other significant classes of compounds is in progress.

4. Experimental

4.1. General procedures

All starting compounds, unless otherwise stated, were purchased. Reactions were run under an atmosphere of dry nitrogen or argon. FT-IR spectra were recorded on a Perkin–Elmer infrared spectrometer, mass spectra on Finnigan MAT instrument, and NMR spectra on a Varian Mercury 400 MHz spectrometer using the residual signal of the solvent as internal standard. Chemical shifts are reported in the δ scale and coupling constants (*J*) in hertz. Optical rotations were recorded on a Perkin–Elmer Polarimeter 343. Solvents were distilled and dried according to standard procedures. All the reactions were performed under a nitrogen atmosphere.

4.2. General procedure (GP1) for the preparation of 1,3-oxazinan-4-ones 3a–3f and 4a–4f

Compound **1** (2 mmol), prepared according to literature,[29] was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at −78 °C. Aldehyde **2** (1 mmol), dissolved in methylene chloride (2 mL), was added followed by a slow addition of BF_3 etherate (1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight while the temperature was allowed to reach room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuum. The reaction mixture was purified by flash chromatography on silica gel. 5-Phenylthio-perhydrooxazin-4ones **3a**–**3f** and **4a**–**4f** were isolated in combined yields and diastereomeric ratios reported in Table 1.

4.2.1. (2*S,5*S**,6*R**)-2,6-Diphenyl-5-phenylthio-[1,3]oxazinan-4-one 3a; (2*R**,5*S**,6*R**)-2,6-diphenyl-5-phenylthio-[1,3]oxazinan-4-one 4a.** The crude reaction mixture

obtained from azadiene **1a** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP1 was subjected to column chromatography (1:1 *EtOAc*/cyclohexane) to give **3a** and **4a** in 90/10 diastereomeric ratio and 35% overall yield.

Compound **3a**: pale yellow solid. Y=32%. Mp 173–174 °C. IR ($CHCl_3$): 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.60–7.10 (m, 15H), 6.30 (br s, 1H), 5.92 (s, 1H), 5.41 (d, J=2.4 Hz, 1H), 3.82 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 137.5, 136.9, 134.6, 133.2, 130.0, 128.8, 128.7, 128.1, 127.9, 127.8, 127.1, 125.9, 86.1, 78.6, 55.4. MS (*m*/*z*): 361, 255, 106, 91, 77. E.A. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 73.29; H, 5.33.

Compound **4a**: Pale yellow oil. Y=3%. IR ($CHCl_3$): 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.78–7.00 (m, 15H), 6.53 (br s, 1H), 6.03 (s, 1H), 5.37 (d, J=3.6 Hz, 1H), 4.03 (d, J=3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.4, 138.0, 136.1, 134.3, 132.9, 129.4, 128.8, 128.7, 128.3, 128.2, 127.7, 126.7, 126.6, 82.0, 73.6, 53.9. MS (*m*/*z*): 361, 255, 106, 91, 77. E.A. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 73.32; H, 5.31.

4.2.2. (2*S,5*S**,6*S**)-2-Phenyl-6-(thiophen-2-yl)-5-phenylthio-[1,3]oxazinan-4-one 3b; (2*R**,5*S**,6*S**)-2-phenyl-6-(thiophen-2-yl)-5-phenylthio-[1,3]oxazinan-4-one 4b.** The crude reaction mixture obtained from azadiene **1a** (2 mmol) and 2-thiophenecarboxaldehyde (0.093 mL, 1 mmol) according to GP1 was subjected to column chromatography (4:6 *EtOAc*/cyclohexane) to give **3b** and **4b** in 40/60 diastereomeric ratio and 38% overall yield.

Compound **3b**: pale yellow oil. Y=15%. IR ($CHCl_3$): 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.43 (m, 7H), 7.33 (dd, J_1=1.0 Hz, J_2=5.0 Hz, 1H), 7.24 (m, 3H), 7.06 (m, 1H), 7.01 (dd, J_1=3.4 Hz, J_2=5.0 Hz, 1H), 6.54 (br s, 1H), 5.93 (s, 1H), 5.60 (dd, J_1=0.6 Hz, J_2=2.4 Hz, 1H), 3.82 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 139.3, 137.1, 134.6, 132.9, 130.0, 128.9, 128.8, 127.8, 127.1, 126.37, 125.9, 125.5, 86.0, 76.3, 55.3. MS (*m*/*z*): 368 (M^++1), 323, 255, 212, 184, 152, 121, 106, 91, 77. E.A. Calcd for $C_{21}H_{19}NOS_2$: C, 69.01; H, 5.24; N, 3.83. Found: C, 70.39; H, 5.34.

Compound **4b**: pale yellow oil. Y=23%. IR ($CHCl_3$): 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–7.38 (m, 8H), 7.33 (br s, 1H), 7.26 (m, 4H), 7.14 (m, 1H), 7.05 (dd, J_1=3.2 Hz, J_2=5.2 Hz, 1H), 5.83 (s, 1H), 5.57 (d, J=4.8 Hz, 1H), 4.23 (dd, J_1=3.6 Hz, J_2=4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 137.6, 137.5, 134.4, 133.5, 129.7, 129.0, 128.8, 127.2, 126.8, 126.7, 81.6, 72.1, 53.4. MS (*m*/*z*): 366 (M^+−1), 322, 255, 212, 186, 152, 121, 106, 77. E.A. Calcd for $C_{21}H_{19}NOS_2$: C, 69.01; H, 5.24; N, 3.83. Found: C, 70.39; H, 5.34.

4.2.3. (2*S,5*S**,6*R**)-2-(4-Methoxy-phenyl)-6-phenyl-5-phenylthio-[1,3]oxazinan-4-one 3c; (2*R**,5*S**,6*R**)-2-(4-methoxy-phenyl)-6-phenyl-5-phenylthio-[1,3]oxazinan-4-one 4c.** The crude reaction mixture obtained from azadiene **1b** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP1 was subjected to column chromatography (1:1 *EtOAc*/cyclohexane) to give **3c** and **4c** in 80/20 diastereomeric ratio and 55% overall yield.

Compound **3c**: pale yellow solid. Y=44%. Mp 181–183 °C. IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.46–7.16 (m, 12H), 6.93 (d, J=8.8 Hz, 2H), 6.45 (br s, 1H), 5.86 (s, 1H), 5.38 (d, J=2.0 Hz, 1H), 3.83 (s, 3H), 3.80 (d, J=2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.5, 160.8, 140.3, 136.9, 134.6, 133.2, 129.2, 128.8, 128.6, 128.1, 126.4, 125.9, 114.1, 85.8, 78.4, 55.4. MS (*m*/*z*): 392 (M^++1), 334, 316, 299, 285, 187, 162, 136, 105, 91, 77. E.A. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95. Found: C, 75.48; H, 6.07.

Compound **4c**: pale yellow solid. Y=11%. IR ($CHCl_3$): 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.20 (m, 12H), 6.90 (d, J=8.6 Hz, 2H), 6.27 (br s, 1H), 5.96 (s, 1H), 5.38 (d, J=3.8 Hz, 1H), 4.08 (d, J=3.8 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.7, 160.7, 136.4, 134.6, 133.1, 130.3, 129.1, 128.5, 128.4, 128.0, 127.9, 127.1, 114.4, 82.1, 73.9, 55.6, 54.1. MS (*m*/*z*): 392 (M^++1), 316, 299, 285, 281, 210, 136, 105, 91, 77. E.A. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95. Found: C, 75.48; H, 6.07.

4.2.4. (2*S,5*S**,6*R**)-2-(2-Triisopropylsilyloxyphenyl)-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 3d; (2*R**,5*S**,6*R**)-2-(2-triisopropylsilyloxyphenyl)-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 4d.** The crude reaction mixture obtained from azadiene **1c** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP1 was subjected to column chromatography (4:6 *EtOAc*/cyclohexane) to give **3d** and **4d** in 85/15 diastereomeric ratio and 48% overall yield.

Compound **3d**: pale yellow oil. Y=41%. IR ($CHCl_3$): 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.62–6.85 (m, 14H), 6.36 (s, 1H), 6.22 (br s, 1H), 5.42 (d, J=2.4 Hz, 1H), 3.84 (d, J=2.4 Hz, 1H), 1.10 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 153.0, 137.1, 134.6, 133.2, 130.3, 128.7, 128.1, 127.8, 127.6, 127.5, 127.2, 125.9, 121.5, 118.0, 80.5, 78.5, 55.5, 18.0, 12.9. MS (*m*/*z*): 534, 427, 385, 279, 234. E.A. Calcd for $C_{32}H_{41}NO_2SSi$: C, 72.27; H, 7.77. Found: C, 74.44; H, 8.00.

Compound **4d**: pale yellow oil. Y=7%. IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.05 (m, 14H), 6.33 (br s, 1H), 6.21 (s, 1H), 5.50 (d, J=4.0 Hz, 1H), 4.10 (d, J=4.0 Hz, 1H), 1.05 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4, 153.4, 135.6, 134.4, 132.9, 130.1, 128.8, 128.5, 128.3, 127.7, 127.4, 126.6, 121.1, 118.5, 77.6, 75.1, 53.4, 18.0, 13.0. MS (*m*/*z*): 534, 427, 385, 279, 234. E.A. Calcd for $C_{32}H_{41}NO_2SSi$: C, 72.27; H, 7.77. Found: C, 74.44; H, 8.00.

4.2.5. (2*S,5*S**,6*R**)-6-Methyl-2-phenyl-5-phenylthio-[1,3]oxazinan-4-one 3e; (2*R**,5*S**,6*R**)-6-methyl-2-phenyl-5-phenylthio-[1,3]oxazinan-4-one 4e.** The crude reaction mixture obtained from azadiene **1a** (2 mmol) and acetaldehyde (0.056 mL, 1 mmol) according to GP1 was subjected to column chromatography (6:4 *EtOAc*/cyclohexane) to give **3e** and **4e** in 50/50 diastereomeric ratio and 51% overall yield.

Compound **3e**: pale yellow oil. Y=25%. IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.70 (m, 2H), 7.45–7.23 (m, 8H), 6.69 (br s, 1H), 5.74 (s, 1H), 4.34 (dq, J_1=6.4 Hz, J_2=2.8 Hz, 1H), 3.51 (d, J=2.8 Hz, 1H), 1.57 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.7, 137.8, 135.1, 133.3, 130.2, 129.3, 129.0, 128.0, 127.3, 86.2, 74.2, 54.6, 18.6. MS (*m*/*z*): 299, 255, 122, 106. E.A. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.34; H, 5.73.

Compound **4e**: yellow solid. Y=26%. Mp 147–148 °C. IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.61 (m, 2H), 7.50–7.15 (m, 8H), 6.67 (br s, 1H), 5.97 (s, 1H), 4.34 (m, 1H), 3.82 (d, J=3.6 Hz, 1H), 1.48 (d, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.0, 138.7, 134.4, 132.8, 129.7, 129.3, 129.1, 128.0, 126.8, 82.0, 69.0, 54.1, 16.8. MS (*m*/*z*): 299, 255, 122, 105, 91, 77. E.A. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.30; H, 5.71.

4.2.6. *tert*-Butyl-3-[(2*S,5*S**,6*R**)-4-oxo-2-phenyl-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 3f; *tert*-butyl-3-[(2*R**,5*S**,6*R**)-4-oxo-2-phenyl-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 4f.** The crude reaction mixture obtained from azadiene **1a** (2 mmol) and *tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (245 mg, 1 mmol) according to GP1 was subjected to column chromatography (4:6 *EtOAc*/cyclohexane) to give **3f** and **4f** in 40/60 diastereomeric ratio and 41% overall yield.

Compound **3f**: yellow oil. Y=16%. IR ($CHCl_3$): 1737, 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.75 (s, 1H), 7.60–7.05 (m, 14H), 6.21 (br s, 1H), 6.00 (s, 1H), 5.63 (dd, J_1=2.0 Hz, J_2=0.8 Hz, 1H), 4.04 (d, J=2.0 Hz, 1H), 1.66 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.2, 149.8, 137.7, 134.5, 133.2, 130.3, 129.1, 128.9, 128.0, 127.9, 127.4, 124.8, 124.7, 123.0, 119.0, 118.1, 116.9, 115.7, 86.5, 84.2, 74.7, 54.1, 28.4. MS (*m*/*z*): 399 (M^+-t-Boc), 334, 255, 202, 106, 91, 77. E.A. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60. Found: C, 69.75; H, 5.62.

Compound **4f**: pale yellow solid. Y=25%. Mp 102–104 °C. IR ($CHCl_3$): 1738, 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.84 (s, 1H), 7.50–7.15 (m, 14H), 6.83 (br s, 1H), 5.78 (s, 1H), 5.67 (dd, J_1=4.8 Hz, J_2=0.8 Hz, 1H), 4.41 (d, J=4.8 Hz, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 149.4, 137.7, 135.4, 134.2, 132.4, 129.6, 128.9, 128.8, 128.7, 127.6, 126.8, 125.2, 124.9, 122.9, 119.1, 115.4, 114.4, 84.3, 81.7, 70.0, 52.4, 28.1. MS (*m*/*z*): 456, 422, 399, 334, 255, 202, 186, 131, 107, 91, 77. E.A. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60. Found: C, 69.77; H, 5.62.

4.3. MW-mediated desulfurization reaction: preparation of 5a as general procedure (GP2)

5-Phenylsulfanyl-perhydrooxazinone **3a** (87 mg, 0.24 mmol), Nickel-Raney (0.6 g), and EtOH (6 mL) were mixed in a 30 mL reaction tube. The tube was sealed and positioned in the reaction cavity. The sealed reaction was irradiated at 150 W for 2 min. The reaction mixture was filtered on Celite, and the solvent evaporated. The crude reaction mixture was purified by flash chromatography (3:7 *EtOAc*/cyclohexane) to give the desired product **5a** in 80% yield.

4.3.1. (2*S,6*S**)-2,6-Diphenyl-[1,3]oxazinan-4-one 5a.** Pale yellow oil. IR (Nujol): 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.51 (m, 2H), 7.43–7.30 (m, 8H), 6.57 (br s, 1H), 5.92 (s, 1H), 5.02 (m, 1H), 2.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 139.6, 137.7, 129.9, 128.8, 128.7, 128.3, 126.9, 125.6, 85.7, 76.6, 39.1. MS (*m*/*z*): 253, 175, 147, 131, 118, 104, 78. E.A. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.96; H, 5.98.

4.3.2. (2*R,6*S**)-2,6-Diphenyl-[1,3]oxazinan-4-one 6a.** The crude reaction mixture obtained from 5-phenylsulfanyl-perhydrooxazinone **4a**, according to GP2, was subjected to a short column chromatography (3:7 *EtOAc*/cyclohexane) to give **6a** in 92% overall yield.

Pale yellow oil. IR (Nujol): 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.60–7.30 (m, 10H), 6.54 (br s, 1H), 5.95 (s, 1H), 5.05 (dd, 1H, J_1=7.2 Hz, J_2=5.8 Hz), 2.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.6, 139.2, 138.4, 129.2, 128.7, 128.6, 128.3, 126.7, 126.1, 81.8, 70.2, 37.6. MS (*m*/*z*): 253, 175, 147, 131, 118, 104, 78. E.A. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.99; H, 5.60.

4.3.3. (2*S,6*S**)-Methyl 4-oxo-2,6-diphenyl-1,3-oxazinane-3-carboxylate 7a.** To a solution of **5a** (253 mg, 1.0 mmol) in THF (10 ml) at 0 °C was added LiHMDS (1 M in THF, 1.0 mmol, 1.0 ml). The reaction mixture was stirred for 20 min, then methyl chloroformate (8 mmol, 0.62 ml) was added. Stirring was maintained for 2 h at the same temperature. A saturated solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The organic phases were dried on Na_2SO_4 and concentrated in vacuum. The carbamate **7a** was obtained in quantitative yield and used as such for the next step.

Compound **7a**: pale yellow oil. IR (Nujol): 1731, 1702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–7.20 (m, 10H), 6.41 (s, 1H), 5.06 (dd, 1H, J_1=7.2 Hz, J_2=5.8 Hz), 3.67 (s, 3H), 2.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.4, 152.8, 138.4, 138.2, 129.3, 128.5, 128.4, 128.3, 126.8, 125.5, 89.5, 75.2, 53.5, 41.5. MS (*m*/*z*): 311, 234, 223. E.A. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 70.83; H, 5.61.

4.3.4. (2*R,6*R**)-Methyl 4-oxo-2,6-diphenyl-1,3-oxazinane-3-carboxylate 8a.** The crude reaction mixture obtained from product **6a** according to the procedure used for **7a** gave **8a** in quantitative yield, which was used as such for the next step.

Compound **8a**: pale yellow oil. IR (Nujol): 1731, 1702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–7.20 (m, 10H), 6.96 (s, 1H), 4.83 (m, 1H), 3.91 (s, 3H), 2.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.4, 153.0, 139.4, 137.3, 129.13, 128.9, 128.7, 128.4, 126.5, 125.6, 86.1, 69.7, 54.1, 40.9. MS (*m*/*z*): 311, 234, 223. E.A. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 70.83; H, 5.61.

4.3.5. Procedure for the preparation of aminol 10a.

4.3.5.1. Step 1: 3-(*N*-benzyl-*N*-methylamino)-1-phenyl-propan-1-ol 9a. Carbamate **7a** and/or **8a** (1 mmol) were dissolved in anhydrous Et_2O (10 mL) at 0 °C. Lithium aluminum hydride (LAH, 1 M in Et_2O, 4 mmol) was added and the mixture was stirred for 2 h. NaOH (10 mL, 5 N) was added and the aqueous phase was washed with ethyl acetate. The extracts were treated with HCl 1 N; aqueous phase was neutralized with NaOH 5 N (pH=10–12) and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent evaporated. Product **9a** so obtained was used without purification for the next step of the synthesis.

Pale yellow oil. IR (Nujol): 3243, 2946, 2843, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.0–7.6 (m, 10H), 4.97 (dd, J_1=3.9 Hz, J_2=7.5 Hz, 1H), 3.70 (d, J=12.7 Hz, 1H), 3.53 (d, J=12.7 Hz, 1H), 2.87 (m, 1H), 2.66 (m, 1H), 2.32 (s, 3H), 1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=144.8, 137.6, 129.0, 128.1, 128.0, 127.2, 126.7, 125.4, 75.4, 62.6, 56.2, 41.6, 34.4. MS (*m*/*z*): 255, 134, 120, 91. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 80.01; H, 8.31.

4.3.5.2. Step 2: hydrogenolysis of 9a. Hydrogenolysis of compound **9a** according to literature procedure furnished aminol **10a** in 78% yield. Spectra are just similar to the literature data.[50]

4.4. Desulfurization reaction by Al/$HgCl_2$ amalgam: preparation of 5b as general procedure (GP3)

Aluminum (4.0 g) and 50 mL of a solution of $HgCl_2$ (1% in H_2O) were stirred for 1 min, the mixture was decanted and the residue was washed with water. The amalgam so prepared was added to a solution of compound **3b** (335 mg, 0.9 mmol) in *i*-PrOH (50 ml) under inert atmosphere. The reaction was stirred overnight until the disappearance of starting materials (TLC test). The mixture was filtered through Celite and the solvent was removed in vacuo. Product **5b** so obtained was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **5b** after purification by a short flash chromatography on silica gel (5:3:2 CH_2Cl_2/cyclohexane/*EtOAc*).

4.4.1. (2*S,6*S**)-2-Phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 5b.** Pale yellow oil. IR ($CHCl_3$): 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–6.95 (m, 8H), 6.37 (br s, 1H), 5.93 (s, 1H), 5.27 (dd, J_1=4.0 Hz, J_2=11.2 Hz, 1H), 2.95 (dd, J_1=11.2 Hz, J_2=17.2 Hz, 1H), 2.86 (dd, J_1=4.0 Hz, J_2=11.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.2, 142.1, 137.3, 130.1, 128.9, 126.9, 126.7, 125.9, 125.0, 85.7, 72.7, 38.9. MS (*m*/*z*): 259, 181, 154, 147, 137, 118, 106, 85, 77. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05. Found: C, 64.96; H, 5.06.

4.4.2. (2*S,6*S**)-*N*-Methyl-2-phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 7b.** To a solution of crude **5b** (0.9 mmol) in THF (10 mL) at 0 °C was added LHMDSA (1 M in THF, 0.9 mL). The reaction was stirred for 20 min, MeI (0.45 mL, 7.2 mmol) was added and the solution warmed to room temperature. Stirring was maintained for 1.5 h at the same temperature. A saturated solution of NH_4Cl was added, the organic solvent removed in vacuo, and the obtained aqueous solution extracted with *EtOAc*. The organic phases were collected, dried on Na_2SO_4, and concentrated in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with CH_2Cl_2/cyclohexane/*EtOAc* 50/30/20. Compound **7b** was obtained in 55% overall yield calculated from product **3b**.

Pale yellow oil. IR ($CHCl_3$): 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.4 (m, 5H), 7.29 (dd, J_1=1.2 Hz, J_2=5.2 Hz, 1H), 7.05 (dd, J_1=1.2 Hz, J_2=4.4 Hz, 1H), 6.97 (dd, J_1=4.4 Hz, J_2=5.2 Hz, 1H), 5.78 (s, 1H), 5.23 (dd, J_1=2.8 Hz, J_2=12.0 Hz, 1H), 3.05 (dd, J_1=12.0 Hz, J_2=16.8 Hz, 1H), 2.90 (dd, J_1=2.8 Hz, J_2=16.8 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.1, 142.0, 136.9, 129.8, 128.8, 127.6, 126.7, 125.9, 125.0, 91.0, 71.9, 39.8, 29.8. MS (*m*/*z*): 273, 259, 196, 167, 137, 118, 110, 91, 77. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53. Found: C, 65.81; H, 5.52.

4.4.3. Synthesis of (2*R,6*S**)-2-phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 6b.** Product **6b**, obtained from **4b** according to GP3, was used for the methylation step without any purification. Identification was performed on an aliquot of the crude reaction mixture prior to purification by a short flash chromatography on silica gel (5:3:2 CH_2Cl_2/cyclohexane/*EtOAc*).

Pale yellow oil. IR ($CHCl_3$): 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.00 (m, 8H), 6.72 (br s, 1H), 5.84 (s, 1H), 5.34 (t, J=6.0 Hz, 1H), 2.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.5, 142.0, 137.8, 129.6, 128.9, 126.9, 126.8, 126.5, 125.8, 81.0, 67.8, 37.0. MS (*m*/*z*): 259, 181, 154, 147, 137, 118, 106, 85, 77. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05. Found: C, 65.01; H, 5.07.

4.4.4. Synthesis of (2*R,6*S**)-*N*-methyl-2-phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 8b.** Crude **6b** was methylated, following the procedure used for **7b**, to give **8b**, after a short column chromatography (CH_2Cl_2/cyclohexane/*EtOAc* 50/30/20) in 58% overall yield calculated from product **4b**.

Pale yellow oil. IR ($CHCl_3$): 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.42 (m, 3H), 7.37 (d, J=2.0 Hz, 2H), 7.29 (dd, J_1=1.6 Hz, J_2=5.2 Hz, 1H), 6.95 (dd, J_1=3.2 Hz, J_2=5.2 Hz, 1H), 6.90 (m, 1H), 6.72 (br s, 1H), 5.78 (s, 1H), 5.12 (dd, J_1=6.0 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 2H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.6, 142.1, 136.4, 129.5, 128.6, 127.4, 126.7, 125.94, 125.13, 87.6, 66.6, 38.3, 31.1. MS (*m*/*z*): 273, 196, 188, 168, 137, 118, 110, 97, 77. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53. Found: C, 68.82; H, 5.51.

4.4.5. Synthesis of aminol *rac*-11b. Ph_2SiH_2 (0.46 mL, 2.5 mmol) and $RhH(CO)(PPh_3)_3$ (1%) were added to a solution of **7b** or **8b** (273 mg, 1.0 mmol) in THF (10 mL) at room temperature and the stirring maintained for 15 h. Disappearance of starting material was verified by TLC (CH_2Cl_2/cyclohexane/*EtOAc* 50/30/20). Aqueous HCl (1 M, 2.50 mL) was added to the crude reaction mixture and the stirring maintained at the same temperature for 4 h. The organic solvent was removed in vacuo and the obtained aqueous

solution extracted with Et_2O. The aqueous phase was basified with NH_4OH (pH=10) and then extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4 and the solvent evaporated.

Compound *rac*-**11b** was obtained in 95% yield calculated from product **7b**. Spectral data are identical to the product obtained from **19b** or **20b** (see below).

4.5. General procedure (GP5) for the preparation of 1,3-oxazinan-4-ones 13a–13e and 14a–14e

Azadiene **1d** (2 mmol), prepared according to literature from (2*S*)-triisopropylsilyloxy-propanal and 2-(phenylthio)acetyl chloride[28] **5**, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at −78 °C. Aldehyde **2** (1 mmol) in methylene chloride (2 mL) was added followed by a slow addition of BF_3 etherate (1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight while the temperature was allowed to reach room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuum. The reaction mixture was purified by flash chromatography on silica gel. 5-Phenylthio-perhydrooxazin-4ones **13a–13e** and **14a–14e** were isolated in combined yields and diastereomeric ratios reported in Table 2.

4.5.1. (2*R*,5*R*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 13a; (2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 14a. The crude reaction mixture obtained from azadiene **1f** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP5 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **13a** and **14a** in 50/50 diastereomeric ratio and 81% overall yield.

Compound **13a**: colorless oil. Y=41%. $[\alpha]_D^{20}$ 13.0 (*c* 0.7, $CHCl_3$). IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.05 (m, 10H), 6.22 (br s, 1H), 5.25 (d, *J*=2.0 Hz, 1H), 5.08 (d, *J*=2.8 Hz, 1H), 4.23 (m, 1H), 3.69 (d, *J*=2.8 Hz, 1H), 1.31 (d, *J*=7.2 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 136.7, 135.0, 132.8, 128.7, 128.0, 127.9, 127.6, 126.0, 85.3, 77.8, 68.8, 56.3, 18.0, 17.9, 15.9, 12.1. MS (*m*/*z*): 486, 442, 399, 379, 336, 239, 211, 188, 135, 77. E.A. Calcd for $C_{27}H_{39}NO_3SSi$: C, 66.76; H, 8.09; N, 2.88. Found: C, 66.86; H, 8.11.

Compound **14a**: colorless oil. Y=40%. $[\alpha]_D^{20}$ −41.5 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.07 (m, 10H), 6.35 (br s, 1H), 5.22 (d, *J*=2.4 Hz, 1H), 4.58 (d, *J*=8.0 Hz, 1H), 3.77 (m, 1H), 3.76 (d, *J*=2.4 Hz, 1H), 1.35 (d, *J*=5.6 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.2, 145.4, 137.0, 133.7, 128.9, 128.6, 128.2, 127.8, 125.7, 87.6, 78.0, 71.5, 55.2, 19.5, 18.1, 18.0, 12.6. MS (*m*/*z*): 486, 442, 379, 336, 284, 239, 211, 188, 135, 77. E.A. Calcd for $C_{27}H_{39}NO_3SSi$: C, 66.76; H, 8.09; N, 2.88. Found: C, 66.82; H, 8.10.

4.5.2. (2*R*,5*R*,6*R*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 13b; (2*S*,5*S*,6*S*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 14b. The crude reaction mixture obtained from azadiene **1d** (2 mmol) and 2-thiophenecarboxaldehyde (0.093 mL, 1 mmol) according to GP5 was subjected to column chromatography (2:8 *EtOAc*/cyclohexane) to give **13b** and **14b** in 60/40 diastereomeric ratio and 90% overall yield.

Compound **13b**: pale yellow oil. Y=54%. $[\alpha]_D^{20}$ +33.5 (*c* 2.9, $CHCl_3$). IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.36 (m, 3H), 7.20 (m, 3H), 7.01 (m, 2H), 6.20 (br s, 1H, NH), 5.46 (d, *J*=2.0 Hz, 1H), 5.09 (d, *J*=3.6 Hz, 1H), 4.19 (dq, J_1=3.6 Hz, J_2=6.0 Hz, 1H), 3.71 (d, *J*=2.0 Hz, 1H), 1.26 (d, *J*=6.0 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.80, 139.61, 135.80, 132.32, 128.84, 127.60, 126.28, 126.03, 125.52, 85.51, 75.69, 68.72, 56.16, 18.02, 15.88, 12.14. MS (*m*/*z*): 492, 448, 379, 336, 187. Anal. Calcd for $C_{25}H_{37}NO_3S_2Si$: C, 61.06; H, 7.58. Found: C, 61.20; H, 7.63.

Compound **14b**: pale yellow oil. Y=36%. $[\alpha]_D^{20}$ −58.6 (*c* 2.5, $CHCl_3$). IR ($CHCl_3$): 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.42–7.20 (m, 6H), 7.02–6.98 (m, 2H), 6.33 (br s, 1H, NH), 5.41 (dd, J_1=1.2 Hz, J_2=2.4 Hz, 1H), 4.60 (d, *J*=8.0 Hz, 1H), 3.77 (d, *J*=2.4 Hz, 1H), 3.68 (m, 1H), 1.31 (d, *J*=6.4 Hz, 3H), 1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.68, 139.66, 134.16, 133.56, 128.71, 127.96, 126.51, 125.54, 124.75, 87.66, 76.07, 71.35, 55.16, 19.43, 18.12, 12.58. MS (*m*/*z*): 491, 446, 379, 336, 217, 186. Anal. Calcd for $C_{25}H_{37}NO_3S_2Si$: C, 61.06; H, 7.58. Found: C, 61.18; H, 7.60.

4.5.3. (2*R*,5*R*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-methyl-5-(phenylthio)-[1,3]oxazinan-4-one 13c; (2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-methyl-5-(phenylthio)-[1,3]oxazinan-4-one 14c. The crude reaction mixture obtained from azadiene **1f** (2 mmol) and acetaldehyde (0.056 mL, 1 mmol) according to GP5 was subjected to column chromatography (2:8 *EtOAc*/cyclohexane) to give **13c** and **14c** in 50/50 diastereomeric ratio and 32% overall yield.

Compound **13c**: pale yellow oil. Y=16%. $[\alpha]_D^{20}$ 40.0 (*c* 2.1, $CHCl_3$). IR ($CHCl_3$): 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (m, 2H), 7.40–7.18 (m, 3H), 6.10 (br s, 1H), 4.90 (d, *J*=3.2 Hz, 1H), 4.20 (dq, J_1=6.0 Hz, J_2=1.8 Hz, 1H), 4.06 (dq, J_1=6.4 Hz, J_2=3.2 Hz, 1H), 3.46 (d, *J*=1.8 Hz, 1H), 1.50 (d, *J*=6.0 Hz, 3H), 1.11 (d, *J*=6.4 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.4, 135.6, 132.4, 129.0, 127.5, 85.4, 73.2, 68.8, 55.1, 18.0, 17.9, 15.7, 12.1. MS (*m*/*z*): 423, 408, 380, 362, 336, 223, 187, 149, 77. E.A. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80; N, 3.31. Found: C, 62.40; H, 8.83.

Compound **14c**: pale yellow oil. Y=16%. $[\alpha]_D^{20}$ −40.7 (*c* 1.35, $CHCl_3$). IR ($CHCl_3$): 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (m, 2H), 7.25 (m, 3H), 6.25 (br s, 1H), 4.39 (d, *J*=7.2 Hz, 1H), 4.14 (dq, J_1=6.4 Hz, J_2=2.4 Hz, 1H), 3.50 (m, 1H), 3.45 (d, *J*=2.4 Hz, 1H), 1.50 (d, *J*=6.4 Hz, 3H), 1.21 (d, *J*=6.0 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.3, 134.5, 133.4, 128.8, 127.7, 87.5, 73.4, 71.3, 54.5, 19.3, 18.1, 18.0, 12.6. MS (*m*/*z*): 423, 408, 380, 362, 336, 222, 186, 149, 77. E.A. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80; N, 3.31. Found: C, 62.42; H, 8.84.

4.5.4. (2*R*,5*R*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(naphthalen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 13d; (2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(naphthalen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 14d. The crude reaction mixture obtained from azadiene **1f** (2 mmol) and 2-naphthaldehyde (156 mg, 1 mmol) according to GP5 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **13d** and **14d** in 50/50 diastereomeric ratio and 41% overall yield.

Compound **13d**: pale yellow oil. Y=20%. $[\alpha]_D^{20}$ −39.7 (*c* 1.40, $CHCl_3$). IR ($CHCl_3$): 1678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.82 (m, 5H), 7.50 (m, 2H), 7.38 (m, 1H), 7.05 (m, 5H), 6.26 (br s, 1H), 5.41 (d, *J*=2.6 Hz, 1H), 5.15 (d, *J*=3.6 Hz, 1H), 4.29 (dq, J_1=6.4 Hz, J_2=3.6 Hz, 1H), 3.83 (d, *J*=2.6 Hz, 1H), 1.36 (d, *J*=6.4 Hz, 3H), 1.08 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 134.8, 134.1, 132.9, 132.8, 132.7, 128.6, 128.1, 127.8, 127.7, 127.6, 126.2, 126.1, 125.2, 123.4, 85.5, 78.0, 68.8, 56.0, 18.1, 18.0, 16.0, 12.1. MS (*m*/*z*): 535, 379, 336, 289, 261, 187. E.A. Calcd for $C_{31}H_{41}NO_3SSi$: C, 69.49; H, 7.71; N, 2.61. Found: C, 69.63; H, 7.73.

Compound **14d**: pale yellow oil. Y=21%. $[\alpha]_D^{20}$ −14.2 (*c* 1.70, $CHCl_3$). IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.85 (m, 5H), 7.55 (m, 2H), 7.38 (m, 1H), 7.22–7.05 (m, 5H), 6.42 (br s, 1H), 5.37 (d, *J*=2.2 Hz, 1H), 4.65 (d, *J*=7.6 Hz, 1H), 3.90 (d, *J*=2.2 Hz, 1H), 3.85 (m, 1H), 1.43 (d, *J*=6.4 Hz, 3H), 1.12 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.1, 134.3, 134.1, 133.7, 132.9, 132.8, 128.5, 128.1, 127.9, 127.8, 127.7, 127.6, 126.2, 126.1, 124.9, 123.2, 87.6, 78.2, 71.5, 55.0, 19.6, 18.1, 18.0, 12.6. MS (*m*/*z*): 535, 379, 336, 289, 261, 187. E.A. Calcd for $C_{31}H_{41}NO_3SSi$: C, 69.49; H, 7.71; N, 2.61. Found: C, 69.62; H, 7.71.

4.5.5. *tert*-Butyl-3-[(2*R*,5*R*,6*S*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-4-oxo-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 13e; *tert*-butyl-3-[(2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-4-oxo-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 14e. The crude reaction mixture obtained from azadiene **1d** (2 mmol) and *tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (245 mg, 1 mmol) according to GP2 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **13e** and **14e** in 63/37 diastereomeric ratio and 55% overall yield.

Compound **13e**: pale yellow oil. Y=35%. $[\alpha]_D^{20}$ +24 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 1738, 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.70 (s, 1H), 7.42–6.98 (m, 9H), 6.23 (br s, 1H), 5.46 (dd, J_1=2.2 Hz, J_2=1.2 Hz, 1H), 5.14 (d, *J*=3.2 Hz, 1H), 4.23 (dq, J_1=3.2 Hz, J_2=6.4 Hz, 1H), 3.92 (d, *J*=2.2 Hz, 1H), 1.68 (s, 9H), 1.30 (d, *J*=6.4 Hz, 3H), 1.08 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 149.5, 135.2, 134.4, 132.4, 128.5, 127.4, 124.6, 122.6, 118.6, 116.5, 115.4, 85.6, 83.9, 73.7, 68.8, 54.5, 28.1, 18.0, 17.9, 15.9, 12.1. MS (*m*/*z*): 567 (M^+−*t*-Bu), 525, 473, 379, 336, 230, 188, 77. E.A. Calcd for $C_{34}H_{50}N_2O_5SSi$: C, 65.14; H, 8.04; N, 4.47. Found: C, 65.41; H, 8.07.

Compound **14e**: pale yellow oil. Y=20%. $[\alpha]_D^{20}$ −42.8 (*c* 1.12, $CHCl_3$). IR ($CHCl_3$): 1737, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (s, 1H), 7.40–7.00 (m, 9H), 6.38 (br s, 1H), 5.41 (dd, J_1=2.4 Hz, J_2=1.2 Hz, 1H), 4.66 (d, *J*=7.2 Hz, 1H), 3.97 (d, *J*=2.4 Hz, 1H), 3.76 (m, 1H), 1.68 (s, 9H), 1.35 (d, *J*=6.4 Hz, 1H), 1.11 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.8, 149.6, 135.3, 133.8, 133.5, 132.5, 128.5, 127.8, 127.7, 124.6, 124.1, 122.7, 118.7, 116.8, 115.4, 87.8, 83.9, 74.1, 71.4, 53.6, 28.2, 19.5, 18.1, 18.0, 12.6. MS (*m*/*z*): 567 (M^+−*t*-Bu), 379, 336, 230, 188, 77. E.A. Calcd for $C_{34}H_{50}N_2O_5SSi$: C, 65.14; H, 8.04; N, 4.47. Found: C, 65.41; H, 8.07.

4.5.6. (2*R*,6*R*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-phenyl-[1,3]oxazinan-4-one 15a. The crude reaction mixture obtained from desulfurization of **13a**, according to GP2, was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **15a** in 98% overall yield. Spectroscopic data are superimposable with the published ones.[16]

4.5.7. (2*S*,6*S*,)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-phenyl-[1,3]oxazinan-4-one 16a. The crude product obtained from desulfurization of **14a** according to GP2 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **16a** in 90% overall yield. Spectra are just similar to literature data.[16]

4.5.8. (2*R*,6*R*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 15b. Product **15b**, obtained from **13b** according to GP3 was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **15b** after purification by flash chromatography on silica gel (2:8 *EtOAc*/cyclohexane).

Compound **15b**: pale yellow oil. $[\alpha]_D^{20}$ +1.9 (*c* 1.3, $CHCl_3$). IR ($CHCl_3$): 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.33 (d, *J*=5.2 Hz, 1H), 7.05 (d, *J*=3.6 Hz, 1H), 7.00 (dd, J_1=3.6 Hz, J_2=5.2 Hz, 1H), 6.38 (br s, 1H, NH), 5.11 (dd, J_1=6.0 Hz, J_2=9.6 Hz, 1H), 5.07 (d, *J* =3.6 Hz, 1H), 4.19 (dq, *J*=3.6 Hz, 6.4 Hz, 1H), 2.77 (m, 2H), 1.19 (d, *J*=6.4 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.18, 142.26, 126.77, 125.88, 124.88, 84.91, 72.13, 68.61, 39.66, 18.01, 15.69, 12.14. MS (*m*/*z*): 384, 340, 322, 202, 187. Anal. Calcd for $C_{19}H_{33}NO_3SSi$: C, 59.49; H, 8.67. Found: C, 60.68; H, 8.84.

4.5.9. (2*S*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 16b. Product **16b**, obtained from **14b** according to GP3 was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **16b** after purification by flash chromatography on silica gel (2:8 *EtOAc*/cyclohexane).

Compound **16b**: pale yellow oil. $[\alpha]_D^{20}$ −1.3 (*c* 2.1, $CHCl_3$). IR ($CHCl_3$): 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.32 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 6.99 (m, 2H), 6.53 (br s, NH), 5.05 (dd, J_1=6.4 Hz, J_2=8.4 Hz, 1H), 4.62 (d, *J*=6.4 Hz, 1H), 3.87 (m, 1H), 2.78 (m, 2H), 1.32 (d, *J*=6.0 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.52, 142.48, 126.70, 125.72, 124.36, 87.33, 72.32, 71.20, 38.95, 19.61, 18.06, 12.59. MS (*m*/*z*): 384, 340, 322, 202, 187. Anal. Calcd for $C_{19}H_{33}NO_3SSi$: C, 59.49; H, 8.67. Found: C, 60.68; H, 8.84.

4.5.10. (2*R*,6*R*)-*N*-Methyl-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 17b. Crude **15b** was methylated according to the procedure described for **7b**. After column chromatography (3:7 *EtOAc*/cyclohexane) **17b** was obtained in 65% overall yield calculated from product **13b**.

Compound **17b**: pale yellow oil. $[\alpha]_D^{20}$ +36.3 (*c* 2.7, $CHCl_3$). IR ($CHCl_3$): 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.31 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 7.00 (m, 2H), 5.03 (dd, J_1=5.6 Hz, J_2=8.4 Hz, 1H), 4.96 (d, J=0.8 Hz, 1H), 4.16 (dq, J_1=0.8 Hz, J_2=6.4 Hz, 1H), 3.06 (s, 3H), 2.76 (m, 2H), 1.17 (d, J=6.4 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.45, 142.42, 126.66, 125.63, 124.53, 90.83, 71.14, 70.44, 40.26, 29.65, 18.03, 16.70, 12.19. MS (*m*/*z*): 397, 354, 216, 137. Anal. Calcd for $C_{20}H_{35}NO_3SSi$: C, 60.41; H, 8.87. Found: C, 62.22; H, 9.14.

4.5.11. (2*S*,6*S*)-*N*-Methyl-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 18b. Crude **16b** was methylated according to the procedure described for **7b**. After column chromatography (3:7 *EtOAc*/cyclohexane) **18b** was obtained in 54% overall yield calculated from product **14b**.

Compound **18b**: pale yellow oil. $[\alpha]_D^{20}$ −67.4 (*c* 2.2, $CHCl_3$). IR ($CHCl_3$): 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.29 (dd, J_1=2.4 Hz, J_2=3.6 Hz, 1H), 6.98 (m, 2H), 5.02 (dd, J_1=3.6 Hz, J_2=10.0 Hz, 1H), 4.87 (d, J=2.4 Hz, 1H), 4.25 (dq, J_1=2.4 Hz, J_2=6.4 Hz, 1H), 2.94 (s, 3H), 2.81 (m, 2H), 1.19 (d, J=6.4 Hz, 3H), 1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.32, 142.87, 126.60, 125.48, 123.93, 90.84, 70.56, 68.87, 39.90, 29.43, 18.05, 16.57, 12.46. MS (*m*/*z*): 397, 354, 216, 137. Anal. Calcd for $C_{23}H_{41}NO_3SSi$: C, 62.82; H, 9.40. Found: C, 62.70; H, 9.38.

4.5.12. Synthesis of optically pure aminoalcohols (*R*)-11b and (*S*)-11b.

4.5.12.1. Step 1: (2*R*,6*R*)-[(*S*)-1-(triisopropylsilyloxy)ethyl]-3-methyl-6-(thiophen-2-yl)-1,3-oxazinane 19b. Ph_2SiH_2 (0.46 mL, 2.5 mmol) and $RhH(CO)(PPh_3)_3$ (1%) were added to a solution of **17b** (1.0 mmol) in THF (10 mL) at room temperature and the stirring maintained for 15 h. Disappearance of starting material was verified by TLC (CH_2Cl_2/cyclohexane/ethyl acetate 50/30/20). An aliquot of the solution was utilized for identification of the reduction product **19b** after removing the solvent and fast purification by a short flash chromatography eluting with cyclohexane/ethyl acetate 90:10 (saturated with NH_3 (g)).

Compound **19b**: pale yellow oil. $[\alpha]_D^{20}$ +35.7 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 2944, 2865, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 6.96 (m, 2H), 4.75 (dd, J_1=2.0 Hz, J_2=11.2 Hz, 1H), 3.99 (m, 1H), 3.92 (d, J=5.2 Hz, 1H), 3.06 (ddd, J_1=2.0 Hz, J_2=4.4 Hz, J_3=12.8 Hz, 1H), 2.88 (dt, J_1=2.8 Hz, J_2=12.8 Hz, 1H), 2.40 (s, 3H), 2.13 (m, 1H), 1.64 (m, 1H), 1.28 (d, J=6.8 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=145.80, 126.12, 124.35, 123.43, 97.06, 75.38, 70.46, 54.80, 36.62, 30.51, 18.78, 18.12, 12.27. MS (*m*/*z*): 383, 340, 235, 182, 123. Anal. Calcd for $C_{20}H_{37}NO_2SSi$: C, 62.61; H, 9.72. Found: C, 64.49; H, 9.99.

4.5.12.2. Step 2: (*R*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol (*R*)-11b. Aqueous HCl (1 M, 2.50 mL) was added to the crude THF solution of **19b** and the stirring maintained at the same temperature for 4 h. The organic solvent was removed in vacuo and the obtained aqueous solution extracted with Et_2O. The aqueous phase was basified with NH_4OH (pH=10) and then extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4 and the solvent evaporated.

The crude reaction mixture was subjected to column chromatography (ethyl acetate/MeOH/NH_4OH 80/19/1) to give (*S*)-**11b** in 68% overall yield calculated on **17b**.

Compound (*R*)-**11b**: pale yellow oil. $[\alpha]_D^{20}$ +13.7 (*c* 2.5, EtOH) [lit. $[\alpha]_D$ +13.3 (*c* 1.05, MeOH)[57]]. IR ($CHCl_3$): 3302, 3103, 2939, 2853, 2793, 1473, 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.20 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H), 6.96 (dd, J_1=4.0 Hz, J_2=5.2 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.19 (dd, J_1=2.8 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.64, 126.53, 123.70, 122.31, 71.92, 50.12, 36.73, 35.88. MS (*m*/*z*): 170, 153, 138, 127, 110, 97, 88. Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65. Found: C, 56.21; H, 7.66.

The same procedure was applied for the preparation of (*S*)-**11b** via reduction product **20b**. (*S*)-**11b** was obtained in 60% overall yield from **18b**.

4.5.12.3. Step 1: (2*S*,6*S*)-[(*S*)-1-(triisopropylsilyloxy)ethyl]-3-methyl-6-(thiophen-2-yl)-1,3-oxazinane 20b. Compound **20b**: pale yellow oil. $[\alpha]_D^{20}$ −17.8 (*c* 2.3, $CHCl_3$). IR ($CHCl_3$): 2944, 2865, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (dd, J_1=2.8 Hz, J_2=3.6 Hz, 1H), 6.96 (m, 2H), 4.73 (dd, J_1=2.8 Hz, J_2=11.6 Hz, 1H), 4.15 (m, 1H), 3.92 (d, J=4.0 Hz, 1H), 3.07 (ddd, J_1=1.6 Hz, J_2=4.4 Hz, J_3=14.4 Hz, 1H), 2.88 (dt, J_1=3.2 Hz, J_2=13.2 Hz, 1H), 2.37 (s, 3H), 2.13 (m, 1H), 1.71 (m, 1H), 1.28 (d, J=6.0 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.17, 126.24, 124.31, 122.89, 96.83, 75.32, 68.14, 54.65, 37.22, 29.81, 18.77, 18.17, 12.60. MS (*m*/*z*): 383, 340, 235, 182, 123. Anal. Calcd for $C_{20}H_{37}NO_2SSi$: C, 62.61; H, 9.72. Found: C, 64.49; H, 9.99.

4.5.12.4. Step 2: (*S*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol (*S*)-11b. $[\alpha]_D^{20}$ −12.0 (*c* 3.0, EtOH). IR ($CHCl_3$): 3302, 3103, 2939, 2853, 2793, 1473, 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.20 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H), 6.96 (dd, J_1=4.0 Hz, J_2=5.2 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.19 (dd, J_1=2.8 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.64, 126.53, 123.70, 122.31, 71.92, 50.12, 36.73, 35.88. MS (*m*/*z*): 170, 153, 138, 127, 110, 97, 88. Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65. Found: C, 57.23; H, 7.88.

Acknowledgements

A.D. thanks Farchemia (Treviglio, Italy) for financial support. M.P., recipient of a grant STM (CNR-Rome) is

indebted to CNR and to Prof. J. M. Aizpurua for the helpful discussions on this paper during his stay at University of Pais Vasco (UPV-EHU), San Sebastian, Spain.

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Nucleophilic aromatic substitutions on 4,5-dicyanopyridazine. Pyrrole and indole systems as carbon nucleophiles

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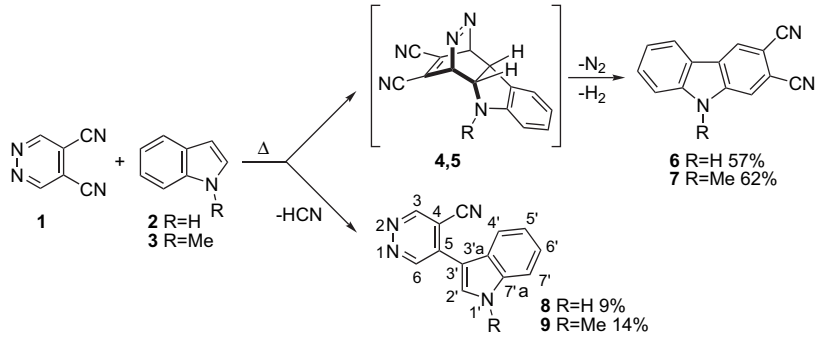
Received 20 July 2006; revised 20 September 2006; accepted 5 October 2006
Available online 31 October 2006

Abstract—4,5-Dicyanopyridazine was found to react with pyrrole and indole counterparts not only as heterocyclic azadiene in inverse electron-demand Hetero Diels–Alder reactions, as previously evidenced, but even as a very reactive heterocyclic electrophile at C-4 carbon, in formal S_NAr2 processes where a CN group acts as leaving group. In particular, operating in acetic acid as solvent, nucleophilic addition–elimination sequences allowed a facile access to pyrrolyl- and indolylpyridazines, through the corresponding 1,4-dihydropyridazine adducts.

1. Introduction

Electron-rich heterocycles with latent enamine functionalities, such as pyrrole and indole derivatives, have been widely exploited in the last 15 years as 2π electron components in inter- and intramolecular inverse electron-demand Hetero Diels–Alder (HDA) reactions with electron-deficient heteroaromatic azadienes and, in particular, the use of 1,2,4,5-tetrazines and 1,2,4-triazines as 4π electron counterparts allowed a facile access to complex indole alkaloids.[1] In this context, 1,2-diazines played a minor role, apart a few exceptions, such as tetramethyl pyridazine-3,4,5,6-tetracarboxylate,[2] polycondensed derivatives as 1,4-dicyanophthalazine[3] and 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]-pyridazine,[4] and indolylalkylpyridazines,[5] which were able to react in intramolecular HDA processes.

Nevertheless, we recently demonstrated that even 4,5-dicyanopyridazine (DCP) (**1**) was able to react as heterocyclic azadiene in intermolecular inverse electron-demand HDA reactions with pyrrole and indole dienophiles.[6] For instance, when DCP was allowed to react with indole (**2**) and *N*-methylindole (**3**) in a sealed tube, respectively, in xylene at 150 °C and chloroform at 110 °C, we succeeded into the isolation in quite satisfactory yields of dicyanocarbazoles **6** and **7** from the primary adducts **4** and **5**, through nitrogen extrusion and aromatization. Anyway, the above HDA reactions had to reckon with competitive S_NAr2 pathways, responsible for the formation of minor amounts of indolylpyridazines **8** and **9** (Scheme 1). Moreover, with great astonishment, attempts to favour the final aromatization step leading to carbazole derivatives by operating in $CHCl_3$ at 110 °C, in the presence of catalytic amounts of palladium on carbon,[7]



Scheme 1.

Keywords: 4,5-Dicyanopyridazine; Pyrrole and indole nucleophiles; Pyrrolylpyridazines and indolylpyridazines; 1,4-Dihydropyridazine adducts; Nucleophilic aromatic substitutions; Addition–elimination processes.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.007

gave rise to the preferential formation of compounds **8** and **9** isolated in 35% and 70% yields, respectively, instead of **6** and **7**.[6]

The displacement of the cyano group in heterocyclic compounds by nucleophiles is rare and only a few cases have been reported concerning 1,2,4-triazinecarbonitriles,[8] 4-quinazolinecarbonitriles,[8b] 1-methyl-4(1*H*)-quinazolinone-2-carbonitrile[9] and 5-arylpyrazine-2,3-dicarbonitriles.[10] In the pyridazine series, to our knowledge, the formal replacement of the nitrile function by phenyl group has been just observed in the reactions of phenylmagnesium chloride with 4-cyano-3(2*H*)-pyridazinone and tetrazolo[1,5-*b*]pyridazine-8-carbonitrile.[11]

On this ground, and with the aim to gain better insight into the possibility to perform nucleophilic aromatic substitutions on the dinitrile **1**, exploiting the reactivity of the cyano group as leaving group, we decided to reinvestigate the behaviour of DCP towards pyrrole and indole systems through suitable modifications of the experimental conditions.

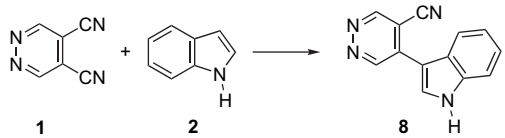
2. Results and discussion

First of all, to elucidate the role of palladium in the nucleophilic substitution pathway, we studied the reactivity of DCP with indole (**2**) (1–1.5 equiv) in the presence of different palladium catalysts, in different solvents and reaction conditions (Table 1). The observed results were quite unclear and the best one was that obtained employing 10% Pd/C in $CHCl_3$ at 50 °C, that afforded **8** in 90% yield (Table 1, entry 1).

At the same time, to investigate the solvent effect, we carried out the above reaction without palladium catalysts in different solvents. While DCP was absolutely inert towards indole in chloroform at 50 °C, operating in acetonitrile at the same temperature compound **8** was obtained as the predominant product (82% yield) after 17 days (Table 1, entries 7 and 8). Anyway, when dinitrile **1** was allowed to react with 1 equiv of **2** in glacial acetic acid for 9 days at room temperature, we succeeded into the isolation of **8** in 91% yield, as the sole reaction product (Table 1, entry 9).

These results clearly show the importance of the acidity in the nucleophilic substitution pathway, likely involving the LUMO of protonated DCP (E_{LUMO}=−5.883 eV) at lower energy with respect to the corresponding orbital of **1** (E_{LUMO}=0.067 eV).[12] Moreover, the acidic medium,

Table 1. Reactions of **1** with indole (**2**)

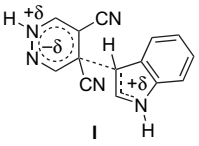


1 **2** **8**

Entry	Catalyst and co-reagents[a]	Solvent	Temp (°C)	Time (days)	**8** Yield[b] (%)
1	10% Pd/C	$CHCl_3$	50	11	90
2	10% Pd/C	MeCN	50	11	—
3	$Pd(PPh_3)_4$ (0.05)	MeCN	rt	11	—
4	$Pd(PPh_3)_2Cl_2$ (0.01), CuI (0.05), K_2CO_3 (1.5)	MeCN	rt	11	52
5	$Pd(OAc)_2$ (0.05), *p*-benzoquinone (1.5)	$CHCl_3$	rt	45	—
6	$Pd(OAc)_2$ (0.05), *p*-benzoquinone (1.5)	AcOH	rt	45	40
7	—	$CHCl_3$	50	12	—
8	—	MeCN	50	17	82
9	—	AcOH	rt	9	91

[a] Molar ratios with respect to **1** are reported in brackets.
[b] Isolated yields.

through protonation of the pyridazine nitrogen, seems to play a crucial role in the competition between HDA and S_NAr2 processes: the stabilization of transition state **I** can, in fact, justify the observed preference for the latter path (Fig. 1).

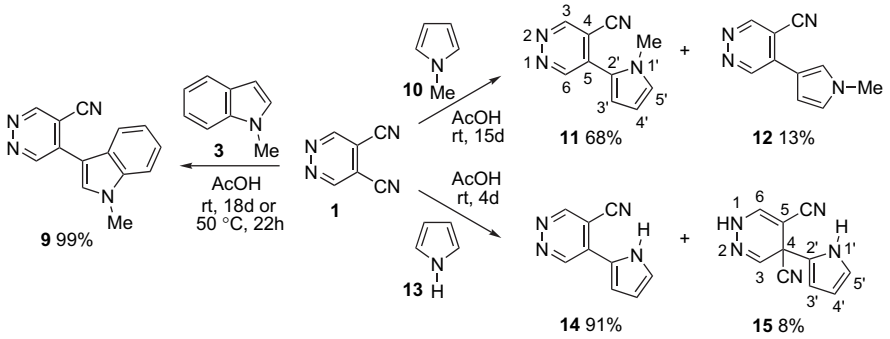


I

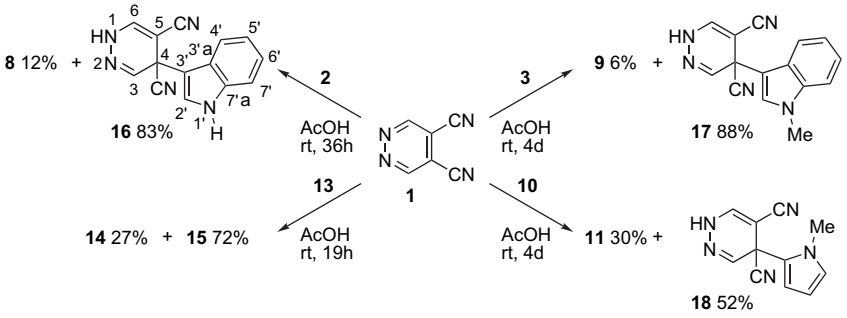
Figure 1.

This observation prompted us to study nucleophilic aromatic substitutions on DCP with indole and pyrrole systems as carbon nucleophiles, operating in glacial acetic acid as solvent.

When 4,5-dicyanopyridazine (**1**) was allowed to react with *N*-methylindole (**3**) (1–1.5 equiv) in AcOH at room temperature for 18 days, 4-cyano-5-(1-methyl-1*H*-indol-3-yl)pyridazine (**9**) was isolated in almost quantitative yield; the same result was achieved by heating at 50 °C for 22 h (Scheme 2). Treatment of **1** with 1.5 equiv of *N*-methylpyrrole (**10**) gave, after 15 days in acetic acid at room temperature, the regioisomeric pyrrolylpyridazines **11** and **12** in 68% and 13% yields,



Scheme 2.



Scheme 3.

respectively (Scheme 2).[13] Operating as above with the more reactive pyrrole (**13**), 4-cyano-5-(1*H*-pyrrol-2-yl)pyridazine (**14**) was isolated after 4 days in 91% yield, together with a minor amount (8%) of 4,5-dicyano-4-(1*H*-pyrrol-2-yl)-1,4-dihydropyridazine (**15**) (Scheme 2).

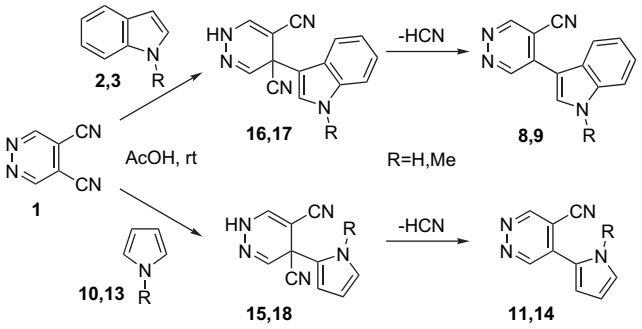
The formation of the 1,4-adduct **15** appeared really interesting to induce further investigations to elucidate the reaction mechanism.

Operating with 1 equiv of indole (**2**) for 36 h at room temperature, we succeeded in the isolation of compounds **8** and **16** in 12% and 83% yields, while *N*-methylindole (**3**) gave after 4 days in the same conditions **9** and **17** in 6% and 88% yields, respectively (Scheme 3).

Analogous results were obtained with stoichiometric amounts of pyrroles **10** and **13**: the former reacted with **1** to give, after 4 days at room temperature, derivatives **11** and **18** in 30% and 52% yields, while the latter afforded in 19 h compounds **14** and **15**, isolated in 27% and 72% yields, respectively (Scheme 3).

The 1,4-dihydropyridazine adducts **15–18** evolved slowly into pyridazine derivatives **8**, **9**, **11** and **14**, through HCN elimination, by simple stirring in AcOH at room temperature.[14]

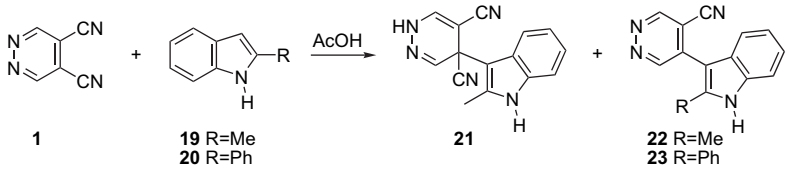
These data clearly show that the formal nucleophilic substitution products **8**, **9**, **11** and **14** are actually the fruit of a two-step process, involving nucleophilic addition and elimination reactions. Regioselective nucleophilic attacks of C-3 and C-2 carbons, respectively, of indole and pyrrole nucleophiles **2**, **3**, **10** and **13** on the strongly electrophilic C-4 carbon of DCP (or, more likely, protonated DCP) lead to intermediates **15–18** that, in turn, evolve into the aromatic species **8**, **9**, **11** and **14** through spontaneous HCN elimination (Scheme 4).



Scheme 4.

Then, to assess applications and limits of this new reactivity of DCP, we decided to study the behaviour of **1** towards different pyrrole and indole derivatives.

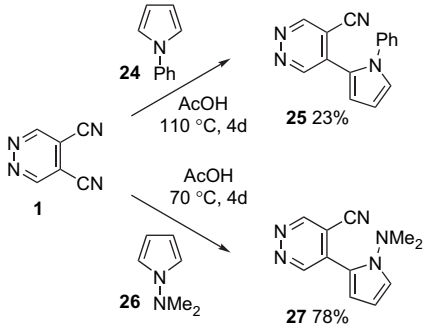
By treatment of **1** with 1 equiv of 2-methylindole (**19**) in acetic acid at room temperature for 16 h, we succeeded into the isolation of adduct **21** in 95% yield, together with a small amount of **22** (3%, Scheme 5, entry 1); on the other hand, operating at 50 °C with 1.5 equiv of **19** for 24 h, the only reaction product was the indolylpyridazine **22** (94%, Scheme 5, entry 2). The steric hindered 2-phenylindole (**20**) reacted with **1** more slowly and at higher temperature (72 h, 70 °C) to give the pyridazine derivative **23** in 88% yield (Scheme 5, entry 3).



entry	indole reagent (equiv)	temp (°C)	time	yield (%)
1	**19** (1)	rt	16 h	**21** 95, **22** 3
2	**19** (1.5)	50	24 h	**21** 0, **22** 94
3	**20** (1.5)	70	72 h	**23** 88

Scheme 5.

Reaction of the dinitrile **1** with the bulky *N*-phenylpyrrole (**24**) (1.5 equiv) was achieved in even more drastic conditions: after 4 days at 110 °C we succeeded into the isolation from a complex reaction mixture of the pyrrolylpyridazine **25** in 23% yield (Scheme 6).

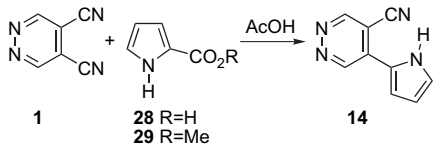


Scheme 6.

The electron-rich *N*-(dimethylamino)pyrrole (**26**) was absolutely inert towards DCP up to 70 °C in $CHCl_3$, in the presence of 10% Pd/C, or MeCN; when the above reaction was performed in AcOH at 70 °C for 4 days the 2-substituted pyrrole **27** was isolated in 78% yield (Scheme 6).

Treatment of DCP with an excess (3 equiv) of electron-deficient pyrrole or indole derivatives, such as *N*-(phenylsulfonyl)indole, *N*-acetylindole, indole-2-carboxylic acid, *N*-(phenylsulfonyl)pyrrole, methyl 1-pyrrolecarboxylate, in AcOH at 110 °C for several days, was absolutely unsuccessful leading to the recovery of unreacted starting materials.

Anyway, when compound **1** was allowed to react with pyrrole-2-carboxylic acid (**28**) (1.5 equiv) at 70 °C in acetic acid for 7 days, we isolated from a complex reaction mixture the (pyrrol-2-yl)pyridazine **14** in 42% yield, identical with the sample obtained from the reaction of **1** with pyrrole (**13**) (Scheme 7, entry 1). The formation of **14** was absolutely unexpected, and could not be ascribed to a decarboxylation process of the acid **28**, which itself proved to be perfectly stable under the reaction conditions. A possible mechanistic rationale could involve a first nucleophilic attack of the oxygen of the carboxylic group on the C-4 carbon of protonated DCP leading to the adduct **31**, through the intermediate **30**; at this level, the following aromatization of the pyridazine ring could be performed not only by HCN elimination but even through deprotonation and carbon–oxygen bond breaking with CO_2 extrusion. This latter possibility produces



entry	pyrrole reagent (equiv)	temp (°C)	time (days)	yield (%)
1	**28** (1.5)	70	7	**14** 42
2	**29** (1.5)	110	2	–

Scheme 7.

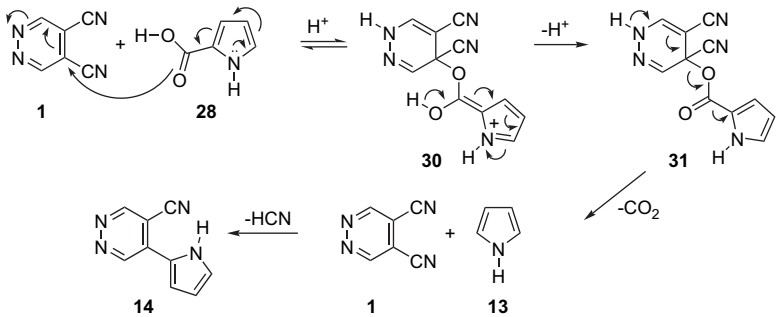
the dinitrile **1** and pyrrole **13**, able to react as previously observed to give **14** (Scheme 8).

This hypothesis could likely find support in the lack of reactivity observed for the corresponding methyl ester **29**, even in more drastic conditions (up to 110 °C, Scheme 7, entry 2). On the basis of the proposed mechanism, the first attack could yet be possible but the substitution of the OH with the OMe group certainly prevents the following evolution of intermediate **30** into **31**.

The structure of pyrrole derivatives **14**, **15**, **18**, **25** and **27**, as regioisomers substituted at position 2, was definitely assigned on the basis of the chemical shifts and multiplicities of the hydrogen atoms of the pyrrole moiety in the proton spectra, through comparison with the corresponding patterns of compounds **11** and **12**, previously characterized.[6]

3. Conclusions

These results clearly show a new facet of the reactivity of 4,5-dicyanopyridazine (**1**) towards pyrrole and indole systems, with interesting mechanistic and synthetic implications. In fact, DCP was not only able to react as heterocyclic azadiene in inverse electron-demand HDA reactions, but can also behave as a very reactive heterocyclic electrophile at C-4 carbon, in formal S_NAr2 processes where a CN group acts as leaving group. In particular, starting from the same reagents, it appears possible to modulate the reaction course by simple variation of the experimental settings. The same pyrrole and indole counterparts can indeed react with DCP as dienophiles at 110–150 °C in chloroform or xylene (sealed tube), leading to dicyano-indoles and –carbazoles, or as carbon nucleophiles, operating in acetic acid in milder



Scheme 8.

conditions (25–110 °C), to afford cyanopyrrolyl- and cyanoindolyl-pyridazines in satisfactory yields through addition–elimination processes.

The study of the general scope as well as synthetic applications of this new methodology is underway in our laboratory.

4. Experimental

4.1. General

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC and flash chromatographies (FC), respectively; petroleum ether (PE) employed for crystallizations and chromatographic workup refers to the fractions of bp 30–50 and 40–70 °C, respectively. IR spectra were recorded as KBr pellets with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 solutions with a Varian Mercuryplus 400 instrument, operating at 400 and 100 MHz, respectively. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer.

4.2. Reactions of DCP (1) with indole (2). General procedure

A mixture of **1** (0.065 g, 0.5 mmol), **2** (0.086 g, 0.75 mmol), Pd catalyst, and in some cases co-reagents, in the specified solvent (1.0 mL) was maintained at the reported temperature under magnetic stirring in a screw-capped tube (Pyrex N. 13). Unless otherwise stated, chromatographic purification (PE/EtOAc 1:1) of the crude product left by evaporation to dryness under reduced pressure afforded 4-cyano-5-(1*H*-indol-3-yl)pyridazine (**8**)[6] (R_f=0.32).

(A) Operating in chloroform at 50 °C in the presence of Pd/C (10%, 0.065 g), the indolylpyridazine **8** (0.099 g, 90%) was isolated as a yellow solid after 11 days.
(B) Performing the above reaction in the presence of $Pd(PPh_3)_2Cl_2$ (0.004 g, 0.006 mmol), CuI (0.005 g, 0.026 mmol) and K_2CO_3 (0.104 g, 0.75 mmol) in acetonitrile at room temperature for 11 days, compound **8** (0.057 g, 52%) was recovered through careful chromatographic resolution.
(C) The indolylpyridazine **8** (0.044 g, 40%) was isolated after 45 days at room temperature, working with $Pd(OAc)_2$ (0.006 g, 0.027 mmol) and *p*-benzoquinone (0.081 g, 0.75 mmol) in glacial acetic acid.
(D) When the above reaction was performed in MeCN at 50 °C for 17 days, without Pd catalysts, chromatographic purification afforded derivative **8** (0.090 g, 82%).
(E) Operating with a stoichiometric amount of **2** (0.059 g, 0.5 mmol) in glacial acetic acid at room temperature for 9 days, pyridazine **8** (0.100 g, 91%) was isolated by filtration from the reaction mixture and washing with dichloromethane.
(F) When the previous reaction was carried out in the same conditions for 36 h, chromatographic resolution (PE/EtOAc 2:1) afforded 4,5-dicyano-4-(1*H*-indol-3-yl)-1,4-dihydropyridazine (**16**) (0.103 g, 83%) as ivory prismatic crystals that yellows with gas evolution above 90 °C and melted at 285–286 °C (from ether) [Found: C, 67.78; H, 3.92; N, 28.62. $C_{14}H_9N_5$ requires C, 68.01; H, 3.67; N, 28.32]; R_f (PE/EtOAc 2:1) 0.30; ν_{max} 3323, 3065, 2247, 2209, 1636, 1612, 1453 cm^{-1}; δ_H 6.90 (s, 1H, H-3), 7.12 (ddd, *J*=8.0, 7.0, and 1.0 Hz, 1H, H-5′), 7.23 (ddd, *J*=8.1, 7.0, and 1.1 Hz, 1H, H-6′), 7.52–7.59 (m, 3H, H-2′, H-4′, H-7′), 7.62 (d, *J*=4.0 Hz, 1H, H-6), 10.46 (br s, 1H, 1-NH), 10.71 (br s, 1H, 1′-NH); δ_C 35.5, 77.8, 113.2, 113.4, 117.7, 118.3, 119.25, 120.8, 123.3, 124.4, 125.3, 132.8, 137.9, 138.6.

The following band gave compound **8** (R_f=0.19, 0.013 g, 12%).

4.3. Reactions of DCP (1) with indoles 3, 19, 20 and pyrroles 10, 13, 24, 26, 28 in glacial acetic acid. General procedure

A mixture of **1** (0.065 g, 0.5 mmol) and the indole or pyrrole derivative in glacial AcOH (0.5 mL) was maintained at the reported temperature under magnetic stirring in a screw-capped tube (Pyrex N. 13).

4.3.1. 4-Cyano-5-(1-methyl-1*H*-indol-3-yl)pyridazine (9) and 4,5-dicyano-4-(1-methyl-1*H*-indol-3-yl)-1,4-dihydropyridazine (17).

(A) Operating with *N*-methylindole (**3**) (0.098 g, 0.75 mmol) at 50 °C for 22 h, compound **9**[6] (R_f=0.33, 0.116 g, 99%) was isolated by chromatographic purification (PE/EtOAc 1:1).
(B) Evaporation to dryness of the mixture coming from reaction of DCP with a stoichiometric amount of *N*-methylindole (**3**) (0.066 g, 0.5 mmol) at room temperature for 18 days afforded exclusively indolylpyridazine **9** (0.116 g, 99%).
(C) Operating as above for 4 days, chromatographic resolution (PE/EtOAc 2:1) afforded the dihydropyridazine **17** (0.115 g, 88%) as yellow-orange needles: mp 211–212 °C (from ether) [Found: C, 68.59; H, 4.26; N, 26.70. $C_{15}H_{11}N_5$ requires C, 68.95; H, 4.24; N, 26.80]; R_f (PE/EtOAc 2:1) 0.26; ν_{max} 3333, 3051, 2934, 2241, 2206, 1628, 1608, 1475, 1445 cm^{-1}; δ_H 3.90 (s, 3H, NMe), 6.88 (s, 1H, H-3), 7.14 (t, *J*=7.9 Hz, 1H, H-5′), 7.28 (t, *J*=7.9 Hz, 1H, H-6′), 7.45 (s, 1H, H-2′), 7.49 (d, *J*=8.0 Hz, 1H, H-7′), 7.55 (d, *J*=8.0 Hz, 1H, H-4′), 7.62 (d, *J*=4.1 Hz, 1H, H-6), 10.49 (br s, 1H, NH); δ_C 33.0, 35.4, 77.7, 111.3, 112.4, 117.7, 118.2, 119.4, 120.8, 123.2, 125.6, 128.4, 132.7, 137.8, 139.1.

The slowest moving fractions yielded the pyridazine **9** (R_f=0.14, 0.007 g, 6%).

4.3.2. 4-Cyano-5-(1-methyl-1*H*-pyrrol-2-yl)pyridazine (11), 4-cyano-5-(1-methyl-1*H*-pyrrol-3-yl)pyridazine (12) and 4,5-dicyano-4-(1-methyl-1*H*-pyrrol-2-yl)-1,4-dihydropyridazine (18).

(A) Chromatographic purification (PE/EtOAc 1:1) of the residue coming from the reaction of **1** and *N*-methylpyrrole (**10**) (0.061 g, 0.056 mL, 0.75 mmol) at room temperature for 15 days allowed to isolate, respectively,

compounds **11**[6] (R_f=0.30, 0.063 g, 68%) and **12**[6] (R_f=0.20, 0.012 g, 13%).

(B) Operating with 1 equiv of **10** (0.041 g, 0.045 mL, 0.5 mmol) for 4 days, chromatographic purification (PE/EtOAc 1:1) gave the adduct **18** (0.055 g, 52%) that crystallized from ether in pale orange needles: mp 110–111 °C (dec) [Found: C, 62.40; H, 4.34; N, 32.87. $C_{11}H_9N_5$ requires C, 62.55; H, 4.29; N, 33.16]; R_f (PE/EtOAc 1:1) 0.42; ν_{max} 3368, 3136, 3105, 3085, 3046, 2977, 2948, 2242, 2210, 1636, 1611, 1465 cm^{-1}; δ_H 3.70 (s, 3H, NMe), 6.08 (dd, J=3.8 and 2.8 Hz, 1H, H-4′), 6.28 (dd, J=3.8 and 1.8 Hz, 1H, H-3′), 6.84 (dd, J=2.8 and 1.8 Hz, 1H, H-5′), 6.91 (s, 1H, H-3), 7.60 (s, 1H, H-6), 10.53 (br s, 1H, NH); δ_C 35.5, 36.7, 76.6, 107.9, 111.4, 117.3, 117.6, 127.0, 128.3, 131.3, 138.4.

The following band yielded compound **11** (R_f=0.30, 0.028 g, 30%).

4.3.3. 4-Cyano-5-(1*H*-pyrrol-2-yl)pyridazine (14) and 4,5-dicyano-4-(1*H*-pyrrol-2-yl)-1,4-dihydropyridazine (15).

(A) The crude product from the reaction of **1** and pyrrole (**13**) (0.050 g, 0.052 mL, 0.75 mmol) at room temperature for 4 days was resolved into two components by chromatographic purification (PE/EtOAc 1:1). The first band gave compound **15** (0.008 g, 8%) as pale yellow prismatic crystals: mp 209–210 °C (from ether) [Found: C, 60.64; H, 3.58; N, 35.37. $C_{10}H_7N_5$ requires C, 60.91; H, 3.58; N, 35.51]; R_f (PE/EtOAc 1:1) 0.31; ν_{max} 3307, 3136, 3099, 3042, 2248, 2217, 1636, 1616, 1499 cm^{-1}; δ_H 6.17 (m, 1H, H-4′), 6.27 (m, 1H, H-3′), 6.85 (s 1H, H-3), 6.94 (m, 1H, H-5′), 7.57 (s, 1H, H-6), 10.36 (br s, 1H, 1-NH), 10.45 (br s, 1H, 1′-NH); δ_C 36.4, 76.6, 108.8, 109.6, 117.5, 117.6, 122.2, 128.7, 131.6, 138.1.

The following one afforded derivative **14** (0.077 g, 91%) as pale yellow needles: mp 207–208 °C (from ether/acetone) [Found: C, 63.24; H, 3.66; N, 32.65. $C_9H_6N_4$ requires C, 63.52; H, 3.55; N, 32.92]; R_f (PE/EtOAc 1:1) 0.20; ν_{max} 3161, 3144, 3095, 2227, 1574, 1535, 1439, 1397 cm^{-1}; δ_H 6.47 (dd, J=4.0 and 2.5 Hz, 1H, H-4′), 7.35 (dd, J=2.5 and 1.4 Hz, 1H, H-5′), 7.48 (dd, J=4.0 and 1.4 Hz, 1H, H-3′), 9.24 (d, J=1.1 Hz, 1H, H-3), 9.69 (d, J=1.1 Hz, 1H, H-6), 11.32 (br s, 1H, NH); δ_C 103.8, 112.7, 116.8, 117.2, 123.9, 126.8, 131.3, 148.2, 152.2.

(B) Operating as above, chromatographic purification of the residue obtained by treatment of **1** with **13** (0.033 g, 0.034 mL, 0.5 mmol) at room temperature for 19 h led to derivatives **15** (R_f=0.31, 0.071 g, 72%) and **14** (R_f=0.20, 0.023 g, 27%), identical with the species previously isolated.

4.3.4. 4,5-Dicyano-4-(2-methyl-1*H*-indol-3-yl)-1,4-dihydropyridazine (21) and 4-cyano-5-(2-methyl-1*H*-indol-3-yl)pyridazine (22).

(A) When DCP was allowed to react with 2-methylindole (**19**) (0.098 g, 0.75 mmol) at 50 °C for 24 h, compound **22** (0.110 g, 94%) was isolated as deep yellow solid by filtration and washing with dichloromethane to remove unreacted **19**: mp 285–286 °C (from acetone) [Found: C, 71.57; H, 3.95; N, 24.21. $C_{14}H_{10}N_4$ requires C, 71.78; H, 4.30; N, 23.92]; ν_{max} 3146, 3050, 2993, 2227, 1564, 1538, 1461 cm^{-1}; δ_H (DMSO-d_6) 2.51 (s, 3H, Me), 7.12 (ddd, J=8.0, 7.0 and 1.0 Hz, 1H, H-5′), 7.19 (ddd, J=8.1, 7.1 and 1.0 Hz, 1H, H-6′), 7.45 (dt, J=8.0 and 1.0 Hz, 1H, H-7′), 7.53 (str d, J=7.9 Hz, 1H, H-4′), 9.57 (d, J=1.2 Hz, 1H, H-3), 9.61 (d, J=1.2 Hz, 1H, H-6), 11.96 (br s, 1H, NH); δ_C (DMSO-d_6) 13.15, 105.0, 110.3, 111.7, 116.1, 118.3, 120.7, 122.3, 126.0, 135.8, 136.8, 138.5, 151.7, 152.8.

(B) Chromatographic resolution (PE/EtOAc 2:1) of the crude coming from reaction of **1** and **19** (0.066 g, 0.5 mmol) at room temperature for 16 h afforded from the first band unreacted **1** (R_f=0.49, 0.003 g), and from the following one the adduct **21** (0.116 g, 89%) as pale yellow needles: mp 283–284 °C (from ether) [Found: C, 69.18; H, 4.56; N, 26.45. $C_{15}H_{11}N_5$ requires C, 68.95; H, 4.24; N, 26.80]; R_f (PE/EtOAc 2:1) 0.35; ν_{max} 3379, 3313, 3081, 2247, 2207, 1635, 1612, 1453 cm^{-1}; δ_H 2.62 (s, 3H, Me), 6.90 (s, 1H, H-3), 7.05 (ddd, J=8.1, 7.0 and 1.1 Hz, 1H, H-5′), 7.13 (ddd, J=8.1, 7.0 and 1.1 Hz, 1H, H-6′), 7.39 (dt, J=8.1 and 0.9 Hz, 1H, H-7′), 7.54 (d, J=4.1 Hz, 1H, H-6), 7.69 (str d, J=8.1 Hz, 1H, H-4′), 10.43 (br s, 1H, 1-NH), 10.52 (br s, 1H, 1′-NH); δ_C 12.75, 34.7, 78.4, 107.4, 111.9, 118.0, 118.7, 118.95, 120.5, 122.2, 127.1, 132.6, 134.7, 136.0, 137.1.

The slowest moving fractions gave pyridazine **22** (R_f=0.21, 0.004 g, 3%), identical with the sample previously isolated.

4.3.5. 4-Cyano-5-(2-phenyl-1*H*-indol-3-yl)pyridazine (23).

When DCP was allowed to react with 2-phenylindole (**20**) (0.145 g, 0.75 mmol) at 70 °C for 3 days, compound **23** (0.105 g, 71%) was isolated by filtration as yellow solid that, after crystallization from acetone, melted at 286–287 °C [Found: C, 76.75; H, 3.84; N, 19.25. $C_{19}H_{12}N_4$ requires C, 77.01; H, 4.08; N, 18.91]; ν_{max} 3102, 3023, 2232, 1558, 1491, 1451 cm^{-1}; δ_H (DMSO-d_6) 7.19 (ddd, J=8.1, 7.1 and 1.0 Hz, 1H, H-5′), 7.29 (ddd, J=8.2, 7.1 and 1.1 Hz, 1H, H-6′), 7.40–7.49 (m, 5H, Ph), 7.56–7.60 (m, 2H, H-4′ and H-7′), 9.35 (d, J=1.2 Hz, 1H, H-6), 9.54 (d, J=1.2 Hz, 1H, H-3), 12.36 (br s, 1H, NH); δ_C (DMSO-d_6) 104.4, 111.7, 112.5, 115.5, 118.9, 121.2, 123.4, 126.7, 128.75, 129.2, 129.4, 131.0, 136.6, 137.1, 139.6, 151.8, 153.4.

Chromatographic purification (PE/EtOAc 2:1) of the residue obtained by evaporation to dryness of the filtrate allowed to isolate a further amount of **23** (R_f=0.29, 0.025 g, 17%).

4.3.6. 4-Cyano-5-(1-phenyl-1*H*-pyrrol-2-yl)pyridazine (25).

Chromatographic workup (toluene/EtOAc 5:1) of the complex reaction mixture obtained by treatment of **1** with *N*-phenylpyrrole (**24**) (0.107 g, 0.75 mmol) at 110 °C for 4 days afforded compound **25** (0.028 g, 23%) as pale orange needles: mp 145–146 °C (from ether/PE) [Found: C, 73.45; H, 3.94; N, 22.45. $C_{15}H_{10}N_4$ requires C, 73.16; H, 4.09; N, 22.75]; R_f (toluene/EtOAc 5:1) 0.35; ν_{max} 3088, 2235, 1564, 1498, 1440 cm^{-1}; δ_H 6.57 (dd, J=3.9 and

2.8 Hz, 1H, H-4′), 7.19 (dd, J=3.9 and 1.6 Hz, 1H, H-3′), 7.34–7.37 (m, 2H, Ar-2H), 7.42 (dd, J=2.7 and 1.6 Hz, 1H, H-5′), 7.44–7.52 (m, 3H, Ar-3H), 8.71 (d, J=1.1 Hz, 1H, H-6), 9.35 (d, J=1.1 Hz, 1H, H-3); δ_C 109.3, 112.1, 116.1, 119.2, 124.5, 126.4, 128.8, 130.6, 130.8, 132.65, 140.0, 150.9, 152.1.

4.3.7. 4-Cyano-5-(1-dimethylamino-1*H*-pyrrol-2-yl)pyridazine (27). Chromatographic purification (PE/EtOAc 3:2) of the reaction crude obtained by treatment of **1** with 1-dimethylaminopyrrole (**26**) (0.083 g, 0.091 mL, 0.75 mmol) at 70 °C for 4 days afforded compound **27** (0.083 g, 78%) as pale yellow prismatic crystals: mp 95–96 °C (from ether) [Found: C, 61.63; H, 4.84; N, 33.15. $C_{11}H_{11}N_5$ requires C, 61.96; H, 5.20; N, 32.84]; R_f (PE/EtOAc 3:2) 0.28; ν_{max} 3109, 2959, 2864, 2829, 2227, 1553, 1450 cm^{-1}; δ_H 2.89 (s, 6H, NMe_2), 6.40 (dd, J=4.2 and 3.0 Hz, 1H, H-4′), 6.89 (dd, J=4.2 and 1.6 Hz, 1H, H-3′), 7.69 (dd, J=3.0 and 1.6 Hz, 1H, H-5′), 9.36 (d, J=1.2 Hz, 1H, H-3), 9.64 (d, J=1.2 Hz, 1H, H-6); δ_C 47.7, 108.8, 110.4, 113.65, 116.7, 121.5, 123.5, 131.6, 151.4, 152.1.

4.3.8. Reaction of 1 with pyrrol-2-carboxylic acid (28). When DCP was allowed to react with pyrrole derivative **28** (0.083 g, 0.75 mmol) at 70 °C for 7 days, compound **14** (R_f=0.20, 0.036 g, 42%) was isolated by chromatographic purification (PE/EtOAc 1:1).

Acknowledgements

Mrs. B. Innocenti and Mr. M. Passaponti are acknowledged for the analytical data. Authors thank the Ente Cassa di Risparmio di Firenze for the grant of the Varian Mercuryplus 400 instrument.

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13. For a previous syntheses of **11** and **12** from **1** and **10**, operating in the presence of Pd/C, see Ref. 6.
14. The same conversion was also observed in the solid state, even if more slowly.

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Tetrahedron 62 (2006) 12288–12296
Tetrahedron

5,6-Bis(dimethylamino)acenaphthylene as an activated alkene and 'proton sponge' in halogenation reactions

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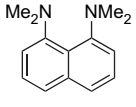
Received 10 July 2006; revised 19 September 2006; accepted 5 October 2006
Available online 27 October 2006

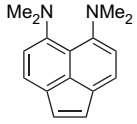
Abstract—It has been shown that 5,6-bis(dimethylamino)acenaphthylene in its reactions with X_2 (X=Cl, Br, I) and *N*-X-succinimides behaves simultaneously as an electron-rich alkene or arene and proton sponge. Thus, addition of bromine or iodine to the C(1)=C(2) bond is followed by immediate dehydrohalogenation leading to the formation of the corresponding 1(2)-(di)halogenoacenaphthylenes in good yields. Reaction with chlorine enables isolation of only 1,4,7-trichloro-5,6-bis(dimethylamino)acenaphthylene. With *N*-halosuccinimides, the halogenation is directed mainly by the steric bulk of the entering halogen and then by solvent polarity thus allowing the regioselective preparation of 1(2)- or 4(7)-(di)halides. Introduction of the third and fourth bromine atoms, but not chlorine, is accomplished by mono-N-demethylation. The pK_a values of some new derivatives of acenaphthene and acenaphthylene proton sponges were measured by competitive transprotonation ^{1}H NMR spectroscopy technique in DMSO. The X-ray molecular structures of 4,7-dichloro-5,6-bis(dimethylamino)acenaphthylene and its monoprotonated form are reported.

1. Introduction

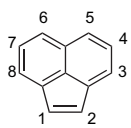
It is well known that 1,8-bis(dimethylamino)naphthalene ('proton sponge', **1**) simultaneously displays properties of a strong neutral organic base[1] and a very weak *N*-nucleophile.[2] At the same time, due to the pronounced electron-donating effect of two NMe_2 groups, the proton sponge is a very active *C*-nucleophile easily reacting with many electrophiles at positions 4(5) or 2(7).[2] Recently, we have described 5,6-bis(dimethylamino)acenaphthylene (**2**),[3] which as an alkene exhibits enhanced activity in [4+2]-cycloaddition reactions with reverse electronic demands.[4] Aside from an activated alkene, acenaphthylene **2** could also be considered as an arene and a proton sponge derivative. In view of this, it seemed rather intriguing to study its behaviour toward typical electrophiles and the scope of the present work is to report on halogenation reactions of **2**.



1



2



3

Keywords: 5,6-Bis(dimethylamino)acenaphthylene; Activated alkenes; Proton sponge; Halogenation; N-demethylation; Basicity; Molecular structure.
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doi:10.1016/j.tet.2006.10.008

2. Results and discussion

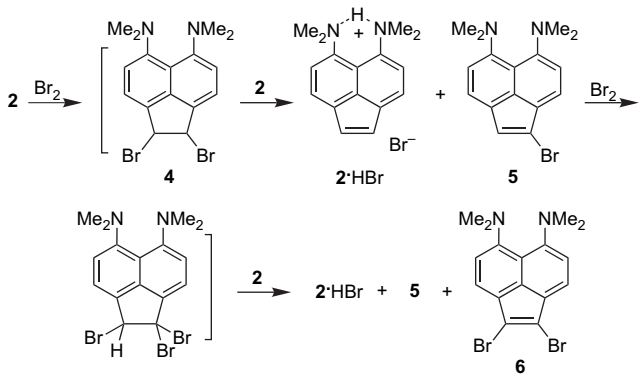
2.1. Bromination

It is known that parent acenaphthylene **3** readily adds 1 equiv of bromine to form 1,2-dibromide and derivatives of **3** with electron-releasing substituents in the naphthalene ring react even faster.[5–7] Though the reaction proceeds with low stereospecificity, it was noted that electron-withdrawing functions in the naphthalene moiety as well as polar solvents favour *trans*-addition.[7] From this, one can assume that reactivity of acenaphthylene sponge **2** toward Br_2 should be rather high. This is indeed the case but the results of bromination turned out to be quite specific.

It came to light that, instead of the expected dibromide **4**, proton sponge **2** yields only unsaturated monobromide **5** and dibromide **6** along with noticeable amounts of regenerated starting material (Scheme 1; Table 1).

Evidently, monobromide **5** is formed as a consequence of dehydrobromination of the initial addition product **4** by means of the starting compound **2** or **4** (cf. data on dehydrohalogenation of 1,2-dihalogenoacenaphthenes by alkali metal alcoholates or pyridine[8,9]). Repeated addition of Br_2 to **5** followed by dehydrobromination results in dibromide **6**.

As seen in Table 1, dibromide **6** predominates in polar protic media (AcOH), which promotes HBr loss. In contrast, monobromide **5** is accumulated in nonpolar solvent (CCl_4 or benzene), presumably because of the heterogeneous conditions.

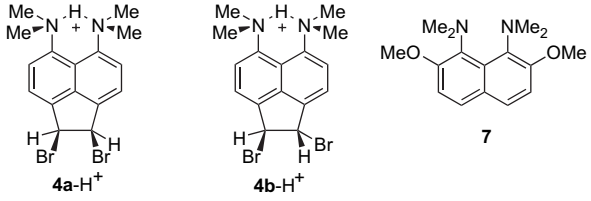


Scheme 1.

Table 1. Interaction of acenaphthylene **2** with molecular bromine

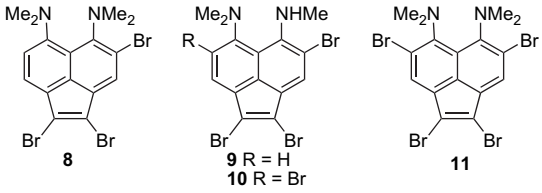
Br_2 (equiv)	T (°C)	Solvent	Reaction time (h)	Mode of addition	Isolated yields (%)			
					2	**5**	**6**	Tarring
0.5	22	CCl_4	1	$Br_2 \rightarrow$ **2**	55	29	4	12
1	22	CCl_4	1	$Br_2 \rightarrow$ **2**	31	37	16	16
1	22	CCl_4	1	**2** $\rightarrow Br_2$	40	30	20	10
1	0	C_6H_6	0.3	$Br_2 \rightarrow$ **2**	30	38	17	15
1	22	AcOH	1	$Br_2 \rightarrow$ **2**	30	20	40	10

To avoid the dehydrobromination reaction, we used the protonated form of compound **2** as starting material. As expected, action of 1 equiv of Br_2 on perchlorate **2**·$HClO_4$ in MeCN after work-up yielded monobromide **5** nearly in quantitative yield. Obviously, the primary addition product in this case is the salt **4**·$HClO_4$, which can be isolated after careful evaporation of acetonitrile. The ^{1}H NMR spectrum of **4**·$HClO_4$ is generally typical for symmetrical 4,5-disubstituted proton sponges and contains two doublets for the aromatic protons at δ 7.85 and 8.00 ppm along with two-proton singlet for the CH(Br)–CH(Br) bridge at 6.16 ppm. At the same time, at δ 3.13 and 3.15 ppm two doublets of equal intensity with $J_{NMe,NH}$=2.6 Hz are observed, indicating magnetic non-equivalence of two pairs of *N*-methyl groups. Clearly, in cations either *cis*-**4a** or *trans*-dibromide **4b**, two CH_3 groups are opposite to the bromine atoms, while the other two are closer to the bridge CH-protons. Unfortunately, these data cannot be assigned to certain isomers.



We further attempted to record the spectrum of the free base **4** immediately in the NMR ampoule after addition of strong base **7**[10] (1 equiv) to a solution of salt **4**·$HClO_4$ (1 equiv) in CD_3CN. However, as a result of very fast dehydrobromination, the final solution contained nothing but cations **5**-H^+ and **7**-H^+. The mechanism of this transformation deserves special investigation since the process may theoretically begin either with elimination of the NH-proton from cation **4**-H^+ followed by dehydrobromination of dibromide **4** (Scheme 2) or, alternatively, with E2-elimination inside the cation **4**-H^+ mediated by the base **7**.[10]

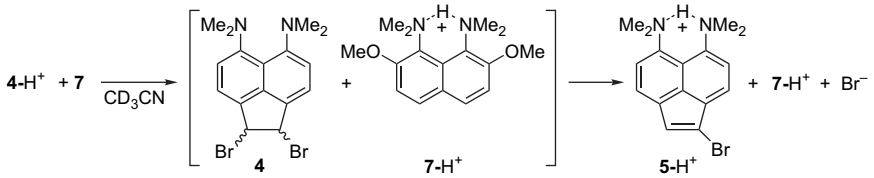
It is known that the proton sponge **1** is brominated selectively by NBS at positions 2 and 7.[11] We found that, unlike **1**, the acenaphthylene **2** under treatment with NBS in chloroform gives a complex mixture of inseparable products. On going from $CHCl_3$ to DMF, the process becomes more controllable and, apart from bromides **5** and **6**, allows the preparation of tri- and tetrabromo derivatives **8**–**10**. Some results of these experiments are collected in Table 2.



As can be seen (Table 2), the five-membered cycle is brominated first and the introduction of the third bromine atom into the naphthalene ring is accomplished by N-demethylation. In parallel with the bromination of acenaphthene, which proceeds in the NBS/DMF system at position 5 (in $CHCl_3$ or CCl_4, only the bridge protons are substituted[12]), we believe that the bromination of **2** under these conditions is realized via an electrophilic substitution pathway. The mechanism for the N-demethylation has been considered previously.[13] Lowering the temperature to −57 °C has practically no effect on the yields (see Table 2). All reactions

Table 2. Interaction of acenaphthylene **2** with NBS in DMF

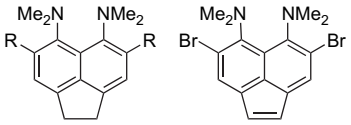
NBS (equiv)	Isolated products (%)					
	T (°C)	**5**	**6**	**8**	**9**	**10**
1	−15	10	9	—	—	—
2	−15	—	12	—	—	—
3	−15	—	4	5	4	—
4	−15	—	—	—	22	—
4	−57	—	—	—	24	—
5	−15	—	—	—	10	10
6	−15	—	—	—	8	13
10	−15	—	—	—	—	1



Scheme 2.

with NBS are characterized by strong tarring, and the compounds obtained are rather labile and prone to decompose when subjected to chromatography. Previously, we have managed to crystallize tribromide **9**, X-ray studies of which proved the functional group arrangement and revealed a very weak intramolecular hydrogen bond (IHB) of the NHN type.[14,15]

Prolonged heating of *N*-trimethyl substituted bromides **9** and **10** with excess of iodomethane followed by treatment with sodium carbonate leads to tetramethyl derivatives **8** and **11** in good yields.



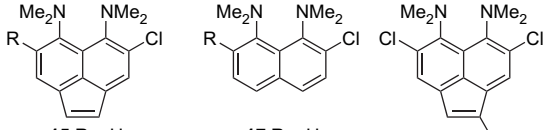
12 R = H
13 R = Br
14

Unlike acenaphthylene **2**, acenaphthene proton sponge **12**[3] under the action of NBS in $CHCl_3$ (even at low temperature) is almost completely turned into tar, which makes impossible the direct synthesis of *ortho*-bromides **13** and **14**. However, in DMF the tarring is hampered and apart from unreacted acenaphthene **12** (64%), the mono-**5** (14%) and dibromoacenaphthylenes **6** (22%) are formed with 2 equiv of NBS at −15 °C as judged by NMR spectroscopic analysis.

Interestingly, bromination of an equimolar mixture of acenaphthylenes **2** and **3** with 1 equiv of bromine in CCl_4 at room temperature gives no chance for the parent acenaphthylene **3**, which remains practically intact and the NMR spectroscopy (in DMSO-d_6) indicates that **2** turns into a mixture of **2** and **5** as hydrobromides.

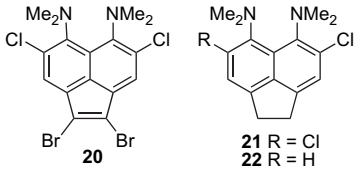
2.2. Chlorination

We have investigated the interaction of acenaphthylene **2** with either *N*-chlorosuccinimide (NCS) or 1-chlorobenzotriazole (CBT). The latter was used earlier for selective *ortho*-chlorination of compound **1**.[16] In contrast to **1**, acenaphthylene **2** reacts with CBT in chloroform giving complex mixture of products. However, in the case of NCS ($CHCl_3$ or DMF, −15 °C), depending on the amount of chlorinating agent (1 or 2 equiv), it is possible to prepare both mono-**15** and dichloride **16**. By analogy, proton sponge **1** reacts with NCS to form mono-**17** and dichlorides **18**. Using for the chlorination molecular chlorine in $CHCl_3$ at 20 °C or −15 °C resulted only in tarrification while on going from chloroform to acetic acid enabled us to isolate trichloride **19** as a single product (5–16% depending on the amount of Cl_2).



15 R = H
16 R = Cl
17 R = H
18 R = Cl
19

Similar to other 2,7-disubstituted derivatives of **1**,[10] dichloride **16** is very inert toward electrophiles that is caused by an almost perpendicular orientation of the NMe_2 group planes relatively the naphthalene π-system and, hence, low activation of the latter (see X-ray data below). For example, **16** does not undergo halogenation with NCS and NBS in chloroform at wide temperature conditions whereas sterically less hindered dibromide **6** reacts with 2 equiv of NCS in $CHCl_3$ to form mixed tetrahalide **20** in 89% yield.



20
21 R = Cl
22 R = H

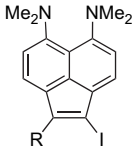
The only products, though in low yield (3–6%), that could be isolated after interaction of acenaphthene **12** with 2 equiv of NCS in $CHCl_3$ turned out to be chloroacenaphthylenes **15** and **16**.

Catalytic hydrogenation (Pd/C, H_2) of dichloride **16** in ethanol gave in near quantitative yield acenaphthene **21** with both the chlorine atoms intact. At the same time, monochloride **15**, taken as free base or perchlorate, readily undergoes protodechlorination (in MeOH, EtOH, EtOAc or THF), giving as a sole product acenaphthene **12**, but not the compound **22**. The reason for the lability of C–Cl bond is not clear in this case.

In contrast to the behaviour of **16**, catalytic hydrogenation of dibromide **6** in the presence of sodium carbonate quantitatively leads to acenaphthene **12**, and the reduction of polyhalide **20** ends up with dichloride **21** in high yield. Therefore, taking into account the possibility of easy oxidation of acenaphthene **12** back into acenaphthylene **2**,[3] the bromine atoms at position(s) 1(2) of **6**, **20** can be selectively removed.

2.3. Iodination

We have found that action of 2 equiv of *N*-iodosuccinimide (NIS) on acenaphthylene **2** even at low temperature ends up with strong tarring along with small fractions (4–8% depending on the solvent) of diiodide **23**. This can be isolated as a labile (especially on sorbents) orange crystalline compound.



23 R = I
24 R = H

Attempted synthesis of monoiodide **24** with 1 equiv of NIS in $CHCl_3$ failed; the only products that could be detected were diiodide **23** (2%) and the starting compound **2** (15%). Also, it was not possible to perform polyiodination of diamine **2** using 3 equiv of NIS in chloroform. However, employing molecular iodine as halogenating agent in AcOH allowed us to prepare iodides **23** and **24** in reasonable yield (Table 3).[17]

Table 3. Iodination of acenaphthylene **2** in different conditions

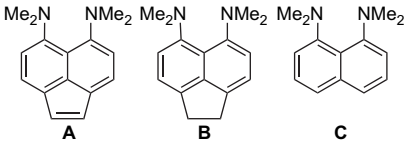
Reagent	Solvent	Equiv	T (°C)	Isolated products (%)	
				23	**24**
NIS	$CHCl_3$	1	−15	2	Traces
		2	−15	4	—
	THF	2	−15	6	—
	DMF	2	−15	8	—
I_2	AcOH	1	20	36	15
		2	20	40	—

As can be seen, acenaphthylene **2** reacts with iodinating agents both via electrophilic substitution and through electrophilic addition–elimination. The very fact of substitution in the five-membered core of acenaphthylene is of principal importance since only single cases of such transformations are known in the literature. Among them are radical nitration of acenaphthylene with dinitrogen tetroxide, leading to 1-nitro- and 1,2-dinitroacenaphthylenes in moderate yield,[18] and electrophilic substitution of trimethylsilyl groups in 1(2)-(bis)trimethylsilyl-acenaphthylenes.[19] The latter approach, in particular, gives 1-iodo- and 1,2-diiodoacenaphthylenes in good yield, although the trimethylsilyl-acenaphthylenes can be prepared from acenaphthylene in at least two steps.[20] The vast majority of other methods to synthesize 1(2)-(di)substituted acenaphthylenes in either case is based on addition–elimination or addition–oxidation sequence (see e.g., preparation of 1-fluoro-[21] and 1-methylthioacenaphthylenes[22]).

2.4. Basicity

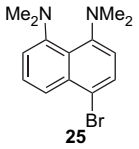
By the competitive transprotonation technique using ^1H NMR spectroscopy,[10] we have measured pK_a values of some synthesized halides and model bases (**1**, **2**, **12**, **18**, **25**) in DMSO. Evidently, the results collected in Table 4 provide not as much information as expected due to the absence of compounds with Cl and Br substituents at the same positions. Even so, it is noticeable that the Br atoms at positions 1 and 2 of the acenaphthylene system (compounds **5** and **6**, cf. also **1** and **25**) lower the basicity to a marked degree, and for the second substituent it is less expressed. On the other hand, the influence of Cl atoms at positions 4 and 7 is much less clear (compounds **15** and **16**). If the first substituent increases the basicity by 0.7 pK_a, the second one lowers it, although the overall basicity is slightly higher than that of unsubstituted **2**. The basicity of tetrahalide **20** (pK_a=3.0) seems to reflect superposition of the above tendencies and is similar to pyridine (pK_a=3.4, DMSO[26]). Interestingly, the influence of chlorine atoms placed in *ortho*-positions to the NMe_2 groups in naphthalene and acenaphthene systems is strictly opposite and decreases the basicity correspondingly by 0.7 and 1.0 pK_a (Table 4). The reason for these differences (repeatedly checked by us) is still unclear.

Table 4. Basicity constants, pK_a, of some synthesized and model compounds (DMSO, 22 °C)



Compound	Structure type	Substituents	pK_a[a]	Refs.
2	**A**	—	4.2	[b,c]
5	**A**	1-Br	2.4	[b]
6	**A**	1,2-Br_2	2.1	[b]
15	**A**	4-Cl	4.9	[b]
16	**A**	4,7-Cl_2	4.4	[b]
20	**A**	1,2-Br_2-4,7-Cl_2	3.0	[b]
12	**B**	—	7.4	[b,d]
21	**B**	4,7-Cl_2	6.4	[b]
1	**C**	—	7.5	23
25	**C**	4-Br	6.5	24
18	**C**	2,7-Cl_2	6.8	25

[a] Accuracy is ±0.05 pK_a.
[b] This work.
[c] This value was corrected in this work; previously reported value is 5.7, Ref. 3.
[d] Corrected in this work; 7.7 in Ref. 3.



25

2.5. General remarks on halogenation of 6

As in the case of other aromatic compounds with the double bond C=C in the side chain, acenaphthylene **2** reacts with molecular bromine, iodine and in known degrees with chlorine, forming addition products to the C(1)=C(2) bond. The cause of this is obvious: substitution in the naphthalene ring is energetically less favourable due to violation of the aromaticity in the intermediate σ-complex. Calculated heats of formation for model protic complexes illustrate this statement (Fig. 1). However, when acenaphthylene **2** is treated by less polarizable and more hard electrophiles such as *N*-halosuccinimides, the factors connected with steric influence and charge control seem to prevail. As shown in Figure 1, maximal negative charge in molecule **2** is localized at the C(4) and C(7) atoms. With this in mind, it is clear that the relatively small chlorine atom enters these sterically hindered positions much readily than more voluminous bromine and iodine do.

2.6. Molecular structure

Preceding X-ray studies of 2,7-disubstituted proton sponges, including dichloride **18**, have revealed that the buttressing effect of *ortho*-substituents causes a decrease in the N···N distance, flattening of the NMe_2 groups and rotating them strongly out of the naphthalene ring plane. To obtain information on how the C(1)=C(2) bridge in the acenaphthylene proton sponge influences the buttressing effect of the *ortho*-chlorine atoms, we have grown crystals of dichloride **16** and its perchlorate **16**·$HClO_4$ suitable for X-ray diffraction analysis. The results, presented in Fig. 2 and in Table 5, clearly demonstrate that in acenaphthylene proton sponge series, the buttressing effect is much more pronounced than in their naphthalene counterparts. Thus, the nitrogen pyramids in **16**, if compared with other proton sponge bases, are planarized to the largest extent (ΣN=355.0°). Furthermore, if at transition from compound **2** to **16** the N···N distance is decreased by 0.078 Å, in the pair of compounds **1**

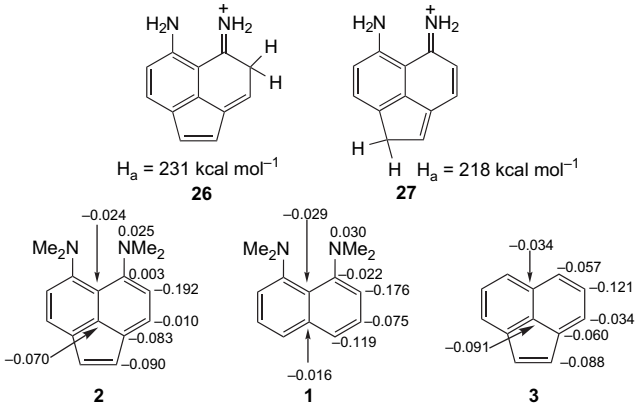


Figure 1. Heats of formation for proton σ-complexes **26** and **27** and distribution of (σ+π)-electron charges at the ring atoms of compounds **2**, **1** and **3** (PM3 method).

and **18** the same difference is equal only to 0.024 Å. Thus, the *ortho*-chlorine atoms make molecule **16** more rigid and flat if compared with **2** (cf. Δ*N* indices, Table 5). The reason for all this is obvious: in the parent proton sponge **1** the NMe_2 groups are already close to each other and only restricted possibilities for their additional approach exist. In contrast, in the acenaphthylene series owing to a tightening effect of the C(1)═C(2) bridge the amino groups are markedly separated and this provides more freedom for geometry changes. The same explanation can be applied to regularities of changing the N···N distance in the protonated forms of proton sponges. Thus, shortening of the N···N distance (given in brackets) for the following base-cation pairs **2**→**2**·H^+ (0.284 Å), **16**→**16**·H^+ (0.279), **1**→**1**·H^+ (0.238),[27] **18**→**18**·H^+ (0.207) moves in accord with the N···N distance in the corresponding bases: **2** (2.955 Å), **16** (2.877), **1** (2.792) and **18** (2.768).

On going from base **16** to perchlorate **16**·$HClO_4$, the compound demonstrates an especially strong contraction (about 10%) of the N···N distance on protonation. This shortening, as it is evident for significant molecular relaxation, along with dimethylamino groups already preorganized for proton abstraction, could be ascribed also for the high basicity of **16**, which is larger than that of **2**. The IHB in cation **16**·H^+ is asymmetric with two unequal asymmetric positions for the bridged proton (disordered H-bonding), though

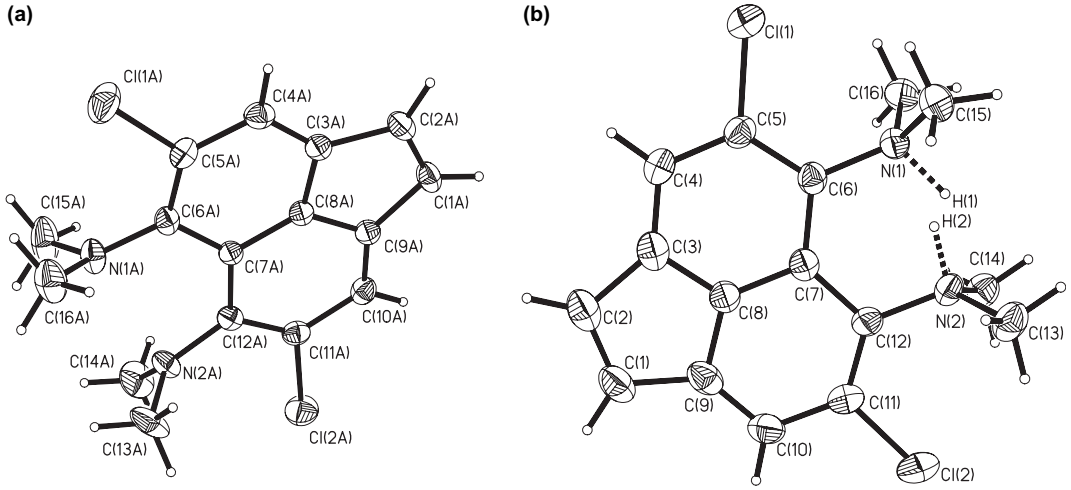


Figure 2. General view and atom numbering scheme for one of the two independent molecules **16** (a) and one independent cation of salt **16**·$HClO_4$ (b); perchlorate-anion is not shown. The ellipsoids for thermal motion are drawn at 30% probability level.

Table 5. Selected structural parametres for investigated and model compounds (lengths in Å, angles in deg)

Compound[a]	**2**	**2**·HBr	**16**[b]	**16**·$HClO_4$	**18**	**18**·HBr
N···N	2.955	2.671	2.877	2.598	2.768	2.561
N–H	—	0.98	—	0.90/0.90[c]	—	1.29
H···N	—	1.75	—	1.82/1.71[c]	—	1.29
∠NHN	—	156	—	144/168[c]	—	165
∠NMe_2-ring[d]	36	84	67	88	71	89
C_{ar}–N[d]	1.395	1.460	1.397	1.452	1.404	1.458
Σ*N*[d,e]	348.3	336.9	355.0	343.2	353.0	342.7
∠C(6)–C(7)–C(12)	129.8	129.1	129.7	127.5	124.5	124.9
C(1)═C(2)	1.339	1.332	1.338	1.361	—	—
Δ*N*[d,f]	0.360	0.041	0.066	0.058	0.051	0.022

[a] Data for compounds **2**, **2**·HBr, **18** and **18**·HBr were accepted from Refs. 27 and 28.
[b] Average data for two independent molecules.
[c] Values for each unequal position of the chelated proton.
[d] Average values.
[e] Sum of CNC angles at the N atoms.
[f] Deviations of N atoms from the mean ring plane.

of 50% occupancy. In summary, the steric influence of the *ortho*-chlorine substituents is opposite to the tightening effect of the CH═CH bridge, which favours weakening of IHB in the corresponding cation.[3,27] Such contradictory tendencies in cation **16**·H^+ result in small but distinct stretching of the C(1)═C(2) bond, which can be considered as a *reversed tightening effect*.

3. Conclusions

It has been shown that the halogenation of the acenaphthylene proton sponge **2** proceeds in a more complex and ambiguous way compared to its naphthalene counterpart **1**. The reaction of **2** with bromine or iodine gives the C(1)═C(2) adduct, which as a result of high basicity of the substrate rapidly undergo E2-elimination, leading to 1-halogeno or 1,2-dihalogeno derivatives. The interaction of **2** with NBS, unlike proton sponge **1**, also proceeds preferentially at the C(1)═C(2) bond. In contrast, the chlorination of **2** with NCS is directed at the *ortho*-positions to the NMe_2 groups, giving 4-chloro- or 4,7-dichlorosubstituted derivatives in excellent yields. In summary, we have at our disposal both 1(2)- and 4(7)-halogeno derivatives of compound **2**, which can be further used in cross-coupling reactions and organometallic syntheses as well as building blocks for supramolecular structures. The existing possibility of fast and reverse change of their high basicity at once by 2–3 orders of magnitude gives them special attractiveness.

4. Experimental

4.1. General

The NMR spectra were recorded on Varian Unity-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) and Brucker DPX-250 (250 MHz for ^{1}H) instruments with $SiMe_4$ as the internal standard. The UV–vis spectra were registered on a Specord M-40 spectrophotometer and the IR spectra were measured on Specord IR-75 spectrometer. Chromatography was carried out on Al_2O_3 with different Brockmann activities and on silica gel L 40/100 μm (Chemapol). The progress of reactions and the purity of products were monitored by TLC on Al_2O_3 and Silufol plates; development with iodine vapour. The melting points were measured in sealed capillaries and are uncorrected. The solvents were purified and dried by standard methods. Commercial NBS (99%, Acros Organics), NCS (99%, Lancaster) and Pd/C (5%, Lancaster) were used. Acenaphthylene **2** was prepared as described earlier,[3] and NIS was synthesized from NBS.[29]

Red plates of dichloride **16** suitable for X-ray diffraction analysis were obtained by isothermic evaporation of its saturated solution in MeOH/$CHCl_3$ (2:1, v/v) at 20 °C. Orange prisms of perchlorate **16**·$HClO_4$ were prepared by the same way using saturated solution of the salt in MeOH. The X-ray diffraction studies were performed at room temperature. The atomic coordinates, bond lengths, bond angles and torsion angles for the structures of **16** and **16**·$HClO_4$ were deposited with the Cambridge Structural Database (CCDC nos. 611178 and 611179, respectively).

4.2. Bromination of 5,6-bis(dimethylamino)acenaphthylene (2) in acetic acid

A solution of Br_2 (0.052 mL, 1 mmol) in AcOH (15 mL) was added for 15 min with stirring to a solution of compound **2** (0.24 g, 1 mmol) in AcOH (15 mL). Then the resulting solution was stirred for 30 min more and the main part of AcOH was distilled off. The residue was diluted with H_2O (20 mL) and neutralized with concd NH_4OH (10 mL). The products were extracted with CCl_4, the extract was concentrated to a minimum volume and chromatographed on silica gel with $CHCl_3$ elution. The first yellow-orange zone with R_f 0.63 gave dark red-brown crystals of 1,2-dibromo-5,6-bis-(dimethylamino)acenaphthylene (**6**), 160 mg (40%), mp 140–141 °C (from MeOH). Found: C, 48.30; H, 4.00; Br, 39.95%. Calcd for $C_{16}H_{16}Br_2N_2$: C, 48.52; H, 4.07; Br, 40.34%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.91 (12H, s, NMe_2), 6.86 (2H, d, *J* 7.8 Hz, H-4, H-7), 7.49 (2H, d, *J* 7.8 Hz, H-3, H-8). ^{13}C NMR ($CDCl_3$, ^1J/Hz) δ ppm: 44.2 (135.8, NMe), 113.3 (157.4, C-4, C-7), 115.5 (C-1, C-2), 116.4 (C-2a, C-8a), 124.8 (161.0, C-3, C-8), 129.7 (C-5a), 130.2 (C-8b), 153.8 (C-5, C-6). UV–vis (MeOH) λ_{max} nm (log ε): 248 (4.17), 275 (4.09), 315 (sh., 3.41), 450 (4.16), end absorption up to 560 nm. Perchlorate **6**·$HClO_4$: brown-orange crystals with mp 150–152 °C (decomp.). ^{1}H NMR (CD_3CN) δ ppm: 3.16 (12H, d, *J* 2.7 Hz, NMe_2), 7.87 (2H, d, *J* 7.7 Hz, H-3, H-8), 7.95 (2H, d, *J* 7.7 Hz, H-4, H-7), 15.98 (1H, br s, NH). ^{1}H NMR (DMSO-d_6) δ ppm: 3.17 (12H, br s, NMe_2), 7.95 (2H, d, *J* 7.5 Hz, H-3, H-8), 8.15 (2H, d, *J* 7.5 Hz, H-4, H-7), 15.52 (1H, br s, NH).

The second yellow zone gave 1-bromo-5,6-bis(dimethylamino)acenaphthylene (**5**) as dark-yellow oil, 60 mg (20%), R_f 0.37. Found: C, 60.30; H, 5.39; Br, 24.92%. Calcd for $C_{16}H_{17}BrN_2$: C, 60.58; H, 5.40; Br, 25.19%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.89 (6H, s, 5-NMe_2), 2.92 (6H, s, 6-NMe_2), 6.82 (1H, d, *J* 7.7 Hz, H-4), 6.88 (1H, s, H-2), 6.92 (1H, d, *J* 7.8 Hz, H-7), 7.46 (1H, d, *J* 7.7 Hz, H-3), 7.53 (1H, d, *J* 7.8 Hz, H-8). UV–vis (MeOH) λ_{max} nm (log ε): 247 (4.16), 270 (4.12), 312 (sh., 3.46), 428 (4.09), end absorption up to 560 nm. Perchlorate **5**·$HClO_4$: brown-yellow crystals with mp 154–156 °C. ^{1}H NMR (CD_3CN) δ ppm: 3.15 (6H, d, *J* 2.5 Hz, 6-NMe_2), 3.18 (6H, d, *J* 2.9 Hz, 5-NMe_2), 7.34 (1H, s, H-2), 7.87 (2H, s, H-7, H-8), 7.87 (1H, d, *J* 7.6 Hz, H-3), 7.96 (1H, d, *J* 7.6 Hz, H-4), 16.07 (1H, br s, NH). ^{1}H NMR (DMSO-d_6) δ ppm: 3.15 (6H, s, 6-NMe_2), 3.19 (6H, d, *J* 2.0 Hz, 5-NMe_2), 7.47 (1H, s, H-2), 7.90 (1H, d, *J* 7.6 Hz, H-3), 7.95 (1H, d, *J* 7.5 Hz, H-8), 8.08 (1H, d, *J* 7.5 Hz, H-7), 8.13 (1H, d, *J* 7.6 Hz, H-4), 15.62 (1H, br s, NH).

4.3. Bromination of perchlorate 2·$HClO_4$ in acetonitrile

A solution of Br_2 (0.103 mL, 2 mmol) in MeCN (5 mL) was added dropwise with vigorous stirring for 15 min to a solution of perchlorate[3] **2**·$HClO_4$ (0.68 g, 2 mmol) in MeCN (5 mL). The reaction mixture was then stirred for 30 min at 20 °C and treated with 10% aqueous solution of sodium carbonate decahydrate (15 mL). The organic layer was separated and the aqueous phase was extracted with chloroform (3×3 mL). The organic phases were then combined and the solvents were removed to give 0.62 g (98%) of compound **5**

with the properties as has the sample prepared above. ^{1}H NMR (CD_3CN) δ ppm: 3.13 (6H, d, J 2.6 Hz, NMe_2), 3.15 (6H, d, J 2.6 Hz, NMe_2), 6.16 (2H, s, H-1, H-2), 7.85 (2H, d, J 7.8 Hz, H-3, H-8), 8.00 (2H, d, J 7.8 Hz, H-4, H-7), 16.50 (1H, br s, NH).

4.4. Bromination of 5,6-bis(dimethylamino)acenaphthylene (2) in DMF

Method A: a solution of NBS (0.53 g, 3 mmol) in DMF (25 mL) was added dropwise with vigorous stirring for 15 min and at −15 °C to a solution of **2** (0.72 g, 3 mmol) in DMF (25 mL). The resulting mixture was diluted with equal volume of water and the reaction products were taken up into hexanes (3×15 mL). The extract was evaporated to dryness at room temperature and the residue was chromatographed on silica gel with $CHCl_3$ elution. This gave 0.11 g (9%) of dibromide **6** and 0.10 g (10%) of monobromide **5** with the properties identical to those of authentic samples.

Method B: a solution of NBS (1.78 g, 20 mmol) in DMF (5 mL) was added with vigorous stirring for 30 min and at −15 °C to a solution of diamine **2** (0.96 g, 4 mmol) in DMF (10 mL). Then the cooling was ceased, the mixture was diluted with water (10 mL), containing several drops of aqueous ammonia, and then extracted with hexanes (4×10 mL). The solvent was removed and the residue was chromatographed (silica gel, CCl_4). The first bright-red fraction with R_f 0.78 gave 0.23 g (10%) of 1,2,4,7-tetrabromo-5-dimethylamino-6-methylamino-acenaphthylene (**10**) as red crystals with mp 152–154 °C (from EtOH/H_2O 1:1, v/v). Found: C, 33.39; H, 2.23; Br, 59.00%. Calcd for $C_{15}H_{12}Br_4N_2$: C, 33.37; H, 2.24; Br, 59.20%. ^{1}H NMR ($CDCl_3$) δ ppm: 3.02 (6H, s, 5-NMe_2), 3.30 (3H, s, 6-NMe), 7.63 (1H, s, H-8), 7.69 (1H, s, H-3), 9.92 (1H, br s, NH). IR ($CHCl_3$) ν cm^{-1}: 3185 (N–H), 3045, 2977, 2965, 2875, 2855 (C–H), 1640, 1602, 1590 (C=C+ring). The second orange fraction with R_f 0.60 gave 0.18 g (10%) of 1,2,4-tribromo-6-dimethylamino-5-methylamino-acenaphthylene (**9**), the properties of which are the same as those of the material prepared earlier.[14]

4.5. 1,2,4-Tribromo- (8) and 1,2,4,7-tetrabromo-5,6-bis(dimethylamino)acenaphthylenes (11)

A solution consisting of tribromide **9** (0.046 g, 0.1 mmol) and MeI (5 mL) was refluxed for 150 h. Then iodomethane was deleted on the water bath, the residue was washed with Et_2O and dissolved in MeCN (5 mL). The resulting solution was treated with 10% aqueous Na_2CO_3 (10 mL) and the product **8** thus formed was extracted with hexanes (3×5 mL). This gave 0.044 g (93%) of red crystalline compound with mp 155–156 °C (from EtOH/H_2O 1:1, v/v). Found: C, 40.03; H, 3.20; Br, 50.61%. Calcd for $C_{16}H_{15}Br_3N_2$: C, 40.43; H, 3.16; Br, 50.53%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.88 (6H, s, 6-NMe_2), 3.06 (6H, s, 5-NMe_2), 6.90 (1H, d, J 7.9 Hz, H-7), 7.44 (1H, d, J 7.9 Hz, H-8), 7.73 (1H, s, H-3). Perchlorate **8**·$HClO_4$: yellow crystals with mp 300–302 °C (decomp. from EtOH). Found: C, 33.45; H, 2.83; Cl+Br, 47.77%. Calcd for $C_{16}H_{16}Br_3ClN_2O_4$: C, 33.40; H, 2.80; Cl+Br, 47.81%. ^{1}H NMR (CD_3CN) δ ppm: 2.26 (6H, d, J 1.1 Hz, 5-NMe_2), 3.34 (6H, d, J 4.2 Hz, 6-NMe_2), 7.91 (1H, d, J 7.7 Hz, H-7), 8.00 (1H, s, H-3), 8.02 (1H, d, J 7.7 Hz, H-8), 16.59 (1H, br s, NH).

Tetrabromide **11** was synthesized analogously and 0.044 g of compound **10** gave 0.037 g (82%) of the product as red crystalline substance with mp 141–142 °C (from EtOH/H_2O 2:1, v/v). Found: C, 34.70; H, 2.56; Br, 57.65%. Calcd for $C_{16}H_{14}Br_4N_2$: C, 34.69; H, 2.55; Br, 57.70%. ^{1}H NMR ($CDCl_3$) δ ppm: 3.02 (12H, s, NMe_2), 7.67 (2H, s, H-3, H-8). Perchlorate **11**·$HClO_4$: yellow crystals, darkened above 260 °C, melting with decomposition at 290–292 °C (from EtOH). Found: C, 29.45; H, 2.30; Cl+Br, 54.25%. Calcd for $C_{16}H_{15}Br_4ClN_2O_4$: C, 29.37; H, 2.31; Cl+Br, 54.26%. ^{1}H NMR (CD_3CN) δ ppm: 3.43 (12H, d, J 2.6 Hz, NMe_2), 8.04 (2H, s, H-3, H-8), 18.84 (1H, br s, NH).

4.6. Bromination of 5,6-bis(dimethylamino)acenaphthene (12) in DMF

A solution of NBS (0.36 g, 2 mmol) in DMF (25 mL) was added dropwise with vigorous stirring for 30 min and at −15 °C to a solution of **12**[3] (0.24 g, 1 mmol) in DMF (10 mL). The resulting mixture was diluted with equal volume of water containing several drops of ammonia and the reaction products were taken up into hexanes (3×10 mL). The solvent was removed and the residue was analyzed by ^{1}H NMR spectroscopy showing the presence of dibromide **6** (22%), monobromide **5** (14%) and the unreacted starting substrate **12** (up to 64%).

4.7. Hydrogenation of 1,2-dibromo-5,6-bis(dimethylamino)acenaphthylene (6)

A suspension consisting of compound **6** (0.39 g, 0.1 mmol), 5% Pd/C (0.02 g), Na_2CO_3·$10H_2O$ (0.50 g) and MeOH (30 mL) was hydrogenated at room temperature and atmospheric pressure for 10 min. Then the catalyst was filtered off, the solution was diluted with the same amount of water and the acenaphthene **12** was extracted with hexanes (3×15 mL). The solvent was removed to give 0.23 g (97%) of compound **12** with the properties as has the sample described previously.[3]

4.8. 4-Chloro-5,6-bis(dimethylamino)acenaphthylene (15)

A solution of NCS (0.53 g, 0.4 mmol) in $CHCl_3$ (50 mL) was added dropwise with intense stirring at −15 °C for 15 min to a solution of acenaphthylene **2** (0.96 g, 4 mmol) in $CHCl_3$ (50 mL). The reaction mass was then washed with water (100 mL), the organic phase was evaporated to dryness and the residue was chromatographed (Al_2O_3 III, *n*-hexane). The main red fraction with R_f 0.89 gave 0.88 g (80%) of compound **15** as red oil. Found: C, 60.98; H, 6.20; Cl, 13.12%. Calcd for $C_{16}H_{17}ClN_2$: C, 70.46; H, 6.24; Cl, 13.03%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.89 (6H, s, 6-NMe_2), 3.06 (6H, s, 5-NMe_2), 6.79 (1H, d, J 5.0 Hz, H-1), 6.92 (2H, m, H-2, H-7), 7.43 (1H, d, J 7.3 Hz, H-8), 7.59 (1H, s, H-3). UV–vis (EtOH) λ_{max} nm (log ε): 245 (4.21), 264 (4.14), 310 (3.45), 402 (3.89), end absorption up to 550 nm. IR (liquid film) ν cm^{-1}: 3100, 3070, 2970, 2915, 2850, 2810, 2780 (C–H), 1600, 1580, 1500, 1450 (C=C+ring). Perchlorate **15**·$HClO_4$: yellow crystals with

mp 265–267 °C (from EtOH). Found: C, 51.45; H, 4.80; Cl, 19.13%. Calcd for $C_{16}H_{18}Cl_2N_2O_4$: C, 51.47; H, 4.83; Cl, 9.03%. ^{1}H NMR (DMSO-d_6) δ ppm: 3.12 (6H, s, 5-NMe_2), 3.36 (6H, d, J 4.3 Hz, 6-NMe_2), 7.16 (1H, d, J 5.4 Hz, H-2), 7.23 (1H, d, J 5.4 Hz, H-1), 7.93 (2H, m, H-3, H-8), 8.16 (1H, d, J 7.7 Hz, H-7), 15.77 (1H, br s, NH).

4.9. 4,7-Dichloro-5,6-bis(dimethylamino)acenaphthylene (16)

Compound **16** was synthesized by analogy using 0.96 g (4 mmol) of **2** and 1.07 g (8 mmol) of NCS. The bright-red fraction with R_f 0.95 gave 1.04 g (85%) of dichloride **16** as red crystals with mp 106–108 °C (from MeOH). Found: C, 62.51; H, 4.80; Cl, 23.19%. Calcd for $C_{16}H_{16}Cl_2N_2$: C, 62.54; H, 5.21; Cl, 23.13%. ^{1}H NMR ($CDCl_3$) δ ppm: 3.01 (12H, s, NMe_2), 6.85 (2H, s, H-1, H-2), 7.50 (2H, s, H-3, H-8). ^{13}C NMR ($CDCl_3$, ^1J/Hz) δ ppm: 43.7 (134.9, NMe), 128.0 (165.8, C-3, C-8), 129.0 (C-2a, C-8a), 129.2 (C-5a), 129.3 (170.9, C-1, C-2), 135.1 (C-8b), 137.6 (C-4, C-7), 147.9 (C-5, C-6). UV–vis (EtOH) λ_{max} nm (log ε): 252 (4.34), 319 (3.55), 334 (3.58), 389 (3.75), 479 (sh., 3.21), end absorption up to 575 nm. Perchlorate **16**·$HClO_4$: yellow crystals, darkened above 234 °C, do not melt up to 300 °C (from EtOH). Found: C, 47.05; H, 4.13; Cl, 26.01%. Calcd for $C_{16}H_{17}Cl_3N_2O_4$: C, 47.12; H, 4.17; Cl, 26.13%. ^{1}H NMR (DMSO-d_6, 70 °C) δ ppm: 3.41 (12H, d, J 2.9 Hz, NMe_2), 7.26 (2H, s, H-1, H-2), 8.01 (2H, s, H-3, H-8), 18.14 (1H, br s, NH).

4.10. 1,2-Dibromo-4,7-dichloro-5,6-bis(dimethylamino)acenaphthylene (20)

A solution of NCS (0.053 g, 0.4 mmol) in $CHCl_3$ (5 mL) was added with stirring at −15 °C for 30 min to a solution of dibromide **6** (0.078 g, 0.2 mmol) in $CHCl_3$ (5 mL). Then the cooling was ceased and the reaction mass was further stirred for 2 h at room temperature. The resulting mixture was washed with the same amount of water, the solvent was removed and the residue was chromatographed (silica gel, chloroform) to give pure halogenide **20** (0.082 g, 89%) as red crystals with mp 132–133 °C (from EtOH). ^{1}H NMR ($CDCl_3$) δ ppm: 3.01 (12H, s, NMe_2), 7.48 (2H, s, H-3, H-8). Perchlorate **20**·$HClO_4$: yellow crystals with mp 305–306 °C (decomp. from EtOH). Found: C, 34.12; H, 2.60; Cl+Br, 47.15%. Calcd for $C_{16}H_{15}Br_2Cl_3N_2O_4$: C, 33.99; H, 2.67; Cl+Br, 47.07%. ^{1}H NMR (DMSO-d_6) δ ppm: 3.34 (12H, br s, NMe_2), 8.04 (2H, s, H-3, H-8), 18.22 (1H, br s, NH).

Hydrogenation of polyhalide **20** was performed by analogy with compound **6**. This gave compound **21** in near quantitative yield.

4.11. 4,7-Dichloro-5,6-bis(dimethylamino)acenaphthene (21)

A suspension consisting of compound **16** (0.31 g, 1 mmol), 5% Pd/C (0.15 g) and EtOH (20 mL) was hydrogenated at room temperature and atmospheric pressure for 30 min. After the catalyst was filtered off, the resulting solution was evaporated to dryness. Yield of acenaphthene **21** was 0.30 g (99%). Pink-beige crystals with mp 135–136 °C (from MeOH). Found: C, 62.15; H, 5.03; Cl, 22.91%. Calcd for $C_{16}H_{18}Cl_2N_2$: C, 62.14; H, 5.82; Cl, 22.98%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.95 (12H, s, NMe_2), 3.26 (4H, s, H-1, H-2), 7.17 (2H, s, H-3, H-8). Perchlorate **21**·$HClO_4$: colourless crystals with mp 230–231 °C (decomp. from EtOH/H_2O 1:1, v/v). Found: C, 46.73; H, 4.22; Cl, 26.08%. Calcd for $C_{16}H_{19}Cl_3N_2O_4$: C, 47.14; H, 4.20; Cl, 26.09%. ^{1}H NMR (DMSO-d_6, 70 °C) δ ppm: 3.37 (12H, d, J 2.6 Hz, NMe_2), 3.44 (4H, s, H-1, H-2), 7.61 (2H, s, H-3, H-8), 18.14 (1H, br s, NH).

4.12. Chlorination of 5,6-bis(dimethylamino)acenaphthene (12) with NCS in chloroform

A solution of NCS (0.134 g, 1 mmol) in $CHCl_3$ (10 mL) was added with stirring at −15 °C for 15 min to a solution of compound **12**[3] (0.120 g, 0.5 mmol) in $CHCl_3$ (10 mL). Then the reaction mixture was washed with water (50 mL), containing several drops of aqueous ammonia, the organic phase was evaporated and the residue was chromatographed (Al_2O_3 III, n-hexane). The first bright-red zone with R_f 0.95 gave red crystals of dichloride **16** (9 mg, 6%) and the second orange zone with R_f 0.89 gave chloride **15** as red oil (4 mg, 3%). The spectral properties of these compounds are identical with those revealed by authentic samples.

4.13. 1,4,7-Trichloro-5,6-bis(dimethylamino)acenaphthylene (19)

A solution of chlorine (0.086 g, 2.4 mmol) in AcOH (5 mL) was added with stirring for 15 min to a solution of **2** (0.288 g, 1.2 mmol) in AcOH (5 mL). The resulting mixture was stirred for an additional hour, diluted with water (10 mL) and neutralized with concd NH_4OH. The reaction products were extracted with CCl_4 (3×5 mL), the solvent was removed and the residue was subjected to TLC (Al_2O_3, n-octane). The red zone with R_f 0.85 gave 0.066 g (16%) of trichloroacenaphthylene **19** as red crystals with mp 54–56 °C (from MeOH). Found: C, 56.20; H, 4.45; Cl, 31.02%. Calcd for $C_{16}H_{15}Cl_3N_2$: C, 56.25; H, 4.45; Cl, 31.13%. ^{1}H NMR ($CDCl_3$) δ ppm: 3.02 (6H, s, NMe_2), 3.04 (6H, s, NMe_2), 6.75 (1H, s, H-2), 7.43 (1H, s, H-3), 7.59 (1H, s, H-8).

4.14. Iodination of 5,6-bis(dimethylamino)acenaphthylene (2) in acetic acid

A solution of I_2 (0.51 mg, 2 mmol) in AcOH (15 mL) was added with stirring for 15 min to a solution of **2** (0.48 g, 2 mmol) in AcOH (15 mL). After that the solution was stirred for 30 min more and the major part of AcOH was distilled off. The residue was diluted with water (20 mL) and concd NH_4OH (10 mL). The products were extracted with CCl_4 (3×20 mL), the extract was evaporated to a minimal volume and chromatographed (silica gel, $CHCl_3$). The first yellow-orange zone with R_f 0.60 gave orange crystals of 5,6-bis(dimethylamino)-1,2-diiodoacenaphthylene (**23**), 0.035 g (36%), mp 95–97 °C (from MeOH). Found: C, 39.20; H, 3.20; I, 51.75%. Calcd for $C_{16}H_{16}I_2N_2$: C, 39.21; H, 3.29; I, 51.78%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.92 (12H, s, NMe_2), 6.85 (2H, d, J 7.7 Hz, H-4,7), 7.39 (2H, d, J 7.7 Hz, H-3, H-8). The second yellow zone with R_f 0.32

allowed to collect 0.011 g (15%) of 5,6-bis(dimethylamino)-1-iodoacenaphthylene (**24**) as orange oil. Found: C, 52.76; H, 4.70; I, 34.76%. Calcd for $C_{16}H_{17}IN_2$: C, 52.76; H, 4.71; I, 34.84%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.90 (6H, s, 6-NMe_2), 2.92 (6H, s, 5-NMe_2), 6.82 (1H, d, *J* 7.7 Hz, H-4), 6.93 (1H, d, *J* 7.3 Hz, H-7), 7.13 (1H, s, H-2), 7.38 (1H, d, *J* 7.7 Hz, H-3), 7.48 (1H, d, *J* 7.3 Hz, H-8).

Acknowledgements

We thank Z. A. Starikova (A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, Moscow) for performing X-ray diffraction study of compounds **16** and **16**·$HClO_4$. This study was in part supported by the Russian Foundation for Basic Research (Project no. 05-03-32110).

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Remote stereocontrol by the sulfinyl group: Mukaiyama aldol reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde in the asymmetric synthesis of β-hydroxyacids and 1,3-diols

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Received 27 June 2006; revised 26 September 2006; accepted 5 October 2006
Available online 31 October 2006

Abstract—(*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]acetaldehyde reacts with different *O*-silylated ketenethioacetals in the presence of $Yb(OTf)_3$ yielding β-hydroxythioesters in high yields and diastereoselectivities. The obtained compounds were readily transformed into β-hydroxyacids and their corresponding diols. These Mukaiyama aldol reactions are a direct evidence of the ability of the sulfinyl group to control 1,5- and 1,6-asymmetric induction processes.

1. Introduction

The aldol reaction is a powerful method of forming carbon–carbon bonds in organic synthesis.[1] The control of the absolute configuration at the new stereogenic centers generated in the reaction is an important task and hundreds of papers and a number of excellent comprehensive reviews have appeared covering this topic.[2] Among these processes, the Mukaiyama reaction[3] has enjoyed a noteworthy development in recent years, and it has become the reaction of choice to attain high stereoselectivity, due to the possibility of using chiral enolates,[4] chiral substrates,[5] and especially chiral catalysts.[6] The ability of the sulfinyl group to control the face-selectivity in many different reactions is well-known.[7] Concerning aldol reactions, the role of the sulfinyl group has been investigated in reactions where this chiral auxiliary is present at the nucleophilic enolate[8–11] as well as at the electrophile.[12] The results obtained from all these studies reveal the efficiency of the sulfinyl group in the stereoselectivity control when it is separated by only one or two bonds from the reaction center (1,2- and 1,3-asymmetric induction processes). Less work has been done in the field of aldol reactions involving remote stereofunctionalization (1,*n*-asymmetric induction processes with $n>3$) controlled by sulfoxides. The most important contributions have been achieved with aromatic aldehydes containing an *ortho*-sulfinyl group,[13–15] which include Mukaiyama reactions.[13b,c,16]

Some years ago we initiated a program to investigate the efficiency of the sulfinyl group to control the stereoselectivity of reactions taking place at remote positions. We have mainly studied 1,4-asymmetric induction processes controlled by the sulfinyl group at the nucleophilic moiety,[17] that proceed with an almost complete control of the stereoselectivity. On the other hand, we have reported the hydrocyanation of γ-sulfinyl aromatic aldehydes, with the sulfur function being at the electrophile.[18] In this context, we have also studied the first 1,5-asymmetric induction processes controlled by the sulfinyl group starting from (*S*)-*ortho*-(*p*-tolylsulfinyl)benzyl alkyl (and aryl) ketones and their corresponding aldehydes,[17e] which involve reduction[19a] and hydrocyanation[19b] reactions with aluminum reagents. These reactions occurred with excellent stereoselectivities and afforded diastereomerically enriched carbinols and cyanohydrins respectively, when they were performed in the presence of $Yb(OTf)_3$. We present herein the first results on the stereoselective Mukaiyama reaction of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde (**1**) with thioester *O*-silyl enolates. They would allow to expand the scope of the 1,5-asymmetric induction reactions controlled by the sulfinyl group and would provide interesting synthetic intermediates with a β-hydroxy carbonylic structure.

2. Results and discussion

Initially, we studied the reaction of the aldehyde **1**[17e] with the *O*-silylated ketenethioacetal **2a**[20] at −78 °C in the

Keywords: Stereoselective Mukaiyama aldol reaction; 1,5- and 1,6-Asymmetric induction; Chiral sulfoxide; Asymmetric synthesis of 3-hydroxyacids.
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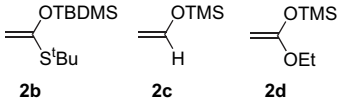
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.010

presence of different Lewis acids (1.2 equiv). Mixtures of the two possible diastereoisomeric adducts, epimers at the hydroxylic carbon, were obtained in all cases (Table 1, entries 1–4 and 6). Diastereoselectivity was low with $BF_3{\cdot}OEt_2$, $TiCl_4$, $AlCl_3$, and ZnI_2 (Table 1, entries 1–4). These reactions did not reach completion and a variable amount of starting material was always recovered. No reaction happened under $MgCl_2$ catalysis, even at higher temperatures and longer reaction times (Table 1, entry 5). The best stereoselectivity was achieved under $Yb(OTf)_3$ catalysis (Table 1, entry 6), as it had been also the case in the reactions of other nucleophiles.[19]

Next, we tried to improve the conversion and stereoselectivity of the reactions performed under $Yb(OTf)_3$ catalysis, by changing the temperature, the solvent, the number of equivalents of the reagents, and the reaction time. The best results were obtained by lowering the temperature (Table 1, entries 6–8) and using acetonitrile[21] as the solvent (entries 11–13), which in its turn, also increased the reactivity. The use of THF as the solvent (Table 1, entries 9 and 10) had no positive influence. Under substoichiometric amounts of $Yb(OTf)_3$ a significant decrease in both the reaction rate and the stereoselectivity, was observed, whereas an increase in the amount of the Lewis acid (2 equiv) scarcely modified the reaction rate. Under the optimum conditions, which were those of entry 12 (3 equiv of **2a**, 1.2 equiv of $Yb(OTf)_3$ in acetonitrile at −40 °C), a 94:6 mixture of diastereoisomers **3** and **4** could be isolated in 86% yield. They were easily separated by flash-column chromatography and the major compound **3** (de >98%) could be isolated in 79% yield.

An increase in the size of the silyloxy group had no significant influence on the reactivity or on the selectivity of these reactions. Thus, *tert*-butyldimethylsilyl derivative **2b**[22] (Scheme 1) gave almost identical results to **2a** under similar conditions. Less nucleophilic species, such as trimethylsilyloxy ethylene, **2c**, were not able to react with **1** in the presence of catalysts, even at room temperature. Analogously, the reaction with ketene acetal **2d**[23] (Scheme 1) did not evolve, which was not unexpected because of the low reactivity of this compound toward 2-(arylsulfinyl)-naphthaldehydes, as had been reported by Toru.[13b]

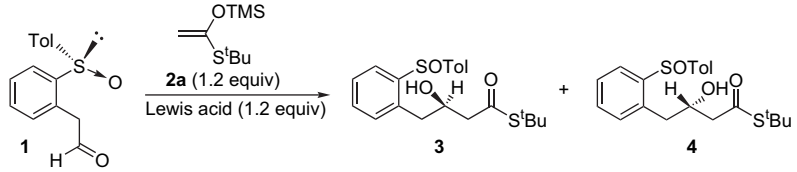


Scheme 1.

Then, we studied the reactions of aldehyde **1** with the substituted *O*-silylated ketenethioacetals (*Z*)-**2e** and (*E*)-**2f**, which would allow the simultaneous formation of two stereogenic centers in one step, providing information about the influence of the remote sulfinyl group in determining the configuration of both centers (1,5- and 1,6-asymmetric induction processes). The reactions were performed under the best conditions of Table 1, acetonitrile being used as the solvent and $Yb(OTf)_3$ as the catalyst. The results are collected in Table 2.

All these reactions afforded only two out of the four possible diastereoisomers. The reactions of sulfinylaldehyde **1** with **2e**[24] in the presence of 1.2 equiv of $Yb(OTf)_3$, were performed at different temperatures (Table 2, entries 1–3), yielding mixtures of *anti* and *syn* α-methyl-β-hydroxythioesters (**5** and **6**), the *anti* isomer **5** being the major one. As expected, the selectivity slightly increased when the temperature became lower and the reaction rate was also diminished. An increase in the number of equivalents of the electrophile had some influence on the reaction rate (shorter reaction times were needed) but not on the stereoselectivity (Table 2, entries 3–5). The use of dichloromethane as the

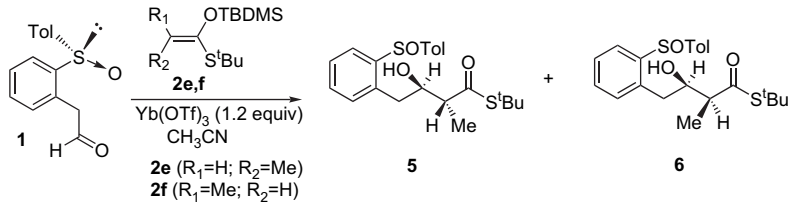
Table 1. Reactions of aldehyde **1** with **2a** catalyzed by Lewis acids



Entry	Solvent	Lewis acid	Temperature (°C)	Time	Conversion (%)[a]	**3**:**4** Ratio[a]
1	CH_2Cl_2	$BF_3{\cdot}OEt_2$[b]	−78	2 h	84	55:45
2	CH_2Cl_2	$TiCl_4$	−78	2 h	87	61:39
3	CH_2Cl_2	$AlCl_3$	−78	2 h	34	66:34
4	CH_2Cl_2	ZnI_2	−78	2 h	72	72:28
5	CH_2Cl_2	$MgCl_2$	rt	5 days	—	—
6	CH_2Cl_2	$Yb(OTf)_3$	−78	2 h	60	88:12
7	CH_2Cl_2	$Yb(OTf)_3$	−40	2 h	83	73:27
8	CH_2Cl_2	$Yb(OTf)_3$	0	2 h	86	61:39
9[c]	THF	$Yb(OTf)_3$	−40	62 h	98	82:18
10	THF	$Yb(OTf)_3$	rt	16 h	98	77:23
11	CH_3CN	$Yb(OTf)_3$	−40	2 h	85	94:6
12[c]	CH_3CN	$Yb(OTf)_3$	−40	1.5 h	100	94:6[d]
13	CH_3CN	$Yb(OTf)_3$	Reflux	2 h	100	83:17

[a] Determined by ^1H NMR spectroscopy.
[b] 2 equiv was used.
[c] 3 equiv of **2a**.
[d] A 77:23 ratio of **3** and **4** was observed by using 0.5 equiv of $Yb(OTf)_3$.

Table 2. Reactions of **1** with *O*-silylated ketenethioacetals **2e** and **2f**



Entry	Enolate (equiv)	Temperature (°C)	Time (h)	Conversion[a] (%)	**5**:**6**[a]
1	**2e** (3)	−40	62	55	78:22
2	**2e** (3)	−10	15	98	74:26
3	**2e** (3)	0	3	100[b]	72:28
4	**2e** (1.5)	0	3	52	72:28
5	**2e** (1.5)	0	6	93	72:28
6[c]	**2e** (1.5)	0	3	—[d]	46:49[e]
7	**2e** (1.5)	rt	3	62	67:33
8	**2f** (3)	0	3	100[f]	83:17
9	**2f** (1.5)	0	7	80	83:17
10	**2f** (3)	−40	120	73	83:17

[a] Determined by ^{1}H NMR spectroscopy.
[b] Combined yield: 71%.
[c] CH_2Cl_2 as the solvent.
[d] Non-evaluated.
[e] A third isomer (5%) was detected.
[f] Combined yield: 73%.

solvent decreased the stereoselectivity, because it afforded nearly equimolar mixtures of *anti*-**5** and *syn*-**6** isomers, along with a third isomer that could be detected by ^{1}H NMR (Table 2, entry 6). The best reaction conditions found for **2e** (Table 2, entries 3 and 5) were also explored with **2f**.[24] In this case the major isomer also was *anti*-**5**, but the stereoselectivity was slightly higher, 83(**5**):17(**6**) at 0 °C (Table 2, entries 8 and 9). When the temperature was lower, the reaction time increased significantly and no change in the stereoselectivity was observed.

Diastereoisomeric mixtures obtained in these reactions could not be separated by column chromatography. However, the major diastereomer **5** could be obtained as a pure compound by crystallization in 40% yield from **2e** and 51% yield from **2e** (Table 2, entries 3 and 8, respectively). All the attempts at −40 °C in THF, in the presence of TBAF as a fluoride source, with the aim of obtaining the *syn* adduct **6** as the major one,[24,25] were unsuccessful.

Configurational assignment of compounds **3**–**6** was carried out as follows:

(1) The configuration of **3** was unequivocally established as [3*R*,(S)*S*] by chemical correlation with alcohol **10** (see later). It allowed us to assign the [3*S*,(S)*S*] configuration for compound **4**.
(2) The oxidation with *m*-CPBA of the 33(**5**):67(**6**) mixture gave two diastereoisomeric sulfones with the same diastereoisomeric ratio as the starting sulfoxides. This result indicated that hydroxysulfoxides **5** and **6** only differed in the configuration of one of the two chiral carbons.
(3) The oxidation with PCC of the above mixture of **5** and **6** afforded two diastereoisomeric ketones, which initially suggested that the starting sulfoxides were epimers at the α-carbon to the thioester group. However, this experience was not conclusive because the composition of the resulting mixture (ca. 1:1) was not identical to that of the starting one (ca. 1:2), thus suggesting partial epimerization of the α-carbon to the thioester group under the reaction conditions. Despite this result, we assumed that both isomers exhibit the same configuration at the hydroxylic carbon because **2e** and **2f** must attack at the same face of the carbonyl group at compound **1**, chelated with $Yb(OTf)_3$, as it was the case of compound **2a**, with a stereoselectivity presumably higher in the former cases due to the bulkier size of the nucleophilic carbon at **2e** and **2f**.
(4) The absolute configuration of the major *anti*-**5** isomer was unequivocally established as [2*R*,3*R*,(S)*S*] by X-ray diffraction studies.[26] Therefore, according to the above considerations we assign the [2*S*,3*R*,(S)*S*] configuration to the minor *syn*-**6**.

Once the configurational assignment of the adducts in the Mukaiyama reactions was unequivocally established, we can conclude that the stereocontrol was very high (from **2a**) or complete (from **2e** and **2f**) at the benzylic carbon (1,5-asymmetric induction process) but only moderate at the α-carbon to the ester group (1,6-asymmetric induction process).

The observed stereoselectivity can be explained by assuming the formation of an eight-membered chelated species between the $Yb(OTf)_3$ and the carbonyl and sulfinyl oxygens at the substrate, as it had been postulated to explain the results obtained in the reduction[19a] and hydrocyanation[19b] of this type of ketosulfoxides. Two conformations can be proposed for this chelated species, **B** (Fig. 1) as the most stable one, because conformation **A** must be strongly unestabilized by steric interactions between the ring and the ligands of the metal. The approach of nucleophile **2a** or **2b** at the pro-*R* face of the carbonyl group in its most stable conformation

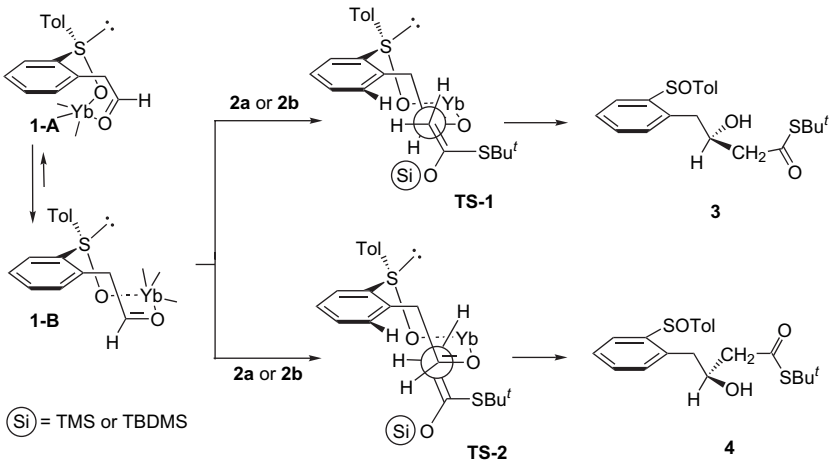


Figure 1. Favored approach of **2a** and **2b** in Mukaiyama aldol reaction of chelated aldehyde **1**.

would yield compound **3** through **TS-1**, whereas the attack at the pro-*S* face would afford **4** through **TS-2**. From Figure 1, it is evident the lower stability of **TS-2**, which would explain the formation of **3** as the major diastereoisomer.

From the above figure it can also be inferred that **TS-2** would be too unstable for substituted enolates, such as **2e** or **2f**, which should evolve in a completely stereoselective manner by attack at the pro-*R* face of the chelated carbonyl through transition states similar to **TS-1**. This fact is in agreement with the complete control of the diastereoselectivity at the hydroxylic center observed for these reactions (Table 2). Different **TS** can be postulated (Fig. 2) differing in the relative arrangement of the C=C and C=O groups. **TS-3** and **TS-5** must be highly unstable due to the strong steric interactions between the ring at **1** and the substituents at **2e** and **2f** adopting an antiperiplanar arrangement with respect to the C=O group. Therefore, the favored transition states are **TS-4** and **TS-4′**, both orientating the H in such an arrangement. As these transition states differ only in the nucleophile face that attacks at the carbonyl group, the obtained products will have the opposite configuration at the attacking nucleophilic carbon. The fact that *anti*-**5** is obtained as the major isomer suggest that the steric interaction of the methylene at the aldehyde with the tetrahedral CH_3 group at the nucleophile, present in **TS-4′**, is stronger than that with the flat olefinic carbon, present in **TS-4**, thus explaining the observed predominance of the *anti*-compounds. From Figure 2 it is easily understood that the *E* or *Z* configuration of the enolates scarcely affects the stereochemical results.[24,27]

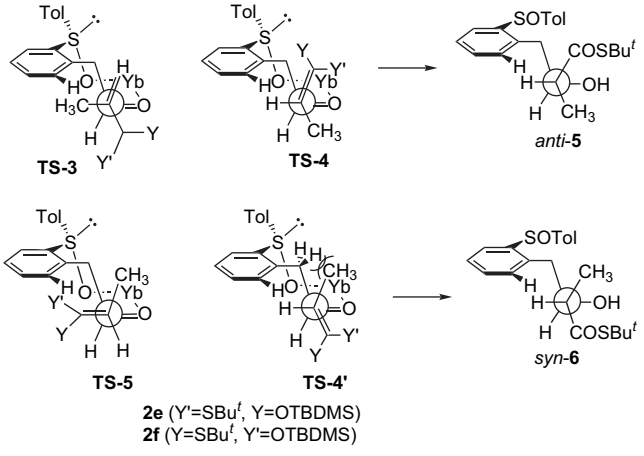
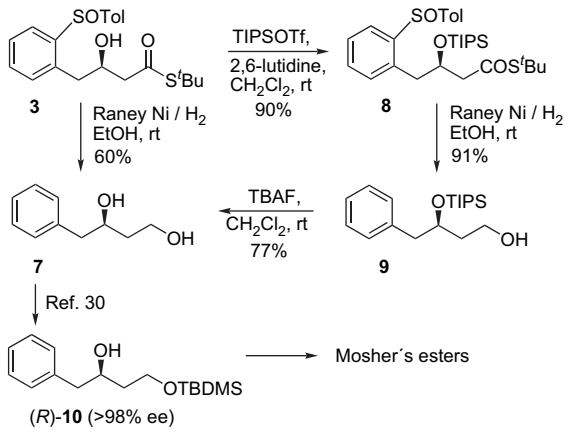


Figure 2. Favored approach of **2e** and **2f** in Mukaiyama aldol reaction of chelated aldehyde **1**.

As the last step of this research we studied the removal of the chiral auxiliary. The reaction of a mixture of **3** and **4** with Raney nickel afforded 4-phenyl-1,3-butanediol (**7**), indicating that the reagent had produced hydrogenolysis of the C–S bond as well as the reduction of the thioester group.[24,28] Reaction of diastereoisomerically pure **3** with Raney nickel under hydrogen atmosphere, yielded compound **7** (60% yield) exhibiting a $[\alpha]_D$ value of +19.0. The protection of the OH group at **3** as a TIPS derivative and further reduction with Raney nickel and desilylation (Scheme 2) also provided compound **7**, but in this case with an $[\alpha]_D$ value of +21.0. This fact suggests that the direct reduction of **3** had taken place with a slight epimerization at the hydroxylic center, as it had been previously reported for other sulfinyl alcohols.[29] Compound **7**, obtained by the indirect way, was transformed into **10**[30] (Scheme 2). The ^{1}H NMR studies on Mosher's esters[31] of compound **10** allowed us to establish the *R* configuration at its hydroxylic carbon as well as its high optical purity (ee >98%). The same configuration must be assigned to its precursor **7**. Therefore, the absolute configuration of **3** was indirectly assigned as [3*R*,(*S*)S], whereas that of [3*S*,(*S*)S] must be assigned to epimer **4**.



Scheme 2.

Desulfinylation and reduction of the thioester moiety with Raney nickel in hydrogen atmosphere were also performed on diastereoisomerically pure **5**, yielding a 83:17 diastereoisomeric mixture of diols **11** and **12** as the result of the partial racemization of the hydroxylic center (Scheme 3). The *anti* stereochemistry of diol **11** was established by comparison of its ^{1}H NMR data with those previously reported for this compound.[32] It can be obtained in its diastereoisomeric pure form by an initial protection of **5** as triisopropylsilyl derivative **13**, reduction with Raney nickel into **14** and final desilylation, as it is indicated in Scheme 3.

Another interesting transformation of hydroxythioester **5** into the corresponding desulfinylated α-methyl-β-hydroxyacid, has been performed (Scheme 4). Hydrolysis of the thioester was readily achieved with lithium hydroxide in THF/H_2O.[33] However, the reaction of the obtained acid **15** with Raney nickel, in order to remove the sulfinyl group, was unsuccessful and the resulting product was unrecoverable. We then protected the sulfinylhydroxyacid **15** as its triisopropylsilyl derivative **16**, which reacted satisfactorily with Raney nickel in very high yield and afforded compound **17**, without apparent racemization at hydroxylic carbon. Desilylation of **17** with HF/pyridine[34] at room temperature afforded the expected hydroxyacid **18** (Scheme 4).

As a conclusion, we have demonstrated that the stereoselectivity of Mukaiyama aldol reactions of aldehydes and *O*-silylated ketenethioacetals can be efficiently controlled by a remote sulfinyl group. The essential role of $Yb(OTf)_3$ as a Lewis catalyst for achieving high level of diastereoselectivity has also been established for these 1,5-asymmetric induction processes. Desulfinylation and further transformation of the resulting isomers provided a new access to interesting carbinols and β-hydroxyacids.

3. Experimental

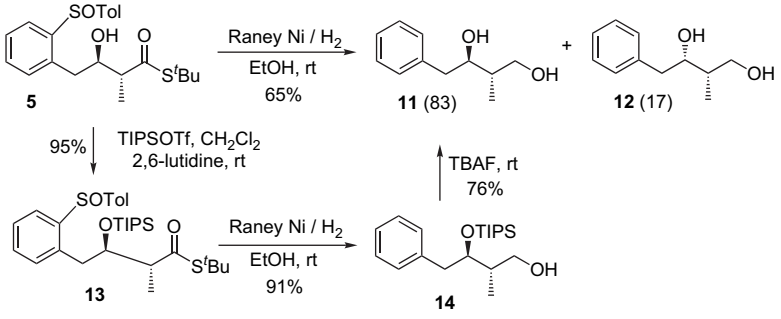
3.1. General methods

NMR spectra were obtained in $CDCl_3$ solutions at 300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively (*J* values are given in hertz). Melting points were measured in open capillary tubes. Mass spectra (MS) were obtained by FAB^+, ES^+ (MeOH+0.1% formic acid) or EI^+ with ionizing voltage of 70 eV. The des were evaluated by integration of well-separated signals of the ^{1}H NMR spectra. All reactions were carried out under an argon atmosphere in anhydrous solvents. THF was distilled from sodium-benzophenone under argon. CH_2Cl_2 was distilled from P_2O_5. Flash-column chromatography was performed using silica gel (230–400 mesh). The silyl thioenolates were synthesized according to the described procedures.

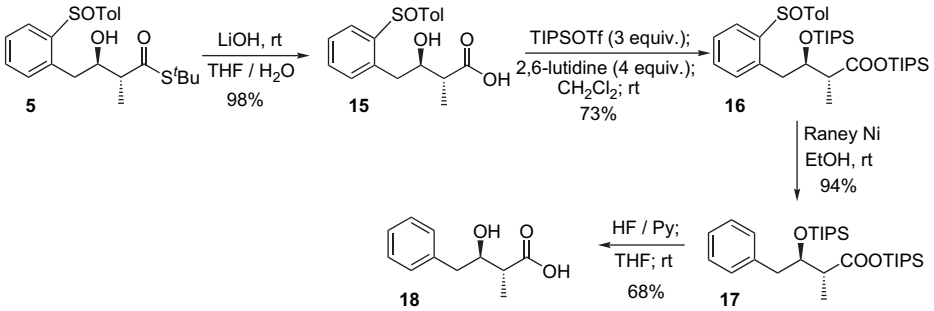
3.2. Mukaiyama aldol reaction. General procedure

A solution of aldehyde **1** (0.39 mmol) and $Yb(OTf)_3$ (0.46 mmol) in CH_3CN (3.4 mL) was stirred at room temperature for 30 min under an argon atmosphere. Then, this solution was cooled to the temperature indicated in each case and the corresponding silyl enol thioester (1.17 mmol) was added. The solution was stirred at the same temperature for the indicated time and then, quenched with an aqueous 1 M solution of HCl. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3.3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash-column chromatography using the eluent specified for each case.

3.2.1. *S-tert*-Butyl [3*R*,(S)*S*]-3-hydroxy-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (3). Compound **3** was obtained



Scheme 3.



Scheme 4.

from **2a** as a 94:6 mixture of **3** and **4** following the above general procedure at −40 °C for 90 min. Combined yield: 86%. Diastereomerically pure **3** was separated by flash-column chromatography (ethyl acetate–hexane 1:2) as a colorless oil. Yield: 79%; $[\alpha]_D^{20}$ −60.4 (*c* 0.2, $CHCl_3$); IR (film): 3386, 1597, 1216, 704 cm^{-1}; ^1H NMR: δ 7.82 (m, 1H), 7.47 and 7.25 (AA′BB′ system, 4H), 7.46–7.39 (m, 2H), 7.30 (m, 1H), 4.14 (ddt, *J* 7.3, 6.9, and 5.3 Hz, 1H), 2.95 (dd, *J* 14.1 and 6.9 Hz, 1H), 2.89 (dd, *J* 14.1 and 5.7 Hz, 1H), 2.57 (dd, *J* 15.6 and 4.8 Hz, 1H), 2.52 (dd, *J* 15.6 and 7.3 Hz, 1H), 2.37 (s, 3H), 1.45 (s, 9H). ^{13}C NMR: δ 199.9, 143.6, 141.8, 141.1, 136.4, 131.5, 131.2, 130.1, 127.8, 126.1, 125.9, 68.5, 50.0, 48.6, 38.1, 29.7, 21.4; MS (FAB$^+$) *m*/*z* 391 (100) $[M+1]^+$, 373 (12) $[M^+–H_2O]$, 307 (23), 91 (20), 89 (20); HRMS $[M+1]^+$: Calcd for $C_{21}H_{27}O_3S_2$: 391.1401; found, 391.1408.

3.2.2. *S*-*tert*-Butyl [3*S*,(S)*S*]-3-hydroxy-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (4). Compound **4** was obtained as the minor adduct, following the above general procedure, from **2a** at different experimental conditions (see Table 1). It was characterized from a 61:39 mixture of **3** and **4**, obtained by flash-column chromatography (ethyl acetate–hexane 1:2). ^1H NMR: (representative parameters) δ 4.13 (m, 1H), 2.94 (dd, *J* 14.5 and 7.0 Hz, 1H), 2.85 (dd, *J* 14.0 and 5.4 Hz, 1H), 2.65–2.43 (m, 2H); ^{13}C NMR: (representative parameters) δ 199.8, 69.4, 51.0.

3.2.3. *S*-*tert*-Butyl [2*R*,3*R*,(S)*S*]-3-hydroxy-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (5). Compound **5** was obtained from **2e** as a 83:17 mixture of **5** and **6**, following the above general procedure at 0 °C for 3 h. The mixture was purified by flash-column chromatography (ethyl acetate–hexane 1:1). Combined yield: 73%. Crystallization (ethyl acetate–hexane) afforded pure **5** as a white solid. Yield: 51%. Mp: 108–110 °C; $[\alpha]_D^{20}$ −85.5 (*c* 2.5, $CHCl_3$); IR (film): 3372, 2924, 1675, 1455 cm^{-1}; ^1H NMR: δ 7.75 (m, 1H), 7.47 and 7.25 (AA′BB′ system, 4H), 7.42–7.31 (m, 3H), 3.73 (m, 1H), 3.08 (d, *J* 7.7 Hz, 1H), 2.98 (dd, *J* 14.1 and 4.4 Hz, 1H), 2.91 (dd, *J* 14.1 and 8.4 Hz, 1H), 2.67 (m, 1H), 2.37 (s, 3H), 1.43 (s, 9H), 1.24 (d, *J* 6.9 Hz, 3H); ^{13}C NMR: δ 204.5, 143.7, 141.7, 141.1, 137.4, 131.2, 131.1, 130.0, 127.7, 126.2, 125.7, 74.2, 53.3, 48.5, 37.1, 29.7, 21.3, 15.0; MS (FAB$^+$) *m*/*z* 405 (100) $[M+1]^+$, 351 (19), 259 (30), 91(17), 89(9); HRMS $[M+1]^+$: Calcd for $C_{22}H_{29}O_3S_2$: 405.1558; found: 405.1572. Anal. Calcd for $C_{22}H_{28}O_3S_2$: C, 65.32; H, 6.98; S, 15.85. Found: C, 65.27; H, 6.88; S, 15.43.

3.2.4. *S*-*tert*-Butyl [2*S*,3*R*,(S)*S*]-3-hydroxy-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]butanethioate (6). Compound **6** was obtained as the minor adduct from **2e**, following the above general procedure at different experimental conditions (see Table 2). It was characterized from a 37:63 mixture of **5** and **6** obtained by flash-column chromatography (ethyl acetate–hexane 1:1). ^1H NMR: (representative parameters) δ 3.89 (m, 1H), 2.91–2.83 (m, 2H), 2.60 (dq, *J* 6.9 and 4.8 Hz, 1H), 1.45 (s, 9H), 1.23 (d, *J* 6.9 Hz, 3H); ^{13}C NMR: (representative parameters) δ 204.3, 74.1, 53.4, 48.2, 36.4, 29.6, 12.7.

3.2.5. (3*R*)-4-Phenylbutane-1,3-diol[35] (7). A 1 M solution of tetrabutylammonium fluoride in THF (0.59 mL, 0.59 mmol) was added to a solution of monoprotected diol **9** (0.12 mmol) in dichloromethane (1 mL) under an argon atmosphere. The reaction mixture was stirred for 18 h and then, quenched with an aqueous 1 M solution of HCl and extracted with dichloromethane (3×3 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:1). Yield: 77%, colorless oil; $[\alpha]_D^{20}$ +21.0 (*c* 0.6, $CHCl_3$); ^1H NMR: δ 7.35–7.20 (m, 5H), 4.09 (m, 1H), 3.92–3.78 (m, 2H), 2.82 (dd, *J* 13.3 and 5.2 Hz, 1H), 2.76 (dd, *J* 13.3 and 7.7 Hz, 1H), 2.38 (br s, 2H), 1.80–1.72 (m, 2H); ^{13}C NMR: δ 137.9, 129.4, 128.6, 126.6, 73.0, 61.7, 44.3, 37.7.

3.2.6. *S*-*tert*-Butyl [3*R*,(S)*S*]-4-[2-(*p*-tolylsulfinyl)phenyl]-3-(triisopropylsilyloxy)butanethioate (8). Triisopropylsilyl trifluoromethanesulfonate (72.9 μL, 0.27 mmol) was added to a solution of **3** (0.18 mmol) in anhydrous dichloromethane (3 mL) and 2,6-lutidine (41.6 μL, 0.36 mmol) under an argon atmosphere, and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (3×3 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4) affording pure **8** as a colorless oil. Yield: 90%; $[\alpha]_D^{20}$ −94.0 (*c* 3.9, $CHCl_3$); IR (film): 2961, 2866, 1680, 1462 cm^{-1}; ^1H NMR: δ 7.98 (m, 1H), 7.49 and 7.23 (AA′BB′ system, 4H), 7.45–7.32 (m, 3H), 4.51 (q, *J* 6.0 Hz, 1H), 3.00 (dd, *J* 14.3 and 6.6 Hz, 1H), 2.95 (dd, *J* 14.3 and 6.2 Hz, 1H), 2.48 (dd, *J* 14.9 and 5.6 Hz, 1H), 2.42 (dd, *J* 14.9 and 6.4 Hz, 1H), 2.35 (s, 3H), 1.43 (s, 9H), 0.96 (m, 21H); ^{13}C NMR: δ 197.7, 143.9, 142.0, 141.8, 136.1, 131.2, 130.7, 130.0, 127.7, 126.2, 124.7, 69.6, 51.4, 48.2, 39.1, 29.7, 21.4, 18.0, 12.5; MS (FAB$^+$) *m*/*z* 547 (50) $[M+1]^+$, 503 (100) $[M^+–CH(CH_3)_2]$; HRMS $[M+1]^+$: Calcd for $C_{30}H_{47}O_3S_2Si$: 547.2735; found, 547.2746.

3.2.7. (*R*)-4-Phenyl-3-(triisopropylsilyloxy)butan-1-ol (9). An excess amount of Raney nickel was added, under hydrogen atmosphere, to a solution of silylated alcohol **8** (85 mg, 0.15 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 16 h, and then, filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. Yield: 91%, colorless oil; $[\alpha]_D^{20}$ −15.0 (*c* 0.6, $CHCl_3$); IR (film): 3355, 3063, 2866, 1463 cm^{-1}; ^1H NMR: δ 7.22–7.07 (m, 5H), 4.25 (m, 1H), 3.84 (m, 1H), 3.64 (m, 1H), 2.95 (dd, *J* 13.2 and 4.9 Hz, 1H), 2.77 (dd, *J* 13.2 and 9.4 Hz, 1H), 2.48 (m, 1H, OH), 1.72 (m, 1H), 1.48 (m, 1H), 1.03 (m, 21H); ^{13}C NMR: 138.2, 129.3, 128.4, 126.0, 73.5, 59.9, 43.2, 36.4, 18.1, 12.6; MS (FAB$^+$) *m*/*z* 323 (27) $[M+1]^+$, 279 (20) $[M–CH(CH_3)_2]^+$, 131 (100), 91 (24); HRMS $[M+1]^+$: Calcd for $C_{19}H_{35}O_2Si$: 323.2406; found, 323.2396.

3.2.8. (2*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-phenylbutan-2-ol (10). It was obtained from diol **7**, following the reported procedure[30] $[\alpha]_D^{20}$ +10.6 (*c* 0.6, $CHCl_3$).

3.2.9. *S*-*tert*-Butyl [2*R*,3*R*,(S)*S*]-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]-3-(triisopropylsilyloxy)butanethioate (13). Triisopropylsilyl trifluoromethanesulfonate (66.8 μL, 0.25 mmol) was added to a solution of **5** (0.16 mmol) in

anhydrous dichloromethane (3 mL) and 2,6-lutidine (38.5 μL, 0.33 mmol) under an argon atmosphere, and the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with water, extracted with CH_2Cl_2 (3×3 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4) affording pure **13** as a colorless oil. Yield: 95%; $[\alpha]_D^{20}$ −110.0 (*c* 4.1, $CHCl_3$); IR (film): 2943, 2866, 1680, 1462 cm^{-1}; ^1H NMR: δ 7.95–7.92 (m, 1H), 7.49 and 7.34 (AA′BB′ system, 4H), 7.42–7.29 (m, 3H), 4.49 (dt, *J* 8.7 and 3.0 Hz, 1H), 2.85–2.29 (m, 2H), 2.76 (dd, *J* 14.3 and 2.6 Hz), 2.34 (s, 3H), 1.46 (s, 9H), 1.23 (d, *J* 7.0 Hz, 3H), 1.04 (m, 7H), 1.89 (m, 14H); ^{13}C NMR: δ 201.6, 144.6, 142.2, 141.4, 137.1, 130.9, 130.5, 129.9, 127.6, 125.9, 124.5, 74.5, 55.0, 48.1, 34.5, 29.8, 21.3, 18.0, 17.9, 17.6, 12.6, 12.3, 9.8. MS (ES^+): 583 (32), 561 (47), 471 (100), 387 (22); HRMS $[M+23]^+$: Calcd for $C_{31}H_{48}O_3NaSiS_2$: 583.2706; found, 583.2704. $[M+1]^+$: Calcd for $C_{31}H_{49}O_3SiS_2$: 561.2886; found, 561.2914.

3.2.10. (2*S*,3*R*)-2-Methyl-4-phenyl-3-(triisopropylsilyloxy)butan-1-ol (14). An excess amount of Raney nickel was added, under hydrogen atmosphere, to a solution of the silylated alcohol **13** (128 mg, 0.23 mmol) in ethanol (4 mL). The reaction mixture was stirred at room temperature for 17 h, and then filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4) affording pure **14** as a colorless oil. Yield: 91%; $[\alpha]_D^{20}$ +11 (*c* 6.4, $CHCl_3$); IR (film): 3384, 3063, 2866, 1463 cm^{-1}; ^1H NMR: δ 7.23–7.07 (m, 5H), 4.15 (ddd, *J* 8.7, 5.5, and 2.4 Hz, 1H), 3.90 (dd, *J* 11.0 and 3.9 Hz, 1H), 3.46 (m, 1H), 2.94 (dd, *J* 13.6 and 5.6 Hz, 1H), 2.85 (dd, *J* 13.6 and 9.1 Hz, 1H), 2.54 (br s, 1H), 1.57 (m, 1H), 1.03 (m, 7H), 0.98 (m, 17H); ^{13}C NMR: δ 138.4, 129.2, 128.4, 126.2, 78.7, 64.4, 41.5, 36.8, 18.2, 18.1, 17.6, 14.8, 12.8, 12.3; HRMS (ES^+) $[M+23]^+$: Calcd for $C_{20}H_{36}O_2NaSi$: 359.2376; found, 359.2369. $[M+1]^+$, Calcd for $C_{20}H_{37}O_2Si$: 337.2557; found, 337.2558.

3.2.11. (2*S*,3*R*)-2-Methyl-4-phenylbutane-1,3-diol (11).[32] A 1 M solution of tetrabutylammonium fluoride in THF (0.95 mL, 0.95 mmol) was added to a solution of monoprotected diol **14** (0.19 mmol) in dichloromethane (2 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 60 h and then filtered through a silica gel pad, which was washed with ethanol, and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:1). Yield: 76%, colorless oil; $[\alpha]_D^{20}$ +49 (*c* 2.3, $CHCl_3$). [Lit.[32] $[\alpha]_D^{25}$ +59 (*c* 0.27, $CHCl_3$)]; ^1H NMR: δ 7.36–7.23 (m, 5H), 3.80–3.74 (m, 2H), 3.67 (dd, *J* 10.9 and 7.1 Hz, 1H), 3.01 (dd, *J* 13.6 and 3.6 Hz, 1H), 2.90 (br s, 71H, OH), 2.66 (dd, *J* 13.6 and 9.5 Hz, 1H), 2.32 (br s, 1H), 1.81 (m, 1H), 1.01 (d, *J* 7 Hz, 3H).

3.2.12. (2*S*,3*R*) and (2*S*,3*S*)-2-Methyl-4-phenylbutane-1,3-diol (11+12).[32] An excess amount of Raney nickel was added, under hydrogen atmosphere, to a solution of the alcohol **5** (85 mg, 0.15 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 18 h, and then filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:1) affording a 83:17 mixture of **11+12**. Yield: 65%, colorless oil; ^1H NMR: (representative parameters of **12**) δ 4.10–4.04 (m, 1H), 2.78 (d, *J* 6.9 Hz, 2H), 1.95–1.87 (m, 1H), 1.04 (d, *J* 6.9 Hz, 3H).

3.2.13. [2*R*,3*R*,(S)*S*]-3-Hydroxy-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]butanoic acid (15). A solution of lithium hydroxide (1.02 mmol) in H_2O (1.5 mL) was added to a solution of **5** (0.17 mmol) in THF (1.5 mL). The reaction mixture was stirred at room temperature for 16 h, and then it was acidified with an aqueous 1 M solution of HCl, and extracted with dichloromethane (3×3 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and the solvent evaporated. Yield: 98%, colorless oil; $[\alpha]_D^{20}$ −28 (*c* 0.5, $CHCl_3$); IR (film): 3356, 2923, 1720, 1594 cm^{-1}; ^1H NMR: δ 7.65 (dd, *J* 8.0 and 1.3 Hz, 1H), 7.44 and 7.23 (AA′BB′ system, 4H), 7.41–7.30 (m, 3H), 3.82 (m, 1H), 3.07 (dd, *J* 14.1 and 8.5 Hz, 1H), 2.98 (dd, *J* 14.1 and 4.1 Hz, 1H), 2.59 (q, *J* 7.0 Hz, 1H), 2.35 (s, 3H), 1.25 (d, *J* 7.2 Hz, 3H); ^{13}C NMR: δ 178.2, 143.1, 141.9, 139.9, 137.6, 131.4, 130.1, 127.8, 126.2, 125.9, 73.5, 44.7, 37.0, 21.4, 14.3; MS (EI^+) *m/z* 315 (75) $[(M+1)-H_2O]^+$, 297 (15), 241 (33), 91 (71); HRMS $[(M+1)-H_2O]^+$: Calcd for $C_{18}H_{19}O_3S$: 315.1055; found: 315.1053.

3.2.14. Triisopropylsilyl [2*R*,3*R*,(S)*S*]-2-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]-3-(triisopropylsilyloxy)butanoate (16). Triisopropylsilyl trifluoromethanesulfonate (142.0 μL, 0.52 mmol) was added to an anhydrous solution of hydroxyacid **15** (0.17 mmol) and 2,6-lutidine (82 μL, 0.70 mmol) in dichloromethane (3 mL), under an argon atmosphere. The reaction mixture was stirred at room temperature for 16 h, and then, quenched with water and extracted with dichloromethane (3×3 mL). The organic extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash-column chromatography (ethyl acetate–hexane 1:4). Yield: 73%, colorless oil; $[\alpha]_D^{20}$ −72.0 (*c* 3.1, $CHCl_3$); IR (film): 2945, 2867, 1715, 1464 cm^{-1}; ^1H NMR: δ 7.80 (m, 1H), 7.45 and 7.20 (AA′BB′ system, 4H), 7.42–7.27 (m, 3H), 4.62 (m, 1H), 3.02–2.87 (m, 2H), 2.54 (m, 1H), 2.33 (s, 3H), 1.33–1.26 (m, 5H), 1.07 (m, 19H), 0.89 (m, 21H); ^{13}C NMR: δ 173.8, 144.8, 142.6, 141.5, 137.0, 130.5, 130.2, 129.9, 127.6, 126.0, 124.2, 74.1, 47.2, 34.7, 21.3, 17.9, 17.8, 12.7, 11.9; MS (FAB^+) *m/z* 645 (27) $[M+1]^+$, 601 (100) $[M-SiCH_3]^+$; HRMS $[M+1]^+$: Calcd for $C_{36}H_{61}O_4SSi_2$: 645.3829; found: 645.3821.

3.2.15. Triisopropylsilyl [2*R*,3*R*]-2-methyl-4-phenyl-3-(triisopropylsilyloxy)butanoate (17). An excess of activated Raney nickel was added to a solution of **16** (0.12 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 14 h under hydrogen atmosphere and then it was filtered through a Celite pad, which was washed with ethanol, and the solvent was evaporated. Yield: 94%, colorless oil; $[\alpha]_D^{20}$ −6.4 (*c* 1.7, $CHCl_3$); IR (film): 3064, 2893, 1708, 1495 cm^{-1}; ^1H NMR: 7.20–7.07 (m, 5H), 4.43 (dt, *J* 8.7 and 3.4 Hz, 1H), 2.80–2.69 (m, 2H), 2.61 (dd, *J* 13.4 and 8.8 Hz, 1H), 1.32–0.79 (m, 45H); ^{13}C NMR: δ 174.0, 139.4, 129.8, 128.1, 126.1, 75.0, 46.9, 39.9, 18.1, 18.0, 17.9, 12.7, 12.0; MS (FAB^+) *m/z* 507 (8) $[M+1]^+$, 463 (100) $[M-CH(CH_3)_2]^+$, 277 (11),

91 (6); HRMS $[M+1]^+$: Calcd for $C_{29}H_{55}O_3Si_2$: 507.3689; found, 507.3677.

3.2.16. [2*R*,3*R*]-3-Hydroxy-2-methyl-4-phenylbutanoic acid (18).[33] To a solution of **17** (0.04 mmol) in THF (2.1 mL) was dropwise added hydrogen fluoride–pyridine (0.47 mL) at 0 °C. The mixture was stirred at room temperature for 17 h, and then, diluted with ether (1 mL) and cooled at 0 °C before slowly adding a saturated aqueous sodium hydrogencarbonate solution until CO_2 evolution ceased. The organic layer was discarded, and the aqueous one was extracted with ether. The combined organic phases were washed with saturated aqueous $CuSO_4$ solution, water, and brine. The organic layer was separated, dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford the acid as a yellow oil. Yield: 68% (^{1}H NMR); ^{1}H NMR: 7.37–7.21 (m, 5H), 3.93 (m, 1H), 2.95–2.59 (m, 3H), 1.32 (d, *J* 7.0 Hz, 3H).

Acknowledgements

We thank the CICYT (Grant BQU2003-04012) for financial support. M.A.F.-I. thanks Comunidad Autónoma de Madrid for a predoctoral fellowship.

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Stereochemistry of substituted isoxazolidines derived from *N*-methyl *C*-diethoxyphosphorylated nitrone

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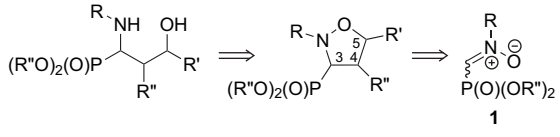
Received 26 June 2006; revised 21 September 2006; accepted 5 October 2006
Available online 27 October 2006

Abstract—Cycloadditions of *N*-methyl-*C*-(diethoxyphosphoryl)nitrone **1a** to cyclic alkenes proceeded regio- and diastereospecifically. Reactions of **1a** with 1,1-disubstituted alkenes led to the regiospecific formation of 5,5-disubstituted isoxazolidines **7/8** in nearly equimolar ratios, whereas additions to *trans*-1,2-disubstituted alkenes gave four isomeric isoxazolidines with up to 80% regioselectivity and moderate (up to 60%) diastereoselectivity. Stereochemistry of the substituted isoxazolidines was established based on the conformational analysis using vicinal H–H, H–P and P–C couplings, and was, in some cases, supported by geminal H–C–P=O coupling and deshielding P=O and C=O effects.

1. Introduction

Isoxazolidines have been found to exhibit antimicrobial activity[1–4] and have been used as enzyme inhibitors.[5–8] Isoxazolidine nucleoside analogues, in which a furanose ring has been replaced by an *N*,*O*-heterocyclic system, are a particularly interesting group of compounds due to their potential antiviral activity.[9–14] Isoxazolidines have also been employed as useful building blocks in the synthesis of various natural and unnatural compounds, including alkaloids, biologically active β-aminoacids, β-lactams, amino sugars, as well as simple 1,3-aminoalcohols owing to the facile cleavage of the N–O bond.[15–17] The 1,3-dipolar cycloaddition of nitrones to alkenes has been the most efficient approach employed for the construction of isoxazolidines, since the stereochemistry of the reaction is predictable, and the mechanism has been established.[15,17,18] A wide range of acyclic and cyclic nitrones have been reacted with substituted alkenes leading to the formation of structurally diverse and highly functionalized nitrogen-containing compounds.[15,16,19] Studies on both inter- and intramolecular nitrone to alkene dipolar cycloadditions have received much interest from a stereochemical point of view, since up to three new stereogenic centres can be created in the isoxazolidines depending on the structural features of the starting materials. Despite the known existence of acyclic nitrones as mixtures of (*E*)- and (*Z*)-isomers, or as single isomer in the case of cyclic analogues, the diastereoselectivity of cycloaddition depends also on the structure of the alkene dipolarophiles. In most cases, cycloadducts were formed in a predictable regio- and stereocontrolled manner due to steric and electronic effects.

Synthesis of functionalized α-aminophosphonates has attracted significant attention, since α-aminophosphonates have been recognized as structural mimetics of natural and unnatural α-aminoacids.[20] Recently, a convenient method for the synthesis of *C*-phosphorylated nitrones **1** has been described and their reactivity in cycloadditions with terminal alkenes has been briefly examined.[21] Substituted 3-phosphorylated isoxazolidines can be employed as key intermediates in the synthesis of functionalized 1-amino-3-hydroxyphosphonates by utilizing the known hydrogenolytic transformation of isoxazolidines into 4-hydroxy-2-aminoacids (Scheme 1).



Scheme 1. Retrosynthesis of substituted α-aminophosphonates from nitrones **1**.

In this paper, a full account of the studies previously communicated[21] is given and the reactivity of nitrone **1a** with di-, tri- and tetrasubstituted alkenes is explored. In particular, 1,2-disubstituted and especially cyclic alkenes were studied in order to obtain particularly interesting, highly functionalized conformationally restricted phosphonate analogues of aminoacids.

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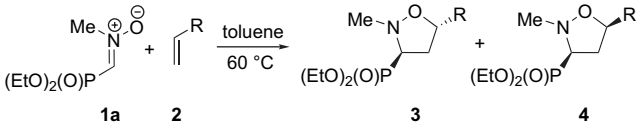
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.011

2. Results and discussion

As reported earlier, the 1,3-dipolar cycloadditions of nitrone **1a** to terminal alkenes were carried out in toluene at 60 °C (Scheme 2, Table 1).[21] Reactions were conducted until the starting nitrone disappeared. The ratios of diastereomeric isoxazolidines **3** and **4** were calculated from the ^{31}P and ^{1}H NMR spectra of crude reaction mixtures.



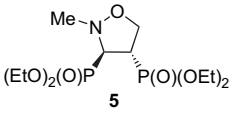
Scheme 2. 1,3-Dipolar cycloadditions of nitrone **1a** and terminal alkenes.

Table 1. Isoxazolidines **3** and **4** produced via Scheme 2

Entry	R	Reaction time (h)	trans/cis ratio (**3**:**4**)	Yield (%)
a	CH_2OH	48	62:38	**3a** (38);[a] **4a** (20)[a]
b	CH_2NHBoc	48	72:28	Inseparable (83)[b]
c	CH_2Br	40	65:35	Inseparable (61)[b]
d	CH_2SiMe_3	40	95:5	**3d** (64)[a]
e	COOMe	24	90:10	**3e** (73)[a]
f	OAc	40	90:10	**3f** (62)[a]
g	Ph	24	90:10	**3g** (60);[a] **4g** (2)[a]
h	$P(O)(OEt)_2$	24	74:19[c]	**3h** (29);[a] **4h** (7)[a]
i	$CH_2P(O)(OEt)_2$	50	74:26	**3i** (23);[a] **4i** (4)[a]

[a] Yield of pure materials obtained after silica gel chromatography.
[b] Yield of pure mixture of two diastereoisomers.
[c] C4-regioisomer **5** (7%) was also produced.

The cycloadditions of nitrone **1a** with terminal alkenes were regiospecific (except for entry h, Table 1) and afforded trans/cis mixtures of *C*5-substituted isoxazolidines **3a–i** and **4a–i** in moderate (65:35) to very good (95:5) diastereoselectivity. When diethyl vinylphosphonate (**2h**) was used, however, the *C*4-regioisomer **5** was also formed, and its presence was detected in the crude product by ^{31}P NMR spectroscopy. Based on the coupling constant value of $^{3}J(P\text{–}C3C4\text{–}P)$=30.5 Hz, which was found to be comparable with a similar coupling observed for **7f** [$^{3}J(P\text{–}C3C3a\text{–}P4)$=25.5 Hz] (vide infra), the trans arrangement of the two phosphonate substituents in **5** was suggested.



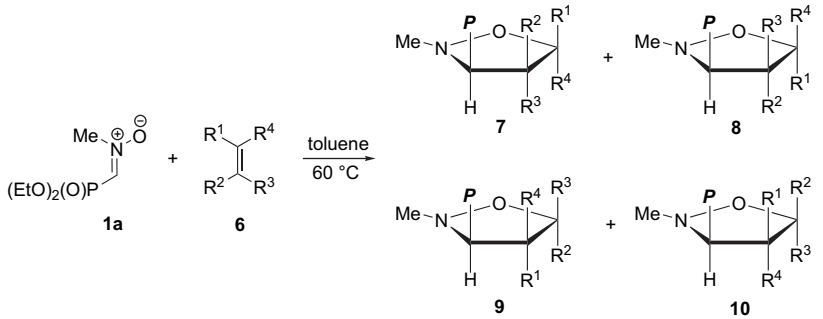
The trans configuration of the major 3,5-substituted isoxazolidines **3** and the cis relationship for minor isomers **4** were already established.[21]

The ratios of isoxazolidines **3** and **4** produced in thermal cycloadditions can be modified by the application of $ZnCl_2$.[19] When nitrone **1a** was reacted with allyl alcohol (**2a**) and allyltrimethylsilane (**2d**) in the presence of an equimolar amount of $ZnCl_2$ at room temperature, mixtures of isoxazolidines **3** and **4** enriched with the cis isomers (20:80 and 55:45, respectively) were produced, as compared to those formed under thermal conditions (Table 1, entries a and d). However, for vinylphosphonate (**2h**) and allylphosphonate (**2i**) no influence of $ZnCl_2$ on the cis/trans ratios of the respective isoxazolidines was noticed.

Having established the stereochemistry of the cycloaddition of **1a** with terminal alkenes, the scope and limitation of this reaction were investigated with di-, tri- and tetrasubstituted alkenes (Scheme 3, Table 2).

Addition of **1a** to cyclic alkenes **6a–6f** was diastereospecific (entries a–f, Table 2), and was also found to be regiospecific for **6c** and **6f** (entries c and f, Table 2). However, a 21:79 mixture of diastereoisomeric products was formed from 3-phospholene **6e**, because a new stereogenic centre at P(6) in the bicyclic system was created (entry e, Table 2). Surprisingly, a single diastereoisomer **7f** was obtained from 2-phospholene **6f**. Cycloadditions with 1,1-disubstituted alkenes **6g**, **6h** and **6i** also occurred regiospecifically (Table 2), however, a negligible diastereoselectivity for **6h** and **6i** was observed (entries h and i). On the other hand, *trans*-1,2-disubstituted alkenes **6j** and **6k** led to mixtures of four isoxazolidines with 54 and 82% regioselectivity and moderate, 20–60% diastereoselectivity (entries j and k, Table 2). Furthermore, treatment of nitrone **1a** with diethyl 2-(propan-2-ylidene)malonate **6l** did not give a cycloaddition product, due to the decomposition of the starting nitrone as was observed after heating the reaction mixture for 20 days.

The mixtures of 3,5,5-trisubstituted isoxazolidines **7h** and **8h** as well as **7i** and **8i** were found to be partially separable, giving fractions enriched with the respective isomers of up to 90% purity. This was sufficient to unambiguously calculate the chemical shifts and coupling constants for each component of the diastereoisomeric pairs of isoxazolidines **7h/8h** and **7i/8i**. Three out of four 3,4,5-trisubstituted isoxazolidines formed from chalcone **6j** and nitrone **1a** were isolated as pure compounds in 12% (**7j**), 50% (**8j**) and 3% (**10j**)



Scheme 3. 1,3-Dipolar cycloadditions of nitrone **1a** and substituted alkenes; **P**=$P(O)(OEt)_2$.

Table 2. Isoxazolidines **7**, **8**, **9** and **10** produced via Scheme 3

Entry	Substituted alkenes **6**				Reaction time	**7**:**8**	**9**:**10**	Yield (%)
	R^1	R^2	R^3	R^4				
a	H	H	$-CH_2CH_2CH_2CH_2-$		18 days	100:0	—	**7a** (100)[a]
b	H	H	$-CH_2CH_2CH_2-$		7 days	100:0	—	**7b** (90)[a]
c	H	H	$-CH_2CH_2O-$		24 h	100:0	—	**7c** (70)[a]
d	H	H	$-CH_2OCH_2-$		24 h	100:0	—	**7d** (71)[a]
e	H	H	$-CH_2P(O)(Ph)CH_2-$		48 h	100:0	—	**7e** (82)[b] (inseparable)[c]
f	H	H	$-P(O)(Ph)CH_2CH_2-$		24 h	100:0	—	**7f** (88)[a]
g	$P(O)(OEt)_2$	H	H	$P(O)(OEt)_2$	24 h	—	—	**7g** (90)[a]
h	$P(O)(OEt)_2$	H	H	COOEt	24 h	46:54	—	Inseparable (90)[b]
i	CH_3	H	H	COOMe	24 h	40:60	—	Inseparable (90)[b]
j	H	C(O)Ph	H	Ph	48 h	20:57	5:18	**7j** (12),[a] **8j** (50),[a] **10j** (3)[a]
k	H	COOEt	H	Ph	48 h	55:36	7:2	**7k** (13),[a] **8k** (7)[a]
l	COOEt	CH_3	CH_3	COOEt	20 days	—	—	Decomposition[d]

[a] Yield of pure materials obtained after silica gel chromatography.
[b] Yield of pure mixture of two diastereoisomers.
[c] A mixture of inseparable *P*(6)-diastereoisomers (21:79) was produced.
[d] Decomposition of the starting nitrone **1a** was observed. The unreacted alkene **6l** was recovered in 80% yield.

yields. On the other hand, only two major diastereoisomers **7k** and **8k**, obtained from ethyl cinnamate **6k**, could be isolated as pure compounds.

The assignment of relative configurations of isoxazolidines has often been difficult due to conformational flexibility of the substituted five-membered ring. The structures of the cycloadducts obtained in this study were established based on conformational analysis. To this end, all vicinal H–H coupling constants and chemical shifts of ring protons were unambiguously extracted from the ^{1}H NMR spectra. In addition, the presence of the diethoxyphosphoryl group at C(3) in the isoxazolidine ring imparted greater stereochemically valuable data over *PCCH*[22,23] and *PCCC*[23–26] vicinal couplings, and appeared to be extremely useful in establishing the stereochemistries of phosphorus-labelled heterocycles.[27,28]

Based on the accepted concerted mechanism of the nitrone to alkene cycloaddition,[15,17,18] the cis-fusion of the rings in the bicyclic isoxazolidines obtained from nitrone **1a** and cyclic alkenes **6a**–**6f** is expected. A set of vicinal couplings found for **7a**: *J*(*H*–C3C3a–*H*)=3.6 Hz, *J*(*H*–C3aC7a–*H*)=4.2 Hz, *J*(*H*–C3aC3–*P*)=16.0 Hz, *J*(*P*–CC–*C*7a)=4.5 Hz and *J*(*P*–CC–*C*4)=11.5 Hz, *J*(*Hax*–C3aC4–*Hax*)=11.0 Hz, *J*(*Hax*–C3aC4–*Heq*)=5.0 Hz, *J*(*Heq*–C7aC7–*Heq*)=4.2 Hz and *J*(*Heq*–C7aC7–*Hax*)=4.2 Hz clearly indicates the stable E_{3a} conformation of the isoxazolidine ring, while the cyclohexane ring exists as a $_{7a}C^5$ chair. In this conformation of the bicyclic **7a**, the diethoxyphosphoryl group is forced to reside in a pseudoaxial position of the isoxazolidine ring. Furthermore, it occupies the same side of the molecule as both bridgehead protons, *H*–C(3a) and *H*–C(7a) (Fig. 1).

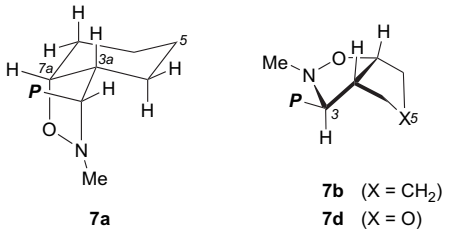


Figure 1. The preferred conformation of **7a**, **7b** and **7d**; **P**=P(O)(OEt)$_2$.

Similar application of the dihedral angle relationships derived from the sets of vicinal couplings found for compounds **7b**–**7f** allowed us to propose stable conformations for these fused isoxazolidines (Table 3, Figs. 1 and 2). This clearly established the cis relationships between the diethoxyphosphoryl group at C(3) and both bridgehead hydrogens at C(3a) and C(6a).

In addition to the various vicinal coupling constants, two other spectral data deserve comments in connection with conformational preferences of **7f** and both isomers of **7e**. Significant deshielding of the *H*–C(3) in **7f** (δ_H=3.79 ppm), as compared to the chemical shifts of the same hydrogen atoms in **7a**–**7e** (2.38–2.99 ppm), undoubtedly results from very close spacial proximity of the P=O group from the phospholane ring and *H*–C(3) (Fig. 2). This observation strongly suggests that the P=O group at P(4) adopts a pseudoaxial position. Less pronounced deshielding of the *H*–C(3) (δ_H=2.99 ppm) and *Hα*–C(4) (δ_H=2.25 ppm) in the major diastereoisomer of **7e** was observed, as compared to the same hydrogens in the minor diastereoisomer (δ_H=2.72 and 1.97 ppm, respectively). On the other hand, the P=O group slightly deshielded the *H*–C(3a) (δ_H=3.65 ppm) and *Hα*–C(6a) (δ_H=4.82 ppm) in the minor diastereoisomer of **7e**.

Moreover, in establishing the conformational features of the isoxazolidine/phospholane fused systems **7e** and **7f** two-bond H–C–P couplings[27] proved very helpful. Thus, the pseudoaxial disposition of phosphoryl oxygen in the phospholane ring of **7f** is further supported by the value of ^2J(PCH)=2.4 Hz found for the H–C_{3a}–P_4=O unit, as illustrated by the respective Newman projection (Fig. 2). For the major and minor diastereoisomers of **7e** two slightly different conformations were assigned based on the analysis of vicinal couplings (Fig. 2). Again, values of the geminal phosphorus–hydrogen couplings [$^2J(PCH_{4\alpha})$=16.8 Hz, $^2J(PCH_{4\beta})$=7.5 Hz for the major **7e** and $^2J(PCH_{4\alpha})$=6.8 Hz, $^2J(PCH_{4\beta})$=15.4 Hz, $^2J(PCH_{6\beta})$=16.4 Hz for the minor **7e**] fully support the already established conformations.

Structures of 3,5,5- and 3,4,5-trisubstituted isoxazolidines (Table 2, entries h–k) were also unequivocally established based on the conformational analysis. The diagnostic vicinal couplings are shown in Table 4.

Table 3. Vicinal couplings for compounds **7b–7f** and their conformations

Vicinal coupling constants (Hz)	Compounds					
	7b	**7c**	**7d**	**7e** (major)	**7e** (minor)	**7f**
J(*P*–C3C4–*C*6*a*)	9.8	10.0	9.5	10.0	6.9	8.8
J(*P*–C3C3a–*C*4)	3.4	3.8	3.4	5.2	8.3	—
J(*P*–C3C3a–*H*)	16.2	17.1	16.0	18.3	20.0	20.1
J(*H*–C3C3a–*H*)	8.0	8.4	7.8	7.0	5.2	5.7
J(*H*–C3aC6a–*H*)	8.0	5.4	7.0	7.0	6.4	5.7
J(*H*–C3aC4–*Hα*)	0	0.9	0	7.0	9.3	—
J(*H*–C3aC4–*Hβ*)	8.0	8.4	6.0	9.2	8.8	—
J(*H*–C6aC6–*Hα*)	0	—	0	5.3	2.0	0
J(*H*–C6aC6–*Hβ*)	3.7	—	3.8	5.3	6.4	4.5
J(*Hβ*–C4C5–*Hα*)	Overlap	11.4	—	—	—	—
J(*Hα*–C4C5–*Hα*)	Overlap	5.4	—	—	—	—
J(*Hβ*–C4C5–*Hβ*)	Overlap	8.4	—	—	—	—
J(*P*5–C4C3a–*H*)	—	—	—	8.7	0	—
J(*P*4–C3aC3–*H*)	—	—	—	—	—	18.9
J(*P*4–C3aC6a–*H*)	—	—	—	—	—	24.0
J(*P*5–C4C3a–*C*3)	—	—	—	6.0	10.6	—
J(*P*5–C4C3a–*C*6*a*)	—	—	—	10.0	9.7	—
J(*P*5–C6C6a–*H*)	—	—	—	18.6	21.2	—
Conformation[a]	E_3/E_5	E_3/E^4	E_3/E_5	$E_3/{}^4T_5$	${}^{6a}E/E_4$	${}^{6a}E/{}^6E$

[a] Isoxazolidine ring/fused ring.

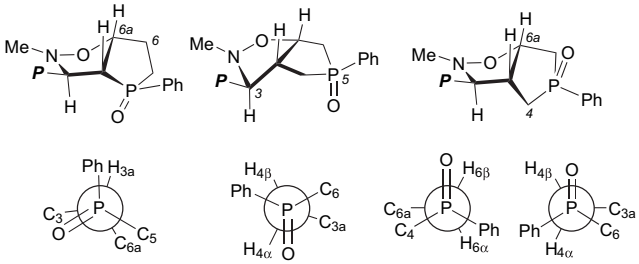
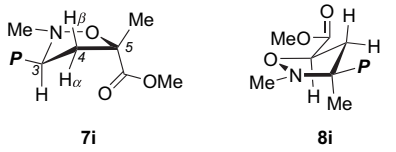


Figure 2. The preferred conformations of **7f** and **7e** (major—left, minor—right); **P**=P(O)(OEt)$_2$.

Furthermore, in some instances the P═O and C═O deshielding effects were observed and they were employed as additional arguments for establishing the relative configurations. For instance, in the E_5 conformation of the isoxazolidine **7i**, the *Hα*–C(4) is shifted downfield (δ_H=3.05 ppm) by the C═O group compared to the same hydrogen atom in diastereoisomer **8i** (δ_H=2.36 ppm). On the other hand, the *Hβ*–C(4) in **8i** (cis-positioned to the COOMe) was shifted downfield (δ_H=3.22 ppm), while in **7i** the respective hydrogen resonated at δ_H=2.49 ppm (Fig. 3).



7i **8i**

Figure 3. The preferred conformations of **7i** and **8i**; **P**=P(O)(OEt)$_2$.

A general tendency of the diethoxyphosphoryl group to occupy pseudoequatorial positions is observed for all isoxazolidines reported herein, except for the compound **7a** in which this substituent is forced to reside in a pseudoaxial position in the chair conformation of the six-membered ring. Moreover, the phenyl group also prefers to be positioned equatorially. In the phospholane rings of compounds **7e** and **7f** this preference is additionally enhanced by pseudoaxial orientation of the P═O group.

3. Conclusions

Cycloadditions of nitrone **1a** to cyclic alkenes led to the formation of single diastereoisomers **7**, in which the diethoxyphosphoryl group is located on the same side of the

Table 4. Vicinal couplings for compounds **7h–k**, **8h–k** and **10j** and their conformations

Vicinal coupling constants (Hz)	Compounds								
	7h	**8h**	**7i**	**8i**	**7j**	**8j**	**10j**	**7k**	**8k**
J(*P*–C3C4–*C*5)	12.0	9.4	8.3	10.6	3.7	5.4	9.2	4.3	5.4
J(*P*–C3C4–*Hα*)	3.3	4.8	4.8	6.6	21.3	—	—	17.4	
J(*P*–C3C4–*Hβ*)	14.4/16.5[a]	16.5	16.8	18.3	—	17.7	17.1	—	13.5
J(*H*–C3C4–*Hα*)	6.6	8.4	7.8	9.3	9.9	—	—	10.2	—
J(*H*–C3C4–*Hβ*)	12.3	9.6	10.5	8.7	—	7.2	8.7	—	7.5
J(*Hα*–C4C5–*Hβ*)	—	—	—	—	9.0	—	—	8.7	—
J(*Hβ*–C4C5–*Hα*)	—	—	—	—	—	7.8	4.2	—	7.0
J(*P*–C5C4–*C*3)	6.0	4.5	—	—	—	—	—	—	—
J(*P*–C5C4–*Hα*)	0.9	17.7	—	—	—	—	—	—	—
J(*P*–C5C4–*Hβ*)	16.5/14.4[a]	11.4	—	—	—	—	—	—	—
J(*P*–C3C4–*C*═O)	—	—	—	—	5.2	4.0	—	6.6	5.4
J(*P*–C3C4–C_{ipso})	—	—	—	—	—	—	0	—	—
Conformation	${}_3E$	E^4	${}_3E$	E^4	E^5	E_5	${}_3T^2$	E^5	${}^1E$

[a] The values cannot be assigned unequivocally.

molecule as both bridgehead hydrogens. Reactions of **1a** with 1,1-disubstituted alkenes appeared to be regiospecific, giving 3,5,5-trisubstituted isoxazolidines **7/8** with low diastereoselectivities. Additions to *trans*-1,2-disubstituted alkenes proceeded with good regio- (up to 80%) and moderate (up to 60%) diastereoselectivity.

Stereochemistry of substituted isoxazolidines has been established based on the conformational analysis using combinations of *H*–CC–*H*, *H*–CC–*P* and *C*–CC–*P* vicinal couplings, H–C–P=O geminal couplings and deshielding effects of the P=O and C=O groups.

As the synthesis of *C*-phosphorylated isoxazolidine cycloadducts is straightforward, and the regio- and stereochemistry of their formation is predictable, they could be used as suitable precursors for the synthesis of various substituted α-aminophosphonates. Studies on the synthesis of enantiomerically pure α-aminophosphonates, including phosphohomoserine, phosphonate analogues of α-hydroxyglutamic acid and proline are currently under investigation in this laboratory, and among others.

4. Experimental

4.1. General

^{1}H NMR spectra were taken in $CDCl_3$ or C_6D_6 on the following spectrometers: Varian Mercury-300 and Bruker DPX (500 MHz) with TMS as an internal standard. ^{13}C and ^{31}P spectra were recorded for $CDCl_3$ or C_6D_6 solution on a Varian Mercury-300 instrument at 75.5 and 121.5 MHz, respectively. ^{1}H{^{31}P} NMR and ^{1}H–^{1}H COSY experiments were applied, when necessary to support spectral assignments. IR spectra were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin–Elmer PE 2400 CHNS analyser.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in various ethyl acetate–hexanes, toluene–isopropanol, toluene–hexanes or chloroform–methanol solvent system. Visualization of spots was effected with iodine vapours.

4.2. General procedure for the cycloaddition of nitrone 1a to alkenes

Nitrone **1a** (1.0 mmol) and an alkene (1.0–10.0 mmol) were stirred in toluene (1–5 mL) at 60 °C and the disappearance of the starting nitrone was monitored by TLC. All volatiles were removed in vacuo and the crude products were purified by chromatography on a silica gel column.

4.3. Diethyl 5-(hydroxymethyl)-2-methylisoxazolidin-3-yl-3-phosphonates (3a and 4a)

From nitrone **1a** (0.914 g, 4.68 mmol) and allyl alcohol (0.64 mL, 9.4 mmol), a mixture of isoxazolidines **3a** and **4a** (1.237 g) was obtained and purified on silica gel with chloroform–MeOH (100:1).

*Compound **3a***: yield 0.45 g, 38%. Colourless oil. IR (film): ν=3400, 2983, 2910, 1444, 1226, 1051, 1023, 970 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.27–4.12 (m, 5H, *H*–C5 and 2×CH_2–O–P), 3.82 (ddAB, J_{AB}=12.0 Hz, J_{3-4}=2.7 Hz, J=0.9 Hz, 1H, C*H*$_2$OH), 3.59 (dAB, J_{AB}=12.0 Hz, J_{3-4}=4.5 Hz, 1H, C*H*$_2$OH), 2.96 (very br s, 1H, CH–P), 2.89 (d, J=0.9 Hz, 3H, C*H*$_3$–N), 2.63–2.34 (m, 2H, P–CH–C*H*$_2$), 2.09 (br s, 1H, OH), 1.36 (t, J=6.9 Hz, 3H, C*H*$_3$–CH_2–O–P), 1.35 (t, J=6.9 Hz, 3H, C*H*$_3$–CH_2–O–P). ^{1}H NMR (C_6D_6, 300 MHz): 4.15–3.97 (m, 3H, CH_2–O–P, *H*–C5), 3.97–3.87 (m, 2H, CH_2–O–P), 3.44 (dAB, J_{AB}=12.0 Hz, J=3.3 Hz, 1H, C*H*$_2$OH), 3.25 (dAB, J_{AB}=12.0 Hz, J=4.5 Hz, 1H, C*H*$_2$OH), 2.93 (s, 3H, C*H*$_3$–N), 2.82 (bdd, $J_{3-4\alpha}$=9.6 Hz, $J_{3-4\beta}$=7.8 Hz, 1H, *H*–C3) 2.47 (dddAB, $J_{P-4\beta}$=18.1 Hz, J_{AB}=12.2 Hz, $J_{3-4\beta}$=7.8 Hz, $J_{5-4\beta}$=7.8 Hz, 1H, *Hβ*–C4), 2.22 (dddAB, J_{AB}=12.2 Hz, $J_{P-4\alpha}$=9.6 Hz, $J_{3-4\alpha}$=9.6 Hz, $J_{5-4\alpha}$=7.8 Hz, 1H, *Hα*–C4), 1.20 (br s, 1H, OH), 1.07 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 77.60 (d, $^3J_{PCCC}$=8.3 Hz, C5), 64.41 (d, $^1J_{PC}$=166.8 Hz, C3), 63.29 (d, J=6.8 Hz, C–O–P), 62.62 (d, J=6.8 Hz, C–O–P), 62.84 (s, C1′), 46.22 (very br d, *C*–N–C–P), 34.09 (br d, $^2J_{PCC}$=2.3 Hz, C4), 16.75 (d, J=5.3 Hz), 16.70 (d, J=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 22.98. Anal. Calcd for $C_9H_{20}NO_5P$: C, 42.69; H, 7.96; N, 5.53. Found: C, 42.59; H, 8.07; N, 5.35.

*Compound **4a***: yield 0.236 g, 20%. Colourless oil. IR (film): ν=3399, 2983, 2911, 1444, 1231, 1047, 1028, 970 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.34 (dddd, $J_{5-4\alpha}$=8.1 Hz, $J_{5-4\beta}$=6.0 Hz, $J_{5-1'a}$=4.8 Hz, $J_{5-1'b}$=2.7 Hz, 1H, *H*–C5), 4.28–4.12 (m, 4H, CH_2–O–P), 3.75 (dAB, J_{AB}=12.0 Hz, $J_{5-1'a}$=2.7 Hz, 1H, *Ha*–C1′), 3.65 (dAB, J_{AB}=12.0 Hz, $J_{5-1'b}$=4.8 Hz, 1H, *Hb*–C1′), 3.07 (ddd, $J_{3-4\alpha}$=9.0 Hz, $J_{3-4\beta}$=7.2 Hz, J_{3-P}=6.3 Hz, 1H, *H*–C3), 2.81 (d, J=0.3 Hz, 3H, C*H*$_3$–N), 2.63 (dddAB, J_{AB}=12.6 Hz, $J_{4\alpha-P}$=12.6 Hz, $J_{4\alpha-3}$=9.0 Hz, $J_{4\alpha-5}$=8.1 Hz, 1H, *Hα*–C4), 2.47 (dddAB, J_{AB}=12.6 Hz, $J_{4\beta-P}$=18.9 Hz, $J_{4\beta-3}$=7.2 Hz, $J_{4\beta-5}$=6.0 Hz, 1H, *Hβ*–C4), 2.46 (br s, 1H, OH), 1.34 (t, J=6.9 Hz, 6H, 2×C*H*$_3$–CH_2–O–P). ^{1}H NMR (C_6D_6, 300 MHz): 4.10–3.84 (m, 5H, CH_2–O–P, *H*-5), 3.69 (dAB, J_{AB}=12.0 Hz, $J_{5-1'a}$=2.7 Hz, 1H, *Ha*–C1′), 3.52 (dAB, J_{AB}=12.0 Hz, $J_{5-1'b}$=4.5 Hz, 1H, *Hb*–C1′), 2.72 (ddd, $J_{3-4\alpha}$=9.0 Hz, $J_{3-4\beta}$=6.9 Hz, J_{3-P}=6.6 Hz, 1H, *H*–C3), 2.57 (s, 3H, CH_3–N), 2.47 (dddAB, J_{AB}=12.9 Hz, $J_{4\beta-P}$=18.6 Hz, $J_{4\beta-3}$=6.9 Hz, $J_{4\beta-5}$=5.7 Hz, 1H, *Hβ*–C4), 2.05 (dddAB, J_{AB}=12.9 Hz, $J_{4\alpha-P}$=13.8 Hz, $J_{4\alpha-3}$=9.0 Hz, $J_{4\alpha-5}$=8.4 Hz, 1H, *Hα*–C4), 1.04 (t, J=7.2 Hz, 6H, 2×C*H*$_3$–CH_2–O–P). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 76.77 (d, $^3J_{PCCC}$=5.3 Hz, C5), 64.30 (d, $^1J_{PC}$=170.5 Hz, C3), 63.24 (s, C1′), 63.13 (d, J=6.8 Hz, C–O–P), 63.00 (d, J=6.8 Hz, C–O–P), 46.04 (d, J=9.8 Hz, *C*–N–C–P), 32.54 (s, C4), 16.70 (d, J=5.3 Hz), 16.68 (d, J=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 23.77. Anal. Calcd for $C_9H_{20}NO_5P$: C, 42.69; H, 7.96; N, 5.53. Found: C, 42.52; H, 8.16; N, 5.86.

4.3.1. Diethyl 5-(*tert*-butoxycarbonylaminomethyl)-2-methylisoxazolidin-3-yl-3-phosphonate (3b and 4b). From nitrone **1a** (0.287 g, 1.47 mmol) and *N*-Boc-allylamine (0.254 g, 1.62 mmol), an inseparable mixture of **3b**

and **4b** (0.43 g, 83%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

*Compounds **3b** and **4b***: colourless oil. IR (film): ν=3316, 2979, 2932, 1711, 1526, 1366, 1250, 1171, 1040, 1027, 970 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.11 (br s, 1H×0.28), 4.79 (very br t, 1H×0.72), 4.30–4.05 (m, 5H), 3.51–3.40 (m, 1H×0.72), 3.40–3.30 (m, 1H×0.28), 3.30–3.15 (m, 1H×0.72), 2.98 (ddd, J=8.7, 8.7, 4.2 Hz, 1H×0.28), 2.86 (d, J=1.2 Hz, 3H×0.72), 2.81 (d, J=0.9 Hz, 3H×0.28), 2.70–2.44 (m, 1H), 2.31–2.13 (m, 1H), 1.44 (s, 9H), 1.36 (t, J=6.9 Hz, 3H×0.28), 1.35 (t, J=6.9 Hz, 3H×0.28), 1.34 (t, J=6.9 Hz, 3H×0.72), 1.33 (t, J=6.9 Hz, 3H×0.72). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 155.91 (C═O, **6b**), 155.90 (C═O, **5b**), 79.44 (s, $C(CH_3)_3$, **5b**), 79.21 (s, $C(CH_3)_3$, **6b**), 76.13 (d, $^{3}J_{PCCC}$=8.3 Hz, C5, **5b**), 74.91 (d, $^{3}J_{PCCC}$=6.8 Hz, C5, **6b**), 64.25 (d, $^{1}J_{PC}$=169.8 Hz, C3, **5b**), 64.22 (d, $^{1}J_{PC}$=170.5 Hz, C3, **6b**), 63.14 (d, J=6.8 Hz, C–O–P, **5b**), 63.00 (d, J=6.8 Hz, C–O–P, **6b**), 62.53 (d, J=6.8 Hz, C–O–P, **6b**), 62.40 (d, J=7.5 Hz, C–O–P, **5b**), 46.20 (d, J=7.5 Hz, *C*–N–C–P, **5b**), 46.13 (d, J=3.8 Hz, *C*–N–C–P, **6b**), 43.03 (s, C1′, **6b**), 42.55 (s, C1′, **5b**), 35.03 (d, $^{2}J_{PCC}$=2.3 Hz, C4, **5b**), 34.71 (d, $^{2}J_{PCC}$=1.5 Hz, C4, **6b**), 28.43 (s, C(CH_3)$_3$, **5b**), 28.46 (s, C(CH_3)$_3$, **6b**), 16.61 (d, J=6.0 Hz, **5b** and **6b**), 16.56 (d, J=5.3 Hz, **5b** and **6b**). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 22.30 (**6b**) and 22.00 (**5b**). Anal. Calcd for $C_{14}H_{29}N_2O_6P$: C, 47.72; H, 8.30; N, 7.95. Found: C, 47.96; H, 8.16; N, 7.84.

4.3.2. Diethyl 5-(bromomethyl)-2-methylisoxazolidin-3-yl-3-phosphonate (3c and 4c). From nitrone **1a** (0.195 g, 1.00 mmol) and allyl bromide (0.173 mL, 2.00 mmol), an inseparable mixture of **3c** and **4c** (0.193 g, 61%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

*Compounds **3c** and **4c***: colourless oil. IR (film): ν=3472, 2981, 2909, 1442, 1239, 1040, 1028, 969 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.42–4.12 (m, 5H, 2×CH_2OP and *H*–C5), 3.54 (dAB, J_{AB}=9.9 Hz, J=5.7 Hz, 1H×0.35), 3.45 (ddAB, J_{AB}=10.8 Hz, J=4.8, 0.6 Hz, 1H×0.65), 3.39 (dAB, J_{AB}=10.8 Hz, J=6.0 Hz, 1H×0.65), 3.38 (dAB, J_{AB}=9.9 Hz, J=7.8 Hz, 1H×0.35), 3.05–2.93 (m, 1H), 2.89 (d, J=1.2 Hz, 3H×0.65), 2.85 (d, J=0.9 Hz, 3H×0.35), 2.83–2.60 (m, 1H), 2.50–2.34 (m, 1H), 1.36 (t, J=7.0 Hz, 3H), 1.35 (t, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 75.99 (d, J=3.0 Hz, C5 in **6c**), 75.89 (d, J=9.1 Hz, C5 in **5c**), 64.46 (d, J=170.0 Hz, C3 in **5c**), 64.21 (d, J=168.3 Hz, C3 in **6c**), 63.36 (d, J=6.0 Hz, **5c**), 63.25 (d, J=6.8 Hz, **6c**), 62.72 (d, J=6.0 Hz, **6c**), 62.64 (d, J=6.8 Hz, **5c**), 46.49 (d, J=3.8 Hz, **6c**), 46.30 (d, J=5.3 Hz, **5c**), 37.47 (d, J=2.3 Hz, **6c**), 37.28 (d, J=2.3 Hz, **5c**), 34.00 (s, C3 in **6c**), 32.89 (s, C3 in **5c**), 16.77 (d, J=5.3 Hz, **5c** and **6c**), 16.72 (d, J=6.0 Hz, **5c** and **6c**). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 23.05 (**6c**) and 22.68 (**5c**). Anal. Calcd for $C_9H_{19}BrNO_4P$: C, 34.19; H, 6.06; N, 4.43. Found: C, 34.10; H, 6.24; N, 4.46.

4.3.3. Diethyl 2-methyl-5-[(trimethylsilyl)methyl]isoxazolidin-3-yl-3-phosphonate (3d and 4d). From nitrone **1a** (0.524 g, 2.69 mmol) and allyltrimethylsilane (0.428 mL, 2.69 mmol), pure **3d** (0.536 g, 64%) and fractions containing mixtures of **3d** and **4d** (0.075 g, 9%) were obtained after chromatography on a silica gel column with chloroform–MeOH (100:1).

*Compound **3d***: colourless oil. IR (film): ν=2955, 2881, 1248, 1054, 1027, 965, 841 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.27–4.13 (m, 4H, CH_2–O–P), 4.08 (dddd, $J_{5-1'b}$=9.1 Hz, $J_{5-4\alpha}$=8.7 Hz, $J_{5-4\beta}$=6.6 Hz, $J_{5-1'a}$=5.7 Hz, 1H, *H*–C5), 2.94 (ddd, $J_{3-4\alpha}$=10.5 Hz, $J_{3-4\beta}$=6.0 Hz, $J_{3\text{-}P}$=1.2 Hz, 1H, *H*–C3), 2.85 (d, J=1.2 Hz, 3H, CH_3–N), 2.53 (dddAB, J_{AB}=12.3 Hz, $J_{4\beta\text{-}P}$=18.9 Hz, $J_{4\beta-5}$=6.6 Hz, $J_{4\beta-3}$=6.0 Hz, 1H, *Hβ*–C4), 2.02 (dddAB, J_{AB}=12.3 Hz, $J_{4\alpha\text{-}P}$=13.5 Hz, $J_{4\alpha-3}$=10.5 Hz, $J_{4\alpha-5}$=8.7 Hz, 1H, *Hα*–C4), 1.35 (t, J=6.9 Hz, 6H, 2×CH_3–CH_2–O–P), 1.07 (dAB, J_{AB}=14.1 Hz, $J_{5-1'a}$=5.7 Hz, 1H, *Ha*–C1′), 0.81 (dAB, J_{AB}=14.1 Hz, $J_{5-1'b}$=9.1 Hz, 1H, *Hb*–C1′), 0.05 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 75.33 (d, $^{3}J_{PCCC}$=6.9 Hz, C5), 64.57 (d, $^{1}J_{PC}$=168.6 Hz, C3), 62.95 (d, J=6.6 Hz, C–O–P), 62.38 (d, J=6.9 Hz, C–O–P), 46.17 (d, J=4.0 Hz, H_3C–N–C–P), 40.21 (d, $^{2}J_{PCC}$=2.9 Hz, C4), 21.87 (s, C1′), 16.63 (d, J=5.7 Hz), −0.81 (s, C(CH_3)$_3$). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 24.12. Anal. Calcd for $C_{12}H_{28}NO_4PSi$: C, 46.58; H, 9.12; N, 4.53. Found: C, 46.49; H, 9.35; N, 4.52.

4.3.4. Methyl 3-(diethoxyphosphoryl)-2-methylisoxazolidin-5-yl-5-carboxylate (3e and 4e). From nitrone **1a** (0.448 g, 2.30 mmol) and methyl acrylate (0.311 mL, 3.45 mmol) pure **3e** (0.473 g, 73%) was obtained by column chromatography (chloroform–MeOH, 100:1), followed by fractions containing mixture of **3e** and **4e** (0.080 g, 12%).

*Compound **3e***: colourless oil. IR (film): ν=3473, 2983, 2913, 1744, 1441, 1222, 1052, 1025, 970 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.56 (dd, $J_{5-4\beta}$=8.4 Hz, $J_{5-4\alpha}$=5.7 Hz, 1H, *H*–C5), 4.26–4.13 (m, 4H, CH_2–O–P), 3.78 (s, 3H, CH_3O(O)C), 3.13 (ddd, $J_{3-4\alpha}$=8.4 Hz, $J_{3-4\beta}$=8.4 Hz, $J_{3\text{-}P}$=3.3 Hz, 1H, *H*–C3), 2.96 (d, J=1.0 Hz, 3H, CH_3–N), 2.88 (dddAB, J_{AB}=12.6 Hz, $J_{4\beta\text{-}P}$=16.8 Hz, $J_{4\beta-3}$=8.4 Hz, $J_{4\beta-5}$=8.4 Hz, 1H, *Hβ*–C4), 2.70 (dddAB, J_{AB}=12.6 Hz, $J_{4\alpha\text{-}P}$=9.6 Hz, $J_{4\alpha-3}$=8.4 Hz, $J_{4\alpha-5}$=5.7 Hz, 1H, *Hα*–C4), 1.36 (t, J=6.9 Hz, 3H, CH_3–CH_2–O–P), 1.35 (t, J=7.0 Hz, 3H, CH_3–CH_2–O–P). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 171.1 (s, C═O), 74.98 (d, $^{3}J_{PCCC}$=8.3 Hz, C5), 63.38 (d, J=6.8 Hz, C–O–P), 63.35 (d, $^{1}J_{PC}$=169.8 Hz, C3), 62.68 (d, J=7.5 Hz, C–O–P), 52.58 (s, *C*H$_3$O(O)C), 46.71 (d, J=5.3 Hz, *C*–N–C–P), 36.53 (d, $^{2}J_{PCC}$=2.3 Hz, C4), 16.66 (d, J=5.3 Hz), 16.60 (d, J=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 21.39. Anal. Calcd for $C_{10}H_{20}NO_6P$: C, 42.71; H, 7.17; N, 4.98. Found: C, 42.76; H, 7.09; N, 4.91.

4.3.5. Diethyl 5-acetoxy-2-methylisoxazolidin-3-yl-3-phosphonate (3f and 4f). From nitrone **1a** (0.510 g, 2.49 mmol) and vinyl acetate (1.00 mL, 10.8 mmol), pure **3f** (0.434 g, 62%) and fractions containing mixture of **3f** and **4f** (0.223 g, 32%) were obtained after column chromatography (chloroform–MeOH, 100:1).

*Compound **3f***: colourless oil. IR (film): ν=2986, 2913, 1752, 1441, 1260, 1235, 1054, 1024, 971 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.28 (dd, $J_{5-4\beta}$=4.2 Hz, $J_{5-4\alpha}$=0.9 Hz, 1H, *H*–C5), 4.28–4.14 (m, 4H, 2×CH_2–O–P), 3.27 (ddd, $J_{3-4\beta}$=11.4 Hz, $J_{3-4\alpha}$=6.9 Hz, $J_{3\text{-}P}$=1.8 Hz, 1H, *H*–C3), 2.99 (d, J=0.8 Hz, 3H, CH_3–N), 2.70 (dddAB, J_{AB}=12.9 Hz, $J_{4\beta\text{-}P}$=17.1 Hz, $J_{4\beta-3}$=11.1 Hz, $J_{4\beta-5}$=4.2 Hz, 1H, *Hβ*–C4),

2.65 (dddAB, J_{AB}=12.9 Hz, $J_{4\alpha-3}$=6.9 Hz, $J_{4\alpha\text{-}P}$=3.0 Hz, $J_{5-4\alpha}$=0.9 Hz, 1H, *Hα*–C4), 2.08 (s, 3H, C*H*$_3$C(O)O), 1.35 (t, *J*=6.9 Hz, 6H, C*H*$_3$–CH$_2$–O–P). ^{1}H NMR (C_6D_6, 300 MHz): 6.28 (d, $J_{5-4\beta}$=4.5 Hz, 1H, *H*–C5), 4.16–4.04 (m, 2H, CH$_2$–O–P), 3.98–3.88 (m, 2H, CH$_2$–O–P), 3.19 (ddd, $J_{3-4\beta}$=12.0 Hz, $J_{3-4\alpha}$=6.6 Hz, $J_{3\text{-}P}$=1.5 Hz, 1H, *H*–C3), 2.98 (s, 3H, CH$_3$–N), 2.54 (dddAB, J_{AB}=12.9 Hz, $J_{4\beta\text{-}P}$=17.4 Hz, $J_{4\beta-3}$=12.0 Hz, $J_{4\beta-5}$=4.5 Hz, 1H, *Hβ*–C4), 2.32 (ddAB, J_{AB}=12.9 Hz, $J_{4\alpha\text{-}P}$=3.0 Hz, $J_{4\alpha-3}$= 6.6 Hz, 1H, *Hα*–C4), 1.55 (s, 3H, C*H*$_3$C(O)O), 1.07 (t, *J*=7.0 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.01 (t, *J*=7.3 Hz, 3H, C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 169.77 (s, C=O), 95.69 (d, $^3J_{PCCC}$=9.5 Hz, C5), 63.66 (d, *J*=6.0 Hz, C–O–P), 62.88 (d, *J*=6.8 Hz, C–O–P), 61.79 (d, $^1J_{PC}$=175.8 Hz, C3), 49.91 (br d, *J*=7.5 Hz, *C*–N–C–P), 39.91 (d, $^2J_{PCC}$=2.3 Hz, C4), 21.58 (s, *C*H$_3$C(O)O), 16.68 (d, *J*=5.3 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 21.84. Anal. Calcd for $C_{10}H_{20}NO_6P$: C, 42.71; H, 7.17; N, 4.98. Found: C, 42.52; H, 7.09; N, 4.97.

4.3.6. Diethyl 2-methyl-5-phenylisoxazolidin-3-yl-3-phosphonate (3g and 4g). From nitrone **1a** (0.635 g, 3.25 mmol) and styrene (0.559 mL, 4.88 mmol), pure **3g** (0.584 g, 60%) and pure **4g** (0.021 g, 2%) were obtained after purification on a silica gel column with chloroform–MeOH (100:1) and toluene–isopropanol (100:1).

Compound ***3g***: colourless oil. IR (film): *ν*=2982, 2908, 1453, 1239, 1053, 1027, 966 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 7.38–7.25 (m, 5H), 5.02 (dd, $J_{5-4\alpha}$=8.4 Hz, $J_{5-4\beta}$=6.9 Hz, 1H, *H*–C5), 4.30–4.14 (m, 4H, 2×CH$_2$–O–P), 3.12 (ddd, $J_{3-4\alpha}$=10.5 Hz, $J_{3-4\beta}$=6.9 Hz, $J_{3\text{-}P}$=1.8 Hz, 1H, *H*–C3), 2.97 (d, *J*=0.8 Hz, 3H, C*H*$_3$–N), 2.88 (dddAB, J_{AB}=12.9 Hz, $J_{4\beta\text{-}P}$=18.6 Hz, $J_{4\beta-3}$=6.9 Hz, $J_{4\beta-5}$= 6.9 Hz, 1H, *Hβ*–C4), 2.48 (dddAB, J_{AB}=12.9 Hz, $J_{4\alpha-3}$= 10.5 Hz, $J_{4\alpha\text{-}P}$=12.9 Hz, $J_{5-4\alpha}$=8.4 Hz, 1H, *Hα*–C4), 1.38 (t, *J*=7.2 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.36 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 138.81 (C$_{ipso}$), 128.44, 128.04, 126.45, 78.81 (d, $^3J_{PCCC}$=7.2 Hz, C5), 64.60 (d, $^1J_{PC}$=168.6 Hz, C3), 63.15 (d, *J*=6.3 Hz, C–O–P), 62.49 (d, *J*=7.2 Hz, C–O–P), 46.24 (br d, *J*=4.0 Hz, H$_3$*C*–N–C–P), 40.32 (d, $^2J_{PCC}$=3.1 Hz, C4), 16.69 (d, *J*=5.7 Hz), 16.62 (d, *J*=5.7 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 23.45. Anal. Calcd for $C_{14}H_{22}NO_4P$: C, 56.18; H, 7.41; N, 4.68. Found: C, 56.16; H, 7.41; N, 4.84.

Compound ***4g***: colourless oil. IR (film): *ν*=2983, 2910, 1672, 1452, 1249, 1053, 1027, 967 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 7.44–7.25 (m, 5H), 5.14 (dd, $J_{5-4\beta}$= 8.7 Hz, $J_{5-4\alpha}$=6.6 Hz, 1H, *H*–C5), 4.25–4.13 (m, 4H, 2×CH$_2$–O–P), 3.23 (ddd, $J_{3-4\beta}$=9.3 Hz, $J_{3-4\alpha}$=8.1 Hz, $J_{3\text{-}P}$=4.2 Hz, 1H, *H*–C3), 2.95 (dddAB, J_{AB}=12.3 Hz, $J_{4\alpha-3}$=8.1 Hz, $J_{4\alpha\text{-}P}$=6.6 Hz, $J_{5-4\alpha}$=6.6 Hz, 1H, *Hα*–C4), 2.93 (d, *J*=0.9 Hz, 3H, C*H*$_3$–N), 2.55 (dddAB, J_{AB}= 12.3 Hz, $J_{4\beta\text{-}P}$=18.6 Hz, $J_{4\beta-3}$=9.3 Hz, $J_{4\beta-5}$=8.7 Hz, 1H, *Hβ*–C4), 1.32 (t, *J*=7.2 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.31 (t, *J*=7.2 Hz, 3H, C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 139.40 (C$_{ipso}$), 128.20, 127.70, 77.31 (d, $^3J_{PCCC}$=8.3 Hz, C5), 65.10 (d, $^1J_{PC}$=172.8 Hz, C3), 63.10 (d, *J*=6.8 Hz, C–O–P), 62.43 (d, *J*=5.3 Hz, C–O–P), 47.07 (d, *J*=9.1 Hz, H$_3$*C*–N–C–P), 41.10 (d, $^2J_{PCC}$=1.5 Hz, C4), 16.49 (d, *J*=6.0 Hz), 16.47 (d, *J*=5.3 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 23.52. Anal. Calcd for $C_{14}H_{22}NO_4P$: C, 56.18; H, 7.41; N, 4.68. Found: C, 56.42; H, 7.67; N, 4.78.

4.3.7. Tetraethyl 2-methylisoxazolidine-3,5-diyl-3,5-bis(phosphonate) (3h and 4h). From nitrone **1a** (0.927 g, 4.75 mmol) and vinylphosphonate (0.741 mL, 4.75 mmol) a mixture of **3h**, **4h** and **5** (1.557 g, 91%) was obtained and subjected to purification on silica gel with chloroform–MeOH (100:1).

Compound ***3h***: yield 0.50 g, 29%. Colourless oil. IR (film): *ν*=3529, 3486, 2983, 2911, 1246, 1047, 1026, 969 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 4.30–4.13 (m, 9H, 4×CH$_2$–O–P and *H*–C5), 3.12 (very br, 1H, *H*–C3), 2.94 (s, 3H, CH$_3$–N), 2.88–2.72 (m, 2H, *Hα*–C4 and *Hβ*–C4), 1.35 (t, *J*=6.9 Hz, 12H, 4×C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 71.80 (d, $^1J_{PC}$=169.0 Hz, $^3J_{PCCC}$=8.3 Hz, C5), 63.89 (d, $^1J_{PC}$=169.0 Hz, $^3J_{PCCC}$=5.3 Hz, C3), 63.38 (d, *J*=6.0 Hz, C–O–P), 63.33 (d, *J*=6.8 Hz, C–O–P), 62.85 (d, *J*=6.8 Hz, C–O–P), 62.72 (d, *J*=6.8 Hz, C–O–P), 46.49 (d, *J*=4.5 Hz, H$_3$*C*–N–C–P), 34.63 (d, $^2J_{PCC}$=0.8 Hz, C4), 16.72 (d, *J*=5.3 Hz), 16.69 (d, *J*=5.3 Hz), 16.67 (d, *J*=5.3 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 21.38 and 20.58. Anal. Calcd for $C_{12}H_{27}NO_7P_2$: C, 40.11; H, 7.57; N, 3.90. Found: C, 39.92; H, 7.79; N, 3.92.

Compound ***4h***: yield 0.113 g, 7%. Colourless oil. IR (film): *ν*=3478, 2985, 2912, 1247, 1047, 1025, 971 cm^{-1}. ^{1}H NMR (C_6D_6, 300 MHz): 4.29–3.90 (m, 9H, 4×CH$_2$–O–P and *H*–C5), 3.02 (dddAB, J_{AB}=12.0 Hz, $J_{4\beta-P3}$=18.0 Hz, $J_{4\beta-P5}$=16.5 Hz, $J_{4\beta-3}$=10.3 Hz, $J_{4\beta-5}$=10.3 Hz, 1H, *Hβ*–C4), 2.79 (s, 3H, C*H*$_3$–N), 2.67 (ddd, $J_{3-4\beta}$=10.3 Hz, $J_{3-4\alpha}$=7.0 Hz, $J_{3\text{-}P}$=3.8 Hz, 1H, *H*–C3), 2.51 (dddAB, J_{AB}=12.0 Hz, $J_{4\alpha-3}$=7.0 Hz, $J_{4\alpha-P3}$=7.0 Hz, $J_{4\alpha-P5}$= 3.3 Hz, $J_{5-4\alpha}$=6.6 Hz, 1H, *Hα*–C4), 1.13 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.07 (t, *J*=7.2 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.05 (t, *J*=7.2 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.03 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 70.56 (d, $^1J_{PC}$=169.8 Hz, $^3J_{PCCC}$=9.8 Hz, C5), 64.52 (d, $^1J_{PC}$= 169.8 Hz, $^3J_{PCCC}$=7.5 Hz, C3), 63.55 (d, *J*=6.8 Hz, C–O–P), 63.22 (d, *J*=6.8 Hz, C–O–P), 63.01 (d, *J*=6.8 Hz, C–O–P), 62.73 (d, *J*=6.8 Hz, C–O–P), 46.80 (d, *J*=6.8 Hz, H$_3$*C*–N–C–P), 35.42 (s, C4), 16.63 (d, *J*=6.0 Hz). ^{31}P NMR (C_6D_6, 121.5 MHz): 21.85 and 21.42. Anal. Calcd for $C_{12}H_{27}NO_7P_2$: C, 40.11; H, 7.57; N, 3.90. Found: C, 39.93; H, 7.62; N, 3.85.

4.3.8. Diethyl 5-[(diethoxyphosphoryl)methyl]-2-methylisoxazolidin-3-yl-3-phosphonate (3i and 4i). From nitrone **1a** (0.713 g, 3.65 mmol) and allylphosphonate (0.640 mL, 3.65 mmol), a mixture of **3i** and **4i** (1.24, 91%) was obtained and purified on silica gel with chloroform–MeOH (100:1).

Compound ***3i***: yield 0.312 g, 23%. Colourless oil. IR (film): *ν*=3471, 2984, 2910, 1237, 1029, 967 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 4.23–3.94 (m, 9H, 4×CH$_2$–O–P and *H*–C5), 2.86 (ddd, $J_{3-4\alpha}$=10.5 Hz, $J_{3-4\beta}$=6.9 Hz, $J_{3\text{-}P}$= 2.1 Hz, 1H, *H*–C3), 2.76 (d, *J*=1.0 Hz, 3H, CH$_3$–N), 2.60 (dddAB, J_{AB}=12.6 Hz, $J_{4\beta\text{-}P}$=19.5 Hz, $J_{4\beta-3}$=6.9 Hz, $J_{4\beta-5}$=6.9 Hz, 1H, *Hβ*–C4), 2.19 (dddAB, J_{AB}=12.6 Hz, $J_{4\alpha\text{-}P}$=12.6 Hz, $J_{4\alpha-3}$=10.5 Hz, $J_{4\alpha-5}$=8.1 Hz, 1H, *Hα*–C4), 2.12 (ddAB, J_{AB}=15.0 Hz, $J_{P\text{-}1'a}$=20.1 Hz, $J_{5-1'a}$=5.1 Hz, 1H, *Ha*–C1′), 1.86 (ddAB, J_{AB}=15.0 Hz, $J_{P\text{-}1'b}$=18.3 Hz,

$J_{5-1'b}$=8.4 Hz, 1H, *Hb*–C1′), 1.25 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.24 (t, *J*=7.2 Hz, 6H, 2×C*H*$_3$–CH$_2$–O–P), 1.23 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 72.08 (d, $^3J_{PCCC}$=7.4 Hz, C5), 64.25 (d, $^1J_{PC}$=168.6 Hz, C3), 63.28 (d, *J*=6.3 Hz, C–O–P), 62.49 (d, *J*=7.2 Hz, C–O–P), 62.04 (d, *J*=6.9 Hz, C–O–P), 61.96 (d, *J*=6.6 Hz, C–O–P), 46.26 (br s, *C*–N–C–P), 38.71 (br s, C4), 30.68 (d, $^1J_{PC}$=140.6 Hz, C1′), 16.73 (d, *J*=5.7 Hz), 16.68 (d, *J*=5.4 Hz), 16.62 (d, *J*=6.0 Hz), 16.60 (d, *J*=6.0 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 26.47 and 22.23. Anal. Calcd for $C_{13}H_{29}NO_7P_2$: C, 41.82; H, 7.83; N, 3.75. Found: C, 41.92; H, 8.03; N, 3.70.

Compound ***4i***: yield 0.061 g, 4%. Colourless oil. IR (film): ν=3471, 2984, 2910, 1237, 1029, 967 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 4.23–3.94 (m, 9H, 4×CH$_2$–O–P and *H*–C5), 2.86 (ddd, $J_{3-4\alpha}$=10.5 Hz, $J_{3-4\beta}$=6.9 Hz, $J_{3\text{-}P}$=2.1 Hz, 1H, *H*–C3), 2.76 (d, *J*=1.0 Hz, 3H, C*H*$_3$–N), 2.60 (dddAB, J_{AB}=12.6 Hz, $J_{4\beta-P}$=19.5 Hz, $J_{4\beta-3}$=6.9 Hz, $J_{4\beta-5}$=6.9 Hz, 1H, *Hβ*–C4), 2.19 (dddAB, J_{AB}=12.6 Hz, $J_{4\alpha-P}$=12.6 Hz, $J_{4\alpha-3}$=10.5 Hz, $J_{4\alpha-5}$=8.1 Hz, 1H, *Hα*–C4), 2.12 (ddAB, J_{AB}=15.0 Hz, $J_{P\text{-}1'a}$=20.1 Hz, $J_{5-1'a}$=5.1 Hz, 1H, *Ha*–C1′), 1.86 (ddAB, J_{AB}=15.0 Hz, $J_{P\text{-}1'b}$=18.3 Hz, $J_{5-1'b}$=8.4 Hz, 1H, *Hb*–C1′), 1.25 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P), 1.24 (t, *J*=7.2 Hz, 6H, 2×C*H*$_3$–CH$_2$–O–P), 1.23 (t, *J*=6.9 Hz, 3H, C*H*$_3$–CH$_2$–O–P). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 72.08 (d, $^3J_{PCCC}$=7.4 Hz, C5), 64.25 (d, $^1J_{PC}$=168.6 Hz, C3), 63.28 (d, *J*=6.3 Hz, C–O–P), 62.49 (d, *J*=7.2 Hz, C–O–P), 62.04 (d, *J*=6.9 Hz, C–O–P), 61.96 (d, *J*=6.6 Hz, C–O–P), 46.26 (br s, *C*–N–C–P), 38.71 (br s, C4), 30.68 (d, $^1J_{PC}$=140.6 Hz, C1′), 16.73 (d, *J*=5.7 Hz, *C*–C–O–P), 16.68 (d, *J*=5.4 Hz), 16.62 (d, *J*=6.0 Hz), 16.60 (d, *J*=6.0 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 26.47 and 22.23. Anal. Calcd for $C_{13}H_{29}NO_7P_2$: C, 41.82; H, 7.83; N, 3.75. Found: C, 42.04; H, 7.62; N, 3.67.

4.3.9. Diethyl octahydro-2-methylbenzo[*d*]isoxazol-3-yl-3-phosphonate (7a). From nitrone **1a** (0.121 g, 0.671 mmol) and cyclohexene (0.68 mL, 6.7 mmol), pure **7a** (0.186 g, 100%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

Compound ***7a***: colourless oil. IR (film): ν=2981, 2934, 2864, 1445, 1248, 1056, 1023, 963 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 4.24–4.10 (m, 4H), 4.08 (q, *J*=4.2 Hz, 1H, *H*–C7a), 2.91 (d, *J*=1.2 Hz, 3H, C*H*$_3$N), 2.70 (dd, J_{3-3a}=3.6 Hz, $J_{3\text{-}P}$=1.5 Hz, 1H, *H*–C3), 2.60 (ddddd, $J_{3a\text{-}P}$=16.0 Hz, *J*=11.0, 5.0, 4.2, 3.6 Hz, 1H, *H*–C3a), 2.02–1.90 (m, 1H), 1.86–1.75 (m, 1H), 1.72–1.59 (m, 2H), 1.52–1.10 (m, 3H), 1.30–1.20 (m, 1H), 1.34 (t, *J*=7.2 Hz, 6H). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 75.48 (d, $^3J_{PCCC}$=4.5 Hz, C7a), 71.45 (d, $^1J_{PC}$=172.0 Hz, C3), 62.78 (d, *J*=6.9 Hz, C–O–P), 62.60 (d, *J*=6.9 Hz, C–O–P), 47.68 (d, *J*=6.9 Hz, H$_3$*C*–N–C–P), 44.22 (d, $^2J_{PCC}$=2.0 Hz, C3a), 30.17 (d, $^3J_{PCCC}$=11.5 Hz, C4), 26.05, 24.00 (d, *J*=1.4 Hz), 20.77, 16.71 (d, *J*=5.7 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 24.26. Anal. Calcd for $C_{12}H_{24}NO_4P$: C, 51.98; H, 8.72; N, 5.05. Found: C, 51.95; H, 8.65; N, 4.89.

4.3.10. Diethyl hexahydro-2-methyl-2*H*-cyclopenta[*d*]-isoxazol-3-yl-3-phosphonate (7b). From nitrone **1a** (0.162 g, 0.830 mmol) and cyclopentene (0.110 mL, 1.24 mmol), pure **7b** (0.190 g, 90%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

Compound ***7b***: colourless oil. IR (film): ν=2950, 2935, 2871, 1442, 1251, 1220, 1054, 1025, 964 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 4.47 (dd, J_{6a-3a}=8.0 Hz, J_{6a-6}=3.7 Hz, 1H, *H*–C6a), 4.25–4.13 (m, 4H), 3.23 (dq, $J_{3a\text{-}P}$=16.2 Hz, J_{3a-3}=8.0 Hz, 1H, *H*–C3a), 2.82 (d, *J*=1.2 Hz, 3H, C*H*$_3$N), 2.38 (br d, J_{3-3a}=8.0 Hz, 1H, *H*–C3), 1.89–1.80 (m, 1H), 1.75–1.60 (m, 4H), 1.50–1.40 (m, 1H), 1.36 (t, *J*=6.9 Hz, 6H). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 83.00 (d, $^3J_{PCCC}$=9.8 Hz, C6a), 72.21 (d, $^1J_{PC}$=162.6 Hz, C3), 63.13 (d, *J*=6.6 Hz, C–O–P), 62.36 (d, *J*=6.9 Hz, C–O–P), 51.68, 45.32, 31.90, 31.57 (d, $^3J_{PCCC}$=3.4 Hz, C4), 23.35, 16.73 (d, *J*=6.0 Hz), 16.69 (d, *J*=6.0 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 23.30. Anal. Calcd for $C_{11}H_{22}NO_4P$: C, 50.18; H, 8.42; N, 5.32. Found: C, 50.01; H, 8.48; N, 5.11.

4.3.11. Diethyl hexahydro-2-methylfuro[3,2-*d*]isoxazol-3-yl-3-phosphonate (7c). From nitrone **1a** (0.327 g, 1.68 mmol) and 2,3-dihydrofuran (0.253 mL, 3.36 mmol), pure **7c** (0.311 g, 70%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

Compound ***7c***: colourless oil. IR (film): ν=2981, 2912, 2879, 1444, 1252, 1226, 1053, 1023, 968 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 5.71 (d, J_{6a-3a}=5.4 Hz, 1H, *H*–C6a), 4.27–4.13 (m, 4H), 4.04 (dd, ^2J=9.0 Hz, *J*=8.4 Hz, 1H, *Hβ*–C5), 3.97 (ddd, *J*=11.4 Hz, ^2J=9.0 Hz, *J*=5.4 Hz, 1H, *Hα*–C5), 3.42 (ddddd, $J_{3a\text{-}P}$=17.1 Hz, J_{3a-3}=8.4 Hz, $J_{3a-4\beta}$=8.4 Hz, J_{3a-6a}=5.4 Hz, $J_{3a-4\alpha}$=0.9 Hz, 1H, *H*–C3a), 2.89 (d, *J*=0.9 Hz, 3H, C*H*$_3$N), 2.66 (br dd, J_{3-3a}=8.4 Hz, $^2J_{3\text{-}P}$=3.0 Hz, 1H, *H*–C3), 2.02 (dddAB, J_{AB}=13.2 Hz, J_{4-5}=11.4 Hz, J_{4-3a}=8.4 Hz, J_{4-5}=8.4 Hz, 1H, *Hβ*–C4), 1.89 (ddAB, J_{AB}=13.2 Hz, J_{4-5}=5.4 Hz, J_{4-3a}=0.9 Hz, 1H, *Hα*–C4), 1.36 (t, *J*=7.0 Hz, 6H). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 106.20 (d, $^3J_{PCCC}$=10.0 Hz, C6a), 68.90 (d, $^1J_{PC}$=164.5 Hz, C3), 66.39 (s, C5), 63.27 (d, *J*=6.8 Hz, C–O–P), 62.49 (d, *J*=7.5 Hz, C–O–P), 51.10 (d, *J*=1.5 Hz, C3a), 45.97 (br s, *C*H$_3$N), 30.77 (d, $^3J_{PCCC}$=3.8 Hz, C4), 16.59 (d, *J*=6.0 Hz), 16.56 (d, *J*=5.3 Hz). ^{31}P NMR (CDCl$_3$, 121.5 MHz): 21.37. Anal. Calcd for $C_{10}H_{20}NO_5P$: C, 45.28; H, 7.60; N, 5.28. Found: C, 45.24; H, 7.63; N, 5.27.

4.3.12. Diethyl hexahydro-2-methylfuro[3,4-*d*]isoxazol-3-yl-3-phosphonate (7d). From nitrone **1a** (0.130 g, 0.670 mmol) and 2,5-dihydrofuran (0.100 mL, 1.34 mmol), pure **7d** (0.126 g, 71%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

Compound ***7d***: colourless oil. IR (film): ν=2979, 2929, 2857, 1250, 1223, 1092, 1052, 1024, 971 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): 4.65 (dd, J_{6a-3a}=7.0 Hz, $J_{6a-6\beta}$=3.8 Hz, 1H, *H*–C6a), 4.25–4.12 (m, 4H), 4.01 (AB, J_{AB}=10.8 Hz, 1H, *Hα*–C6), 3.97 (dAB, J_{AB}=9.9 Hz, 1H, *Hα*–C4), 3.58 (dAB, J_{AB}=9.9 Hz, $J_{3a-4\beta}$=6.0 Hz, 1H, *Hβ*–C4), 3.55–3.40 (dddd, $J_{3a\text{-}P}$=16.0 Hz, J_{3a-3}=7.8 Hz, J_{3a-6a}=7.0 Hz, $J_{3a-4\beta}$=6.0 Hz, 1H, *H*–C3a), 3.42 (dAB, J_{AB}=10.8 Hz, $J_{6a-6\beta}$=3.8 Hz, 1H, *Hβ*–C6), 2.86 (d, *J*=1.0 Hz, 3H, C*H*$_3$N), 2.65 (d, J_{3-3a}=7.8 Hz, 1H, *H*–C3), 1.36 (t, *J*=7.1 Hz, 3H), 1.35 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75.5 MHz): 82.02 (d, $^3J_{PCCC}$=9.5 Hz, C6a), 72.45 (s, C6), 71.84 (s, $^3J_{PCCC}$=3.4 Hz, C4), 70.86 (d,

$^{1}J_{PC}$=157.7 Hz, C3), 63.32 (d, J=6.3 Hz, C–O–P), 62.55 (d, J=6.9 Hz, C–O–P), 53.63, 45.27, 16.76 (d, J=5.7 Hz), 16.72 (d, J=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 22.26. Anal. Calcd for $C_{10}H_{20}NO_5P$: C, 45.28; H, 7.60; N, 5.28. Found: C, 45.33; H, 7.66; N, 5.13.

4.3.13. Diethyl hexahydro-2-methyl-5-oxo-5-phenyl-2*H*-phospholo[3,4-*d*]isoxazol-3-yl-3-phosphonate (7e). From nitrone **1a** (0.530 g, 2.72 mmol) and 3-phospholene **6e** (0.484 g, 2.72 mmol), pure **7e** (0.608 g, 82%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

*Compound **7e***: colourless oil. IR (film): ν=3447, 2981, 2927, 1657, 1439, 1392, 1250, 1232, 1162, 1025, 970 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.9–7.8 (m, 1H), 7.75–7.65 (m, 2H), 7.6–7.48 (m, 2H), 4.82 (dddd, $J_{6a–P5}$=21.6 Hz, $J_{6a–3a}$=6.4 Hz, $J_{6a–6\beta}$=6.4 Hz, $J_{6a–6\alpha}$=2.0 Hz, 1H×0.21, *H*–C6a), 4.68 (dddd, $J_{6a–P5}$=18.9 Hz, $J_{6a–3a}$=7.0 Hz, $J_{6a–6\beta}$=5.4 Hz, $J_{6a–6\alpha}$=5.4 Hz, 1H×0.79, *H*–C6a), 4.28–4.13 (m, 4H), 3.65 (ddddd, $J_{3a–P3}$=20.1 Hz, $J_{3a–4\alpha}$=9.3 Hz, $J_{3a–4\beta}$=8.8 Hz, $J_{3a–6a}$=6.4 Hz, $J_{3a–3}$=5.2 Hz, 1H×0.21, *H*–C3a), 3.35 (dddddd, $J_{3a–P3}$=18.3 Hz, $J_{3a–P5}$=8.7 Hz, $J_{3a–4\beta}$=9.2 Hz, $J_{3a–4\alpha}$=7.0 Hz, $J_{3a–6a}$=7.0 Hz, $J_{3a–3}$=7.0 Hz, 1H×0.79, *H*–C3a), 2.99 (dd, $J_{3–3a}$=7.0 Hz, $^{2}J_{3–P3}$=2.5 Hz, 1H×0.79, *H*–C3), 2.94 (d, J=1.2 Hz, 3H×0.79, CH_3N), 2.90 (d, J=1.0 Hz, 3H×0.21, CH_3N), 2.72 (dd, $J_{3–3a}$=5.2 Hz, $^{2}J_{3–P3}$=3.1 Hz, 1H×0.21, *H*–C3), 2.55 (dddd, $^{2}J_{4\beta–P5}$=15.4 Hz, $J_{4\beta–4\alpha}$=15.4 Hz, $J_{4\beta–3a}$=8.8 Hz, $^{4}J_{HH}$=1.0 Hz, 1H×0.21, *Hβ*–C4), 2.45 (dddd, $^{2}J_{6\beta–P5}$=16.4 Hz, $^{2}J_{6\beta–6\alpha}$=16.4 Hz, $J_{6\beta–6a}$=6.4 Hz, $^{4}J_{HH}$=1.0 Hz, 1H×0.21, *Hβ*–C6), 2.40–2.30 (m, 2H×0.79 from *H*–C6 and 1H×0.21 from *Hα*–C6), 2.36 (ddd, $^{2}J_{4\beta–4\alpha}$=15.9 Hz, $J_{4\beta–3a}$=9.2 Hz, $^{2}J_{4\beta–P5}$=7.5 Hz, 1H×0.79, *Hβ*–C4), 2.25 (ddd, $^{2}J_{4\alpha–P5}$=16.8 Hz, $^{2}J_{4\alpha–4\beta}$=15.9 Hz, $J_{4\alpha–3a}$=7.0 Hz, 1H×0.79, *Hα*–C4), 1.97 (ddd, $J_{4\alpha–4\beta}$=15.4 Hz, $J_{4\alpha–3a}$=9.3 Hz, $^{2}J_{4\alpha–P5}$=6.8 Hz, 1H×0.21, *Hα*–C4), 1.35 (t, J=6.9 Hz, 3H), 1.34 (t, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 131.97 (d, J=2.9 Hz), 131.60 (d, J=92.5 Hz, C_{ipso}×0.79), 131.30 (d, J=92.8 Hz, C_{ipso}×0.21), 130.14 (d, J=10.3 Hz, C×0.21), 129.58 (d, J=10.0 Hz, C×0.79), 128.64 (d, J=11.7 Hz, C×0.79), 128.43 (d, J=12.0 Hz, C×0.21), 79.13 (dd, J=9.7, 6.9 Hz, C6a×0.21), 78.05 (dd, J=10.0, 10.0 Hz, C6a×0.79), 72.67 (dd, $^{1}J_{PC}$=169.0 Hz, J=10.6 Hz, C3×0.21), 72.44 (dd, $^{1}J_{PC}$=164.0 Hz, J=6.0 Hz, C3×0.79), 63.20 (d, J=6.6 Hz, C×0.21), 62.92 (d, J=6.3 Hz, C×0.79), 62.45 (d, J=6.9 Hz, C×0.79), 62.28 (d, J=6.9 Hz, C×0.21), 48.33 (d, J=9.7, 1.6 Hz, C3a×0.21), 47.73 (d, J=10.3 Hz, C3a×0.79), 45.90 (d, J=3.4 Hz, CH_3N×0.21), 45.49 (s, CH_3N×0.79), 35.09 (dd, $^{1}J_{PC}$=64.4 Hz, J=8.3 Hz, C4×0.21), 32.70 (dd, $^{1}J_{PC}$=65.0 Hz, J=5.2 Hz, C4×0.79), 32.38 (d, $^{1}J_{PC}$=64.7 Hz, C6×0.21), 32.04 (d, $^{1}J_{PC}$=65.3 Hz, C6×0.79), 16.35 (d, J=5.3 Hz), 16.29 (d, J=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 63.68 (d, J=5.8 Hz, 1P×0.21), 61.69 (d, J=4.3 Hz, 1P×0.79), 21.28 (d, J=4.3 Hz, 1P×0.79), 20.93 (d, J=5.8 Hz, 1P×0.21). Anal. Calcd for $C_{16}H_{25}NO_5P_2$: C, 51.48; H, 6.75; N, 3.75. Found: C, 51.55; H, 6.72; N, 3.67.

4.3.14. Diethyl hexahydro-2-methyl-4-oxo-4-phenyl-2*H*-phospholo[2,3-*d*]isoxazol-3-yl-3-phosphonate (7f). From nitrone **1a** (0.195 g, 1.00 mmol) and 2-phospholene **6f** (0.178 g, 1.00 mmol), pure **7f** (0.329 g, 88%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

*Compound **7f***: colourless oil. IR (film): ν=3467, 2981, 2931, 1650, 1440, 1241, 1183, 1113, 1055, 1023, 971 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.75–7.65 (m, 2H), 7.6–7.45 (m, 3H), 4.74 (ddd, $J_{6a–P4}$=24.0 Hz, $J_{3a–6a}$=5.7 Hz, $J_{6a–6\beta}$=4.5 Hz, 1H, *H*–C6a), 4.30–4.10 (m, 4H), 3.79 (ddd, $J_{3–P4}$=18.9 Hz, $J_{3–3a}$=5.7 Hz, $^{2}J_{3-P}$=1.8 Hz, 1H, *H*–C3), 3.12 (dddd, $J_{3a–P3}$=20.1 Hz, $J_{3a–3}$=5.7 Hz, $J_{3a–6a}$=5.7 Hz, $^{2}J_{3–P4}$=2.4 Hz, 1H, *H*–C3a), 2.98 (d, J=1.2 Hz, 3H, CH_3N), 2.55–2.40 (m, 1H, *H*–C5), 2.40–2.25 (m, 2H, *H*–C5 and *H*–C6), 1.95–1.80 (m, 1H, *H*–C6), 1.29 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 132.97 (d, $^{1}J_{PC}$=92.8 Hz, C_{ipso}), 132.20 (d, J=2.6 Hz), 129.58 (d, J=9.4 Hz), 128.99 (d, J=11.7 Hz), 81.56 (dd, $J_{C6a–P3}$=8.8 Hz, $J_{C6a–P4}$=5.0 Hz, C6a), 64.31 (d, $^{1}J_{PC}$=168.6 Hz, C3), 63.32 (d, J=6.3 Hz), 62.91 (d, J=6.6 Hz), 48.69 (dd, $^{1}J_{P4–C3a}$=66.5 Hz, $^{2}J_{C3a–P3}$=2.5 Hz, C3a), 45.79 (d, J=4.0 Hz, CH_3N), 24.64 (d, $^{1}J_{P4–C5}$=66.4 Hz, C5), 24.88 (d, $J_{P4–C6}$=7.7 Hz, C6), 16.61 (d, J=5.4 Hz), 16.53 (d, J=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 56.04 (d, J=25.6 Hz) and 22.02 (d, J=25.6 Hz). Anal. Calcd for $C_{16}H_{25}NO_5P_2$: C, 51.48; H, 6.75; N, 3.75. Found: C, 51.41; H, 7.03; N, 3.57.

4.3.15. Hexaethyl 2-methylisoxazolidin-3-yl-3,5,5-tris(phosphonate) (7g). From nitrone **1a** (0.104 g, 0.335 mmol) and **6g** (0.065 g, 0.335 mmol), pure **7g** (0.152 g, 90%) was obtained after purification on silica gel with chloroform–MeOH (100:1).

*Compound **7g***: colourless oil. IR (film): ν=3492, 2984, 2913, 1256, 1019, 973 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.40–4.12 (m, 12H), 3.4–3.0 (m, 3H, *H*–C3 and *H*–C4), 2.98 (d, J=1.0 Hz, 3H, CH_3N), 1.36 (t, J=6.9 Hz, 6H), 1.35 (t, J=3 Hz, 3H), 1.34 (t, J=6.9 Hz, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 78.66 (ddd, $^{1}J_{PC}$=160.0, 160.0 Hz, $^{3}J_{PCCC}$=11.8 Hz, C5), 64.55 (br d, $^{1}J_{PC}$=162.6 Hz, C3), 64.26 (d, J=6.9 Hz), 64.17 (d, J=6.9 Hz), 64.03 (d, J=6.6 Hz), 63.87 (d, J=6.6 Hz), 63.71 (d, J=6.4 Hz), 62.61 (d, J=6.9 Hz), 46.50 (s, CH_3N), 40.03 (s, C4), 16.76 (d, J=4.0 Hz), 16.70 (d, J=5.4 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 20.69, 18.12 (AB, J_{AB}=56.7 Hz) and 17.40 (AB, J_{AB}=56.7 Hz). Anal. Calcd for $C_{16}H_{36}NO_{10}P_3$: C, 38.79; H, 7.32; N, 2.83. Found: C, 38.95; H, 7.40; N, 2.83.

4.3.16. Ethyl 3,5-bis(diethoxyphosphoryl)-2-methylisoxazolidine-5-carboxylate (7h and 8h). From nitrone **1a** (0.195 g, 1.00 mmol) and **6h** (0.237 g, 1.00 mmol), a mixture of **7h** and **8h** (0.39 g, 90%) was obtained after purification on silica gel (chloroform–MeOH, 100:1). Further purification on silica gel with hexane–isopropanol (50:1) gave fractions enriched with **7h** (0.074 g, **7h**/**8h**=90:10) and **8h** (0.053 g, **8h**/**7h**=85:15).

*Compound **7h***: colourless oil. IR (film): ν=3490, 2984, 2912, 1733, 1260, 1040, 1023, 973 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.40–4.10 (m, 10H), 3.25–2.95 (m, 3H), 3.01 (d, J=1.2 Hz, 3H), 1.39–1.30 (m, 15H). ^{1}H NMR (C_6D_6, 300 MHz): 4.30–3.80 (m, 10H), 3.55 (dddAB, J_{AB}=12.3 Hz, $J_{P5–4}$=16.5 Hz, $J_{P3–4}$=14.4 Hz, $J_{4–3}$=12.3 Hz, 1H, *Hβ*–C4), 3.39 (dddAB, J_{AB}=12.3 Hz, $J_{4–3}$=6.6 Hz, $J_{P3–4}$=

3.3 Hz, J_{P5-4}=0.9 Hz, 1H, *Hα*–C4), 3.15 (ddd, $J_{3-4\beta}$=12.3 Hz, $J_{3-4\alpha}$=6.6 Hz, $^2J_{P3-3}$=0.9 Hz, 1H, *H*–C3), 3.16 (s, 3H), 1.11 (t, *J*=7.1 Hz, 3H), 1.10 (t, *J*=7.1 Hz, 3H), 1.07 (t, *J*=7.1 Hz, 3H), 0.96 (t, *J*=0.97 Hz, 3H), 0.92 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 169.54 (d, ^2J=11.5 Hz, C=O), 82.12 (dd, $^1J_{PC}$=165.5 Hz, $^3J_{P3-C5}$=12.0 Hz, C5), 64.40 (d, *J*=6.8 Hz), 64.24 (d, *J*=6.8 Hz), 63.87 (d, *J*=6.8 Hz), 63.67 (dd, $^1J_{PC}$=168.3 Hz, $^3J_{P5-C3}$=6.0 Hz, C3), 62.70 (d, *J*=6.8 Hz), 62.64, 47.60 (d, *J*=2.9 Hz), 41.18 (d, *J*=1.5 Hz), 16.63 (d, *J*=6.0 Hz), 14.28. ^{31}P NMR ($CDCl_3$, 121.5 MHz): 20.45 and 16.10. Anal. Calcd for $C_{15}H_{31}NO_9P_2$: C, 41.77; H, 7.24; N, 3.25. Found: C, 41.97; H, 7.32; N, 3.25.

Compound ***8h***: colourless oil. IR (film): *ν*=3491, 2984, 2912, 1734, 1260, 1040, 1024, 973 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.40–4.10 (m, 10H), 3.35–3.30 (m, 3H), 2.98 (s, 3H), 1.39–1.26 (m, 15H). ^{1}H NMR (C_6D_6, 300 MHz): 4.25–3.85 (m, 10H), 3.77 (dddAB, J_{AB}=13.2 Hz, J_{P3-4}=16.5 Hz, J_{P5-4}=11.4 Hz, J_{4-3}=9.6 Hz, 1H, *Hβ*–C4), 3.45 (dddAB, J_{AB}=12.3 Hz, J_{P5-4}=17.7 Hz, J_{4-3}=8.4 Hz, J_{P3-4}=4.8 Hz, 1H, *Hα*–C4), 3.25 (br dd, $J_{3-4\beta}$=9.6 Hz, $J_{3-4\alpha}$=8.4 Hz, 1H, *H*–C3), 3.10 (d, *J*=0.6 Hz, 3H), 1.08 (t, *J*=7.1 Hz, 3H), 1.07 (t, *J*=7.1 Hz, 3H), 1.00 (t, *J*=7.1 Hz, 3H), 0.99 (t, *J*=7.1 Hz, 3H), 0.97 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 169.44 (d, ^2J=8.0 Hz, C=O), 82.01 (dd, $^1J_{PC}$=160.0 Hz, $^3J_{P3-C5}$=9.4 Hz, C5), 64.77 (dd, $^1J_{PC}$=163.0 Hz, $^3J_{P5-C3}$=4.5 Hz, C3), 64.49 (d, *J*=6.8 Hz), 64.19 (d, *J*=6.8 Hz), 63.65 (d, *J*=6.0 Hz), 62.58 (d, *J*=6.8 Hz), 62.38, 46.01, 39.89, 16.67 (d, *J*=5.3 Hz), 16.60 (d, *J*=5.3 Hz), 14.33. ^{31}P NMR ($CDCl_3$, 121.5 MHz): 20.98 and 16.29. Anal. Calcd for $C_{15}H_{31}NO_9P_2$: C, 41.77; H, 7.24; N, 3.25. Found: C, 41.91; H, 7.08; N, 3.18.

4.3.17. Methyl 3-diethoxyphosphoryl-2,5-dimethylisoxazolidine-5-carboxylate (7i and 8i). From nitrone **1a** (0.39 g, 2.00 mmol) and **6i** (1.0 mL, 10.0 mmol), a mixture of **7i** and **8i** (0.529 g, 90%) was obtained after purification on silica gel (chloroform–MeOH, 100:1). Further purification on silica gel with toluene–isopropanol (100:1) gave fractions enriched with **8i** (0.033 g, **8i/7i**=95:5) and **7i** (0.10 g, **7i/8i**=50:50).

Compound ***7i***: colourless oil. IR (film): *ν*=2473, 2984, 1737, 1444, 1238, 1203, 1053, 1024, 969 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.27–4.07 (m, 4H), 3.77 (s, 3H), 3.15 (ddd, $J_{3-4\beta}$=10.5 Hz, $J_{3-4\alpha}$=7.8 Hz, $^2J_{3-P}$=3.0 Hz, 1H, *H*–C3), 3.05 (ddd, ^2J=12.6 Hz, J_{4-3}=7.8 Hz, J_{4-P}=4.8 Hz, 1H, *Hα*–C4), 2.92 (d, *J*=1.2 Hz, 3H), 2.49 (ddd, J_{4-P}=16.8 Hz, ^2J=12.6 Hz, J_{4-3}=10.5 Hz, 1H, *Hβ*–C4), 1.56 (s, 3H), 1.36 (t, *J*=7.2 Hz, 3H), 1.33 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 173.7 (C=O), 81.59 (d, *J*=10.6 Hz, C5), 64.53 (d, $^1J_{PC}$=169.0 Hz, C3), 63.35 (d, *J*=6.0 Hz), 62.63 (d, *J*=6.8 Hz), 52.76 (s, *C*H$_3$), 46.94 (d, *J*=4.5 Hz, *C*H$_3$N), 43.21 (d, *J*=2.3 Hz, C4), 23.77, 16.67 (d, *J*=6.0 Hz), 16.63 (d, *J*=5.3 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 22.33. Anal. Calcd for $C_{11}H_{22}NO_6P$: C, 44.74; H, 7.51; N, 4.74. Found: C, 44.63; H, 7.81; N, 4.61.

Compound ***8i***: colourless oil. IR (film): *ν*=2473, 2984, 1737, 1444, 1238, 1203, 1053, 1024, 969 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.27–4.07 (m, 4H), 3.77 (s, 3H,), 3.22 (ddd, J_{P-4}=18.3 Hz, ^2J=12.9 Hz, J_{4-3}=9.3 Hz, 1H, *Hβ*–C4), 3.00 (ddd, $J_{4\beta-3}$=9.3 Hz, $J_{4\alpha-3}$=9.3 Hz, *J*=1.5 Hz, 1H, *H*–C3), 2.92 (d, *J*=1.2 Hz, 3H), 2.36 (ddd, ^2J=12.9 Hz, J_{4-3}=9.3 Hz, J_{P-4}=6.6 Hz, 1H, *Hα*–C4), 1.50 (s, 3H), 1.35 (t, *J*=7.2 Hz, 3H), 1.32 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 174.40 (C=O), 81.03 (d, *J*=8.3 Hz), 64.76 (d, $^1J_{PC}$=165.3 Hz, C3), 63.35 (d, *J*=6.0 Hz), 62.41 (d, *J*=6.8 Hz), 52.64 (s, *C*H$_3$), 45.85 (d, *J*=2.3 Hz, *C*H$_3$N), 42.18 (d, *J*=2.3 Hz, C4), 23.55, 16.60 (d, *J*=5.3 Hz), 16.53 (d, *J*=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 22.12. Anal. Calcd for $C_{11}H_{22}NO_6P$: C, 44.74; H, 7.51; N, 4.74. Found: C, 44.84; H, 7.73; N, 4.73.

4.3.18. Phosphonates obtained from 1a and chalcone (7j–10j). From nitrone **1a** (0.781 g, 4.00 mmol) and **6j** (0.833 g, 4.00 mmol), pure **7j** (0.201 g, 12%), **8j** (0.825 g, 50%) and **10j** (0.044 g, 3%) were obtained after purification on silica gel with ethyl acetate–hexane (2:1).

4.3.18.1. Diethyl 5-benzyl-2-methyl-4-phenylisoxazolidin-3-yl-3-phosphonate 7j. Mp 79–80 °C, colourless needles. IR (KBr): *ν*=2975, 2919, 1681, 1446, 1246, 1224, 1048, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.9–7.83 (m, 2H), 7.6–7.5 (m, 1H), 7.4–7.38 (m, 4H), 7.35–7.2 (m, 3H), 5.69 (d, J_{4-5}=9.0 Hz, 1H, *H*–C5), 4.45 (ddd, J_{4-P}=21.3 Hz, J_{4-3}=9.9 Hz, J_{4-5}=9.0 Hz, 1H, *H*–C4), 4.19–4.08 (m, 2H), 4.05–3.85 (m, 2H), 3.75 (dd, J_{4-3}=9.9 Hz, $^2J_{3-P}$=7.2 Hz, 1H, *H*–C3), 3.08 (d, *J*=0.9 Hz, 3H, C*H*$_3$N), 1.26 (t, *J*=6.9 Hz, 3H), 1.02 (t, *J*=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 195.14 (d, *J*=5.2 Hz, C=O), 137.98 (C_{ipso}), 137.59 (C_{ipso}), 133.32, 128.65, 128.58, 128.48, 128.44, 126.79, 82.83 (d, $^3J_{PCCC}$=3.7 Hz, C5), 69.34 (d, $^1J_{PC}$=172.6 Hz, C3), 63.45 (d, *J*=6.6 Hz), 62.82 (d, *J*=7.2 Hz), 58.43 (s, C4), 47.55 (d, *J*=8.9 Hz, *C*H$_3$N), 16.53 (d, *J*=6.0 Hz), 16.20 (d, *J*=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 18.88. Anal. Calcd for $C_{21}H_{26}NO_5P$: C, 62.52; H, 6.50; N, 3.47. Found: C, 62.52; H, 6.65; N, 3.66.

4.3.18.2. Diethyl 5-benzyl-2-methyl-4-phenylisoxazolidin-3-yl-3-phosphonate 8j. IR (film): *ν*=2985, 2909, 1680, 1596, 1449, 1252, 1240, 1027, 969 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.70–7.67 (m, 2H), 7.55–7.4 (m, 1H), 7.4–7.2 (m, 7H), 5.20 (d, J_{4-5}=7.8 Hz, 1H, *H*–C5), 4.71 (ddd, J_{4-P}=17.7 Hz, J_{4-5}=7.8 Hz, J_{4-3}=7.2 Hz, 1H, *H*–C4), 4.25–4.08 (m, 4H), 3.86 (dd, J_{4-3}=7.2 Hz, $^2J_{3-P}$=6.0 Hz, 1H, *H*–C3), 3.06 (s, 3H, C*H*$_3$N), 1.28 (t, *J*=7.2 Hz, 3H), 1.17 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 196.98 (s, *J*=4.0 Hz, C=O), 137.17 (C_{ipso}), 136.20 (C_{ipso}), 133.76, 128.81, 128.73, 128.66, 128.52, 127.05, 83.33 (d, $^3J_{PCCC}$=5.4 Hz, C5), 69.03 (d, $^1J_{PC}$=174.6 Hz, C3), 63.38 (d, *J*=6.6 Hz), 62.94 (d, *J*=6.9 Hz), 61.39 (d, *J*=1.7 Hz, C4), 47.06 (d, *J*=12.6 Hz, *C*H$_3$N), 16.62 (d, *J*=6.0 Hz), 16.42 (d, *J*=6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 22.67. Anal. Calcd for $C_{21}H_{26}NO_5P$: C, 62.52; H, 6.50; N, 3.47. Found: C, 62.62; H, 6.57; N, 3.64.

4.3.18.3. Diethyl 4-benzyl-2-methyl-5-phenylisoxazolidin-3-yl-3-phosphonate 10j. Colourless oil. IR (film): *ν*=2982, 2930, 1690, 1447, 1247, 1240, 1025, 971 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.0–7.94 (m, 2H), 7.6–7.5 (m, 1H), 7.5–7.24 (m, 7H), 5.10 (d, J_{4-5}=4.2 Hz, 1H, *H*–C5), 4.64 (ddd, J_{4-P}=17.1 Hz, J_{4-3}=8.7 Hz, J_{4-5}=4.2 Hz, 1H, *H*–C4), 4.20–3.80 (m, 4H), 3.13 (dd, J_{4-3}=8.7 Hz, $^2J_{3-P}$=3.0 Hz, 1H, *H*–C3), 3.02 (d, *J*=1.2 Hz, 3H, C*H*$_3$N),

1.29 (t, J=7.2 Hz, 3H), 1.07 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 196.56 (s, C=O), 140.85 (C_{ipso}), 134.97 (C_{ipso}), 133.28, 129.33, 128.92, 128.43, 128.23, 127.54, 86.31 (d, $^3J_{PCCC}$=9.2 Hz, C5), 74.36 (d, $^1J_{PC}$= 162.9 Hz, C3), 63.89 (d, J=6.3 Hz), 62.34 (d, J=6.6 Hz), 53.99 (C4), 46.18 (CH_3N), 16.61 (d, J=6.3 Hz), 16.27 (d, J=6.3 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 20.95. Anal. Calcd for $C_{21}H_{26}NO_5P$: C, 62.52; H, 6.50; N, 3.47. Found: C, 62.28; H, 6.52; N, 3.70.

4.3.19. Phosphonates obtained from 1a and ethyl cinnamate (7k–10k). From nitrone **1a** (0.781 g, 4.00 mmol) and **6h** (0.705 g, 4.00 mmol), pure **7k** (0.192 g, 13%) and **8k** (0.103 g, 7%) were obtained after purification on silica gel with ethyl acetate–hexane (2:1).

4.3.19.1. Ethyl 3-diethoxyphosphoryl-2-methyl-5-phenylisoxazolidine-4-carboxylate 7k. Colourless oil. IR (film): ν=2983, 2909, 1737, 1455, 1378, 1243, 1187, 1050, 1027, 971 cm^{-1}. ^{1}H NMR (C_6D_6, 300 MHz): 7.45–7.40 (m, 2H), 7.15–7.00 (m, 3H), 5.82 (d, J=8.7 Hz, 1H, *H*–C5), 4.20–3.95 (m, 6H, 2×CH_2OP and CH_2–CH_3), 3.51 (ddd, J=17.4, 10.2, 8.7 Hz, 1H, *H*–C4), 3.45 (dd, J=10.2, 6.8 Hz, 1H, *H*–C3), 2.89 (s, 3H), 1.11 (t, J=7.0 Hz, 6H), 0.99 (t, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 169.17 (d, J=6.6 Hz, C=O), 137.57 (C_{ipso}), 128.50, 128.37, 126.57, 82.11 (d, $^3J_{PCCC}$=4.6 Hz, C5), 67.97 (d, $^1J_{PC}$=169.2 Hz, C3), 63.14 (d, J=6.8 Hz), 63.10 (d, J=6.6 Hz), 61.37 (s, CH_3CH_2O(O)C), 56.72 (s, C4), 46.83 (d, J=7.4 Hz, CH_3N), 16.55 (d, J=5.4 Hz), 16.49 (d, J=5.7 Hz), 14.07 (s, CH_3CH_2O(O)C). ^{13}C NMR (C_6D_6, 75.5 MHz): 169.79 (d, J=6.6 Hz, C=O), 137.01 (C_{ipso}), 129.14, 128.90, 127.50, 82.92 (d, $^3J_{PCCC}$=4.3 Hz, C5), 69.05 (d, $^1J_{PC}$=167.2 Hz, C3), 63.48 (d, J=6.3 Hz), 63.31 (d, J=6.6 Hz), 61.67 (s, CH_3CH_2O(O)C), 57.90 (s, C4), 47.14 (d, J=7.2 Hz, CH_3N), 17.05 (d, J=6.0 Hz), 16.97 (d, J=5.7 Hz), 14.50 (s, CH_3CH_2O(O)C). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 19.32. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.06; N, 3.77. Found: C, 55.04; H, 7.30; N, 3.96.

4.3.19.2. Ethyl 3-diethoxyphosphoryl-2-methyl-5-phenylisoxazolidine-4-carboxylate 8k. Colourless oil. IR (film): ν=2983, 2910, 1735, 1447, 1375, 1253, 1180, 1024, 971 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.47–7.42 (m, 2H), 7.40–7.25 (m, 3H), 5.26 (d, J_{5-4}=7.0 Hz, 1H, *H*–C5), 4.30–4.10 (m, 6H), 3.69 (dd, J_{3-4}=7.5 Hz, $J_{3\text{-}P}$= 5.7 Hz, 1H, *H*–C3), 3.64 (ddd, $J_{4\text{-}P}$=13.5 Hz, J_{4-3}=7.5 Hz, J_{4-5}=7.0 Hz, 1H, *H*–C4), 3.00 (d, J=0.6 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H), 1.26 (t, J=7.0 Hz, 3H), 1.24 (t, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 170.85 (d, J=5.4 Hz, C=O), 137.99 (C_{ipso}), 128.51, 128.39, 126.68, 81.57 (d, $^3J_{PCCC}$=5.4 Hz, C5), 68.20 (d, $^1J_{PC}$=173.8 Hz, C3), 63.62 (d, J=6.6 Hz), 62.86 (d, J=6.9 Hz), 61.78 (s, CH_3CH_2O-(O)C), 59.38 (s, C4), 46.88 (d, J=11.5 Hz, CH_3N), 16.57 (d, J=6.0 Hz), 14.36 (s, CH_3CH_2O(O)C). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 21.84. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.06; N, 3.77. Found: C, 54.86; H, 7.20; N, 4.00.

4.4. General procedure for the cycloaddition of nitrone 1a to alkene in the presence of $ZnCl_2$

Nitrone **1a** (1.0 mmol) and alkene (2.0 mmol) in methylene chloride (2 mL) were stirred at room temperature in the presence of $ZnCl_2$ (1.00 mmol) until the nitrone disappeared. Crude product was purified by column chromatography on silica gel.

4.4.1. Isoxazolidines 3a and 4a. From nitrone **1a** (1.03 g, 5.28 mmol) and allyl alcohol (0.720 mL, 10.56 mmol), pure **3a** (0.633 g, 47%) and **4a** (0.045 g, 3%) were obtained after purification by column chromatography.

4.4.2. Isoxazolidines 3d and 4d. From nitrone **1a** (0.256 g, 1.31 mmol) and alkene **2d** (0.416 mL, 2.62 mmol), pure **3d** (0.081 g, 20%) and **4d** (0.028 g, 7%) were obtained, after purification by column chromatography.

*Compound **4d***: IR (film): ν=2981, 2955, 2911, 1249, 1050, 1027 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.30–4.13 (m, 5H, H-C5 and 2×CH_2–O–P), 3.10 (ddd, $J_{3-4\beta}$=9.0 Hz, $J_{3-4\alpha}$=8.4 Hz, $J_{3\text{-}P}$=4.8 Hz, 1H, *H*–C3), 2.78 (d, J=0.9 Hz, 3H, CH_3–N), 2.60 (dddAB, J_{AB}=12.3 Hz, J=6.6 Hz, $J_{4\alpha-3}$= 8.4 Hz, J=5.4 Hz, 1H, *Hα*–C4), 2.03 (dddAB, J_{AB}= 12.3 Hz, $J_{4\beta\text{-}P}$=18.6 Hz, $J_{4\beta-5}$=9.3 Hz, $J_{4\beta-3}$=9.0 Hz, 1H, *Hβ*–C4), 1.34 (t, J=7.1 Hz, 6H, 2×CH_3–CH_2–O–P), 1.07 (dAB, J_{AB}=14.1 Hz, $J_{5-1'a}$=6.0 Hz, 1H, *Ha*–C1′), 0.87 (dAB, J_{AB}=14.1 Hz, $J_{5-1'b}$=8.3 Hz, 1H, *Hb*–C1′), 0.05 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 73.82 (d, $^3J_{PCCC}$=7.5 Hz, C5), 64.71 (d, $^1J_{PC}$=169.0 Hz, C3), 62.95 (d, J=6.6 Hz, C–O–P), 62.48 (d, J=6.8 Hz, C–O–P), 46.31 (d, J=4.5 Hz, H_3C–N–C–P), 40.34 (d, $^2J_{PCC}$=3.8 Hz, C4), 21.98 (s, C1′), 16.63 (d, J=5.5 Hz, *C*–C–O–P), −0.70 (s, C(CH_3)$_3$). ^{31}P NMR ($CDCl_3$, 121.5 MHz): 24.42. Anal. Calcd for $C_{12}H_{28}NO_4PSi$: C, 46.58; H, 9.12; N, 4.53. Found: C, 46.37; H, 9.23; N, 4.52.

Acknowledgements

The author is indebted to Professor Andrzej E. Wróblewski for constant support, fruitful discussions and helpful suggestions during the preparation of this manuscript. Mrs. Małgorzata Pluskota and Mrs. Jolanta Płocka are acknowledged for their technical assistance. The author is also grateful to Dr. Maria Zabłocka from Polish Academy of Sciences in Łódź for an authentic sample of 1-oxo-1-phenyl-2-phospholene. This work was supported by the Medical University of Łódź internal funds (502-13-332 and 503-3014-1).

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Reactions of 3,10-epoxycyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,6,8,13-tetraene: a new intramolecular 1,5-oxygen migration

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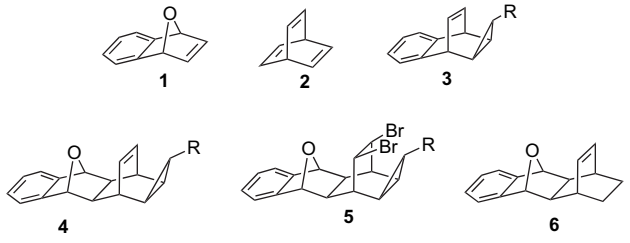
Received 18 June 2006; revised 18 September 2006; accepted 5 October 2006
Available online 31 October 2006

Abstract—Bromination of 3,10-epoxycyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,6,8,13-tetraene gave 13-bromo-11-oxapentacyclo[8.7.0.0^{2,4}.0^{12,17}]-heptadeca-4,6,8-triene-3-ol, 12-bromo-1,2,3,4-tetrahydro-1,4-ethano-antracen-11-ol, 13-hydroxy-3,14-dibromotetracyclo[10.2.2.0^{2,11}.0^{4,9}]-hexadeca-2,4,6,8,10-pentaene, and 13-hydroxy-3,10,14-tribromotetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10-pentaene by cleavage of the carbon–oxygen bonds and intramolecular 1,5-migration of the oxygen atom of 1,4-epoxide. Reactions of epoxide 14,18-dioxahexacyclo[10.3.2.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,15}]octadeca-4,6,8-triene obtained from 3,10-epoxycyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,6,8,13-tetraene gave also similar products, in acidic media. Compound 3,10-epoxycyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,6,8,13-tetraene was converted into tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2(11),3,9-triene in two ways. The reactions, especially intramolecular oxygen migration, are discussed.

1. Introduction

Molecular rearrangements occur in some reactions of organic compounds. According to the processes desired in the synthesis, rearrangements may be of value or a disadvantage for researchers. These rearrangements depend on the structures of the compounds and reaction conditions.[1] Oxabenzonorbornadiene (**1**), barralene (**2**), and benzhomobarralene derivative **3** give skeleton rearrangements.[1a,2] The structures of compounds **4** and **6** include both oxabenzonorbornane and barrelene derivatives as annulated structures. Dibromide **5**[3] was selectively formed in the bromination of compound **4** by neighboring group participation of the oxygen atom in **4** (Scheme 1).



Scheme 1.

The structure of 3,10-epoxycyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,6,8,13-tetraene (**6**) is similar to that of **4** as it includes 1,4-epoxide, an isolated double bond, and a benzene ring as functional groups. Its reactions with reagents such as bromine and *meta*-chloroperbenzoic acid (*m*-CPBA) will be important. Its importance is the following: (1) From which face does bromine or *m*-CPBA attack the double bond in **6**? (2) How does epoxide act in **6** when the reagents such as Br_2 or *m*-CPBA react with the double bond? Does a *cis*-dibromide **7** similar to **5** happen? Or does this epoxide in **6** rearrange? (3) Does anthracene derivative **8** obtained from **6**, by elimination of water? At the same time, **8** is an adduct of cyclohexadiene and was obtained by two different ways (from reactions of 1,3-cyclohexadiene with naphthyne and 1,4-naphthoquinone separately).[4] (4) It will also be possible that the aromatic ring shifts from terminal ring to the central ring in the same compound if **9** is obtained from **6** by reduction reactions from **6** (Scheme 2). Therefore, reactions of the compound **6** with these reagents were investigated separately.

2. Results and discussion

Adduct **6** was obtained from the Diels–Alder cycloaddition reaction of 1,4-dihydronaphthalene-1,4-epoxide with cyclohexadiene.[3] Adduct **6** was reacted with Br_2 (1.1 equiv) in a CCl_4 solution at 0 °C for 30 min (Scheme 3). It was seen that adduct **6** was absent in the ^{1}H NMR spectrum of the reaction mixture. Careful PLC (preparative thick-layer chromatography) allowed us to isolated two products, **10** and **11**.

Keywords: Aromatization; Bromination; Epoxide; Epoxidation; Naphthyne; Oxygen migration; Rearrangement; Reduction.
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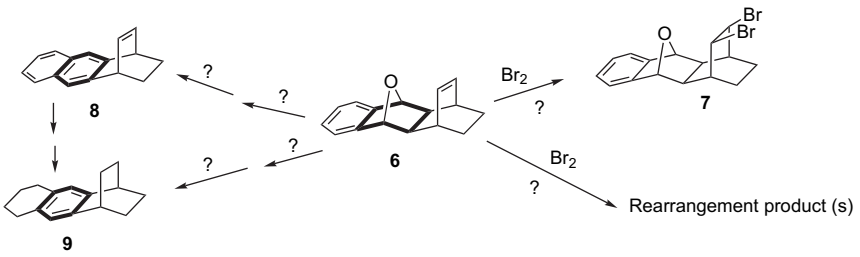
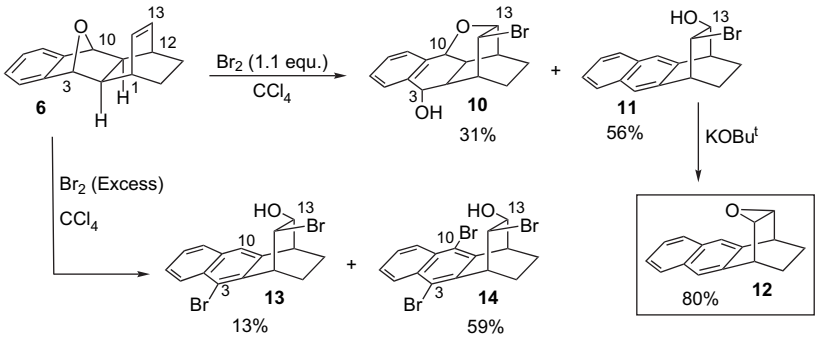
doi:10.1016/j.tet.2006.10.012



Scheme 2.



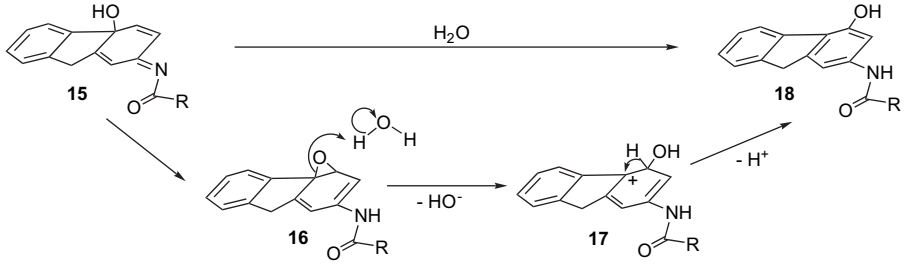
Scheme 3.

On the basis of the NMR spectra of these compounds, it was determined that they are asymmetrical structures, but it was not easy to establish their exact configurations. NMR spectroscopic data of **11** indicated that it is a naphthalene derivative with Br and OH functional groups. To confirm the configuration of Br and OH groups in **11**, compound **11** was reacted with potassium *tert*-butoxide to give epoxide **12**. Epoxide **12**[4a] has a symmetrical structure and its structure is consistent with its NMR spectra (Scheme 3). To determine the exact structures of **10** and **11**, X-ray crystallographic analyses were carried out.[5] We assumed that **10** might be formed during PLC by the hydrolysis of intermediate bromide (probable **24**, Scheme 5) whose structure is not known.

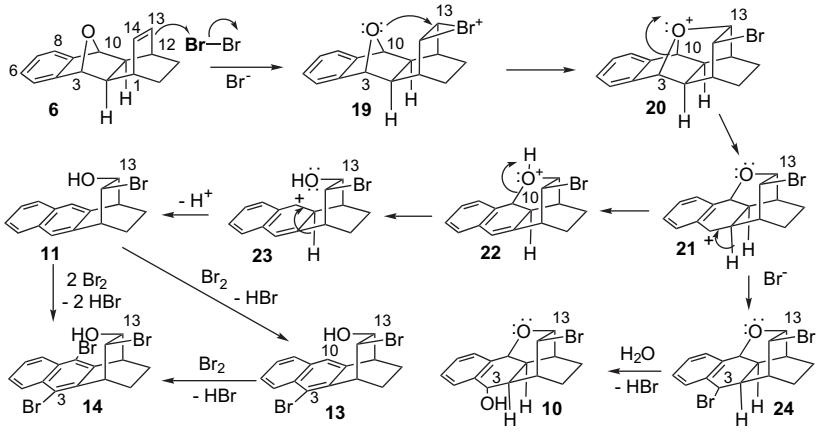
In a similar manner, adduct **6** was reacted with excess Br_2. After evaporation of excess Br_2 and solvent, dibromide **13** and tribromide **14** were isolated in this bromination reaction by column chromatography (Scheme 3). The ^{1}H NMR spectrum of dibromide **13** showed absorptions at δ 8.29 (d), 7.81 (d), 7.64 (s), and 7.63–7.27 (m), with relative intensities of 1:1:1:2. However, dibromide **13** does not have a symmetrical structure and exhibits ten lines in the aromatic and six lines in the aliphatic regions of its ^{13}C NMR spectrum. One of the five quaternary carbons should be CBr and other substituent groups (Br and OH) should be at the bridgehead as in **11**. The region of Br at aromatic carbon (C_3) was regarded as compound **13** because greater steric effect(s) can occur between the Br and OH groups in it and its intermediate(s) if Br is at C_{10} rather than the other position (if Br is at C_3). Tribromide **14** does not have a symmetrical structure and is consistent with its NMR spectra.

In the reactions of compound **6** with bromine, the epoxide ring of **6** is opened and tetrahydrofuran rings occur in this structure, as in **10**, by intramolecular 1,5-migration of the oxygen atom. Then halohydrins **11**, **13**, and **14** occur by the aromatization of these structures.

Intramolecular 1,5-migration of the oxygen atom and formation of tetrahydrofuran derivative are important in the bromination of **6**. There are intramolecular oxygen migrations.[6] One of them is migration of the oxygen atom, which is observed in the conversion of compound **15** to compound **18**.[6b] According to the data, epoxide (oxa norcaradiene) **16** was formed by nucleophilic attack of oxygen, and then **18** was formed (via **17**) by ring opening of epoxide and aromatization of ring in this reaction (Scheme 4). The migration of the oxygen atom in the formation of **18** is an intramolecular 1,2-migration and is similar to that of **6**. However, the



Scheme 4.

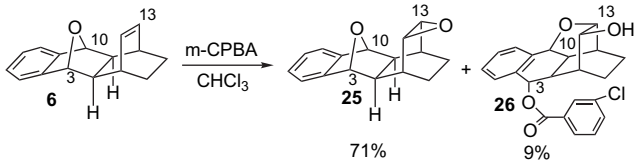


Scheme 5.

intramolecular 1,5-migration of the oxygen atom is a new oxygen migration.

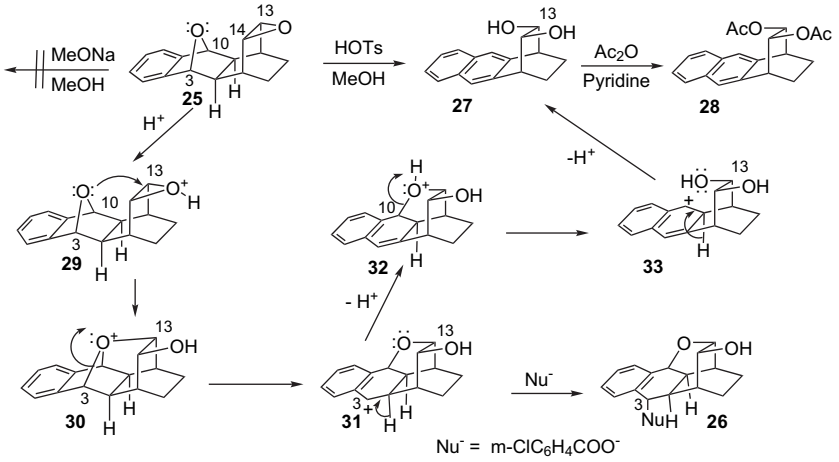
To rationalize the formation of compounds **10**, **11**, **13**, and **14**, we propose the following reaction mechanism as favorable mechanism. As shown in the bromination of compound **5**,[3] bromine can attack the double bond in **6** from the *exo* face (Scheme 5). A bridged bromonium ion **19** is produced and the oxygen of the epoxide acts as a nucleophile to yield **20**. Intermediate **21** is produced from **20** by the opening of the epoxide ring. Br^- can attack intermediate **21** to give **24** (probable) as a nucleophile. Intermediate **24** whose structure is not known may hydrolyze to give **10**. Intermediate **21** is converted into **11** through intermediates **22** and **23** by aromatization of the ring. As reported in the literature,[7] bromine is added to naphthalene and its derivatives, and then brominated naphthalenes are produced by the elimination of HBr. Compound **11** is a naphthalene derivative, and bromine will be added to its ring, which is electron-rich. Compound **11** is converted into **13** by the addition of Br_2 and then the elimination of HBr. Compound **14** can be formed by either the addition of 2 equiv of Br_2 to **11** and then the elimination of 2 equiv of HBr or the addition of Br_2 to **13** and then the elimination of HBr.

As mentioned above, bromine attacks the double bond in **4** and **6** from the *exo* face. *m*-CPBA can attack the double bound in **6** by approach from *exo* and *endo* (toward 1,4-epoxide) faces. To investigate the approach of *m*-CPBA to the double bond in **6** and to confirm the intramolecular 1,5-migration of the oxygen atom, compound **6** was reacted with *m*-CPBA (Scheme 6). In this epoxidation, epoxide **25** and ester **26**[8] were obtained. According to its NMR data such as HETCOR and COSY, **25** has a symmetrical structure and is consistent with the proposed structure. In the formation of epoxide **25**, *m*-CPBA also attacks the double bond in **6**. As shown in Scheme 7, ester **26** is a secondary product formed from **25**.



Scheme 6.

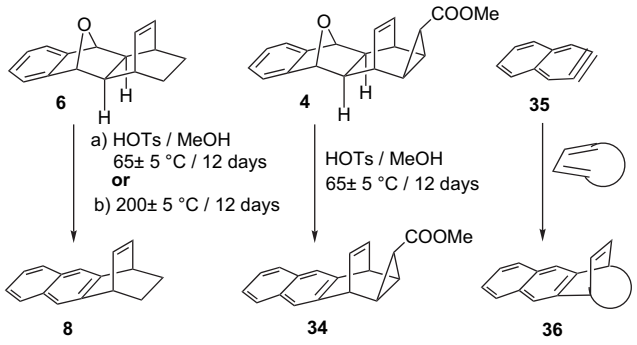
Epoxide **25** was refluxed with TsOH (*p*-toluenesulfonic acid) in MeOH for 1 week (Scheme 7). In this reaction, only diol **27** was obtained and epoxide **25** was not present. However, when the opening of the ring of epoxide **25** with NaOMe in similar conditions was attempted, we isolated only unreacted starting material.



Scheme 7.

For the formation of diol **27**, we can propose the following reaction mechanism as favorable mechanism. The fact that no product with OMe was observed in either of them by the opening of 1,2-epoxide, which shows that the oxygen of 1,4-epoxide only attacked the 1,2-epoxide as a nucleophile. First, 1,2-epoxide is protonated with TsOH and it converts into structure **31** via **29** and **30** because it is more strained than the 1,4-epoxide.[9] Intermediate **31** can convert into both **32**, by the departure of the proton and the formation of a double bond, and **26** by the attack of a nucleophile. Ester **26**,[8] a substitution product, was obtained in the epoxidation of compound **6** because *m*-chlorobenzoic acid (*m*-ClC_6H_4COOH) or *m*-chlorobenzoate (*m*-$ClC_6H_4COO^-$) transferred from *m*-CPBA is present. Intermediate **32**, a protonated tetrahydrofuran derivative, can convert into diol **27** via **33** by the opening of the tetrahydrofuran ring, the departure of the proton, and aromatization of ring. The synthesis and structure of diacetate **28** also confirm diol **27**.

A compound such as epoxide **6** reacted with acids gives an aromatic product by the elimination of water.[10] Epoxide **6** was reacted with TsOH in a methanol solution at 65±5 °C (in a sealed tube) for 12 days and only an anthracene derivative **8** was isolated (Scheme 8). However, anthracene derivative **8** was also obtained when epoxide **6** was heated at 200±5 °C (in a sealed tube) for 12 days. In a similar manner, the reaction of compound **4** with TsOH in a methanol solution at 65±5 °C (in a sealed tube) for 12 days gave only an anthracene derivative **34** (Scheme 8). According their NMR data, both **8**[4a] and **34** have symmetrical structures. Aromatic protons of **34** resonate as an AA′BB′ system and a singlet. Compounds **8** and **34** represented by a generic structure **36** are adducts of naphthyne with cyclohexadiene and 7-methoxycarbonylcycloheptatriene, respectively, and they were obtained from adducts **6** and **4**, which were synthesized from reactions of 1,4-dihydronaphthalene-1,4-epoxide with cyclohexadiene and 7-methoxycarbonylcycloheptatriene, respectively.[3] However, a diol derivative of **34** was synthesized from reaction of 1,4-naphthoquinone with 7-methoxycarbonylcycloheptatriene as adduct.[11] Therefore, 1,4-dihydronaphthalene-1,4-epoxide can act as a synthetic equivalent of naphthyne.



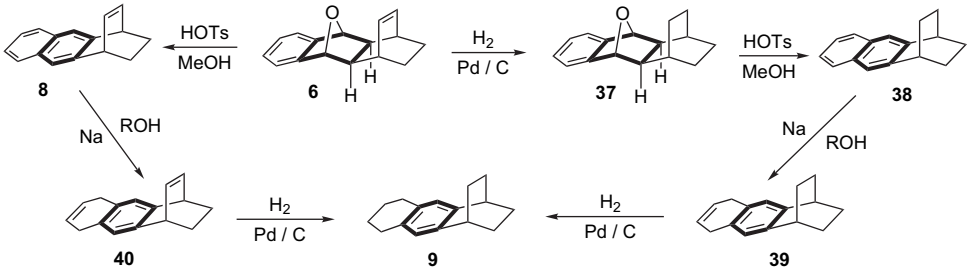
Scheme 8.

In compound **6**, aromatic and olefinic double bonds can be reduced, and these reduced products will be interesting. With this in mind, reduction reactions of **6** were investigated in two ways. One synthetic path is via **6**, **37**, **38**, **39**, and **9**, while the other is via **6**, **8**, **40**, and **9** (Scheme 9). Catalytic hydrogenation of compound **6** quantitatively gave **37** (Scheme 9). Reaction of compound **37** with TsOH gave anthracene derivative **38** in 72% yield. The data of **38**[4a] and **39** are in complete agreement with the proposed structures. We performed the reductions of aromatic compounds such as naphthalene with alkali metals and *tert*-butyl alcohol in high yield at room temperature.[12] Reduction reactions of **8** and **38** with Na/^{t}BuOH were carried out separately. Reduction of **8** produced a mixture of **8** and **40** while reduction of **38** produced a mixture of **38** and **39**. These mixtures could not be separated by chromatographic methods. Unsubstituted aromatic rings of **8** and **38** were reduced in these reactions because their electron densities are less than the others.[13] Catalytic hydrogenations of **39** and **40** in these mixtures gave compound **9** in high yields (Scheme 9). The aromatic protons of **9**, **39**, and **40** resonate at 6.91, 6.98, and 6.98 ppm, respectively, as singlets.

There is an aromatic ring in compounds **6** and **9**, but these aromatic rings are in different units of these structures. Therefore, the aromatic ring in **6** was transferred into another ring in **9** by chemical reactions.

3. Conclusion

The reaction of compound **6** with Br_2 (1.1 equiv) gave tetrahydrofuran derivative **10** and anthracene derivative **11**, while with excess Br_2 it gave anthracene derivatives **13** and **14**. As shown in Scheme 5, compounds **13** and **14** are not primary products and they are formed from **11**. Compound **10** is formed by the cleavage of a carbon–oxygen bond and intramolecular 1,5-migration of the oxygen atom of 1,4-epoxide. Compound **11** can also be formed from products and intermediate(s) such as **21** and **24** by cleavage of the tetrahydrofuran rings in them. Reactions of epoxide **25** obtained from **6** also gave similar products, **26** and **27**, in acidic media. In these reactions, the observed intramolecular 1,5-migration of the oxygen atom of 1,4-epoxide is important and new.



Scheme 9.

Compounds **8** and **34** represented by a generic structure **36** were formed from the reactions of **6** and **4** with TsOH, are adducts of naphthyne with cyclohexadiene and 7-methoxycarbonylcycloheptatriene, respectively. Therefore, 1,4-dihydronaphthalene-1,4-epoxide can be used as a synthetic equivalent of naphthyne.

Compound **6** was converted into **9** by reactions of TsOH and reduction. Aromatic rings are found in different units in the structures of **6** and **9**. Therefore, the aromatic ring in **6** was transferred into another ring in **9** by these reactions.

4. Experimental

4.1. General methods

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Melting points were determined on Thomas-Hoover capillary melting apparatus and are uncorrected. IR spectra were obtained from solutions in 0.1 mm cells with a *Perkin–Elmer* spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a 200 (50) and 400 (100)-MHz *Varian spectrometer*; δ in parts per million, Me_4Si as the internal standard. Mass spectra were determined on VG ZabSpec, double focusing, magnetic sector (100.000 resolution) max. range 1000 for EI and 10,000 for HRMS. Elemental analyses were performed on Carlo Erba 1106 apparatus. All column chromatography was performed on silica gel (60-mesh, Merck). PLC is preparative thick-layer chromatography: 1 mm of silica gel 60 PF (Merck) on glass plates.

4.2. Bromination of the compound 6 with bromine (1.1 equiv)

To a stirred solution of compound **6** (200 mg, 0.89 mmol) in CCl_4 (20 mL) was added Br_2 (158 mg, 0.99 mmol, in 1 mL of CCl_4) dropwise at 0 °C over 5 min. The mixture was stirred for 30 min, and then the solvent was evaporated. According to the NMR spectrum of the residue, compound **6** was absent. The residue was submitted to PLC with ether/hexane (1:1). Compounds **11**[5b] (150 mg, 0.50 mmol, 56%) and **10**[5a] (90 mg, 0.28 mmol, 31%) were isolated pure.

4.3. Treatment of halohydrine 11 with ^{t}BuOK

To a stirred solution of compound **11**[5b] (520 mg, 1.72 mmol) in dry tetrahydrofuran (40 mL) was added ^{t}BuOK (1.5 g, 13.40 mmol) at room temperature. The mixture was stirred for 5 days. After the evaporation of solvent, a cold solution of NH_4Cl (5%, 100 mL) was added. The mixture was extracted with $CHCl_3$ (3×50 mL). The combined organic layer was dried over $CaCl_2$ and filtered by a small column (2–3 g silica gel). After the evaporation of solvent, epoxide **12**[4a] (305 mg, 1.37 mmol, 80%) was crystallized from $CHCl_3$/hexane as white crystals.

4.3.1. 14-Oxo-1*S*(*R*),12*R*(*S*),13*S*(*R*),15*R*(*S*)-pentacyclo-[10.3.2.0^{2,11}.0^{4,9}.0^{13,15}]heptadeca-2(11),3,5,7,9-pentaene (12). Mp 166–168 °C (lit. 173–174 °C[4a]); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91–7.85 (AA′ of AA′BB′, aromatic, 2H), 7.61 (s, aromatic, 2H), 7.53–7.47 (BB′ of AA′BB′, aromatic, 2H), 3.68–3.66 (m, 2H), 3.60–3.54 (m, 2H), 1.98–1.88 (m, methylenic, 2H), 1.57–1.48 (m, methylenic, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.5 (C), 135.1 (C), 129.6 (CH), 127.1 (CH), 124.3 (CH), 52.0 (CH), 39.1, 24.9; Anal. Calcd for $C_{16}H_{14}O$: C 86.45, H 6.35; found: C 86.29, H 6.37.

4.4. Bromination of the compound 6 with excess bromine

To a stirred solution of compound **6** (1 g, 4.46 mmol) in CCl_4 (45 mL) was added Br_2 (2–3 mL, excess) dropwise at 0 °C over 5 min. The temperature of the bath was allowed to rise gradually to room temperature. After the addition of Br_2 was completed, the reaction mixture was stirred for 19 h. Solvent and excess Br_2 were evaporated. Chromatography of the residue on silica gel (60 g) with hexane/ether (10/1) gave the first fraction tribromide **14** (1.2 g, 2.61 mmol, 59%) and the second fraction dibromide **13** (186 mg, 0.57 mmol, 13%).

4.4.1. 1(*R*)*S*,12(*S*)*R*,13(*R*)*S*,14(*R*)*S*-13-Hydroxy-3,14-dibromotetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10-pentaene (13). Mp 178–180 °C; white crystal from ethyl acetate/hexane; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (d, aromatic, J=8.3 Hz, 1H), 7.81 (d, aromatic, J=6.7 Hz, 1H), 7.64 (s, aromatic, 1H), 7.63–7.27 (m, aromatic, 2H), 4.36 (m, CH-O, 1H), 3.39 (m, 1H), 4.01 (m, 1H), 3.14 (m, 1H), 2.39 (m, methylenic, 1H), 1.95 (m, methylenic, 1H), 1.84 (br d, J=6.5 Hz, OH, 1H), 1.69–1.40 (m, methylenic, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6 (C), 138.5 (C), 136.0 (C), 133.7 (C), 129.8 (CH), 129.6 (CH), 128.9 (CH), 128.4 (CH), 126.8 (CH), 121.5 (C), 81.7 (CH-O), 60.0 (CH), 45.2 (CH), 44.8 (CH), 25.0 (CH_2), 20.9 (CH_2); *m*/*z*: 384.2/382.3/380.2 (61/41/41), 259.2/257.2 (54/47), 194.2/192.2/191.2 (22/16/15), 178.2/179.2 (100/52), 166.2/165.2/164.2 (13/29/6); IR ($CHCl_3$) 3301, 3270, 3062, 2939, 2869, 1496, 1419, 1326, 1257, 1187, 1064, 1033, 933, 887, 794, 775, 686 cm^{-1}. HRMS: Anal. Calcd for $C_{16}H_{14}O^{79}Br_2$ 381.9568, found 381.9557.

4.4.2. 1(*R*)*S*,12(*S*)*R*,13(*R*)*S*,14(*R*)*S*-13-Hydroxy-3,10,14-tribromotetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10-pentaene (14). Mp 171–173 °C; white crystal from ethyl acetate/pentane; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.37–8.32 (m, aromatic, 2H), 7.68–7.60 (m, aromatic, 2H), 4.44 (m, CH-O, 1H), 4.07 (m, 1H), 3.91 (m, 1H), 3.83 (m, 1H), 2.39 (m, methylenic, 1H), 1.97 (m, methylenic, 1H), 1.83 (br d, J=5.5 Hz, OH, 1H), 1.70–1.27 (m, methylenic, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.0 (C), 138.7 (C), 134.6 (C), 134.4 (C), 130.1 (CH), 129.9 (CH), 129.7 (CH), 129.0 (CH), 123.9 (C), 121.4 (C), 81.8 (CH-O), 59.0 (CH), 45.3 (2CH), 23.8 (CH_2), 20.5 (CH_2); *m*/*z*: 464.1/462.2/460.2/452.2 (35/76/76/35), 384.2/382.2/380.2 (18/34/20), 339.1/337.1 (35/48), 259.2/258.2/256.2 (50/86/81), 192.2/191.2/189.2 (31/35/37), 179.2/178.2 (40/100), 165.2/163.2 (48/23); IR ($CHCl_3$) 3284, 3228, 3096, 2916, 2869, 1592, 1492, 1446, 1323, 1253, 1192, 1176, 1076, 1038, 930, 761, 700, 684 cm^{-1}. HRMS: Anal. Calcd for $C_{16}H_{13}O^{79}Br_3$ 459.8673, found 459.8686.

4.5. Reaction of the compound 6 with *m*-CPBA

A solution of *m*-CPBA (2.392 g, 10.40 mmol) whose water is 25% in $CHCl_3$ (50 mL) was dried over Na_2SO_4 and filtered. To this solution was added compound **6** (1.164 g,

5.20 mmol). After stirring at room temperature for 1 day, the reaction mixture was washed with a solution of NaOH (0.5%, 500 mL) and water (500 mL), dried over Na_2SO_4, and the solvent was evaporated. The reaction mixture was crystallized from $CHCl_3$/ether, and epoxide **25** (735 mg, 3.10 mmol, 59%) was obtained as colorless crystals. The residue was submitted to preparative thick-layer chromatography (PLC) with ethyl acetate/hexane (1/1). Epoxide **25** (150 mg, 0.60 mmol, 12%) and compound **26**[8] (468 mg, 1.20 mmol, 9%) were obtained.

4.5.1. 1*R*(*S*),2*R*(*S*),3*R*(*S*),10*S*(*R*),11*S*(*R*),12*S*(*R*),13*S*(*R*),15*R*(*S*)-14,18-Dioxahexacyclo[10.3.2.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,15}]-octadeca-4,6,8-triene (25). Mp 202–204 °C; colorless crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.22 (AA′ of AA′BB′, aromatic, 2H), 7.15–7.13 (BB′ of AA′BB′, aromatic, 2H), 5.22 (s, epoxide, H_3–H_{10}, 2H), 3.29 (br s, epoxide, H_{13}–H_{15}, 2H), 2.46 (br s, bridgehead, H_1–H_{12}, 2H), 1.86 (br s, H_2–H_{11}, 2H), 1.75 (br d, A of AABB, J=8.1 Hz, methylenic, 2H), 1.06 (br d, B of AABB, J=8.1 Hz, methylenic, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (C), 126.8 (CH), 119.1 (CH), 82.7 (CH, C_3–C_{10}), 52.3 (CH, C_{14}–C_{15}), 43.8 (CH, C_1–C_{12}), 31.3 (CH, C_2–C_{11}), 24.0 (CH_2); IR ($CHCl_3$) 3077, 3023, 2939, 2861, 1457, 1419, 1272, 1133, 1079 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found: C 79.76, H 6.68.

4.6. Reaction of epoxide 25 with TsOH

A mixture of epoxide **25** (335 mg, 1.40 mmol), TsOH (200 mg, 1.16 mmol), and MeOH (50 mL) was refluxed for 1 week. After the solvent of the mixture was evaporated, water (50 mL) was added and it was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL), dried over $CaCl_2$, and the solvent was evaporated. Diol **27** (175 mg, 73%) was crystallized from ethyl acetate.

4.6.1. 1(*R*)*S*,12(*S*)*R*,13(*S*)*R*,14(*S*)*R*-Tetracyclo-[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10-pentaene-13,14-diol (27). Mp 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.80 (AA′ of AA′BB, aromatic, 2H), 7.66 (s, aromatic, 1H), 7.64 (s, aromatic, 1H), 7.47–7.42 (BB′ of AA′BB, aromatic, 2H), 3.84 (br s, OCH, 1H), 3.62 (br s, OCH, 1H), 3.20 (m, bridgehead, 1H), 3.15 (m, bridgehead, 1H), 2.19 (m, methylenic, 1H), 1.92 (m, methylenic, 1H), 1.72 (m, OH, 1H), 1.59 (tt, J=12.7, 4.03 Hz, 1H), 1.31 (m, methylenic, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4 (C), 137.4 (C), 133.2 (C), 133.0 (C), 127.8 (CH), 127.7 (CH), 125.7 (2CH), 124.7 (CH), 123.1 (CH), 79.7 (C–O), 78.8 (C–O), 42.8, 42.1, 23.7, 17.7.

4.7. Synthesis of diacetate 28

Diol **27** (600 mg, 2.50 mmol) was allowed to react at room temperature for 3 days with pyridine (2 mL) and acetic anhydride (Ac_2O) (3 mL). The reaction mixture was poured into dilute aqueous HCl (100 g) with ice and checked with pH paper. It was extracted with $CHCl_3$ (2×40 mL), the extract was washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL), and dried over $CaCl_2$. The solvent was evaporated and diacetate **28** (486 mg, 1.50 mmol, 60%) was obtained in a refrigerator from $CHCl_3$/hexane as white crystals.

4.7.1. 1(*R*)*S*,12(*S*)*R*,13(*S*)*R*,14(*S*)*R*-14-(Acetyloxy)tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10-pentaen-13-yl acetate (28). Mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (AA′ of AA′BB′, aromatic, 2H), 7.70 (s, aromatic, 1H), 7.61 (s, aromatic, 1H), 7.50–7.44 (BB′ of AA′BB′, aromatic, 2H), 5.06 (t, J=2.6 Hz, H_{14}, 1H), 4.80–4.76 (m, H_{13}, 1H), 3.43–3.41 (m, bridgehead, H_{12}, 1H), 3.33–3.30 (m, bridgehead, H_{13}, 1H), 2.33–2.00 (m, methylenic, 2H), 2.17 (s, methyl, 3H), 1.91 (s, methyl, 3H), 1.62 (tt, J=12.5, 4.03 Hz, methylenic, 1H), 1.45–1.33 (m, methylenic, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (CO), 170.5 (CO), 137.8 (C), 137.4 (C), 133.3 (C), 133.2 (C), 128.0 (CH), 127.8 (CH), 125.8 (CH), 125.7 (CH), 124.0 (CH), 123.5 (CH), 77.8 (C–O), 77.7 (C–O), 39.3 (CH), 39.0 (CH), 23.4 (CH), 21.5 (CH_3), 21.3 (CH_3), 18.6 (CH); IR ($CHCl_3$) 3055, 3018, 2953, 2872, 1739, 1371, 1245, 1214, 1054, 1039, 879, 752 cm^{-1}; Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06, H 6.21; found: C 73.81, H 6.23.

4.8. Synthesis of anthracene derivative 8[4a] from 6

This product **8** was synthesized in two different ways.

(a) A mixture of compound **6** (591 mg, 2.46 mmol), TsOH (156 mg, 0.91 mmol), and MeOH (20 mL) in a sealed tube was heated at 95±5 °C for 12 days. The other parts of the reaction were studied in the same manner as for epoxide **25**. $CHCl_3$ (3×50 mL) was used in the extraction and anthracene derivative **8** was obtained as 350 mg (1.70 mmol, 69%).

(b) Compound **6** (112 mg, 0.50 mmol) was heated at 200±5 °C for 12 days alone. After the reaction mixture with silica gel (2–3 g) was filtered by $CHCl_3$ and the solvent was evaporated, **8** (55 mg, 0.20 mmol, 40%) was obtained.

4.8.1. 1(*R*)*S*,12(*S*)*R*-Tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10,13-hexaene (8). Mp 102–104 °C (lit. 112–114 °C[4a]); white crystals were obtained from $CHCl_3$/hexane; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86–7.80 (AA′ of AA′BB′, aromatic, 2H), 7.63 (s, aromatic, 2H), 7.48–7.42 (BB′ of AA′BB′, aromatic, 2H), 6.63 (m, olefinic, 2H), 4.09 (m, bridgehead, 2H), 1.73–1.60 (m, methylenic, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8 (C), 137.1 (CH), 134.2 (C), 129.4 (CH), 126.9 (CH), 122.3 (CH), 42.2, 28.1; Anal. Calcd for $C_{16}H_{14}$: C 93.16, H 6.84; found: C 92.99, H 6.86.

4.9. Synthesis of anthracene derivative 34

A mixture of compound **4**[3] (125 mg, 0.43 mmol), TsOH (160 mg, 0.93 mmol), and MeOH (25 mL) in a sealed tube was heated at 95±5 °C for 12 days. The other parts of the reaction were studied in the same manner as for epoxide **25**. $CHCl_3$ (3×50 mL) was used in the extraction and chromatography of the residue on PLC with hexane/ether (7/3) given as an anthracene derivative **34** (80 mg, 0.29 mmol, 67%).

4.9.1. 1(*R*)*S*,12(*S*)*R*,13(*S*)*R*,14(*R*)*S*-Methylpentacyclo-[10.3.2.0^{2,11}.0^{4,9}.0^{13,15}]heptadeca-2,4,6,8,10,16-hexaene-14-carboxylate (34). Mp (amorf) 146–148 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80–7.72 (AA′ of AA′BB′, aromatic, 2H), 7.61 (s, aromatic, 2H), 7.47–7.27 (BB′ of AA′BB′, aromatic, 2H), 6.26 (m, olefinic, 2H), 4.20 (m, bridgehead,

2H), 3.67 (s, OMe, 3H), 1.98–1.92 (m, cyclopropane, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.4 (CO), 144.9 (C), 134.0 (C), 133.5 (CH), 129.5 (CH), 127.4 (CH), 123.3 (CH), 53.5 (OMe), 42.7, 28.5, 27.5; IR ($CHCl_3$) 3080, 3029, 3004, 2953, 1710, 1676, 1625, 1497, 1472, 1319, 1242, 1191, 1165, 1114, 1063, 936, 885, 757 cm^{-1}; Anal. Calcd for $C_{19}H_{16}O_2$: C 82.55, H 5.84; found: C 82.24, H 5.81.

4.10. Catalytic hydrogenation of the compound 6

Into a 250 mL, two necked, round-bottomed flask fitted with a spinbar were placed 60 mg of Pd/C (5%) catalyst and **6** (1.04 g, 5.00 mmol) in ethyl acetate (100 mL). One of the necks was attached to a hydrogen manifold with a three-way stopcock and the other neck was capped with a rubber septum, degassed and flushed with hydrogen gas, while stirring magnetically. After stirring for 9 h the solution was decanted to separate it from the catalyst, and the solvent was evaporated. Compound **37** was quantitatively obtained and crystallized from hexane as white crystals.

4.10.1. 2*R*(*S*),3*R*(*S*),10*S*(*R*),11*S*(*R*)-3,10-Epoxytetracyclo-[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,6,8-triene (37). Mp 127–129 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.21 (AA′ of AA′BB′, aromatic, 2H), 7.19–7.12 (BB′ of AA′BB′, aromatic, 2H), 5.17 (s, epoxide, 2H), 1.94–1.87 (m, 4H), 1.70 (m, 2H), 1.62–1.30 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.0 (C), 128.1 (CH), 120.7 (CH), 84.3 (OCH), 44.7, 29.7, 28.7, 24.2; IR ($CHCl_3$) 2914, 1458, 1351, 1247, 1208, 1023, 965, 919, 850, 758, 657 cm^{-1}; Anal. Calcd for $C_{16}H_{18}O$: C 84.91, H 8.02; found: C 84.68, H 8.05.

4.11. Synthesis of anthracene derivative 38[4a]

This reaction was also studied in the same manner as for compound **6**. Compound **37** (904 mg, 4.00 mmol), TsOH (172 mg, 1.00 mmol), and MeOH (25 mL) were used for this reaction. Compound **38** (600 mg, 72%) was obtained and crystallized from ethanol.

4.11.1. Tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2,4,6,8,10-pentaene (38). Mp 111–113 °C (lit. 112–113 °C[4a]); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91–7.84 (AA′ of AA′BB′, aromatic, 2H), 7.65 (s, aromatic, 2H), 7.52–7.45 (BB′ of AA′BB′, aromatic, 2H), 3.17 (m, bridgehead, 2H), 1.97–1.91 (m, methylenic, 4H), 1.59–1.54 (m, methylenic, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.4 (C), 134.8 (C), 129.5 (CH), 127.7 (CH), 123.2 (CH), 36.2 (CH), 28.5 (CH_2); Anal. Calcd for $C_{16}H_{18}$: C 91.37, H 8.63; found: C 91.28, H 8.65.

4.12. Reduction of anthracene derivative 8

Anthracene derivative **8** (340 mg, 1.65 mmol) and ^{t}BuOH (2 mL) were dissolved in dry ether (30 mL). Excess metallic Na (1 g, 43.48 mmol), in small pieces, was added over 10 min. After stirring at room temperature for 4 days, unreacted Na and solid ^{t}BuOK were removed by filtration and washed with ether (40 mL). The solution was poured into water (100 mL) and the mixture formed was shaken. The organic layer was separated, and the water layer was extracted twice with ether (2×30 mL). The combined organic layer was washed with water (20 mL), dried over $CaCl_2$, and then the solvent was evaporated. A mixture of **8** and **40** (278 mg) was obtained (**8**:**40**=1:9). They were not isolated by chromatographic methods.

4.12.1. 1(*R*)*S*,12(*S*)*R*-Tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2(10),3,5,8,13-pentaene (40). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.98 (s, aromatic, 2H), 6.57–6.53 (m, olefinic, 2H), 5.95 (s, olefinic, 2H), 3.94 (m, bridgehead, 2H), 3.41 (s, methylenic, 4H), 1.68–1.54 (m, methylenic, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.3 (C), 137.3 (CH), 132.4 (C), 127.0 (CH), 124.6 (CH), 41.0, 31.0, 28.1.

4.13. Reduction of anthracene derivative 38

This reaction was also studied in the same manner as for compound **8**. A mixture of anthracene derivative **38** (600 mg, 2.88 mmol), ^{t}BuOH (2 mL), dry ether (40 mL), and excess metallic Na (6 equiv) was stirred for 1 week. A mixture of **38** and **39** (430 mg) was obtained (**38**:**39**=1:6). They were also not isolated by chromatographic methods.

4.13.1. Tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2(10),3,5,8-tetraene (39). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.98 (s, aromatic, 2H), 5.98 (s, olefinic, 2H), 3.46 (br s, methylenic, 4H), 3.00 (m, bridgehead, 2H), 1.83 (bd, A of AB, J= 8.2 Hz, methylenic, 4H), 1.47 (bd, B of AB, J=8.2 Hz, methylenic, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2 (C), 133.3 (C), 129.0 (CH), 125.5 (CH), 35.7, 28.6, 20.4.

4.14. Synthesis of compound 9

This compound was synthesized by two ways.

(a) Catalytic hydrogenation of the compound **39**: This reaction was also studied in the same manner as for compound **6**. A mixture of compounds **38** and **39** (300 mg, **38**:**39**=1:6), Pd/C (25 mg, 5%) catalyst, and ethyl acetate (30 mL) were used for this reaction. The residue was submitted to PLC with hexane and compound **9** (75 mg) was obtained and crystallized from ethanol.
(b) Catalytic hydrogenation of the compound **40**: This reaction was also studied in the same manner as for compound **37**. A mixture of compounds **8** and **40** (300 mg, **8**:**40**=1:9), Pd/C (25 mg, 5%) catalyst, and ethyl acetate (40 mL) were used for this reaction. The residue was submitted to PLC with hexane and compound **9** (155 mg) was obtained and crystallized from ethanol.

4.14.1. Tetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-2(11),3,9-triene (9). Mp 88–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.91 (s, aromatic, 2H), 2.95 (m, bridgehead, 2H), 2.86–2.80 (m, methylenic, 4H), 1.89–1.78 (m, methylenic, 8H), 1.46 (br d, B of AB, J=8.0 Hz, methylenic, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6 (C), 136.2 (C), 126.2 (CH), 35.7, 31.4, 28.6, 25.5; IR ($CHCl_3$) 2929, 2864, 1466, 1143, 893, 630 cm^{-1}; *m/z*: 213.1/212.0 (8/49), 185.0/184.0/182.9 (8/60/100), 169.0 (12), 156.0 (16), 142.0/140.9 (24/86), 128.0 (22), 114.9 (20), 18.41 (100); Anal. Calcd for $C_{16}H_{22}$: C 89.65, H 10.35; found: C 89.60, H 10.37.

Acknowledgements

The authors are indebted to the Department of Chemistry (Atatürk University) for financial support, associate

Professor Dr. Cavit Kazaz for technical assistant and associate Professor Dr. Thomas J. Cronin (SUNY Cobleskill, NY) for proofread.

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Tetrahedron 62 (2006) 12326–12333
Tetrahedron

Efficient and selective oxidation of methyl substituted cycloalkanes by heterogeneous methyltrioxorhenium–hydrogen peroxide systems

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Received 15 February 2006; revised 20 September 2006; accepted 5 October 2006
Available online 27 October 2006

Abstract—Polymer-supported methyltrioxorhenium (MTO) systems are efficient catalysts for the oxidative functionalisation of cyclohexane and cyclopentane derivatives with H_2O_2 as oxygen donor. Using poly(4-vinyl)pyridine and poly(4-vinyl)pyridine-*N*-oxide as MTO supports, cycloalkanol, cycloalkanediol, cycloalkanone and ω-hydroxy methyl ketone derivatives were obtained in different yields depending on the experimental conditions. Interestingly, cycloalkane dimers were selectively recovered in acceptable to good yields when the oxidation was performed with polystyrene-microencapsulated MTO catalyst. The EPR investigation suggests that the homolytic cleavage of the CH_3–Re bond with formation of $CH_3^{\bullet}$ radicals occurs inside the polystyrene capsule, indicating a possible role of methyl radical in the cycloalkane dimerisation pathway.

1. Introduction

In the last years increasing attention was directed to the use of methyltrioxorhenium (CH_3ReO_3, MTO)[1] in oxidative reactions, in conjunction with hydrogen peroxide (H_2O_2) as oxygen donor, due to the excellent catalytic properties showed by this system.[2] Among the various MTO catalysed reactions, the oxidation of hydrocarbons to alcohols and ketones is of relevant interest because of industrial and environmental concerns.[3,4] This reaction proceeds through the formation of the monoperoxo [$MeRe(O)_2O_2$] (**A**) and the bis-peroxo [$MeReO(O_2)_2$] (**B**) η^2-rhenium complexes that have been isolated and fully characterised by single-crystal X-ray analysis (Fig. 1).[5] In molecular solvents, the complex **A** was found to be more reactive than **B**, while the opposite occurs for reactions driven in ionic liquids.[6] Theoretical and computational studies have been performed to elucidate the geometrical features of the transition state involved in this oxidation. Specifically, the oxygen transfer from complexes **A** and/or **B** to the substrate was always described by a concerted process requiring a butterfly-like transition state similar to that previously suggested for cyclic organic peroxides such as dimethyldioxirane (DMDO).[7,8] Heterogeneous rhenium catalysts behave in a similar way:[9] for example, the same **A** and **B** complexes were intermediates in the epoxidation of alkenes with H_2O_2, catalysed by MTO supported on silica tethered with polyethers.[9c] The heterogenation of MTO on polymeric supports is an important tool because it allows an easier recovery of the catalyst, decreases the toxicity of reaction wastes and sometimes improves the reactivity.[10] The heterogeneous systems used in the present paper have been prepared either by heterogenation of MTO on easily available polymers bearing nitrogen atoms as anchorage sites, such as poly(4-vinylpyridine) (PVP) and poly(4-vinylpyridine)-*N*-oxide (PVPN), [2% or 25% cross-linked with divinylbenzene (PVP-2/MTO **I**, PVP-25/MTO **II** and PVPN-2/MTO **III**, respectively; Fig. 2)][11] or by physical microencapsulation on polystyrene of both MTO or its adduct with 2-aminomethyl pyridine (PS/MTO **IV** and PS/MTO-L **V**, respectively; Fig. 2).[12]

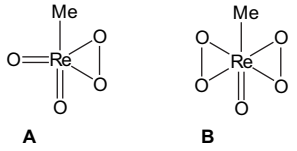

Figure 1. Peroxo η^2-rhenium complexes.

Keywords: Heterogeneous catalysis; Methyltrioxorhenium; Radical reactions; EPR spectroscopy.
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0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.10.013

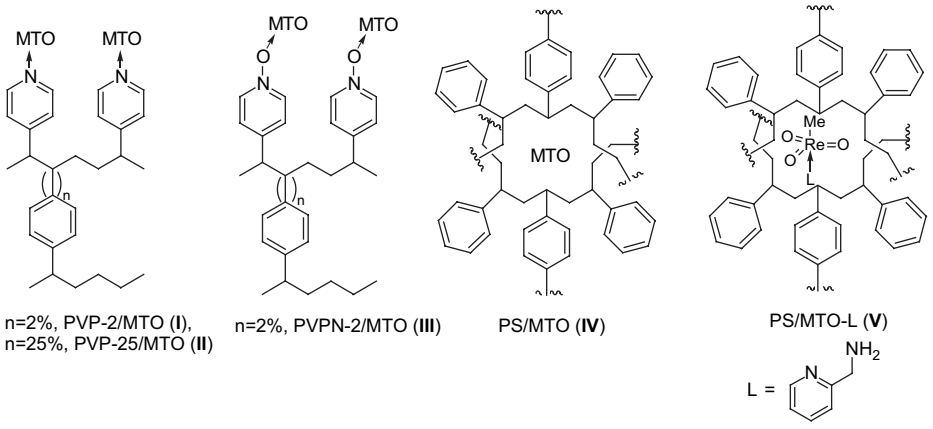
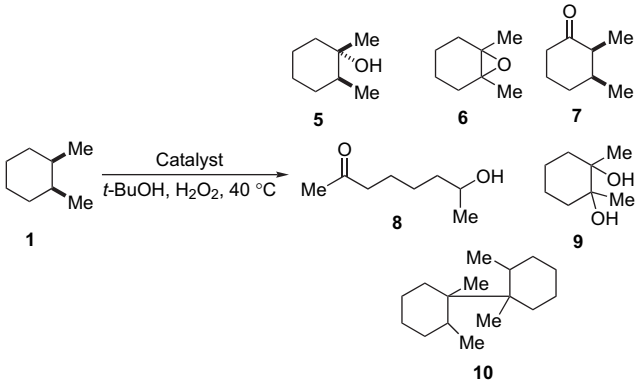
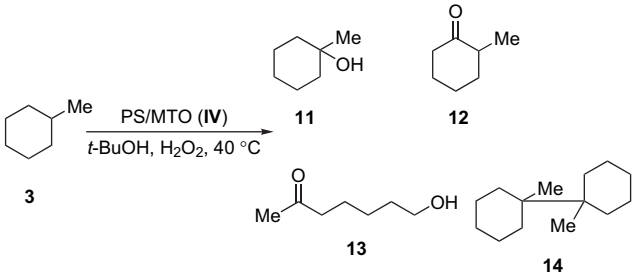


Figure 2. Sketches of polymer-supported MTO catalysts **I**–**V**.

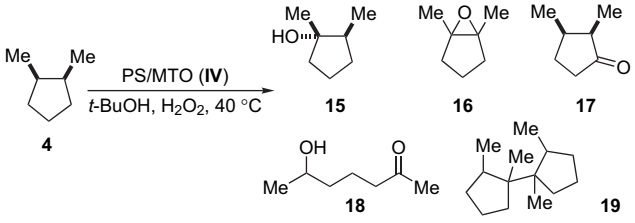
These systems showed high catalytic activity and selectivity in the oxidation of aromatic derivatives,[13] pyrrolidines,[14] alkenes and terpenes,[15] including the oxygen atom insertion into the C–H sigma bond of hydrocarbons, both in molecular solvents[16] and ionic liquids.[17] As a result of our ongoing studies, herein we report on the oxidative derivatisation of different cycloalkane derivatives, namely stereoisomeric *cis*- and *trans*-1,2-dimethylcyclohexanes **1** and **2**, methylcyclohexane **3** and *cis*-1,2-dimethylcyclopentane **4**, with heterogeneous MTO and H_2O_2 in *tert*-butanol (*t*-BuOH). A different reaction pathway was observed depending on the catalyst used for the transformation. Alcohols or products obtained from further oxidation of alcohols, including ring-opened ω-hydroxy methyl ketones were obtained with poly(4-vinylpyridine) catalysts **I**–**III**. The oxidation of the same substrates with the PS/MTO **IV** catalytic system afforded, unexpectedly, cycloalkane dimers in appreciable amounts (**10**, **14** and **19**, Schemes 1–4). The Electron Paramagnetic Resonance (EPR) investigation showed that the homolytic cleavage of the Re–CH_3 bond preferentially occurs inside the polystyrene capsule, thus suggesting



Scheme 1. Products from catalytic MTO-based oxidations of *cis*-1,2-dimethylcyclohexane **1**.

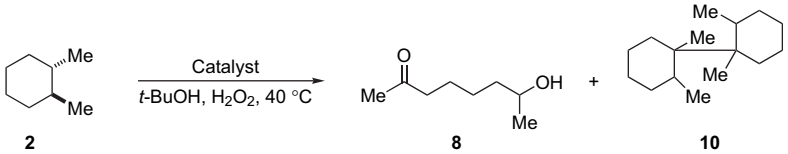


Scheme 3. Products from catalytic MTO-based oxidation of methylcyclohexane **3**.



Scheme 4. Products from catalytic MTO-based oxidation of *cis*-1,2-dimethylcyclopentane **4**.

a possible role of the methyl radical in the cycloalkane dimerisation pathway. To the best of our knowledge this is the first example in the literature dealing with the presence of a radical pathway in oxidation reactions with MTO and H_2O_2. Noteworthy, the effect of the polystyrene microcapsule environment on the reactivity of MTO appears to be finely tuned by the presence of nitrogen containing ligand bonded to rhenium atom and able to change its stereoelectronic properties. As an example, cycloalkane dimers were not recovered when the oxidation was repeated in the presence of the catalytic system PS/MTO-L **V**, obtained by the microencapsulation of previously formed complex between MTO and 2-aminomethyl pyridine[15a] (Fig. 2).



Scheme 2. Products from catalytic MTO-based oxidations of *trans*-1,2-dimethylcyclohexane **2**.

2. Results and discussion

The results of the oxidation of stereoisomeric *cis*- and *trans*-1,2-dimethylcyclohexanes **1** and **2**, methylcyclohexane **3** and *cis*-1,2-dimethylcyclopentane **4** in *t*-BuOH with H_2O_2, catalysed by heterogeneous MTO-based catalysts, are reported in Schemes 1–4 and Tables 1–3. Oxidations with MTO under similar homogeneous conditions were performed as references. In the absence of catalyst, less than 5% conversion of substrates took place under otherwise identical conditions.

2.1. Homogeneous MTO catalysed reactions

The oxidation of stereoisomeric *cis*- and *trans*-1,2-dimethylcyclohexanes, **1** and **2** was initially studied as a representative example of oxidation of cycloalkane derivatives with MTO under homogeneous conditions. Treatment of **1** (1.0 mmol) with an excess of H_2O_2 (4.0–6.0 equiv) and MTO (2% w/w) in *t*-BuOH at 40 °C, afforded a quantitative conversion of the substrate to give (*E*)-1,2-dimethylcyclohexanol **5** as the main reaction product, besides 1,6-dimethyl-7-oxabicyclo[4.1.0]heptane (1,2-dimethyl cyclohexan-oxide) **6**, 2,3-dimethylcyclohexanone **7** and the ω-hydroxy methyl ketone **8** as side-products (Scheme 1, Table 1, entry 1).[18] The 1,2-dimethylcyclohexandiol **9** was also detected in very low amount by gas-chromatography–mass-spectrometry (GC–MS) analysis.

Table 1. Oxidation of *cis*-1,2-dimethylcyclohexane **1** with MTO and heterogeneous MTO catalysts **I–V**

Entry	Catalyst	Conversion (%)	Yield (%)[a]					
			5	**6**	**7**	**8**	**9**	**10**
1	MTO	>98	65	18	7[b]	5[b]	—	—
2	PVP-2/MTO (**I**)	>98	22	—	—	68	—	—
3	PVP-25/MTO (**II**)	>98	48	9[b]	—	3[b]	35	—
4	PVPN-2/MTO (**III**)	45	60	—	—	—	—	—
5	PS/MTO (**IV**)	>98	12[b]	26	—	4[b]	—	53
6[c]	PS/MTO (**IV**)	9	—	—	—	—	—	12[b]
7	PS/MTO-L (**V**)	80	65	—	—	—	—	—

[a] Calculated from isolated product.
[b] Calculated by GC–MS analysis.
[c] Without hydrogen peroxide.

Table 2. Oxidation of *trans*-1,2-dimethylcyclohexane **2** with MTO and heterogeneous MTO catalysts **I–IV**

Entry	Catalyst	Conversion (%)	Yield[a] (%)	
			8	**10**
1	MTO	>98	>98	—
2	PVP-2/MTO (**I**)	>98	>95	—
3	PVP-25/MTO (**II**)	>98	>98	—
4	PVPN-2/MTO (**III**)	>98	>98	—
5	PS/MTO (**IV**)	>98	7[b]	78

[a] Calculated from isolated product.
[b] Calculated by GC–MS analysis.

Cyclohexanol **5** was clearly formed by oxygen atom insertion at the tertiary C–H bond. Such selectivity is similar to that previously observed during the oxidation of 1,2-dimethylcycloalkanes with stoichiometric DMDO derivatives, invoking the formation of a concerted butterfly-like transition state.[19] The appearance of epoxide **6** is notable and suggests a multifunctional catalytic behaviour for MTO under these experimental conditions. In fact, compound **6** was probably obtained via epoxidation of 1,2-dimethylcyclohexene (not shown) generated in situ by elimination of a water molecule from **5**, due to the known Lewis and Brönsted acidity of MTO.[2] In agreement with this hypothesis, appreciable amounts of 1,2-dimethylcyclohexene were obtained by treating **5** with catalytic amount of MTO in the absence of H_2O_2. A similar behaviour was previously observed in the oxidation of dimethylcyclohexane derivatives with H_2O_2 in the presence of Fe(II) complexes.[20] The remarkable selectivity of oxygen atom insertion at the tertiary over secondary C–H bonds, despite the high reactivity of MTO, is confirmed by the higher yield of tertiary alcohol **5** and its derivative **6**, in comparison with cyclic ketone **7** (necessarily produced by the oxidation of the secondary C–H bond) (see Table 1, entry 1). The presence of little amounts of ω-hydroxy methyl ketone **8** is worthy of note. It is reasonable to suggest that this compound arises from the over-oxidation of the diol **9** followed by C–C oxidative ring-cleavage. To the best of our knowledge, with the exception of our recent study on the degradation of aromatic moieties to ring-opened muconic acid derivatives in lignin and lignin model compounds,[21] no further data were reported in literature dealing with the oxidative cleavage of the C–C bond by H_2O_2 and MTO. The highest selectivity was observed during the oxidation of *trans*-1,2-dimethylcyclohexanes **2** under similar experimental conditions. In this latter case, the ω-hydroxy methyl ketone **8** was obtained as the only recovered product, with quantitative conversion of substrate and high yield (Scheme 2, Table 2, entry 1). The highest reactivity of the carbon atoms bearing an axial hydrogen towards the approaching metal peroxides **A** and **B**, explains the selective formation of this over-oxidation product from substrate **2**. It must be emphasised that, beyond the synthetic interest due to their potential biological applications, as far as we are aware there are no examples of chemical procedures to obtain ω-hydroxy ketones starting from saturated cyclic hydrocarbons.

2.2. Polymer-supported MTO catalysed reactions

The oxidation of stereoisomeric *cis*- and *trans*-1,2-dimethylcyclohexanes, **1** and **2** (1.0 mmol) was performed with an excess of H_2O_2 (4.0–6.0 equiv) and the appropriate catalyst

Table 3. Oxidation of methylcyclohexane **3** and *cis*-1,2-dimethylcyclopentane **4** with MTO supported on polystyrene (PS/MTO, **IV**)

Entry	Catalyst	Substrate	Conversion (%)	Yield (%)[a]								
				11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
1	PS/MTO (**IV**)	**3**	>98	3[b]	16	35	42	—	—	—	—	—
2	PS/MTO (**IV**)	**4**	>98	—	—	—	—	4[b]	6[b]	2[b]	20	68

[a] Calculated from isolated product.
[b] Calculated by GC–MS analysis.

(10% w/w) in *t*-BuOH at 40 °C. All polymer-supported MTO systems **I**–**V**[11,12,15a] showed high efficiency in the oxidation of stereoisomeric *cis*- and *trans*-1,2-dimethylcyclohexanes, **1** and **2**, giving a different distribution of products depending on the chemical and physical properties of the catalyst used in the transformation (Schemes 1 and 2, Tables 1 and 2). In particular, in the family of poly(4-vinylpyridine)-based catalysts **I**–**III**, the reticulation grade of the polymeric support as well as its oxidation state appeared to be relevant parameters for the selectivity of the reaction. Thus, the oxidation of **1** with low-reticulated PVP-2/MTO **I** afforded the ω-hydroxy methyl ketone **8** as the main reaction product besides low amount of cyclohexanol **5** (Table 1, entry 2). On the other hand, treatment of **1** with high-reticulated PVP-25/MTO **II** afforded alcohols **5** and **9** in high yields, compounds **6** and **8** being recovered as side-products (Table 1, entry 3). Finally, cyclohexanol **5** was obtained as the only recovered product in the presence of PVPN-2/MTO **III**. Only in this last case a low conversion of the substrate was observed (Table 1, entry 4). The significant effects of the reticulation grade and of the oxidation of pyridine nitrogen atom of the support, on the reactivity and selectivity of MTO, are in accordance with the data previously obtained in the oxidation of alkanes, alkenes and phenol derivatives.[11,12,16] Unexpectedly, when the oxidation of **1** was performed using microencapsulated catalyst PS/MTO **IV**, the dimeric derivative, 1,1′,2,2′-tetramethyl-1,1′-bi(cyclohexyl) **10**, was obtained as the main reaction product in 53% yield (Table 1, entry 5). Bis-cyclohexane derivatives are usually obtained by photochemical oxidation of the corresponding cyclohexanes through a radical pathway[22a] but, to date, there are no examples of the possible appearance of a radical mechanism during oxidations performed with MTO and H_2O_2. Moreover, compound **10** was recovered, even if in low yield, also in the absence of H_2O_2 by treating compound **1** with PS/MTO **IV** (Table 1, entry 6). This involves a direct role of microencapsulated MTO in the dimerisation process. As known, the reactivity of MTO in several oxidative functionalisations can be tuned by the presence of Lewis bases coordinating the metal centre. This trend was confirmed by the result obtained in the oxidation of **1** with microencapsulated catalyst PS/MTO-L **V** (Table 1, entry 7): in this case no trace of dimeric derivative **10** was detected, alcohol **5** being recovered in 65% yield.

We then studied the oxidation of *trans*-1,2-dimethylcyclohexane **2**: in this case the ω-hydroxy methyl ketone **8** was obtained as the only recovered product, with both quantitative conversion of substrate and high yield, independent of the poly(4-vinylpyridine)-based catalyst used for the reaction (Scheme 2, Table 2, entries 2–4). Under homogeneous conditions the system evidenced quite an analogous behaviour (Table 2, entry 1). Again, the dimer 1,1′,2,2′-tetramethyl-1,1′-bi(cyclohexyl) **10** was obtained as the main reaction product in the presence of microencapsulated PS/MTO **IV** catalyst, thus confirming the peculiar reactivity of this system.

To further evaluate the generality of the dimerisation process, we studied two novel methyl substituted cycloalkanes, such as methylcyclohexane **3** and *cis*-1,2-dimethylcyclopentane **4**, in the presence of PS/MTO **IV** and H_2O_2. Treatment of **3** (1.0 mmol) with an excess of H_2O_2 (4.0–6.0 equiv) and PS/MTO **IV** (10% w/w) in *t*-BuOH at 40 °C afforded a quantitative conversion of substrate to give the ring-opened derivative 7-hydroxy-2-heptanone **13** and the dimeric compound 1,1′-dimethyl-1,1′-bi(cyclohexyl) **14** as the main reaction products, besides low amount of 2-methylcyclohexanone **12** and 1-methylcyclohexanol **11** (Scheme 3, Table 3, entry 1).

In a similar way, the dimeric compound 1,1′,2,2′-tetramethyl-1,1′-bi(cyclopentyl) **19** was obtained in high yield, by the oxidation of *cis*-1,2-dimethylcyclopentane **4** with PS/MTO **IV** and H_2O_2, besides the 6-hydroxyheptan-2-one **18** as side product, and traces of 1,2-dimethylcyclopentanol **15**, 1,5-dimethyl-6-oxabicyclo[3.1.0]hexane **16** and 2,3-dimethylcyclopentanone **17** (Scheme 4, Table 3, entry 2). Thus, the oxidative dimerisation of cycloalkane derivatives during the oxidation with the PS/MTO **IV** and H_2O_2 system, was an operative process irrespective of the substitution pattern and the size of the alkane ring to be oxidised.

2.3. EPR investigation

In order to understand the formation of dimers **10**, **14** and **19** during the oxidation of stereoisomeric cyclohexane and cyclopentane derivatives with polymer-microencapsulated MTO catalyst **IV**, an EPR investigation was performed on freshly prepared catalysts **I**–**V** at 25 °C. The EPR spectra of MTO and the uncharged resins were also recorded.

MTO has high thermal stability, since it decomposes only above 300 °C, however, it slowly decomposes by radical pathway under daylight and it is very sensitive to UV radiation. In particular, photolytic reactions lead to a homolytic cleavage of the carbon–rhenium bond, with the formation of CH_3• and •ReO_3 radicals.[22b] Since no EPR signals were observed on pure MTO, we assume that no significant catalyst decomposition takes place under our experimental conditions.

The EPR spectrum of poly(4-vinylpyridine) catalysts **I**–**III** showed a very broad isotropic signal (g=2.299, ΔH_{pp}~1450 G). The same signal was also observed in the pure polymer, and it is probably due to metal contaminants. Similarly, the EPR spectrum of pure polystyrene resin showed an isotropic sharp signal (g=1.978, ΔH_{pp}=11.3 G, Fig. 3 line a).

When MTO was encapsulated into PS resin (catalyst **IV**), the EPR spectrum showed the same signal observed in pure resin; in addition, four resonance lines not equally spaced and having different amplitudes and widths appeared at g~2.00 (Fig. 3, line b). The absence of symmetry about the centre of resonances indicates anisotropy of both g and A tensors.[23] Thus, the quartet was simulated by the spectrum of a CH_3• radical with axial anisotropy of both g and A tensors ($g\perp$=2.0028, $g\|$=2.0069, $A\perp$=10.4 G, A$\|$=11.7 G), linewidth $\Delta H\perp$=5.1 G and $\Delta H\|$=4.0 G (Fig. 3, line b′).

The literature reports the g and A tensor anisotropy for the CH_3• radical in Ar, Kr and CO matrices at liquid He temperatures,[23] attributing it to interaction with the hosts. In our case, the anisotropy of g tensor was higher (Δg=0.0041 against Δg=0.0005 of CH_3• in CO matrix[23]) and indicates

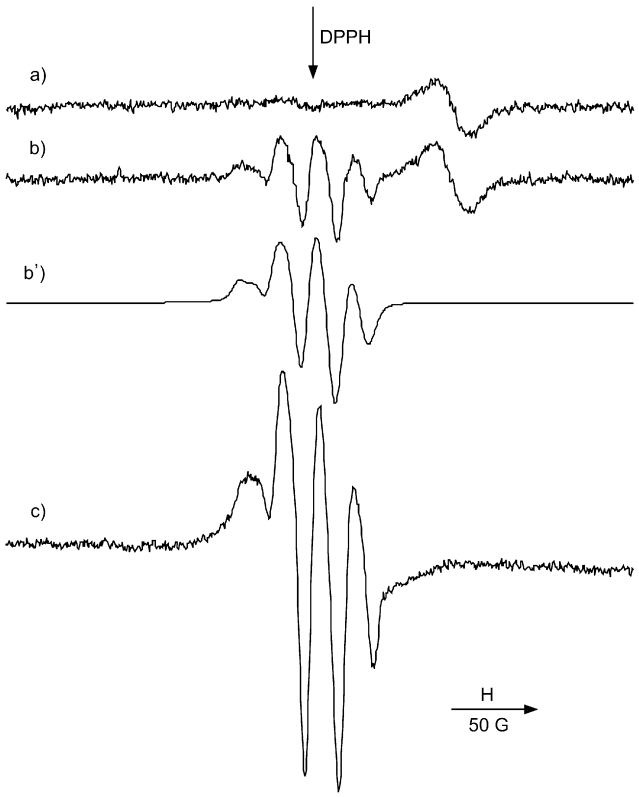


Figure 3. X-band EPR spectra, recorded at 298 K, of: PS resin (line a); PS/MTO (line b, experimental; line b′, simulated); PS/MTO after treatment with H_2O_2 (line c).

a significant interaction between methyl radical and PS resin; the much lower value of the hyperfine coupling constants with respect to the value reported for 'free' CH_3• (A=23 G),[24] confirms that such interaction strongly affects the electronic distribution on methyl radicals. The fact that MTO dispersed in polystyrene matrix interacts with the surroundings was also confirmed by the results of FTIR analyses previously performed in our laboratories;[11] in fact microencapsulated PS/MTO **IV** showed the lowest ν(ReO) stretching vibration frequencies (ν_s 953, ν_{as} 911 cm^{-1}) with respect to either polymer-supported MTO systems **I–III** (ν_s 963–964, ν_{as} 923–932 cm^{-1}) or pure MTO (ν_s=998, ν_{as} 959 cm^{-1}). As expected, polymer-supported MTO systems (**I–IV**) showed vibration frequency values lower than those for MTO, thus suggesting that the π-bonded hydrocarbon ligands cause the lowering of the Re–O bond order, probably due to their electron-donating ability. A similar correlation between the π-donor qualities of the ring ligand and the decreasing of the rhenium–oxygen bond order in the (η^5-C_5Me_5)ReO_3 half-sandwich complex, if compared with MTO, was already observed by *Herrmann* and coworkers.[25a]

Previously, methyl radicals formed by cleavage of carbon–rhenium bonds were observed, only in solution, after photolysis of organorhenium(VII) oxides[26] [R–ReO_3, with R=CH_3, C_2H_5, η^1-mesityl, C_6H_5, η^5-C_5H_5, η^5-$C_5H_4(CH_3)$ and η^5-$C_5(CH_3)_5$]. In those cases, methyl radicals were detected by using a spin trap molecule. To the best of our knowledge, PS/MTO shows the first example of stable methyl radicals from cleavage of the Re–CH_3 bond.

The signal of •ReO_3 centre was not observed in the EPR spectrum, probably due to the fast formation of perovskite ReO_3.[27] After treatment with H_2O_2, the EPR signals of the pure polymer disappeared, while the amount of CH_3• radicals increased from 1.2×10^{15} spin/g on PS/MTO to 1.3×10^{16} spin/g, corresponding to a molar ratio CH_3•/MTO= 0.1% (Fig. 3, line c). For what concerns this spectrum, the presence of small amounts of peroxo radicals[24] could explain the difference in the relative intensity of the four resonance lines with respect to that observed in untreated PS/MTO.

The signal of CH_3• radical was observed neither with PVP catalysts **I–III** nor with PS/MTO-L **V**. The absence of CH_3–Re cleavage in poly(4-vinylpyridine)-based systems is probably due to the stabilising effect of the nitrogen ligands on the metal–carbon bond. Analogous reasons concerning the stabilising role of the bidentate ligand 2-aminomethyl pyridine (L, in Fig. 2) on the behaviour of MTO, could be used to justify the absence of the radical pathway with catalyst **V**.

The identification of CH_3• radical in PS/MTO **IV**, associated to the increase of the radical amount after addition of the oxidant, can be reasonably correlated to the formation of dimers **10**, **14** and **19** by using the microencapsulated catalyst. The mechanism of the dimer formation was not further investigated. However, since the coupling of two CH_3• radicals is not favoured,[25b] it can be thought that the methyl radical in solution abstracts one hydrogen atom from the substrate, with formation of methane and a tertiary alkyl radical, directly available for the dimerisation process.

Finally, in the investigated reactions, the solvent (*t*-BuOH) probably plays a relevant role,[28] as it can be deduced from the fact that the oxidation of 1,2-dimethylcyclohexane catalysed by polymer-MTO catalysts **I–IV** gave the alcohol **5** as the only recovered product, in ionic liquids.[17]

3. Conclusions

MTO and polymer-supported MTO systems **I–V** are shown to be efficient catalysts for the oxidative functionalisation of cyclohexane and cyclopentane derivatives with H_2O_2 as oxygen atom donor. Different reaction pathways were observed depending on the nature of the polymeric support. In the case of catalysts **I–III**, obtained by heterogenation of MTO on poly(4-vinyl)pyridine and poly(4-vinylpyridine)-*N*-oxide resins, the reaction proceeded through a concerted oxygen insertion from the intermediate peroxo complexes **A** and **B**[5] into the very reactive tertiary C–H bonds, to give the corresponding cycloalkanol derivatives. Due to the multifunctional catalytic properties of MTO, elimination of water molecule, epoxidation of the resulting double bond, nucleophilic ring-opening reactions of the epoxide ring and oxidative C–C bond cleavage were also operative processes. The selectivity of the reactions was found to be correlated both to the structural properties of the poly(4-vinyl)pyridine support and to the stereochemical properties of the substrate. Noteworthy, a different reaction pathway was observed with microencapsulated catalyst **IV**, leading to the formation of a cycloalkane dimer, irrespective of the

nature of the substrate, in yields ranging from acceptable to good. Moreover, dimeric compounds were also recovered, although in low yields, by treating cycloalkanes with PS/MTO **IV** in the absence of H_2O_2, showing a direct role of microencapsulated MTO on the dimerisation process.

The EPR analysis showed that homolytic cleavage of the CH_3–Re bond selectively occurs for catalyst **IV**, leading to the formation of a PS-trapped methyl radical. On the basis of these data it is reasonable to suggest the intervention of a radical pathway in the formation of the cycloalkane dimers. The radical pathway observed with catalyst **IV** can be suppressed by modulating the chemical reactivity of microencapsulated MTO as in the case of catalyst **V** containing the Lewis adduct [MTO·2-aminomethyl pyridine]. Thus, a large panel of reaction products can be obtained during the oxidation of stereoisomeric cycloalkane derivatives with MTO-based heterogeneous catalysts, the selectivity of the transformation being tuned by different experimental parameters, such as the nature of the support, the reaction solvent and the stereochemical properties of the substrate. Further work is in progress in order to better evaluate the synthetic potentiality of the microencapsulated MTO catalyst **IV** for the oxidation of hydrocarbons and hydrocarbon derivatives with H_2O_2 in *t*-BuOH.

4. Experimental

4.1. General remarks

All commercial products were of the highest available grade and were used as such. NMR spectra were recorded on a Bruker (AC 200 MHz). When necessary, chromatographic purification was performed on columns packed with silica gel, 230–400 mesh, for flash technique. In order to evaluate the scaling-up of our catalytic procedure, the oxidation of *cis*-1,2-dimethylcyclohexane **1** with catalyst **I** (PVP-2/MTO) was repeated on the scale of 10 mmol of substrate, and working under the same experimental conditions: neither substantial changes in the reaction selectivity nor sensible variations of reaction yields were observed.

4.2. Preparation of supported catalysts I–IV[11a,12]

MTO (256 mg, 1.0 mmol) was added to a suspension of the appropriate resin (0.5 g, loading factor=2) in ethanol (4 mL). The mixture was allowed for stirring for 1 h. The solvent was removed by filtration, and the catalyst washed with ethyl acetate and finally dried under high vacuum.

FTIR (KBr), ν (Re–O) cm^{-1}: **I**: 963, 923; **II**: 964, 932; **III**: 924; **IV**: 953, 911.

4.3. Preparation of supported catalyst V

The preparation of [MTO·2-aminomethyl pyridine] adduct was performed according to a published method.[15a] Briefly, 0.5 mmol of 2-aminomethyl pyridine was added to 1.0 mmol of MTO in toluene (10 mL) at room temperature. A yellow precipitate was immediately formed. The reaction mixture was concentrated, cooled to −35 °C and the precipitate isolated by filtration. The microencapsulation on polystyrene of the so obtained adduct was performed analogously as previously published.[15a]

4.4. Typical oxidative reaction

One millimole of *cis*- and *trans*-1,2-dimethylcyclohexanes, **1** and **2**, respectively, dissolved in *t*-BuOH (2.0 mL) was added with MTO (2.4 mg, 2% w/w) or supported catalysts **I–V** (11.2 mg, 10% w/w) and H_2O_2 (4.0–6.0 equiv). The mixture was heated at 40 °C and allowed for stirring for 72 h. Catalysts were recovered by filtration at the end of the reaction, when the reaction was performed under heterogeneous conditions. A low amount of MnO_2 was added to decompose the excess of oxidant and the solvent was evaporated after filtration of the oxide. The reaction products were fully characterised by GC–MS, ^1H and ^{13}C NMR analyses and by comparison with authentic samples.[18]

4.4.1. 1,2-Dimethylcyclohexanol 5.[29] ^1H NMR ($CDCl_3$) δ 1.71–1.16 (m, 9H), 1.50 (s, 1H), 1.05 (s, 3H), 0.88 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 73.05, 42.28, 41.35, 32.01, 25.28, 24.01, 20.69, 15.31. GC–MS *m/z* (%): 128 (20), 113 (25), 95 (25), 85 (60), 71 (100).

4.4.2. 1,6-Dimethyl-7-oxabicyclo[4.1.0]heptane 6.[30] ^1H NMR ($CDCl_3$) δ 2.10–1.28 (m, 8H), 1.22 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 62.25, 32.18, 22.13, 20.75. GC–MS *m/z* (%): 126 (20), 110 (25), 95 (73), 81 (60), 69 (100).

4.4.3. 2,3-Dimethylcyclohexanone 7.[31] ^1H NMR ($CDCl_3$) δ 2.6–1.5 (m, 8H), 0.98 (d, J=9 Hz, 3H), 0.85 (d, J=9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 213.62, 48.75, 40.12, 36.62, 30.78, 22.85, 11.62, 11.51. GC–MS *m/z* (%): 126 (37), 111 (28), 98 (30), 83 (80), 55 (100).

4.4.4. 7-Hydroxyoctan-2-one 8. ^1H NMR ($CDCl_3$) δ 3.15 (br s, 1H), 3.42–3.34 (m, 1H), 2.45 (t, J=6.8 Hz, 2H), 2.14 (s, 3H), 1.58–1.25 (m, 6H), 1.20 (d, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 207.68, 65.25, 43.15, 42.98, 28.76, 25.33, 24.18, 23.12. GC–MS *m/z* (%): 101 (55), 83 (15), 59 (78), 43 (100).

4.4.5. 1,2-Dimethylcyclohexane-1,2-diol 9.[32] ^1H NMR ($CDCl_3$) δ 2.06 (br s, 2H), 1.70–1.25 (m, 8H), 1.22 (s, 6H), 1.15 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 74.32, 36.40, 23.20, 22.10. GC–MS *m/z* (%): 145 (4), 127 (30), 111 (28), 71 (55), 43 (100).

4.4.6. 1,1′,2,2′-Tetramethyl-1,1′-bi(cyclohexyl) 10. ^1H NMR ($CDCl_3$) δ 2.28–2.10 (m, 2H), 1.75–1.20 (m, 16H), 0.94 (s, 6H), 0.85 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 38.65, 36.82, 33.24, 29.80, 23.62, 21.85, 17.40, 15.82. GC–MS *m/z* (%): 111 (75), 69 (100), 55 (20), 43 (50).

4.4.7. 1-Methylcyclohexanol 11. ^1H NMR ($CDCl_3$) δ 2.3 (br s, 1H), 1.65–1.30 (m, 10H), 1.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 69.85, 39.45, 29.15, 24.35, 22.68. GC–MS *m/z* (%): 114 (9), 99 (28), 81 (25), 71 (100), 58 (25).

4.4.8. 2-Methylcyclohexanone 12.[33] ^1H NMR ($CDCl_3$) δ 2.40–2.08 (m, 5H), 1.80–1.65 (m, 3H), 1.33–1.38 (m, 1H), 1.05 (d, J=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 214.01, 45.81, 41.65, 35.98, 28.22, 25.67, 14.58. GC–MS *m/z* (%): 112 (35), 97 (25), 81 (54), 69 (100), 56 (50).

4.4.9. 7-Hydroxy-2-heptanone 13. ^{1}H NMR ($CDCl_3$) δ 1.33–1.40 (m, 2H), 1.54–1.62 (m, 4H), 2.14 (s, 3H), 2.19 (br, 1H), 2.45 (m, 2H), 3.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 23.35, 25.20, 29.80, 32.29, 43.52, 62.35, 209.32. GC–MS *m*/*z* (%): 101 (60), 83 (16), 59 (84), 43 (100).

4.4.10. 1,1′-Dimethyl-1,1′-bi(cyclohexyl) 14. ^{1}H NMR ($CDCl_3$) δ 1.64–1.55 (m, 8H), 1.47–1.07 (m, 12H), 0.81 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 38.10, 30.34, 26.61, 20.34, 16.61. GC–MS *m*/*z* (%): 97 (100), 69 (20), 55 (75), 43 (25).

4.4.11. 1,2-Dimethylcyclopentanol 15.[29] ^{1}H NMR ($CDCl_3$) δ 1.98–1.50 (m, 6H), 1.87 (br s, 1H), 1.21–1.14 (m, 1H), 1.11 (s, 3H), 0.84 (d, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 81.00, 44.62, 39.98, 31.75, 22.78, 20.48, 15.36. GC–MS *m*/*z* (%): 114 (5), 99 (12), 85 (30), 71 (100), 43 (60).

4.4.12. 1,5-Dimethyl-6-oxabicyclo[3.1.0]hexane 16.[34] ^{1}H NMR ($CDCl_3$) δ 1.81–1.73 (m, 2H), 1.70–1.65 (m, 2H), 1.38–1.22 (m, 2H), 1.22 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 62.97, 35.41, 17.01, 16.84. GC–MS *m*/*z* (%): 112 (60), 97 (80), 71 (50), 69 (49), 43 (100).

4.4.13. 2,3-Dimethylcyclopentanone 17. ^{1}H NMR ($CDCl_3$) δ 2.23–1.75 (m, 5H), 1.38–1.29 (m, 1H), 0.93 (d, J=7.1 Hz, 3H), 0.90 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 218.04, 47.05, 39.25, 35.38, 28.66, 16.74, 11.22. GC–MS *m*/*z* (%): 112 (50), 97 (22), 81 (75), 69 (100), 55 (82).

4.4.14. 6-Hydroxyheptan-2-one 18. ^{1}H NMR ($CDCl_3$) δ 3.87 (m, 1H), 3.11 (br s, 1H), 2.49 (t, J=6.8 Hz, 2H), 2.10 (s, 3H), 1.63 (m, 2H), 1.43 (m, 2H), 1.19 (d, J=6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 207.98, 68.22, 43.68, 42.95, 29.12, 28.75, 19.22. GC–MS *m*/*z* (%): 101 (58), 83 (14), 59 (80), 43 (100).

4.4.15. 1,1′,2,2′-Tetramethyl-1,1′-bi(cyclopentyl) 19. ^{1}H NMR ($CDCl_3$) δ 1.83–1.72 (m, 2H), 1.65–1.45 (m, 8H), 1.38–1.26 (m, 2H), 1.10–0.99 (m, 2H), 0.92 (s, 6H), 0.89 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 45.18, 38.42, 38.05, 36.22, 21.14, 15.28, 14.77. GC–MS *m*/*z* (%): 97 (100), 69 (22), 55 (73), 43 (58).

4.5. EPR analysis

The EPR spectra were recorded on samples in powdered form. Pure MTO and resins were studied as received. Heterogeneous catalysts **I–V** were prepared as previously described. The H_2O_2-treated samples were prepared by suspending the catalyst (1 g) in *t*-BuOH (30 mL), then H_2O_2 (5 equiv) was added and the suspension was maintained under stirring for 1 h. At the end, the catalyst was recovered by filtration and allowed to dry in air. For all samples, spectra were recorded at 25 °C on an X-band CW EPR Bruker EMX spectrometer. The g values were determined by standardisation with α,α′-diphenyl-β-picryl hydrazyl (DPPH), g=2.0036±0.0003. The spin concentration, expressed as spin/g of catalyst, was calculated with a ±10% accuracy by double integration of the resonance lines and referring the area under the absorption curve to that of the standard Bruker weak pitch (10^{13}±5% spin/cm); then the weight of sample filling 1 cm length of EPR cavity was determined. Care was taken in order to ensure that the sensitive part of the EPR cavity (1 cm length) was always full; no variations were observed in the density of samples. All the experimental spectra were fitted by the 6/9/91 DOS version of the SIM14S simulation program.

Acknowledgements

Italian MIUR (PRIN-COFIN 2003) is acknowledged for financial support. Prof. Roberto Scotti (University of Milano-Bicocca, Milano, Italy) is acknowledged for helpful discussion about EPR investigation.

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Tetrahedron 62 (2006) 12334–12339
Tetrahedron

Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols

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Received 8 September 2006; revised 29 September 2006; accepted 2 October 2006
Available online 27 October 2006

Abstract—Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols has been established starting from 2-benzyloxymethylpyrrolidin-2-one framework, which is derived from commercially available *trans*-(2*S*,4*R*)-4-hydroxyproline. The single diastereomer having a trans–cis relative configuration with C_2 and C_3 and C_3 and C_4 is constructed in two one-pot functional group transformations of Grignard addition/dehydration and epoxidation/isomerization as the key steps in moderate yield.

1. Introduction

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline, it possesses three functional groups that can be easily modified and they are 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks such as monocycles (pyrrole,[2a] pyrrolidine,[2b,c,l] piperidine[2d] and azanucleoside[2e]), fused or bridged bicycles (pyrrolizidine[2f] or azabicycles[2g,h,m]), polycycles,[2i–k,n] macrocycle,[2o] etc. using an efficient modification technique.

Recently, we have introduced a facile and straightforward approach toward monocyclic pyrrolidine (anisomycin)[2l] and piperidine (α-conhydrine),[2m] bicyclic bridged 7-azabicyclo[2.2.1]heptane (epibatidine)[2n] and pyrrolophane (streptorubin B core),[2o] bicyclic fused hexahydro-1*H*-indol-3-one (pancracine)[2p] and acyclic γ-amino acid (statin and vigabatrin®)[2q,r] skeleton system via some easy functional group transformations, intramolecular basic alkylation, acidic aldol condensation, ring-closing metathesis and regioselective Baeyer–Villiger oxidation of different 2-substituted pyrrolidin-4-one framework employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material.

To demonstrate the synthetic utility of our methodology and explore the application to the synthesis of 2-substituted pyrrolidin-4-one, synthetic studies toward (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols were investigated (Fig. 1). Our interest in synthesizing 4-aryl-3-hydroxyprolinol (4-aryl-3-hydroxy-2-hydroxymethylpyrrolidine) skeleton was piqued on the different biological properties and because it is with the motif of 3-hydroxyl group and is a key intermediate for preparing many important skeletons of substituted piperidines and prolines.[3] Prolinol is an α-aminoalcohol with a unique nature inducing specific electronic and geometric features. The presence of such a ring in the chemical structure restricts conformational flexibility, which may efficiently modify binding affinity to its target. In addition, this peptidomimetic compound is expected to be more stable to hydrolysis by metabolic enzymes.

(2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinol *trans*-(2*S*,4*R*)-4-hydroxyproline

Figure 1. Structures of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinol and *trans*-(2*S*,4*R*)-4-hydroxyproline.

2. Results and discussion

2.1. Retrosynthetic analysis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols 1a–d

We now wish to report an easy and straightforward synthesis of (2*S*)-2-benzyloxymethylpyrrolidin-4-one **3** leading to four (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d** by two remarkable one-pot transformations as shown in Scheme 1. One

Keywords: (2*R*,3*S*,4*S*)-4-Aryl-3-hydroxyprolinols; *trans*-(2*S*,4*R*)-4-Hydroxyproline; One-pot reaction; Grignard addition/dehydration; Epoxidation/isomerization.
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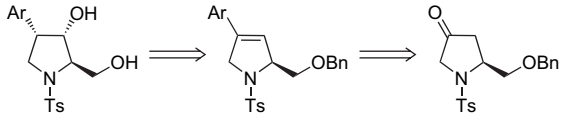
doi:10.1016/j.tet.2006.10.002

is the access to produce (2*S*)-4-aryl-2-benzyloxymethyl-2,5-dihydropyrroles **2a–d** by the Grignard addition of compound **3** and subsequent boron trifluoride etherate mediated dehydration of the resulting tertiary alcohols. The other is a specific step from olefins **2a–d** to diols **1a–d** by stereochemical epoxidation and followed by boron trifluoride etherate mediated isomerization of the resulting epoxides.

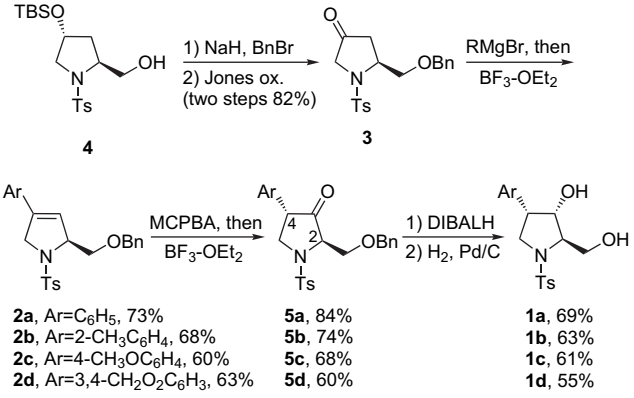


a, Ar=C_6H_5; **b**, Ar=2-$CH_3C_6H_4$; **c**, Ar=2-$CH_3OC_6H_4$; **d**, Ar=3,4-$CH_2O_2C_6H_3$

Scheme 1. Retrosynthetic analysis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**.

2.2. Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols 1a–d

In a previous report,[2m–q] synthesis of prolinol **4** from *trans*-(2*S*,4*R*)-4-hydroxyproline provided a 90% overall yield with purification done only once via a facile four-step reaction. As shown in Scheme 2, prolinol **4** was first transformed into ketone **3** (82% yield in two steps) by *O*-benzylation and Jones oxidation under the standard conditions. With enough amounts of ketone **3**, conversion of ketone **3** into olefins **2a–d** was further examined.



Scheme 2. Synthetic approach toward (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**.

Treatment of ketone **3** with different arylmagnesium bromide reagents (a, Ar=C_6H_5; b, Ar=2-$CH_3C_6H_4$; c, Ar=4-$CH_3OC_6H_4$; d, Ar=3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran provided a pair of diastereoisomers (ca. 1:1 ratio) without any induction onto the stereoselectivity.[4a] Following this similar approach, attempts to form a sole tertiary alcohol under a variety of conditions (prolonged reaction time, diverse temperature, different solvents) were unsuccessful.[4]

With these results in hand, the direct one-pot conversion for the reaction of ketone **3** with four arylmagnesium bromide reagents and subsequent dehydration of the resulting tertiary alcohols with boron trifluoride etherate yielded compounds **2a–d** in 60–73% overall yield. During the one-pot process, 4-aryl-2-benzyloxymethyl-2,3-dihydropyrrole framework was not observed. In the other way, one-pot reaction of ketone **3** with methylmagnesium bromide and followed by dehydration was also examined. Treatment of 4-hydroxy-4-methyl-2-benzyloxymethylpyrrolidine yielded 4-methyl-2-benzyloxymethyl-2,5-dihydropyrrole in trace amounts under the acidic conditions (e.g., boron trifluoride etherate, aluminum chloride and Dean–Stark distillation). Based on these results, we envisioned that aryl group is an important substituent, which easily provides a stable benzylic cation in the dehydration process. However, 4-methyl-2-benzyloxymethyl-2,5-dihydropyrrole was carried out in 34% yield by the basic dehydration of this tertiary alcohol with mesyl chloride and pyridine.

To investigate the relative stereochemistry of diols **1a–d** at C_2 and C_3 and C_3 and C_4 positions, epoxidation of olefins **2a–d** and isomerization of the resulting epoxides **2aa–da** were studied in the next stage. Epoxidation of model substrate **2a** with *m*-chloroperoxybenzoic acid afforded a sole epoxide **2aa** with three contiguous asymmetric centers in 92% yield. The structural stereochemistry of epoxide **2aa** was determined by single-crystal X-ray analysis (Diagram 1).[5] According to the provided epoxide **2aa**, we envisioned that stereoselective epoxidation of olefin **2a** was strongly affected by the steric hindrance of 2-benzyloxymethyl group.[6] Both 4-phenyl and 2-benzyloxymethyl groups in the structure of epoxide **2aa** could be arranged as *cis* configuration. Next, ketone **5a** was afforded by the selective isomerization of trisubstituted epoxide **2aa** via hydride shift in 91% yield.[7] Therefore, the stereochemical assignment of ketone **5a** at C_2 and C_4 centers was made the trans configuration.

For the epoxidation of olefins **2c–d** with electron-donating groups, the desired epoxides **2ca–da** could not be obtained and complex products were isolated during silica gel chromatography. With the previous experiences in mind,[8] we envisioned that the problem was solved by the one-pot reaction. Therefore, ketones **5a–d** were yielded via the one-pot reaction of olefins **2a–d** with the combination of *m*-chloroperoxybenzoic acid and followed by boron trifluoride etherate in 60–84% overall yield. Ketones **5a–d** must be purified by recrystallization from dichloromethane and methanol because the generated racemic mixture was observed by the epimerization of C_2 or C_4 position during silica gel-mediated chromatographic purification.

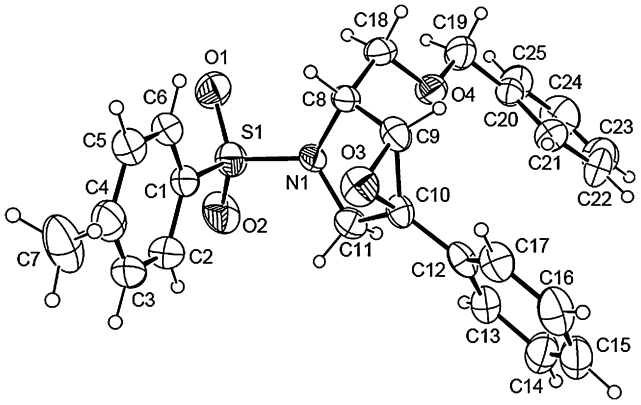


Diagram 1. X-ray crystallography of epoxide **2aa**.

Briefly, ketones **5a–d** were obtained via the stereoselective epoxidation of olefins **2a–d** with *m*-chloroperoxybenzoic acid and followed by isomerization of the resulting epoxides **2aa–da** with boron trifluoride etherate. Two one-pot procedures of Grignard addition/dehydration and epoxidation/isomerization were monitored by TLC until the reaction was completed. The overall simple procedure was achieved within one working day.

With the requisite ketones **5a–d** in hand, we examined the reduction of ketones **5a–d**. When the model substrate **5a** was treated with sodium borohydride or lithium aluminum hydride under different temperatures, two diastereoisomers were obtained in a 2:3 ratio. Therefore, reduction of ketone **5a** with diisobutylaluminum hydride at −78 °C afforded the sole benzyl alcohol **5aa**. Other benzyl alcohols **5ba–da** were also afforded by this reduction. Finally, hydrogenolysis of the benzyl alcohols **5aa–da** with a catalytic amount of 10% palladium on activated carbon yielded (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**. According to the literature reports,[9] the coupling constant (J_{H3-H4} value) with cis configuration was approximately determined to be about 2.8–4.2 Hz in the prolinol or proline skeleton.[3f,9c,h] In comparison with the prolinols **1a–d**, we believe that the relative stereochemical centers at C_3 and C_4 positions were also assigned by correlation of the H_3–H_4 coupling constant (e.g., **1a**, δ 4.45, J_{H3-H4}=4.0 Hz). Thus, the assignment of three contiguous stereocenters on pyrrolidine framework of compounds **1a–d** was made the trans–cis configuration.

3. Conclusion

In summary, we have developed two one-pot Grignard addition/dehydration and epoxidation/isomerization as the key transformations for synthesizing (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d** with potential biological activities. Further application of this methodology to the synthesis of 4-methyl-3-hydroxyproline (4-HMP), which is the common constituent of the active echinocandin family,[10] is now underway.

4. Experimental

4.1. General

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.2. (2*S*)-2-Benzyloxymethyl-1-(4-methylphenylsulfonyl)pyrrolidin-4-one (3)

A solution of prolinol **4** (7.7 g, 20.0 mmol) in tetrahydrofuran (100 mL) was added to a rapidly stirred suspension of sodium hydride (1.60 g, 60%, 40.0 mmol) in tetrahydrofuran (30 mL). After the reaction mixture was stirred at room temperature for 20 min, a solution of benzyl bromide (5.0 g, 29.0 mmol) in tetrahydrofuran (100 mL) was added. The reaction mixture was stirred at refluxed temperature for 20 h. The resulting mixture was cooled to room temperature, quenched with aqueous ammonium chloride solution (15%, 10 mL) and concentrated. The residue was extracted with ethyl acetate (3×150 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product. Without further purification, excess Jones reagent (15 mL) was added to a stirred solution of resulting benzyl compound in acetone (200 mL) at 0 °C. The mixture was stirred for 20 min and treated with 2-propanol (10 mL) to destroy the unreacted oxidizing reagent. After the solvent was removed, the residue was diluted with water (10 mL) and extracted with diethyl ether (3×150 mL). The combined organic layers were dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate=4:1) afforded compound **3** (5.9 g, two steps 82%). White solid; mp=118–119 °C; $[\alpha]_D^{25}$ +41.10 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 2959, 1766, 1312, 1141, 1094, 688 cm^{-1}; FAB-MS: $C_{19}H_{22}NO_4S$ *m*/*z* (%)=91 (100), 155 (19), 224 (36), 238 (52), 360 (M^++1, 17); HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1272; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.5 Hz, 2H), 7.32–7.26 (m, 5H), 7.16 (d, *J*=8.5 Hz, 2H), 4.43 (d, *J*=12.0 Hz, 1H), 4.43–4.38 (m, 1H), 4.37 (d, *J*=12.0 Hz, 1H), 3.78 (dd, *J*=3.5, 9.5 Hz, 1H), 3.76 (s, 2H), 3.52 (dd, *J*=3.5, 9.5 Hz, 1H), 2.43 (s, 3H), 2.39–2.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.09, 144.08, 137.39, 135.36, 130.01 (2×), 128.41 (2×), 127.75, 127.31 (2×), 127.07 (2×), 73.37, 73.22, 56.84, 53.92, 40.47, 21.52; Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.41; H, 6.01; N, 3.71.

4.3. A representative procedure with one-pot reaction for the preparation of olefins 2a–d

A solution of different arylmagnesium bromide reagents (1.0 M in tetrahydrofuran, 1 mL, 1.0 mmol) was added to a stirred solution of ketone **3** (180 mg, 0.5 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred at room temperature for 2 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (1 mL) was added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. Water (2 mL) and ethyl acetate (10 mL) were added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure to yield the crude compound. Purification on silica gel (hexane/ethyl acetate=8:1–4:1) afforded olefins **2a–d** in 60–73% overall yield.

4.3.1. 2-Benzyloxymethyl-4-phenyl-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2a). Viscous oil; $[\alpha]_D^{24}$ −12.45 (*c* 0.043, $CHCl_3$); IR ($CHCl_3$) 2360, 1636, 1345, 1163, 1092, 754, 695 cm^{-1}; FAB-MS: $C_{25}H_{26}NO_3S$ *m*/*z* (%)=91 (100), 137 (28), 154 (20), 298 (6), 420 (M^++1, 15); HRMS (ESI, M^++1) calcd for $C_{25}H_{26}NO_3S$ 420.1633,

found 420.1632; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=8.5 Hz, 2H), 7.36–7.26 (m, 12H), 6.14 (br d, J=2.0 Hz, 1H), 4.70–4.65 (m, 1H), 4.62–4.54 (m, 1H), 4.59 (s, 2H), 4.43 (d, J=14.0 Hz, 1H), 4.03 (dd, J=4.0, 9.5 Hz, 1H), 3.63 (t, J=9.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.71, 138.13, 137.15, 134.06, 132.35, 129.84 (2×), 128.64 (2×), 128.48, 128.40 (2×), 127.70 (2×), 127.68, 127.50 (2×), 125.52 (2×), 122.14, 73.96, 73.67, 67.13, 55.80, 21.50. Anal. Calcd for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34. Found: C, 71.68; H, 6.29; N, 3.57.

4.3.2. 2-Benzyloxymethyl-4-(2-methylphenyl)-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2b). Viscous oil; $[\alpha]_D^{26}$ −12.20 (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2359, 1634, 1160, 668 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for $C_{26}H_{28}NO_3S$ 434.1790, found 434.1791; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.5 Hz, 2H), 7.36–7.28 (m, 7H), 7.20–7.12 (m, 3H), 7.00 (d, J=7.5 Hz, 1H), 5.75 (dd, J=2.0, 4.0 Hz, 1H), 4.76–4.73 (m, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.58 (d, J=12.0 Hz, 1H), 4.44 (ddd, J=2.0, 5.0, 14.5 Hz, 1H), 4.36 (dt, J=2.0, 14.5 Hz, 1H), 3.97 (dd, J=3.5, 9.0 Hz, 1H), 3.68 (dd, J=7.0, 9.0 Hz, 1H), 2.42 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.67, 138.17, 138.08, 135.90, 134.26, 132.98, 130.82, 129.77 (2×), 128.37 (2×), 127.99, 127.87, 127.63 (3×), 127.51 (2×), 125.93, 125.81, 73.81, 73.59, 67.46, 57.92, 21.51, 20.88. Anal. Calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28; N, 3.23. Found: C, 72.19; H, 6.12; N, 3.44.

4.3.3. 2-Benzyloxymethyl-4-(4-methoxyphenyl)-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2c). Viscous oil; $[\alpha]_D^{26}$ +61.67 (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2922, 2358, 1652, 1515, 1344, 1162, 1094, 817, 590 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for $C_{26}H_{28}NO_4S$ 450.1739, found 450.1740; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.38–7.27 (m, 7H), 7.22 (d, J=9.0 Hz, 2H), 6.85 (d, J=9.0 Hz, 2H), 6.00 (br d, J=2.0 Hz, 1H), 4.66–4.64 (m, 1H), 4.59 (s, 2H), 4.54 (ddd, J=2.0, 5.0, 13.5 Hz, 1H), 4.40 (dt, J=2.0, 13.5 Hz, 1H), 4.02 (dd, J=4.0, 9.0 Hz, 1H), 3.80 (s, 3H), 3.62 (t, J=8.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.72, 143.63, 138.17, 136.55, 134.08, 129.80 (2×), 128.37 (2×), 127.68 (2×), 127.64, 127.48 (2×), 126.81 (2×), 125.08, 119.90, 113.98 (2×), 74.07, 73.64, 67.09, 55.89, 55.29, 21.48. Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.61; H, 5.83; N, 3.35.

4.3.4. 2-Benzyloxymethyl-4-(3,4-dioxymethylenephenyl)-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2d). Viscous oil; $[\alpha]_D^{26}$ −38.32 (*c* 0.007, $CHCl_3$); IR ($CHCl_3$) 2360, 1635, 1558, 668 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for $C_{26}H_{26}NO_5S$ 464.1532, found 464.1535; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.38–7.27 (m, 7H), 6.81 (d, J=1.5 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.70 (dd, J=1.5, 8.0 Hz, 1H), 5.97 (d, J=2.0 Hz, 1H), 5.95 (s, 2H), 4.66–4.61 (m, 1H), 4.59 (s, 2H), 4.50 (ddd, J=2.0, 5.0, 14.0 Hz, 1H), 4.37 (d, J=14.0 Hz, 1H), 4.01 (dd, J=4.0, 9.0 Hz, 1H), 3.63 (t, J=8.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.00, 147.83, 143.69, 138.14, 136.68, 134.07, 129.83 (2×), 128.40 (2×), 127.70 (2×), 127.68, 127.50 (2×), 126.67, 120.65, 119.47, 108.23, 105.77, 101.25, 73.96, 73.65, 67.02, 55.93, 21.51. Anal. Calcd for $C_{26}H_{25}NO_5S$: C, 67.37; H, 5.44; N, 3.02. Found: C, 67.50; H, 5.70; N, 3.21.

4.4. A general representative procedure with one-pot reaction for the preparation of ketones 5a–d

m-Chloroperoxybenzoic acid (70 mg, 75%, 0.3 mmol) was added to a solution of olefins **2a–d** (0.2 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 3–5 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (1 mL) was added to a stirred solution of the resulting epoxides **2aa–da** at 0 °C. The reaction mixture was stirred at room temperature for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude products under reduced pressure. Recrystallization from dichloromethane and methanol yielded the ketones **5a–d**. Besides ketone **5a**, it is worthy of note that ketones **5b–d** are slow in producing some epimers under the deuterated chloroform condition.

4.4.1. 4-Benzyloxymethyl-3-(4-methylphenylsulfonyl)-1-phenyl-6-oxa-3-aza-bicyclo[3.1.0]hexane (2aa). White solid; mp=115–116 °C; $[\alpha]_D^{28}$ +27.48 (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) 2925, 2358, 1634, 1453, 1342, 1163, 1096, 814 cm^{-1}; FAB-MS: $C_{25}H_{26}NO_4S$ *m/z* (%)=91 (100), 298 (20), 328 (15), 436 (M$^+$+1, 13); HRMS (ESI, M$^+$+1) calcd for $C_{25}H_{26}NO_4S$ 436.1582, found 436.1584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=8.0 Hz, 2H), 7.32–7.27 (m, 10H), 7.18 (dd, J=2.0, 8.0 Hz, 2H), 4.58 (d, J=11.5 Hz, 1H), 4.52 (d, J=11.5 Hz, 1H), 4.12 (t, J=4.0 Hz, 1H), 4.03 (d, J=12.5 Hz, 1H), 3.86 (d, J=4.0 Hz, 2H), 3.78 (d, J=12.5 Hz, 1H), 3.60 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.54, 137.75, 135.36, 133.21, 129.60 (2×), 128.53, 128.47 (2×), 128.39 (2×), 127.78, 127.70 (2×), 127.53 (2×), 126.05 (2×), 73.74, 71.19, 65.99, 65.49, 61.10, 51.35, 21.60. Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 69.03; H, 5.92; N, 3.51. Single-crystal X-ray diagram: crystal of epoxide **2aa** was grown by slow diffusion of ethyl acetate into a solution of compound **2aa** in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system. a=7.778(16) Å, b=16.074(3) Å, c=18.523(4) Å, V=2315.7(8) Å^3, Z=4, d_{calcd}=1.249 mg/m^3, absorption coefficient 0.170 mm^{-1}, $F(000)$=920, 2θ range (2.20–25.99°), wR_2=0.1304.

4.4.2. 2-Benzyloxymethyl-4-phenyl-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5a). White solid; mp=124–125 °C; $[\alpha]_D^{27}$ −4.05 (*c* 0.037, $CHCl_3$); IR ($CHCl_3$) 2358, 1764, 1348, 1165, 1091, 815, 662, 549 cm^{-1}; FAB-MS: $C_{25}H_{26}NO_4S$ *m/z* (%)=91 (100), 155 (11), 314 (29), 328 (10), 341 (15), 436 (M$^+$+1, 11); HRMS (ESI, M$^+$+1) calcd for $C_{25}H_{26}NO_4S$ 436.1582, found 436.1584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.0 Hz, 2H), 7.36–7.23 (m, 10H), 7.03 (dd, J=2.0, 8.0 Hz, 2H), 4.52 (d, J=12.0 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.23 (dd, J=9.0, 9.5 Hz, 1H), 4.09 (dd, J=2.5, 10.0 Hz, 1H), 3.94

(dd, J=2.0, 10.0 Hz, 1H), 3.81 (dd, J=9.0, 9.5 Hz, 1H), 3.77 (dd, J=2.0, 2.5 Hz, 1H), 3.52 (dd, J=9.0, 9.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.44, 144.26, 137.66, 134.54, 133.54, 129.93 (2×), 128.91 (2×), 128.36 (2×), 128.05 (2×), 127.78, 127.70 (2×), 127.69, 127.44 (2×), 73.66, 70.24, 64.70, 53.37, 51.60, 21.57. Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 68.61; H, 5.89; N, 3.57.

4.4.3. 2-Benzyloxymethyl-4-(2-methylphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5b). Viscous oil; $[\alpha]_D^{27}$ −2.31 (c 0.01, $CHCl_3$); IR ($CHCl_3$) 2360, 1771, 1346, 1159, 1088, 760 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_4S$ 450.1739, found 450.1743; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J=8.1 Hz, 2H), 7.32–7.25 (m, 7H), 7.20–7.13 (m, 3H), 6.99 (d, J=7.2 Hz, 1H), 4.50 (d, J=10.8 Hz, 1H), 4.44 (d, J=10.8 Hz, 1H), 4.27 (dd, J=9.0, 9.6 Hz, 1H), 4.06 (dd, J=2.4, 10.2 Hz, 1H), 3.96 (dd, J=2.4, 10.2 Hz, 1H), 3.85 (dd, J=9.0, 9.6 Hz, 1H), 3.80 (dd, J=2.4, 2.7 Hz, 1H), 3.50 (dd, J=9.0, 9.6 Hz, 1H), 2.45 (s, 3H), 2.15 (s, 3H); Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.87; H, 6.39; N, 3.43.

4.4.4. 2-Benzyloxymethyl-4-(4-methoxyphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5c). Viscous oil; $[\alpha]_D^{29}$ −12.53 (c 0.006, $CHCl_3$); IR ($CHCl_3$) 2355, 1761, 1345, 1162, 1090, 766 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_5S$ 466.1688, found 466.1689; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=8.1 Hz, 2H), 7.39–7.18 (m, 7H), 6.85 (d, J=9.0 Hz, 2H), 6.63 (d, J=9.0 Hz, 2H), 4.50 (d, J=10.8 Hz, 1H), 4.43 (d, J=10.8 Hz, 1H), 4.22 (dd, J=9.0, 9.6 Hz, 1H), 4.08 (dd, J=2.4, 10.2 Hz, 1H), 3.94 (dd, J=2.4, 10.2 Hz, 1H), 3.79 (s, 3H), 3.80–3.76 (m, 2H), 3.27 (dd, J=9.0, 9.6 Hz, 1H), 2.46 (s, 3H). Anal. Calcd for $C_{26}H_{27}NO_5S$: C, 67.08; H, 5.85; N, 3.01. Found: C, 66.83; H, 5.60; N, 2.84.

4.4.5. 2-Benzyloxymethyl-4-(3,4-dioxymethylenephenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5d). Viscous oil; $[\alpha]_D^{29}$ −16.32 (c 0.008, $CHCl_3$); IR ($CHCl_3$) 2356, 1760, 1350, 1160, 1095 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{26}NO_6S$ 480.1481, found 480.1481; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=8.1 Hz, 2H), 7.39–7.25 (m, 5H), 7.20–7.16 (m, 2H), 6.78 (d, J=8.1 Hz, 1H), 6.52 (d, J=1.2 Hz, 1H), 6.43 (dd, J=1.2, 8.1 Hz, 1H), 5.96 (s, 2H), 4.38 (d, J=10.8 Hz, 1H), 4.36 (d, J=10.8 Hz, 1H), 4.18 (dd, J=9.0, 9.6 Hz, 1H), 4.03 (dd, J=2.4, 10.2 Hz, 1H), 3.96 (dd, J=2.4, 10.2 Hz, 1H), 3.76 (dd, J=9.0, 9.6 Hz, 1H), 3.75 (dd, J=1.8, 2.4 Hz, 1H), 3.22 (dd, J=9.0, 9.6 Hz, 1H), 2.42 (s, 3H).

4.5. A representative procedure for the preparation of diols 1a–d

A solution of diisobutylaluminum hydride (1.0 M in hexane, 0.3 mmol) was added to a solution of ketones **5a–d** (0.1 mmol) in tetrahydrofuran (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h. The total procedure was monitored by TLC until the reaction was completed. Methanol (0.5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude benzyl alcohols **5aa–da** under reduced pressure. Palladium (10%) on activated carbon (30 mg) was added to a stirred solution of the resulting benzyl alcohols **5aa–da** in methanol (10 mL). Hydrogen was bubbled into the mixture for 10 min and stirring of the reaction mixture was continued for 10 h at room temperature. The catalyst was filtered through a short plug of Celite and washed with methanol (2×20 mL). The combined organic layers were evaporated to afford crude products. Purification on silica gel (hexane/ethyl acetate=2:1–1:1) afforded diols **1a–d**.

4.5.1. 2-Hydroxymethyl-4-phenyl-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1a). White solid; mp=158–159 °C; $[\alpha]_D^{28}$ +23.82 (c 0.019, $CHCl_3$); IR ($CHCl_3$) 3430, 2358, 1634, 1339, 1160, 1089, 663 cm^{-1}; FAB-MS: $C_{18}H_{22}NO_4S$ m/z (%)=91 (100), 136 (13), 154 (10), 316 (30), 341 (5), 348 (M^++1, 7); HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1269, found 348.1267; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J=8.0 Hz, 2H), 7.37–7.26 (m, 5H), 7.13 (d, J=8.5 Hz, 2H), 4.45 (t, J=4.0 Hz, 1H), 4.14 (dd, J=5.5, 12.0 Hz, 1H), 4.11 (dd, J=4.0, 12.0 Hz, 1H), 3.92 (dd, J=11.5, 12.0 Hz, 1H), 3.88 (dd, J=8.0, 11.5 Hz, 1H), 3.76 (dd, J=4.0, 10.0 Hz, 1H), 2.66 (ddd, J=4.0, 8.0, 12.0 Hz, 1H), 2.46 (s, 3H), 1.68 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.08, 134.74, 134.17, 130.01 (2×), 128.79 (2×), 128.27 (2×), 127.65, 127.53 (2×), 75.68, 65.57, 62.63, 51.07, 48.65, 21.58. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.50; H, 6.23; N, 4.30.

4.5.2. C3 isomer of compound 1a. Viscous oil; $[\alpha]_D^{28}$ +10.68 (c 0.009, $CHCl_3$); IR ($CHCl_3$) 3432, 2916, 2849, 1636, 1159, 543 cm^{-1}; FAB-MS: $C_{18}H_{22}NO_4S$ m/z (%)=91 (100), 136 (18), 154 (16), 316 (26), 341 (8), 348 (M^++1, 6); HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1269, found 348.1268; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.30–7.23 (m, 3H), 7.07 (d, J=8.5 Hz, 2H), 4.18 (dd, J=5.0, 12.0 Hz, 1H), 4.04 (dd, J=8.0, 9.5 Hz, 1H), 3.98 (dd, J=3.0, 12.0 Hz, 1H), 3.88 (dd, J=8.0, 10.0 Hz, 1H), 3.75 (ddd, J=4.5, 5.0, 8.0 Hz, 1H), 3.39 (dd, J=9.5, 10.0 Hz, 1H), 3.05 (dd, J=10.0, 10.0 Hz, 1H), 2.48 (s, 3H), 2.10 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.19, 137.49, 132.94, 129.95 (2×), 128.86 (2×), 127.72 (2×), 127.57, 127.37 (2×), 77.55, 62.73, 61.33, 51.70, 49.98, 21.60. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.42; H, 5.83; N, 4.32.

4.5.3. 2-Hydroxymethyl-4-(2-methylphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1b). White solid; mp=167–168 °C; $[\alpha]_D^{27}$ +16.67 (c 0.009, $CHCl_3$); IR ($CHCl_3$) 3428, 2920, 1635, 1338, 1160, 1091, 661, 545 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_4S$ 362.1426, found 362.1427; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 7.19–7.14 (m, 4H), 4.40 (br s, 1H), 4.11 (br s, 2H), 3.97 (t, J=12.0 Hz, 1H), 3.87 (dd, J=5.0, 10.5 Hz, 1H), 3.76 (dd, J=7.0, 12.0 Hz, 1H), 2.78 (br s, 1H), 2.72–2.67 (m, 1H), 2.46 (s, 3H), 2.03 (br s, 1H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.07, 136.52, 134.40, 132.27, 130.84, 129.95 (2×), 127.62, 127.58 (2×), 127.48, 126.21,

73.49, 65.70, 62.66, 50.82, 45.19, 21.53, 19.36. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.38; H, 6.80; N, 3.61.

4.5.4. 2-Hydroxymethyl-4-(4-methoxyphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1c). Viscous oil; $[\alpha]_D^{26}$ +25.57 (*c* 0.009, $CHCl_3$); IR ($CHCl_3$) 3455, 2920, 1611, 1515, 1340, 1160, 1033, 817 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_5S$ 378.1375, found 378.1377; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.05 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 4.38 (br s, 1H), 4.11 (br s, 2H), 3.89–3.80 (m, 2H), 3.78 (s, 3H), 3.76–3.73 (m, 1H), 2.94 (br s, 1H), 2.64–2.59 (m, 1H), 2.46 (s, 3H), 2.42 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.01, 144.03, 134.19, 129.98 (2×), 129.31 (2×), 127.53 (2×), 126.43, 114.21 (2×), 75.65, 65.56, 62.63, 55.28, 51.28, 47.92, 21.57. Anal. Calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71. Found: C, 60.22; H, 6.29; N, 3.90.

4.5.5. 2-Hydroxymethyl-4-(3,4-dioxymethylenephenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1d, rotamer). Viscous oil; $[\alpha]_D^{26}$ +10.39 (*c* 0.008, $CHCl_3$); IR ($CHCl_3$) 3445, 2933, 1504, 1338, 1160, 1037, 663 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_6S$ 392.1168, found 392.1171; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.4 Hz, 2H), 7.39 (d, *J*=8.4 Hz, 2H), 6.77 (d, *J*=8.1 Hz, 1H), 6.63 (br s, 1H), 6.52 (dd, *J*=1.2, 8.1 Hz, 1H), 5.97 (s, 2H), 4.39 (br s, 1H), 4.16 (br s, 2H), 3.97–3.93 (m, 1H), 3.85–3.80 (m, 2H), 3.73–3.69 (m, 1H), 2.83 (br s, 1H), 2.66–2.62 (m, 1H), 2.45 (s, 3H).

Acknowledgements

The authors would like to thank the National Science Council (NSC-95-2113-M-390-003-MY2) of the Republic of China for financial support. We also thank Prof. Michael Y. Chiang (National Sun Yat-Sen University) for structural determination of epoxide **2aa** by X-ray diffraction analysis.

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Tetrahedron 62 (2006) 12340–12344

Anthracene derivatives bearing sulfur atoms or selenium atoms as fluorescent chemosensors for Cu^{2+} and Hg^{2+}: different selectivity induced from ligand immobilization onto anthracene

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Received 14 July 2006; revised 29 September 2006; accepted 2 October 2006
Available online 27 October 2006

Abstract—Two new selenium containing anthracene derivatives and two new sulfur containing anthracene derivatives were synthesized as fluorescent chemosensors for Hg^{2+} and Cu^{2+}. Compound **1** displayed a highly selective chelation enhanced fluorescence quenching (CHEQ) effect only with Cu^{2+}, on the other hand, compounds **3** and **4** displayed highly selective chelation enhanced fluorescence (CHEF) effects only with Hg^{2+} among the metal ions examined.

1. Introduction

Fluoroionophores chemically communicate ion concentrations and are the subjects of substantial investigation for metal ion analysis.[1] The advent of ligand engineering has introduced a more systematic approach to the design of chemosensors with new selectivities and signal transduction schemes. Selenacrown[2] or selenium containing cyclophane[3] have been studied actively by various groups due to the large covalent radius and greater polarizability of selenium compared to oxygen, nitrogen and sulfur, which could influence the conformational as well as complexation properties of these compounds. Another reason can be the accessibility of ^{77}Se NMR for the investigation of structural properties of selenium containing compounds. Selenium containing hosts have been reported to display strong affinities with Hg^{2+} or Ag^{+}.[3e,4] Recently, a calix[4](diseleno)crown ether[4] as well as organoselenium-bridged bis(β-cyclodextrin)s[5] have been also reported. However, as far as we are aware, there has not been any report regarding a fluorescent chemosensor containing selenium atoms as a binding site for metal ions.

We report herein two new selenium containing anthracene derivatives and two new sulfur containing anthracene derivatives as fluorescent chemosensors for Hg^{2+} and Cu^{2+}. Four different host compounds **1**–**4** have been synthesized to compare the binding affinities of sulfur containing ligand and selenium ligand towards various metal ions. Compound **1** displayed a highly selective chelation enhanced fluorescence quenching (CHEQ) effect only with Cu^{2+}, on the other hand, compounds **3** and **4** displayed highly selective chelation enhanced fluorescence (CHEF) effects only with Hg^{2+} among the metal ions examined. Especially, compounds **1** and **2**, 9,10-isomer and 1,8-isomer, respectively, showed quite different emission patterns and selectivity towards metal ions; a large CHEQ effect was observed with $\mathbf{1}\cdot Cu^{2+}$, on the other hand, a large CHEF effect along with a red shift (~40 nm) was observed in the case of $\mathbf{2}\cdot Cu^{2+}$. We observed high selectivity for compound **1** with Cu^{2+}, which is relatively a simple host compound. Furthermore, 1,8-isomer (**2**) containing same ligand displayed quite different binding selectivity towards metal ions.

2. Results and discussion

1,8-Bis(bromomethyl)anthracene (**6**) was first synthesized following the procedures of Gunnlaugsson[6] and Nakagawa.[7] Treatment of compounds **5** and **6** with K_2CO_3 and ethanethiol in chloroform led to 9,10-bis(ethylthiamethyl)anthracene (**1**) and 1,8-bis(ethylthiamethyl)anthracene (**2**) in 83% and 72% yield, respectively, after purification by flash chromatography using ethyl acetate/hexane (1:2) (Scheme 1). For the synthesis of 1,8-diselenanthracenometacyclophane (**3**) and 1,8-diselenanthraceno-2,6-pyridinophane (**4**), 2,6-bis-(selenocyanatomethyl)benzene (**7**) and 2,6-bis(selenocyanatomethyl)pyridine (**8**) were synthesized following the published procedure.[3c,d] Either compound **7** or **8** was reacted with 9,10-bis(bromomethyl)anthracene (**5**) and sodium

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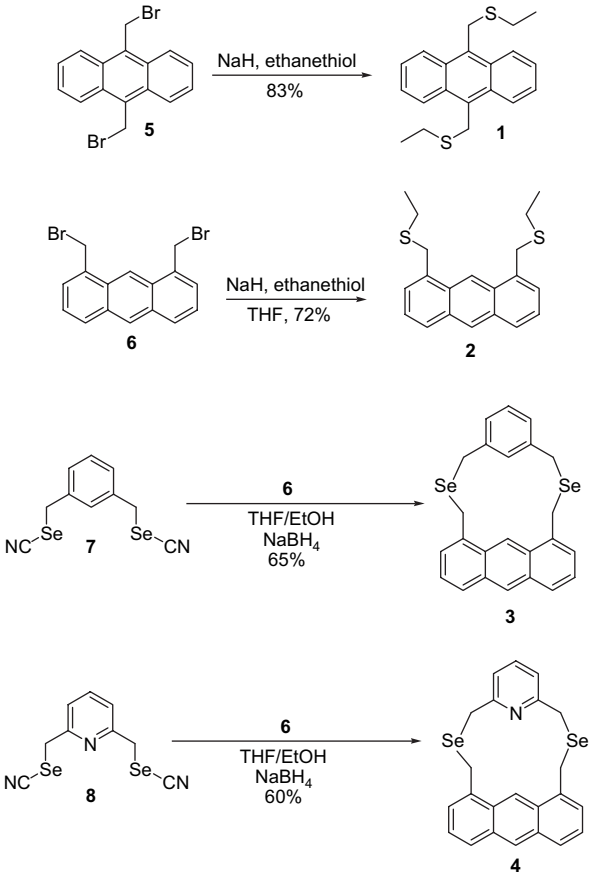
doi:10.1016/j.tet.2006.10.001

borohydride in THF/ethanol (4:1, v/v) to give compound **3** or **4**, respectively, as yellow crystalline compound after recrystallization from chloroform.



Scheme 1. Syntheses of compounds **1**, **2**, **3** and **4**.

Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cs^+, Cu^{2+}, K^+, Li^+, Hg^{2+}, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+} and Zn^{2+} ions were used to evaluate the metal ion binding properties of compounds **1**, **2**, **3** and **4** in acetonitrile/chloroform (4:1, v/v). Using these metal ions (100 equiv), compound **1** (6 μM) displayed a CHEQ effect only with Cu^{2+} (Fig. 1). As the amounts of Cu^{2+} were increased, the fluorescent intensities (Fig. 2) as well as UV absorptions (Fig. 3) of compound **1** were consequently

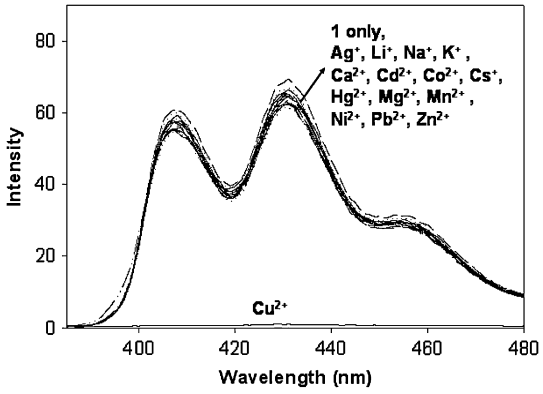


Figure 1. Changes in the fluorescence emission spectra of compound **1** (6 μM) upon the addition of 100 equiv of metal ions in $CH_3CN/CHCl_3$ (4:1, v/v) (excitation at 379 nm, excitation and emission slit width=1.5 nm).

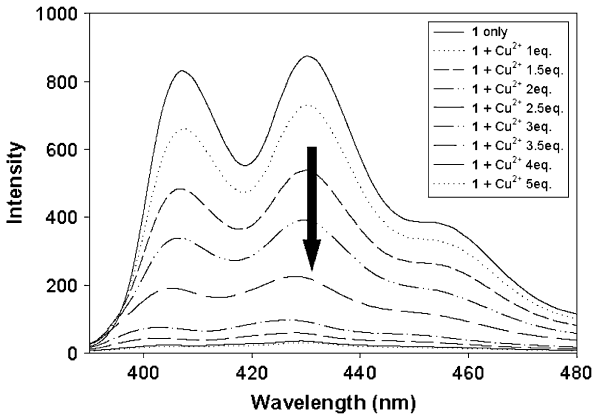


Figure 2. Fluorescent titrations of compound **1** (1 μM) with Cu^{2+} in $CH_3CN/CHCl_3$ (4:1, v/v). (excitation at 379 nm, excitation and emission slit width=5 nm).

decreased. These observations of UV along with fluorescent data support the fact that there is an additional π–Cu^{2+} interaction in the case of 9,10-isomer (**1**). Similar interaction between the silver ion and the anthracene moiety was reported by our group[8] and Desvergne group.[9] Therefore, compound **1** may provide three potential binding sites, namely two sulfur atoms and an additional π–cation interaction. From the fluorescent titrations (Fig. 2), the association constant for Cu^{2+} was calculated as 238 000 M^{-1}.[10] An overall emission change of 100-fold was observed for Cu^{2+}. Thia-anthracene derivative bearing $SCH_2CH_2CH_2S$ spacer at the 9,10-positions of anthracene was reported by Ostaszewski et al.,[11] which was reported to display a selective fluorescence change with Ag^+. The selectivity of compound **1** with Cu^{2+} can be productively compared with that of the compound reported by Ostaszewski.

On the other hand, 1,8-isomer (**2**) (6 μM) showed CHEF effects with Cu^{2+}, Hg^{2+} and Ag^+ among the metal ions examined (Fig. 4). In the absence of metal ions, compound **2** displayed its maximum intensity at 417 nm. Upon the addition of these metal ions, significant red shifts (Cu^{2+}, 40 nm; Hg^{2+}, 13 nm; Ag^+, 17 nm) were observed in their fluorescent spectra. Unlike 9,10-isomer (**1**), 1,8-isomer (**2**) displayed a similar red shift (367–390 nm) in its UV spectra upon the addition of Cu^{2+}. The red shift of fluorescence emission

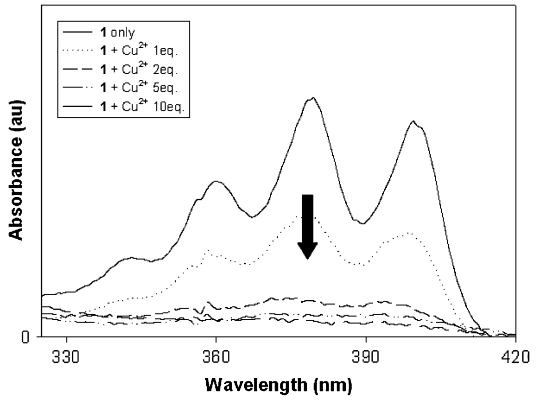


Figure 3. Changes in the UV absorption spectra of compound **1** (20 μM) upon the addition of Cu^{2+} in $CH_3CN/CHCl_3$ (4:1, v/v).

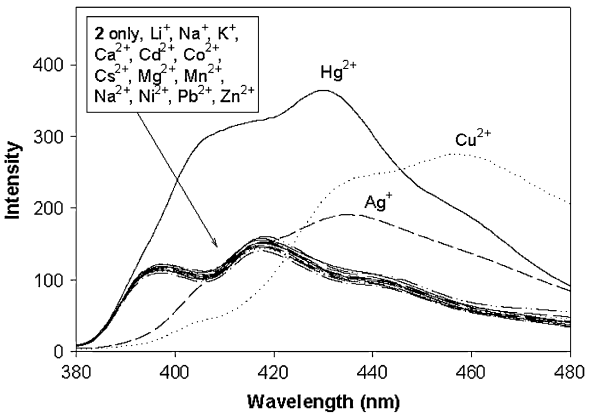


Figure 4. Changes in the fluorescence emission spectra of compound **2** (6 μM) upon the addition of 100 equiv of metal ions in $CH_3CN/CHCl_3$ (4:1, v/v) (excitation at 368 nm, excitation and emission slit width=5 nm).

is closely related to the red shift of absorption peak upon the addition of Cu^{2+} ion because the less excitation energy will induce the less emission energy.

As shown in Figure 4, there was a unique change in the emission spectrum upon the addition of Cu^{2+}. A new red-shifted peak at 457 nm was observed and ratiometric changes were observed as the amount of Cu^{2+} was increased. A ratiometric sensor allows a calibration curve, which is independent of the sample condition e.g. the concentration of the sensor, etc. Furthermore, ratiometric fluorescence measurements can increase the selectivity and the sensitivity of the detection. The addition of Ag^+ caused similar changes in the fluorescent emission spectra of compound **2**; the λ_{max} at 417 moved to 434 nm upon the addition of Ag^+. The job plots indicate 1:1 binding between these hosts and Hg^{2+} (S-Figure 1). From the fluorescent titrations, the association constants for Cu^{2+} (Fig. 5), Ag^+ and Hg^{2+} were calculated as 146 000, 71 200 and 24 000 M^{-1}, respectively.[10]

Figure 6 explains the opposite fluorescence changes of compounds **1** and **2** upon the addition of Cu^{2+}. These results explain that relatively simple hosts, such as compounds **1** and **2**, can display effective selectivity towards metal ions. Even though there have been many reports regarding fluorescent

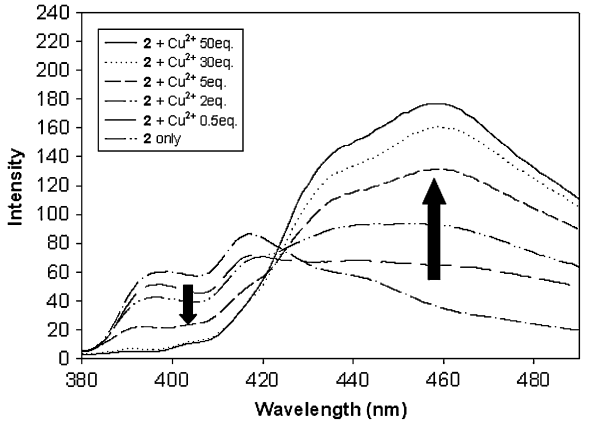


Figure 5. Fluorescent titrations of compound **2** (3 μM) with Cu^{2+} in $CH_3CN/CHCl_3$ (4:1, v/v). (excitation at 368 nm, excitation and emission slit width=5 nm).

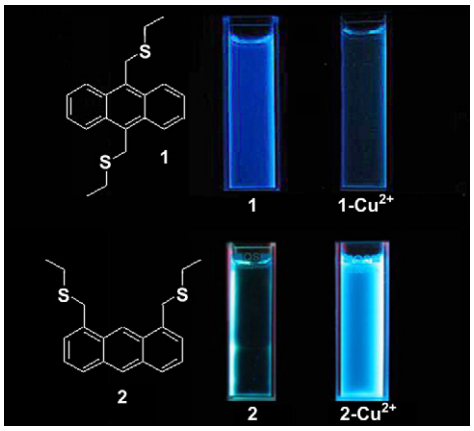


Figure 6. Changes in the fluorescence compounds **1** and **2** (10 μM) upon the addition of 50 equiv of $Cu(ClO_4)_2$ in $CH_3CN/CHCl_3$ (4:1, v/v).

chemosensors for Cu^{2+}, relatively few examples are available as OFF–ON type sensors or ratiometric sensors for Cu^{2+}.[12]

On the other hand, compounds **3** and **4** displayed highly selective CHEF effects with Hg^{2+} among the metal ions examined (Figs. 7 and 8). The association constants were

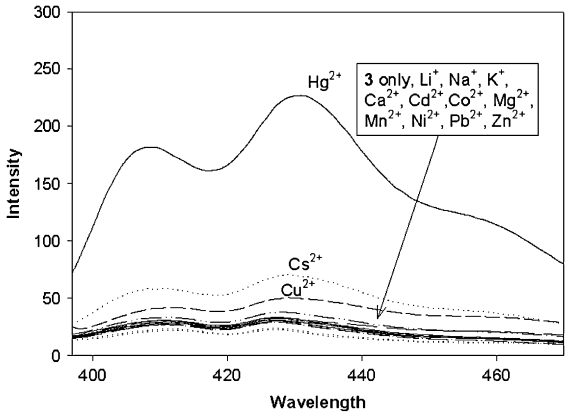


Figure 7. Changes in the fluorescence emission spectra of compound **3** (6 μM) upon the addition of 100 equiv of metal ions in $CH_3CN/CHCl_3$ (4:1, v/v) (excitation at 377 nm, excitation and emission slit width=5 nm).

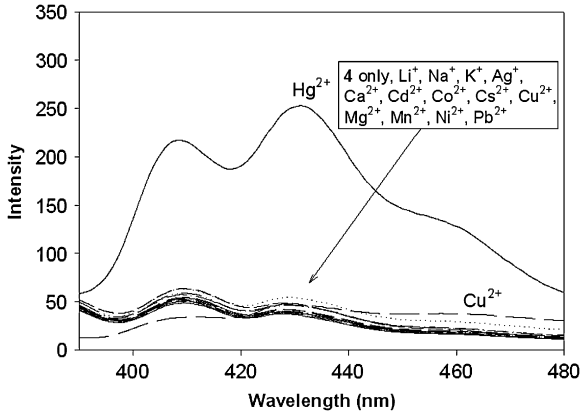


Figure 8. Changes in the fluorescence emission spectra of compound **4** (6 μM) upon the addition of 100 equiv of metal ions in $CH_3CN/CHCl_3$ (4:1, v/v) (excitation at 377 nm, excitation and emission slit width=5 nm).

calculated as 36 000 and 44 000 M^{-1}, respectively.[10] The job plots indicate 1:1 binding between host compounds **3** and **4** and Hg^{2+} (S-Figure 1). Even though pyridine moiety contains additional nitrogen for the binding with Hg^{2+}, the association constants turned out to be very similar.

3. Conclusion

In conclusion, two new selenium containing anthracene derivatives (**3**, **4**) and two new sulfur containing anthracene derivatives (**1**, **2**) were synthesized as fluorescent chemosensors for metal ions. Compound **1**, which contains three potential binding sites, two sulfur atoms and an additional π–cation interaction, displayed a selective fluorescent quenching effect with Cu^{2+}. On the other hand, the 1,8-isomer (**2**) displayed a unique red-shifted and enhanced fluorescent effects upon the addition of Cu^{2+}. Compounds **3** and **4** displayed a highly selective CHEF effect with Hg^{2+} among the metal ions examined. It is worth noting that the anthracene moiety in these hosts acts not only as a fluorescent source but also as a template for introducing the binding selectivity.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a thickness of 0.25 mm. Preparative TLC was performed using Merck 60 F_{254} plates with the thickness of 1 mm.

Melting points were measured using a Büchi 530 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 250 MHz or Varian 500 MHz. Chemical shifts were given in parts per million and coupling constants (*J*) in Hertz. UV absorption spectra were obtained on UVIKON 933 Double Beam UV–vis Spectrometer. Fluorescence emission spectra were obtained using RF-5301/PC Spectrofluorophotometer (Shimadzu).

4.1.1. 9,10-Bis(ethylthiamethyl)anthracene (1). *Procedure A*. To a reaction mixture of ethanethiol (62 mg, 1.0 mmol) in THF (20 mL) was added NaH (48 mg, 2.0 mmol) at 0 °C. After stirring for 20 min at 0 °C, 9,10-bis(bromomethyl)anthracene (**5**)[6] (100 mg, 0.28 mmol) was added to the reaction mixture. After additional stirring for 1 h at room temperature, the reaction mixture was poured into 50 mL of water and extracted with $CHCl_3$. The organic layer was then separated, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica gel (2:1, hexane/ethyl acetate) afforded compound **1** (76 mg, 83%) as a yellow solid: mp 75–78 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (d, J=8.8 Hz, 2H), 8.35 (d, J=8.8 Hz, 2H), 7.56 (m, 4H), 4.78 (s, 4H), 2.74 (q, J=7.8 Hz, 4H), 1.40 (t, J=7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.4, 133.4, 128.3, 127.5, 35.6, 29.9, 15.1; HRMS (FAB) m/z=326.1166 $(M+H)^+$, Calcd for $C_{20}H_{22}S_2$=326.1163. Anal. Calcd for $C_{20}H_{22}S_2$: C, 73.57; H, 6.79. Found: C, 73.44; H, 6.83.

4.1.2. 1,8-Bis(ethylthiamethyl)anthracene (2). Application of procedure A to 1,8-bis(bromomethyl)anthracene (**6**)[7] (100 mg, 0.28 mmol) afforded compound **2** (66 mg, 72%) as a yellow solid: mp 80–83 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.03 (s, 1H), 8.45 (s, 1H), 7.91 (d, J=4.0 Hz, 2H), 7.38 (m, 4H), 4.33 (s, 4H), 2.56 (q, J=7.3 Hz, 4H), 1.33 (t, J=7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.5, 132.4, 129.8, 128.3, 128.2, 126.6, 125.0, 120.0, 34.6, 29.9, 14.8; HRMS (FAB) m/z=349.1062 $(M+H+Na)^+$, Calcd for $C_{20}H_{22}S_2Na$=349.1061.

4.1.3. 1,8-Diselenanthracenometacyclophane (3). *Procedure B*. 2,6-Bis(selenocyanatomethyl)benzene (**7**) (158 mg, 0.5 mmol) and 1,8-bis(bromomethyl)anthracene (**6**) (181 mg, 0.5 mmol) were each dissolved separately in a mixture of 80% freshly distilled THF and 20% absolute ethanol to a total volume of 50 mL and thoroughly degassed with Ar. They were added separately but simultaneously from two constant addition funnels over 20 h into 95 mL freshly distilled THF and 5 mL of absolute ethanol containing an excess (150 mg) of $NaBH_4$ at room temperature under Ar. The resulting solution was filtered and concentrated to dryness. The solid was treated with 100 mL of benzene. The benzene solution was evaporated to dryness to yield a yellow crystalline solid, which was recrystallized from $CHCl_3$ (152 mg, 65%): mp 196–200 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.37 (s, 1H), 8.30 (s, 1H), 7.92 (br s, 7.92), 7.79 (d, J=8.3 Hz, 2H), 7.44 (d, J=6.8 Hz, 2H), 7.44 (dd, J=8.4 Hz, J=6.8 Hz, 2H), 7.20 (t, hidden, 1H), 7.11 (d, partially hidden, 2H), 4.15 (s, 4H), 3.91 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.4, 133.9, 132.2, 129.6, 129.3, 128.3 128.2, 128.0, 127.8, 125.3, 118.9, 29.0, 24.9 ($^2J_{Se-C}$=23.6 Hz); ^{77}Se NMR ($CDCl_3$, 95 MHz) δ 330.9; HRMS (FAB) m/z=467.9909 $(M+H)^+$, Calcd for $C_{24}H_{20}Se_2$=467.9900. Anal. Calcd for $C_{24}H_{20}Se_2$: C, 61.18; H, 4.32. Found: C, 60.96; H, 4.52.

4.1.4. 1,8-Diselenanthraceno-2,6-pyridinophane (4). Application of procedure B to 2,6-bis(selenocyanatomethyl)pyridine (150 mg, 0.5 mmol) and 1,8-bis(bromomethyl)anthracene (**6**) (181 mg, 0.5 mmol) gave compound **4** as a yellow crystalline solid after recrystallization from $CHCl_3$ (140 mg, 60%): mp ~250 °C, decomposed; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.89 (s, 1H), 8.29 (s, 1H), 7.79 (d, J=8.4 Hz, 2H), 7.54 (t, J=7.6 Hz, 1H), 7.40 (d, J=6.6 Hz, 2H), 7.23 (dd, J=8.4 Hz, J=6.6 Hz, 2H), 7.04 (d, J=7.6 Hz, 2H), 4.40 (s, 4H), 4.05 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.85, 137.3, 134.4, 132.3, 129.5, 128.3, 127.7, 127.2, 125.4, 121.8, 120.9, 30.4, 26.1 ($^2J_{Se-C}$= 24.7 Hz); ^{77}Se NMR ($CDCl_3$, 95 MHz) δ 319.2; HRMS (EI) m/z=468.9852 $(M)^+$, Calcd for $C_{23}H_{19}NSe_2$=468.9845. Anal. Calcd for $C_{23}H_{19}NSe_2$: C, 59.11; H, 4.10; N, 3.00. Found: C, 59.13; H, 4.26; N, 2.83.

4.2. Preparation of fluorometric metal ion titration solutions

Stock solutions (1 mM) of the metal perchlorate salts (for Cd(II), chloride salt was used) were prepared using CH_3CN. Stock solutions of compound **1** or **2** (0.6 mM)

were prepared in $CHCl_3$. Test solutions were prepared by placing 40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock and diluting the solution to 4 mL with $CH_3CN/CHCl_3$ to make 4:1 ratio.

For all measurements, excitation was at 379 nm (for compound **1**), 368 nm (for compound **2**) or 377 nm (for compounds **3** and **4**). Both excitation and emission slit widths were either 1.5 nm or 5 nm.

Acknowledgements

This work was supported by the SRC programme of the Korea Science and Engineering Foundation (KOSEF) (R11-2005-008-02001-0), Basic Science Research of KOSEF (R01-2006-000-10001-0) and BK21. We also thank KBSI in Taejon, Korea, for their instrumentation assistance (FAB mass spectra).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.001.

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Studies on the synthetic utility of [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines: efficient synthesis of fused ring cyclooctanoids

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Received 1 August 2006; revised 15 September 2006; accepted 28 September 2006
Available online 27 October 2006

Dedicated with respect to Professor M. V. George on the occasion of his 78th birthday

Abstract—A study on the synthetic utility of [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines is described. 5–8 Fused oxa-bridged cyclooctanoids, the products of the above methodology undergo facile Diels–Alder reaction, dipolar cycloaddition, Luche reduction and selective hydrogenation over Pd/C leading to functionalized molecules, which can be transformed to oxa-bridged fused cyclooctanoids. We have shown that the carbon framework of the molecules can be directly expanded from the product, thus enhancing the synthetic versatility of the products.

1. Introduction

Strategies towards the synthesis of fused ring heterocycles and carbocycles are important as they are found in structurally complex natural products possessing potent and selective biological activities. Moreover, functionalized heterocycles are well utilized in the development and practise of modern medicinal chemistry. Though significant achievements have been made in the synthesis of medium sized heterocycles, designing efficient, short routes for the stereoselective construction of cyclooctanoids is an interesting challenge in synthetic organic chemistry.[1,2] The discovery of new, complex and architecturally interesting cyclooctane bearing frameworks from nature, particularly from microbial and other exotic sources sustains unabated interest in cyclooctanoid synthesis.[1] Some bioactive cyclooctanoids are shown in Figure 1.

Eight-membered rings are notoriously difficult to prepare because of the unfavourable entropic and enthalpic effects, as well as the propensity for transannular interactions.[3] Fragmentation of complex bicyclic systems,[4a–d] metal-mediated synthesis[4e] and acyclic ring closures[4f] are the commonly used methods. [3,3] Sigmatropic rearrangements[4g,h] of smaller rings to such skeletons and transition metal-mediated cycloadditions[5] provide another interesting route to cyclooctanoids. Among the various methods for the synthesis of eight-membered rings,[6] higher-order cycloadditions[7] are important because of their ability to produce complex molecules with extensive functionality in a single step with good control over the creation of new stereocentres. Many of the strategies towards cyclooctanoids have been developed in the context of a specific target, but their generality, operational simplicity and regio-and stereocontrol element still remain to be fully delineated.

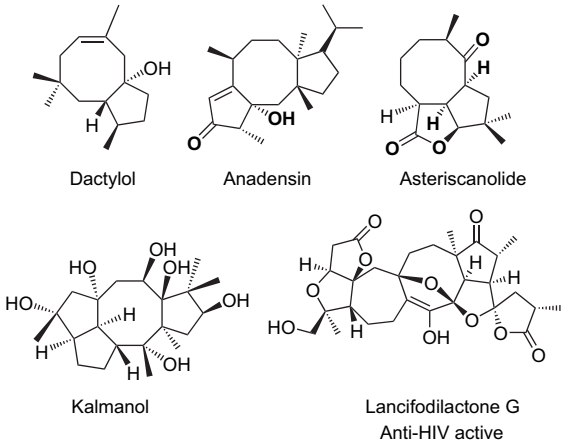

Figure 1. Some of the biologically active cyclooctanoids.

Keywords: [6+3] Cycloaddition; Diels–Alder reaction; Luche reduction; Hydrogenation; Oxa-bridged fused cyclooctanoids.
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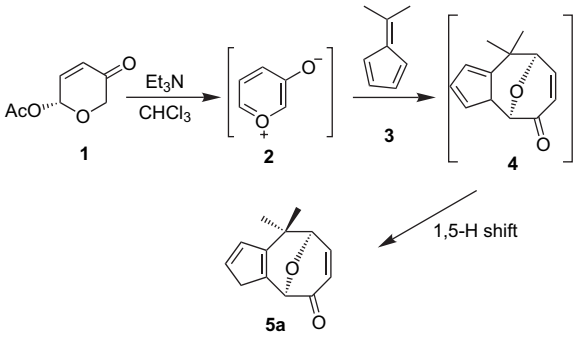
doi:10.1016/j.tet.2006.09.102

We have recently reported a facile [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines leading to the formation of 5–8 fused oxa-bridged cyclooctanoids (Scheme 1).[8] The [6+3] adducts obtained by the present methodology contain an α,β-unsaturated ketone, an oxa-bridge and a cyclopentadiene functionality, which make these adducts potentially amenable to a number of synthetic transformations. In addition, depending on the type of fulvene and 3-oxidopyrylium betaine used, manipulations can also be carried out in the eight-membered ring. We have carried out synthetic transformations of the adduct obtained by the above methodology with an aim to show the synthetic utility of the reaction and our results are described in this communication.



Scheme 1.

2. Results and discussion

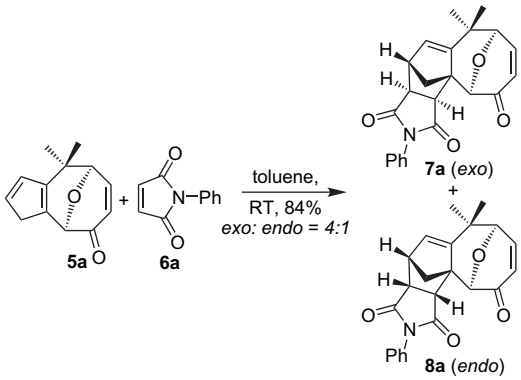
Our investigations involved the synthetic transformations of the [6+3] adduct **5a** in order to check the feasibility of the novel methodology. We have carried out transformations at three points in the molecule viz the cyclopentadiene part, α,β-unsaturated ketone functionality and at the stereocentre in the eight-membered ring corresponding to the C-6 substituent in the fulvene.

2.1. Synthetic transformations in the cyclopentadiene part

The cyclopentadiene part of **5a** can undergo cycloaddition reactions with a variety of partners and the adducts obtained can be synthetically manipulated as per our target. Keeping this aim in mind, at first we carried out the Diels–Alder cycloaddition reactions of the adduct with some selected dienophiles. The reaction of [6+3] adduct **5a** with *N*-phenyl maleimide **6a** in toluene at rt proceeded smoothly affording a 4:1 mixture of *exo* and *endo* adducts **7a** and **8a**, respectively, in 84% yield (Scheme 2).

The structure assigned to the products **7a** and **8a** was supported by spectral analysis. Finally the structure of the adducts was unambiguously proved by the single crystal X-ray analysis of *exo* adduct **7a** (Fig. 2).[9]

Similar reactivity was observed with other selected dienophiles and the results are summarized in Table 1. These results show that the 5–8 fused cyclooctanoid having the cyclopentadiene moiety can undergo facile [4+2]



Scheme 2.

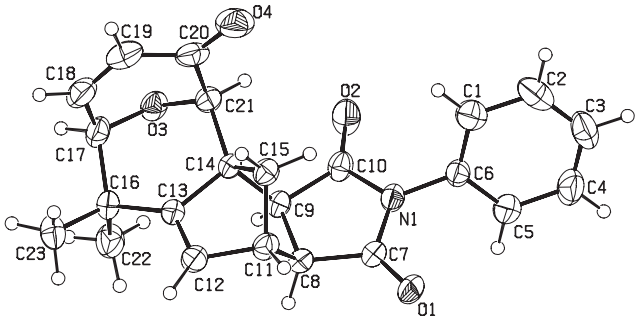
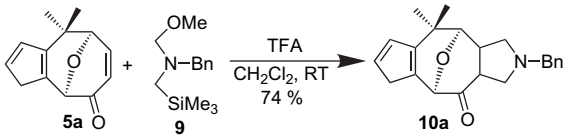


Figure 2. ORTEP plot for X-ray crystal structure of **7a**.

cycloaddition with a variety of dienophiles. In the case of **6c**, only the *exo* adduct was isolated; the *endo* adduct was found to decompose during purification. The reaction of **6e** with **5a** afforded an inseparable mixture of **7e** and **8e** in 3:1 ratio. The adducts obtained are potentially amenable to a number of synthetic transformations and can be manipulated to cyclooctanoid molecules of biological significance.

2.2. Chemistry of the α,β-unsaturated carbonyl part

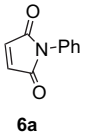
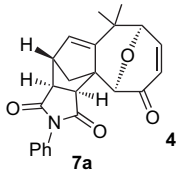
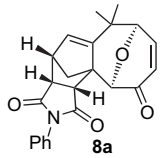
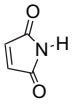
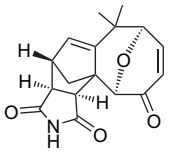
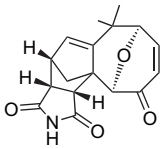
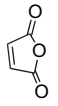
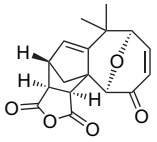
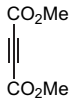
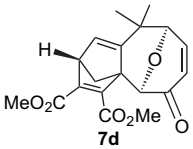
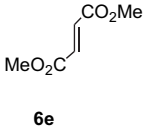
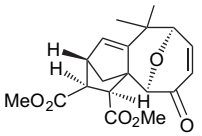
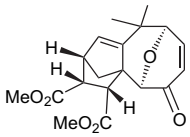
The α,β-unsaturated carbonyl group of the eight-membered ring is an easily functionalizable part and it is possible to add a new carbocyclic or heterocyclic ring to the molecule through appropriate transformations. Along this line, we have carried out the dipolar cycloaddition of the azomethine ylide[10] generated from *N*-methoxy methyl *N*-(trimethylsilylmethyl)benzylamine in the presence of trifluoroacetic acid. The reaction afforded the 5–8–5 fused system **10a** in 74% yield by selective reaction at the α,β-unsaturated ketone (Scheme 3).



Scheme 3.

The reaction was carried out with **5b** and **5c** and similar results were obtained (Table 2). The products **10a–c** have a unique 5–8–5 fused system, which can be manipulated

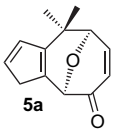
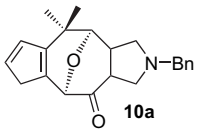
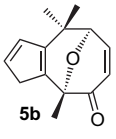
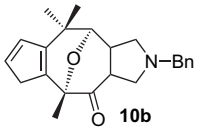
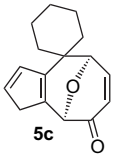
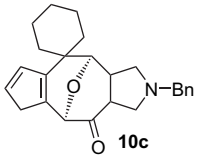
Table 1. [4+2] Cycloaddition of [6+3] adduct **5a** with some selected dienophiles

Dienophile	Products		Yield (%)
	exo Adduct	*endo* Adduct	
 **6a**	 **7a** 4 : 1	 **8a**	84
 **6b**	 **7b** 3.2 : 1	 **8b**	64
 **6c**	 **7c**		64
 **6d**	 **7d**		70
 **6e**	 **7e** 3 : 1	 **8e**	81

Reaction conditions: [6+3] adduct (1.0 equiv), dienophile (1.2 equiv), toluene, 50 °C, 8 h.

further towards bioactive molecules. By selecting a three carbon dipole such as oxyallyl cation or TMM, the corresponding 5–8–5 system analogous to the natural product kalmanol[11] (see Fig. 1) can be synthesized.

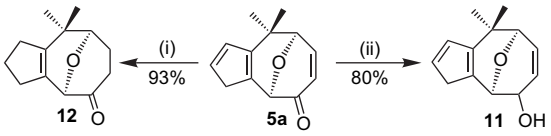
Table 2. Azomethine ylide addition to [6+3] cycloadduct

Entry	[6+3] Adduct	Product	Yield (%)
1	 **5a**	 **10a**	74
2	 **5b**	 **10b**	78
3	 **5c**	 **10c**	76

Reaction conditions: [6+3] adduct (1.0 equiv), **9** (1.2 equiv), TFA (catalytic), CH_2Cl_2, RT, 3 h.

2.3. Selective reduction

Luche reduction[12] of **5a** afforded the allylic alcohol **11** in 80% yield. The allylic alcohol **11** can be appropriately functionalized to the cyclooctanoid target of interest. On hydrogenation of **5a** over Pd/C at 1 atm, two disubstituted double bonds got reduced affording the product **12** with a tetrasubstituted double bond. The above transformations are illustrated in Scheme 4.

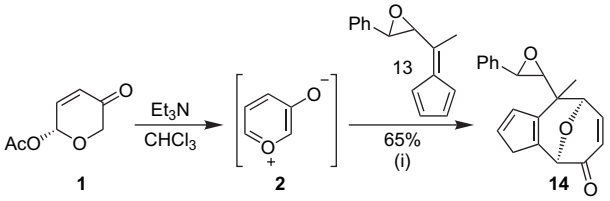


Scheme 4. (i) H_2 (1 atm), Pd–C (catalytic), ethyl acetate, rt, 6 h; (ii) $NaBH_4$ (3 equiv), 0.4 M Ce^{3+} in MeOH, rt, 4 h.

It is to be noted that the olefinic part of **12** can be readily opened leading to a 11-membered molecule analogous to that of neodolabelline natural products.[13]

2.4. Synthetic manipulations through C-6 functionalized fulvenes

We have also utilized functionalized fulvenes for the [6+3] cycloaddition with pyrylium betaines. The cycloaddition of 6-epoxyphenyl-6-methyl fulvene **13** with 3-oxidopyrylium betaine **2** afforded **14** in 66% yield (Scheme 5). The epoxide functionality of **14** can be opened with appropriate nucleophiles towards molecules similar to asteriscanolide (see Fig. 1).[14]



Scheme 5. (i) Fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

3. Conclusions

In conclusion, we have shown that 5–8 fused oxa-bridged molecules, obtained through [6+3] cycloaddition of fulvenes with 3-oxidopyrylium betaines, can be easily functionalized towards the synthesis of cyclooctanoid molecules of interest. The carbon framework of the molecules can be expanded directly from the product, thus enhancing the synthetic versatility of the products and these can act as key intermediates in the synthesis of fused cyclooctanoid natural products. It is presumed that by using appropriately functionalized fulvenes and oxidopyrylium betaines, the present methodology can be utilized in the synthesis of cyclooctanoid natural products. It is to be noted that some of the naturally occurring oxa-bridged cyclooctanoids, lancifodilactones, exhibit interesting biological activity such as cytotoxicity and anti-HIV activity.[15] In this context and in the general importance of fused cyclooctanoids, the methodology is very promising

and may lead to novel biologically active synthetic molecules. We have also shown that the 5–8 fused cyclooctanoid products are versatile molecules having multiple points for functionalization and can be synthetically manipulated easily. Further work along this line is in progress.

4. Experimental

4.1. General

All reactions were carried out in oven dried glassware under nitrogen atmosphere. Progress of the reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light or by staining with Enholm yellow solution. Column chromatography was done using 100–200 mesh silica gel and appropriate mixtures of petroleum ether (60–80 °C) and ethyl acetate for elution. The solvents were removed using a Buchi rotary evaporator. The IR spectra were recorded on Nicolet FT-IR spectrometer. NMR spectra were recorded on a Bruker FT-NMR spectrometer using $CDCl_3$ or $CDCl_3$–CCl_4 mixture (7:3) as solvent. TMS was used as internal standard and chemical shifts are in δ-scale. High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. Abbreviations used in ^{1}H NMR are: s, singlet; t, triplet; q, quartet and m, multiplet.

4.2. General procedure for the synthesis of compounds 7a–e and 8a–e

Dimethyl fulvene (250 mg, 2.36 mmol), pyranulose acetate (441.8 mg, 2.86 mmol) and dry triethylamine (285.8 mg, 2.86 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 5% ethyl acetate–hexane mixture as eluent to afford the [6+3] cycloadduct **5a** as a pale yellow crystalline solid (350 mg, 74%). The cycloadduct (100 mg, 0.50 mmol) was then treated with dienophile (0.55 mmol) in toluene at 50 °C in a Schlenk tube and stirred under nitrogen for 8 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue when subjected to chromatography on a silica gel (60–120 mesh) column using ethyl acetate–hexane mixture as eluent afforded the products in good yield.

4.2.1. Data for compounds 7a and 8a, total yield 84% (ratio 7a/8a=4:1).

4.2.1.1. Compound 7a. Colourless crystalline solid. Mp=232–234 °C. R_f (50% EtOAc–hexane) 0.47. IR (KBr) ν_{max}: 2959, 1776, 1708, 1498, 1376, 1187, 1067, 934, 866, 725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.28 (m, 5H), 7.11 (dd, 1H, J_1=4.2 Hz, J_2=10.6 Hz), 6.18 (d, 1H, J=2.8 Hz), 6.10 (d, 1H, J=10.6 Hz), 5.22 (s, 1H), 4.12 (d, 1H, J=3.7 Hz), 3.32 (s, 1H), 3.11 (d, 1H, J=6.8 Hz), 2.94 (d, 1H, J=7.23 Hz), 1.43 (m, 4H), 1.15 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 175.9, 149.7, 131.5, 129.2, 128.8, 126.6, 126.5, 75.4, 74.9, 53.1, 50.5, 48.0, 44.8, 43.9, 39.5, 30.3, 24.1. HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO_4$: 375.1471. Found: 375.1476. Anal. Calcd for $C_{23}H_{21}NO_4$: C 73.58, H 5.64, N 3.73. Found: C 73.69, H 5.57, N 4.05.

4.2.1.2. Compound 8a. Colourless crystalline solid. Mp=82–85 °C. R_f (50% EtOAc–hexane) 0.36. IR (KBr) ν_{max}: 2974, 2928, 1774, 1712, 1501, 1377, 1176, 1068, 929, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.17 (m, 5H), 7.03 (dd, 1H, J_1=4.2 Hz, J_2=10.5 Hz), 6.13 (d, 1H, J=2.8 Hz), 6.00 (d, 1H, J=10.5 Hz), 4.75 (s, 1H), 4.00 (d, 1H, J=4.0 Hz), 3.55–3.50 (m, 1H), 3.33 (d, 2H, J=7.9 Hz), 1.44–1.31 (m, 1H), 1.25–1.17 (m, 1H), 1.09 (s, 3H), 1.06 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 175.9, 175.1, 152.5, 150.5, 129.5, 129.0, 128.4, 126.2, 126.1, 79.1, 76.3, 56.6, 54.7, 52.1, 48.8, 43.5, 39.1, 30.1, 25.6. HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO_4$: 375.1471. Found: 375.1478.

4.2.2. Data for compounds 7b and 8b, total yield 64% (ratio 7b/8b=3.2:1).

4.2.2.1. Compound 7b. Pale yellow viscous liquid. R_f (50% EtOAc–hexane) 0.30. IR (KBr) ν_{max}: 3232, 2922, 2855, 1715, 1468, 1339, 1270, 1190, 1102, 932 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.12 (dd, 1H, J_1=4.3 Hz, J_2=10.5 Hz), 6.13–6.08 (m, 2H), 5.17 (s, 1H), 4.11 (d, 1H, J=4.1 Hz), 3.23 (s, 1H), 3.00 (d, 1H, J=7.0 Hz), 2.83 (d, 1H, J=6.9 Hz), 1.45 (d, 1H, J=10.2 Hz), 1.38 (s, 3H), 1.16 (s, 3H), 1.10 (d, 1H, J=10.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 177.8, 177.2, 153.1, 149.9, 130.9, 126.1, 75.1, 74.5, 52.0, 51.6, 49.0, 43.8, 43.6, 29.9, 23.8. HRMS (EI) *m/z* calcd for $C_{17}H_{17}NO_4$: 299.1158. Found: 299.1168.

4.2.2.2. Compound 8b. Pale yellow solid. Mp=231–233 °C. R_f (50% EtOAc–hexane) 0.29. IR (KBr) ν_{max}: 3227, 2979, 2876, 1769, 1712, 1686, 1351, 1192, 1068, 929 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.06 (dd, 1H, J_1=4.2 Hz, J_2=10.5 Hz), 6.05–5.97 (m, 2H), 4.66 (s, 1H), 4.03 (d, 1H, J=3.4 Hz), 3.41–3.36 (m, 1H), 3.14–3.11 (m, 2H), 1.45 (d, 1H, J=8.9 Hz), 1.25 (d, 1H, J=8.9 Hz), 1.23 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 176.8, 150.7, 148.4, 129.9, 125.6, 76.3, 75.7, 56.2, 55.4, 53.3, 49.5, 44.2, 43.5, 27.8, 22.6. HRMS (EI) *m/z* calcd for $C_{17}H_{17}NO_4$: 299.1158. Found: 299.1176.

4.2.3. Data for compound 7c. Pale yellow solid. Mp=247–249 °C. R_f (30% EtOAc–hexane) 0.14. IR (KBr) ν_{max}: 2974, 2938, 1779, 1687, 1498, 1223, 1083, 918, 862 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (dd, 1H, J_1=4.2 Hz, J_2=10.6 Hz), 6.15 (d, 1H, J=2.6 Hz), 6.08 (d, 1H, J=10.6 Hz), 4.99 (s, 1H), 4.11 (d, 1H, J=3.9 Hz), 3.33 (s, 1H), 3.27 (d, 1H, J=7.4 Hz), 3.11 (d, 1H, J=7.4 Hz), 1.36 (d, 1H, J=8.6 Hz), 1.35 (s, 3H), 1.16 (s, 3H), 1.13 (d, 1H, J=8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 173.5, 151.7, 149.8, 130.6, 125.1, 74.2, 73.5, 50.4, 48.9, 44.4, 43.9, 41.8, 29.3, 28.8, 22.9. HRMS (EI) *m/z* calcd for $C_{17}H_{16}O_5$: 300.0998. Found: 300.0970.

4.2.4. Data for compound 7d. Pale yellow solid. Mp=110–112 °C. R_f (30% EtOAc–hexane) 0.20. IR (KBr) ν_{max}: 2953, 2866, 1717, 1634, 1434, 1279, 1212, 1114, 1063, 1021 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (dd, 1H, J_1=4.3 Hz, J_2=10.5 Hz), 6.46 (d, 1H, J=2.9 Hz), 5.98 (d, 1H, J=10.5 Hz), 4.86 (s, 1H), 4.01 (d, 1H, J=3.9 Hz),

3.77 (s, 3H), 3.71 (d, 1H, J=4.3 Hz), 3.67 (s, 3H), 2.18 (d, 1H, J=6.9 Hz), 1.54 (d, 1H, J=6.9 Hz), 1.16 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 165.8, 164.3, 158.9, 155.3, 150.5, 149.2, 134.4, 126.2, 75.8, 72.2, 60.5, 52.5, 52.3, 49.5, 39.9, 29.4, 24.3. HRMS (EI) m/z calcd for $C_{19}H_{20}O_6$: 344.1260. Found: 344.1226.

4.2.5. Data for compounds 7e and 8e, *exo* and *endo* (3:1). Pale yellow viscous liquid. R_f (30% EtOAc–hexane) 0.23. IR (KBr) ν_{max}: 2953, 2871, 1738, 1702, 1434, 1382, 1259, 1068, 1017, 929, 867 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (dd, 1H, J_1=4.3 Hz, J_2=10.5 Hz), 6.05 (d, 1H, J=10.5 Hz), 5.91 (d, 1H, J=2.5 Hz), 4.33 (s, 1H), 4.07 (d, 1H, J=4.1 Hz), 3.80 (s, 3H), 3.65 (s, 3H), 3.44 (t, 1H, J=4.1 Hz), 3.16–3.10 (m, 2H), 1.83 (d, 1H, J=9.1 Hz), 1.42 (s, 3H), 1.13 (s, 3H), 0.94 (d, 1H, J=9.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 172.9, 172.8, 152.0, 149.9, 147.1, 129.4, 125.9, 123.0, 75.5, 52.1, 52.0, 51.7, 49.1, 47.1, 43.9, 39.1, 30.1, 23.8. HRMS (EI) m/z calcd for $C_{19}H_{22}O_6$: 346.1416. Found: 346.1421.

4.3. Typical procedure for the synthesis of compounds 10a–c

The cycloadduct **5a** (100 mg, 0.50 mmol) and *N*-methoxy methyl *N*-(trimethylsilylmethyl)benzylamine (130.6 mg, 0.55 mmol) were taken in anhydrous dichloromethane and cooled to 0 °C. A catalytic quantity of TFA was added and the mixture was stirred under an argon atmosphere for 4 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 20% ethyl acetate–hexane mixture as eluent to afford the product **10a** as a colourless viscous liquid (124 mg, 74%).

4.3.1. Data for compound 10a. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.58. IR (KBr) ν_{max}: 2964, 2917, 2799, 1717, 1568, 1449, 1367, 1078, 1022, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.16 (m, 5H), 6.39 (d, 1H, J=5.2 Hz), 6.29 (d, 1H, J=5.2 Hz), 4.54 (s, 1H), 3.54 (d, 1H, J=5.2 Hz), 2.99–2.85 (m, 5H), 2.74–2.68 (m, 4H), 2.46–2.41 (m, 1H), 1.29–1.19 (m, 3H), 1.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 148.4, 134.1, 130.4, 129.6, 129.1, 128.6, 127.6, 126.1, 79.2, 78.7, 76.4, 60.4, 55.5, 43.8, 40.7, 39.8, 30.4, 24.6, 23.7. HRMS (FAB) m/z calcd for $C_{22}H_{25}NO_2$: 335.1885. Found (M+1): 335.95.

4.3.2. Data for compound 10b. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.61. IR (KBr) ν_{max}: 2958, 2929, 2798, 1719, 1674, 1498, 1455, 1372, 1255, 1095, 1027, 856 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.12 (m, 5H), 6.43–6.14 (m, 2H), 3.72–3.51 (m, 3H), 2.96–2.88 (m, 5H), 2.73–2.65 (m, 3H), 1.48 (s, 3H), 1.39–1.19 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1, 148.0, 133.8, 130.3, 128.8, 128.6, 128.3, 128.1, 127.3, 127.2, 126.7, 79.5, 79.1, 60.1, 59.7, 59.4, 55.5. HRMS (FAB) m/z calcd for $C_{23}H_{27}NO_2$: 349.2042. Found (M+1): 350.19.

4.3.3. Data for compound 10c. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.67. IR (KBr) ν_{max}: 2930, 2858, 1718, 1671, 1454, 1375, 1185, 1151, 1080, 968 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–6.89 (m, 5H), 6.49–6.10 (m, 2H), 4.12 (d, 1H, J=4.8 Hz), 3.63–3.55 (m, 2H), 3.35–3.32 (m, 3H), 3.16–2.78 (m, 4H), 2.57–2.54 (m, 2H), 1.41–1.24 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.7, 133.4, 130.5, 129.3, 128.9, 128.6, 128.3, 128.2, 127.3, 76.9, 75.9, 72.9, 71.8, 60.1, 59.9, 55.1, 53.9, 49.7, 43.3, 40.5, 32.0, 29.3, 25.6, 22.4, 21.9. HRMS (FAB) m/z calcd for $C_{25}H_{29}NO_2$: 375.2198. Found (M+1): 376.22.

4.4. Typical procedure for the synthesis of 11

The cycloadduct **5a** (100 mg, 0.50 mmol) was dissolved in 0.4 M ceric nitrate solution in methanol and cooled to 0 °C. A stoichiometric amount of $NaBH_4$ (56.7 mg, 1.5 mmol) was added and the mixture was allowed to stir for 5 h at rt. The reaction mixture was quenched with water, the solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 30% ethyl acetate–hexane mixture as eluent to afford the product **11** as a colourless viscous liquid (82 mg, 80%).

4.4.1. Data for compound 11. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.32. IR (KBr) ν_{max}: 3412, 2964, 2907, 1624, 1383, 1274, 1171, 1073, 976, 914, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (d, 1H, J=4.2 Hz), 6.39 (d, 1H, J=4.2 Hz), 5.89–5.86 (d, 1H, J=10.5 Hz), 5.68–5.63 (d, 1H, J=10.4 Hz), 4.69 (d, 1H, J=6.0 Hz), 4.63 (s, 1H), 3.93 (d, 1H, J=1.5 Hz), 3.26–2.89 (m, 2H), 1.29 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 133.1, 131.7, 130.0, 129.3, 128.1, 75.9, 71.3, 67.0, 43.1, 38.8, 28.2, 23.4. HRMS (EI) m/z calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1002.

4.5. Typical procedure for the synthesis of 12

The cycloadduct **5a** (100 mg, 0. 50 mmol) was dissolved in anhydrous ethyl acetate. A catalytic amount of Pd–C (10%) was added and the reaction mixture was stirred under H_2 atmosphere at rt. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 10% ethyl acetate–hexane mixture as eluent to afford the product as a white crystalline solid (96 mg, 93%).

4.5.1. Data for compound 12. Colourless crystalline solid. Mp=107–110 °C R_f (50% EtOAc–hexane) 0.71. IR (KBr) ν_{max}: 2959, 2854, 1727, 1459, 1363, 1243, 1070, 1052, 888 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (s, 1H), 3.93–3.88 (m, 1H), 2.73–2.65 (m, 2H), 2.39–2.31 (m, 4H), 1.84–1.91 (m, 4H), 1.25 (d, 3H, J=5.4 Hz), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.3, 142.3, 129.1, 82.6, 75.1, 37.8, 35.3, 33.7, 31.5, 27.1, 22.7, 21.6, 21.1. HRMS (EI) m/z calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1330.

4.6. Typical procedure for the synthesis of 14

6-Epoxyphenyl-6-methyl fulvene (100 mg, 0. 48 mmol), pyranulose acetate (89.9 mg, 0.58 mmol) and dry triethylamine (58.6 mg, 0.58 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure

and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 5% ethyl acetate–hexane mixture as eluent to afford the product as a pale yellow viscous liquid (96 mg, 65%).

4.6.1. Data for compound 14. Yield 65%, pale yellow viscous liquid. IR (KBr) ν_{max}: 3067, 2928, 1690, 1610, 1497, 1376, 1246, 1158, 1066, 1012, 978 cm^{-1}. ^1H NMR: δ 1.30 (s, 3H), 2.95 (m, 2H), 3.69 (d, 1H, J=1.92 Hz), 3.77 (d, 1H, J=1.92 Hz), 4.64 (d, 1H, J=5.59 Hz), 4.81 (s, 1H), 5.99 (d, 1H, J=10.47 Hz), 6.38 (d, 2H, J=3.72 Hz), 6.95 (m, 1H), 7.32–7.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.2, 146.3, 137.1, 133.7, 133.6, 130.5, 129.3, 128.5, 128.1, 125.8, 125.6, 124.7, 124.6, 73.1, 68.5, 67.7, 56.1, 40.9, 29.3, 16.1. HRMS (EI) *m/z* calcd for $C_{20}H_{18}O_3$: 306.1256. Found: (M+) 306.1274.

Acknowledgements

K.S.K thank Council of Scientific and Industrial Research (CSIR), New Delhi for research fellowship. The authors thank Dr. R. Luxmi Varma, Ms. S. Viji, Ms. Soumini Mathew and Mr. Thirumalai Kumaran for the NMR and high-resolution mass spectral analyses. Thanks are due to CSIR, New Delhi for financial assistance [Task force project-CMM-005 on specialty chemicals].

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Tetrahedron 62 (2006) 12351–12356

A new access to quinazolines from simple anilines

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Received 21 July 2006; revised 5 September 2006; accepted 28 September 2006
Available online 25 October 2006

Abstract—A new synthetic pathway to quinazolines is described. This new method uses hexamethylenetetramine in TFA and potassium ferricyanide in aqueous ethanolic KOH, starting from simple *N*-protected anilines. The method affords substituted quinazolines with high selectivities and good yields, reducing reaction-time and work-up operations.

1. Introduction

In the last few years, we have been interested in synthesizing benzoquinazolinic derivatives in search of new antiproliferative drugs. The interest in the quinazolinic structure, due to its wide range of biological activities,[1] led to a number of different synthetic pathways to access this nucleus (e.g., Niementowski's synthesis,[2] Bischler's synthesis,[3] and Riedel's synthesis).[4] However, all these methods suffer from the disadvantage that the starting naphthylamines need an appropriate *ortho* functional group in order to cyclize to the pyrimidine ring of the quinazoline nucleus.

During our studies we found a novel ring closure of the benzoquinazoline system starting from simple naphthylamines.[5] This new synthetic approach consisted in reacting the appropriate *N*-protected α-naphthylamines or β-naphthylamines with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA), followed by treatment with potassium ferricyanide in aqueous ethanolic potassium hydroxide to give, respectively, benzo[*f*]quinazoline or benzo[*h*]quinazoline in good yield. The final products were achieved via the corresponding dihydrobenzoquinazoline intermediates, which were directly reacted with the oxidizing agent without intermediate isolation.

This method represents a new improved and straightforward route to the benzoquinazoline nucleus. To expand the scope of this method in order to access new heterocyclic scaffolds, in this paper we also describe further investigations on simple anilines to find an efficient synthetic route to quinazolines. Particular attention was paid to study the various parameters of this new synthetic strategy in order to standardize the reaction conditions.

2. Results and discussion

To verify if the HMTA/TFA/$K_3Fe(CN)_6$ method could have widespread application and to set up standard reaction conditions, *N*-protected anilines were chosen as starting products. The protection of the amino group is necessary because it is well known that aromatic amines treated with HMTA in TFA gave only Tröger's bases.[6] As a general procedure, the *N*-protected aniline was treated with HMTA in TFA, and then directly refluxed in aqueous ethanolic potassium hydroxide with potassium ferricyanide.

In order to investigate reaction conditions avoiding *para* formylation, 4-methylaniline was chosen as reference compound: in fact, as reported in the literature,[7] aniline itself undergoes only *para* formylation. Even the HMTA/TFA/$K_3Fe(CN)_6$ method runs through an initial formylation step,[5] but this must occur at the *ortho*-position in order to achieve the desired pyrimidine annulation. In fact the reaction mechanism involves aminomethylation at both the *ortho*-position and the nitrogen atom of the carbamoyl group. The successive dehydrogenation of *ortho*-aminomethyl to aldimino group promotes an intramolecular cyclization to dihydropyrimidine ring. Finally oxidative dehydrogenation of the dihydropyrimidine derivative affords the desired quinazoline (Scheme 1).

To constrain *ortho* formylation and then pyrimidine ring closure, 4-methylaniline (**1a**) was first tested with the amino

Keywords: Quinazoline; Synthesis; Substituent effects.
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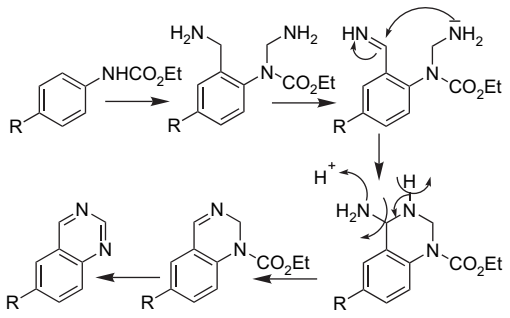
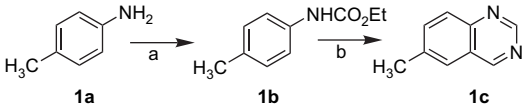
doi:10.1016/j.tet.2006.09.103



Scheme 1. Proposed reaction mechanism.

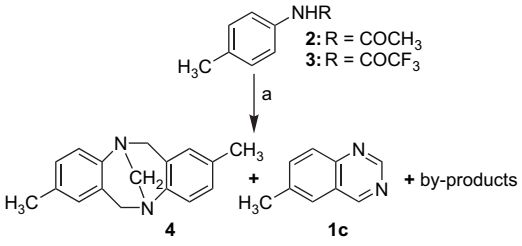
group protected as an ethyl carbamate. Thus, the *N*-protected 4-methylaniline (**1b**) gave 6-methylquinazoline (**1c**) in good yield (49%) (Scheme 2).



Scheme 2. Reagents and conditions: (a) $ClCO_2Et$, THF, 98% and (b) (1) HMTA, TFA and (2) KOH aqueous EtOH, $K_3Fe(CN)_6$, 49%.

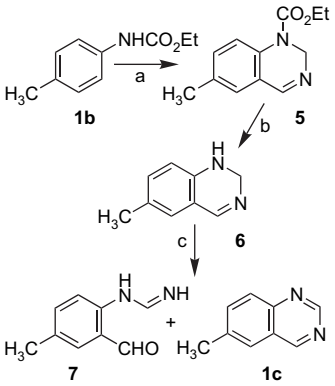
The reaction was even attempted with different protecting groups on the amino function and different acid conditions to evaluate their influence on the reaction course.

If the amino group was protected as an acetyl or trifluoroacetyl (**2** and **3**), the HMTA/TFA/$K_3Fe(CN)_6$ reaction afforded a complex mixture, in which the quinazoline **1c** was present in low concentration together with the Tröger's base **4** and other unidentified by-products (Scheme 3). In this case, the acid hydrolysis of the protecting groups became competitive with cyclization: the portion of still protected molecules yielded the final quinazoline, while the portion of deprotected molecules gave rise to the Tröger's base and other unidentified by-products.



Scheme 3. Influence of N-protection on reaction products (A). Reagents and conditions: (a) (1) HMTA, TFA and (2) KOH aqueous EtOH, $K_3Fe(CN)_6$.

On the other hand, the ethyl carbamate group is stable in TFA in such a way to afford the *N*-protected dihydroquinazoline intermediate from which the final quinazoline is derived. Hence, the stability of the *N*-protected intermediate is crucial for the quinazoline formation: in our hypothesis, the intermediate arising from N-deprotection is not stable in acid conditions, owing to the hydrolysis of the imine bond, and does not survive long enough to be aromatized to the quinazoline nucleus. To prove this hypothesis, compound **1b** was reacted with HMTA in TFA and the stable intermediate **5** was hydrolyzed in alkaline medium to dihydroquinazoline **6**, immediately isolated from the reaction mixture and kept in toluene solution, due to its high instability (Scheme 4).



Scheme 4. Influence of N-protection on reaction products (B). Reagents and conditions: (a) HMTA, TFA, 80%; (b) KOH aqueous, 92%; and (c) AcOH, 13% (**7**) and 13% (**1c**).

Compound **6** in acid solution was converted into a mixture of the quinazoline **1c** and formamidine **7**: compound **1c** derived from spontaneous oxidation of **6**,[8] while compound **7** derived from the hydrolysis of the imine bond of dihydropyrimidine ring.[9] Therefore, to avoid undesired side reactions, it is essential that the amino group of the starting anilines remained protected until the aromatization step: this condition is satisfied only when ethyl carbamate, stable in the strong acid conditions needed for the initial cyclization step, is used.

The influence of different acid conditions on the HMTA/TFA/$K_3Fe(CN)_6$ reaction was also studied. Performing the reaction in acetic acid or in a mixture of formic and acetic acids, no reaction occurred, while in methanesulfonic acid, the reaction afforded the same complex mixture as observed with acyl as the protecting group (Scheme 3). This fact was ascribed to the strength of the acid medium, which causes partial hydrolysis of the amino protection. Even diluting methanesulfonic acid with another acid (e.g., acetic acid), a complex mixture was obtained, while dilution with a solvent (e.g., THF) led to no reaction.

Using TFA in lower quantity, the reaction did not reach completion, while dilution with solvent led to no reaction.

Finally, the reaction was attempted even on compound **1a**, but, as expected,[6] in TFA only the Tröger's base **4** was isolated, while in acetic acid a mixture of the quinazoline **1c** and formamidine **7** was obtained, demonstrating that intermediate **6** could be formed but is not stable in acid conditions.

Various *N*-carbethoxy anilines were submitted as starting materials to the HMTA/TFA/$K_3Fe(CN)_6$ synthetic pathway to test its applicability.

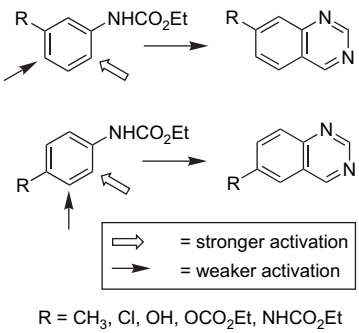
The course of the reaction and the obtained products depend on the starting aniline: in fact, in this study we worked with anilines substituted with activating and deactivating groups in order to understand their influence on reactivity and orientation.

If starting anilines have position 4 substituted with *ortho*/*para*-directing groups (such as methyl, methoxy, chloro, and amino groups), the quinazoline nucleus was obtained in moderate to good yields. For example, the *N*-protected 4-methylaniline (**1b**), 4-chloroaniline (**8b**), 4-methoxyaniline (**9b**), and 4-*O*-carbethoxyaniline (**10b**) gave, respectively, 6-methyl (**1c**), 6-chloro (**8c**), 6-methoxy (**9c**), and 6-hydroxyquinazoline (**10c**) (Scheme 2 and Table 1, entries 1–3). In particular compound **10b**, in which both amino and hydroxyl groups were protected with ethyl chloroformiate, gave only 6-hydroxyquinazoline with deprotection of the hydroxyl function during the oxidative step (entry 3), while compound **11b** carrying only N-protection led to a complex reaction mixture (entry 4). Moreover, it was observed that in the case of 1,4-phenylendiamine (**12a**), despite the presence of two amino functions, only one pyrimidine ring was formed to give 6-aminoquinazoline (**12c**) (Table 1, entry 5).

As expected, if starting anilines have position 4 substituted with deactivating groups, such as nitro or carboxylic groups, no reaction was observed (Table 1, entries 6 and 7).

The influence of methoxy or amino substitution on position 3 of aniline was also tested: even if the *para* position was free, only quinazoline formation was observed, probably due to the activation of the *para* position in the respect of the 3-substituent. From *N*-protected 3-methoxyaniline (**15b**), *N*,*N*′-diprotected 1,3-phenylenediamine (**16b**), and *N*,*N*′-diprotected 2-methyl-1,3-phenylenediamine (**17b**), respectively, 7-methoxy (**15c**), 7-aminoquinazoline (**16c**), and 7-amino-8-methylquinazoline (**17c**) were obtained (Table 1, entries 8–11). In particular, no trace of the isomeric 5-aminoquinazoline was recovered in the reaction mixture of entry 9, so proving the regioselectivity of pyrimidine annulation. This high regioselectivity was again observed in the presence of further substituents: when the reaction was carried out on *N*,*N*′-diprotected 1,3-phenylenediamines susbstituted in 4 position with methyl group (**18b**), and methoxy group (**19b**), only 7-amino-6-methylquinazoline (**18c**), and 7-amino-6-methoyquinazoline (**19c**) were achieved without traces of the other two possible quinazoline isomers (Table 1, entries 11 and 12). This last observation demonstrates the selectivity of the reaction toward the *para* position with respect to the second amino group, and/or a steric hindrance exerted by the *meta* substituent.

The effect of aniline substituents on the reaction course is summarized in Scheme 5.

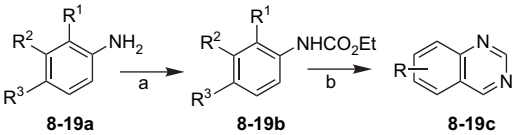


Scheme 5. Effect of aniline substituents.

3. Conclusions

We report further investigations on a versatile and improved method[5] for the synthesis of substituted quinazoline derivatives to verify its general applicability. This new method uses HMTA in TFA and potassium ferricyanide in aqueous ethanolic KOH, starting from anilines with the amino group protected as an ethyl carbamate, without isolating reaction intermediates. Both *N*-ethoxycarbonyl protection and TFA are crucial to the success of the reaction. Various 6- and 7-substituted quinazolines were obtained in yields higher than that previously reported:[10–14] even when the yields were comparable, the old methods were time and solvent-consuming, running through almost 4–5 steps. Moreover, our method starts from cheaper and easily available starting materials. Finally, three new methyl- or methoxy-7-aminoquinazoline was synthesized. This novel method afforded

Table 1. Reaction products[a]



Entry	Starting amine				Intermediate carbamate				Product		Yield
	R^1	R^2	R^3		R^1	R^2	R^3				
1	H	H	Cl	**8a**	H	H	Cl	**8b**	6-Chloroquinazoline	**8c**	15
2	H	H	OCH_3	**9a**	H	H	OCH_3	**9b**	6-Methoxyquinazoline	**9c**	19
3	H	H	OH	**10a**	H	H	OCO_2Et	**10b**	6-Hydroxyquinazoline	**10c**	24
4	H	H	OH	**11a**	H	H	OH	**11b**	Complex mixture		
5	H	H	NH_2	**12a**	H	H	$NHCO_2Et$	**12b**	6-Aminoquinazoline	**12c**	54
6	H	H	NO_2	**13a**	H	H	NO_2	**13b**	No reaction		
7	H	H	COOH	**14a**	H	H	COOH	**14b**	No reaction		
8	H	OCH_3	H	**15a**	H	OCH_3	H	**15b**	7-Methoxyquinazoline	**15c**	22
9	H	NH_2	H	**16a**	H	$NHCO_2Et$	H	**16b**	7-Aminoquinazoline	**16c**	45
10	CH_3	NH_2	H	**17a**	CH_3	$NHCO_2Et$	H	**17b**	7-Amino-8-methylquinazoline	**17c**	38
11	H	NH_2	CH_3	**18a**	H	$NHCO_2Et$	CH_3	**18b**	7-Amino-6-methylquinazoline	**18c**	44
12	H	NH_2	OCH_3	**19a**	H	$NHCO_2Et$	OCH_3	**19b**	7-Amino-6-methoxyquinazoline	**19c**	43

[a] Reagents and conditions: (a) $ClCO_2Et$, THF; (b) (1) HMTA, TFA and (2) KOH aqueous EtOH, $K_3Fe(CN)_6$.

substituted quinazolines with high selectivities and good yields, reducing reaction-time and work-up operations.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp MFB-595-010M melting point apparatus and are uncorrected. Analytical TLC was performed on pre-coated 60 F_{254} silica gel plates (0.25 mm; Merck) developing with a $CHCl_3$/MeOH mixture (9:1). Preparative column chromatography was performed using silica gel 60 (0.063–0.100 mm; Merck), eluting with $CHCl_3$. ^1H NMR spectra were recorded on a Bruker AMX300 spectrometer with TMS as an internal standard. Chemical shift values are reported in parts per million and coupling constants are reported in hertz. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer. HRMS spectra were obtained using an ESI-TOF Mariner 5220 (Applied Biosystem) mass spectrometer with direct injection of the sample and collecting data in the positive ion mode. GC–MS analysis of samples were carried out using a Varian CP-3800 gas chromatograph with a Mass Selective Detector (EI), equipped with an Agilent HP-INNOWax column (30 m length, 0.25 mm I.D., and 0.25 μm film thickness) using helium as carrier gas (1 mL/min) and a temperature program from 100 °C (3 min) to 300 °C (10 °C/min) for a total run length of 28 min. Elemental analyses were performed on a Perkin–Elmer 2400 Analyser and are within ±0.4% of theoretical values.

Analytical data for compounds **1c**,[10] **8c**,[11] **9c**,[10] **10c**,[12] **12c**,[13] **15c**,[10] and **16c**[14] were compared with literature data.

For the synthesis of carbamates **1b** and **8–19b**, and for experiments with different acids, see the Supplementary data.

4.2. General procedures for quinazolines

A mixture of carbamate **1b** or **8–19b** (5 mmol) and HMTA (35 mmol) in TFA (35 mL) was refluxed for 1 h. After cooling, the mixture was diluted with 4 M HCl (200 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in aqueous ethanolic (water/EtOH, 1/1) 10% KOH (300 mL), added of $K_3Fe(CN)_6$ (12.5 g, 38 mmol) and refluxed for 4 h. After cooling, the mixture was diluted with water (300 mL), extracted with organic solvent (see below) (5×100 mL), and the organic phase was evaporated under reduced pressure.

4.2.1. 6-Methylquinazoline (1c). Extraction solvent: toluene; yield: 49%; mp: 62 °C (lit.[10] 62–63 °C); ^1H NMR ($CDCl_3$): δ 9.32 (s, 1H, 4-H), 9.27 (s, 1H, 2-H), 7.95 (d, J=8.6 Hz, 1H, 8-H), 7.76 (dd, J=8.6, 1.8 Hz, 1H, 7-H), 7.69 (d, J=1.8 Hz, 1H, 5-H), 2.58 (s, 3H, CH_3); HRMS (ESI-TOF) for $C_9H_9N_2$ (M^++1): calcd: 145.0760, found: 145.0674. Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.00; H, 5.50; N, 19.50.

4.2.2. 6-Chloroquinazoline (8c). Extraction solvent: toluene; yield: 15%; mp: 137 °C (lit.[11] 143 °C); ^1H NMR ($CDCl_3$): δ 9.36 (s, 1H, 4-H), 9.34 (s, 1H, 2-H), 8.02 (d, J=9.0 Hz, 1H, 8-H), 7.94 (d, J=2.2 Hz, 1H, 5-H), 7.87 (dd, J=9.0, 2.2 Hz, 1H, 7-H); HRMS (ESI-TOF) for $C_8H_6{}^{35}ClN_2$ (M^++1): calcd: 165.0214, found: 165.0197. Anal. Calcd for $C_8H_5ClN_2$: C, 58.38; H, 3.06; Cl, 21.54; N, 17.02. Found: C, 58.34; H, 3.09; Cl, 21.51; N, 17.06.

4.2.3. 6-Methoxyquinazoline (9c). Extraction solvent: cyclohexane; yield: 19%; mp: 71 °C (lit.[10] 71–72 °C); ^1H NMR ($CDCl_3$): δ 9.29 (s, 1H, 4-H), 9.20 (s, 1H, 2-H), 7.94 (d, J=9.2 Hz, 1H, 8-H), 7.56 (dd, J=9.2, 2.8 Hz, 1H, 7-H), 7.13 (d, J=2.5 Hz, 1H, 5-H), 3.95 (s, 3H, OCH_3); HRMS (ESI-TOF) for $C_9H_9N_2O$ (M^++1): calcd: 161.0709, found: 161.0622. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.06; N, 17.52.

4.2.4. 6-Hydroxyquinazoline (10c). After washing with chloroform (3×100 mL), the aqueous solution was neutralized with 1 M HCl, extracted with EtOAc (3×100 mL), and evaporated under reduced pressure. Yield: 24%; mp: 235 °C (lit.[12] 239 °C); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, 4-H), 9.18 (s, 1H, 2-H), 8.14 (d, J=2.5 Hz, 1H, 5-H), 7.99 (d, J=9.1 Hz, 1H, 8-H), 7.61 (dd, J=9.1, 2.5 Hz, 1H, 7-H); HRMS (ESI-TOF) for $C_8H_7N_2O$ (M^++1): calcd: 147.0553, found: 147.0693. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.68; H, 4.17; N, 19.17.

4.2.5. 6-Aminoquinazoline (12c). Extraction solvent: toluene; yield: 54%; mp: 212 °C (lit.[13] 213 °C); ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H, 4-H), 9.13 (s, 1H, 2-H), 7.90 (d, J=9.1 Hz, 1H, 8-H), 7.35 (dd, J=9.1, 2.6 Hz, 1H, 7-H), 6.95 (d, J=2.6 Hz, 1H, 5-H); HRMS (ESI-TOF) for $C_8H_8N_3$ (M^++1): calcd: 146.0713, found: 146.0693. Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.23; H, 4.80; N, 28.97.

4.2.6. 7-Methoxyquinazoline (15c). Extraction solvent: cyclohexane; yield: 22%; mp: 90 °C (lit.[10] 87 °C); ^1H NMR (MeOD-d_4): δ 9.30 (s, 1H, 4-H), 9.10 (s, 1H, 2-H), 7.97 (d, J=9.0 Hz, 1H, 5-H), 7.53 (dd, J=9.0, 2.5 Hz, 1H, 6-H), 7.31 (d, J=2.5 Hz, 1H, 8-H), 4.01 (s, 3H, OCH_3); HRMS (ESI-TOF) for $C_9H_9N_2O$ (M^++1): calcd: 161.0709, found: 161.0699. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.53; H, 5.00; N, 17.50.

4.2.7. 7-Aminoquinazoline (16c). Extraction solvent: toluene; yield: 45%; mp: 190 °C (lit.[14] 190.5–191 °C); ^1H NMR (MeOD-d_4): δ 9.01 (s, 1H, 4-H), 8.84 (s, 1H, 2-H), 7.79 (d, J=8.9 Hz, 1H, 5-H), 7.16 (dd, J=8.9, 2.0 Hz, 1H, 6-H), 6.90 (d, J=2.0 Hz, 1H, 8-H); HRMS (ESI-TOF) for $C_8H_8N_3$ (M^++1): calcd: 146.0713, found: 146.0589. Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.23; H, 4.85; N, 28.92.

4.2.8. 7-Amino-8-methylquinazoline (17c). Extraction solvent: toluene; yield: 38%; mp: 163 °C; ^1H NMR (MeOD-d_4): δ 8.96 (s, 1H, 4-H), 8.90 (s, 1H, 2-H), 7.65 (d, J=8.8 Hz, 1H, 5-H or 6-H), 7.16 (d, J=8.8 Hz, 1H, 5-H or 6-H), 2.43 (s, 3H, CH_3); IR (KBr) 3450, 3370, 3025, 2930, 2865, 1620, 1520, 1490, 1375, 1270, 1145, 1035, 940, 825 cm^{-1}; HRMS (ESI-TOF) for $C_9H_{10}N_3$ (M^++1): calcd: 160.0869, found: 160.0781. Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.94; H, 5.68; N, 26.38.

4.2.9. 7-Amino-6-methylquinazoline (18c). Extraction solvent: toluene; yield: 44%; mp: 175 °C; ^{1}H NMR (DMSO-d_6): δ 9.01 (s, 1H, 4-H), 8.91 (s, 1H, 2-H), 7.64 (s, 1H, 5-H or 8-H), 7.38 (s, 1H, 5-H or 8-H), 2.30 (s, 3H, CH_3); IR (KBr) 3430, 3345, 3030, 2930, 2865, 1625, 1530, 1345, 1235, 1145, 1100, 1015, 950, 845 cm^{-1}; HRMS (ESI-TOF) for $C_9H_{10}N_3$ (M^++1): calcd: 160.0869; found: 160.0912. Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.01; H, 5.67; N, 26.32.

4.2.10. 7-Amino-6-methoxyquinazoline (19c). Extraction solvent: EtOAc; yield: 43%; mp: 163 °C; ^{1}H NMR ($CDCl_3$): δ 9.01 (s, 1H, 4-H), 9.00 (s, 1H, 2-H), 7.07 (s, 1H, 5-H or 8-H), 7.00 (s, 1H, 5-H or 8-H), 4.02 (s, 3H, OCH_3); IR (KBr) 3420, 3395, 3040, 2930, 2865, 1690, 1575, 1490, 1380, 1320, 1235, 1215, 1170, 1025, 905, 835 cm^{-1}; HRMS (ESI-TOF) for $C_9H_{10}N_3O$ (M^++1): calcd: 176.0818, found: 176.0685. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.68; H, 5.22; N, 24.02.

4.3. Synthesis from compounds 2 and 3

A mixture of carbamate **2**[15] or **3**[16] (5 mmol) and HMTA (35 mmol) in TFA (35 mL) was refluxed for 1 h. After cooling, the mixture was diluted with 4 M HCl (200 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in aqueous ethanolic (water/EtOH, 1/1) 10% KOH (300 mL), added with $K_3Fe(CN)_6$ (12.5 g, 38 mmol) and refluxed for 4 h. After cooling, the mixture was diluted with water (300 mL), extracted with toluene (5×100 mL), and the organic phase was evaporated under reduced pressure to give a complex mixture, in which **1c** and Tröger's bases **4** were detectable by NMR analysis: ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, **1c**-4-H), 9.27 (s, 1H, **1c**-2-H), 7.95 (d, J=8.6 Hz, 1H, **1c**-8-H), 7.76 (dd, J=8.6, 1.8 Hz, 1H, **1c**-7-H), 7.69 (d, J=1.8 Hz, 1H, **1c**-5-H), 7.02 (d, J=8.8 Hz, 2H, **4**-3-H and 9-H or 4-H and 10-H), 6.96 (d, J=8.8 Hz, 2H, **4**-3-H and 9-H or 4-H and 10-H), 6.70 (s, 2H, **4**-1-H and 7-H), 4.64 (d, J=16.6 Hz, 2H, **4**-6-H and 12-H), 4.30 (s, 2H, **4**-N–CH_2–N), 4.10 (d, J=16.6 Hz, 2H, **4**-6-H and 12-H), 2.21 (s, 6H, 2H, **4**-2-CH_3 and 8-CH_3), 2.58 (s, 3H, **1c**-CH_3); peak assignment was made by comparison with NMR spectrum of an authentic sample of **4** prepared from literature method.[6]

4.4. Ethyl 6-methyl-2*H*-quinazoline-1-carboxylate (5)

A mixture of **1b** (1.0 g, 5.6 mmol) and HMTA (5.5 g, 39.1 mmol) in TFA (40 mL) was refluxed for 1 h. After cooling, the mixture was diluted with 4 M HCl (200 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in water (200 mL), neutralized with $NaHCO_3$, and extracted with EtOAc (3×100 mL). The organic phase was evaporated under reduced pressure, and the solid was crystallized from cyclohexane to give **5** (0.98 g, 80%). ^{1}H NMR (DMSO-d_6): δ 8.32 (t, J=2.0 Hz, 1H, 4-H), 7.58 (d, J=8.3 Hz, 1H, 8-H), 7.35 (dd, J=8.3, 1.6 Hz, 1H, 7-H), 7.29 (d, J=1.6 Hz, 1H, 5-H), 5.29 (d, J=2.0 Hz, 2H, 2-H), 4.23 (q, J=7.1 Hz, 2H, COOCH_2CH$_3$), 2.35 (s, 3H, CH_3), 1.29 (t, J=7.1 Hz, 3H, COOCH$_2$$CH_3$). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.09; H, 6.42; N, 12.88.

4.5. 6-Methyl-1,2-dihydroquinazoline (6)

A solution of **5** (0.95 g, 4.3 mmol) in 10% KOH (200 mL) was refluxed for 2 h. After cooling, the mixture was extracted with toluene (3×100 mL) and the organic phase was evaporated under reduced pressure to give **6** (0.58 g, 92%). ^{1}H NMR (DMSO-d_6): δ 7.95 (t, J=1.6 Hz, 1H, 4-H), 6.96 (dd, J=8.1, 1.5 Hz, 1H, 7-H), 6.92 (d, J=1.5 Hz, 1H, 5-H), 6.45 (d, J=8.1 Hz, 1H, 8-H), 5.86 (d, J=1.6 Hz, 1H, NH), 4.77 (d, J=1.6 Hz, 2H, 2-H), 2.14 (s, 3H, CH_3). Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.00; H, 6.86; N, 19.14. Compound **6** easily decomposed if not kept in aprotic or non-polar solvent, such as toluene.

4.6. *N*-(2-Formyl-4-methylphenyl)formamidine (7)

A solution of **6** (0.55 g, 3.8 mmol) in acetic acid (30 mL) was refluxed for 1 h. After cooling, the mixture was diluted with water (100 mL), neutralized with $NaHCO_3$, and extracted with toluene (3×80 mL). The organic phase was evaporated under reduced pressure and the residue was analyzed by GC–MS, identifying **1c** (t_R=12.7 min) and **7** (t_R=13.9 min) as reaction products. The residue was further purified by column chromatography to give, in order of elution, **1c** (7.1 mg, 13%); GC–MS (EI): m/z 144, 117, 89, 90, 63 (see above for other analytical data) and **7** (7.9 mg, 13%); ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, CHO or CH=NH), 9.27 (s, 1H, CHO or CH=NH), 7.95 (d, J=8.6 Hz, 1H, 6-H), 7.76 (dd, J=8.6, 1.8 Hz, 1H, 5-H), 7.69 (d, J=1.8 Hz, 1H, 3-H), 2.58 (s, 3H, CH_3); GC–MS (EI): m/z 136, 135, 107, 106, 77; HRMS (ESI-TOF) for $C_9H_{11}N_2O$ (M^++1): calcd: 163.0866, found: 163.0901. Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.66; H, 6.18; N, 17.30.

Acknowledgements

The present work has been carried out with financial supports of the Italian Ministry for University and Research (MIUR), Rome, Italy.

Supplementary data

Experimental details for compounds **1b** and **8**–**19b**, and experiments with different acids can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.103.

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Microwave induced one-pot synthesis of fluorenespiro[9.3′]-(4′-aryl)pyrrolidine/pyrrolizidine/tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione derivatives

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Received 9 July 2006; revised 11 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—A versatile one-pot method for the synthesis of new dispiro heterocycles is described using an intermolecular [3+2] cycloaddition reaction. The reaction gives excellent yields when carried out under solvent-free microwave irradiation.

1. Introduction

Concerted cycloaddition processes represent a powerful and often highly controlled entry into a wide variety of heterocyclic systems. Additional features associated with these processes include mild conditions, versatility and in particular, the ability to gain rapid access to complex, polycyclic ring frameworks.[1]

The 1,3-dipolar cycloaddition reaction of azomethine ylides with olefinic and acetylenic dipolarophiles offers an excellent route for the construction of pyrrolidines, pyrrolines, and pyrroles.[2–4] The chemistry of azomethine ylides has gained significance in recent years as it serves as an important route for the construction of nitrogen containing five-membered heterocycles, which are often central ring systems of numerous natural products.[5]

In addition, there has been considerable interest in the microwave irradiation protocol for rapid synthesis of a variety of organic compounds due to the selective absorption of microwave energy by polar molecules.[6]

2. Results and discussion

In our previous work,[7] we reported the facile syntheses of novel dispiropyrrolidines and pyrrolizidines in fairly good yields under microwave irradiation and classical heating method.

Our research group has been largely involved in the synthesis of pyrrolidine, pyrrolizidine, and thiazolidine derivatives through [3+2] cycloaddition reactions,[8–10] which are found in many naturally occurring alkaloids and known to possess several significant biological activity.[11]

Herein, we wish to report full details and studies related to the scope and limitations of our [3+2] reaction. In order to investigate the scope and the limitations of the new 1,3-dipolar cycloaddition reaction for the preparation of pyrrolidine, pyrrolizidine, and thiazolidine derivatives, the 1,2-diketone necessary for the generation of azomethine ylide was varied.

The reaction of non-stabilized azomethine ylide (generated in situ from the decarboxylative condensation of ninhydrin and sarcosine) with the dipolarophiles **3a–e** in refluxing methanol furnished dispiro heterocycles **4a–e** in moderate yields (50–56%) (Scheme 1).

The structures of these products were assigned on the basis of their IR, NMR (^{1}H and ^{13}C) as well as elemental analyses. In particular, the regiochemistry proposed for the product **4b** was established on the basis of its ^{1}H NMR spectrum exhibiting a doublet of doublet at δ 4.88 (J=8.3, 9.6 Hz) for the benzylic proton. If the other isomer **5b** was formed, one would expect a singlet instead of a doublet for the benzylic proton. The ^{13}C NMR spectrum of **4b** showed two peaks at δ 68.8 and 83.0 ppm due to the two spiro carbons. The indane-1,3-dione carbonyl carbons resonated at δ 197.3 and 203.6 ppm. The mass spectrum of **4b** showed a molecular ion peak at m/z 455 (M^+), which further confirms the

Keywords: 1,3-Dipolar cycloaddition; Pyrrolidine; Pyrrolizidine; Thiazole; Microwave; Solid-support.
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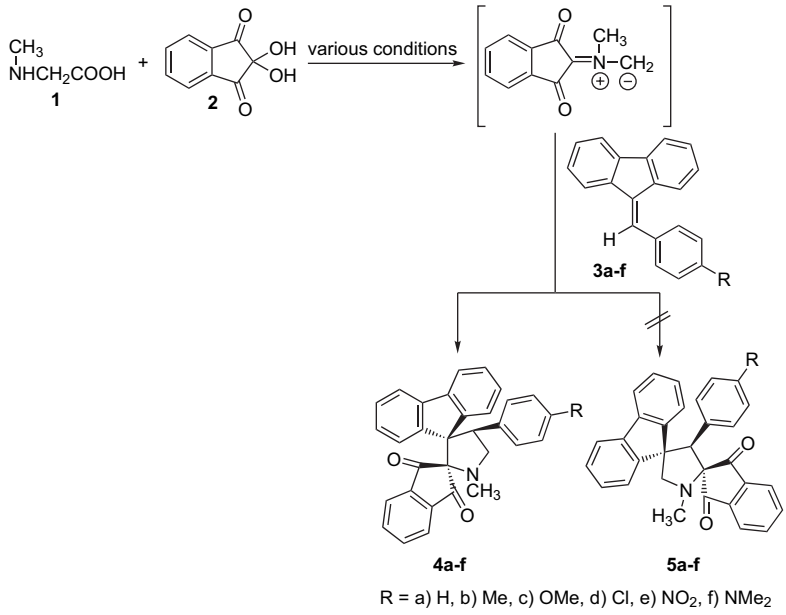
doi:10.1016/j.tet.2006.09.105



Scheme 1.

formation of the cycloadduct. Identical results were furnished by other compounds **4b–f** with identical stereochemistry. The structure of **4c** could unequivocally be established by X-ray single crystal analysis,[12] which proves the regiochemistry (Fig. 1).

In the case of **3f** as dipolarophile, the reaction was extremely sluggish affording only starting material. To gain insight into this unsuccessful cycloaddition, the reaction was subjected to microwave irradiation (600 W) in methanol. Low yield was still encountered as summarized in Table 1.

Finally, we submitted the reactants **3f**, **1**, and **2** to solvent-free microwave irradiation (600 W) ground with and without K-10 Montmorillonite clay (Methods C and D). We found that the yields of all products increased from modest to excellent (50–56% to 84–94%). In particular, to our surprise, the yield of **4f** increased drastically from 5% (Method A) to 88% (Method D) in short reaction time.

Having the best conditions in hand, we examined next the reaction of the same dipolarophile with non-stabilized azomethine ylides generated from cyclic secondary amino acids, proline or thiazolidine-4-carboxylic acid with ninhydrin (Scheme 2).

As observed in the earlier case, the yields of [3+2] cycloaddition reaction of **3a–f** with ninhydrin and proline or thiazolidine-4-carboxylic acid did not improve by the Methods A and B. However, when the above reaction was carried out under solvent-free conditions, by irradiating the reactants under microwave (600 W) with and without K-10 Montmorillonite clay, the products were obtained in excellent yields with high regioselectivity and in a short duration of time (Table 2).

The cycloadducts were characterized by spectral and elemental analyses. The ^{1}H NMR spectrum of **7d** showed a doublet for the benzylic proton at δ 4.37. The methylene protons of the pyrrolizidine ring system showed a multiplet in the region δ 1.25–3.08. The ^{13}C NMR spectrum of **7d** exhibits two peaks at δ 198.7 and 200.1 ppm for the carbonyl carbons of indane-1,3-dione ring system. Finally the structure of the product **7d** was confirmed by a peak at *m*/*z* 501.5 (M^{+}) in mass spectrum and it showed satisfactory elemental analysis.

In conclusion, we have developed a simple, one-pot and new method for the synthesis of dispiropyrrolidine/pyrrolizidine/

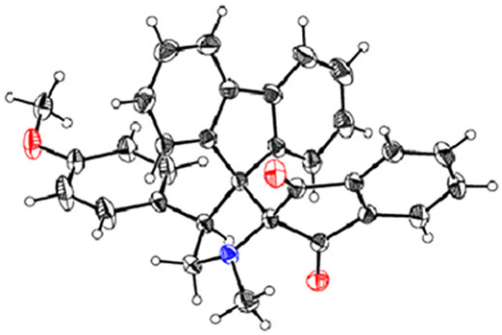
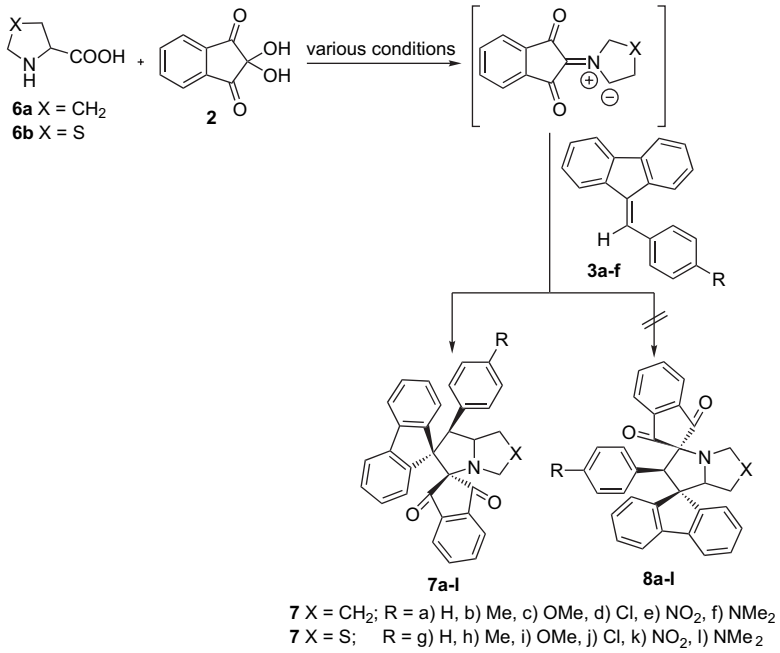


Figure 1. ORTEP diagram of **4c**.

Table 1. Influence of conventional heating and microwave irradiation on 1,3-dipolar cycloaddition reaction of **3a–f** with **1** and **2**

4	*Method A*		*Method B*		*Method C*		*Method D*	
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
a	2.0	52	6.0	55	3.0	84	2.5	88
b	1.0	55	5.0	57	2.0	78	2.0	84
c	1.5	52	8.0	54	2.5	85	3.0	87
d	2.0	50	5.5	53	3.0	89	3.5	90
e	1.0	56	5.0	60	2.0	91	2.5	94
f	2.0	5	9.0	15	4.0	80	3.0	88

Method A: conventional methanol reflux; *Method B*: methanol/MW; *Method C*: K-10 Montmorillonite clay/MW; *Method D*: neat/MW.



Scheme 2.

Table 2. Influence of conventional heating and microwave irradiation on 1,3-dipolar cycloaddition reaction of **3a–f** with **6** and **2**

7	*Method A*		*Method B*		*Method C*		*Method D*	
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
a	1.5	55	5.0	58	3.0	78	2.5	83
b	1.0	57	4.5	60	3.0	82	3.0	85
c	1.5	60	4.8	62	2.5	80	3.0	84
d	2.0	59	5.2	65	3.5	85	2.5	89
e	1.0	62	4.0	64	3.0	87	3.5	90
f	2.5	7	6.0	20	3.5	77	3.0	81
g	3.0	50	5.5	58	4.0	80	3.5	85
h	2.5	57	6.0	60	3.5	83	4.0	87
i	3.5	56	6.0	64	4.5	86	3.7	90
j	4.0	52	5.5	64	4.5	81	4.0	89
k	3.0	63	5.0	66	4.0	88	4.5	93
l	5.0	5	8.0	18	6.0	80	5.5	87

Method A: conventional methanol reflux; *Method B*: methanol/MW; *Method C*: K-10 Montmorillonite clay/MW; *Method D*: neat/MW.

pyrrolo[1,2-*c*]thiazole derivatives by [3+2] cycloaddition methodology. Of the various conditions employed, the solvent-free and solid-support approach accelerated by microwave irradiation was found to be synthetically useful in achieving high yields with substantial reduction in time when compared to conventional heating.

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on JEOL 400 MHz and 100 MHz, respectively. MS spectra were recorded on a Finnigan MAT-8230 GC-Mass spectrometer.

3.2. General procedure for the synthesis of dispiro heterocycles

Method A: A solution of ninhydrin **2** (1 mmol), sarcosine **1**/proline **6a**/thiazolidine-4-carboxylic acid **6b** (1 mmol), and 9-arylidene fluorenes **3a–f** (1 mmol) was refluxed in methanol. Completion of the reaction was evidenced by TLC analysis. The solvent was removed in vacuo. The crude product was subjected to column chromatography using petroleum ether–ethyl acetate as an eluent.

Method B: A solution of ninhydrin **2** (1 mmol), sarcosine **1**/proline **6a**/thiazolidine-4-carboxylic acid **6b** (1 mmol), and 9-arylidene fluorenes **3a–f** (1 mmol) in methanol was irradiated under microwave conditions (600 W). After completion of the reaction, the solvent was evaporated and the crude product was subjected to column chromatography using petroleum ether–ethyl acetate as an eluent.

Method C: A mixture of ninhydrin **2** (1 mmol), sarcosine **1**/proline **6a**/thiazolidine-4-carboxylic acid **6b** (1 mmol), and 9-arylidene fluorenes **3a–f** (1 mmol) was ground with K-10 Montmorillonite clay and irradiated under microwave conditions (600 W). After completion of the reaction, the product was extracted with dichloromethane, the organic layer dried over $MgSO_4$, the solvent removed in vacuo and the residue crystallized from methanol.

Method D: A mixture of ninhydrin **2** (1 mmol), sarcosine **1**/proline **6a**/thiazolidine-4-carboxylic acid **6b** (1 mmol), and 9-arylidene fluorenes **3a–f** (1 mmol) was ground and irradiated under microwave conditions (600 W). After completion of the reaction, the mixture was allowed to stand at room temperature until it solidified and the product was recrystallized from methanol.

3.2.1. Fluorenespiro[9.3′]-1-*N*-methyl-(4′-phenyl)pyrrolidinespiro[2′.2″]indan-1″,3″-dione (4a). Pale yellow solid,

mp 177–179 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.69–8.12 (17H, m, Ph), 4.91 (1H, dd, J=8.3, 9.6 Hz, C*H*Ph), 4.24 (1H, dd, J=7.2, 8.3 Hz, NCH_2), 3.90 (1H, dd, J=7.2, 9.6 Hz, NCH_2), 2.58 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 203.6, 197.2, 142.8, 141.8, 141.7, 141.3, 140.8, 139.9, 136.3, 135.5, 129.5, 128.4, 128.1, 128.0, 127.2, 126.6, 126.4, 124.8, 122.6, 122.1, 119.6, 119.1, 82.9, 68.8, 57.5, 51.3, 36.3; m/z 441 (M^+). Anal. Calcd for $C_{31}H_{23}NO_2$: C, 84.35; H, 5.21; N, 3.17%. Found: C, 84.55; H, 5.35; N, 2.98%.

3.2.2. Fluorenespiro[9.3′]-1-*N*-methyl-(4′-*p*-methylphenyl)pyrrolidinespiro[2′.2″]indan-1″,3″-dione (4b). Yellow solid, mp 176–178 °C; ν_{max} (KBr): 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.58–8.12 (16H, m, Ph), 4.88 (1H, dd, J=8.3, 9.6 Hz, C*H*Ph), 4.21 (1H, dd, J=7.0, 8.3 Hz, NCH_2), 3.88 (1H, dd, J=7.0, 9.6 Hz, NCH_2), 2.57 (3H, s, NCH_3), 2.04 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 203.6, 197.3, 143.0, 141.8, 141.7, 141.3, 140.8, 139.9, 135.9, 135.5, 133.1, 129.6, 128.3, 128.1, 127.9, 126.6, 126.4, 124.8, 122.6, 122.2, 119.6, 119.1, 83.00, 68.8, 57.7, 50.9, 36.3, 20.8; m/z 455 (M^+). Anal. Calcd for $C_{32}H_{25}NO_2$: C, 84.39; H, 5.49; N, 3.08%. Found: C, 84.58; H, 5.60; N, 3.18%.

3.2.3. Fluorenespiro[9.3′]-1-*N*-methyl-(4′-*p*-methoxyphenyl)pyrrolidinespiro[2′.2″]indan-1″,3″-dione (4c). Yellow solid, mp 185–186 °C; ν_{max} (KBr): 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.53–7.62 (16H, m, Ph), 4.71 (1H, dd, J=8.2, 9.8 Hz, C*H*Ph), 4.02 (1H, dd, J=7.4, 8.2 Hz, NCH_2), 3.86 (1H, dd, J=7.4, 9.8 Hz, NCH_2), 3.64 (3H, s, OCH_3), 2.41 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 200.7, 199.9, 143.2, 142.1, 135.8, 134.2, 133.6, 130.9, 130.3, 130.1, 129.9, 128.7, 128.0, 127.8, 127.7, 127.3, 126.0, 122.6, 122.0, 120.9, 119.0, 116.6, 113.4, 113.3, 112.5, 71.0, 73.9, 52.0, 54.8, 48.5, 31.7; m/z 471 (M^+). Anal. Calcd for $C_{32}H_{25}NO_3$: C, 81.53; H, 5.31; N, 2.97%. Found: C, 81.75; H, 5.47; N, 3.08%.

3.2.4. Fluorenespiro[9.3′]-1-*N*-methyl-(4′-*p*-chlorophenyl)pyrrolidinespiro[2′.2″]indan-1″,3″-dione (4d). Pale yellow solid, mp 182–184 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.64–7.84 (16H, m, Ph), 4.80 (1H, dd, J=8.4, 9.4 Hz, C*H*Ph), 4.30 (1H, dd, J=7.1, 8.4 Hz, NCH_2), 3.92 (1H, dd, J=7.1, 9.4 Hz, NCH_2), 2.53 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 199.3, 198.0, 141.3, 140.2, 140.1, 139.5, 138.7, 136.7, 130.8, 128.4, 128.2, 128.1, 127.8, 127.6, 127.1, 126.9, 126.2, 124.2, 123.0, 120.5, 120.2, 119.4, 118.1, 117.8, 110.2, 80.8, 69.4, 57.2, 52.2, 34.2; m/z 475.5 (M^+). Anal. Calcd for $C_{31}H_{22}NO_2Cl$: C, 78.23; H, 4.63; N, 2.94%. Found: C, 78.48; H, 4.79; N, 3.09%.

3.2.5. Fluorenespiro[9.3′]-1-*N*-methyl-(4′-*p*-nitrophenyl)-pyrrolidinespiro[2′.2″]indan-1″,3″-dione (4e). Yellow solid, mp 190 °C; ν_{max} (KBr): 1741 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.45–7.56 (16H, m, Ph), 4.84 (1H, dd, J=8.4, 10.0 Hz, C*H*Ph), 4.36 (1H, dd, J=7.3, 8.4 Hz, NCH_2), 3.81 (1H, dd, J=7.3, 10.0 Hz, NCH_2), 2.35 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 203.5, 198.9, 141.2, 133.8, 130.9, 130.5, 130.0, 128.8, 128.4, 128.1, 127.8, 127.4, 125.0, 124.6, 124.0, 123.7, 122.4, 121.6, 121.5, 120.8, 119.8, 116.9, 115.2, 114.8, 113.1, 111.2, 79.7, 68.2, 56.3, 51.1, 36.1; m/z 486 (M^+). Anal. Calcd for $C_{31}H_{22}N_2O_4$: C, 76.54; H, 4.53; N, 5.76%. Found: C, 76.70; H, 4.68; N, 5.92%.

3.2.6. Fluorenespiro[9.3′]-1-*N*-methyl-(4′-*p*-*N*,*N*-dimethylphenyl)pyrrolidinespiro[2′.2″]indan-1″,3″-dione (4f). Yellow solid, mp 175–177 °C; ν_{max} (KBr): 1738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.50–7.44 (16H, m, Ph), 4.80 (1H, dd, J=8.7, 9.6 Hz, C*H*Ph), 4.39 (1H, dd, J=7.4, 8.7 Hz, NCH_2), 3.84 (1H, dd, J=7.4, 9.6 Hz, NCH_2), 2.80 (6H, s, NCH_3), 2.43 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 202.6, 197.2, 141.8, 141.5, 138.3, 137.6, 136.6, 133.2, 132.0, 131.1, 130.2, 129.4, 128.8, 128.2, 127.9, 127.3, 126.1, 125.6, 124.1, 123.6, 122.6, 121.7, 120.1, 119.2, 116.7, 110.3, 70.5, 67.9, 55.5, 52.4, 34.7, 34.4, 33.2; m/z 484 (M^+). Anal. Calcd for $C_{33}H_{28}N_2O_2$: C, 81.82; H, 5.78; N, 5.78%. Found: C, 82.06; H, 5.97; N, 5.63%.

3.2.7. Fluorenespiro[9.3′]-(4′-phenyl)pyrrolizidinespiro [2′.2″]indan-1″,3″-dione (7a). Pale yellow solid, mp 158–160 °C; ν_{max} (KBr): 1745 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.45–7.17 (17H, m, Ph), 4.53–4.55 (1H, m, H_b), 4.33 (1H, d, J=9.6 Hz, C*H*Ph), 1.30–2.94 (6H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 202.0, 200.1, 141.2, 132.8, 132.0, 130.0, 128.4, 128.1, 127.8, 125.7, 125.3, 125.1, 124.4, 124.0, 123.7, 122.4, 121.6, 121.5, 120.8, 119.8, 116.9, 116.1, 115.2, 114.8, 113.1, 73.1, 70.8, 57.1, 46.5, 34.1, 31.8, 30.4; m/z 467 (M^+). Anal. Calcd for $C_{33}H_{25}NO_2$: C, 84.79; H, 5.35; N, 2.99%. Found: C, 85.03; H, 5.49; N, 2.84%.

3.2.8. Fluorenespiro[9.3′]-(4′-*p*-methylphenyl)pyrrolizidinespiro[2′.2″]indan-1″,3″-dione (7b). Yellow solid, mp 156–157 °C; ν_{max} (KBr): 1738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.62–7.81 (16H, m, Ph), 4.58–4.60 (1H, m, H_b), 4.52 (1H, d, J=9.4 Hz, C*H*Ph), 2.37 (3H, s, CH_3), 1.26–2.17 (6H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 199.9, 198.8, 142.5, 140.5, 139.3, 136.7, 132.7, 130.5, 130.3, 129.1, 129.0, 128.5, 128.3, 127.7, 127.4, 127.2, 126.5, 125.9, 125.6, 125.2, 124.8, 124.4, 121.0, 120.4, 119.2, 118.9, 110.6, 80.6, 76.3, 56.3, 47.3, 34.6, 34.1, 33.0; m/z 481 (M^+). Anal. Calcd for $C_{34}H_{27}NO_2$: C, 84.82; H, 5.61; N, 2.91%. Found: C, 85.08; H, 5.48; N, 3.06%.

3.2.9. Fluorenespiro[9.3′]-(4′-*p*-methoxyphenyl)pyrrolizidinespiro[2′.2″]indan-1″,3″-dione (7c). Pale yellow solid, mp 163–165 °C; ν_{max} (KBr): 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.34–8.34 (16H, m, Ph), 4.63–4.69 (1H, m, H_b), 4.35 (1H, d, J=9.5 Hz, C*H*Ph), 3.55 (3H, s, OCH_3), 2.13–3.08 (6H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 204.0, 198.4, 158.2, 142.3, 141.4, 141.0, 140.8, 140.3, 139.9, 135.4, 135.2, 131.7, 130.8, 129.5, 129.4, 128.1, 126.6, 126.4, 125.0, 124.2, 125.6, 122.1, 119.4, 119.1, 114.0, 112.7, 73.8, 69.9, 56.5, 54.8, 47.3, 33.7, 31.8, 30.0; m/z 497 (M^+). Anal. Calcd for $C_{34}H_{27}NO_3$: C, 82.09; H, 5.43; N, 2.82%. Found: C, 82.33; H, 5.63; N, 2.70%.

3.2.10. Fluorenespiro[9.3′]-(4′-*p*-chlorophenyl)pyrrolizidinespiro[2′.2″]indan-1″,3″-dione (7d). Pale yellow solid, mp 140 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.59–8.33 (16H, m, Ph), 4.62–4.67 (1H, m, H_b), 4.37 (1H, d, J=9.5 Hz, C*H*Ph), 1.25–3.08 (6H, m, pyrrolizidine); δ_C

(100 MHz, $CDCl_3$) 200.1, 198.7, 141.4, 139.3, 137.2, 136.3, 135.4, 133.9, 130.7, 129.7, 129.5, 128.8, 128.4, 127.4, 127.1, 126.7, 126.5, 125.6, 124.9, 124.3, 123.7, 122.2, 120.3, 119.8, 119.6, 119.2, 73.6, 69.6, 56.6, 47.2, 34.0, 31.7, 30.1; *m/z* 501.5 (M^+). Anal. Calcd for $C_{33}H_{24}NO_2Cl$: C, 78.96; H, 4.78; N, 2.79%. Found: C, 79.18; H, 4.95; N, 2.64%.

3.2.11. Fluorenespiro[9.3′]-(4′-*p*-nitrophenyl)pyrrolizidinespiro[2′.2″]indan-1″,3″-dione (7e). Yellow solid, mp 160–162 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.44–7.25 (16H, m, Ph), 4.49–4.51 (1H, m, H_b), 4.33 (1H, d, *J*=9.6 Hz, C*H*Ph), 1.34–2.90 (6H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 202.1, 199.7, 142.3, 141.4, 139.3, 136.8, 135.9, 130.7, 129.4, 128.3, 128.0, 127.8, 127.3, 126.0, 125.1, 124.5, 124.1, 123.9, 122.0, 121.7, 121.5, 119.7, 117.8, 116.4, 114.4, 110.5, 54.9, 46.0, 31.3, 31.1, 30.5; *m/z* 512 (M^+). Anal. Calcd for $C_{33}H_{24}N_2O_4$: C, 77.34; H, 4.68; N, 5.47%. Found: C, 77.56; H, 4.86; N, 5.34%.

3.2.12. Fluorenespiro[9.3′]-(4′-*p*-*N*,*N*-dimethylphenyl)-pyrrolizidinespiro[2′.2″]indan-1″,3″-dione (7f). Pale yellow solid, mp 152–154 °C; ν_{max} (KBr): 1738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.60–7.59 (16H, m, Ph), 4.55–4.58 (1H, m, H_b), 4.30 (1H, d, *J*=9.4 Hz, C*H*Ph), 2.53 (6H, s, CH_3), 1.30–2.94 (6H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 198.0, 194.6, 141.6, 140.4, 137.0, 136.6, 136.3, 136.0, 135.8, 134.7, 133.7, 133.0, 131.5, 128.0, 126.5, 126.1, 125.8, 125.7, 121.9, 120.1, 119.1, 118.2, 117.4, 115.9, 110.1, 107.6, 56.5, 45.5, 35.6, 35.0, 34.5, 33.0, 32.6; *m/z* 510 (M^+). Anal. Calcd for $C_{35}H_{30}N_2O_2$: C, 82.35; H, 5.88; N, 5.49%. Found: C, 82.54; H, 6.08; N, 5.34%.

3.2.13. Fluorenespiro[9.3′]-(4′-phenyl)tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione (7g). Pale yellow solid, mp 169–170 °C; ν_{max} (KBr): 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.70–7.91 (17H, m, Ph), 4.72–4.74 (1H, m, H_b), 4.51 (1H, d, *J*=8.7 Hz, C*H*Ph), 4.19 (1H, d, *J*=7.4 Hz, NCH_2), 3.70 (1H, d, *J*=7.4 Hz, NCH_2), 3.45 (1H, dd, *J*=4.0, 10.0 Hz, SCH_2), 3.20 (1H, dd, *J*=5.4, 10.0 Hz, SCH_2); δ_C (100 MHz, $CDCl_3$) 203.5, 195.0, 143.0, 142.4, 137.0, 136.1, 135.5, 134.1, 132.3, 131.8, 129.6, 129.5, 129.2, 129.0, 128.5, 128.0, 127.2, 126.5, 126.1, 124.9, 123.3, 122.0, 121.9, 121.0, 120.0, 115.8, 67.9, 65.3, 61.8, 54.3, 52.2, 35.5; *m/z* 485 (M^+). Anal. Calcd for $C_{32}H_{23}NO_2S$: C, 79.17; H, 4.74; N, 2.88%. Found: C, 79.43; H, 4.90; N, 2.74%.

3.2.14. Fluorenespiro[9.3′]-(4′-*p*-methylphenyl)tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione (7h). Yellow solid, mp 174–175 °C; ν_{max} (KBr): 1742 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.59–8.36 (16H, m, Ph), 4.95–4.97 (1H, m, H_b), 4.46 (1H, d, *J*=8.6 Hz, C*H*Ph), 4.28 (1H, d, *J*=7.6 Hz, NCH_2), 3.79 (1H, d, *J*=7.6 Hz, NCH_2), 3.49 (1H, dd, *J*=3.3, 10.2 Hz, SCH_2), 3.19 (1H, dd, *J*=5.5, 10.2 Hz, SCH_2), 2.05 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 203.4, 196.3, 142.1, 141.3, 141.0, 139.8, 136.4, 135.7, 135.5, 131.5, 129.3, 128.3, 128.1, 126.6, 126.5, 124.7, 122.8, 122.3, 119.6, 119.2, 81.9, 73.9, 73.1, 55.8, 51.3, 37.0, 20.7; *m/z* 499 (M^+). Anal. Calcd for $C_{33}H_{25}NO_2S$: C, 79.35; H, 5.01; N, 2.80%. Found: C, 79.56; H, 5.20; N, 2.68%.

3.2.15. Fluorenespiro[9.3′]-(4′-*p*-methoxyphenyl)tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione (7i). Yellow solid, mp 181–183 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.52–7.83 (16H, m, Ph), 4.81–4.83 (1H, m, H_b), 4.55 (1H, d, *J*=8.6 Hz, C*H*Ph), 4.35 (1H, d, *J*=7.6 Hz, NCH_2), 3.63 (3H, s, OCH_3), 3.53 (1H, d, *J*=7.6 Hz, NCH_2), 3.40 (1H, dd, *J*=3.4, 9.8 Hz, SCH_2), 3.23 (1H, dd, *J*=5.5, 9.8 Hz, SCH_2); δ_C (100 MHz, $CDCl_3$) 199.5, 193.9, 139.7, 137.9, 135.0, 134.2, 132.7, 132.5, 131.8, 129.3, 128.8, 128.4, 127.3, 126.1, 124.8, 124.2, 123.8, 123.2, 122.1, 121.5, 121.1, 120.9, 119.0, 115.8, 113.1, 112.5, 79.9, 72.1, 69.0, 58.2, 54.7, 52.1, 35.6; *m/z* 515 (M^+). Anal. Calcd for $C_{33}H_{25}NO_3S$: C, 76.89; H, 4.85; N, 2.72%. Found: C, 77.11; H, 4.66; N, 2.85%.

3.2.16. Fluorenespiro[9.3′]-(4′-*p*-chlorophenyl)tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione (7j). Pale Yellow solid, mp 172–174 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.71–7.94 (16H, m, Ph), 4.53–4.55 (1H, m, H_b), 4.45 (1H, d, *J*=8.5 Hz, C*H*Ph), 4.21 (1H, d, *J*=8.0 Hz, NCH_2), 3.80 (1H, d, *J*=8.0 Hz, NCH_2), 3.40 (1H, dd, *J*=4.0, 9.8 Hz, SCH_2), 3.17 (1H, dd, *J*=5.6, 9.8 Hz, SCH_2); δ_C (100 MHz, $CDCl_3$) 203.9, 201.6, 144.1, 141.9, 140.0, 136.5, 135.0, 134.4, 132.5, 131.2, 129.6, 129.1, 128.4, 127.9, 127.0, 126.5, 126.3, 125.6, 124.3, 123.7, 123.0, 122.4, 121.6, 119.0, 115.8, 113.9, 69.3, 68.0, 63.6, 57.2, 52.4, 34.4; *m/z* 519.5 (M^+). Anal. Calcd for $C_{32}H_{22}NO_2SCl$: C, 73.92; H, 4.23; N, 2.69%. Found: C, 74.18; H, 4.42; N, 2.53%.

3.2.17. Fluorenespiro[9.3′]-(4′-*p*-nitrophenyl)tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione (7k). Yellow solid, mp 185–187 °C; ν_{max} (KBr): 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.64–7.81 (16H, m, Ph), 4.55–4.58 (1H, m, H_b), 4.50 (1H, d, *J*=8.6 Hz, C*H*Ph), 4.10 (1H, d, *J*=7.8 Hz, NCH_2), 3.85 (1H, d, *J*=7.8 Hz, NCH_2), 3.41 (1H, dd, *J*=3.8, 10.0 Hz, SCH_2), 3.23 (1H, dd, *J*=5.5, 10.0 Hz, SCH_2); δ_C (100 MHz, $CDCl_3$) 204.7, 197.1, 142.0, 141.5, 140.6, 139.0, 137.9, 137.1, 136.0, 133.6, 133.2, 131.3, 129.0, 128.8, 127.7, 127.0, 126.6, 125.3, 124.7, 124.6, 123.3, 123.0, 120.2, 117.9, 116.2, 71.8, 66.4, 62.3, 58.9, 55.2, 37.1; *m/z* 530 (M^+). Anal. Calcd for $C_{32}H_{22}N_2O_4S$: C, 72.45; H, 4.15; N, 5.28%. Found: C, 72.70; H, 4.28; N, 5.10%.

3.2.18. Fluorenespiro[9.3′]-(4′-*p*-*N*,*N*-dimethylphenyl)-tetrahydropyrrolo[1,2-*c*]thiazolespiro[2′.2″]indan-1″,3″-dione (7l). Yellow solid, mp 166–168 °C; ν_{max} (KBr): 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.53–7.28 (16H, m, Ph), 4.50–4.52 (1H, m, H_b), 4.47 (1H, d, *J*=8.6 Hz, C*H*Ph), 4.25 (1H, d, *J*=7.7 Hz, NCH_2), 3.90 (1H, d, *J*=7.7 Hz, NCH_2), 3.39 (1H, dd, *J*=3.6, 10.0 Hz, SCH_2), 3.18 (1H, dd, *J*=5.6, 10.0 Hz, SCH_2), 2.70 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.0, 196.6, 1432.5, 139.6, 138.7, 136.5, 134.4, 134.1, 133.2, 133.1, 132.2, 128.0, 127.6, 127.1, 126.6, 125.0, 121.3, 120.7, 119.8, 119.2, 118.9, 117.2, 115.9, 110.8, 108.2, 106.6, 67.0, 65.7, 61.5, 56.7, 54.0, 37.1, 36.7, 36.6, 35.8, 35.5; *m/z* 528 (M^+). Anal. Calcd for $C_{34}H_{28}N_2O_2S$: C, 77.27; H, 5.30; N, 5.30%. Found: C, 77.48; H, 5.50; N, 5.42%.

Acknowledgements

R.D.R.S.M and J.J. thank CSIR (SRF), New Delhi for financial support.

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Tetrahedron 62 (2006) 12363–12374

Asymmetric oxidation of enol phosphates to α-hydroxy ketones by (salen)manganese(III) complex. Effects of the substitution pattern of enol phosphates on the stereochemistry of oxygen transfer

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Received 30 June 2006; revised 11 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—This paper presents a study of enantioselective catalytic oxidation of a variety of differently substituted, cyclic (*E*) and acyclic (*Z*)-enol phosphates. The asymmetric oxidation of acyclic (*Z*)-enol phosphates containing alkoxy substituents in the phosphate group **2a**, **c**, **e**–**g**, **i**, and **j** and *Z*-configured enol phosphates containing aryloxy substituents in the phosphate group **2b**, **d**, and **h** afforded optically active α-hydroxy ketones **4a**–**j** of opposite configuration with good to high enantioselectivity. The influence of electronic and steric effects of the enol phosphate substituents on the stereoselectivity of oxidation was studied.

1. Introduction

The α-hydroxy carbonyl unit is found in many biologically active natural products such as sugars and antibiotics.[1] Enantiomerically pure α-hydroxy carbonyl compounds are also important synthons for the asymmetric synthesis of natural products.[1a,2] Consequently, efficient methods for the construction of enantiomerically pure, or at least enriched, α-hydroxy carbonyl derivatives are in demand.[3] This class of compounds has been prepared by both nonoxidative[4] and oxidative methods.[3a,b,5] Among the latter, the asymmetric oxidation of enolate or enol ethers using chiral *N*-sulfonyloxaziridine[3a] or a Sharpless dihydroxylation catalyst[3b] has been applied with success. Epoxidation is among the most useful oxidation reactions, since the epoxides may be transformed by stereoselective ring opening into highly functionalized products.[6] A recent major advance in catalytic enantioselective epoxidation is oxidation of prochiral unsaturated compounds with readily accessible (salen) Mn(III) complexes. It has been demonstrated that these complexes are highly enantioselective catalysts for the epoxidation of various conjugated substituted olefins,[7] enol ethers,[5a,8] and esters.[5a,8a] These epoxy derivatives were easily converted into optically active α-hydroxy carbonyl compounds.

Enol phosphates constitute a class of important organic compounds exhibiting biological activity.[9] They are very easy to prepare.[10] However, the utility of enol phosphates in organic synthesis is still limited.[11]

We have previously described the application of cyclic enol phosphates in the stereoselective synthesis of newly functionalized polycyclic compounds including functionalized enol phosphates with an allyl hydroxy group. We also found that epoxidation of these compounds led to α-hydroxy ketones.[12] We then elaborated methodology, based on epoxy phosphate intermediates,[12,13] for an alternative general synthesis of acyclic and cyclic α-hydroxy carbonyl compounds.[14]

In a recent paper[15] we showed that readily available enol phosphates can be stereoselectively oxidized to α-hydroxy ketones with high enantioselectivity using (salen) Mn(III) Jacobsen's catalyst **1**[16] (Fig. 1). We observed that reactions

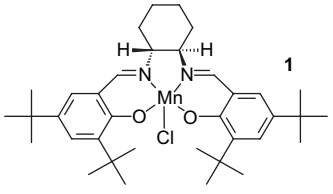

Figure 1. (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-*cyclo*-hexanediamino manganese(III) chloride.

Keywords: Enol phosphates; Asymmetric oxidation; α-Hydroxy ketones; Jacobsen's catalyst.
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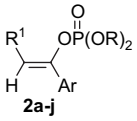
doi:10.1016/j.tet.2006.09.100

of asymmetric epoxidation of enol phosphates bearing phenoxy instead of ethoxy substituents at phosphorus led to α-hydroxy ketones of opposite configuration to that of other α-hydroxy carbonyl compounds obtained. We decided to develop these studies, which could provide an insight into factors controlling stereoinduction in the epoxidation of enol phosphates.

2. Results and discussion

We first prepared a set of enol phosphates **2** (Table 1), substituted with phenyl in the α-position and alkyl or phenyl in the β-position, which would afford the more persistent α-hydroxy ketones. Besides the phosphates containing ethoxy groups at phosphorus atom, the phosphorus compounds with bulky alkoxy and phenoxy groups at phosphorus were also chosen for oxidation. This allowed us to test the influence of steric and electronic aspects of the substrates on the stereochemistry of their asymmetric epoxidation. All compounds **2a**–**j** were obtained by the reaction of dialkyl (R=Et, *i*-Pr, and *t*-$BuCH_2$) and diaryl (R=Ph and *p*-MeO–Ph) phosphorochloridates with enolate anions. The latter were generated from the appropriate ketones by action of LDA.[10d]

Table 1. Acyclic *Z*-enol phosphates **2**



2a-j

2	R^1	Ar	R
a	Me	Ph	Et
b	Me	Ph	Ph
c	Et	Ph	Et
d	Et	Ph	Ph
e[a]	Et	Ph	*t*-$BuCH_2$
f	Pr	Ph	Et
g	Pr	Ph	*i*-Pr
h	Pr	Ph	4-$MeOC_6H_4$
i[a]	Ph	Ph	Et
j	Me	4-$MeOC_6H_4$	Et

[a] Mixture of *E* and *Z* isomers.

Most enol phosphates **2** were formed as single isomers. All compounds had *Z*-configuration, assigned on the basis of ^1H NMR spectral analysis and in particular for compound **2g** on the observation of a positive nuclear Overhauser effect (NOE)—a 3% increase in area for the vinyl proton cis to phenyl.[17] *Z*-Configuration of the other enol phosphates was determined by comparison of the chemical shift of vinyl protons and the coupling constant ($^4J_{PH}$) observed for **2g** and **2a**–**d**, **f**, and **h**–**j**[18] and additionaly by a NOESY experiment carried out on compound **2d**.

Catalytic oxidation of phosphates **2a**–**j** was carried out with NaOCl in phosphate buffer (pH∼11) as oxygen source, 4-phenylpyridine *N*-oxide (PPNO) as additive and 7% of (salen) Mn(III) complex **1** as catalyst.[7b,19] The best conversion of enol phosphates to α-hydroxy ketones was achieved in the oxidation performed at 0 °C for 24 h. Opening of the intermediate epoxides **3** was carried out with 25% CF_3COOH at 5 °C (Scheme 1) and pure α-hydroxy ketones **4** were obtained by flash chromatography. All the results of epoxidation of enol phosphates **2** are summarized in Table 2.

(*Z*)-Configured enol phosphates **2a**, **c**, **f**, **g**, and **j** with an alkyl substituent β to the phosphate group afforded *S* enantiomers of the corresponding α-hydroxy ketones **4a**, **c**, **f**, and **j** with high ee (83–96%) (entries 1, 3, 6, 7, and 10).

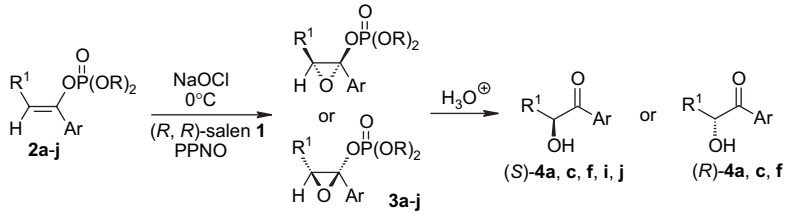
Catalytic oxidation of enol phosphate **2i** containing a phenyl group in both α- and β-positions gave the benzoin **4i** with 89% ee (entry 9), whereas oxidation of diphenyl substituted silyl enol ether by chiral complex **1** led to the formation of benzoin with only 12% ee.[5a]

To test the steric influence of the phosphoryloxy group on asymmetric induction and enantioselectivity, enol phosphates with bulkier isopropoxy (R=*i*-Pr, R^1=Pr) **2g** and neopentoxy substituents (R=*t*-$BuCH_2$, R^1=Et) **2e** were selected. Compound **2g** afforded (*S*)-configured α-hydroxy ketone **4g** with 88% ee, which is only a slightly better value than for **2f** (R=Et, R^1=Pr), ee=83% (entries 6 and 7). For compound **2e** enantioselectivity is very low (13% estimated

Table 2. Enantioselective synthesis of α-hydroxy ketones **4a**, **4c**, **4f**, **4i**, and **4j** by catalyst (*R*,*R*)-(−) salen Mn(III) **1** with NaOCl

Entry	Substrate	Product	Yield[a](%)	ee[b](%)	Config.[c] of **4**
1	**2a**	**4a**	57	96	*S*-(−)
2	**2b**	**4a**	47	68	*R*-(+)
3	**2c**	**4c**	50	93	*S*-(−)
4	**2d**	**4c**	58	81	*R*-(+)
5	**2e**	**4c**	50	13[d]	*S*-(−)
6	**2f**	**4f**	58	83	*S*-(−)
7	**2g**	**4f**	70	88	*S*-(−)
8	**2h**	**4f**	50	68	*R*-(+)
9	**2i**	**4i**	56	89	*S*-(+)
10	**2j**	**4j**	60	87	*S*-(−)

[a] Yield of pure, isolated compounds **4** (not optimized) based on enol phosphates **2**.
[b] Determined by HPLC analysis (Chiracel OD, for details see Section 4) using racemic compounds as references.
[c] Configurations were assessed by comparison of sign of the optical rotation with literature data, for **4f** in analogy to the elution order of the enantiomers of **4a** and **4c** (see Section 4).
[d] Enantiomeric excess was estimated by comparison of values of optical rotation of *S*-(−)-α-hydroxy ketones **4f**.



Scheme 1. Asymmetric oxidation of enol phosphates **2** by (*R*,*R*)-(−) salen Mn(III) catalyst **1**.

on optical rotation of **4c** compared to reported data), but the starting enol phosphate **2e** is a mixture of *Z* and *E* isomers.

Enol phosphates **2b**, **d**, and **h**, bearing phenoxy groups at phosphorus, afforded *R* enantiomers of α-hydroxy ketones **4a**, **c**, and **f** with enantiomeric excess of 68–81% (Table 2, entries 2, 4, and 8). Comparing the absolute configuration of these products with the *S* configuration of **4a**, **c**, and **f** obtained from enol phosphates **2a**, **c**, **f**, and **g** (entries 1, 3, 6, and 7) reveals that the change of R substituent in phosphate group from Alk (**2a**, **c**, **f**, and **g**) to Ar (**2b**, **d**, and **h**) leads to the opposite absolute configuration of α-hydroxy ketones formed, and has influence on the enantioselectivity of the oxidation. Decrease in enantioselectivity was observed for **2b**—68% ee compared to 96% ee for **2a**; 81% ee for **2d** versus 93% ee for **2c** and 68% ee for **2h** compared to 83–88% ee for **2f** and **g** (entries 1–4 and 6–8). Oxidation of the enol phosphate with electronically modified phenoxy groups (R=4-MeOC$_6$H$_4$) **2h** afforded the corresponding α-hydroxy ketone **4f** of *R* configuration (entry 8). This stereochemical result confirms that the phenoxy substituents in enol phosphates are responsible for the opposite sense of asymmetric induction in these oxidations.

In order to determine the usefulness of enol phosphates as prochiral substrates for metal-catalyzed oxidation by a chiral oxygen complex, and to test the influence of the substitution pattern of the enol phosphate substrates on the stereochemistry, further studies with cyclic compounds were undertaken. We chose bi- and tricyclic systems containing enol phosphate and aromatic moieties. Similar α-hydroxy ketones simulate functionalities in natural products.[20]

The corresponding enol phosphates **5a**–**f** (Fig. 2) were prepared according to the procedure described above. Pure **5a**–**f** were the subject of asymmetric epoxidation, performed as before and after hydrolysis of the intermediate epoxides **6** the α-hydroxy ketones **7** were obtained and isolated by flash chromatography (Fig. 3). Their enantiomeric purity was determined by chiral HPLC (Table 3).

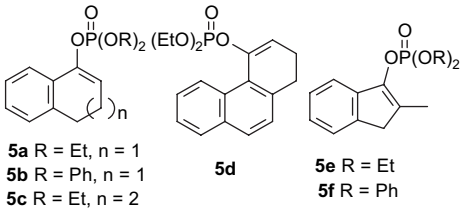


Figure 2. Cyclic *E*-enol phosphates **5**.

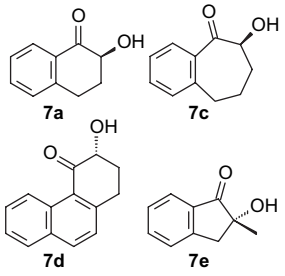


Figure 3. Cyclic α-hydroxy ketones **7**.

Table 3. Enantioselective synthesis of α-hydroxy ketones **7a** and **7c**–**e** by catalyst (*R*,*R*)-(−) (salen) Mn(III) **1** with NaOCl

Entry	Substrate	Product	Yield[a](%)	ee[b](%)	Config. of **6**[c]
1	**5a**	**7a**	37	89	*S*-(−)
2	**5b**	**7a**	35	88	*S*-(−)
3	**5c**	**7c**	54	94	*S*-(+)[d]
4	**5d**	**7d**	22	81	*R*-(+)[d]
5	**5e**	**7e**	57	69	*R*-(+)
6	**5f**	**7e**	49	60	*R*-(+)

[a] Yield of isolated pure compounds **7** (not optimized) based on enol phosphates **5** (see text).
[b] Determined by HPLC analysis (Chiracel OD, for details see Section 4) using racemic compounds as references.
[c] Configurations were assessed by comparison of the sign of optical rotation with literature data (see Section 4).
[d] Absolute configurations were assigned by comparing circular dichroism (CD) spectra of the purified α-hydroxy ketones **7c** and **7d** to the CD spectrum of (*S*)-2-hydroxy tetralone **7a** (see Supplementary information).

The degree of conversion of cyclic enol phosphates **5a**, **b**, and **d** to α-hydroxylated products **7a** and **d** is not as good as for phosphates **5c**, **e**, and **f** (Table 3). Low yields of **7a** and **d** are due in part to the participation of an aromatization pathway leading to the corresponding naphthalene and phenanthrene derivatives.[7c]

Oxidation of enol phosphates **5a**, **b**, and **c** afforded (*S*)-(−)-2-hydroxy tetralone **7a** and (*S*)-(+)-2-hydroxy benzosuberone **7c** in high enantioselectivity 88–94% (Table 3, entries 1–3). High enantioselectivity 81% was also observed for the oxidation of the enol phosphate **5d** but for **7d** the *R* configuration prevailed (Table 3, entry 4).

Stereoselectivity of the oxidation of tetrasubstituted enol phosphates **5e** and **f** leading to (*R*)-(+)-2-hydroxy-2-methyl-1-indanone **7e** is substantially lower at 69–60% ee (Table 3, entries 5 and 6).

The change of substituents RO in the phosphate group from EtO (**5a** and **e**) to PhO (**5b** and **f**) had no influence on the absolute configuration of products **7** (Table 3 entries 1, 2 and 5, 6).

The results presented in Tables 2 and 3 demonstrate that the degree of enantioselectivity and absolute configuration of α-hydroxy ketones in the catalytic oxidation of enol phosphates **2** and **5** by Jacobsen's chiral oxo complex is controlled by the substitution pattern of these phosphates, and particularly by the steric and electronic factors of the phosphate group in enol compounds. In order to rationalize the stereochemical results we have analyzed the mechanistic models proposed for metal-catalyzed asymmetric oxidation of trisubstituted olefins. Generally two proposals for the mechanism of oxygen-atom transfer from metal oxo complexes have been considered. One invokes substrate attack at both the metal and oxo centers to form an oxametallacycle intermediate.[21] The other widely accepted mechanism involves direct substrate attack at the oxo ligand with concerted or stepwise C–O bond formation.[19b,22] Two approaches of the olefin to the metal–oxygen bond have been proposed (Fig. 4): side-on along the direction of the chiral diamine bridge **b** (Jacobsen model)[23] and a skewed side-on attack **c** or **c′** along the metal C=N ligand of the diamine bridge (Katsuki model),[7e,g,h] which is more adequate for oxofunctionalization of trisubstituted olefins.

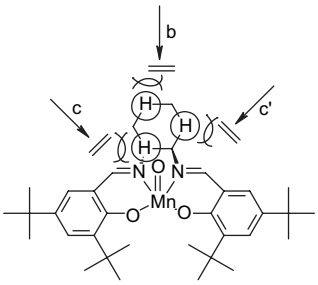
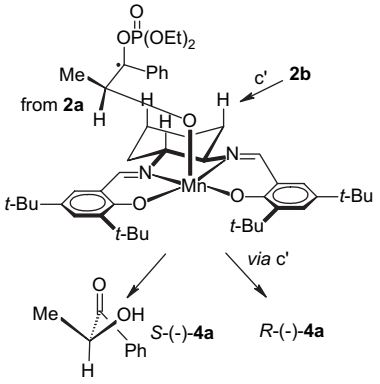


Figure 4. The view of the olefin approaches to the metal–oxygen bond.

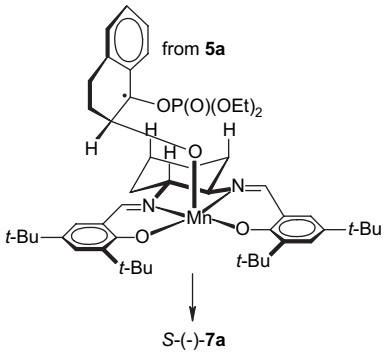
Oxidation of (*Z*) acyclic enol phosphates, containing alkoxy substituents at the phosphorus atom **2a**, **c**, **e–g**, **i**, and **j** led to the formation of *S*-configured α-hydroxy ketones. This means that one of the two possible enantiofacial orientations of these enol phosphates is favored. Following the suggestion by Adam[5a] we considered a skewed side-on approach of the enol phosphate to the oxo ligand of the catalyst, which would avoid steric and electronic interaction between the substrate's substituents and its salen framework. This enantiofacial approach, illustrated in Scheme 2, should lead to *S*-configured α-hydroxy ketones, in accord with our experimental data.



Scheme 2. Mechanistic proposal for the oxidation of enol phosphates **2a** and **2b** by the oxo-metal complex of catalyst **1**.

Enol phosphates with PhO groups at the phosphorus atom **2b**, **d**, and **h** display the opposite facial selectivity in the resulting α-hydroxy ketones. Again we considered the privileged enantiofacial orientation of enol phosphates, which means that the phosphate groups should avoid the arene rings of the salen ligand. The opposite configuration of α-hydroxy ketones **4a**, **c**, and **f** obtained from **2b**, **d**, and **h**, and the lower enantioselectivity in the oxidation of these substrates compared with the enantioselectivity of α-hydroxy ketones **4a**, **c**, and **f** derived from **2a**, **c**, **f**, and **g** can suggest that approach along trajectory **c′** is also possible (Scheme 2). A similar proposal explaining the stereoselectivity of catalytic oxidation of some aromatic derivatives has been reported in the literature.[7f]

The stereochemistry of epoxides obtained from the Mn–salen catalyzed oxidation of 1- or 2-methyl-3,4-dihydronaphthalene has been rationalized by taking the electronic effects of the aromatic moiety into consideration.[7e] So we proposed the approach of enol phosphate tetralone derivatives **5a** and **b** and enol phosphate benzosuberone derivative **5c** to the metal–oxo bond, shown in Scheme 3. In this approach the electronic interactions between salen benzene ring and arene substituents, including phenoxy groups in compound **5b**, orients these unsaturated substituents away from the salen benzene ring.



Scheme 3. Mechanistic proposal for the oxidation of the phosphate **5a** by the oxo-metal complex of catalyst **1**.

The α-hydroxy ketones of opposite configuration (*R*) **7d–e** were formed from catalytic epoxidation of the enol phosphate derivatives of 2,3-dihydro-phenanthren-4-one **5d** and of 2-methyl indanone **5e** and **f**. Such stereochemical results can be analyzed in terms of electronic as well as steric interactions of bulkier aromatic substituent with the salen framework. The lower enantiomeric excesses of 2-hydroxy-2-methyl indanone **7e** correlate with the poorer stereoselectivity of manganese-assisted oxidation of tetrasubstituted olefins.[7c] Thus, we have considered the top-on approach (the olefin and salen-ligand planes parallel)[7c] of enol phosphates **5d–f** to the oxo-metal catalyst.

Likely transition states were proposed for oxygen transfer from oxo Mn–salen complex to olefin to form the possible radical[22] or metallaoxetane intermediates.[21b] Adam et al. considered a metallaoxetane mechanism as more adequate for the oxofunctionalization of silyl enol ethers and ketene acetals to the corresponding α-hydroxy ketones and α-hydroxy acetals.[5a] It seems reasonable to assume on the basis of presented data for salen Mn-catalyzed epoxidation of enol phosphates, that direct attack of enol phosphate on an (oxo) manganese species generates a radical intermediate, which collapses to the epoxide, which then transposes to an α-hydroxy ketone.

3. Conclusion

We have shown that a variety of readily available (*Z*) and (*E*)-enol phosphates **2** and **5** are good synthons in the stereoselective syntheses of the corresponding α-hydroxy ketones **4** and **7**. Asymmetric epoxidation of these phosphates using Jacobsen's (salen) Mn(III) complex afforded α-hydroxy ketones **4** and **7** in high enantioselectivity up to 96%.

Our results demonstrate that absolute configuration of these target compounds is controlled by steric bulk and electronic aspects of the phosphate group in enol phosphates. By choosing the right substituents in the remote phosphate group of acyclic (*Z*)-enol phosphate **2** ArO or AlkO, both enantiomers of α-hydroxy ketones **4** may be obtained with

the same chiral catalyst. In contrast bulky aromatic groups display an influence on the enantioselectivity as well as on the sense of stereoselectivity of catalytic oxidation of cyclic (*E*)-enol phosphates **5**.

4. Experimental

4.1. General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200.13, 50.32, and 81.02 MHz, respectively (using deuterochloroform as solvent) unless otherwise noted. IR spectra were measured on an Ati Mattson Infinity FT IR 60. GC spectra were performed on a Hewlett–Packard 5890. MS spectra (EI, CI, and HRMS) were recorded on a Finnigan MAT 95 spectrometer. Microanalyses were carried out on EA1108 apparatus. Melting points were measured with PHMK Boetius (VEB Analytik Dresden) apparatus. Optical rotation values were measured in 100 mm cell on Perkin Elmer 241 MC under Na lamp radiation. The enantiomeric ratios were determined by HPLC analysis on the commercially available column Chiracel OD under conditions specified.

Chromatographic purification was performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with an indicated eluent. Chemicals and solvents were obtained from commercial sources and distilled or dried according to standard methods. The products were characterized by comparison of their data with those of known samples or by their spectral data.

4.1.1. Phosphoric acid diethyl ester 1-phenyl-propenyl ester 2a.[10d] General procedure. To a solution of freshly prepared LDA (21 mmol) in THF (50 mL) at −78 °C was added propiophenone (2.68 g, 20 mmol) in THF solution (10 mL) and the mixture was stirred under an Ar atmosphere for 1 h, then the solution of diethylphosphorochloridate (5.1 g, 30 mmol) in THF (5 mL) was dropped at the same temperature. The mixture was stirred and allowed to warm slowly to room temperature. After 1 h of stirring at ambient temperature the solvent was evaporated, the residue was dissolved in ether, washed with saturated NH_4Cl and water and dried ($MgSO_4$). Evaporation of solvent afforded the crude reaction mixture, which was analyzed by ^{1}H and ^{31}P NMR spectroscopy. Pure enol phosphate was obtained from column chromatography with petroleum ether–EtOAc (5:1 v/v) as single isomer, yellow oil (4.9 g, 91%); R_f 0.34 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2984, 2911, 2866, 1665, 1445, 1392, 1269, 1165, 1027, 979; δ_H (200 MHz, $CDCl_3$) 7.51–7.45 (2H, m, Ph), 7.35–7.24 (3H, m, Ph), 5.65 (1H, dq, *J*=7.0, 2.2 Hz, C=CH), 4.06 (4H, q, *J*=7.3 Hz, OCH_2CH_3), 1.87 (3H, dd, *J*=7.0, 3.0 Hz, C=CCH_3), 1.22 (6H, t, *J*=7.1 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 146.6 (d, *J*=9.1 Hz, POC=CH), 135.5 (*ipso*-Ph), 127.9, 127.8, 125.0 (Ph), 111.9 (d, *J*=5.9 Hz, POC=CH), 64.0 (d, *J*=5.9 Hz, $POCH_2CH_3$), 15.7 (d, *J*=6.8 Hz, $POCH_2CH_3$), 11.5 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −5.6; MS (CI-isobutane): *m/z* (%) 271 (80) $[M+H]^+$, 155 (100).

4.1.2. Phosphoric acid diphenyl ester 1-phenyl-propenyl ester 2b.[23] Single isomer, yellow oil (85%); R_f 0.51 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3061, 1667, 1591, 1490, 1294, 1216, 1189, 1024, 954, 764, 689; δ_H (200 MHz, $CDCl_3$) 7.51–7.45 (2H, m, Ph), 7.33–7.26 (7H, m, Ph, PhO), 7.19–7.11 (6H, m, PhO), 5.74 (1H, dq, *J*=7.0, 2.0 Hz, C=CH), 1.85 (3H, dd, *J*=7.0, 3.1 Hz, C=CCH_3); δ_C (50.3 MHz, $CDCl_3$) 150.3 (d, *J*=7.2 Hz, *ipso*-PhO), 146.8 (d, *J*=9.6 Hz, POC=CH), 134.8 (*ipso*-Ph), 129.5, 128.1, 125.1 (Ph, PhO), 119.8 (d, *J*=4.9 Hz, POPh), 112.6 (d, *J*=6.8 Hz, POC=CH), 11.5 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −16.98; MS (CI-isobutane): *m/z* (%) 367 (36) $[M+H]^+$, 251 (100), 95 (10).

4.1.3. Phosphoric acid diethyl ester 1-phenyl-but-1-enyl ester 2c. Single isomer, colorless oil (90%); R_f 0.25 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2980, 2934, 2874, 1660, 1494, 1446, 1273, 1165, 1099, 980, 767; δ_H (200 MHz, $CDCl_3$) 7.53–7.49 (2H, m, Ph), 7.35–7.26 (3H, m, Ph), 5.56 (1H, dt, *J*=7.3, 2.0 Hz, C=CH), 4.06 (4H, q, *J*=7.2 Hz, OCH_2CH_3), 2.38 (2H, dquint, *J*=7.5, 2.5 Hz, C=CCH_2), 1.23 (6H, t, *J*=7.1 Hz, OCH_2CH_3), 1.08 (3H, t, *J*=7.5 Hz, C=CCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 145.2 (d, *J*=9 Hz, POC=CH), 135.5 (*ipso*-Ph), 127.9, 127.8, 125.1 (Ph), 119.4 (d, *J*=6.4 Hz, POC=CH), 64.0 (d, *J*=5.9 Hz, $POCH_2CH_3$), 19.4 (CH_2), 15.7 (d, *J*=6.9 Hz, $POCH_2CH_3$), 13.4 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −5.64; MS (EI, 15 eV): *m/z* (%) 284 (38) $[M]^+$, 155 (100), 130 (42). Anal. calcd for $C_{14}H_{21}O_4P$ (284.29): C, 59.15; H, 7.44; P, 10.89. Found: C, 58.59; H, 7.71; P, 10.53%.

4.1.4. Phosphoric acid diphenyl ester 1-phenyl-but-1-enyl ester 2d. Single isomer, yellow oil (72%); R_f 0.42 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3062, 2968, 1590, 1489, 1299, 1216, 1189, 1042, 1011, 959, 765; δ_H (200 MHz, $CDCl_3$) 7.51–7.46 (2H, m, Ph), 7.40–7.32 (7H, m, Ph, PhO), 7.22–7.10 (6H, m, PhO), 5.64 (1H, dt, *J*=7.4, 1.8 Hz, C=CH), 2.33 (2H, dquint, *J*=7.5, 2.5 Hz, C=CCH_2), 1.04 (3H, t, *J*=7.5 Hz, C=CCH_2CH_3); NOESY (^{1}H–^{1}H): cross peak [5.64 (C=CH) and 7.51–7.46 (*o*-Ph)]; δ_C (50.3 MHz, $CDCl_3$) 150.3 (d, *J*=7.2 Hz, *ipso*-PhO), 145.4 (d, *J*=9.5 Hz, POC=CH), 132.7 (*ipso*-Ph), 129.6, 129.5, 129.3, 128.3, 128.1 (Ph, PhO), 125.3 (d, *J*=6.3 Hz, POPh), 119.8 (d, *J*=4.7 Hz, POC=CH), 19.4 (CH_2), 14.2 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −17.0; MS (CI-isobutane): *m/z* (%) 381 (56) $[M+H]^+$, 251 (100); calcd for $C_{22}H_{21}O_4P$ $[M]^+$: 380.1177; found $[M]^+$: 380.1179.

4.1.5. Phosphoric acid 2,2-dimethyl-propyl ester 1-phenyl-but-1-enyl ester 2e. Prepared as the mixture *E*/*Z* (1:1.5), a dark yellow oil (30%); R_f 0.6 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2980, 2870, 1671, 1668, 1495, 1440, 1394, 1360, 1275, 1268, 1200, 1165, 1020, 890, 880; δ_H (200 MHz, $CDCl_3$) 7.54–7.46 (2H, m, Ph), 7.45–7.40 (2H, m, Ph), 7.39–7.28 (6H, m, Ph), 5.68 (1H, dt, *J*=7.8, 2.6 Hz, C=CH, '*E*'), 5.57 (1H, dt, *J*=7.2, 2.1 Hz, C=CH, '*Z*'), 3.86–3.59 (8H, m, OCH_2C), 2.40 (2H, dquint, *J*=7.5, 2.5 Hz, C=CCH_2, '*Z*'), 2.17 (2H, dquint, *J*=7.6, 2.3 Hz, C=CCH_2, '*E*'), 1.08 (3H, t, *J*=7.5 Hz, C=CCH_2CH_3), 1.03 (3H, t, *J*=7.5 Hz, C=CCH_2CH_3), 0.89 (9H, m, CCH_3), 0.86 (9H, m, CCH_3); δ_C (50.3 MHz, $CDCl_3$) 146.9 (d, *J*=9.1 Hz, POC=CH, '*E*'), 145.5 (d, *J*=8.9 Hz, POC=CH, '*Z*'), 134.7 (*ipso*-Ph), 128.1, 127.8, 127.5, 125.5 (Ph), 118.2 (d, *J*=6.2 Hz, POC=CH, '*E*'), 116.9

(d, J=7.0 Hz, POC=*C*H, '*Z*'), 78.0, 77.8 (d, J=7.1 Hz, $POCH_2$), 32.1 (d, J=8.8 Hz, $C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 20.5 (CH_2, '*Z*'), 19.8 (CH_2, '*E*'), 15.1 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −5.55 (*Z*), −5.46 (*E*); MS (EI, 15 eV): *m/z* (%) 368 (35) $[M]^+$, 239 (100), 117 (25); calcd for $C_{20}H_{33}O_4P$ $[M]^+$: 368.2116; found $[M]^+$: 368.2109.

4.1.6. Phosphoric acid diethyl ester 1-phenyl-pent-1-enyl ester 2f. Single isomer, yellowish oil (76%); R_f 0.20 (2:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2981, 2934, 2900, 1670, 1471, 1369, 1280, 1028, 1013, 980, 801; δ_H (200 MHz, $CDCl_3$) 7.53–7.42 (2H, m, Ph), 7.36–7.26 (3H, m, Ph), 5.58 (1H, dt, J=7.3, 2.0 Hz, C=CH), 4.07, 4.06 (4H, 2q, J=7.2 Hz, OCH_2CH_3), 2.34 (2H, dq, J=7.4, 2.5 Hz, C=CCH_2), 1.49 (2H, q, J=7.5 Hz, C=CCH_2CH_2), 1.23 (6H, t, J=7.1 Hz, OCH_2CH_3), 0.97 (3H, t, J=7.3 Hz, C=$CCH_2CH_2CH_3$); δ_C (50.3 MHz, $CDCl_3$) 145.7 (d, J=9 Hz, POC=CH), 135.5 (*ipso*-Ph), 127.9, 127.5, 125.2 (Ph), 117.4 (d, J=6.1 Hz, POC=*C*H), 63.6 (d, J=6.0 Hz, $POCH_2CH_3$), 28.7, 22.3 (CH_2), 15.7 (d, J=6.5 Hz, $POCH_2CH_3$), 13.7 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −5.3; MS (CI-isobutane): *m/z* (%) 299 (100) $[M+H]^+$, 155 (12); calcd for $C_{15}H_{23}O_4P$ $[M]^+$: 298.1334; found $[M]^+$: 298.1331.

4.1.7. Phosphoric acid diisopropyl ester 1-phenyl-pent-1-enyl ester 2g. Single isomer, yellowish oil (90%); R_f 0.44 (2:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2980, 2934, 2873, 1649, 1450, 1386, 1267, 1179, 1010; δ_H (200 MHz, $CDCl_3$) 7.53–7.49 (2H, m, Ph), 7.37–7.26 (3H, m, Ph), 5.57 (1H, dt, J=7.4, 2.0 Hz, C=CH), 4.65 (2H, octet, J=6.3 Hz, $OCHCH_3$), 2.37 (2H, dq, J=7.3, 2.5 Hz, C=CCH_2), 1.51 (2H, sext, J=7.4 Hz, C=$CCH_2CH_2CH_3$), 1.31 (6H, t, J=6.1 Hz, $OCHCH_3$), 1.19 (6H, t, J=6.1 Hz, $OCHCH_3$), 0.99 (3H, t, J=7.3 Hz, C=$CCH_2CH_2CH_3$); δ_C (50.3 MHz, $CDCl_3$) 145.9 (d, J=9.2 Hz, POC=CH), 135.8 (*ipso*-Ph), 127.9, 127.8, 125.4 (Ph), 117.5 (d, J= 6.0 Hz, POC=*C*H), 72.8, 72.7 (d, J=6.0 Hz, $CH(CH_3)_2$), 28.1 (CH_2), 23.6, 23.5, 23.3, 23.2 ($CH(CH_3)_2$), 22.2 (CH_2), 13.7 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −7.3; MS (CI-isobutane): *m/z* (%) 327 (100) $[M+H]^+$, 183 (20). Anal. calcd for $C_{17}H_{27}O_4P$ (326.37): C, 62.56; H, 8.34; P, 9.49. Found: C, 61.90; H, 8.48; P, 10.05%.

4.1.8. Phosphoric acid bis-(4-methoxy-phenyl) ester 1-phenyl-pent-1-enyl ester 2h. Single isomer, yellowish oil (78%); R_f 0.70 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3060, 3028, 2983, 2909, 1660, 1495, 1275, 1130, 1052, 1031, 979; δ_H (200 MHz, $CDCl_3$) 7.50–7.46 (2H, m, Ph), 7.29–7.26 (3H, m, Ph), 7.02 (4H, d, J=9.0 Hz, 4-MeO–C_6H_4O), 6.78 (4H, d, J=9.1 Hz, 4-MeO–C_6H_4O), 5.63 (1H, dt, J=7.4, 1.8 Hz, C=CH), 3.76 (6H, s, OCH_3), 2.23 (2H, dq, J=7.4, 2.6 Hz, C=CCH_2), 1.44 (2H, sext, J=7.3 Hz, $CH_2CH_2CH_3$), 0.89 (3H, t, J=7.3 Hz, C=$CCH_2CH_2CH_3$); δ_C (50.3 MHz, $CDCl_3$) 156.9 (*ipso*-Ph), 152.5 (d, J=9.0 Hz, *ipso*-4-MeO–C_6H_4O), 144.4 (d, J=9.0 Hz, POC=CH), 128.2, 125.6 (Ph, 4-MeO–C_6H_4O) 121.0 (d, J=4.7 Hz, POC_6H_4–MeO), 118.3 (d, J=6.2 Hz, POC=*C*H), 114.6 (4-MeO–C_6H_4O), 55.6 (CH_3O), 28.1, 22.3 (CH_2), 13.8 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −15.99; MS (CI-isobutane): *m/z* (%) 455 (100) $[M+H]^+$; calcd for $C_{25}H_{27}O_6P$ $[M]^+$: 454.1545; found $[M]^+$: 454.1542.

4.1.9. Phosphoric acid 1,2-diphenyl-vinyl ester diethyl ester 2i.[17a,24] The mixture *E*/*Z* isomers (1/10), yellowish oil (75%); R_f 0.33 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2988, 2845, 1667, 1495, 1410, 1370, 1270, 1020, 980; δ_H (200 MHz, $CDCl_3$) 7.69–7.62 (4H, m, Ph), 7.45–7.09 (6H, m, Ph), 6.72 (1H, d, J=2.7 Hz, C=CH, '*E*'), 6.41 (1H, d, J=1.2 Hz, C=CH, '*Z*'), 4.22–4.06 (4H, m, OCH_2CH_3, '*E*'), 4.05–3.78 (4H, m, OCH_2CH_3, '*Z*'), 1.30 (6H, dt, J=7.0, 1.1 Hz, OCH_2CH_3, '*E*'), 1.11 (6H, dt, J=7.1, 1.2 Hz, OCH_2CH_3, '*Z*'); δ_C (50.3 MHz, $CDCl_3$) 145.2 (d, J=9.0 Hz, POC=CH), 136.3 (*ipso*-Ph), 134.5 (d, J=6 Hz, *ipso*-Ph), 129.0, 128.3, 127.5, 127.0, 126.3 (Ph), 117.2 (d, J=8.4 Hz, POC=*C*H, '*E*'), 116.0 (d, J=7.0 Hz, POC=*C*H, '*Z*'), 64.3 (d, J=6.1 Hz, $POCH_2CH_3$), 15.9 (d, J=7.6 Hz, $POCH_2CH_3$); δ_P (81.0 MHz, $CDCl_3$) −6.08 (*Z*), −5.5 (*E*); MS (CI-isobutane): *m/z* (%) 333 (100) $[M+H]^+$, 105 (18).

4.1.10. Phosphoric acid diethyl ester 1-(4-methoxy-phenyl)-propenyl ester 2j.[25] Single isomer, yellow oil (85%); R_f 0.25 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2980, 2961, 1667, 1505, 1260, 1022, 1007, 814; δ_H (200 MHz, $CDCl_3$) 7.44–7.41 (2H, 5 lines, Ar), 6.86–6.81 (2H, 6 lines, Ar), 5.52 (1H, dq, J=7.0, 2.0 Hz, C=CH), 4.06 (4H, dsext, J=7.1, 1.8 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 1.86 (3H, dd, J=7.0, 3.0 Hz, C=CCH_3), 1.25 (6H, t, J=7.0 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 144.3 (d, J=9.0 Hz, POC=CH), 140.5 (*ipso*-Ar), 127.8, 125.2 (Ar), 112.9 (d, J=6.0 Hz, POC=*C*H), 114.7 (Ar), 64.4 (d, J=5.5 Hz, $POCH_2CH_3$), 52.8 (CH_3O), 14.9 (d, J=6.6 Hz, $POCH_2CH_3$), 11.8 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −4.37; MS (EI, 15 eV): *m/z* (%) 300 (50) $[M]^+$, 155 (22), 146 (100).

4.1.11. Phosphoric acid 3,4-dihydro-naphthalen-1-yl ester diethyl ester 5a.[26] Yellow oil (85%); R_f 0.37 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2949, 2888, 2835, 1650, 1470, 1270, 1162, 1038, 952, 737; δ_H (200 MHz, $CDCl_3$) 7.42–7.38 (1H, m, Ph), 7.23–7.07 (3H, m, Ph), 5.87 (1H, dt, J=4.6, 1.7 Hz, C=CH), 4.19 (4H, 2q, J=7.4 Hz, OCH_2CH_3), 2.78 (2H, t, J=7.4 Hz, CH_2), 2.33–2.42 (2H, m, CH_2), 1.33 (6H, t, J=7.1 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 144.8 (d, J=7.7 Hz, POC=CH), 136.2 (C^{4a}–Ar), 130.1 (d, J=6.5 Hz, C^{8a}–Ar), 127.8, 127.0, 126.1, 121.0 (Ar), 110.3 (d, J=3.7 Hz, POC=*C*H), 64.1 (d, J=5.9 Hz, $POCH_2CH_3$), 27.0, 21.6 (CH_2), 15.8 (d, J=6.5 Hz, $POCH_2CH_3$); δ_P (81.0 MHz, $CDCl_3$) −5.7; MS (CI-isobutane): *m/z* (%) 283 (10) $[M+H]^+$, 157 (100); calcd for $C_{14}H_{19}O_4P$ $[M]^+$: 282.1020; found $[M]^+$: 282.1016.

4.1.12. Phosphoric acid 3,4-dihydro-naphthalen-1-yl ester diphenyl ester 5b. Yellowish oil (86%); R_f 0.70 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3068, 2939, 1649, 1590, 1488, 1299, 1187, 1083, 956, 765; δ_H (200 MHz, $CDCl_3$) 7.41–7.12 (14H, m, PhO, Ar), 6.01 (1H, dt, J=4.6, 2.0 Hz, C=CH), 2.83 (2H, t, J=8.0 Hz, CH_2), 2.37–2.49 (2H, m, CH_2); δ_C (50.3 MHz, $CDCl_3$) 150.4 (d, J=7.5 Hz, *ipso*-PhO), 145.1 (d, J=8.2 Hz, POC=CH), 136.3 (C^{4a}–Ar), 129.8 (C^{8a}–Ar), 129.6, 128.1, 127.6, 126.3, 125.3, 121.3 (PhO, Ar), 120.0 (d, J=4.9 Hz, POPh), 111.4 (d, J=4.0 Hz, POC=*C*H), 27.0, 21.8 (CH_2); δ_P (81.0 MHz, $CDCl_3$) −17.0; MS (CI-isobutane): *m/z* (%) 379 (40) $[M+H]^+$, 251 (100). Anal. calcd for $C_{22}H_{19}O_4P$ (378.36): C, 69.84; H, 5.06; P, 8.18. Found: C, 69.40; H, 5.01; P, 8.04%.

4.1.13. Phosphoric acid 8,9-dihydro-7*H*-benzocyclohepten-5-yl ester diethyl ester 5c. Yellowish oil (79%); R_f 0.32 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3060, 2983, 2932, 2861, 1648, 1449, 1272, 1119, 1030, 972, 903, 771; δ_H (200 MHz, $CDCl_3$) 7.57–7.52 (1H, m, Ph), 7.29–7.14 (3H, m, Ph), 6.08 (1H, dt, J=6.4, 2.5 Hz, C=CH), 4.19 (4H, dquint, J=7.5, 3.0 Hz, OCH_2CH_3), 2.72 (2H, t, J=6.2 Hz, CH_2), 2.08–2.02 (4H, m, CH_2), 1.29 (6H, t, J=7.1 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 146.4 (d, J=8.8 Hz, PO*C*=CH), 142.3 (C^{9a}–Ar), 135.4 (d, J=4.7 Hz, C^{4a}–Ar), 129.8, 129.2, 127.6, 126.9 (Ar), 117.1 (d, J=4.7 Hz, POC=*C*H), 65.1 (d, J=6.0 Hz, $POCH_2CH_3$), 34.3, 32.6, 25.5 (CH_2), 16.9 (d, J=6.8 Hz, $POCH_2CH_3$); δ_P (81.0 MHz, $CDCl_3$) −5.4; MS (CI-isobutane): *m/z* (%) 297 (100) $[M+H]^+$, 155 (8). Anal. calcd for $C_{15}H_{21}O_4P$ (296.30): C, 60.80; H, 7.14; P, 10.45. Found: C, 60.55; H, 7.33; P, 10.34%.

4.1.14. Phosphoric acid 1,2-dihydro-phenanthren-4-yl ester diethyl ester 5d. Yellowish oil (85%); R_f 0.20 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2957, 2924, 2869, 1688, 1460, 1279, 1260, 1090, 799; δ_H (200 MHz, $CDCl_3$) 8.63 (1H, dt, J=8.5, 1.2 Hz, Ar), 7.79–7.67 (2H, m, Ar), 7.49–7.27 (3H, m, Ar), 6.14 (1H, dt, J=5.6, 2.4 Hz, C=CH), 4.10 (4H, dquint, J=7.1, 1.7 Hz, OCH_2CH_3), 2.92–2.84 (2H, m, CH_2), 2.38–2.26 (2H, m, CH_2), 1.23 (6H, dt, J=7.1, 1.1 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 147.4 (d, J=8.0 Hz, PO*C*=CH), 137.3 (C^{IV}–Ar), 133.4 (C^{IV}–Ar), 129.8 (C^{IV}–Ar), 128.8, 128.5, 126.0, 124.8 (Ar), 119.2 (C^{IV}–Ar), 113.4 (d, J=4.7 Hz, POC=*C*H), 64.4 (d, J=5.9 Hz, $POCH_2CH_3$), 29.8, 22.6 (CH_2), 16.1 (d, J=6.5 Hz, $POCH_2CH_3$); δ_P (81.0 MHz, $CDCl_3$) −5.96; MS (CI-isobutane): *m/z* (%) 333 (100) $[M+H]^+$, 155 (8). Anal. calcd for $C_{18}H_{21}O_4P$ (332.33): C, 65.05; H, 6.37; P, 9.32. Found: C, 65.56; H, 6.12; P, 9.02%.

4.1.15. Phosphoric acid diethyl ester 2-methyl-3*H*-inden-1-yl ester 5e. Yellow oil (87%); R_f 0.5 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3047, 2983, 2911, 1647, 1463, 1395, 1300, 1136, 1051, 983, 911, 763; δ_H (200 MHz, $CDCl_3$) 7.43–7.13 (4H, m, Ar), 4.26 (4H, dquint, J=7.2, 1.4 Hz, OCH_2CH_3), 3.29 (2H, d, J=4.4 Hz, CH_2), 2.14 (3H, d, J=2.9 Hz, CH_3), 1.37 (6H, t, J=7.1 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 143.2 (d, J=7.7 Hz, PO*C*=CCH_3), 139.8 (d, J=3.6 Hz, C^{7a}–Ar), 139.7 (C^{3a}–Ar), 126.5 (d, J=6.3 Hz, POC=*C*CH_3), 126.1, 124.5, 123.7, 117.6 (Ar), 64.4 (d, J=6.0 Hz, $POCH_2CH_3$), 38.7 (CH_2), 15.9 (d, J=6.7 Hz, $POCH_2CH_3$), 12.1 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −5.19; MS (CI-isobutane): *m/z* (%) 283 (100) $[M+H]^+$, 256 (16). Anal. calcd for $C_{14}H_{19}O_4P$ (282.27): C, 59.57; H, 6.78; P, 10.97. Found: C, 59.51; H, 7.02; P, 10.78%.

4.1.16. Phosphoric acid diphenyl ester 2-methyl-3*H*-inden-1-yl ester 5f. White solid, mp 67 °C (68%); R_f 0.66 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3050, 2932, 1657, 1441, 1353, 1274, 1167, 1031, 967, 898, 721; δ_H (200 MHz, $CDCl_3$) 7.42–7.13 (14H, m, Ar, PhO), 3.31 (2H, d, J=4.5 Hz, CH_2), 2.07 (3H, d, J=3.0 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 150.5 (d, J=7.5 Hz, POPh), 143.2 (d, J=9.9 Hz, PO*C*=CCH_3), 139.7 (C^{3a}–Ar), 139.2 (d, J=2.1 Hz, C^{7a}–Ar), 129.6 (PhO), 127.2 (d, J=6.7 Hz, POC=*C*CH_3), 126.3 (Ar), 125.4 (PhO), 124.8, 123.4 (Ar), 120.0 (d, J=4.8 Hz, POPh), 117.6 (Ar), 38.8 (CH_2), 12.0 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −16.8; MS (CI-isobutane): *m/z* (%) 379 (100) [M+H], 95 (8). Anal. calcd for $C_{22}H_{19}O_4P$ (378.36): C, 69.84; H, 5.06; P, 8.18. Found: C, 69.92; H, 5.12; P, 7.97%.

4.2. Syntheses of racemic α-hydroxy ketones 4 and 7

4.2.1. Epoxidation procedure.[27]

4.2.1.1. Phosphoric acid diethyl ester 2-phenyl-3-methyl-oxiranyl ester 3a. To a solution of enol phosphate **2a** (810 mg, 3 mmol) in methylene chloride (30 mL) was added a solution of *m*-chloroperbenzoic acid (1 g, 6 mmol) in CH_2Cl_2 (30 mL) at −20 °C, with stirring. The reaction mixture was stirred at this temperature until enol phosphate disappeared (monitored by TLC). Then the reaction mixture was washed with sodium thiosulfate (10%, 2×10 mL), saturated $NaHCO_3$ (2×5 mL), and water (10 mL) and dried ($MgSO_4$). Evaporation of solvent afforded the crude epoxide **3a**. Colorless oil (755 mg, 88%); R_f 0.54 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2987, 2885, 2807, 1450, 1274, 1167, 1064, 1028, 699; δ_H (200 MHz, $CDCl_3$) 7.52–7.47 (2H, m, Ph), 7.40–7.33 (3H, m, Ph), 4.07, 4.06 (4H, 2q, J=7.3 Hz, OCH_2CH_3), 3.04 (1H, dq, J=5.3, 1.9 Hz, POCOC(*H*)CH_3), 1.56 (3H, d, J=5.3 Hz, POCOC(H)C*H*$_3$), 1.26 (3H, dt, J=7.1, 1.1 Hz, OCH_2CH_3), 1.16 (3H, dt, J=7.1, 1.1 Hz, OCH_2CH_3); δ_C (50.3 MHz, $CDCl_3$) 136.1 (*ipso*-Ph), 128.9, 127.9, 125.3 (Ph), 88.6 (d, J=9.0 Hz, PO*C*OC(H)CH_3), 68.8 (d, J=6.7 Hz, POCO*C*(H)CH_3), 64.0 (d, J=5.9 Hz, $POCH_2CH_3$), 15.8 (t, J=6.5 Hz, $POCH_2CH_3$), 10.0 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −3.97; MS (CI-isobutane): *m/z* (%) 287 (100) $[M+H]^+$, 211 (38), 151 (34), 135 (16); calcd for $C_{13}H_{19}O_5P$ $[M]^+$: 286.0970; found $[M]^+$: 286.0962.

4.2.1.2. Phosphoric acid diphenyl ester 2-phenyl-3-methyl-oxiranyl ester 3b. Yellow oil (74%); R_f 0.61 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3068, 2910, 1588, 1491, 1395, 1312, 1214, 1128, 1092, 959, 773; δ_H (200 MHz, $CDCl_3$) 7.53–7.05 (15H, m, Ph, OPh), 3.11 (1H, dq, J=5.3, 1.9 Hz, POCOC(*H*)CH_3), 1.54 (3H, d, J=5.3 Hz, POCOC(H)C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 156.7 (d, J=7.0 Hz, *ipso*-PhO), 135.3 (*ipso*-Ph), 129.6, 128.3, 125.4 (Ph, PhO), 120.1 (d, J=4.4 Hz, POPh), 87.8 (d, J=9.0 Hz, PO*C*OC(H)CH_3), 72.2 (d, J=6.7 Hz, POCO*C*(H)CH_3), 17.1 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −15.3; MS (CI-isobutane): *m/z* (%) 383 (100) $[M+H]^+$, 289 (4); calcd for $C_{21}H_{19}O_5P$ $[M]^+$: 382.0970; found $[M]^+$: 382.0965.

4.2.1.3. Phosphoric acid diethyl ester 2-phenyl-3-ethyl-oxiranyl ester 3c. Colorless oil (85%); R_f 0.5 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2967, 1449, 1259, 1031, 816, 699; δ_H (200 MHz, $CDCl_3$) 7.50–7.45 (2H, m, Ph), 7.40–7.33 (3H, m, Ph), 4.07, 4.06 (4H, 2q, J=7.3 Hz, OCH_2CH_3), 2.85 (1H, dt, J=6.2, 1.9 Hz, POCOC(*H*)CH_2), 1.87 (2H, quint, J=7.2 Hz, POCOC(H)C*H*$_2$), 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.14 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.09 (3H, t, J=7.3 Hz, POCOC(H)CH_2C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 136.1 (*ipso*-Ph), 128.8, 128.1, 125.7 (Ph), 86.3 (d, J=8.8 Hz, PO*C*OC(H)CH_2), 67.3 (d, J=6.9 Hz, POCO*C*(H)CH_2), 63.9 (d, J=5.7 Hz, $POCH_2CH_3$), 20.8 (CH_2), 15.7 (t, J=6.6 Hz, $POCH_2CH_3$), 9.8 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −4.29; MS (CI-isobutane): *m/z* (%)

301 (100) $[M+H]^+$, 155 (12), 149 (8); calcd for $C_{14}H_{21}O_5P$ $[M]^+$: 300.1126; found $[M]^+$: 300.1119.

4.2.1.4. Phosphoric acid diphenyl ester 2-phenyl-3-ethyl-oxiranyl ester 3d. Yellow oil (80%); R_f 0.7 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3032, 2990, 1595, 1460, 1297, 1187, 946, 790; δ_H (200 MHz, $CDCl_3$) 7.51–7.04 (2H, m, Ph), 7.36–7.09 (13H, Ph, OPh), 2.93 (1H, dt, J=6.2, 2.1 Hz, POCOC(*H*)CH_2), 1.83 (2H, quint, J=7.5 Hz, POCOC(H)C*H*$_2$), 1.04 (3H, t, J=7.5 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 156.7 (d, J=7.0 Hz, *ipso*-PhO), 134.4 (*ipso*-Ph), 129.7, 129.1, 128.3, 127.9, 125.8 (Ph, PhO), 125.0 (d, J=4.8 Hz, POPh), 86.8 (d, J=8.5 Hz, PO*C*OC(H)CH_2), 68.2 (d, J=6.7 Hz, POCO*C*(H)CH_2), 20.2 (CH_2), 13.5 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −15.48; MS (CI-isobutane): *m/z* (%) 397 (100) $[M+H]^+$, 155 (12), 149 (10), 95 (15); calcd for $C_{22}H_{21}O_5P$ $[M]^+$: 396.1126; found $[M]^+$: 396.1119.

4.2.1.5. Phosphoric acid 2,2-dimethyl-propyl ester 2-phenyl-3-ethyl-oxiranyl ester 3e. Colorless oil (30%); R_f 0.55 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2952, 2901, 1460, 1310, 1225, 1165, 885; δ_H (200 MHz, $CDCl_3$) 7.58–7.41 (2H, m, Ph), 7.39–7.27 (3H, m, Ph), 3.68 (4H, d, J=4.6 Hz, OC*H*$_2$C$(CH_3)_3$), 2.87 (1H, dt, J=5.0, 2.0 Hz, POCOC(*H*)CH_2), 1.92 (2H, q, J=7.6 Hz, POCOC(H)C*H*$_2$), 1.11 (3H, t, J=7.5 Hz, CH_2CH_3), 0.93, 0.86 (18H, 2×s, C$(CH_3)_3$); δ_C (50.3 MHz, $CDCl_3$) 133.2 (*ipso*-Ph), 128.5, 128.1, 127.5, 126.1 (Ph), 83.1 (d, J=8.0 Hz, PO*C*OC(H)CH_2), 78.4 (t, J=7.0 Hz, POCH_2), 67.1 (t, J=7.0 Hz, POCO*C*(H)-CH_2), 32.3 (d, J=6.7 Hz, *C*$(CH_3)_3$), 25.9 (C(*C*$H_3)_3$), 21.2 (CH_2), 15.5 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −4.06; MS (CI-isobutane): *m/z* (%) 385 (100) $[M+H]^+$, 239 (40); calcd for $C_{20}H_{33}O_5P$ $[M]^+$: 384.2065; found $[M]^+$: 384.2057.

4.2.1.6. Phosphoric acid diethyl ester 2-phenyl-3-propyl-oxiranyl ester 3f. Colorless oil (90%); R_f 0.3 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2970, 2860, 1498, 1244, 1052, 997, 756; δ_H (200 MHz, $CDCl_3$) 7.52–7.45 (2H, m, Ph), 7.42–7.28 (3H, m, Ph), 4.07, 4.06 (4H, 2q, J=7.3 Hz, OC*H*$_2$CH$_3$), 2.90 (1H, dt, J=6.0, 2.0 Hz, POCOC(*H*)CH_2), 1.91–1.80 (2H, m, POCOC(H)C*H*$_2$), 1.56 (2H, sext, J=7.3 Hz, CH_2C*H*$_2$), 1.26 (3H, dt, J=7.1, 1.1 Hz, OCH_2C*H*$_3$), 1.16 (3H, dt, J=7.0, 1.1 Hz, OCH_2C*H*$_3$), 1.01 (3H, t, J=7.3 Hz, CH_2CH_2C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 136.1 (*ipso*-Ph), 128.9, 128.3, 125.8 (Ph), 85.2 (d, J=8.8 Hz, PO*C*OC(H)CH_2), 66.4 (d, J=7.0 Hz, POCO*C*(H)CH_2), 63.9 (d, J=5.4 Hz, PO*C*H$_2$CH$_3$), 29.3, 19.1 (CH_2), 15.9 (t, J=6.6 Hz, POCH$_2$*C*H$_3$), 13.8 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −3.93; MS (CI-isobutane): *m/z* (%) 315 (100) $[M+H]^+$, 155 (10); calcd for $C_{15}H_{23}O_5P$ $[M]^+$: 314.1283; found $[M]^+$: 314.1281.

4.2.1.7. Phosphoric acid diisopropyl ester 2-phenyl-3-propyl-oxiranyl ester 3g. Colorless oil (83%); R_f 0.5 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2975, 2901, 2877, 1460, 1305, 1270, 1035, 983, 701; δ_H (200 MHz, $CDCl_3$) 7.52–7.48 (2H, m, Ph), 7.46–7.34 (3H, m, Ph), 4.60 (2H, septet, J=6.3 Hz, OC*H*CH$_3$), 2.88 (1H, dt, J=6.0, 1.8 Hz, POCOC(*H*)CH_2), 1.93–1.81 (2H, m, POCOC(H)C*H*$_2$), 1.57 (2H, sext, J=7.1 Hz, CH_2C*H*$_2$), 1.27 (3H, dd, J=6.1, 4.0 Hz, OCHC*H*$_3$), 1.12 (3H, d, J=6.0 Hz, OCHC*H*$_3$), 1.00 (3H, t, J=7.3 Hz, C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 136.1 (*ipso*-Ph), 128.8, 128.3, 127.8, 125.4 (Ph), 87.3 (d, J=8.5 Hz, PO*C*OC(H)CH_2), 72.8 (d, J=6.0 Hz, PO*C*H$(CH_3)_2$), 64.4 (d, J=7.2 Hz, POCO*C*(H)CH_2), 29.3 (CH_2), 23.5, 23.4, 23.25, 23.2 (CH(*C*H$_3)_2$), 20.1 (CH_2), 13.8 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −6.09; MS (CI-isobutane): *m/z* (%) 343 (100) $[M+H]^+$, 183 (16); calcd for $C_{17}H_{27}O_5P$ $[M]^+$: 342.1596; found $[M]^+$: 342.1593.

4.2.1.8. Phosphoric acid bis-(4-methoxy-phenyl) ester 2-phenyl-3-propyl-oxiranyl ester 3h. Yellow oil (55%); R_f 0.57 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2961, 1503, 1253, 1185, 1035, 967, 833; δ_H (200 MHz, $CDCl_3$) 7.51–7.43 (2H, m, Ph), 7.35–7.26 (3H, Ph), 7.09–6.95 (4H, m, 4-MeOC_6H_4O), 6.82–6.75 (4H, m, 4-MeOC_6H_4O), 3.77 (6H, s, OCH_3), 2.94 (1H, dt, J=6.0, 1.9 Hz, POCOC(*H*)CH_2), 1.77 (2H, q, J=7.0 Hz, POCOC(H)C*H*$_2$), 1.49 (2H, sext, J=7.4 Hz, CH_2C*H*$_2$CH$_3$), 0.96 (3H, t, J=7.4 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 156.8 (*ipso*-4-MeO-C_6H_4O), 135.7 (*ipso*-Ph), 129.1, 128.6, 128.3, 126.0 (Ph, 4-MeOC_6H_4O), 120.9 (d, J=4.8 Hz, POC_6H_4–OMe), 114.5 (4-MeOC_6H_4O), 87.5 (d, J=8.3 Hz, PO*C*OC(H)CH_2), 66.3 (d, J=7.0 Hz, POCO*C*(H)CH_2), 55.5 (CH_3O), 29.3, 19.2 (CH_2), 13.7 (CH_3); δ_P (81.0 MHz, $CDCl_3$) −14.78; MS (CI-isobutane): *m/z* (%) 471 (100) $[M+H]^+$, 311 (12); calcd for $C_{25}H_{27}O_7P$ $[M]^+$: 470.1494; found $[M]^+$: 470.1487.

4.2.1.9. Phosphoric acid diethyl ester 2-phenyl-3-phenyl-oxiranyl ester 3i. Colorless oil (55%); R_f 0.55 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2983, 2870, 1456, 1394, 1271, 1165, 1035; δ_H (200 MHz, $CDCl_3$) 7.64–7.60 (2H, m, Ph), 7.58–7.52 (2H, m, Ph), 7.51–7.29 (6H, m, Ph), 3.97 (1H, s, POCOC(*H*)Ph), 3.88 (4H, dq, J=7.1, 2.9 Hz, OC*H*$_2$CH$_3$), 1.14, 1.13 (6H, dt, J=7.1, 0.6 Hz, OCH_2C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 133.5 (*ipso*-Ph), 129.3, 129.1, 128.7, 128.6 (Ph), 81.1 (d, J=8.0 Hz, PO*C*OC(H)Ph), 80.2 (d, J=7.6 Hz, POCO*C*(H)Ph), 64.2 (d, J=5.4 Hz, PO*C*H$_2$CH$_3$), 15.9 (t, J=6.6 Hz, POCH$_2$*C*H$_3$); δ_P (81.0 MHz, $CDCl_3$) −4.04; MS (CI-isobutane): *m/z* (%) 349 (100) $[M+H]^+$, 333 (10), 243 (16), 195 (40), 155 (74); calcd for $C_{18}H_{21}O_5P$ $[M]^+$: 348.1126; found $[M]^+$: 348.1121.

4.2.1.10. Phosphoric acid 2,3-dihydro-1a*H*-1-oxa-cyclopropa[*a*]naphthalen-7b-yl ester diethyl ester 6a. Yellowish oil (88%); R_f 0.25 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2970, 2870, 1450, 1410, 1285, 1150, 1070, 1053, 980; δ_H (200 MHz, $CDCl_3$) 7.30–7.27 (3H, m, Ar), 7.14–7.09 (1H, m, Ar), 4.40 (1H, d, J=3.0 Hz, POCOC(*H*)CH_2), 4.20 (4H, dquint, J=7.1, 0.6 Hz, OC*H*$_2$CH$_3$), 2.80–2.52 (2H, m, CH_2), 2.43–2.30 (1H, m, CH_2), 1.87 (1H, ddd, J=14.8, 12.9, 6.1 Hz, C*H*$_2$), 1.36, 1.35, 1.34, 1.33 (6H, 4t, J=7.1 Hz, OCH_2C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 131.7 (C^{IV}–Ar), 130.3 (C^{IV}–Ar), 129.8, 129.4, 127.8, 127.3 (Ar), 79.1 (d, J=6.0 Hz, PO*C*OCH), 64.4 (d, J=6.0 Hz, PO*C*H$_2$CH$_3$), 63.4 (d, J=5.0 Hz, POCO*C*H), 30.9, 27.4 (CH_2), 15.9 (d, J=6.6 Hz, POCH$_2$*C*H$_3$); δ_P (81.0 MHz, $CDCl_3$) −6.09; MS (CI-isobutane): *m/z* (%) 299 (100) $[M+H]^+$, 283 (20), 155 (36); calcd for $C_{14}H_{19}O_5P$ $[M]^+$: 298.0970; found $[M]^+$: 298.0964.

4.2.1.11. Phosphoric acid 2,3-dihydro-1a*H*-1-oxa-cyclopropa[*a*]naphthalen-7b-yl ester diphenyl ester 6b. Orange oil (52%); R_f 0.66 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3030, 2896, 1591, 1456, 1217, 1128, 1042, 908,

735; δ_H (200 MHz, $CDCl_3$) 8.07–8.02 (1H, m, Ar), 7.55–7.47 (1H, m, Ar), 7.39–7.09 (12H, m, Ar, Ph), 4.39 (1H, d, J=2.8 Hz, POCOC(*H*)CH_2), 2.85–2.55 (2H, m, CH_2), 2.48–2.36 (1H, m, CH_2), 1.87 (1H, ddd J=14.1, 13.1, 6.1 Hz, C*H*$_2$); δ_C (50.3 MHz, $CDCl_3$) 150.4 (d, J=7.0 Hz, *ipso*-OPh), 136.5 (C^{IV}–Ar), 129.7 (C^{IV}–Ar), 129.6 (OPh), 128.2, 128.0, 127.3, 127.0 (Ar), 125.4 (OPh), 120.4 (OPh), 82.8 (d, J=6.4 Hz, PO*C*OCH), 66.5 (d, J=4.0 Hz, POCO*C*H), 30.8, 27.3 (CH_2); δ_P (81.0 MHz, $CDCl_3$) −17.3; MS (EI): *m*/*z* (%) 394 (4) $[M]^+$, 300 (44), 250 (66), 144 (46), 94 (100); calcd for $C_{22}H_{19}O_5P$ $[M]^+$: 394.0970; found $[M]^+$: 394.0969.

4.2.1.12. Phosphoric acid diethyl ester 1a,2,3,4-tetrahydro-1-oxa-benzo[*a*]cyclopropa[*c*]cyclohepten-8b-yl ester 6c. Yellow oil (60%); R_f 0.45 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 2995, 2880, 1440, 1310, 1270, 1160, 1038, 980; δ_H (200 MHz, $CDCl_3$) 7.77–7.71 (1H, m, Ph), 7.31–7.25 (3H, m, Ph), 3.91 (4H, m, OC*H*$_2$CH$_3$), 3.31 (1H, ddd, J=13.9, 12.1, 6.3 Hz, POCOC(*H*)CH_2), 2.73–2.67 (2H, m, CH_2), 2.08–1.90 (4H, m, CH_2), 1.29, 1.28 (6H, 2t, J=7.1 Hz, OCH$_2$C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 137.8 (C^{4a}–Ar), 132.6 (C^{8a}–Ar), 129.6, 129.3, 128.7, 126.7 (Ar), 84.2 (d, J=6.1 Hz, PO*C*OCH), 64.1 (d, J=5.4 Hz, PO*C*H$_2$CH$_3$), 60.6 (d, J=4.6 Hz, POCO*C*H), 30.7, 27.0, 22.6 (CH_2), 15.7 (d, J=4.8 Hz, POCH$_2$*C*H$_3$); δ_P (81.0 MHz, $CDCl_3$) −6.23; MS (CI-isobutane): *m*/*z* (%) 313 (100) $[M+H]^+$, 297 (18), 155 (16); calcd for $C_{15}H_{21}O_5P$ $[M]^+$: 312.1126; found $[M]^+$: 312.1128.

4.2.2. Hydrolysis of epoxides 3 and 6.

4.2.2.1. 2-Hydroxy-1-phenyl-1-propan-1-one 4a.[5a] To a solution of **3a** (755 mg, 2.64 mmol) in diethyl ether (10 mL), trifluoroacetic acid (2 mL) in water (10 mL) was added with stirring at 5 °C. The reaction was stirred and monitored by TLC. After 24–48 h the reaction mixture was diluted with chloroform, washed with saturated $NaHCO_3$ and water and dried ($MgSO_4$). After removal of the solvent the crude product was purified by column chromatography with petroleum ether/EtOAc as an eluent (5:1 v/v) to give 309 mg (78% yield) of product as colorless liquid; R_f 0.52 (2:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 7.95–7.91 (2H, m, Ph), 7.63–7.46 (3H, m, Ph), 5.16 (1H, q, J=7.0 Hz, C*H* (OH)), 3.04 (1H, br s, OH), 1.45 (3H, d, J=7.0 Hz, CH_3); MS (CI-isobutane): *m*/*z* (%) 151 (100) $[M+H]^+$, 133 (16), 123 (32).

4.2.2.2. 2-Hydroxy-1-phenyl-1-butan-1-one 4c.[5a] Colorless liquid; yield 76%; R_f 0.69 (2:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 7.93–7.88 (2H, m, Ph), 7.66–7.57 (1H, m, Ph), 7.53–7.45 (2H, m, Ph), 5.16 (1H, dd, J=6.8, 3.8 Hz, C*H* (OH)), 3.70 (1H, br s, OH), 1.85 (1H, qdd, J=7.4, 7.0, 3.8 Hz, CH_2), 1.61 (1H, septet, J=7.0 Hz, CH_2), 0.93 (3H, t, J=7.4 Hz, CH_3); MS (CI-isobutane): *m*/*z* (%) 165 (100) $[M+H]^+$, 147 (10), 136 (18).

4.2.2.3. 2-Hydroxy-1-phenyl-1-pentan-1-one 4f.[28] Colorless liquid; yield 55%; R_f 0.75 (1:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 7.91–7.88 (2H, 2 lines, Ph), 7.60–7.44 (3H, m, Ph), 5.07 (1H, dd, J=6.7, 3.2 Hz, C*H* (OH)), 3.66 (1H, br s, OH), 1.81 (1H, dq, J=3.2, 5.9 Hz, CH_2), 1.60–1.34 (3H, m, HC*H*–C*H*$_2$), 0.89 (3H, t, J=7.0 Hz, CH_3); δ_C (50.3 MHz, $CDCl_3$) 202.1 (C=O), 133.6 (*ipso*-Ph), 133.8, 128.7, 128.4 (Ph), 72.8 (CH(OH), 37.8, 18.1 (CH_2), 13.7 (CH_3); MS (CI-isobutane): *m*/*z* (%) 179 (100) $[M+H]^+$, 163 (16), 105 (10).

4.2.2.4. 2-Hydroxy-1,2-diphenyl-ethanone 4i.[29] White solid, mp 135 °C; yield 73%; R_f 0.62 (1:1 petroleum ether–EtOAc); δ_H (200 MHz, CD_3OD) 7.98–7.93 (2H, m, Ph), 7.56–7.26 (8H, m, Ph), 6.11 (1H, s, C*H* (OH)), 4.87 (1H, br s, OH); MS (CI-isobutane): *m*/*z* (%) 213 (100) $[M+H]^+$, 195 (74).

4.2.2.5. 2-Hydroxy-1-(4-methoxyphenyl)-propan-1-one 4j.[30] Colorless liquid; yield 48%; R_f 0.5 (1:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 7.91 (2H, d, J=8.9 Hz, Ph), 6.96 (2H, d, J=8.9 Hz, Ph), 5.10 (1H, q, J=7.0 Hz, C*H* (OH)), 3.88 (3H, s, OCH_3), 3.25 (1H, br s, OH), 1.43 (3H, d, J=7.0 Hz, CH_3); MS (CI-isobutane): *m*/*z* (%) 181 (100) $[M+H]^+$, 163 (16), 135 (20).

4.2.2.6. 2-Hydroxy-3,4-dihydro-2*H*-naphthalen-1-one 7a.[29] Colorless liquid; yield 68%; R_f 0.49 (1.5:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 8.10–7.97 (1H, m, Ph), 7.62–7.31 (3H, m, Ph), 4.40 (1H, dd, J=13.4, 5.4 Hz, C*H* (OH)), 3.99 (1H, br s, OH), 3.26–2.97 (2H, m, CH_2), 2.60–2.48 (1H, m, CH_2), 2.04 (1H, ddd, J=17.4, 12.5, 5.3 Hz, CH_2); MS (CI-isobutane): *m*/*z* (%) 163 (100) $[M+H]^+$, 157 (36), 145 (32).

4.2.2.7. 6,7,8,9-Tetrahydro-6-hydroxy-5*H*-benzocyclohepten-5-one 7c.[31] Colorless liquid; yield 60%; R_f 0.55 (1:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 7.95–7.90 (1H, m, Ph), 7.50–7.22 (3H, m, Ph), 4.50 (1H, dd, J=10.0, 5.4 Hz, C*H*(OH)), 4.00 (1H, br s, OH), 3.03–2.90 (2H, m, CH_2), 2.53–2.33 (1H, m, CH_2), 2.30–2.09 (1H, m, CH_2), 1.90–1.59 (2H, m, CH_2); MS (CI-isobutane): *m*/*z* (%) 177 (100) $[M+H]^+$, 157 (36), 145 (32).

4.2.2.8. 2,3-Dihydro-3-hydroxy-1*H*-phenanthren-4-one 7d. Dark yellow oil; yield 66%; R_f 0.58 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} 3454, 2962, 1664, 1260, 1089, 1021, 800; δ_H (200 MHz, $CDCl_3$) 9.35 (1H, d, J=8.6 Hz, Ar), 7.97 (1H, d, J=8.4 Hz, Ar), 7.83 (1H, d, J=8.1 Hz, Ar), 7.66 (1H, dd, J=7.4, 8.1 Hz, Ar), 7.53 (1H, t, J=7.4 Hz, Ar), 7.31 (1H, d, J=8.4 Hz, Ar), 4.48 (1H, dd, J=5.0, 13.6 Hz, C*H*–OH), 4.31 (1H, br s, OH), 3.99 (1H, ddd, J=4.3, 13.0, 17.3 Hz, CH_2), 3.20 (1H, dd, J=4.0, 17.5 Hz, CH_2), 2.61 (1H, dd, J=5.8, 6.1 Hz, CH_2), 2.16 (1H, ddd, J=4.8, 12.8, 17.5 Hz, CH_2); δ_C (50.3 MHz, $CDCl_3$) 201.6 (C=O), 146.5 (C^{IV}–Ar), 135.0 (Ar), 132.5 (C^{IV}–Ar), 131.2 (C^{IV}–Ar), 129.1 (Ar), 128.4 (Ar), 126.7 (Ar), 126.2 (Ar), 125.8 (Ar), 124.8 (C^{IV}–Ar), 73.8 (CHOH), 32.2 (CH_2), 29.1 (CH_2); MS (CI-isobutane): *m*/*z* (%) 213 (100) $[M+H]^+$; calcd for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.0916; found $[M+H]^+$: 213.0910.

4.2.2.9. 2-Hydroxy-2-methyl 1-indanone 7e.[32] White solid, mp 49 °C; yield 65%; R_f 0.54 (1:1 petroleum ether–EtOAc); δ_H (200 MHz, $CDCl_3$) 7.77 (1H, d, J=7.6 Hz, Ph), 7.67 (1H, m, Ph), 7.49–7.36 (2H, m, Ph), 3.27 (2H, s, CH_2), 2.48 (1H, br s, OH), 1.44 (3H, s, CH_3); MS (CI-isobutane): *m*/*z* (%) 163 (100) $[M+H]^+$, 145 (16).

4.3. General procedure for asymmetric oxidation

To a stirred solution of NaOCl (4 mL, 7 equiv) and phosphate buffer (4 mL, pH=11) the mixture of appropriate enol phosphate (1.1 mmol, 1 equiv), 4-phenylpyridine *N*-oxide (PPNO) (30 mol %), and (salen) Mn(III) complex **1** (7 mol %) in 4 mL CH_2Cl_2 was added at −10 °C. The stirring of the reaction mixture was continued at 0 °C for 18 h (the reaction was monitored by TLC), *n*-hexane (40 mL) was added, organic layer was separated, washed with distilled water and dried ($MgSO_4$). Evaporation of solvent afforded crude epoxide, which was diluted with Et_2O and treated with CF_3COOH in H_2O (10 mL) at 0 °C. Stirring was continued until TLC analysis revealed the complete consumption of epoxide. Then the mixture was washed with $NaHCO_3$, $CHCl_3$ was added, the organic layer was separated, washed with water and dried. After removal of the solvent the residue was subjected to silica gel column chromatography with hexane–ethyl acetate (3:1 v/v) as the eluent, to afford pure, optically active α-hydroxy ketones **4** and **7**. Spectral data of **4** and **7** as described.

4.3.1. Determination of the enantiomeric purity of compounds 4 and 7. The enantiomeric ratios were determined by HPLC analysis on Chiracel OD column. All runs were carried out at room temperature.

4.3.1.1. HPLC conditions for compounds 4 (Table 2 in text). *S*-(−)-**4a** Entry 1: 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 17.3 (*S*), t_R [min] 19.8 (*R*), absolute configuration of product determined by comparison of sign of optical rotation to the literature value (*S*)-**4a**: $[\alpha]_D^{20}$ −82.7 (*c* 3.6, $CHCl_3$); lit. $[\alpha]_D^{20}$ −80.9 (*c* 2.0, $CHCl_3$), ee=95%;[33a] $[\alpha]_D^{20}$ −58.3 (*c* 2.0, $CHCl_3$), ee=62%.[33b]

R-(+)-**4a**, Entry 2: 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 17.7 (*S*), t_R [min] 20.1 (*R*), $[\alpha]_D^{20}$ +65.4 (*c* 0.75, $CHCl_3$); lit. (*R*)-**4a**: $[\alpha]_D^{20}$ +81.0 (*c* 1.5, $CHCl_3$);[30] $[\alpha]_D^{20}$ +82.2 (*c* 2.0, $CHCl_3$), ee=96%.[34]

S-(−)-**4c** Entry 3: 4% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 14.7 (*S*), t_R [min] 17.8 (*R*), $[\alpha]_D^{20}$ −29.3 (*c* 1.1, $CHCl_3$); lit. (*S*)-**4c**: $[\alpha]_D^{20}$ −30.78 (*c* 2.24, $CHCl_3$), ee=95% was determined by Eu(hfc)$_3$ NMR shift reagent of acetate derivative.[33a]

R-(+)-**4c** Entry 4: 4% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 14.5 (*S*), t_R [min] 19.0 (*R*), $[\alpha]_D^{20}$ +40.54 (*c* 0.3, $CHCl_3$).

S-(−)-**4c** Entry 5: $[\alpha]_D^{20}$ −3.8 (*c* 0.5, $CHCl_3$).

S-(−)-**4f** Entry 6: 3% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 16.1 (*S*), t_R [min] 22.5 (*R*), $[\alpha]_D^{20}$ −14.0 (*c* 0.3, $CHCl_3$); lit.[35] (*S*)-acetate derivative of **4f**: $[\alpha]_D^{20}$ +1.9 (*c* 0.8, acetone), (*R*)-acetate derivative of **4f**: $[\alpha]_D^{20}$ −2.3 (*c* 0.5, acetone), ee=50%.

S-(−)-**4f** Entry 7: 3% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 18.8 (*S*), t_R [min] 24.5 (*R*), $[\alpha]_D^{20}$ −19.9 (*c* 2.4, $CHCl_3$).

R-(+)-**4f** Entry 8: 3% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 19.7 (*S*), t_R [min] 23.3 (*R*), $[\alpha]_D^{20}$ +17.3 (*c* 1.3, $CHCl_3$).

S-(+)-**4i** Entry 9: 5% *i*-PrOH in hexane, 0.4 mL/min; t_R [min] 38.5 (*S*), t_R [min] 57.6 (*R*), $[\alpha]_D^{20}$ +138.4 (*c* 0.25, $CHCl_3$); lit. (*S*)-**4i**: $[\alpha]_D^{20}$ +114.9 (*c* 1.5, acetone), ee=95%.[33]

S-(−)-**4j** Entry 10: 0.25% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 221.6 (*S*), t_R [min] 215.5 (*R*), $[\alpha]_D^{20}$ −30.7 (*c* 0.87, $CHCl_3$); lit. (*S*)-**4j**: $[\alpha]_D^{20}$ −33.4 (*c* 1.05, MeOH).[30]

4.3.1.2. HPLC conditions for compounds 7 (Table 3 in text). *S*-(−)-**7a** Entry 1: 0.5% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 31.9 (*S*), t_R [min] 29.3 (*R*), $[\alpha]_D^{20}$ −16.6 (*c* 0.35, $CHCl_3$); lit.[4a] (*S*)-**7a**: $[\alpha]_D^{20}$ −8.6 (*c* 1.0, CH_2Cl_2), ee=99%, (kinetic resolution, HPLC-Chiralcel OB-H).

S-(−)-**7a** Entry 2: 0.5% *i*-PrOH in hexane, 0.5 mL/min; t_R [min] 31.9 (*S*), t_R [min] 29.4 (*R*), $[\alpha]_D^{20}$ −12.0 (*c* 0.2, $CHCl_3$).

S-(+)-**7c** Entry 3: 2.25% *i*-PrOH in hexane, 0.3 mL/min; t_R [min] 32.6 (*S*), t_R [min] 28.1 (*R*), absolute configuration of product determined by comparing circular dichroism (CD) spectrum of the purified α-hydroxy ketone **7c** to the CD spectrum of (*S*)-2-hydroxy tetralone **7a**, $[\alpha]_D^{20}$ +44.2 (*c* 4.4, $CHCl_3$); lit.[29] *R*-**7c** ($[\alpha]_D^{20}$ +72.5 (*c* 1.0, EtOH)) at 94% ee, [(CHIRALPAK AD (20% *i*-PrOH in hexane, 0.8 mL/min)], t_R [min] 20.9 (*S*), t_R [min] 15.5 (*R*); lit.[31] 95% ee (Chiral SFC AD, 10% MeOH/CO_2, 1.5 mL/min, t_R [min] 7.1 (*S*), t_R [min] 9.5 (*R*)).

R-(+)-**7d** Entry 4: 5% *i*-PrOH in hexane, 0.4 mL/min, t_R [min] 34.3 (*S*), t_R [min] 45.2 (*R*), absolute configuration of product determined by comparing circular dichroism (CD) spectrum of the purified α-hydroxy ketone **7d** to the CD spectrum of (*S*)-2-hydroxy tetralone **7a**, $[\alpha]_D^{20}$ +17.5 (*c* 0.4, $CHCl_3$).

R-(+)-**7e** Entry 5: hexane–EtOH–*i*-PrOH (98:1.6:0.4 v/v), 0.2 mL/min, t_R [min] 65.9 (*S*), t_R [min] 74.3 (*R*), absolute configuration of product determined by comparison of sign of optical rotation to the literature value $[\alpha]_D^{20}$ +19.8 (*c* 3.1, $CHCl_3$); lit.[32a] (*R*)-**7e**: $[\alpha]_D^{20}$ +33.4 (*c* 1.4, $CHCl_3$) at 78% ee (chiral GC); lit[32b] (*R*)-**7e**: $[\alpha]_D^{25}$ +20.0 (*c* 2.0, MeOH) at 81% ee; (*S*)-**7e**: $[\alpha]_D^{25}$ −22.7 (*c* 1.62, MeOH) at 85% ee, (Daicel Chiracel OB-H, 35% *i*-PrOH in hexane, 1.5 mL/min, t_R [min] 8.2 (*S*), t_R [min] 4.2 (*R*)).

R-(+)-**7e** Entry 6: hexane–EtOH–*i*-PrOH (98:1.6:0.4 v/v), 0.2 mL/min, t_R [min] 63.5 (*S*), t_R [min] 71.5 (*R*), $[\alpha]_D^{20}$ +7.5 (*c* 0.48, $CHCl_3$).

Acknowledgements

Financial support by the Ministry of Science and Higher Education of Poland (Grant No 3 T09A 083 29; 2005–2008) is gratefully acknowledged. The authors thank Prof. A. Skowrońska for her helpful discussion.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.100.

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Tetrahedron 62 (2006) 12375–12379

Organocatalytic synthesis of dipyrromethanes by the addition of *N*-methylpyrrole to aldehydes

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Received 21 June 2006; revised 8 September 2006; accepted 28 September 2006
Available online 25 October 2006

Abstract—The reaction of aldehydes with *N*-methylpyrrole carried out in the presence of catalytic pyrrolidinium tetrafluoroborate at room temperature affords the corresponding dipyrromethanes and minor amounts of tripyrranes. This new, mild, and convenient process represents the first organocatalytic synthesis of dipyrromethanes. The products are obtained in chemical yields similar to those obtained with existing methods, which, however, require either a much larger excess of heterocycle (when aldehydes are employed as starting materials), or more drastic reaction conditions (when aldehyde equivalents are used as starting materials) than those employed here. A mechanism is proposed to explain the course of this reaction.

1. Introduction

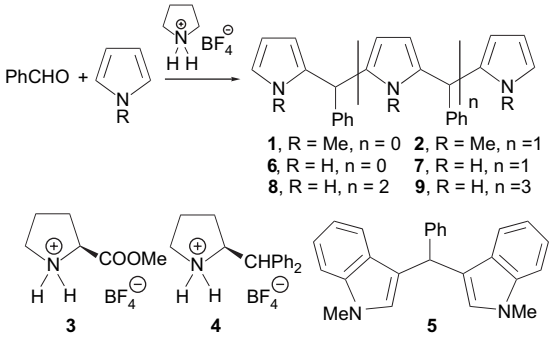
In the context of organic catalysis,[1a] iminium ion formation by reaction of a carbonyl compound with a secondary amine in acidic medium is a ubiquitous mode of activation of carbonyl substrates toward addition of electrophiles.[1b] Based on this approach we here disclose a new, mild synthesis of dipyrromethanes by addition of *N*-methylpyrrole to aldehydes catalyzed by the tetrafluoroborate salts of pyrrolidines.

Dipyrromethanes are important compounds used, inter alia, as building blocks for the synthesis of porphyrins and calix[*n*]phyrins.[2] Some dipyrromethanes have applications as flavors or food additives.[3] These compounds are generally obtained by acid-catalyzed addition of pyrroles and pyrrole derivatives to aldehydes[4] or aldehyde equivalents such as oxazines.[5] However, in the case of the reaction involving aldehydes (generally carried out at room temperature), a very large excess of heterocycle is necessary (typically, 50–100 mol equiv with respect to the aldehyde; sometimes the heterocycle is used as the reaction solvent); when oxazines are involved, the excess of heteroaromatic compound can be drastically reduced to 4 mol equiv, but much harsher reaction conditions (300 mol % of acidic promoter, high reaction temperatures) are required for the reaction to proceed in acceptable yields (28–62%).[5]

The present method improves the previous protocols in that the products are obtained directly from the aldehydes under mild reaction conditions, with a relatively small excess of *N*-methylpyrrole, and in the presence of a substoichiometric amount of promoter.

2. Results and discussion

The reaction of *N*-methylpyrrole with benzaldehyde (1 mmol) in the presence of 10 mol % of pyrrolidinium tetrafluoroborate salt[6] in aqueous THF afforded after 24 h at room temperature *N*-methyl-2-[1-phenyl-1-(2′-*N*-methylpyrrolyl)-methyl]-pyrrole **1** in 57% yield (Scheme 1, and entry 1 of Table 1). 'Tripyrrane' **2**, the major by-product usually observed in these dipyrromethane syntheses,[4,5] was also isolated in 25% yield as a 1:1 mixture of *meso*- and *d,l*-diastereoisomers.



Scheme 1. Reaction of *N*-methylpyrrole and *N*-methylindole with benzaldehyde.

Keywords: Catalysis; Organocatalysis; Heterocycles; Dipyrromethanes; Nucleophilic addition.
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doi:10.1016/j.tet.2006.09.104

Table 1. Synthesis of dipyrromethane **1** and tripyrrane **2** from benzaldehyde and *N*-methylpyrrole (*N*MP) catalyzed by pyrrolidine/HBF_4 (**P**/HBF_4) and other catalysts at room temperature

Entry	PhCHO (mol equiv)	*N*MP (mol equiv)	Catalyst	Catalyst (mol %)	THF/H_2O	*t* (h)	% Yield of **1**	% Yield of **2**
1	1	5	**P**/HBF_4	10	20:3	24	57	25
2	3	1	**P**/HBF_4	20	20:3	48	—	—
3	1	1	**P**/HBF_4	20	20:3	48	—	—
4	1	10	**P**/HBF_4	10	20:3	24	66	19
5	1	5	**P**/HBF_4	20	20:3	24	54	25
6	1	5	**P**/HBF_4	10	100:0	24	35	23
7	1	5	**P**/HBF_4	10	50:50	24	54	28
8	1	5	**3**/HBF_4	20	20:3	48	49	27
9	1	5	**4**/HBF_4	20	20:3	48	40	31

The influence exerted by reagent stoichiometry on the reaction outcome was examined by varying the amounts of benzaldehyde, *N*-methylpyrrole, and catalyst (entries 2–5 of Table 1). It was discovered that a small excess of heterocycle was necessary for the reaction to occur, and that, as expected, the higher the heterocycle/aldehyde molar ratio the better the yield of dipyrromethane **1**. Indeed with a 1:3 or 1:1 pyrrole/aldehyde ratio (entries 2 and 3), the dipyrromethane derivative was not formed in significant yield, even if 20 mol % was used. However, by employing 10 mol equiv of *N*-methylpyrrole, in the presence of 10 mol % of catalyst, the yield of **1** was increased to 66% (entry 4).

Doubling the amount of catalyst did not improve the yield or the **1/2** ratio (54% yield of **1** vs 57% yield, entry 5 vs entry 1). Increasing the water content in the solvent from 13 to 50% did not affect the reaction outcome, while the use of anhydrous THF led to a decrease in the yields of **1** and **2**, and in the **1/2** ratio (entries 6 and 7 of Table 1), possibly pointing to the role of water in the reaction mechanism (see below).

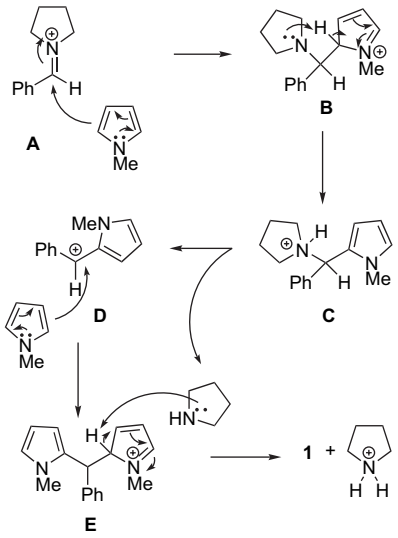
Other catalysts having pyrrolidine-related structure such as the tetrafluoroborate salts of methyl prolinate **3** and 2-(diphenylmethyl)pyrrolidine **4** were also shown to promote the reaction (entries 8 and 9).

However, while catalyst **3**/HBF_4 behaved very similarly to pyrrolidine, the use of the much more sterically hindered catalyst **4**/HBF_4 depressed the yields of **1** and **2** and the **1/2** ratio. Finally, it was found that the catalysts obtained by reacting pyrrolidine with other strong acids (HCl, $HClO_4$, CF_3SO_3H) were much less effective, if at all, than the pyrrolidine/HBF_4 combination.[7]

The pyrrolidinium tetrafluoroborate-catalyzed reaction was then extended to other heterocyclic compounds (Scheme 1).

By reacting benzaldehyde with *N*-methylindole under the reaction conditions of entry 1, Table 1, *N*-methyl-3-[1-phenyl-1-(3′-*N*-methylindolyl)methyl]-indole **5** was isolated as the only product in 33% yield.[8] On the other hand, the reaction of benzaldehyde with pyrrole led to a mixture of adducts featuring two (**6**, 20% yield), three (**7**, 30% yield), four (**8**, 20% yield), and five (**9**, 23% yield) pyrrole units, readily separated by flash chromatography, and identified by mass spectrometry and comparison of their ^1H NMR spectra with those reported in the literature.[4]

A possible reaction mechanism accounting for the formation of dipyrromethane **1** is proposed in Scheme 2. Iminium ion **A**, formed by condensation of the catalyst with benzaldehyde, undergoes addition of *N*-methylpyrrole to afford adduct **B**. Aromatization of the pyrrole nucleus occurs through deprotonation by the lone pair of the pyrrolidine nitrogen to afford intermediate **C** (this step can also be mediated by the water present in the reaction medium and acting as proton shuttle). Adduct **C** can then release the pyrrolidine precatalyst and the relatively stable carbenium ion **D**. The latter undergoes attack of a second molecule of *N*-methylpyrrole to afford adduct **E**. Deprotonation by pyrrolidine (to aromatize the second heterocyclic unit) generates product **1** and the catalytically active protonated pyrrolidine.



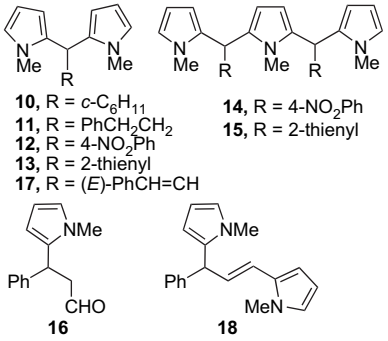
Scheme 2. Proposed mechanism for the reaction of *N*-methylpyrrole with benzaldehyde.

This is transformed into iminium ion **A** by reaction with the aldehyde to start a new catalytic cycle. Tripyrrane **2** can arise from addition of dipyrromethane **1** to carbenium ion **D**.

On the basis of this mechanism, it was anticipated that aromatic aldehydes should react better than aliphatic aldehydes in this process, since, in the case of the aromatic substrates, the formation of carbenium ion **D** would be favored by

delocalization of the positive charge on the phenyl ring. This turned out to be the case.

Indeed, when cyclohexane carboxaldehyde and phenylpropanal were used instead of benzaldehyde, dipyrromethanes **10** and **11** were isolated in 33 and 13% yields, respectively (Scheme 3).[9,10] In both cases no traces of the corresponding tripyrranes were detected. On the contrary, 4-nitrobenzaldehyde and 2-thiophene carboxyaldehyde reacted nicely with *N*-methylpyrrole to afford the corresponding dipyrromethanes **12**[5a] and **13**[10] in 61 and 59% isolated yields, respectively. These products were accompanied by the corresponding tripyrranes **14** and **15**,[10] obtained in 11 and 30% yields, respectively, after a straightforward chromatographic separation.



Scheme 3. Reaction of *N*-methylpyrrole with different aldehydes.

Finally, the reaction of cinnamaldehyde with *N*-methylpyrrole was investigated. It was recently reported by MacMillan and co-workers that, in the presence of the trifluoroacetate salt of a chiral pyrrolidine derived from phenylalanine, cinnamaldehyde underwent exclusively conjugate addition of *N*-methylpyrrole to afford 3-(2-*N*-methylpyrrolyl)-3-phenylpropanal **16** (THF/water 20:3, room or low temperature, 3–72 h) in a highly stereoselective fashion.[11] However, when the reaction was repeated in the presence of pyrrolidine/HBF_4 (0.1 mmol) as catalyst, no traces of adduct **16** were observed, even by analysis of the crude reaction mixture performed at different reaction times. Rather, dipyrromethane **17** was isolated as the major reaction product in 30% yield (Scheme 3). It was accompanied by minor amounts of other compounds, among which adduct **18** could be detected.[12] We do not have at present any rationalization to explain why our reaction follows this unusual course, which however is in agreement with our mechanistic hypothesis.

3. Conclusion

In conclusion the first organocatalytic synthesis of dipyrromethanes has been achieved by the reaction of aldehydes with *N*-methylpyrrole in the presence of catalytic amounts of pyrrolidinium tetrafluoroborate. This convenient method represents an improvement with respect to previous protocols because the products are obtained directly from the aldehydes under mild reaction conditions, with a relatively small excess of *N*-methylpyrrole, and in the presence of a catalytic amount of promoter.

4. Experimental

4.1. General methods

TLC was performed on Merck silica gel 60 TLC plates F254 and visualized using UV or phosphomolybdic acid. Flash chromatography was carried out on silica gel (230–400 mesh).

^{1}H NMR spectra were recorded on Bruker instruments at 300 or 500 MHz in chloroform-*d* ($CDCl_3$) unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm; ^{13}C NMR spectra were recorded at 75 or 125 MHz and were referenced to 77.0 ppm in $CDCl_3$.

IR spectra were recorded on thin film or as solution in CH_2Cl_2 or as KBr pellet.

Products **1**,[5a] **2**,[5a] **5**,[8] **6**,[4d] **12**,[5a] **16**,[11] are known compounds, completely characterized; they had physical and spectral properties in agreement with literature data.

Products **7**,[4f] **8**,[4f] **9**,[4f] and **18**[12b] are known compounds but NMR data are not reported in the original works; the characterization of those compounds is reported in Section 4 of the present work.

4.2. Synthesis of the catalysts

To a stirred solution of pyrrolidine (0.18 ml, 2.2 mmol) in dry Et_2O (8 mL) a 54% w/w solution of HBF_4 in diethylether (0.37 ml, 2.7 mmol) was added at 0 °C. After the reaction mixture was allowed to stir at room temperature for 30 min, the solvent was evaporated to give a very thick oil. Treatment with pentane afforded a waxy, low melting point solid. ^{1}H NMR analysis showed that this compound was a single species, which did not contain either free HBF_4 (whose proton resonates in $CDCl_3$ at 11.5 ppm) or unprotonated pyrrolidine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.4 (br s, 2H), 3.20 (m, 4H), 1.95 (m, 4H).

Following a similar procedure catalysts **3** and **4** were prepared.

Catalyst **3**: ^{1}H NMR (300 MHz, acetone d_6): δ 4.77 (m, 1H), 3.86 (s, 3H), 3.70 (m, 2H), 2.58 (m, 1H), 2.20 (m, 3H).

Catalyst **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 10H), 6.3 (br s, 2H), 4.40 (br s, 1H), 4.10 (m, 1H), 3.30 (m, 4H), 2.00 (m, 3H), 1.90 (m, 1H).

4.3. General procedure for the synthesis of dipyrromethanes

In a typical experiment benzaldehyde (1 mmol) was added to a stirred solution of pyrrolidine/HBF4 (0.1 mmol) in 3.0 mL of THF/water 20:3. After 10 min *N*-methylpyrrole (5 mmol) was added and the mixture was stirred at room temperature for 24 h. Aqueous work-up followed by purification by flash chromatography with a hexane/ethyl acetate mixture allowed the isolation of *N*-methyl-2-[1-phenyl-1-(2′-*N*-methylpyrrolyl)-methyl]-pyrrole **1** in 57% yield and 'tripyrrane' **2** in 25% yield.

4.3.1. Compound 1.[5a] LC–ESI-MS 251 (M+1), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 3H), 7.19–7.10 (m, 2H), 6.60 (m, 2H), 6.06 (t, J=8.5 Hz, 2H), 5.55 (m, 2H), 5.31 (s, 1H), 3.40 (s, 6H), yellow solid, mp 85–86 °C (lit.,[5a] 86.5 °C).

4.3.2. Compound 2.[5a] LC–ESI-MS 419 (M+1), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.21 (m, 6H), 7.19–7.12 (m, 4H), 6.57 (m, 2H), 6.02 (t, J=9.5 Hz, 2H), 5.45 (m, 2H), 5.35 (m, 2H), 5.23 (s, 2H), 3.40 (s, 6H), 3.10 (s, 3H), yellow solid.

4.3.3. Compound 7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 2H), 7.70 (br s, 1H), 7.20 (m, 10H), 6.61 (m, 2H), 6.10 (m, 2H), 5.80 (m, 2H), 5.70 (m, 2H), 5.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 133.6, 128.5, 128.4, 125.9, 121.2, 118.2, 108.0, 107.0, 106.3, 50.1. (Found: C, 82.70; H, 6.13; N, 11.18. $C_{26}H_{23}N_3$ requires C, 82.73; H, 6.14; N, 11.13%.) LC–ESI-MS 378 (M+1), viscous solid.

4.3.4. Compound 8. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 2H), 7.65 (br s, 2H), 7.20 (m, 15H), 6.60 (m, 2H), 6.10 (m, 2H), 5.85 (m, 2H), 5.70 (m, 4H), 5.30 (m, 2H), 5.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 141.1, 133.6, 132.0, 128.5, 128.1, 126.4, 125.7, 121.2, 119.2, 118.1, 108.0, 107.2, 107.0, 106.3, 106.1, 53.1, 50.1. (Found: C, 83.51; H, 6.08; N, 10.48. $C_{37}H_{32}N_4$ requires C, 83.43; H, 6.06; N, 10.52%.) LC–ESI-MS 533 (M+1), low melting point solid.

4.3.5. Compound 9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 2H), 7.60 (br s, 3H), 7.20 (m, 20H), 6.60 (m, 2H), 6.10 (m, 2H), 5.80 (m, 2H), 5.70 (m, 6H), 5.25 (m, 2H), 5.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 141.4, 134.1, 133.0, 129.5, 128.1, 126.7, 125.1, 122.2, 119.2, 118.1, 109.4, 108.0, 107.5, 107.1, 106.9, 106.3, 106.0, 53.1, 50.1. (Found: C, 83.77; H, 5.99; N, 10.23. $C_{48}H_{41}N_5$ requires C, 83.81; H, 6.01; N, 10.18%.) LC–ESI-MS 688 (M+1), low melting point solid.

4.3.6. Compound 10. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (m, 2H), 6.04 (t, J=6.5 Hz, 2H), 5.94 (m, 2H), 3.70 (d, J=10 Hz, 1H), 3.55 (s, 6H), 2.08 (m, 1H), 1.80–1.50 (m, 6H), 1.20 (m, 2H), 0.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.4, 121.0, 107.1, 106.3, 42.6, 42.0, 34.0, 32.3, 26.6, 26.5. (Found: C, 79.71; H, 9.47; N, 10.88. $C_{17}H_{24}N_2$ requires C, 79.64; H, 9.44; N, 10.93%.) LC–ESI-MS 257 (M+1), low melting point solid.

4.3.7. Compound 11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 6.50 (m, 2H), 6.03 (t, J=4.5 Hz, 2H), 5.92 (m, 2H), 3.90 (t, J=11 Hz, 1H), 3.35 (s, 6H), 2.65 (t, J=12 Hz, 2H), 2.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 133.6, 128.5, 128.4, 125.9, 121.2, 107.0, 106.3, 36.2, 34.8, 33.9, 33.7. (Found: C, 81.93; H, 7.96; N, 10.08. $C_{19}H_{22}N_2$ requires C, 81.97; H, 7.97; N, 10.06%.) LC–ESI-MS 279 (M+1), low melting point solid.

4.3.8. Compound 12.[5a] LC–ESI-MS 296 (M+1), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J=11 Hz, 2H), 7.30 (d, J=11 Hz, 2H), 6.60 (m, 2H), 6.01 (t, J=5.5 Hz, 2H), 5.45 (m, 2H), 5.35 (s, 1H), 3.40 (s, 6H), yellow solid, mp 119–121 °C (lit.,[5a] 123 °C).

4.3.9. Compound 14. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J=10 Hz, 4H), 7.30 (d, J=10 Hz, 4H), 6.58 (m, 2H), 6.05 (m 2H), 5.45 (m, 2H), 5.35 (m, 2H), 3.38 (s, 6H), 3.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 147.2, 142.5, 137.6, 128.9, 126.9, 121.2, 108.0, 107.0, 106.3, 55.2, 33.9, 30.7. (Found: C, 68.37; H, 5.35; N, 13.73. $C_{29}H_{27}N_5O_4$ requires C, 68.36; H, 5.34; N, 13.74%.) LC–ESI-MS 510 (M+1), yellow solid, mp 191–193 °C.

4.3.10. Compound 13. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J=6 Hz, 1H), 6.90 (dd, J=6 Hz, J=4 Hz, 1H), 6.70 (d, J=4 Hz, 1H), 6.52 (m, 2H), 6.05 (m, 2H), 5.65 (m, 2H), 5.55 (s, 1H), 3.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 138.5, 137.1, 128.9, 126.9, 120.2, 108.6, 106.3, 49.2, 33.6. (Found: C, 70.31; H, 6.31; N, 10.89. $C_{15}H_{16}N_2S$ requires C, 70.27; H, 6.29; N, 10.93%.) LC–ESI-MS 257 (M+1), yellow solid, mp 110–111 °C.

4.3.11. Compound 15. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J=5 Hz, 2H), 6.90 (t, J=5 Hz, 2H), 6.65 (d, J=5 Hz, 2H), 6.53 (m, 2H), 6.02 (m, 2H), 5.65 (m, 2H), 5.55 (m, 2H), 5.50 (s, 2H), 3.41 (s, 6H), 3.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 141.5, 138.5, 137.1, 128.9, 127.0, 126.9, 120.2, 108.6, 106.3, 47.2, 33.6, 32.7. (Found: C, 69.53; H, 5.81; N, 9.77. $C_{25}H_{25}N_3S_2$ requires C, 69.57; H, 5.84; N, 9.74%.) LC–ESI-MS 432 (M+1), yellow solid, mp 157–159 °C.

4.3.12. Compound 17. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.18 (m, 6H), 6.66 (m, 2H), 6.25 (d, J=19 Hz, 1H), 6.12 (m, 2H), 5.87 (m, 2H), 4.87 (m, 1H), 3.52 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 137.6, 131.5, 128.9, 126.9, 123.2, 111.2, 107.0, 106.3, 102.3, 47.7, 33.8. (Found: C, 82.61; H, 7.31; N, 10.11. $C_{19}H_{20}N_2$ requires C, 82.57; H, 7.29; N, 10.14%.) LC–ESI-MS 277 (M+1), waxy solid.

4.3.13. Compound 18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.20 (m, 6H), 6.63 (m, 2H), 6.35 (m, 2H), 6.15 (m, 3H), 4.83 (m, 1H), 3.53 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 142.9, 137.8, 131.4, 131.0, 128.8, 126.9, 123.2, 111.2, 107.3, 107.0, 106.8, 106.1, 102.3, 48.1, 34.1, 33.0. (Found: C, 82.55; H, 7.27; N, 10.16. $C_{19}H_{20}N_2$ requires C, 82.57; H, 7.29; N, 10.14%.) LC–ESI-MS 277 (M+1), waxy solid.

Acknowledgements

This work was supported by University of Milan, Italy and MIUR.

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6. The catalyst was prepared by adding a commercially available 54% solution of HBF_4 in diethylether to an equimolar amount of pyrrolidine also dissolved in dry diethylether. After 30 min stirring at room temperature under nitrogen, the solvent was evaporated under vacuum. ^1H NMR analysis showed that this compound was a single species, which did not contain either free HBF_4 or unprotonated pyrrolidine. The catalyst was used as obtained.
7. This different behavior of the pyrrolidine salts as catalysts was only partially matched by that of the free acids employed for catalyst preparation. For instance, HBF_4 behaved almost identically to pyrrolidine/HBF_4 (**1**, 60%; **2**, 24%); $HClO_4$ was less effective than HBF_4 (**1**, 43%; **2**, 21%); pyrrolidine/$HClO_4$ did not promote any reaction at all.
8. For a recently reported example of addition of *N*-methylindole to aldehydes catalyzed by gold(III) chloride and leading to product **5** see: Nair, V.; Abhilash, K. G.; Vidya, N. *Org. Lett.* **2005**, *7*, 5857–5859.
9. The possibility that these aliphatic aldehydes can also undergo formation of the corresponding unreactive enamines under the reaction conditions can also be invoked to explain the observed low yields. In agreement with this hypothesis is the observation that 3-phenylpropanal reacts more sluggishly than cyclohexane carboxyaldehyde, because the latter is less prone to enamine formation than the former.
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Chemo-, regio- and stereoselective 1,3-dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones over 3,5-bis(arylidene)-1-methylpiperidin-4-ones: synthesis of highly substituted novel spiro-isoxazolidines

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Received 16 June 2006; revised 14 September 2006; accepted 28 September 2006
Available online 25 October 2006

Abstract—1,3-Dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones to 3,5-bis-(arylidene)-1-methylpiperidin-4-ones affords novel mono- and bis-spiroisoxazolidines in moderate yields. In general, this reaction predominantly yields mono-spiroisoxazolidine, wherein the oxygen of the nitrone is linked to the β-carbon of the benzylidene moiety, while 3,5-bis-(2-chloro- and 3-nitro-benzylidene)-1-methylpiperidin-4-ones afford predominantly bis-spiroisoxazolidines. The cycloaddition of mono-spiroisoxazolidines occurs with facial diastereoselectivity to furnish bis-spiroisoxazolidines. The nitrogen in the heterocyclic ring of the 3,5-bis-(arylidene)-1-methylpiperidin-4-ones facilitates the cycloaddition through transannular (N···C═O) and/or homoconjugative (N···C═C) interactions.

1. Introduction

The 1,3-dipolar cycloaddition of nitrones with olefinic dipolarophiles proceeds through a concerted mechanism yielding highly substituted isoxazolidines with generation of as many as three new contiguous stereogenic centres in a single step.[1] Isoxazolidines are potential precursors for biologically important compounds such as amino sugars,[1] alkaloids,[2,3] β-lactams[3] and amino acids,[4] and exhibit antibacterial and antifungal activities.[5] Among the dipoles, nitrones have been extensively used as they readily undergo both inter- and intra-molecular 1,3-dipolar cycloaddition with olefins.[5]

The 1,3-dipolar cycloaddition of exocyclic olefins with nitrones result in highly substituted spiro-isoxazolidines[6] and they have also been transformed into complex heterocycles.[7] Heterocycles with piperidine sub-structures display important biological activities, such as cytotoxic[9] and anticancer,[8] besides being useful as synthons in the construction of alkaloid natural products.[10]

The above importance of isoxazolidine and piperidine sub-structures and our interest in the synthesis of novel heterocycles[11,12] led us to investigate the cycloaddition of a series of 3,5-bis-(arylidene)-1-methylpiperidin-4-ones **1** with *C*-aryl-*N*-phenylnitrones **2** (Scheme 1). These heterocycles with isoxazolidine and piperidine sub-structures **3**–**7** could exhibit important biological properties. Incidentally, it is of interest to examine the influence of: (i) the electronic and steric effects of the substituents of the aryl rings of **1** and (ii) the influence of intra-molecular interactions in **1** on the reactivity and/or selectivities of the cycloaddition. It is pertinent to note that this work is the first investigation on the dipolar cycloaddition of 3,5-bis-(arylidene)-1-methylpiperidin-4-ones **1**.

2. Results and discussion

The 1,3-dipolar cycloaddition of 3,5-bis-(arylidene)-1-methylpiperidin-4-ones, **1a**–**o**, with nitrones, **2a** and **2b** (4 molar equiv), affords mono- and bis-spiroisoxazolidines (Scheme 1). This reaction proceeds cleanly without any decomposition furnishing only isoxazolidines along with unreacted **1** and **2**. This cycloaddition affords five mono- and bis-spiroisoxazolidines with different regio- and stereochemistry, each dipolarophile, **1a**–**o** giving one to a maximum of four products (Table 1).

The isolated yield of the products (Table 1) discloses that this cycloaddition occurs chemoselectively furnishing mono-isoxazolidine **3**(β_t) predominantly, ascribable to the steric hindrance exerted by the mono spiro-isoxazolidine ring for the second cycloaddition leading to bis-isoxazolidines. This reaction is also: (i) regioselective, as **3**(β_t) with

Keywords: Nitrones; Piperidone; Spiro-isoxazolidines; 1,3-Dipolar cycloaddition; Transannular interaction.
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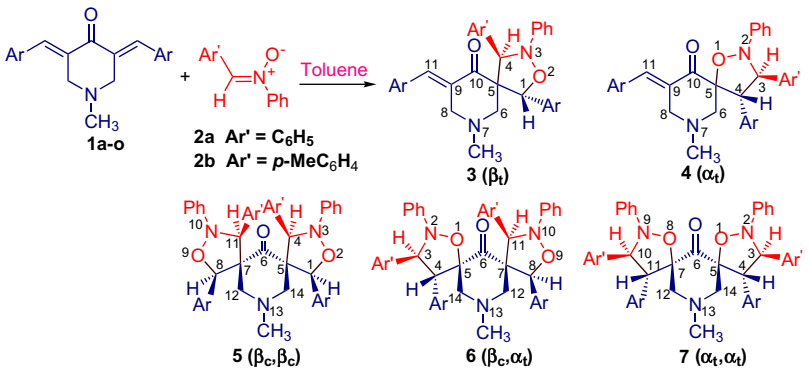
doi:10.1016/j.tet.2006.09.106



Comp	Ar	Ar'
a	C_6H_5	C_6H_5
b	*p*-ClC_6H_4	C_6H_5
c	*p*-MeC_6H_4	C_6H_5
d	*p*-$MeOC_6H_4$	C_6H_5
e	*p*-FC_6H_4	C_6H_5
f	*o*-ClC_6H_4	C_6H_5
g	*o*-MeC_6H_4	C_6H_5
h	*o*-$MeOC_6H_4$	C_6H_5
i	2-Thienyl	C_6H_5
j	*m*-$O_2NC_6H_4$	C_6H_5
k	C_6H_5	*p*-MeC_6H_4
l	*p*-ClC_6H_4	*p*-MeC_6H_4
m	*p*-MeC_6H_4	*p*-MeC_6H_4
n	*o*-MeC_6H_4	*p*-MeC_6H_4
o	1-Naphthyl	*p*-MeC_6H_4

Scheme 1. Synthesis of spiro-isoxazolidines.

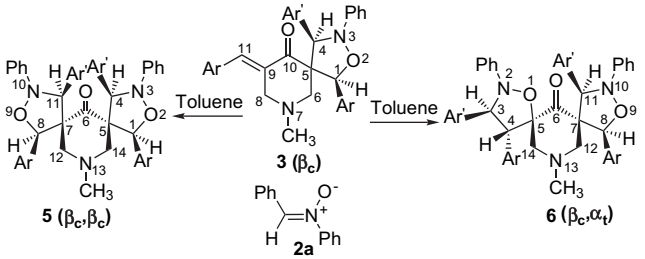
Table 1. Yield of isoxazolidines

Compd	Isolated yield of cycloadducts (%)[a]			
	3	**4**	**5** and **6** (ratio[b])	**7**
a	34	—	17 (Only **6**)	—
b	31	5	15 (1:0.4)	—
c	39	—	18 (1:0.5)	7
d	31	—	16 (1:0.4)	—
e	31	—	10 (1:0.9)	—
f	20	—	30 (Only **6**)	—
g	24	7	15 (1:0.5)	—
h	36	—	—	—
i	30	8	—	—
j	18	—	17 (Only **6**)	—
k	26	—	9 (1:0.5)	—
l	23	—	7 (Only **5**)	—
m	37	—	16 (1:0.4)	—
n	32	7	—	—
o	20	—	—	—

[a] Besides the products, only the unreacted reactants were found and recovered.
[b] The yield ratio of inseparable mixtures estimated from ^{1}H NMR signal intensities of the isolated mixture.

the oxygen of the nitrone added to the β-carbon of the dipolarophile predominating over **4**(α_t) and (ii) stereoselective, as the two aryl rings of **3**(β_t) are trans (vide infra). The regiochemistry of each cycloaddition product is indicated by the letters, α and β, while the trans or cis stereochemical relationship between the aryls in the isoxazolidine rings is indicated by the subscript, *t* or *c*, respectively. The regioselectivity is in accord with the polarisation of the C=C bond enabling the more electron-deficient β-carbon to preferentially react with the electron-rich oxygen of the nitrone. The yield of the bis-isoxazolidines is, in general, in the order: **5**(β_c,β_c)>**6**(β_c,α_t)>**7**(α_t,α_t) revealing the preference of the same regiochemistry in the mono- as well as bis-isoxazolidines, except in the case of **1a**, **1f** and **1j**, where only **6**(β_c,α_t) was obtained. The origin for the deviation of **1a**, **1f** and **1j** from the above general trend is unclear.

That the reaction proceeds stereoselectively is evident from the predominant formation of mono-isoxazolidine, **3**(β_t) in most of the cases (Table 1) explicable by the concerted reaction of (*E*)-nitrone over **1** (Scheme 2). The cis-relationship between the *C*-aryl rings of the isoxazolidine rings of **5** and one of the isoxazolidine rings of **6** is ascribable to the concerted reaction of (*Z*)-nitrone over the mono-isoxazolidine. It is pertinent to note that the *C*,*N*-diarylnitrones exist preferentially in (*Z*)-configuration with the aryl rings trans to each other. If the relative amounts of the nitrones in (*Z*)- and (*E*)-configuration determine the amounts of *cis*- and *trans*-isoxazolidines formed, then *cis*-isoxazolidines should be predominantly formed. The formation of **3**(β_t) as the major product in most cases suggests that either **3**(β_c) isomerises to **3**(β_t) via retro-cycloaddition or the cycloaddition of (*E*)-nitrone proceeds through a transition state of lower free energy and the (*Z*)- and (*E*)-nitrones interconvert[13] rapidly.



Scheme 2. Formation of bis-isoxazolidines from **3**(β_c).

The mono-isoxazolidine, **3**(β_c) could not be isolated from the reaction mixture to infer whether it isomerises to its trans isomer **3**(β_t), as **3**(β_c) is rapidly converted to the bis-isoxazolidines (vide infra). In a separate experiment, **3m**(β_t), was subjected to reaction with nitrone **2b** (as excess nitrone was employed in the reaction between **1m** and **2b**) under the same reaction conditions as employed for the reaction between **1** and **2** for 10 h. Under these conditions **3m**(β_t) remained unchanged and neither isomerisation to its cis isomer **3m**(β_c), nor formation of bis-spiroisoxazolidine was found showing that **3m**(β_t) is very stable. In the case of **1h** and **1o** with *o*-anisyl and 1-naphthyl, respectively, the mono-isoxazolidine **3**(β_t) is formed as the only product, ascribable to the steric effect due to the *o*-methoxy and naphthyl ring, respectively.

Column chromatography of the product mixture affords pure **4**(α_t) and in one case, **7**(α_t,α_t) along with an inseparable mixture of **3**(β_t), **5**(β_c,β_c) and **6**(β_c,α_t) with almost identical R_f values. However, the mixture of **3**(β_t), **5**(β_c,β_c) and **6**(β_c,α_t) upon crystallisation in alcohol furnishes pure **3**(β_t) in most cases. The bis-spiroisoxazolidines, **5**(β_c,β_c) and **6**(β_c,α_t) remaining as a mixture could not be separated. However, **6f**(β_c,α_t) could be obtained as crystals, since **5f**(β_c,β_c) is not formed in this case. The structural elucidation for all the spiro-isoxazolidines was achieved using ^{1}H, ^{13}C and 2D NMR spectroscopic techniques as described in detail for **3m**(β_t), **4g**(α_t), **5c**(β_c,β_c), **6f**(β_c,α_t) and **7c**(α_t,α_t). In the case of **5c**(β_c,β_c) and **6f**(β_c,α_t), the NMR spectroscopic study was performed on the mixture.

The ^{1}H NMR spectrum of 7-methyl-1,4-bis(4-methylphenyl)-9-[(4-methylphenyl)-methylidene]-3-phenyl-2-oxa-3,7-diazaspiro[4.5]decan-10-one **3m**(β_t) has two singlets at 6.28 and 5.03 ppm assignable to H-1 and H-4, respectively, as evident from the HMBC spectrum, wherein the signal of H-4, but not H-1, displays a HMBC correlation with the N–Ph *ipso* carbon at 151.6 ppm (Fig. 1). The doublet of doublets at 2.04 (J=12, 2 Hz) and a doublet at 2.79 ppm (J=12 Hz) are assigned to the 6-CH_2 protons. Similarly, 8-CH_2 protons also occur as doublet of doublets at 2.96 ppm (J=14, 2 Hz) and doublet at 3.82 (J=14 Hz). The assignments of 6- and 8-CH_2 are supported by the fact that 8-CH_2 protons exhibit a HMBC correlation with the benzylidene carbon at 136.1 ppm, while the 6-CH_2 protons show HMBC correlations with the spiro and the methine (C-4) carbons, respectively, at 66.8 and 79.6 ppm. The benzylidene and the N–CH_3 protons appear as singlets at 6.53 and 2.28 ppm, respectively. The aromatic protons appear as a multiplet in the range 6.91–7.20 ppm. The structure for **3m**(β_t) arrived from the single crystal X-ray study (Fig. 2) and NMR spectroscopic studies are in good agreement. The structure shown in Figure 2 reveals that H-1 and H-4 are trans and the piperidone and the isoxazolidine rings are in half-chair and envelope forms, respectively.

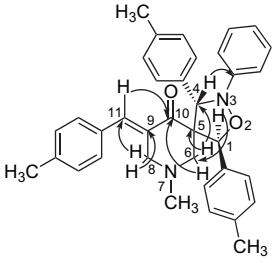


Figure 1. Selected HMBC correlations of **3m**(β_t).

The ^{1}H NMR spectrum of 7-methyl-4-(2-methylphenyl)-9-[(2-methylphenyl)-methylidene]-2,3-diphenyl-1-oxa-3,7-diazaspiro[4.5]decan-10-one **4g**(α_t) has two singlets at 2.01 and 2.09 ppm due to the methyls in the aryl ring. The N–CH_3 and benzylidene protons appear as singlets at 2.28 and 7.76 ppm. The C,H-COSY correlation of the benzylidene proton assigns the carbon at 136.5 ppm to C-11. Further, H-11 shows a HMBC correlation (Fig. 3) with the carbon at 56.5 ppm and the carbonyl at 195.3 ppm assigning the former to C-8. The C,H-COSY spectrum assigns the 8-CH_2 protons to the doublets at 3.76 and 3.24 ppm (J=14 Hz). The 6-CH_2 protons appear as doublets at 2.38 and 2.72 ppm (J=13 Hz) and show: (i) a C,H-COSY correlation with the carbon at 61.2 ppm due to C-6 and (ii) a HMBC correlation with the carbon at 83.0 ppm due to the spiro-carbon C-5. The 8-CH_2 protons show a HMBC correlation with a carbon at 137.2 ppm assigning it to C-9. The N–CH_3 carbon appears at 45.9 ppm, while the methyls of the aromatic rings give signals at 20.4 and 20.8 ppm. The doublets at 4.59 and 5.05 ppm (J=8 Hz) can be assigned, respectively, to H-3 and H-4, as a HMBC correlation was found between the carbonyl carbon and the proton at 5.05 ppm. The J value of 8 Hz shows trans relationship between H-3 and H-4.

The N–CH_3 protons and the aromatic protons of 13-methyl-1,8-bis(4-methylphenyl)-3,4,10,11-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one **5c**(β_c,β_c) appear as a singlet at 2.24 ppm and a multiplet in the range 6.83–8.25 ppm, respectively. This compound has a symmetrical structure, wherein the 12- and 14-CH_2 are in identical environments. The two protons of each: H-12 and H-14 give rise to doublets at 2.46 and 2.63 ppm (J=13 Hz), which show a C,H-COSY correlation with the carbon at 57.5 ppm assigning it to C-12,14. The singlet at 5.41 ppm is assigned to H-4,11 on the basis of its HMBC correlation with the quaternary carbon of N–Ph at 152.9 ppm (Fig. 4). The other singlet at 5.57 ppm can be readily assigned to H-1,8 and, as expected, these protons do not display HMBC correlation with the *ipso* carbon of N–Ph. Further, H-1,8 and H-4,11 show HMBC correlations with the carbonyl and α-carbons at 199.2 and 67.2 ppm rendering the assignment of the latter to C-5,7. The C,H-COSY correlations and the chemical shifts of H-1,8 and H-4,11 assign the carbon signals at 87.9 and 80.5 ppm to C-1,8 and C-4,11, respectively. The N–CH_3 carbon signal appears at 45.4 ppm.

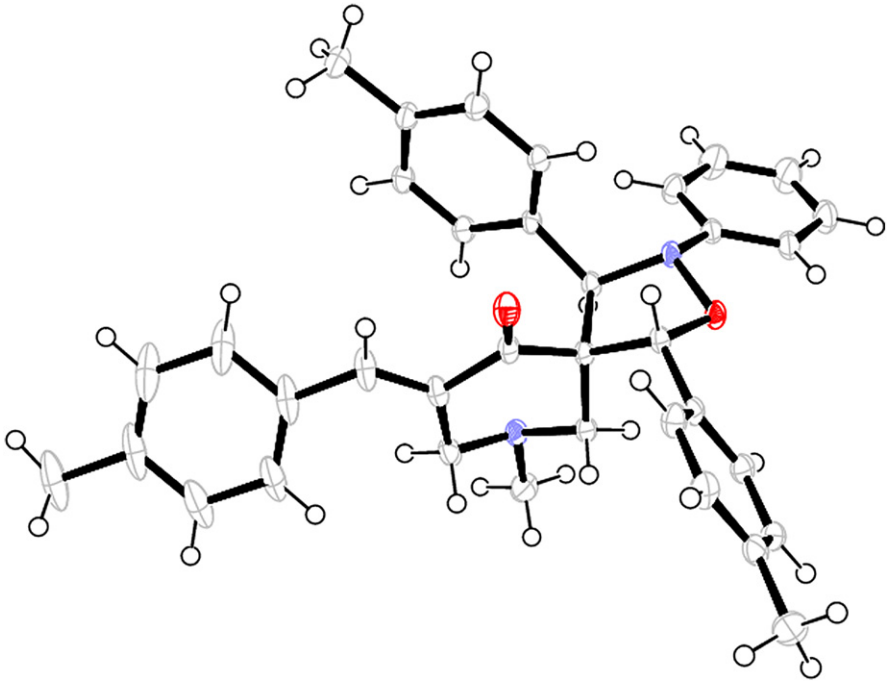


Figure 2. ORTEP diagram of **3m**(β_t).

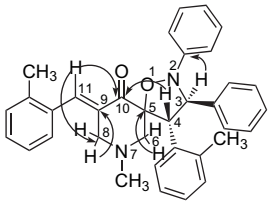


Figure 3. Selected HMBC correlations of **4g**(α_t).

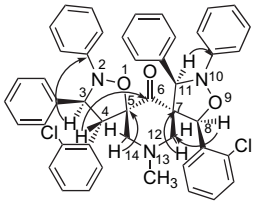


Figure 5. Selected HMBC correlations of **6f**(β_c,α_t).

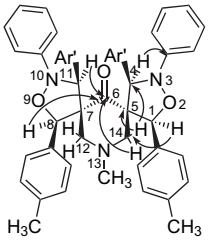


Figure 4. Selected HMBC correlations of **5c**(β_c,β_c).

The ^{1}H NMR spectrum of 4,8-bis(2-chlorophenyl)-13-methyl-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one **6f**(β_c,α_t) show doublets at 4.55 and 5.38 ppm (J=7 Hz), related by a H,H-COSY correlation, which can be assigned to H-3 and H-4, respectively. The distinct assignment of these protons to H-3 and H-4 is evident from the HMBC correlation of the signal at 5.38 ppm with the carbonyl at 201.1 ppm (Fig. 5). Further the J value of 7 Hz suggests that these hydrogens are in trans relationship. The singlets at 6.72 and 6.03 ppm are assigned to H-8 and H-11, respectively, as evident from HMBC correlation of H-11 (and not H-8) with the N–Ph *ipso* carbon at 149.2 ppm. The 12-CH_2 protons give a doublet at 1.99 ppm (J=10 Hz) and a multiplet at 1.60–1.63 ppm, while the 14-CH_2 protons give doublets at 1.96 and 2.99 ppm (J=12 Hz). These assignments are evident from the HMBC correlations of: (i) H-8 with the methylenic carbon at 58.1 ppm (ii) 12-CH_2 protons with the carbon at 65.9 ppm and (iii) 14-CH_2 protons with the carbon at 85.4 ppm. Hence the signals at 58.1, 65.9 and 85.4 ppm can be readily assigned to C-12, C-7 and C-5, respectively. From the C,H-COSY spectrum and the proton chemical shifts, the signals of C-3, C-4 and C-14 are assigned to 79.8, 54.4 and 60.3 ppm, respectively. The aromatic protons appear as a multiplet in the range 6.93–8.03 ppm and the N–CH_3 protons appear as a singlet at 1.50 ppm.

The structure of **6f**(β_c,α_t) deduced from NMR spectroscopic study is also further confirmed by the X-ray crystallographic study of a single crystal (Fig. 6). The structure in Figure 6 shows that the piperidin-4-one ring adopts a chair conformation, while both the spiro-isoxazolidine rings are in envelope conformation with the heteroatoms, viz. nitrogen and oxygen lying out of plane. Further, it is seen that H-3 and H-4 are in trans, while the aryl rings at C-8 and C-11 are in cis-relationship.

13-Methyl-4,11-bis(4-methylphenyl)-2,3,9,10-tetraphenyl-1,8-dioxa-2,9,13-triazadispiro [4.1.4.3]tetradecan-6-one **7c**(α_t,α_t) has a symmetrical structure as **5c**, with the complementary regiochemistry, oxygen attached to the α-carbon.

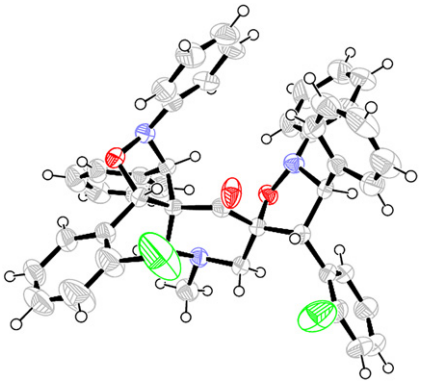


Figure 6. ORTEP diagram of **6f**(β_c,α_t).

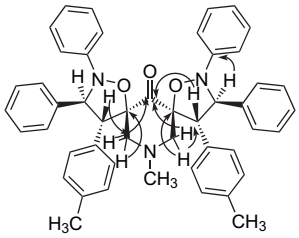


Figure 7. Selected HMBC correlations of **7c**(α_t,α_t).

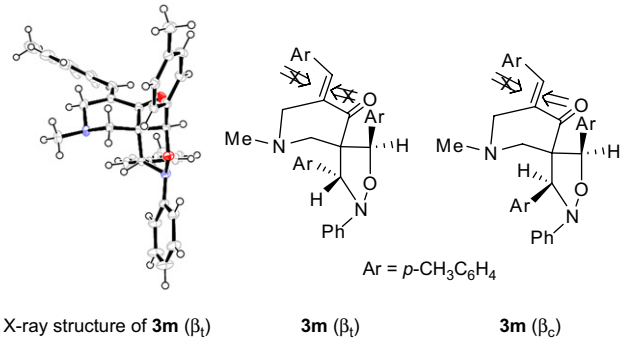
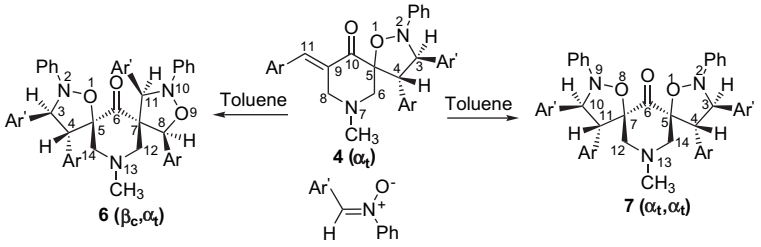


Figure 8.

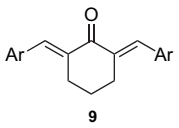
The assignment of the proton and carbon signals of the heterocyclic rings of **7c**(α_t,α_t) has been done by straightforward considerations as done for the other compounds. Thus the doublets 4.73 and 4.68 ppm (J=7 Hz) have been assigned to H-3,10 and H-4,11, respectively. The N–CH_3 protons appear as a singlet at 2.31 ppm and the aromatic protons appear as a multiplet in the range 6.88–7.38 ppm. A doublet at 2.91 ppm (J=13 Hz) can be assigned to one of the methylenic protons, H-12,14 and a doublet at 1.91 (J=13 Hz) is assigned to the other. The N–CH_3 and the spiro-carbons, C-5,7 are observed at 45.9 and 87.5 ppm, respectively. The carbonyl carbon appears at 203.3 ppm. From the C,H-COSY and HMBC spectra, it is clear that C-3,10 and C-4,11 appear at 60.2 and 77.2 ppm, respectively (Fig. 7). The signals at 61.8 and 21.5 ppm are assigned to the methylenic carbons C-12,14 and the methyl carbons of the aryl rings.

The stereochemical relationship between the aryls in **5**(β,β), whether they are *cis* [**5**(β_c,β_c)] or *trans* [**5**(β_t,β_t)], could not be deduced from NMR studies. X-ray studies could not be performed, as efforts to separate and crystallise **5**(β,β) did not succeed. However, this stereochemical information was indirectly obtained from the fact that the reaction of pure **3m**(β_t) with nitrone **2a**, under the conditions employed for the reaction of **1m** with nitrone failed to afford both **5**(β,β) and **6**(β_c,α_t). If the aryls in the isoxazolidine rings of **5**(β,β) are in trans relationship as **3**(β_t), then the reaction of **3**(β_t) with nitrone should give **5**(β,β). This probably can be taken as an indirect evidence for the cis-relationship between the aryl rings, viz. **5**(β_c,β_c), which might arise from the cycloaddition of (*Z*)-nitrone over the mono-isoxazolidine **3**(β_c) with *cis* aryl rings (Scheme 2). However, **3**(β_c) was not detected even in traces in the reaction of **1** and **2**. Probably, **3**(β_c) with both the aryl rings oriented on the same side might be more reactive towards the second cycloaddition than **3**(β_t) with the aryl rings at C-1 and C-4 in a trans relationship. That this reactivity difference could arise from the possibility of steric effects due to the 1- and 4-aryls impeding the cycloaddition on both the faces of the C=C bond of **3**(β_t) is evident from the crystal structure of **3m**(β_t) oriented appropriately in Figure 8. In contrast, in the case of **3**(β_c), the attack of the nitrone from the bottom side of the C=C bond is not much hindered by the 4-aryl oriented away. This, in turn, also explains the facial diastereoselectivity encountered during the second cycloaddition of **3**(β_c) to afford the symmetrical bis-isoxazolidine, **5**(β_c,β_c). The **3**(β_c) might have completely been converted into the bis-isoxazolidines leading to the absence of **3**(β_c) in the reaction mixture. The bis-spiroisoxazolidine **6**(β_c,α_t) could arise from the further cycloaddition of either mono-isoxazolidines, **3**(β_c) or **4**(α_t) or both, while the bis-spiroisoxazolidine **7**(α_t,α_t) could be formed from the cycloaddition of **4**(α_t) (Schemes 2 and 3).

The foregoing results reveal that the chemo-, regio- and stereo-selectivities of the cycloaddition are, in general, influenced by the steric and electronic nature of the substituents on the aryl rings of **1** and the stereochemistry of the initially formed mono-isoxazolidine. Further, the nitrogen of the



Scheme 3. Formation of bis-isoxazolidines from **4**(α_t).



9

Figure 9.

piperidin-4-one ring is found to be responsible for the reactivity of **1** towards the cycloaddition as evident from the fact that the nitrone **2** failed to react with 2,6-bis-(arylidene)-cyclohexanones **9** (Fig. 9) under the reaction conditions employed for the reaction of **1** with **2**. Probably, the nitrogen of **1** influences the polarity of the enone moiety by the overlap of its lone pair orbital with the p-orbital of the carbonyl carbon (transannular interaction)[14] and/or the p-oribtal of the α-carbon of the C=C bond (homoconjugation) rendering the cycloaddition facile.

3. Conclusions

The cycloaddition of *C*-aryl-*N*-phenylnitrones over 3,5-bis-(arylidene)-1-methyl-piperidin-4-ones **1** proceeds chemo-, regio- and stereoselectively affording mono- and bis-spiroisoxazolidines, the former predominating, with the oxygen of the nitrone attached to the β-carbon of the benzylidene moiety. The sterically bulky groups such as 1-naphthyl and *o*-anisyl in **1** lead to the formation of solely mono-spiroisoxazolidines. The cycloaddition of mono-spiroisoxazolidines to furnish bis-spiroisoxazolidines displays facial diastereoselectivity ascribable to steric control. The transannular and/or homoconjugative interactions in dienone **1** render the cycloaddition facile relative to the cycloaddition over **9**. The dipolar cycloaddition of 3,5-bis-(arylidene)-1-methyl-piperidin-4-ones with other 1,3-dipoles is under progress in our group.

4. Experimental

4.1. General

Melting points were recorded using open capillary tubes and are uncorrected. The ^{1}H, ^{13}C, DEPT, H–H COSY, C–H COSY and HMBC spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in case of solids and $CHCl_3$ in case of viscous liquids). The single crystal X-ray data set for **3m** was collected on Bruker Kappa X8 APPEX II diffractometer with Mo Kα (λ=0.71073 Å) radiation. Scan range was $2.22^\circ \leq \theta \leq 33.00^\circ$. Single crystal X-ray data set for **6f** was collected on Enraf–Nonius (CAD4) diffractometer with Mo Kα (λ=0.71073 Å) radiation. Scan range was $2.02^\circ \leq \theta \leq 24.97^\circ$. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyser. Silica gel (60–120 mesh) column chromatography was performed using pet ether (60–80 °C)–ethyl acetate as an eluent. The starting compounds (**1**) were prepared according to the reported procedure.[8]

4.2. Cycloaddition of *C*-aryl-*N*-phenylnitrones with 3,5-bis-(arylidene)-1-methyl-piperidin-4-ones

General procedure. A mixture of **1** (1 mmol) and the nitrone **2** (4 mmol) in toluene (15 mL) was refluxed for 10 h. The solvent was evaporated under reduced pressure and the product separated through column chromatography using pet ether–ethyl acetate as an eluent.

4.2.1. 7-Methyl-1,3,4-triphenyl-9-(phenylmethylidene)-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3a). Obtained as yellow solid; yield: 0.140 g (34%); mp 168–169 °C; IR (KBr): 1682, 1601, 1501, 1480, 1263, 1168, 1071 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.03 (1H, d, J=12 Hz, H_{6A}), 2.28 (3H, s, N–CH_3), 2.83 (1H, dd, J=12, 2 Hz, H_{6B}), 2.96 (1H, dd, J=14, 2 Hz, H_{8B}), 3.87 (1H, d, J=14 Hz, H_{8A}), 5.07 (1H, s, H_4), 6.34 (1H, s, H_1), 6.60 (1H, s, C*H*Ar), 6.73–8.33 (20H, m, Ph); δ_C (75 MHz, $CDCl_3$) 46.8 (N–*C*H_3), 57.7 (C_8), 60.4 (C_6), 67.2 (C_5), 80.2 (C_4), 81.0 (C_1), 114.6 (*C*H), 122.3 (*C*H), 126.9 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 129.0 (*C*H), 129.2 (*C*H), 129.4 (*C*H), 130.5 (*C*H), 134.2 (*C*), 135.4 (C_9), 135.7 (*C*), 136.4 (C_{11}), 138.9 (*C*), 150.5 (*C*), 198.1 (*C*=O). Anal. calcd for $C_{33}H_{30}N_2O_2$: C, 81.45; H, 6.21; N, 5.76. Found: C, 81.51; H, 6.27; N, 5.70.

4.2.2. 13-Methyl-2,3,4,8,10,11-hexaphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6a). Obtained as a viscous liquid; yield: 0.100 g (17%); IR ($CHCl_3$): 1725, 1600, 1493, 1459, 1265, 1090 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29–1.39 (1H, m, H_{12B}), 1.33 (3H, s, N–CH_3), 1.77 (1H, d, J=13 Hz, H_{14A}), 2.11 (1H, dd, J=11, 2 Hz, H_{12A}), 2.51 (1H, dd, J=13, 2 Hz, H_{14B}), 4.42 (1H, d, J=6 Hz, H_3), 4.49 (1H, d, J=6 Hz, H_4), 6.05 (1H, s, H_{11}), 6.39 (1H, s, H_8), 6.68–8.38 (30H, m, Ph); δ_C (75 MHz, $CDCl_3$) 43.2 (N–*C*H_3), 58.1 (C_4), 59.0 (C_{12}), 60.4 (C_{14}), 66.9 (C_7), 72.6 (C_{11}), 80.3 (C_3), 81.9 (C_8), 86.6 (C_5), 114.6 (*C*H), 118.0 (*C*H), 122.8 (*C*H), 125.9 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 128.0 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.6 (*C*H), 130.0 (*C*H), 132.0 (*C*H), 135.2 (*C*), 137.6 (*C*), 138.5 (*C*), 142.9 (*C*), 148.9 (*C*), 151.1 (*C*), 204.9 (*C*=O). Anal. calcd for $C_{46}H_{41}N_3O_3$: C, 80.79; H, 6.04; N, 6.14. Found: C, 80.87; H, 6.00; N, 6.19.

4.2.3. 1-(4-Chlorophenyl)-9-[(4-chlorophenyl)methylidene]-7-methyl-3,4-diphenyl-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3b). Obtained as yellow solid; yield: 0.120 g (31%); mp 200–202 °C; IR (KBr): 1681, 1598, 1490, 1359, 1265, 1170, 1089 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.00 (1H, d, J=12 Hz, H_{6A}), 2.30 (3H, s, N–CH_3), 2.79 (1H, d, J=12 Hz, H_{6B}), 2.94 (1H, dd, J=14, 2 Hz, H_{8B}), 3.76 (1H, d, J=14 Hz, H_{8A}), 5.03 (1H, s, H_4), 6.30 (1H, s, H_1), 6.64 (1H, s, C*H*Ar), 6.92–7.98 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 45.3 (N–*C*H_3), 52.9 (C_8), 55.8 (C_6), 65.7 (C_5), 78.8 (C_4), 78.9 (C_1), 115.0 (*C*H), 116.4 (*C*H), 127.6 (*C*H), 127.9 (*C*H), 128.0 (*C*H), 128.3 (*C*H), 128.9 (*C*H), 129.3 (*C*H), 129.4 (*C*H), 133.1 (*C*), 133.6 (*C*), 133.9 (*C*), 134.6 (C_9), 135.0 (*C*), 135.8 (C_{11}), 137.3 (*C*), 151.2 (*C*), 197.3 (*C*=O). Anal. calcd for $C_{33}H_{28}Cl_2N_2O_2$: C, 71.35; H, 5.08; N, 5.04. Found: C, 71.28; H, 5.01; N, 5.11.

4.2.4. 4-(4-Chlorophenyl)-9-[(4-chlorophenyl)methylidene]-7-methyl-2,3-diphenyl-1-oxa-2,7-diazaspiro[4.5]decan-10-one (4b). Obtained as white solid; yield: 0.019 g (5%); mp 189–191 °C; IR (KBr): 1667, 1586, 1475, 1333 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.23 (3H, s, N–CH_3), 2.39 (1H, d, 12 Hz, H_{6A}), 2.78 (1H, d, J=12 Hz, H_{6B}), 3.42 (1H, d, 14 Hz, H_{8A}), 3.91 (1H, d, J=14 Hz, H_{8B}), 4.63 (1H, d, J=7 Hz, H_3), 4.76 (1H, d, J=7 Hz, H_4), 7.56 (1H, s, C*H*Ar), 6.59–7.83 (17H, m, Ph); δ_C (75 MHz, $CDCl_3$) 45.9 (N–*C*H$_3$), 56.7 (C_8), 60.9 (C_4), 61.7 (C_6), 77.2 (C_3), 85.2 (C_5), 117.1 (*C*H), 118.4 (*C*H), 127.5 (*C*H), 128.8 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 131.4 (*C*H), 135.7 (C_{11}), 137.3 (C_9), 139.7 (*C*), 139.8 (*C*), 140.2 (*C*), 149.1 (*C*), 149.5 (*C*), 150.3 (*C*), 196.0 (*C*=O). Anal. calcd for $C_{33}H_{28}Cl_2N_2O_2$: C, 71.35; H, 5.08; N, 5.04. Found: C, 74.31; H, 5.01; N, 5.12.

4.2.5. Compounds 5b and 6b.[15] Obtained as a viscous liquid; overall yield: 0.085 g; yield: **5b**, 11%; **6b**, 4%. Anal. calcd for **5b** and **6b** mixture $C_{46}H_{39}Cl_2N_3O_3$: C, 73.40; H, 5.22; N, 5.58. Found: C, 73.46; H, 5.15; N, 5.49.

4.2.6. 1,8-Bis(4-chlorophenyl)-13-methyl-3,4,10,11-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5b).[16] δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, N–CH_3), 2.39 (2H, d, 13 Hz, $H_{12A,14A}$), 2.73 (2H, d, 13 Hz, $H_{12B,14B}$), 5.45 (2H, s, $H_{4,11}$), 5.65 (2H, s, $H_{1,8}$), 6.92–7.98 (30H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.0 (N–*C*H$_3$), 58.0 ($C_{12,14}$), 65.7 ($C_{5,7}$), 78.7 ($C_{4,11}$), 85.7 ($C_{1,8}$), 197.3 (*C*=O).

4.2.7. 4,8-Bis(4-chlorophenyl)-13-methyl-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6b). δ_H (300 MHz, $CDCl_3$) 1.39 (3H, s, N–CH_3), 1.40–1.49 (1H, m, H_{12B}), 1.84–1.88 (1H, m, H_{12A}), 1.91 (1H, d, J=13 Hz, H_{14A}), 2.61 (1H, d, J=13 Hz, H_{14B}), 4.40 (1H, d, J=6 Hz, H_3), 4.53 (1H, d, J=6 Hz, H_4), 6.08 (1H, s, H_{11}), 6.42 (1H, s, H_8), 6.92–7.98 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 43.2 (N–*C*H$_3$), 56.1 (C_{12}), 57.5 (C_4), 60.4 (C_{14}), 66.9 (C_7), 72.2 (C_{11}), 81.3 (C_3), 82.1 (C_8), 86.4 (C_5), 114.6 (*C*H), 118.1 (*C*H), 122.6 (*C*H), 124.7 (*C*H), 127.9 (*C*H), 128.0 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 128.8 (*C*H), 129.1 (*C*H), 130.5 (*C*H), 131.2 (*C*H), 131.3 (*C*H), 131.8 (*C*H), 132.0 (*C*H), 132.7 (*C*H), 133.9 (*C*), 134.6 (*C*), 135.0 (*C*), 136.7 (*C*), 137.3 (*C*), 142.7 (*C*), 148.8 (*C*), 151.1 (*C*), 204.8 (*C*=O).

4.2.8. 7-Methyl-1-(4-methylphenyl)-9-[(4-methylphenyl)-methylidene]-3,4-diphenyl-2-oxa-3,7-diazaspiro[4.5]-decan-10-one (3c). Obtained as yellow solid; yield: 0.157 g (39%); mp 174–175 °C; IR (KBr): 1677, 1600, 1511, 1488, 1263, 1168, 1074 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.06 (1H, d, J=12 Hz, H_{6A}), 2.29 (3H, s, N–CH_3), 2.36 (6H, s, CH_3), 2.82 (1H, dd, J=12, 2 Hz, H_{6B}), 2.98 (1H, dd, J=13, 2 Hz, H_{8B}), 3.83 (1H, d, J=13 Hz, H_{8A}), 5.06 (1H, s, H_4), 6.30 (1H, s, H_1), 6.54 (1H, s, C*H*Ar), 6.91–7.54 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.6 (*C*H$_3$), 21.8 (*C*H$_3$), 46.8 (N–*C*H$_3$), 57.8 (C_8), 60.3 (C_6), 67.1 (C_5), 80.2 (C_4), 81.1 (C_1), 116.1 (*C*H), 122.2 (*C*H), 126.8 (*C*H), 128.1 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 129.4 (*C*H), 129.5 (*C*H), 130.7 (*C*H), 132.6 (*C*), 132.7 (*C*), 133.5 (C_9), 136.5 (C_{11}), 137.9 (*C*), 139.1 (*C*), 139.6 (*C*), 150.6 (*C*), 197.9 (*C*=O). Anal. calcd for $C_{35}H_{34}N_2O_2$: C, 81.68; H, 6.66; N, 5.44. Found: C, 81.75; H, 6.74; N, 5.36.

4.2.9. Compounds 5c and 6c.[15] Obtained as a viscous liquid; overall yield: 0.098 g; yield: **5c**, 12%; **6c**, 6%. Anal. calcd for $C_{48}H_{45}N_3O_3$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.07; H, 6.30; N, 5.95.

4.2.10. 13-Methyl-1,8-bis(4-methylphenyl)-3,4,10,11-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5c). δ_H (300 MHz, $CDCl_3$) 2.24 (3H, s, N–CH_3), 2.28 (6H, s, CH_3), 2.46 (2H, d, 13 Hz, $H_{12A,14A}$), 2.63 (2H, d, 13 Hz, $H_{12B,14B}$), 5.41 (2H, s, $H_{4,11}$), 5.57 (2H, s, $H_{1,8}$), 6.83–8.25 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.8 (*C*H$_3$), 45.4 (N–*C*H$_3$), 57.5 ($C_{12,14}$), 67.2 ($C_{5,7}$), 80.5 ($C_{4,11}$), 87.9 ($C_{1,8}$), 114.9 (*C*H), 126.5 (*C*H), 127.8 (*C*H), 128.8 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.8 (*C*H), 131.2 (*C*H), 138.0 (*C*), 138.7 (*C*), 140.2 (*C*), 152.9 (*C*), 199.2 (*C*=O).

4.2.11. 13-Methyl-4,8-bis(4-methylphenyl)-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6c). δ_H (300 MHz, $CDCl_3$) 1.18–1.30 (1H, m, H_{12B}), 1.37 (3H, s, N–CH_3), 1.74 (1H, d, J=12 Hz, H_{14A}), 2.09 (1H, d, J=13 Hz, H_{12A}), 2.22 (6H, s, CH_3), 2.53 (1H, d, J=12 Hz, H_{14B}), 4.40 (1H, d, J=6 Hz, H_3), 4.43 (1H, d, J=6 Hz, H_4), 6.07 (1H, s, H_{11}), 6.40 (1H, s, H_8), 6.91–7.67 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.0 (*C*H$_3$), 20.1 (*C*H$_3$), 43.3 (N–*C*H$_3$), 58.1 (C_{12}), 59.2 (C_{14}), 59.2 (C_4), 66.8 (C_7), 74.0 (C_{11}), 81.6 (C_3), 83.1 (C_8), 86.6 (C_5), 114.6 (*C*H), 117.8 (*C*H), 122.8 (*C*H), 126.4 (*C*H), 126.8 (*C*H), 127.5 (*C*H), 128.0 (*C*H), 128.1 (*C*H), 128.5 (*C*H), 128.8 (*C*H), 129.2 (*C*H), 129.4 (*C*H), 129.7 (*C*H), 129.8 (*C*H), 130.0 (*C*H), 130.7 (*C*H), 136.4 (*C*), 136.5 (*C*), 137.6 (*C*), 137.7 (*C*), 138.1 (*C*), 138.7 (*C*), 148.9 (*C*), 149.2 (*C*), 204.9 (*C*=O).

4.2.12. 13-Methyl-4,11-bis(4-methylphenyl)-2,3,9,10-tetraphenyl-1,8-dioxa-2,9,13-triazadispiro[4.1.4.3]tetradecan-6-one (7c). Obtained as white solid; yield: 0.042 g (7%); mp 190–192 °C; IR (KBr): 1645, 1610, 1500, 1463 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.91 (2H, d, 13 Hz, $H_{12B,14B}$), 1.98 (3H, s, N–CH_3), 2.31 (6H, s, CH_3), 2.91 (2H, d, 13 Hz, $H_{12A,14A}$), 4.68 (2H, d, J=7 Hz, $H_{4,11}$), 4.73 (2H, d, J=7 Hz, $H_{3,10}$), 6.88–7.38 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.5 (*C*H$_3$), 45.9 (N–*C*H$_3$), 60.22 ($C_{3,10}$), 61.8 ($C_{12,14}$), 77.2 ($C_{4,11}$), 87.5 ($C_{5,7}$), 118.3 (*C*H), 123.1 (*C*H), 127.5 (*C*H), 128.0 (*C*H), 128.7 (*C*H), 129.0 (*C*H), 129.6 (*C*H), 130.0 (*C*H), 134.6 (*C*), 137.4 (*C*), 140.8 (*C*), 149.8 (*C*), 203.3 (*C*=O). Anal. calcd for $C_{48}H_{45}N_3O_3$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.91; H, 6.32; N, 5.82.

4.2.13. 1-(4-Methoxyphenyl)-9-[(4-methoxyphenyl)-methylidene]-7-methyl-3,4-diphenyl-2-oxa-3,7-diazaspiro-[4.5]decan-10-one (3d). Obtained as yellow solid; yield: 0.122 g (31%); mp 178–180 °C; IR (KBr): 1675, 1598, 1488, 1361, 1251, 1170, 1029 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.07 (1H, d, J=12 Hz, H_{6A}), 2.27 (3H, s, N–CH_3), 2.81 (1H, d, J=12 Hz, H_{6B}), 2.97 (1H, d, J=14 Hz, H_{8B}), 3.79 (3H, s, OCH_3), 3.77–3.85 (1H, m, H_{8A}), 3.81 (3H, s, OCH_3), 5.08 (1H, s, H_4), 6.27 (1H, s, H_1), 6.56 (1H, s, C*H*Ar), 6.69–7.67 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 46.9

(N–CH_3), 54.5 (C_8), 55.7 (OCH_3), 55.8 (OCH_3), 57.7 (C_6), 67.2 (C_5), 80.2 (C_4), 81.1 (C_1), 113.9 (*C*H), 114.3 (*C*H), 116.1 (*C*H), 122.2 (*C*H), 126.8 (*C*H), 127.8 (*C*H), 128.2 (*C*H), 129.0 (*C*H), 129.3 (*C*H), 132.3 (C_9), 132.6 (*C*), 133.3 (*C*), 136.6 (C_{11}), 139.3 (*C*), 143.1 (*C*), 160.7 (*C*), 161.1 (*C*), 197.6 (*C*=O). Anal. calcd for $C_{35}H_{34}N_2O_4$: C, 76.90; H, 6.27; N, 5.12. Found: C, 76.83; H, 6.21; N, 5.18.

4.2.14. Compounds 5d and 6d.[15] Obtained as a viscous liquid; overall yield: 0.090 g; yield: **5d**, 11%; **6d**, 5%. Anal. calcd for $C_{48}H_{45}N_3O_5$: C, 77.50; H, 6.10; N, 5.65. Found: C, 77.41; H, 6.17; N, 5.61.

4.2.15. 1,8-Bis(4-methoxyphenyl)-13-methyl-3,4,10,11-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]-tetradecan-6-one (5d). δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, N–CH_3), 2.52 (2H, d, 13 Hz, $H_{12A,14A}$), 2.71 (2H, d, 13 Hz, $H_{12B,14B}$), 3.82 (6H, s, OCH_3), 5.48 (2H, s, $H_{4,11}$), 5.63 (2H, s, $H_{1,8}$), 6.69–7.76 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 45.6 (N–*C*H_3), 55.7 (O*C*H_3), 58.0 ($C_{12,14}$), 67.0 ($C_{5,7}$), 80.5 ($C_{4,11}$), 87.8 ($C_{1,8}$), 113.9 (*C*H), 114.6 (*C*H), 122.0 (*C*H), 127.8 (*C*H), 128.1 (*C*H), 128.8 (*C*H), 129.3 (*C*H), 130.9 (*C*H), 132.1 (*C*), 136.8 (*C*), 159.8 (*C*), 160.7 (*C*), 199.0 (*C*=O).

4.2.16. 4,8-Bis(4-methoxyphenyl)-13-methyl-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]-tetradecan-6-one (6d). δ_H (300 MHz, $CDCl_3$) 1.39–1.44 (1H, m, H_{12B}), 1.45 (3H, s, N–CH_3), 1.82 (1H, d, *J*=12 Hz, H_{14A}), 1.93 (1H, d, *J*=9 Hz, H_{12A}), 2.60 (1H, d, *J*=12 Hz, H_{14B}), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.45 (1H, d, *J*=6 Hz, H_3), 4.51 (1H, d, *J*=6 Hz, H_4), 6.15 (1H, s, H_{11}), 6.43 (1H, s, H_8), 6.69–7.67 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.8 (N–*C*H_3), 54.5 (C_{12}), 55.7 (O*C*H_3), 55.8 (O*C*H_3), 58.9 (C_4), 60.3 (C_{14}), 67.0 (C_7), 74.1 (C_{11}), 81.7 (C_3), 83.2 (C_8), 87.8 (C_5), 113.4 (*C*H), 114.9 (*C*H), 116.5 (*C*H), 117.9 (*C*H), 121.4 (*C*H), 121.7 (*C*H), 122.2 (*C*H), 126.0 (*C*H), 127.6 (*C*H), 129.3 (*C*H), 129.5 (*C*H), 129.9 (*C*H), 130.2 (*C*H), 130.3 (*C*H), 130.9 (*C*H), 132.1 (*C*), 132.3 (*C*), 132.6 (*C*), 133.2 (*C*), 138.3 (*C*), 150.3 (*C*), 159.3 (*C*), 160.7 (*C*), 206.5 (*C*=O).

4.2.17. Compounds 3e, 5e and 6e.[15–17] Obtained as a viscous liquid; overall yield: 0.186 g; yield: **3e**, 31%; **5e**, 5%; **6e**, 5%.

4.2.18. 1-(4-Fluorophenyl)-9-[(4-fluorophenyl)methylidene]-7-methyl-3,4-diphenyl-2-oxa-3,7-diazaspiro[4.5]-decan-10-one (3e). δ_H (300 MHz, $CDCl_3$) 1.92 (1H, d, *J*=12 Hz, H_{6A}), 2.32 (3H, s, N–CH_3), 2.72 (1H, d, *J*=12 Hz, H_{6B}), 2.96 (1H, d, *J*=15 Hz, H_{8B}), 3.08 (1H, d, *J*=15 Hz, H_{8A}), 4.96 (1H, s, H_4), 6.23 (1H, s, H_1), 6.40 (1H, s, C*H*Ar), 6.63–8.22 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 45.3 (N–*C*H_3), 52.9 (C_8), 56.2 (C_6), 65.6 (C_5), 78.7 (C_4), 79.1 (C_1), 134.4 (C_{11}), 135.3 (C_9), 197.4 (*C*=O).

4.2.19. 1,8-Bis(4-fluorophenyl)-13-methyl-3,4,10,11-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5e). δ_H (300 MHz, $CDCl_3$) 2.31 (3H, s, N–CH_3), 2.33 (2H, d, 13 Hz, $H_{12A,14A}$), 2.64 (2H, d, 13 Hz, $H_{12B,14B}$), 5.38 (2H, s, $H_{4,11}$), 5.58 (2H, s, $H_{1,8}$), 6.63–8.22 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.0 (N–*C*H_3), 58.9 ($C_{12,14}$), 65.6 ($C_{5,7}$), 78.7 ($C_{4,11}$), 85.8 ($C_{1,8}$), 196.5 (*C*=O).

4.2.20. 4,8-Bis(4-fluorophenyl)-13-methyl-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6e). δ_H (300 MHz, $CDCl_3$) 1.30–1.35 (1H, m, H_{12B}), 1.33 (3H, s, N–CH_3), 1.76 (1H, d, *J*=13 Hz, H_{14A}), 2.08–2.11 (1H, m, H_{12A}), 2.48 (1H, d, *J*=13 Hz, H_{14B}), 4.32 (1H, d, *J*=6 Hz, H_3), 4.46 (1H, d, *J*=6 Hz, H_4), 6.02 (1H, s, H_{11}), 6.35 (1H, s, H_8), 6.63–8.22 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 43.2 (N–*C*H_3), 55.8 (C_{12}), 58.8 (C_4), 60.4 (C_{14}), 66.8 (C_7), 73.9 (C_{11}), 82.1 (C_3), 82.9 (C_8), 86.5 (C_5), 206.7 (*C*=O).

4.2.21. 1-(2-Chlorophenyl)-9-[(2-chlorophenyl)methylidene]-7-methyl-3,4-diphenyl-2-oxa-3,7-diazaspiro[4.5]-decan-10-one (3f). Obtained as yellow solid; yield: 0.079 g (20%); mp 200–203 °C; IR (KBr): 1724, 1598, 1488, 1263, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.01–2.04 (1H, m, H_{6A}), 2.50 (3H, s, N–CH_3), 2.59 (1H, d, *J*=12 Hz, H_{6B}), 3.00 (1H, d, *J*=15 Hz, H_{8B}), 3.26 (1H, d, 15 Hz, H_{8A}), 5.64 (1H, s, H_4), 5.87 (1H, s, H_1), 7.79 (1H, s, C*H*Ar), 6.93–8.03 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.5 (N–*C*H_3), 56.4 (C_8), 63.0 (C_6), 67.2 (C_5), 79.2 (C_4), 84.1 (C_1), 114.8 (*C*H), 121.9 (*C*H), 126.1 (*C*H), 126.3 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 129.6 (*C*H), 129.8 (*C*H), 129.9 (*C*H), 130.0 (*C*H), 130.1 (*C*H), 133.5 (*C*), 133.9 (*C*), 134.0 (C_{11}), 134.8 (*C*), 135.2 (C_9), 135.4 (*C*), 138.2 (*C*), 151.2 (*C*), 198.7 (*C*=O). Anal. calcd for $C_{33}H_{28}Cl_2N_2O_2$: C, 71.35; H, 5.08; N, 5.04. Found: C, 71.43; H, 5.02; N, 5.12.

4.2.22. 4,8-Bis(2-chlorophenyl)-13-methyl-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6f). Obtained as white solid; yield: 0.156 g (30%); mp 182–184 °C; IR (KBr): 1720, 1596, 1490, 1452, 1267, 1035 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.50 (3H, s, N–CH_3), 1.60–1.63 (1H, m, H_{12B}), 1.96 (1H, d, *J*=12 Hz, H_{14A}), 1.99 (1H, d, *J*=10 Hz, H_{12A}), 2.99 (1H, d, *J*=12 Hz, H_{14B}), 4.55 (1H, d, *J*=7 Hz, H_3), 5.38 (1H, d, *J*=7 Hz, H_4), 6.03 (1H, s, H_{11}), 6.72 (1H, s, H_8), 6.93–8.03 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.5 (N–*C*H_3), 54.4 (C_4), 58.1 (C_{12}), 60.3 (C_{14}), 65.9 (C_7), 74.7 (C_{11}), 79.8 (C_3), 81.4 (C_8), 85.4 (C_5), 113.8 (*C*H), 117.8 (*C*H), 121.1 (*C*H), 123.9 (*C*H), 126.6 (*C*H), 126.7 (*C*H), 127.2 (*C*H), 127.5 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 128.9 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 129.6 (*C*H), 133.9 (*C*), 135.5 (*C*), 135.8 (*C*), 138.2 (*C*), 139.1 (*C*), 149.2 (*C*), 150.1 (*C*), 201.1 (*C*=O). Anal. calcd for $C_{46}H_{39}Cl_2N_3O_3$: C, 73.40; H, 5.22; N, 5.58. Found: C, 73.47; H, 5.15; N, 5.65.

4.2.23. 7-Methyl-1-(2-methylphenyl)-9-[(2-methylphenyl)methylidene]-3,4-diphenyl-2-oxa-3,7-diazaspiro[4.5]-decan-10-one (3g). Obtained as a viscous liquid; yield: 0.100 g (24%); IR ($CHCl_3$): 1681, 1598, 1488, 1454, 1261, 1172 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.93 (3H, s, CH_3), 2.01 (3H, s, CH_3), 2.04–2.11 (1H, m, H_{6A}), 2.21 (3H, s, N–CH_3), 2.65 (1H, d, *J*=12 Hz, H_{6B}), 2.91 (1H, d, *J*=14 Hz, H_{8B}), 3.06 (1H, d, 14 Hz, H_{8A}), 4.88 (1H, s, H_4), 6.40 (1H, s, H_1), 7.69 (1H, s, C*H*Ar), 6.80–7.91 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 18.7 (*C*H_3), 25.8 (*C*H_3), 43.7 (N–*C*H_3), 54.2 (C_8), 55.9 (C_6), 66.2 (C_5), 79.6 (C_4), 81.3 (C_1), 114.8 (*C*H), 122.8 (*C*H), 125.8 (*C*H), 126.1 (*C*H), 127.1 (*C*H), 128.1 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 129.3 (*C*H), 129.4 (*C*H), 130.0 (*C*H), 130.2 (*C*H), 130.7 (*C*H), 131.2 (*C*H),

133.3 (*C*), 134.6 (*C*), 135.1 (C_9), 136.1 (*C*), 136.5 (C_{11}), 136.6 (*C*), 137.5 (*C*), 150.8 (*C*), 195.3 (*C*=O). Anal. calcd for $C_{35}H_{34}N_2O_2$: C, 81.68; H, 6.66; N, 5.44. Found: C, 81.60; H, 6.70; N, 5.51.

4.2.24. 7-Methyl-4-(2-methylphenyl)-9-[(2-methylphenyl)methylidene]-2,3-diphenyl-1-oxa-3,7-diazaspiro[4.5]decan-10-one (4g). Obtained as a viscous liquid; yield: 0.027 g (7%); IR ($CHCl_3$): 1640, 1577, 1465, 1440 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.28 (3H, s, N–CH_3), 2.38 (1H, d, 13 Hz, H_{6A}), 2.72 (1H, d, *J*=13 Hz, H_{6B}), 3.24 (1H, d, 14 Hz, H_{8A}), 3.76 (1H, d, *J*=14 Hz, H_{8B}), 4.59 (1H, d, *J*=8 Hz, H_3), 5.04 (1H, d, *J*=8 Hz, H_4), 7.67 (1H, s, C*H*Ar), 6.81–8.01 (17H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.4 (CH_3), 20.8 (CH_3), 45.9 (N–CH_3), 56.2 (C_4), 56.5 (C_8), 61.2 (C_6), 78.0 (C_3), 83.0 (C_5), 117.0 (*C*H), 122.2 (*C*H), 124.5 (*C*H), 124.9 (*C*H), 126.2 (*C*H), 126.3 (*C*H), 126.8 (*C*H), 127.4 (*C*H), 127.7 (*C*H), 127.9 (*C*H), 129.3 (*C*H), 129.7 (*C*H), 133.3 (*C*H), 134.1 (*C*), 135.0 (*C*), 136.1 (*C*), 136.5 (C_{11}), 137.0 (*C*), 137.2 (C_9), 138.5 (*C*), 148.2 (*C*), 195.3 (*C*=O). Anal. calcd for $C_{35}H_{34}N_2O_2$: C, 81.68; H, 6.66; N, 5.44. Found: C, 81.77; H, 6.59; N, 5.38.

4.2.25. Compounds 5g and 6g.[15] Obtained as a viscous liquid; overall yield: 0.085 g; yield: **5g**, 10%; **6g**, 5%. Anal. calcd for $C_{48}H_{45}N_3O_3$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.92; H, 6.43; N, 5.96.

4.2.26. 13-Methyl-1,8-bis(2-methylphenyl)-3,4,10,11-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5g).[16] δ_H (300 MHz, $CDCl_3$) 2.01 (6H, s, CH_3), 2.21 (3H, s, N–CH_3), 2.89 (2H, d, 11 Hz, $H_{12A,14A}$), 3.53 (2H, d, 11 Hz, $H_{12B,14B}$), 5.54 (2H, s, $H_{4,11}$), 5.70 (2H, s, $H_{1,8}$), 6.80–7.91 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.8 (CH_3), 44.5 (N–CH_3), 56.2 ($C_{12,14}$), 65.2 ($C_{5,7}$), 80.3 ($C_{4,11}$), 85.2 ($C_{1,8}$), 199.0 (*C*=O).

4.2.27. 13-Methyl-4,8-bis(2-methylphenyl)-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6g). δ_H (300 MHz, $CDCl_3$) 1.37–1.42 (1H, m, H_{12B}), 1.38 (3H, s, N–CH_3), 2.01 (1H, d, *J*=13 Hz, H_{14A}), 2.17 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.60–2.83 (1H, m, H_{12A}), 2.85–2.94 (1H, m, H_{14B}), 4.39 (1H, d, *J*=7 Hz, H_3), 5.01 (1H, d, *J*=7 Hz, H_4), 5.88 (1H, s, H_{11}), 6.54 (1H, s, H_8), 6.80–7.83 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 18.9 (CH_3), 19.3 (CH_3), 43.1 (N–CH_3), 55.5 (C_4), 56.2 (C_{12}), 60.9 (C_{14}), 65.2 (C_7), 74.3 (C_{11}), 81.3 (C_3), 81.4 (C_8), 85.2 (C_5), 113.7 (*C*H), 118.5 (*C*H), 121.9 (*C*H), 125.8 (*C*H), 126.0 (*C*H), 127.0 (*C*H), 127.6 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 129.5 (*C*H), 129.6 (*C*H), 130.2 (*C*H), 130.9 (*C*H), 134.8 (*C*), 134.9 (*C*), 135.1 (*C*), 136.5 (*C*), 137.2 (*C*), 137.5 (*C*), 148.2 (*C*), 150.8 (*C*), 206.9 (*C*=O).

4.2.28. 1-(2-Methoxyphenyl)-9-[(2-methoxyphenyl)methylidene]-7-methyl-3,4-diphenyl-2-oxa-3,7-diazaspiro-[4.5]decan-10-one (3h). Obtained as yellow solid; yield: 0.141 g (36%); mp 176–178 °C; IR (KBr): 1677, 1600, 1461, 1436, 1249, 1160, 1022 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.00 (1H, d, 12 Hz, H_{6A}), 2.41 (3H, s, N–CH_3), 2.44 (1H, d, *J*=12 Hz, H_{6B}), 2.99 (1H, dd, *J*=14, 1 Hz, H_{8B}), 3.09 (1H, d, 14 Hz, H_{8A}), 3.46 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.56 (1H, s, H_4), 5.62 (1H, s, H_1), 7.93 (1H, s, C*H*Ar), 6.67–8.08 (18H, m, Ph); δ_C (75 MHz, $CDCl_3$) 43.7 (N–CH_3), 53.0 (OCH_3), 53.8 (C_8), 54.4 (OCH_3), 56.0 (C_6), 65.4 (C_5), 79.2 (C_4), 82.7 (C_1), 107.6 (*C*H), 109.6 (*C*H), 113.1 (*C*H), 118.8 (*C*H), 119.0 (*C*H), 120.3 (*C*H), 123.1 (*C*H), 124.0 (*C*H), 124.9 (*C*H), 126.4 (*C*H), 126.5 (*C*H), 127.3 (*C*H), 127.4 (*C*H), 127.8 (*C*H), 129.0 (*C*), 129.5 (*C*), 130.1 (C_{11}), 131.7 (C_9), 138.0 (*C*), 151.3 (*C*), 155.5 (*C*), 157.5 (*C*), 196.4 (*C*=O). Anal. calcd for $C_{35}H_{34}N_2O_4$: C, 76.90; H, 6.27; N, 5.12. Found: C, 76.83; H, 6.35; N, 5.17.

4.2.29. 7-Methyl-3,4-diphenyl-1-(2-thienyl)-9-[2-thienylmethylidene]-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3i). Obtained as yellow solid; yield: 0.127 g (30%); mp 146–148 °C; IR (KBr): 1670, 1563, 1490, 1367, 1267, 1174, 1052 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.38 (1H, d, 13 Hz, H_{6A}), 2.40 (3H, s, N–CH_3), 2.77 (1H, d, *J*=13 Hz, H_{6B}), 3.10 (1H, d, *J*=15 Hz, H_{8B}), 3.30 (1H, d, 15 Hz, H_{8A}), 5.34 (1H, s, H_4), 5.81 (1H, s, H_1), 7.77 (1H, s, C*H*Ar), 6.86–7.85 (16H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.3 (N–CH_3), 54.7 (C_8), 57.3 (C_6), 65.7 (C_5), 79.6 (C_4), 85.2 (C_1), 114.0 (*C*H), 120.9 (*C*H), 124.0 (*C*H), 124.3 (*C*H), 125.4 (*C*H), 126.3 (*C*H), 126.7 (*C*H), 127.0 (*C*H), 127.5 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 129.3 (*C*H), 130.5 (*C*), 132.8 (C_9), 136.0 (C_{11}), 136.8 (*C*), 137.3 (*C*), 150.8 (*C*), 196.6 (*C*=O). Anal calcd for $C_{29}H_{26}N_2O_2S_2$: C, 69.85; H, 5.26; N, 5.62. Found: C, 69.80; H, 5.20; N, 5.69.

4.2.30. 7-Methyl-2,3-diphenyl-4-(2-thienyl)-9-[2-thienylmethylidene]-1-oxa-2,7-diazaspiro[4.5]decan-10-one (4i). Obtained as a viscous liquid; yield: 0.035 g (8%); IR ($CHCl_3$): cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.32 (3H, s, N–CH_3), 2.58 (1H, d, 13 Hz, H_{6A}), 2.88 (1H, d, *J*=13 Hz, H_{6B}), 3.33 (1H, d, 15 Hz, H_{8A}), 3.98 (1H, d, *J*=15 Hz, H_{8B}), 4.72 (1H, d, *J*=10 Hz, H_3), 5.02 (1H, d, *J*=10 Hz, H_4), 7.87 (1H, s, C*H*Ar), 6.82–7.88 (15H, m, Ph); δ_C (75 MHz, $CDCl_3$) 46.3 (N–CH_3), 57.4 (C_8), 58.6 (C_4), 58.9 (C_6), 76.7 (C_3), 85.3 (C_5), 116.2 (*C*H), 122.7 (*C*H), 125.4 (*C*H), 127.5 (*C*H), 127.6 (*C*H), 128.4 (*C*H), 128.9 (*C*H), 129.2 (*C*H), 129.5 (*C*H), 130.0 (*C*H), 130.4 (*C*H), 131.8 (*C*), 134.4 (C_{11}), 137.7 (C_9), 138.7 (*C*), 139.8 (*C*), 151.7 (*C*), 194.0 (*C*=O). Anal calcd for $C_{29}H_{26}N_2O_2S_2$: C, 69.85; H, 5.26; N, 5.62. Found: C, 69.92; H, 5.20; N, 5.69.

4.2.31. Compounds 3j and 6j.[15–17] Obtained as a viscous liquid; overall yield: 0.153 g; yield: **3j**, 18%; **6j**, 17%.

4.2.32. 7-Methyl-1-(3-nitrophenyl)-9-[(3-nitrophenyl)-methylidene]-3,4-diphenyl-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3j). δ_H (300 MHz, $CDCl_3$) 2.18 (1H, d, 12 Hz, H_{6A}), 2.30 (3H, s, N–CH_3), 2.57 (1H, d, *J*=12 Hz, H_{6B}), 3.01 (1H, d, *J*=14 Hz, H_{8B}), 3.41 (1H, d, 14 Hz, H_{8A}), 5.21 (1H, s, H_4), 5.65 (1H, s, H_1), 7.67 (1H, s, C*H*Ar), 6.85–7.99 (16H, m, Ph); δ_C (75 MHz, $CDCl_3$) 44.0 (N–CH_3), 53.7 (C_8), 58.3 (C_6), 65.1 (C_5), 78.6 (C_4), 84.8 (C_1), 131.8 (C_9), 136.5 (C_{11}), 196.1 (*C*=O).

4.2.33. 13-Methyl-4,8-bis(3-nitrophenyl)-2,3,10,11-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6j). δ_H (300 MHz, $CDCl_3$) 1.30 (1H, *J*=12 Hz, H_{12B}), 1.34 (3H, s, N–CH_3), 1.92 (1H, d, *J*=12 Hz, H_{14A}),

2.12 (1H, d, J=12 Hz, H_{12A}), 2.54 (1H, d, J=12 Hz, H_{14B}), 4.41 (1H, d, J=6 Hz, H_3), 5.01 (1H, d, J=6 Hz, H_4), 6.04 (1H, s, H_{11}), 6.37 (1H, s, H_8), 6.85–7.99 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 43.9 (N–CH_3), 57.9 (C_4), 58.2 (C_{12}), 60.1 (C_{14}), 66.8 (C_7), 73.9 (C_{11}), 81.3 (C_3), 83.1 (C_8), 86.4 (C_5), 204.7 (C=O).

4.2.34. Compounds 3k, 5k and 6k.[15–17] Obtained as a viscous liquid; overall yield: 0.156 g; yield: **3k**, 26%; **5k**, 6%; **6k**, 3%.

4.2.35. 7-Methyl-4-(4-methylphenyl)-1,3-diphenyl-9-[phenylmethylidene]-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3k). δ_H (300 MHz, $CDCl_3$) 2.01 (1H, d, 12 Hz, H_{6A}), 2.21 (3H, s, CH_3), 2.27 (3H, s, N–CH_3), 2.81 (1H, d, J=12 Hz, H_{6B}), 2.95 (1H, dd, J=14, 2 Hz, H_{8B}), 3.88 (1H, d, 14 Hz, H_{8A}), 5.01 (1H, s, H_4), 5.99 (1H, s, H_1), 6.61 (1H, s, CHAr), 6.67–7.81 (19H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.1 (CH_3), 46.9 (N–CH_3), 55.7 (C_6), 57.6 (C_8), 67.3 (C_5), 78.7 (C_4), 81.2 (C_1), 135.3 (C_9), 136.0 (C_{11}), 198.0 (C=O).

4.2.36. 13-Methyl-4-(3-methylphenyl)-11-(4-methylphenyl)-1,3,8,10-tetraphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5k). δ_H (300 MHz, $CDCl_3$) 2.21 (6H, s, CH_3), 2.30 (3H, s, N–CH_3), 2.41 (2H, d, 13 Hz, $H_{12A,14A}$), 2.69 (2H, d, 13 Hz, $H_{12B,14B}$), 5.49 (2H, s, $H_{4,11}$), 5.62 (2H, s, $H_{1,8}$), 6.67–7.81 (26H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.9 (CH_3), 45.1 (N–CH_3), 57.9 ($C_{12,14}$), 67.3 ($C_{5,7}$), 79.8 ($C_{4,11}$), 87.8 ($C_{1,8}$), 199.3 (C=O).

4.2.37. 13-Methyl-3,11-bis(4-methylphenyl)-2,4,8,10-tetraphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (6k). δ_H (300 MHz, $CDCl_3$) 1.21–1.28 (1H, m, H_{12B}), 1.38 (3H, s, N–CH_3), 1.73 (1H, d, J=13 Hz, H_{14A}), 2.12–2.14 (1H, m, H_{12A}), 2.23 (6H, s, CH_3), 2.51 (1H, d, J=13 Hz, H_{14B}), 4.42 (1H, d, J=6 Hz, H_3), 5.10 (1H, d, J=6 Hz, H_4), 6.01 (1H, s, H_{11}), 6.42 (1H, s, H_8), 6.67–7.81 (28H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.5 (CH_3), 20.7 (CH_3), 43.1 (N–CH_3), 56.1 (C_{12}), 57.4 (C_4), 60.1 (C_{14}), 66.7 (C_7), 72.1 (C_{11}), 82.1 (C_3), 83.0 (C_8), 86.1 (C_5), 204.8 (C=O).

4.2.38. Compounds 3l and 5l.[15–17] Obtained as a viscous liquid; overall yield: 0.123 g; yield: **3l**, 23%; **5l**, 7%.

4.2.39. 1-(4-Chlorophenyl)-9-[(4-chlorophenyl)methylidene]-7-methyl-4-(4-methylphenyl)-3-phenyl-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3l). δ_H (300 MHz, $CDCl_3$) 2.00 (1H, d, 12 Hz, H_{6A}), 2.22 (3H, s, CH_3), 2.31 (3H, s, N–CH_3), 2.77 (1H, d, J=12 Hz, H_{6B}), 2.91 (1H, dd, J=14, 2 Hz, H_{8B}), 3.79 (1H, d, 14 Hz, H_{8A}), 5.06 (1H, s, H_4), 6.31 (1H, s, H_1), 6.63 (1H, s, CHAr), 6.70–7.80 (17H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.6 (CH_3), 46.0 (N–CH_3), 53.1 (C_8), 56.9 (C_6), 65.7 (C_5), 78.9 (C_4), 81.0 (C_1), 134.7 (C_9), 135.7 (C_{11}), 197.9 (C=O).

4.2.40. 1,8-Bis(4-chlorophenyl)-13-methyl-4-(3-methylphenyl)-11-(4-methylphenyl)-3,10-diphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5l). δ_H (300 MHz, $CDCl_3$) 2.23 (6H, s, CH_3), 2.29 (3H, s, N–CH_3), 2.31 (2H, d, 13 Hz, $H_{12A,14A}$), 2.66 (2H, d, 13 Hz, $H_{12B,14B}$), 5.42 (2H, s, $H_{4,11}$), 5.61 (2H, s, $H_{1,8}$), 6.70–7.80 (26H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.7 (CH_3), 44.8 (N–CH_3), 58.1 ($C_{12,14}$), 67.4 ($C_{5,7}$), 80.4 ($C_{4,11}$), 87.4 ($C_{1,8}$), 199.2 (C=O).

4.2.41. 7-Methyl-1,4-bis(4-methylphenyl)-9-[(4-methylphenyl)methylidene]-3-phenyl-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3m). Obtained as yellow solid; yield: 0.153 g (37%); mp 174–175 °C; IR (KBr): 1677, 1600, 1490, 1361, 1261, 1170, 1064 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.03 (1H, dd, 12, 2 Hz, H_{6A}), 2.28 (3H, s, N–CH_3), 2.35 (6H, s, CH_3), 2.36 (3H, s, CH_3), 2.79 (1H, d, J=12 Hz, H_{6B}), 2.96 (1H, dd, J=14, 2 Hz, H_{8B}), 3.82 (1H, d, J=14 Hz, H_{8A}), 5.03 (1H, s, H_4), 6.28 (1H, s, H_1), 6.53 (1H, s, CHAr), 6.91–7.20 (17H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.1 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 45.3 (N–CH_3), 52.9 (C_8), 56.3 (C_6), 66.8 (C_5), 79.6 (C_4), 80.9 (C_1), 116.2 (CH), 126.9 (CH), 128.9 (CH), 129.3 (CH), 129.4 (CH), 129.5 (CH), 129.8 (CH), 130.6 (CH), 134.7 (C_9), 134.8 (C), 136.0 (C), 136.1 (C_{11}), 136.5 (C), 138.0 (C), 138.7 (C), 149.2 (C), 151.6 (C), 196.6 (C=O). Anal. calcd for $C_{36}H_{36}N_2O_2$: C, 81.79; H, 6.86; N, 5.30. Found: C, 81.86; H, 6.81; N, 5.34.

4.2.42. Compounds 5m and 6m.[15] Obtained as a viscous liquid; overall yield: 0.100 g; yield: **5m**, 11%; **6m**, 5%. Anal. calcd for $C_{50}H_{49}N_3O_3$: C, 81.16; H, 6.67; N, 5.68. Found: C, 81.10; H, 6.60; N, 5.62.

4.2.43. 13-Methyl-4-(3-methylphenyl)-1,8,11-tris(4-methylphenyl)-3,10-diphenyl-2,9-dioxa-3,10,13-triazadispiro[4.1.4.3]tetradecan-6-one (5m). δ_H (300 MHz, $CDCl_3$) 2.20–2.26 (2H, m, $H_{12A,14A}$), 2.23 (12H, s, CH_3), 2.24 (3H, s, N–CH_3), 2.68 (2H, d, 13 Hz, $H_{12B,14B}$), 5.37 (2H, s, $H_{4,11}$), 5.56 (2H, s, $H_{1,8}$), 6.72–8.32 (26H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.0 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 44.0 (N–CH_3), 58.8 ($C_{12,14}$), 65.6 ($C_{5,7}$), 78.9 ($C_{4,11}$), 86.4 ($C_{1,8}$), 113.5 (CH), 126.1 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 130.0 (CH), 136.0 (C), 136.4 (C), 136.5 (C), 138.7 (C), 151.7 (C), 197.7 (C=O).

4.2.44. 13-Methyl-3,4,8,11-tetrakis(4-methylphenyl)-2,10-diphenyl-1,9-dioxa-2,10,13-triazadispiro[4.1.4.3]-tetradecan-6-one (6m). δ_H (300 MHz, $CDCl_3$) 1.39 (3H, s, N–CH_3), 1.40 (1H, J=12 Hz, H_{12B}), 1.96 (1H, d, J=13 Hz, H_{14A}), 2.17 (1H, d, J=12 Hz, H_{12A}), 2.29 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.60 (1H, d, J=13 Hz, H_{14B}), 4.43 (1H, d, J=6 Hz, H_3), 4.46 (1H, d, J=6 Hz, H_4), 6.10 (1H, s, H_{11}), 6.42 (1H, s, H_8), 6.59–7.93 (27H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.4 (CH_3), 21.5 (CH_3), 44.8 (N–CH_3), 59.2 (C_{12}), 60.6 (C_4), 61.8 (C_{14}), 68.2 (C_7), 73.8 (C_{11}), 81.3 (C_3), 83.2 (C_8), 87.9 (C_5), 114.6 (CH), 117.8 (CH), 121.5 (CH), 124.0 (CH), 127.6 (CH), 128.1 (CH), 128.4 (CH), 129.2 (CH), 129.6 (CH), 129.8 (CH), 133.1 (C), 135.6 (C), 136.1(C), 136.9 (C), 137.2 (C), 137.4 (C), 137.5 (C), 137.9 (C), 150.1 (C), 150.5 (C), 206.2 (C=O).

4.2.45. 7-Methyl-1-(2-methylphenyl)-4-(4-methylphenyl)-9-[(2-methylphenyl)methylidene]-3-phenyl-2-oxa-3,7-diazaspiro[4.5]decan-10-one (3n).[16] Obtained as a viscous liquid; yield: 0.130 g (32%); IR ($CHCl_3$): 1680, 1563, 1499, 1362, 1267, 1174, 1059 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.09 (1H, d, 12 Hz, H_{6A}), 2.25 (3H, s, N–CH_3), 2.27 (3H, s, CH_3), 2.29 (6H, s, CH_3), 2.85 (1H, dd, J=12,

2 Hz, H_{6B}), 2.89 (1H, d, J=14 Hz, H_{8B}), 3.85 (1H, d, 14 Hz, H_{8A}), 5.09 (1H, s, H_4), 6.26 (1H, s, H_1), 6.45 (1H, s, C*H*Ar), 6.67–7.71 (17H, m, Ph); δ_C (75 MHz, $CDCl_3$) 20.3 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 44.6 (N–CH_3), 52.3 (C_8), 56.7 (C_6), 65.8 (C_5), 78.6 (C_4), 81.9 (C_1), 135.6 (C_9), 136.2 (C_{11}), 197.2 (*C*=O). Anal. calcd for $C_{36}H_{36}N_2O_2$: C, 81.79; H, 6.86; N, 5.30. Found: C, 81.72; H, 6.90; N, 5.37.

4.2.46. 7-Methyl-4-(2-methylphenyl)-3-(4-methylphenyl)-9-[(2-methylphenyl)methylidene]-2-phenyl-1-oxa-2,7-diazaspiro[4.5]decan-10-one (4n). Obtained as a viscous liquid; yield: 0.029 g (7%); IR ($CHCl_3$): 1667, 1545, 1478, 1360 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.09 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.30 (3H, s, N–CH_3), 2.36 (3H, s, CH_3), 2.43 (1H, d, 13 Hz, H_{6A}), 2.88 (1H, d, J=13 Hz, H_{6B}), 3.31 (1H, d, 14 Hz, H_{8A}), 3.84 (1H, d, J=14 Hz, H_{8B}), 4.63 (1H, d, J=8 Hz, H_3), 5.10 (1H, d, J=8 Hz, H_4), 7.76 (1H, s, C*H*Ar), 6.87–7.54 (17H, m, Ph); δ_C (75 MHz, $CDCl_3$) 19.9 (CH_3), 20.5 (CH_3), 21.1 (CH_3), 45.5 (N–CH_3), 55.6 (C_8), 56.0 (C_4), 60.8 (C_6), 77.3 (C_3), 83.8 (C_5), 196.2 (*C*=O), 118.1 (*C*H), 123.2 (*C*H), 125.5 (*C*H), 125.8 (*C*H), 127.1 (*C*H), 127.2 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 128.9 (*C*H), 129.4 (*C*H), 130.3 (*C*H), 130.6 (*C*H), 133.1 (*C*), 133.9 (*C*), 134.6 (*C*), 135.1 (C_{11}), 137.3 (C_9), 137.9 (*C*), 138.1 (*C*), 149.2 (*C*). Anal. calcd for $C_{36}H_{36}N_2O_2$: C, 81.79; H, 6.86; N, 5.30. Found: C, 81.73; H, 6.92; N, 5.36.

4.2.47. 7-Methyl-4-(4-methylphenyl)-1-(1-naphthyl)-9-(1-naphthylmethylidene)-3-phenyl-2-oxa-3,7-diazaspiro-[4.5]decan-10-one (3o).[16] Obtained as a viscous liquid; yield: 0.076 g (20%); IR ($CHCl_3$): 1677, 1598, 1500, 1361, 1263, 1170, 1063 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.88 (1H, d, 12 Hz, H_{6A}), 2.21 (1H, d, J=12 Hz, H_{8B}), 2.30 (3H, s, N–CH_3), 2.33 (3H, s, CH_3), 2.80 (1H, d, 12 Hz, H_{8A}), 2.96 (1H, dd, J=12, 2 Hz, H_{6B}), 5.01 (1H, s, H_4), 6.31 (1H, s, H_1), 8.02 (1H, s, C*H*Ar), 6.90–8.50 (23H, m, Ph); δ_C (75 MHz, $CDCl_3$) 28.7 (CH_3), 43.5 (N–CH_3), 55.0 (C_8), 60.9 (C_6), 66.7 (C_5), 78.8 (C_4), 82.8 (C_1), 134.4 (C_9), 136.3 (C_{11}), 198.5 (*C*=O). Anal. calcd for $C_{42}H_{36}N_2O_2$: C, 83.97; H, 6.04; N, 4.66. Found: C, 84.05; H, 5.97; N, 4.74.

4.3. X-ray crystallographic determination of 3m and 6f

The isoxazolidines **3m** and **6f** were recrystallised from ethanol–ethyl acetate (1:1) mixture. X-ray diffraction data for **3m** were collected using a Bruker Kappa X8 APPEX II diffractometer with graphite-monochromated Mo Kα radiation 0.71073 Å. The temperature of the crystal was maintained at the selected value (100 K) by means of a 7000 series Cryostream cooling device to within an accuracy of $\pm$1. For **6f**, the data were collected at room temperature on an Enraf–Nonius MACH 3 four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å) in Madurai Kamaraj University. The data collection, integration and data reduction for **3m** was performed using Bruker SMART and Bruker SAINT programs whereas for **6f** it was performed using CAD-4 EXPRESS and XCAD4 programs. An empirical absorption correction was applied using μ scan method. The unit cell parameters were determined by a least square fitting of randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method. The structure was solved by direct methods (SHELXS 97) and subsequent Fourier synthesis and refined by full matrix least squares on SHELXL 97 for all nonhydrogen atoms for **3m** and **6f**. All hydrogen atoms were placed in calculated positions.

4.3.1. Compound 3m. $C_{36}H_{36}N_2O_2$, M=528.67, monoclinic, space group $P21/c$, a=10.7182(14) Å, b=14.7010(19) Å, c=18.582(2) Å, V=2897.4(7) $Å^3$, Z=4, $F(000)$=1128, μ=0.075 mm^{-1}, D_c=1.212 g/cm^3. The reflections collected were 79817 of which 10863 unique [R(int)=0.0493]; 8102 reflections $I>2\sigma(I)$, R_1=0.0725 and wR_2=0.1925 for 8102 [$I>2\sigma(I)$] and R_1=0.1013 and wR_2=0.2348 for all (10863) intensity data. Goodness of fit=1.098, residual electron density in the final Fourier map was 0.649 and -0.455 $eÅ^{-3}$. CCDC number is 608816.

4.3.2. Compound 6f. $C_{46}H_{39}Cl_2N_3O_3$, M=752.70, monoclinic, space group $P21/n$, a=10.992(4) Å, b=25.671(10) Å, c=14.545(6) Å, V=3845(3) $Å^3$, Z=4, $F(000)$=1576, μ=0.215 mm^{-1}, D_c=1.300 mg/m^3. The reflections collected were 7464 of which 6747 unique [R(int)=0.0480]; 2784 reflections $I>2\sigma(I)$, R_1=0.0534 and wR_2=0.1123 for 2784 [$I>2\sigma(I)$] and R_1=0.1833 and wR_2=0.1560 for all (6747) intensity data. Goodness of fit=1.002, residual electron density in the final Fourier map was 0.431 and -0.531 $eÅ^{-3}$. CCDC number is 608817.

Acknowledgements

S.P. thanks the Council of Scientific and Industrial Research, New Delhi for a major research project No. 01(1926/04/EMR II) and the Department of Science and Technology, New Delhi for funds under (i) IRHPA programme for the purchase of a high resolution NMR spectrometer and (ii) FIST programme and the University Grants Commission, New Delhi for funds under the DRS and ASIST programmes. The measurements on **3m** were carried out at ICMMO (Institut de Chimie Moléculaire d'Orsay, France) diffractometer service.

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15. Total isolated yield of inseparable mixtures is split into yields of individual compounds using ^{1}H NMR signal intensities.
16. For these compounds existing as mixture, identification of all signals of the aromatic carbons proved difficult.
17. The elemental analysis not done as they occur as mixture of compounds with different molecular formula.

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Tetrahedron 62 (2006) 12392–12397
Tetrahedron

A novel synthesis of hexahydroazoninoindoles using activated alkynes in an azepine ring expansion

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Received 23 May 2006; revised 9 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—The manuscript describes a novel and efficient protocol for the synthesis of hexahydroazoninoindoles, based on the tandem cleavage–cyclisation reaction of hexahydroazepinoindoles with activated alkynes.

1. Introduction

Monocyclic and annulated medium-ring *N*-containing heterocycles are an important class of compounds, occurring in a wide range of natural and synthetic products.[1] There is a sound basis for their appeal in pharmacological research; they are of moderate size giving rise to their potential as ligands for receptors, and they offer semi-restricted conformational flexibility allowing considerable scope for selective binding with a range of functional groups.[2] The term 'medium ring' by origin is applied to alicyclic compounds having a ring size in the range 8–11;[3] however, it is now also used to describe heterocyclic systems. Most of the evidence available regarding the difficulties associated with the formation of medium rings comes from experimental studies.[4] The direct formation of these ring sizes (in particular, the nine-membered rings) from acyclic precursors is entropically and enthalpically disfavoured. The efficient construction of medium-sized cycles is a challenge and has therefore attracted considerable attention during the past years.[5] This paper describes the first successful example of the hexahydroazepine (HHAz) ring expansion under the action of activated acetylenes.

2. Discussion

We have recently worked out the alkyne-induced tetrahydropyridine (THP) ring expansion protocol for the synthesis of differently annulated tetrahydroazocines.[6,7] The starting hexahydroazepine derivatives **1**–**4** were synthesised according to the literature procedure.[8] The protocol includes the Fisher indolisation reaction leading to the carbazolone A, its oximation, followed by the Beckmann rearrangement and reduction of the resulting cyclic amide, yielding the *NH*-hexahydroazepino[4,3-*b*]indole B, its acylation and subsequent reduction, leading to the target derivatives **1**–**4**.

The isomeric hexahydroazepino[3,4-*b*]indole scaffold (also promising from the viewpoint of the seven-membered ring expansion) was built according to the strategy illustrated in Scheme 2.

6-Fluoro-2,3,4,9-tetrahydro-1*H*-1-carbazolone **5** was also synthesised according to a previously described method.[9] Its oximation was followed by the Beckmann rearrangement of **6**, yielding amide **7** as the sole product. Analogously to the Scheme 1, **7** was reduced, yielding *NH*-hexahydroazepino[3,4-*b*]indole **8**, which was acetylated (yielding **9**) or benzoylated (yielding **10**). The reduction of **9** and **10** provided *N*-ethyl (**11**) and *N*-Bn- (**12**) hexahydroazepino-[3,4-*b*]indoles correspondingly.

Azepine derivatives **1**–**4** and **11**,**12** were treated with methyl propiolate (MP) or dimethyl acetylene dicarboxylate (DMAD) in methanol at room temperature. The reaction with MP proceeded smoothly in all cases, giving the corresponding azoninoindoles **13**–**18** as the sole products in high preparative yields (Scheme 3). A mechanism similar to that suggested for azocine formation[6] seems plausible for the HHAz ring expansion.

The reaction of the compounds **1**–**3** with DMAD along with the formation of the target azonines **19**–**21** provided 3-methoxymethyl indoles **22**–**24** (Scheme 4). The latter compounds are the products of the tandem cleavage process, involving one molecule of solvent and are most likely formed analogously to the previously described route for the THP derivatives.[10] Compounds **22**–**24** were formed as single

Keywords: Medium-ring heterocycles; Fused indoles; Michael addition; Ring expansion; Azonine.
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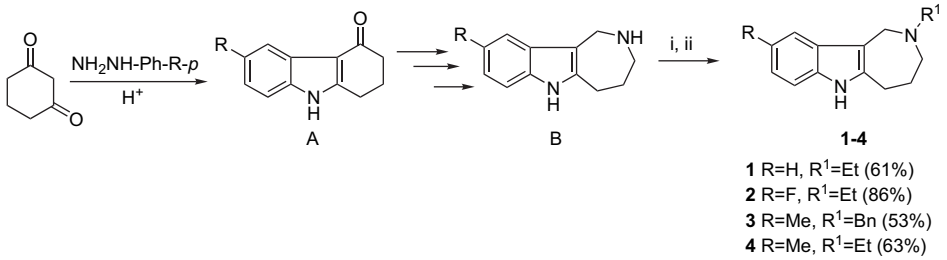
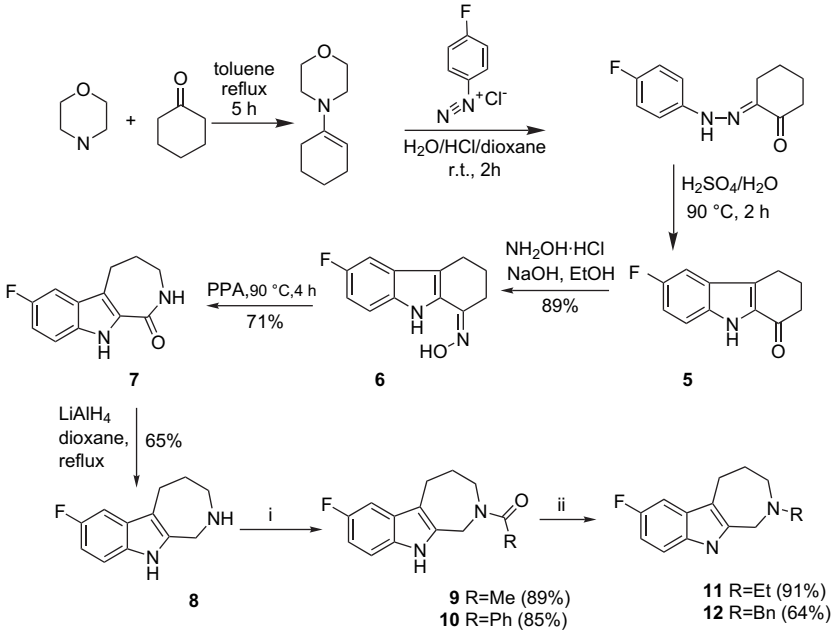
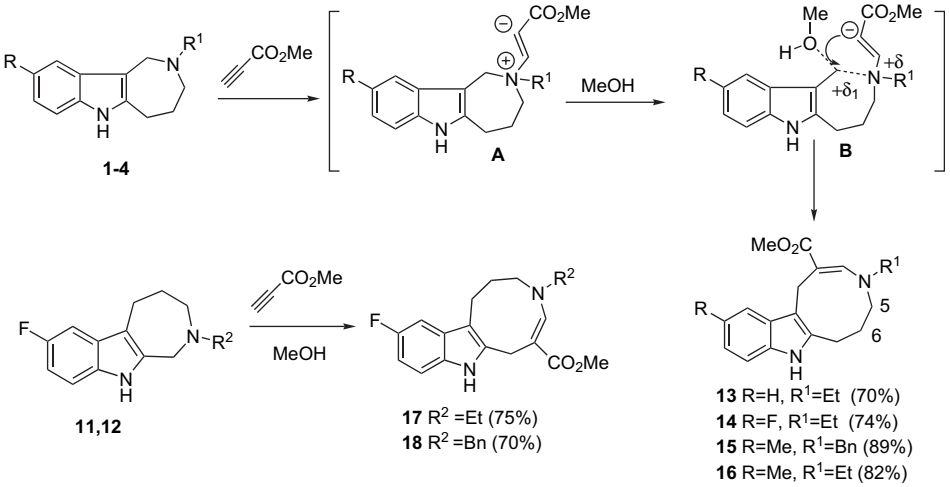
doi:10.1016/j.tet.2006.09.107



Scheme 1. Reagents and conditions: (i) Ac_2O (for **1**,**2**,**4**) or $PhCOCl/NEt_3$ (for **3**); (ii) $LiAlH_4$/dioxane.



Scheme 2. Reagents and conditions: (i) Ac_2O (for **9**) or $PhCOCl/NEt_3$ (for **10**); (ii) $LiAlH_4$/dioxane, reflux, 5 h.

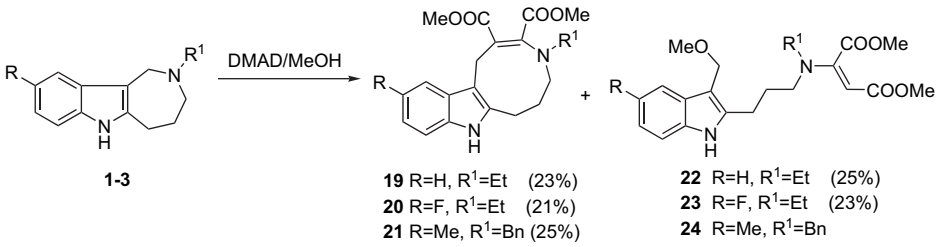


Scheme 3.

isomers of the enamine fragment (derived from the NMR data), more detailed study of their stereochemistry being out of the scope of this paper.

To perform an unequivocal structural assignment and elucidate its three-dimensional structure, X-ray crystallographic analysis was carried out on a suitable monocrystal of hexahydroazonino[5,6-*b*]indole **16** obtained by recrystallisation from ethyl acetate by slow evaporation at room temperature.[11] The refined X-ray crystal structure of **16** is shown in Figure 1.

The nine-membered ring of the molecule has a twisted bath conformation. The N(2)–C(10) is shorter than the



Scheme 4. Compound **24** was not isolated in pure form (see Section 4 for details).

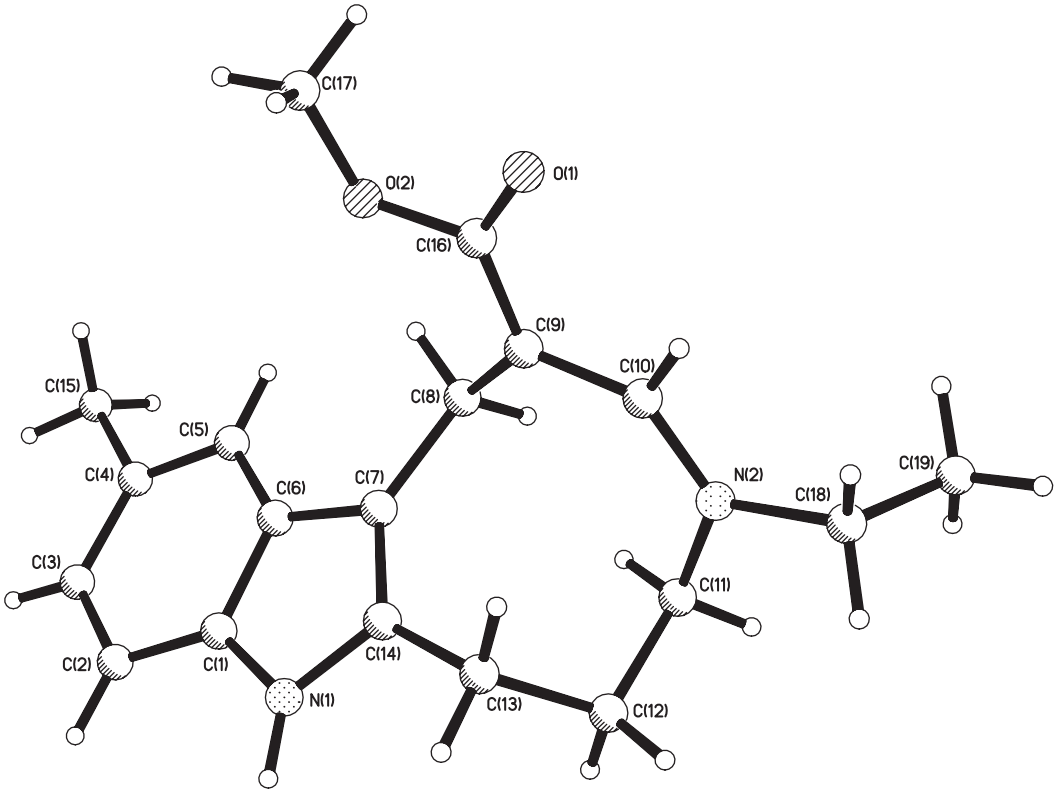


Figure 1. X-ray crystal structure of **16**.

N(2)–C(11) bond (1.366 and 1.442 Å, respectively), indicating the presence of conjugation in the enamine (N(2)–C(10)–C(11)) fragment. CCDC 608173 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44 1223/336 033. E-mail: deposit@ccdc.cam.ac.uk].

3. Conclusion

We have developed a new and original approach towards azoninoindoles—compounds, which are hardly available by other synthetic means. To the best of our knowledge this is the first example of a seven-membered *N*-heterocycle expansion leading to the formation of the azonine derivative. The ease of formation of the hydrogenated eight and nine-membered rings by this reaction encourages us to apply it to the synthesis of other medium-sized *N*-heterocycles.

4. Experimental

4.1. General

All solvents were distilled and dried before use, DMAD and MP were purchased from ACROS ORGANICS and were used without any additional purification. Column chromatography was performed with alumina oxide 60 from Fluka. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, at 25 °C or in DMSO-d_6 solutions at 40 °C, using a 300 MHz NMR spectrometer operating at 300 and 75 MHz correspondingly, peak positions are given in parts per million (δ) with tetramethylsilane used as the internal standard. Mass-spectra were registered using ESI or EI techniques.

4.2. General experimental procedure for the synthesis of azoninoindoles 13–18

To a stirred solution of azepinoindole **1**–**4** or **11**,**12** (1 mmol) in dry methanol (15 mL) at 25 °C, methyl propiolate (1.2 mmol) was added and stirring was continued for an

Table 1. Yields and some physico-chemical properties for compounds **13–23**

No.	Yield, %	Mp, °C	IR, cm^{-1}	Element analysis (calculated/found)	
13	70	179–181	1658 (C═O), 3271 (N–H)	C 72.46%, H 7.43%, N 9.39%/C 72.66%, H 7.21%, N 9.02%	$C_{18}H_{22}N_2O_2$
14	74	193–195	1661 (C═O), 3352 (N–H)	C 68.34%, H 6.69%, N 8.85%/C 67.91%, H 6.65%, N 8.63%	$C_{18}H_{21}FN_2O_2$
15	89	62–64	1669 (C═O), 3317 (N–H)	C 76.98%, H 7.00%, N 7.48%/C 76.59%, H 6.79%, N 7.56%	$C_{24}H_{26}N_2O_2$
16	82	204–206	1661 (C═O), 3265 (N–H)	C 73.05%, H 7.74%, N 8.97%/C 73.26%, H 7.65%, N 8.64%	$C_{19}H_{24}N_2O_2$
17	74	216–218	1655 (C═O), 3117 (N–H)	C 68.34%, H 6.69%, N 8.85%/C 67.95%, H 6.32%, N 8.46%	$C_{18}H_{21}FN_2O_2$
18	75	180–181	1650 (C═O), 3200 (N–H)	C 73.00%, H 6.13%, N 7.40%/C 73.32%, H 6.08%, N 7.35%	$C_{23}H_{23}FN_2O_2$
19	23	155–157	1670 (C═O), 3379 (N–H)	C 67.40%, H 6.79%, N 7.86%/C 67.30%, H 7.06%, N 8.00%	$C_{20}H_{24}N_2O_4$
20	21	183–185	1669 (C═O), 3372 (N–H)	C 64.16%, H 6.19%, N 7.48%/C 64.46%, H 6.06%, N 7.82%	$C_{20}H_{23}FN_2O_4$
21	25	176–178	1723 (C═O), 3373 (N–H)	C 72.20%, H 6.53%, N 6.48%/C 72.56%, H 6.19%, N 6.32%	$C_{26}H_{28}N_2O_4$
22	25	131–133	1673 (C═O), 3261 (N–H)	C 64.93%, H 7.27%, N 7.21%/C 65.05%, H 7.39%, N 7.55%	$C_{21}H_{28}N_2O_5$
23	23	121–123	1685 (C═O), 3300 (N–H)	C 62.06%, H 6.70%, N 6.89%/C 62.45%, H 7.12%, N 7.22%	$C_{21}H_{27}FN_2O_5$

additional 1 h (TLC monitoring). Methanol was evaporated under reduced pressure and the resulting residues were recrystallised from ethyl acetate to give compounds **13–16** or **17**,**18** correspondingly.

Yields and some physico-chemical properties of the products can be found in Table 1.

4.2.1. Methyl 4-ethyl-1,4,5,6,7,8-hexahydroazonino[5,6-*b*]indole-2-carboxylate (13). ^{1}H NMR (DMSO-d_6), ppm: δ 1.15 (3H, t, J=7.2 Hz, CH_3–Et), 1.79 (2H, m, CH_2), 2.82 (2H, m, CH_2), 3.25 (2H, q, J=7.2 Hz, CH_2–Et), 3.51 (3H, s, OCH_3), 3.60 (2H, m, CH_2), 3.90 (2H, s, CH_2-1), 6.98 (2H, m, H-11+H-10), 7.23 (1H, d, J=7.7 Hz, H-9), 7.44 (1H, d, J=7.7 Hz, H-12), 7.68 (1H, s, H-3), 10.60 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 15.4, 21.2, 23.1, 29.9, 45.4, 51.2, 51.3, 92.0, 107.9, 110.9, 118.2, 118.9, 129.7, 129.4, 134.6, 135.8, 150.9, 170.2. EIMS m/z (%): 298 (M^+, 80), 269 (10), 239 (15), 225 (30), 209 (10), 180 (20), 168 (70), 156 (40), 143 (30), 115 (15), 82 (20), 68 (10), 58 (100), 42 (45).

4.2.2. Methyl 4-ethyl-11-fluoro-1,4,5,6,7,8-hexahydroazonino[5,6-*b*]indole-2-carboxylate (14). ^{1}H NMR (DMSO-d_6), ppm: δ 1.13 (3H, t, J=7.2 Hz, CH_3–Et), 1.79 (2H, m, CH_2), 2.81 (2H, m, CH_2), 3.24 (2H, q, J=7.2 Hz, CH_2–Et), 3.51 (3H, s, OCH_3), 3.59 (2H, m, CH_2), 3.83 (2H, s, CH_2-1), 6.80 (1H, ddd, $^{1,3}J$=9.0 Hz, $^{1,3}J$=9.0 Hz, $^{1,4}J$=2.3 Hz, H-10), 7.41 (1H, dd, $^{1,3}J$=10.2 Hz, $^{1,4}J$= 2.3 Hz, H-12), 7.21 (1H, dd, $^{1,3}J$=8.7 Hz, $^{1,4}J$=4.5 Hz, H-9), 7.64 (1H, s, H-3), 10.81 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 15.5 (CH_3), 21.5 (CH_2), 23.3 (CH_2), 29.9 (CH_2), 45.6 (CH_2), 51.1 (OCH_3), 51.2 (CH_2), 92.0 (C), 102.6 (d, J=23 Hz, CH-12), 108.3 (d, J=25 Hz, CH-10), 108.4 (C), 111.6 (d, J=10 Hz, CH-9), 129.7 (C), 131.3 (C), 138.3 (C), 150.7 (CH-3), 157.2 (d, J=231 Hz, CH-11), 170.2 (COO). EIMS m/z (%): 316 (M^+, 100), 285 (15), 257 (15), 243 (20), 198 (10), 174 (20), 161 (10).

4.2.3. Methyl 4-benzyl-11-methyl-1,4,5,6,7,8-hexahydroazonino[5,6-*b*]indole-2-carboxylate (15). ^{1}H NMR ($CDCl_3$), ppm.: δ 1.79 (2H, m, CH_2), 2.45 (3H, s, CH_3), 2.93 (2H, m, CH_2), 3.60 (2H, m, CH_2), 3.66 (3H, s, OCH_3), 4.05 (2H, s, CH_2), 4.37 (2H, s, CH_2Ph), 6.95 (1H, d, J=8.1 Hz, H-10), 7.14 (3H, m, 3H–Ar), 7.27 (3H, m, 3H–Ar), 7.41 (1H, s, H-12), 7.51 (1H, s, H-3), 7.82 (1H, s, H-8). ^{13}C NMR (DMSO), ppm: δ 23.6, 29.4, 31.2, 31.5, 46.9, 51.1, 59.8, 94.2, 107.2, 110.5, 117.8, 122.0, 126.7, 127.8 (2×C), 128.9, 129.1 (2×C), 129.6, 133.1, 135.8, 138.9, 151.6, 170.2. EIMS m/z (%): 374 (M^+, 30), 283 (100), 251 (25), 223 (15), 195 (15), 182 (30), 170 (40), 157 (20), 144 (20), 120 (10), 91 (100), 65 (100).

4.2.4. Methyl 4-ethyl-11-methyl-1,4,5,6,7,8-hexahydroazonino[5,6-*b*]indole-2-carboxylate (16). ^{1}H NMR (DMSO-d_6), ppm: δ 1.15 (3H, t, J=7.1 Hz, CH_3–Et), 1.78 (2H, m, CH_2), 2.37 (3H, s, CH_3), 2.81 (2H, m, CH_2), 3.20 (2H, m, CH_2–Et), 3.51 (3H, s, OCH_3), 3.60 (2H, m, CH_2), 3.86 (2H, s, CH_2-1), 6.81 (1H, dd, $^{1,3}J$=8.2 Hz, $^{1,4}J$= 1.4 Hz, H-10), 7.11 (1H, d, $^{1,3}J$=8.2 Hz, H-9), 7.21 (1H, br s, H-12), 7.67 (1H, s, H-3), 10.38 (1H, s, H-8). ^{13}C NMR ($CDCl_3$), ppm: δ 15.1 (CH_3), 21.2 (CH_2), 21.4 (CH_3), 23.4 (CH_2), 25.6 (CH_3), 29.8 (CH_2), 45.5 (CH_2), 51.8 (CH_2), 108.1 (C), 109.7 (CH), 117.6 (CH), 122.4 (CH), 128.1 (2×C), 129.49 (C), 132.6 (C), 134.7 (C), 151.9 (CH-3), 170.3 (C═O). EIMS: m/z (%): 312 (M^+, 80), 283 (15), 269 (20), 253 (20), 239 (30), 226 (15), 196 (20), 182 (50), 168 (75), 140 (40), 115 (10), 97 (30), 84 (20), 73 (10), 58 (100), 45 (20).

4.2.5. Methyl 4-ethyl-11-fluoro-1,2,3,4,7,8-hexahydroazonino[5,6-*b*]indole-6-carboxylate (17). ^{1}H NMR ($CDCl_3$), ppm: δ 1.21 (3H, t, J=7.2 Hz, CH_3–Et), 1.80 (2H, m, CH_2), 2.86 (2H, m, CH_2), 3.23 (2H, q, J=7.2 Hz, CH_2–Et), 3.60 (2H, m, CH_2-3), 3.66 (3H, s, OCH_3), 4.03 (2H, s, CH_2-7), 6.83 (1H, ddd, $^{1,3}J$=8.7 Hz, $^{1,3}J$=10.0 Hz, $^{1,4}J$=2.3 Hz, H-10), 7.10 (1H, dd, $^{1,3}J$=10.0 Hz, $^{1,4}J$= 2.3 Hz, H-12), 7.15 (1H, dd, $^{1,3}J$=8.7 Hz, $^{1,4}J$=4.3 Hz, H-9), 7.65 (1H, s, H-5), 7.98 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 15.6 (CH_3), 18.8 (CH_2), 25.5 (CH_2), 30.1 (CH_2), 45.4 (CH_2), 51.2 (OCH_3), 52.6 (CH_2-7), 88.7 (C-6), 102.1 (d, J=23 Hz, CH-12), 108.4 (d, J=25 Hz, CH-10), 111.4 (d, J=10 Hz, CH-9), 110.6 (C), 129.7 (C), 131.5 (C), 135.8 (C), 151.3 (CH-5), 157.1 (d, J=230 Hz, C-11), 170.1 (COO). EIMS m/z (%): 316 (M^+, 70), 301 (10), 255 (15), 243 (30), 227 (15), 198 (20), 186 (50), 161 (30), 142 (50), 121 (10), 96 (20), 84 (40), 58 (100), 45 (30).

4.2.6. Methyl 4-benzyl-11-fluoro-1,2,3,4,7,8-hexahydroazonino[5,6-*b*]indole-6-carboxylate (18). ^{1}H NMR (DMSO-d_6), ppm: δ 1.66 (2H, m, CH_2), 2.47 (2H, m, CH_2), 2.78 (2H, m, CH_2), 3.51 (3H, s, OCH_3), 4.02 (2H, s, CH_2), 4.46 (2H, s, CH_2Ph), 6.77 (1H, ddd, $^{1,3}J$=9.2 Hz, $^{1,3}J$=9.2 Hz, $^{1,4}J$=2.3 Hz, H-10), 7.11–7.31 (7H, m, Ar), 7.81 (1H, s, H-5), 10.84 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 19.1 (CH_2), 25.3 (CH_2), 29.6 (CH_2), 46.4 (CH_2), 51.3 (OCH_3), 60.0 (CH_2), 90.1 (C-6), 102.2 (d, J=22 Hz, CH-12), 108.3 (d, J=25 Hz, CH-10), 110.7 (C), 111.4 (d, J=10 Hz, CH-9),

127.9 (CH), 128.0 (2×CH), 129.1 (2×CH), 129.6 (C), 131.6 (C), 135.6 (C), 138.7 (C), 152.1 (CH), 157.2 (d, J=230 Hz, C-11), 170.1 (COO). ESI MS: 379 (M^++1).

4.3. General experimental procedure for the synthesis of azoninoindoles 19–21 and 3-alkoxyalkylindoles 22–24

To a stirred solution of azepinoindole **1**–**3** (1 mmol) in dry methanol (15 mL) at 25 °C, DMAD (1.2 mmol) was added and stirring was continued for additional 3–4 h (TLC monitoring). Methanol was evaporated under reduced pressure and the resulting residues were purified using column chromatography (1:2 ethyl acetate/hexane mixture as eluent) providing compounds **19** and **22** (for **1**), **20** and **23** (for **2**) or **21** and **24**[12] (for **3**). Yields and some physico-chemical properties of the products can be found in Table 1.

4.3.1. Dimethyl 4-ethyl-1,4,5,6,7,8-hexahydroazonino-[5,6-*b*]indole-2,3-dicarboxylate (19). ^{1}H NMR ($CDCl_3$), ppm: δ 1.03 (3H, t, J=7.2 Hz, CH_3–Et), 1.77 (2H, m, CH_2), 2.76 (2H, q, J=7.2 Hz, CH_2–Et), 2.83 (2H, m, CH_2), 3.08 (2H, m, CH_2), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.03 (2H, s, CH_2-1), 7.09 (2H, m, H-11+H-10), 7.26 (1H, d, J=7.6 Hz, H-9), 7.50 (1H, d, J=7.6 Hz, H-12), 7.83 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 15.2 (CH_3), 22.6 (CH_2), 24.1 (CH_2), 27.1 (CH_2), 44.5 (CH_2), 52.3 (OCH_3), 52.4 (OCH_3), 55.6 (CH_2), 108.3 (C), 111.0 (CH), 117.9 (CH), 118.8 (CH), 120.5 (CH), 124.3 (C), 128.1 (C), 135.4 (C), 135.6 (C), 151.2 (C), 166.4 (COO), 169.3 (COO). EIMS m/z (%): 356 (M^+, 60), 327 (10), 297 (60), 267 (30), 252 (10), 237 (30), 226 (10), 209 (20), 180 (30), 168 (40), 156 (60), 143 (45), 128 (20), 115 (20), 77 (10), 58 (100), 45 (30).

4.3.2. Dimethyl 4-ethyl-11-fluoro-1,4,5,6,7,8-hexahydroazonino[5,6-*b*]indole-2,3-dicarboxylate (20). ^{1}H NMR ($CDCl_3$), ppm: δ 0.98 (3H, t, J=7.2 Hz, CH_3–Et), 1.78 (2H, m, CH_2), 2.74 (2H, q, J=7.2 Hz, CH_2–Et), 2.93 (2H, m, CH_2), 3.06 (2H, m, CH_2), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.96 (2H, s, CH_2), 6.82 (1H, ddd, $^{1,3}J$=9.0 Hz, $^{1,3}J$=9.0 Hz, $^{1,4}J$=2.3 Hz, H-10), 7.13 (2H, m, H-12+H-9), 7.74 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 15.2 (CH_3), 21.9 (CH_2), 23.9 (CH_2), 27.2 (CH_2), 44.6 (CH_2), 52.3 (OCH_3), 52.4 (OCH_3), 55.5 (CH_2), 102.6 (d, J=22 Hz, CH-12), 108.3 (d, J=26 Hz, CH-10), 108.6 (C), 111.8 (d, J=10 Hz, CH-9), 122.4 (C), 128.3 (C), 132.3 (C), 138.0 (C), 151.7 (C-3), 157.2 (d, J=231 Hz, C-11), 166.4 (COO), 169.31 (COO). EIMS, m/z (%): 374 (M^+, 100), 345 (20), 315 (100), 285 (30), 227 (10), 198 (20), 174 (30), 161 (30), 148 (10), 58 (40), 45 (10).

4.3.3. Dimethyl 4-benzyl-11-methyl-1,4,5,6,7,8-hexahydroazonino[5,6-*b*]indole-2,3-dicarboxylate (21). ^{1}H NMR ($CDCl_3$), ppm: δ 1.74 (2H, m, CH_2), 2.43 (3H, s, CH_3), 3.08 (4H, m, CH_2+CH_2), 3.67 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.95 (2H, s, CH_2), 3.99 (2H, s, CH_2), 6.84 (1H, d, $^{1,3}J$=8.3 Hz, H–Ar), 7.15–7.28 (7H, m, Ar), 7.60 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 21.8 (CH_3), 22.7 (CH_2), 24.6 (CH_2), 27.0 (CH_2), 52.1 (OCH_3), 52.4 (OCH_3), 54.8 (CH_2), 57.0 (CH_2), 107.6 (C), 110.8 (CH), 117.7 (CH), 122.1 (CH), 127.1 (C), 127.6 (CH), 128.4 (C), 128.7 (2×CH), 128.7 (2×CH), 134.1 (2×C), 135.4 (C), 139.0 (C), 150.4 (C), 165.8 (COO), 169.7 (COO). EIMS, m/z (%): 432 (M^+, 30), 341 (40), 281 (25), 170 (20), 91 (100).

4.3.4. Dimethyl 2-(ethyl{3-[3-(methoxymethyl)-1*H*-indol-2-yl]propyl}amino)-2-butenedioate (22). ^{1}H NMR ($CDCl_3$), ppm: δ 1.11 (3H, t, J=7.2 Hz, CH_3–Et), 1.95 (2H, m, CH_2), 2.75 (2H, m, CH_2), 3.03–3.15 (4H, m, CH_2+CH_2–Et), 3.37 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.60 (3H, s, CH_2+C═CH), 7.12 (2H, m, Ar), 7.30 (1H, d, J=7.5 Hz, Ar), 7.60 (1H, d, J=7.5 Hz, Ar), 8.46 (1H, s, NH). EIMS, m/z (%): 388 (M^+, 70), 356 (90), 327 (20), 297 (100), 267 (20), 237 (20), 202 (50), 186 (15), 170 (50), 143 (30), 130 (10), 59 (10), 45 (10).

4.3.5. Dimethyl 2-(ethyl{3-[5-fluoro-3-(methoxymethyl)-1*H*-indol-2-yl]propyl}amino)-2-butenedioate (23).[13] ^{1}H NMR ($CDCl_3$), ppm: δ 1.11 (3H, t, J=7.2 Hz, CH_3–Et), 1.97 (2H, m, CH_2), 2.78 (2H, m, CH_2), 3.09 (4H, m, CH_2+CH_2–Et), 3.37 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.53 (2H, s, CH_2), 4.57 (1H, s, C═CH), 6.86 (1H, ddd, $^{1,3}J$=9.0 Hz, $^{1,3}J$=9.0 Hz, $^{1,4}J$=2.3 Hz, Ar), 7.21 (2H, m, Ar), 8.46 (1H, s, H-8). ^{13}C NMR (DMSO-d_6), ppm: δ 12.9 (CH_3), 23.2 (CH_2), 27.5 (CH_2), 45.0 (CH_2), 49.5 (CH_2), 50.5 (OCH_3), 52.8 (OCH_3), 57.0 (OCH_3), 64.4 (CH_2), 82.4 (CH), 103.1 (d, J=23 Hz, CH–Ar), 108.4 (C), 108.7 (d, J=26 Hz, CH–Ar), 112.0 (d, J=10 Hz, CH–Ar), 129.1 (C), 132.3 (C), 140.5 (C), 154.3 (C), 156.9 (d, J=231 Hz, C–F), 165.6 (COO), 167.6 (COO). EIMS, m/z (%): 406 (M^+, 10), 374 (20), 315 (35), 285 (10), 202 (70), 188 (100), 161 (100), 148 (60), 133 (20), 112 (20), 96 (40), 82 (25), 68 (40), 58 (70), 45 (100).

Acknowledgements

The authors thank the Russian Foundation for Basic Research for financial support (grants # 05-03-08149-ofi-a and 05-03-32211-a).

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11. Crystal structure analysis for **16**: $C_{19}H_{24}N_2O_2$, M_r=312.40 g mol^{-1}, monoclinic, space group $P2(1)/n$, a=8.070(6), b=13.347(8), c=15.845(9) Å, α=90°, β=90.54(5)°, γ=90°, V=1706.6(19) Å^3, Z=4, ρ=1.216 g cm^3, μ=0.079 mm^{-1}, F(000)=672, crystal size: 0.41×0.24×0.04 mm. Crystal data were collected on a Cad-4 diffractometer (λCu Kα radiation, graphite monochromator; ω scanning). A total of 3241 reflections ($1.29<\theta<25.98°$) were collected of which 2876 were unique (R(int)=0.0801). The structure was solved with the program SHELXS-97[14] and refined using SHELXL-97[15] to R_1=0.0662 and $wR(F^2)$=0.1580 for 2876 reflections with $I>2\sigma(I)$; max/min residual electron density 0.325 and −0.299 eÅ^{-3}.
12. In the case of the reaction of **3** with DMAD the formation of the indole derivative **24** was demonstrated only by the LC–MS analysis of the reaction mixture; our attempts to isolate it, using column chromatography failed.
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Tetrahedron 62 (2006) 12398–12407
Tetrahedron

Stereoselective Diels–Alder reactions of 3-phosphonopropenoyl derivatives of 1,3-oxazolidin-2-ones

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Received 21 April 2006; revised 13 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—Dienophiles of the general structure $(EtO)_2P(O)CH{=}CHCOX$ have been prepared, where X represents an oxazolidinone chiral auxiliary. Use of the (*S*)-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one auxiliary gave Diels–Alder adducts with several cyclic and acyclic dienes. The crystal structures of the main cyclohexa-1,3-diene and 2,3-dimethylbutadiene adducts formed during reactions in the presence of dialkylaluminium halides are consistent with a reaction, which is stereoselectively *endo* with respect to the carbonyl group and occurs on the less hindered face of the dienophile when aluminium is chelated between the two carbonyl groups.

1. Introduction

Phosphonic acids and their derivatives are of interest as analogues of functional groups such as phosphate esters and carboxylic acids and of the transition states for ester and amide hydrolysis.[1] Several synthetic methods have been devised for the stereoselective synthesis of compounds in which a phosphonic acid or ester group is attached to a chiral centre.[2] Typical approaches include the addition of $R_2P(O)H$ species to aldehydes or imines to give hydroxy- or aminophosphonates,[3] the attack of electrophiles on carbanions that are stabilised by an adjacent phosphorus atom[4] and the use of asymmetric addition reactions of unsaturated phosphonates (e.g., dihydroxylation[5] and aminohydroxylation).[6]

Despite the ability to control the formation of up to four chiral centres, the Diels–Alder reaction has seldom been used as a method for the stereoselective synthesis of phosphonic acid derivatives. Simple vinylphosphonates tend to show only limited dienophilicity and so the most promising phosphonate dienophiles are those containing an additional electron-withdrawing group.[7] Evans has shown that acryloyl derivatives of 1,3-oxazolidinone chiral auxiliaries undergo rapid and highly stereoselective Diels–Alder reactions in the presence of dialkylaluminium halides.[8] Analogous derivatives of the parent 4,5-unsubstituted, achiral 1,3-oxazolidinone system have also featured in numerous reports employing chiral Lewis acids.[9] In this paper, we discuss the preparation and Diels–Alder chemistry of 3-phosphonopropenoyl derivatives of oxazolidinones.

2. Results and discussion

3-(Diethoxyphosphinoyl)prop-2-enoic acid (**1**), prepared by hydrolysis of its methyl ester,[10] was coupled directly to oxazolidinones **2a**–**e** by the general approach of Knol and Feringa,[11] using 2-chloro-1-methylpyridinium iodide in the presence of triethylamine (Scheme 1). The low yield of the *N*-acyloxazolidinone **3d** is attributed to the poor solubility of the chiral auxiliary **2d** in dichloromethane. We found that *N*-acyloxazolidinone **3e** was crystalline, whereas the other oxazolidinone chiral auxiliaries that we acylated using acid **1** gave oily products.

We next examined the Diels–Alder reactions of these *N*-acyloxazolidinones with excess cyclopentadiene in dichloromethane at room temperature. ^{31}P NMR spectra of the crude products, in $CDCl_3$ solution, indicated conversion of the starting vinylphosphonate dienophiles **3** (δ_P ca. 15) into alkylphosphonates (δ_P 30–33). The reactions can generate four stereoisomeric products, but in the case of the achiral dienophile **3a** these include two pairs of enantiomers and hence ^{31}P and ^1H NMR spectra of the crude product showed only two diasteroisomeric components, with δ_P 32.0 (70%) and 31.2 (30%). The four-component mixtures were not straightforward to separate by flash chromatography, but when the reaction between **3a** and cyclopentadiene was performed at low temperature in the presence of Et_2AlCl,

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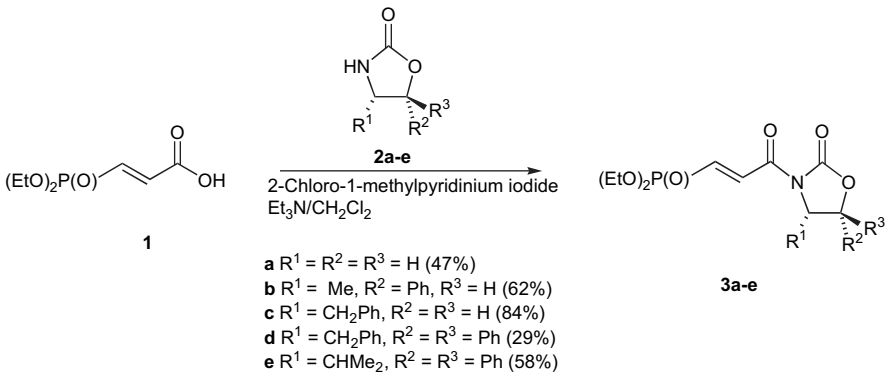
doi:10.1016/j.tet.2006.09.099



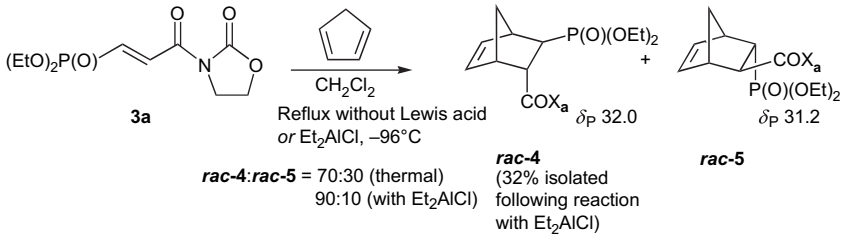
Scheme 1. Formation of 3-(3-phosphonopropenoyl)-1,3-oxazolidin-2-one derivatives **3a**–**e**.

the diastereoisomer ratio increased to 90:10 and the major diastereoisomer *rac*-**4** with δ_P 32.0 was isolated (Scheme 2). The ^{1}H NMR spectrum of *rac*-**4** included distinctive doublets of doublets of doublets for both the CHP and CHCO environments, with similar coupling constants to those of analogous esters and ketones that have *exo*-phosphonate and *endo*-carbonyl groups.[7a]

The 4-isopropyl-5,5-diphenyloxazolidin-2-one chiral auxiliary **2e** is known to be excellent at conferring crystallinity on its *N*-acyl derivatives whilst being easy to remove and recover;[12] furthermore, the crotonyl derivative of **2e** has been reported to react highly selectively in a Lewis acid-induced Diels–Alder reaction with cyclopentadiene.[13] We therefore selected the Diels–Alder reactions of dienophile **3e** for further study, using several dienes both under thermal conditions (refluxing dichloromethane) and employing dialkylaluminium chlorides as Lewis acid promoters, at low temperatures, typically −96 °C (Table 1).

^{31}P NMR spectroscopy showed that the Lewis acid-promoted Diels–Alder reactions of **3e** with cyclohexa-1,3-diene, 2,3-dimethylbutadiene and 2-methylbutadiene all occurred with high selectivity (>95% of the main stereoisomer), whereas mixtures of products were formed with cyclopenta-1,3-diene and in the thermal reactions with all four dienes. X-ray diffraction was used to confirm the structure of cycloadducts derived from three of the dienes.

The reactions of **3e** with cyclopentadiene showed relatively low stereoselectivity and gave four cycloadducts (δ_P 32.3, 32.1, 31.4 and 31.2). These were difficult to separate, but



Scheme 2. *endo* Selectivity in the reaction of dienophile **3a** with cyclopentadiene.

Table 1. Diels–Alder reactions of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e**

Diene	Conditions[a]	Selectivity (from ^{31}P NMR)	δ_P (Principal product)	Structure of principal product (isolated yield)
Cyclopenta-1,3-diene	CH_2Cl_2 reflux 60 h	66:17:9:6	32.3	**6**
	Me_2AlCl, −96 °C, 40 min	37:34:17:12	32.1	**7**
	Et_2AlCl, −96 °C, 10 min	47:32:12:9	32.3	**6** (22%)
Cyclohexa-1,3-diene	CH_2Cl_2 reflux 48 h	60:23:14:3	31.8	
	Et_2AlCl, −96 °C, 20 min	100:0:0:0	31.5	**10** (71%)
	Me_2AlCl, −78 °C, 40 min	97:3:0:0	31.5	**10** (61%)
2,3-Dimethylbuta-1,3-diene	Et_2AlCl, −96 °C, 20 min	100:0	31.0	**11** (58%)
	Me_2AlCl, −96 °C, 20 min	100:0	31.0	**11** (69%)
	CH_2Cl_2 reflux 72 h	80:20	31.4, 31.0	**12** (70%), 11 (12%)
2-Methylbuta-1,3-diene	CH_2Cl_2 reflux 48 h	57:23:20:0	31.2	
	Me_2AlCl, −96 °C, 40 min	100:0:0:0	30.9	**13** (76%)
cyclo-Octa-1,3-diene	Et_2AlCl, −70 °C, 20 min	75:15:10	33.2	**14** (59%)[b]

[a] Me_2AlCl and Et_2AlCl were used in excess (typically 3 equiv relative to **3e**).
[b] The main product **14** is formed by conjugate addition of Et_2AlCl to compound **3e**, rather than by Diels–Alder reaction.

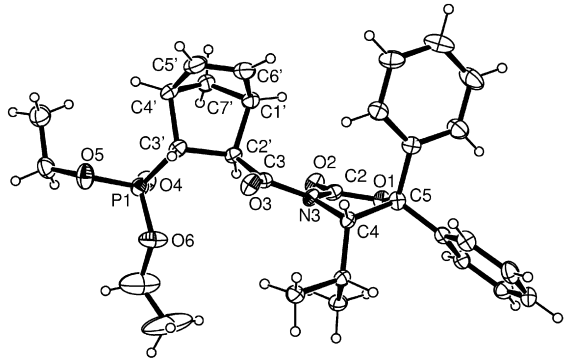


Figure 1. Molecular structure of (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **6**.

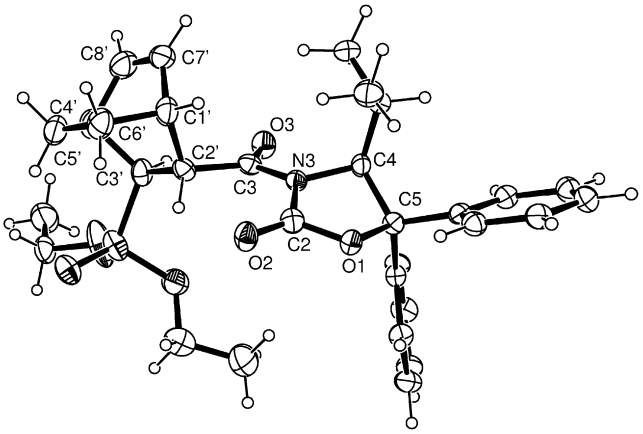
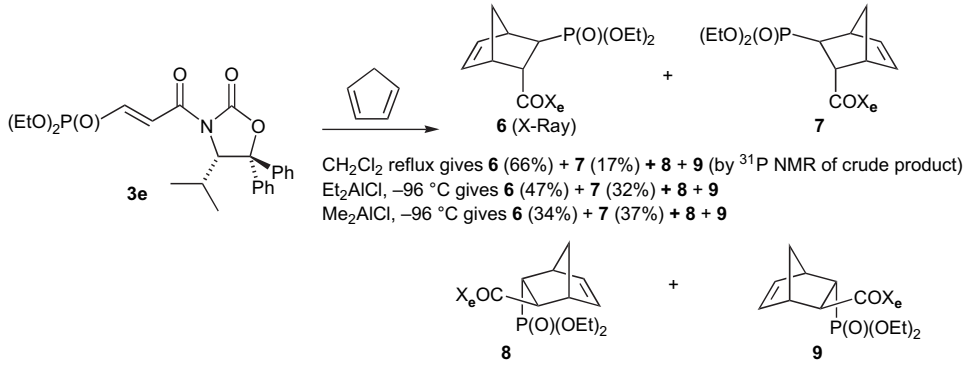


Figure 2. Molecular structure of (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **10**.

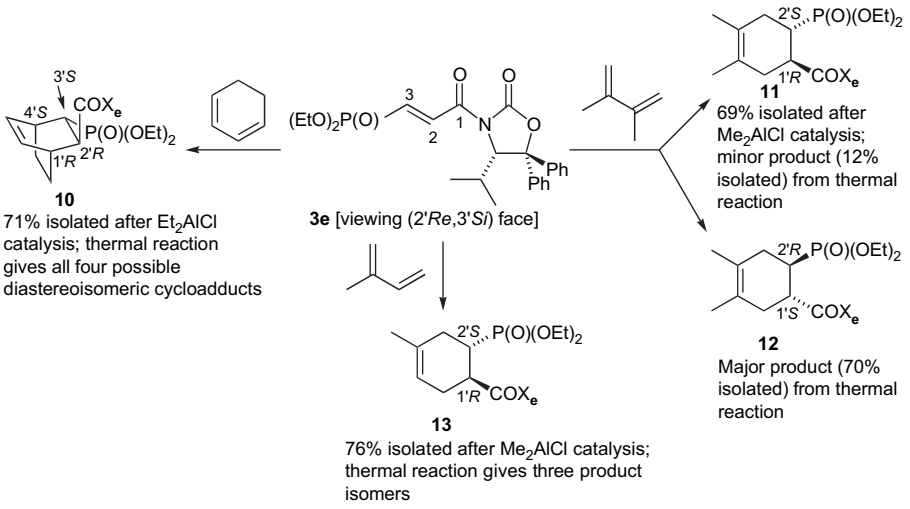
the cycloadduct with δ_P 32.3 could be obtained as a single stereoisomer following flash chromatography and recrystallisation. The ^{1}H NMR spectrum of this product resembled that of *rac*-**4**, again suggesting an *endo*-directed carbonyl and *exo*-directed P═O group, and an X-ray crystal structure (Fig. 1) showed the (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-configuration given in Scheme 3 (structure **6**). This is the favoured product of the thermal reaction and corresponds to attack on the (2′*Si*,3′*Re*)-face of the dienophile, which is the less hindered face of the conformer with the two C═O dipoles opposed to one another. The same product **6** was formed in lower proportions when Lewis acids were used; with Me_2AlCl the product with δ_P 32.1, considered to be the other C═O *endo* adduct **7**, was marginally favoured over **6**. We presume that the Lewis acids chelated between the two carbonyl groups activate the dienophile **3e** towards formation of adduct **7**, in direct analogy with Evans's proposals for simple acryloyloxazolidinones.[8] However, the formation of significant quantities of the diastereoisomer **6**, even when a large excess of Lewis acid was used, suggests that chelation of the Lewis acid is not mandatory for rapid addition of **3e** to cyclopentadiene.

An X-ray crystal structure of the cyclohexadiene adduct **10** (Fig. 2) that was isolated following the Et_2AlCl-mediated reaction established the (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-configuration shown in Scheme 4. This confirmed that the trans relationship between the phosphonate and carbonyl groups of the dienophile is preserved and that the favoured mode of addition is '*endo*' with respect to the carbonyl group and '*exo*' with respect to the phosphonate. Furthermore, the favoured product corresponds to attack on the less hindered (2′*Re*,3′*Si*)-face of the dienophile, assuming that the aluminium chelates between the two carbonyl groups as proposed by Evans.[8]

An X-ray crystal structure (Fig. 3) was also determined for the predominant Diels–Alder adduct **11** formed from 2,3-dimethylbutadiene and the dienophile **3e** when Lewis acid was used. The product has the (4*S*,1′*R*,2′*S*)-configuration; after allowing for the different numbering schemes in compounds **10** and **11** its stereochemistry is directly analogous to that of the cyclohexadiene adduct, again indicating attack on the (2′*Re*,3′*Si*) face of the dienophile. The substitution pattern of the diene does not permit '*endo*' and '*exo*' modes of attack to be distinguished in this case. The carbocyclic ring in **5a** has a half-chair conformation, similar to that of cyclohexene itself:[14] the carbonyl and phosphonate groups are trans to one another and each is pseudo-equatorial. In the ^{31}P-decoupled ^{1}H NMR spectrum of the adduct, both protons H-1′ and H-2′ appeared as triplets of doublets with triplet splittings of 10–11 Hz, consistent with involvement in axial–axial couplings with neighbours on either side, suggesting that the solution phase conformation is similar to that adopted in the crystal. One of the four OCH_2 protons is shifted upfield in this adduct and appears as a multiplet at δ 3.5; examination of the crystal structure shows that one of these hydrogen atoms is so positioned that it could be shielded by the magnetic anisotropy of a phenyl group.



Scheme 3. Possible products from the reaction of dienophile **3e** with cyclopentadiene.



Scheme 4. Stereoselective Diels–Alder reactions of the dienophile **3e**.

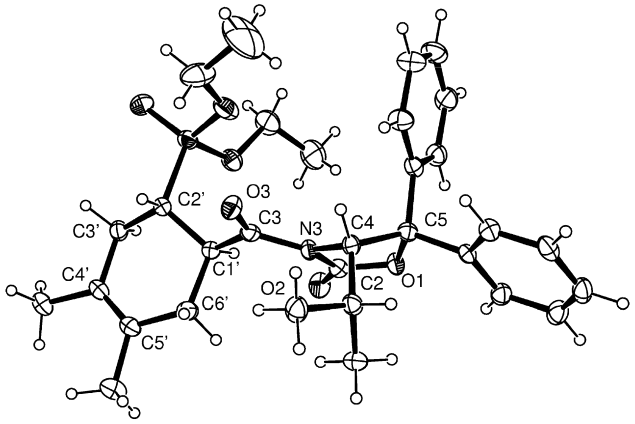


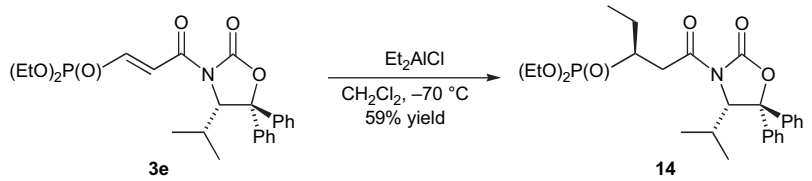
Figure 3. Molecular structure of (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11**.

When the Diels–Alder reaction between **3e** and 2,3-dimethylbutadiene was performed under thermal conditions, the above product **11** could again be isolated, but the main product was the (4*S*,1′*S*,2′*R*) diastereoisomer **12**; the NMR spectra of the two isomers were rather similar, but in the ^{1}H NMR spectrum of **12** all four OCH_2 protons appeared together as a multiplet near δ 4.0. Neither of the two diastereoisomeric adducts **11** and **12** underwent any isomerisation when heated in the presence of excess 2,3-dimethylbutadiene under the conditions employed for the thermal reaction. Thus the opposite selectivity observed in the Lewis-acid and thermal reactions was not a consequence of a switch to thermodynamic control in the latter case. The thermal reaction occurs on a non-chelated acyloxazolidinone and may take place by preferential, kinetically controlled attack on the (2*Si*,3*Re*) face of the dienophile, through a transition state in which the two carbonyl groups are antiparallel. Comparison of the ^{31}P NMR spectra of the crude cycloadduct mixtures indicate that the preferred products formed in the reactions of cyclohexa-1,3-diene and isoprene also change on switching from Lewis acid to thermal conditions.

Lewis acid-induced reaction of the dienophile **3e** with 2-methylbuta-1,3-diene (isoprene) gave a single Diels–Alder adduct **13**. From the ^{13}C and HSQC spectra the two olefinic carbons could be identified. The one with δ_C 118.3 had one attached hydrogen atom and was not coupled to ^{31}P, whereas the one with δ_C 132.7 had no attached hydrogen and had a 12 Hz coupling to ^{31}P. This implies a 1,4-relationship between the methyl and carbonyl substituents on the cyclohexene ring: thus the regiochemical preference is analogous to that seen in reactions of isoprene with simple acryloyloxazolidinones,[8] demonstrating the dominance of the electron-withdrawing effect of carbonyl group over that of the phosphinoyl group.

It is likely that the isoprene adduct **13** that is formed under Lewis acidic conditions has the (1′*R*,2′*S*)-configuration analogous to that seen in the crystal structure of the closely related 2,3-dimethylbutadiene adduct **11**. Support for this proposal is provided by the similar ^{1}H NMR spectra of the two compounds, each of which has one of the OCH_2 protons shifted ca. 0.3 ppm upfield of the other three.

A Diels–Alder reaction with *cyclo*-octa-1,3-diene was attempted in the presence of diethylaluminium chloride, but it was found that this particular diene was much less reactive than cyclohexa-1,3-diene and at −96 °C most of the dienophile remained unchanged. Upon increasing the reaction temperature to −70 °C it was possible to observe the complete consumption of starting material and the formation of new phosphorus-containing products, of which the main components, with δ_P 33.2, 33.3 and 30.0, were formed in a 75:15:10 ratio. The principal product **14** (Scheme 5) was crystallised and was shown by NMR spectroscopy, mass spectrometry and X-ray diffraction (Fig. 4) to have arisen by conjugate addition of an ethyl group at the β-position with respect to the carbonyl group. The observed (*S*)-configuration of the newly formed chiral centre in **14** indicates that ethyl group is preferentially transferred to the (2*Re*,3*Si*) face of the C=C double bond. The same three products were produced when the dienophile **3e** was treated with diethylaluminium chloride at −70 °C in the absence of any diene. Conjugate additions of diethylaluminium chloride to alk-2-enoyloxazolidinones without phosphinoyl substituents have been observed by Evans and co-workers;[8] synthetic applications were later developed by Rück and Kunz, who



Scheme 5. Conjugate addition of Et_2AlCl to **3e**.

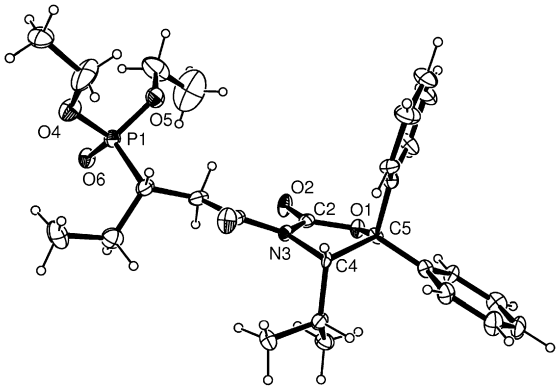
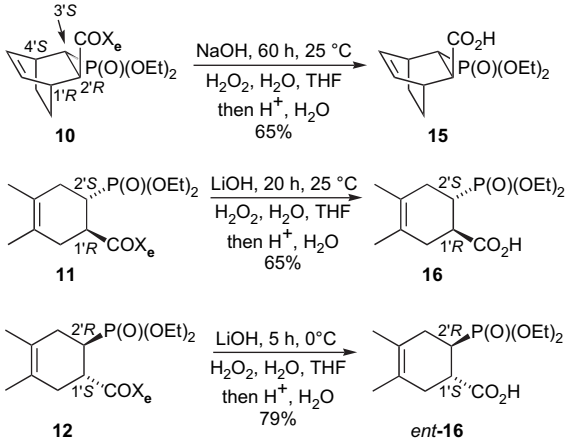


Figure 4. Molecular structure of (4*S*,3′*S*)-3-[3-(diethoxyphosphinoyl)pentanoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **14**.

found that such reactions typically generate significant amounts of minor stereoisomers.[15]

We have examined the removal of the 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one chiral auxiliary from adducts **10**, **11** and **12** (Scheme 6), using similar conditions to those described by Seebach for the cleavage of the 2-methyl-3-propanoyl derivatives of oxazolidinone **2e**.[13] The hydrolysis reactions were monitored by TLC and were found to be slow compared to Seebach's compounds, probably as a consequence of greater steric hindrance in the cycloadducts. Simple aqueous work up procedures provided the corresponding carboxylic acids **15**, **16** and *ent*-**16**, thus confirming the diastereoisomeric relationship between cycloadducts **11** and **12**.



Scheme 6. Removal of chiral auxiliaries from Diels–Alder adducts **10**, **11** and **12**.

3. Conclusions

(*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** has been found to participate in Diels–Alder reactions with a selection of dienes, giving adducts, which are often highly crystalline and easy to obtain in isomerically pure form, thus providing a new approach to the production of highly functionalised phosphonic acid derivatives of defined configuration. The dialkylaluminium chloride-accelerated reactions typically show similar facial preferences to those seen in the reactions of simple *N*-alkenoyloxazolidinones, but reactions with cyclopentadiene are rather unselective.

4. Experimental

4.1. Materials and general procedures

'Petrol' refers to the fraction of petroleum spirit with bp 40–60 °C. Dichloromethane was distilled from calcium hydride before use. The temperature of −96 °C was obtained using methanol and liquid nitrogen. Flash chromatography was performed on BDH silica gel (33–70 μm). All new compounds were >95% pure as assessed by TLC and high field NMR. Melting points were determined using a Reichert hot stage microscope and are uncorrected. Specific rotations were determined on an Optical Activity Ltd AA-1000 or Jasco P-1010 polarimeter with a path length of 0.5 dm. IR spectra were recorded using a Shimadzu FTIR 8300; samples were prepared as films by evaporation of CH_2Cl_2 solutions on NaCl plates. NMR spectra were recorded on Jeol EX270 and Bruker AM250, AMX400 or AMX600 spectrometers. FAB mass spectra were recorded on a ZAB-SE4F machine at the School of Pharmacy, University of London; other mass spectra were obtained by the EPSRC National Service in Swansea.

4.2. Typical procedure for oxazolidinone acylation: preparation of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 3e

(*S*)-4-Isopropyl-5,5-diphenyloxazolidin-2-one (2.00 g, 7.11 mmol) was added to a solution of (*E*)-3-(diethoxyphosphinoyl)prop-2-enoic acid[10] (1.85 g, 8.89 mmol) in dry dichloromethane (5 mL). Triethylamine (2.96 mL, 21.2 mmol) and 2-chloro-1-methylpyridinium iodide (2.72 g, 10.6 mmol) were added to the mixture, which was stirred for 72 h at room temperature. Dichloromethane (80 mL) was then added to the mixture before it was washed with aqueous $NaHCO_3$ (4×40 mL), dried ($MgSO_4$) and the solvent was evaporated to leave a yellow solid. Flash chromatography (CH_2Cl_2–EtOAc, 97.5:2.5) afforded the *title compound* **3e** (1.93 g, 58%) as a white crystalline solid, mp 178–180 °C (from EtOAc–petrol); $[\alpha]_D$ −188 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} (film) 1690 (C═O) and 1782 (C═O); δ_H (270 MHz, $CDCl_3$) 0.77 (d, 3H, *J* 7 Hz, CH_3CHMe),

0.90 (d, 3H, *J* 7 Hz, CH_3CHMe), 1.34 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$O), 1.95–2.07 (m, 1H, Me$_2$C*H*), 4.14 (quintet, 4H, *J* 7 Hz, 2×CH$_3$CH_2O), 5.44 (d, 1H, *J* 3 Hz, NCH), 6.96 (dd, 1H, *J* 19, 17 Hz, CH=), 7.24–7.46 (m, 10H, 2×Ph), 7.90 (dd, 1H, *J* 21, 19 Hz, CH=); δ_P (109 MHz, $CDCl_3$) 15.2; δ_C (101 MHz, $CDCl_3$) 16.70 (CH_3), 16.76 (2×CH_3), 22.18 (CH_3), 30.49 (*C*Me$_2$), 63.06 (d, $^2J_{C-P}$ 6 Hz, 2×CH_2O), 65.27 (CHN), 90.20 (C–O) [125.92, 126.23, 128.49, 128.85, 129.17, 129.43, together aromatic C], 133.28 (d, $^1J_{C-P}$ 186 Hz, PC=), 135.35 (d, $^2J_{C-P}$ 10 Hz, CO*C*=), 138.27 (C-1 of Ph), 142.31 (C-1 of Ph), 152.88 (OCON), 163.44 (d, $^3J_{C-P}$ 28 Hz, C–*C*=O); *m*/*z* (ESI) found: $[M+NH_4]^+$ 489.2146. $C_{25}H_{34}N_2O_6P$ requires 489.2149.

4.2.1. 3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-1,3-oxazolidin-2-one 3a. Flash chromatography [gradient from CH_2Cl_2–Et_2O (3:1) to (3:2)] gave **3a** (47% yield) as a colourless oil; ν_{max}/cm^{-1} (film) 1686 (C=O) and 1779 (C=O); δ_H (250 MHz, $CDCl_3$) 1.38 (t, 6H, *J* 7 Hz, 2×CH_3), 4.07–4.23 (m, 6H, 2×CH_2OP+CH_2N), 4.49 (t, 2H, *J* 8 Hz, CH_2OCO), 7.02 (dd, 1H, *J* 19, 17 Hz, C=C*H*CO), 7.98 (dd, 1H, *J* 21, 17 Hz, C=C*H*P); δ_P (101 MHz, $CDCl_3$) 15.0; δ_C (101 MHz, $CDCl_3$) 16.66 (d, $^3J_{C-P}$ 6 Hz, *C*H_3CH$_2$O), 42.97 (CH_2N) [62.90, 63.08, 63.14, together 3×CH_2], 132.71 (d, *J* 186 Hz, PC=), 135.49 (d, *J* 10 Hz, CO*C*=), 153.56 (O–CO–N), 163.59 (d, *J* 28 Hz, C–*C*O–N); *m*/*z* (FAB) found: $[M+H]^+$ 278.0780. $C_{10}H_{17}NO_6P$ requires 278.0794.

4.2.2. (4*S*,5*R*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 3b. Flash chromatography [CH_2Cl_2–Et_2O, gradient from (2:1) to (3:2)] gave **3b** (62% yield) as a colourless oil; $[\alpha]_D^{36}$ −20.6 (*c* 2, $CHCl_3$); ν_{max}/cm^{-1} (film) 1686 (C=O) and 1782 (C=O); δ_H (250 MHz, $CDCl_3$) 0.95 (d, 3H, *J* 7 Hz, NCH–CH_3), 1.38 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$), 4.18 (quint, 4H, *J* 7 Hz, 2×CH_2OP), 4.82 (quint, 1H, *J* 7 Hz, NC*H*–CH$_3$), 5.73 (d, 1H, *J* 7 Hz, PhC*H*O), 7.03 (dd, 1H, *J* 19 and 17 Hz, C=C*H*CO), 7.29–7.44 (m, 5H, Ph), 8.01 (dd, 1H, *J* 21 and 17 Hz, C=C*H*P); δ_P (101 MHz, $CDCl_3$) 15.1; δ_C (101 MHz, $CDCl_3$) 14.82 (4-Me), 16.72 (d, $^3J_{C-P}$ 6 Hz, *C*H_3CH$_2$O), 55.48 (C-4), 63.20 (d, $^2J_{C-P}$ 6 Hz, CH_2O), 79.78 (C-5), 126.05 (Ph), 129.17 (Ph), 129.34 (Ph), 132.84 (d, $^1J_{C-P}$ 186 Hz, PC=), 133.30 (Ph quaternary C), 136.00 (d, $^2J_{C-P}$ 9 Hz, CO*C*=), 153.02 (O–CO–N), 163.31 (d, $^3J_{C-P}$ 28 Hz, C–*C*O–N); *m*/*z* (EI) found: M^+ 367.1184. $C_{17}H_{22}NO_6P$ requires 367.1185.

4.2.3. (*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-benzyl-1,3-oxazolidin-2-one 3c. Flash chromatography [gradient from CH_2Cl_2–Et_2O (2:1) to (3:2)] gave **3c** (84% yield) as a colourless oil; $[\alpha]_D^{36}$ +52.2 (*c* 2.26, $CHCl_3$); ν_{max}/cm^{-1} (film) 1684 (C=O) and 1782 (C=O); δ_H (250 MHz, $CDCl_3$) 1.38 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$), 2.82 (dd, 1H, *J* 13 and 9 Hz, *H*CHPh), 3.35 (dd, 1H, *J* 13 and 3 Hz, HC*H*Ph), 4.12–4.30 (m, 6H, 3×CH_2O), 4.69–4.79 (m, 1H, NC*H*–CH$_2$), 7.06 (dd, 1H, *J* 19 and 17 Hz, C=C*H*CO), 7.19–7.38 (m, 5H, Ph), 7.99 (dd, 1H, *J* 21 and 17 Hz, C=C*H*P); δ_P (101 MHz, $CDCl_3$) 15.8; δ_C (101 MHz, $CDCl_3$) 16.72 (d, $^3J_{C-P}$ 6 Hz, *C*H_3CH$_2$O), 37.93 (*C*H_2Ph), 55.69 (C-4), 63.24 (d, $^2J_{C-P}$ 6 Hz, CH_2O), 66.96 (C-5), 127.86 (Ph), 129.41 (Ph), 129.79 (Ph), 132.84 (d, $^1J_{C-P}$ 186 Hz, PC=), 135.25 (Ph quaternary C), 135.93 (d, $^2J_{C-P}$ 10 Hz, CO*C*=), 153.43 (O–CO–N), 163.54 (d, $^3J_{C-P}$ 28 Hz, C–*C*O–N); *m*/*z* (FAB) found: $[M+H]^+$ 368.1268. $C_{17}H_{23}NO_6P$ requires 368.1263.

4.2.4. (*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-benzyl-5,5-diphenyl-1,3-oxazolidin-2-one 3d. Flash chromatography in CH_2Cl_2–EtOAc (85:15) gave **3d** (29% yield) as a colourless oil; $[\alpha]_D^{36}$ −218 (*c* 1.2, CH_2Cl_2); ν_{max}/cm^{-1} (film) 1786 (C=O) and 1688 (C=O); δ_H (270 MHz, $CDCl_3$) 1.32 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$), 2.76 (dd, 1H, *J* 14 and 8 Hz, *H*CHPh), 2.87 (dd, 1H, *J* 14 and 5 Hz, HC*H*Ph), 4.12 (quintet, 4H, *J* 7 Hz, 2×CH_2O), 4.65 (dd, 1H, *J* 8 and 5 Hz, NC*H*–CH$_2$), 6.70–6.75 (m, 2H, Ar–H), 6.86 (dd, 1H, *J* 19 and 17 Hz, C=C*H*CO), 7.07–7.44 (m, 13H, Ar–H), 7.85 (dd, 1H, *J* 21 and 17 Hz, C=C*H*P); δ_P (109 MHz, $CDCl_3$) 15.1; *m*/*z* (ESI) found: $[M+NH_4]^+$ 537.2155. $C_{29}H_{34}N_2O_6P$ requires 537.2149.

4.3. Typical procedure for Lewis acid-promoted Diels–Alder reaction: preparation of (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 10

(*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.200 g, 0.424 mmol) was dissolved in dry dichloromethane (2 mL). The solution was cooled to −96 °C under nitrogen. Cyclohexa-1,3-diene (1.0 mL, 10.5 mmol) and 1.8 M diethylaluminium chloride in toluene (0.37 mL, 0.66 mmol) were added to the solution, which was stirred for 20 min at −96 °C. The reaction mixture was then poured into 2 M HCl (90 mL). It was extracted with dichloromethane (40 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (4×20 mL), followed by 0.4 M aqueous potassium sodium (+)-tartrate (40 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. Analysis of the residue by ^{31}P NMR showed complete conversion of dienophile into a single product. Flash chromatography (EtOAc–petrol, 7:3) yielded the *title compound* **10** (0.166 g, 71%) as a white solid. Recrystallisation from dichloromethane–petrol gave colourless needles, mp 201–202 °C, $[\alpha]_D$ −73.7 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} (film) 1706 (C=O) and 1779 (C=O); δ_H (400 MHz, CD_2Cl_2, assignments supported by COSY) 0.67 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.75 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.81 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 0.96–1.08 (m, 4H, CH_3CH$_2$O+H-8′$_a$), 1.2–1.3 (m, 1H, H-7′$_a$), 1.69–1.77 (m, 1H, H-7′$_b$), 1.89–1.96 (m, 1H, C*H*Me$_2$), 2.00–2.08 (1H, m, H-8′$_b$), 2.37 (ddt, 1H, *J* 19, 7, 2 Hz, CHP), 2.78–2.80 (m, 1H, H-1′), 3.00–3.02 (m, 1H, H-4′), 3.40–3.50 (m, 1H, CH–O), 3.56–3.66 (m, 1H, CH–O), 3.7–3.8 (m, 3H, CH_2O+CHC=O), 5.37 (d, 1H, *J* 3 Hz, NCH), 5.93 (t, 1H, *J* 7 Hz, H-6′), 6.41 (tt, 1H, *J* 7, 1 Hz, H-5′), 7.17–7.45 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 31.5; δ_C (101 MHz, CD_2Cl_2, assignments supported by HSQC) 16.18 (*C*H_3CHMe), 16.58 (2×*C*H_3CH$_2$O), 20.59 (C-8′), 22.01 (*C*H_3CHMe), 25.59 (C-7′), 30.03 (C-1′), 30.74 (*C*HMe$_2$), 35.31 (d, $^1J_{C-P}$ 141 Hz, *C*P), 35.45 (d, $^2J_{C-P}$ 5 Hz, C-4′), 43.32 (d, $^2J_{C-P}$ 4 Hz, *C*H–C=O), 61.62 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 61.92 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 64.68 (*C*HN), 89.29 (O–*C*Ph$_2$), 125.71 (Ph), 126.12 (Ph), 128.25 (Ph), 128.79 (Ph), 128.91 (Ph), 129.28 (Ph), 129.88 (C-6′), 137.54 (d, $^3J_{C-P}$ 18 Hz, C-5′), 138.77 (Ph quaternary C), 143.12 (Ph

quaternary C), 152.62 (O–*C*=O–N), 173.25 (d, $^3J_{C-P}$ 4 Hz, C–*C*O–N); *m*/*z* (ESI) found: [M+H$^+$] 552.2517. $C_{31}H_{39}NO_6P$ requires 552.2510.

4.3.1. (1′*R,2′*R**,3′*S**,4′*S**)-[3-(Diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-oxazolidin-2-one *rac*-4.** 3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-1,3-oxazolidin-2-one **3a** (228 mg, 0.822 mmol) was dissolved in CH_2Cl_2 (2 mL) under nitrogen and cooled to −96 °C before being treated with excess cyclopenta-1,3-diene (2 mL) followed by 1.8 M Et_2AlCl in toluene (0.64 mL, 1.15 mmol). The reaction mixture was stirred at −96 °C for 20 min, then 10% aqueous sodium potassium tartrate solution (20 mL) was added to the reaction mixture, which was allowed to attain room temperature. The mixture was extracted with CH_2Cl_2 (20 mL) and the organic layer was washed with 2 M hydrochloric acid (30 mL) followed by saturated aqueous $NaHCO_3$ (30 mL). Drying ($MgSO_4$) and evaporation of the organic phase gave the crude product (190 mg). Flash chromatography with CH_2Cl_2–EtOAc (1:3) gave the major Diels–Alder product *rac*-**4** (86.5 mg, 31%) as a colourless oil with the following properties; ν_{max}/cm^{-1} (film) 1696 (C=O) and 1777 (C=O); δ_H (250 MHz, $CDCl_3$) 1.30 (t, 6H, *J* 7 Hz, 2×C*H*$_3$CH$_2$O), 1.43 (d, 1H, *J* 9 Hz, H-7′), 1.93 (d, 1H, *J* 9 Hz, H-7′), 2.36 (ddd, 1H, *J* 15.5, 6.0 and 1.8 Hz, H-3′), 3.18–3.22 (m, 1H, H-4′), 3.49 (br s, 1H, H-1′), 3.88–4.16 (m, 6H, C*H*$_2$N+2×C*H*$_2$O), 4.30 (ddd, 1H, *J* 18, 6 and 3.4 Hz, H-2′), 4.43 (t, 2H, *J* 8 Hz, C*H*$_2$OCO), 5.81 (dd, 1H, *J* 5 and 3 Hz, H-5), 6.41 ('t', 1H, *J* 5 Hz, H-6′) and 6.43 (t, 1H, *J* 5 Hz, H-5′); δ_P (101 MHz, $CDCl_3$) 32.0; δ_C (63 MHz, $CDCl_3$, assignments by ^{1}H–^{13}C correlation) 16.5 (*C*H$_3$CH$_2$O), 16.6 (*C*H$_3$CH$_2$O), 38.1 (d, $^1J_{C-P}$ 142 Hz, C-3′), 43.0 (C-4), 44.9–45.1 (m, C-2′ and C-4′), 47.3 (C-1′), 48.7 (C-7′), 61.7–62.1 (m, 3×OCH$_2$), 132.0 (C-6′), 139.7 (d, $^3J_{C-P}$ 15 Hz, C-5′), 153.3 (O–*C*O–N), 172.6 (C–*C*O–N); *m*/*z* (FAB) found: [M+H$^+$] 344.1250. $C_{15}H_{23}NO_6P$ requires 344.1263.

4.3.2. (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-[3-(Diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 6. (*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl) prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.060 g, 0.089 mmol) was dissolved in dry dichloromethane (1.0 mL). The solution was cooled to −96 °C under nitrogen. Cyclopentadiene (1.0 mL) and 1.8 M diethylaluminium chloride in toluene (0.343 mL, 0.617 mmol) were added to the solution, which was stirred for 10 min. The reaction mixture was then poured into 2 M HCl (75 mL). It was extracted with dichloromethane (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (2× 20 mL) followed by 0.4 M aqueous potassium sodium (+)-tartrate (20 mL). The organic phase was dried ($MgSO_4$) and the solvent was then removed by rotary evaporation. The residue was then subjected to flash chromatography using ethyl acetate–petrol (70:30), followed by recrystallisation from dichloromethane–petrol to give the cycloadduct **6** (0.015 g, 22%) as a white solid, mp 151–155 °C, $[\alpha]_D$ −199 (*c* 0.18, $CHCl_3$); following further recrystallisation the product was obtained as colourless, orthorhombic plates, mp 165–167 °C; ν_{max}/cm^{-1} (film) 1697 (C=O) and 1771 (C=O); δ_H (400 MHz, $CDCl_3$) 0.78 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 0.85 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 1.22–1.32 (m, 7H, 2×C*H*$_3$CH$_2$O+H-7′$_a$), 1.82 (d, 1H, *J* 9 Hz, H-7′$_b$), 1.98–2.04 (m, 1H, C*H*Me$_2$), 2.30 (ddd, 1H, *J* 16, 6, 1.6 Hz, H-3′, on decoupling ^{31}P simplifies to dd, *J* 6, 1.3 Hz), 2.75–2.79 (m, 1H, HCC=), 3.09–3.13 (m, 1H, HCC=), 4.03–4.19 (m, 4H, 2×CH$_2$O), 4.30 (ddd, 1H, *J* 18, 6, 3 Hz, H-2′, on decoupling ^{31}P simplifies to dd, *J* 6, 3 Hz), 4.84 (dd, 1H, *J* 5, 3 Hz, HC=), 5.19 (d, 1H, *J* 4 Hz, NC*H*), 6.22 (dd, 1H, *J* 5, 3 Hz, HC=), 7.24–7.57 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 32.3; *m*/*z* (ESI) found: [M+H]$^+$ 538.2345. $C_{30}H_{37}NO_6P$ requires 538.2353.

4.3.3. (4*S*,1′*R*,2′*S*)-[2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 11. A solution of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.200 g, 0.414 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −96 °C under nitrogen. 2,3-Dimethylbuta-1,3-diene (0.5 mL, 4.4 mmol) and 1.0 M dimethylaluminium chloride in hexane (1.32 mL, 1.32 mmol) were added to the solution, which was stirred for 20 min. The reaction mixture was then poured into 2 M HCl (45 mL). It was extracted with $CHCl_3$ (50 mL). The organic phase was washed with brine, dried ($MgSO_4$) and the solvent was then evaporated to leave the crude product (0.27 g). ^{31}P NMR showed the consumption of the starting dienophile **3e** and the formation of a single product, δ_P 31.0. Flash chromatography (CH_2Cl_2–EtOAc, 85:15) yielded the *title compound* **11** (163 mg, 69%) as a white foam. Slow evaporation of a solution of **11** in ethyl acetate–petrol (1:4) gave colourless, monoclinic crystals, mp 135–139 °C, $[\alpha]_D^{25}$ −62.1 (*c* 0.98, $CHCl_3$); ν_{max}/cm^{-1} (film) 1716 (C=O) and 1782 (C=O); δ_H (400 MHz, $CDCl_3$, assignments supported by COSY) 0.76 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 0.91 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 0.97 (t, 3H, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.21 (t, 3H, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.62 (s, 6H, 2×C*H*$_3$C=C), 1.92–2.00 (m, 1H, C*H*Me$_2$), 2.07–2.43 (m, 4H, 2×CH$_2$C=C), 2.47 (m, 1H, simplifies to td, *J* 11, 6 Hz upon decoupling ^{31}P, C*H*P=O), 3.45–3.52 (m, 1H, OCH), 3.74–3.87 (m, 3H, 3×OCH), 4.11 (tt, 1H, *J* 10, 6 Hz, simplifies to td, *J* 10, 6 Hz upon decoupling ^{31}P, C*H*–C=O), 5.45 (d, 1H, *J* 3 Hz, NCH), 7.25–7.53 (m, 10H, 2×Ph), δ_P (109 MHz, $CDCl_3$) 31.0; δ_C (101 MHz, $CDCl_3$, assignments supported by DEPT and HSQC) 16.11 (d, *J* 6 Hz, *C*H$_3$CH$_2$O), 16.30 (*C*H$_3$CH), 16.40 (d, *J* 6 Hz, *C*H$_3$CH$_2$O), 18.62 (2×*C*H$_3$C=C), 22.09 (*C*H$_3$CH), 30.21 (*C*HMe$_2$), 30.51 (d, $^2J_{C-P}$ 5 Hz, *C*H$_2$CHP=O), 31.94 (d, $^1J_{C-P}$ 140 Hz, *C*H–P=O), 35.76 (d, $^3J_{C-P}$ 6 Hz, *C*H$_2$–CHC=O), 38.76 (d, $^2J_{C-P}$ 4 Hz, *C*H–C=O), 61.08 (d, $^2J_{C-P}$ 7 Hz, *C*H$_2$O), 61.63 (d, $^2J_{C-P}$ 6 Hz, *C*H$_2$O), 64.18 (*C*H–N), 88.96 (Ph$_2$*C*–O), 123.15 (CH$_3$*C*=C), 124.31 (d, $^3J_{C-P}$ 13 Hz, CH$_3$*C*=C), 125.98 (Ph), 126.08 (Ph), 127.89 (Ph), 128.34 (Ph), 128.40 (Ph), 128.78 (Ph), 138.57 (quaternary C of Ph), 142.32 (quaternary C of Ph), 152.33 (O*C*ON), 174.62 (d, $^3J_{C-P}$ 5 Hz, CH–*C*O–N); *m*/*z* (ESI) found: [M+H]$^+$ 554.2669. $C_{31}H_{41}NO_6P$ requires 554.2666.

4.3.4. Reaction of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)-prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 3e with 2,3-dimethylbuta-1,3-diene in the absence of Lewis acid. A mixture of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.050 g, 0.11 mmol), 2,3-dimethylbuta-1,3-diene (0.50 mL, 4.4 mmol) and CH_2Cl_2 (0.5 mL) was heated

under reflux for 72 h. The solvent was evaporated and the residue was separated by flash chromatography with EtOAc–petrol (3:7) to give first (4*S*,1′*S*,2′*R*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **12** (0.041 g, 70%) as a white foam and then (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11** (0.007 g, 12%) as a white foam.

(4*S*,1′*S*,2′*R*)-[2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **12** had mp 47–49 °C, $[\alpha]_D$ −143 (*c* 1.17, $CHCl_3$); ν_{max}/cm^{-1} (film) 1714 (C=O) and 1786 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 (d, 3H, *J* 7 Hz, CH_3CHMe), 1.02 (d, 3H, *J* 7 Hz, CH_3CHMe), 1.24–1.47 (m, 11H, 2×CH_3CH$_2$O+CH_3C=C+2×CHC=), 1.57 (s, 3H, CH_3C=C), 1.97–2.05 (m, 1H, C*H*Me$_2$), 2.22–2.24 (m, 2H, CH$_2$C=C), 2.47–2.54 (m, 1H, C*H*P=O), 4.05–4.15 (m, 5H, 2×OCH$_2$+C*H*CO), 5.33 (d, 1H, *J* 3 Hz, NCH), 7.27–7.50 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 31.4; δ_C (101 MHz, $CDCl_3$) 16.70, 16.81 (d, *J* 6 Hz), 18.70, 18.96, 21.70, 30.14, 31.06 (d, *J* 4 Hz), 33.11 (d, *J* 142 Hz), 35.30 (d, *J* 12 Hz), 38.34, 61.84 (d, *J* 7 Hz), 62.30 (d, *J* 6 Hz), 66.04, 89.92, 123.35, 124.33 (d, *J* 13 Hz), 126.02, 126.16, 128.36, 128.85, 128.92, 129.21, 138.32, 143.03, 153.53, 175.18 (d, *J* 5 Hz); *m*/*z* (ESI) found: $[M+H]^+$ 554.2670. $C_{31}H_{41}NO_6P$ requires 554.2666.

(4*S*,1′*R*,2′*S*)-[2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11** was identical by ^1H and ^{31}P NMR to the major product of the Lewis acid-induced Diels–Alder reaction described in the previous experiment.

4.3.5. (4*S*,1′*R*,2′*S*)-[2-(Diethoxyphosphinoyl)-4-methylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 13. A solution of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.200 g, 0.424 mmol in dry CH_2Cl_2 (2 mL) was cooled to −96 °C under nitrogen. Isoprene (1.0 mL, 10.0 mmol) and 1.0 M dimethylaluminium chloride in hexane (1.32 mL, 1.32 mmol) were added to the solution, which was stirred for 40 min. The reaction mixture was then poured into 2 M HCl (45 mL). It was extracted with $CHCl_3$ (50 mL) and the organic layer was washed with brine (40 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated to leave the crude product (0.23 g). ^{31}P NMR showed only two peaks δ_P ($CDCl_3$) 15.2 (5%, unreacted dienophile) and 30.9 (95%, product). Flash chromatography (EtOAc–CH_2Cl_2, 96:4) gave the *title compound* **13** (0.174 g, 76%) as a white solid, mp 73–75 °C, $[\alpha]_D^{25}$ −21.7 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 1703 (C=O) and 1772 (C=O); δ_H (400 MHz, $CDCl_3$) 0.74 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.89 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.98 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.21 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.67 (s, 3H, CH_3C=C), 1.93–1.97 (m, 1H, C*H*Me$_2$), 2.13–2.55 (m, 5H, 2×CH_2–C=C+CHP), 3.48–3.54 (m, 1H, OCH), 3.77–3.86 (m, 3H, 3×OCH), 4.01–4.10 (m, 1H, CHC=O), 5.37–5.39 (m, 1H, CH=C), 5.44 (d, 1H, *J* 3 Hz, NCH), 7.25–7.53 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 30.9; δ_C (101 MHz, $CDCl_3$) 16.13 (d, $^3J_{C-P}$ 6 Hz, *C*H$_3$CH$_2$O), 16.23 (*C*H$_3$CHMe), 16.39 (d, $^3J_{C-P}$ 6 Hz, *C*H$_3$CH$_2$O), 22.05 (*C*H$_3$CHMe), 23.15 (*C*H$_3$C=), 28.92 (d, J_{C-P} 5 Hz, *C*H$_2$–C=), 30.06 (d, J_{C-P} 12 Hz, *C*H$_2$–C=), 30.21 (*C*Me$_2$), 31.67 (d, $^1J_{C-P}$ 141 Hz, *C*H–P=O), 37.83 (d, J_{C-P} 5 Hz, *C*H–C=O), 61.17 (d, $^2J_{C-P}$ 7 Hz, CH$_2$O), 61.70 (d, $^2J_{C-P}$ 6 Hz, CH$_2$O), 64.21 (N*C*H–CO), 88.97 (CO–*C*Ph$_2$), 118.30 (H*C*=C) [125.51, 125.90, 125.98, 126.06, 127.89, 128.35, 128.41, 128.78, together aromatic *C*H], 132.47 (d, $^3J_{C-P}$ 12 Hz, Me*C*=C), 138.55 (quaternary C of Ph), 142.36 (quaternary C of Ph), 152.31 (N–*C*O–O), 174.74 (d, $^3J_{C-P}$ 6 Hz, C–*C*O–N); *m*/*z* (ESI) found: $[M+H]^+$ 540.2506. $C_{30}H_{39}NO_6P$ requires 540.2510.

4.4. (4*S*,3′*S*)-3-[3-(Diethoxyphosphinoyl)pentanoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 14

(*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.100 g, 0.212 mmol) was dissolved in dry dichloromethane (2 mL). The solution was cooled to −70 °C under nitrogen. Diethylaluminium chloride 1.8 M in toluene (1.0 mL) was added to the solution, which was stirred for 20 min at −70 °C. The reaction mixture was then poured into 2 M HCl (45 mL), then extracted with dichloromethane (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (2×20 mL) followed by 0.4 M aqueous potassium sodium (+)-tartrate (20 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. ^{31}P NMR on the residue indicated that the starting material had been converted into three products δ_P (109 MHz, $CDCl_3$) 33.2 (72%), 33.3 (21%) and 30.0 (7%). Flash chromatography (EtOAc–petrol, 7:3) afforded a white solid, which was recrystallised from EtOAc–petrol to give the *title compound* **14** (0.066 g, 59%), mp 145–149 °C; repeated recrystallisation from EtOAc–petrol gave colourless, orthorhombic crystals, mp 149–151 °C, $[\alpha]_D^{25}$ −144 (*c* 0.36, $CHCl_3$); ν_{max}/cm^{-1} (film) 1705 (C=O) and 1784 (C=O); δ_H (400 MHz, $CDCl_3$) 0.76 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.89 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.97 (t, 3H, *J* 7 Hz, CH_3CH$_2$CHP), 1.22 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.23 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.44–1.56 (m, 1H, CH_2CHP), 1.70–2.04 (m, 1H, CH_2CHP), 1.95–2.03 (m, 1H, C*H*Me$_2$), 2.34–2.45 (m, 1H, CHP), 3.07–3.18 (m, 2H, CH_2CO), 3.97–4.04 (m, 4H, 2×CH_2O), 5.37 (d, 1H, *J* 3 Hz, NC*H*), 7.26–7.49 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 33.2; δ_C (101 MHz, $CDCl_3$, assignment by DEPT and ^1H–^{13}C correlation) 12.07 (d, $^3J_{C-P}$ 8 Hz, *C*H$_3$CH$_2$CHP), 16.38 (*C*H$_3$CH), 16.41 (*C*H$_3$CH$_2$O), 16.43 (*C*H$_3$CH$_2$O), 21.82 (*C*H$_3$CHMe), 22.10 ($^2J_{C-P}$ 4 Hz, *C*H$_2$CHP), 29.91 (*C*HMe$_2$), 32.67 (d, $^1J_{C-P}$ 142 Hz, *C*HP), 34.29 (*C*H$_2$CO), 61.51 (d, $^2J_{C-P}$ 7 Hz, *C*H$_2$O), 61.73 (d, $^2J_{C-P}$ 6 Hz, *C*H$_2$O), 64.90 (*C*HN), 89.37 (O–*C*Ph$_2$), 125.49 (Ph), 125.88 (Ph), 127.98 (Ph), 128.39 (Ph), 128.63 (Ph), 128.88 (Ph), 128.95 (Ph), 138.07 (quaternary C of Ph), 142.26 (quaternary C of Ph), 152.84 (O*C*=O), 171.08 (d, $^3J_{C-P}$ 16 Hz, C*C*=O); *m*/*z* (ESI) found: $[M+H]^+$ 502.2351. $C_{27}H_{37}NO_6P$ requires 502.2353.

4.4.1. (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-(Diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid 15. (4*S*,1′*R*,2′*R*,-3′*S*,4′*S*)-[3-(Diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **10** (19.8 mg, 0.0359 mmol) was dissolved in a mixture of THF (0.2 mL) and EtOH (0.2 mL). NaOH 1 M (0.05 mL) was added followed by 35% aqueous H_2O_2 (0.05 mL) and

the mixture was stirred for 60 h at 25 °C. Na_2SO_3 (50 mg) was then added, the organic solvents were removed by rotary evaporation and the residue was diluted with 1 M NaOH (10 mL) and filtered. The filtrate was washed with Et_2O (2×10 mL); the aqueous phase was acidified to pH 2 using 2 M HCl, then saturated with NaCl and extracted with $CHCl_3$ (5×20 mL). Drying ($MgSO_4$) and evaporation of the $CHCl_3$ extracts gave the *title compound* **15** (6.7 mg, 65%) as a white crystalline mass, mp 120–122 °C, $[\alpha]_D^{25}$ +20.1 (*c* 0.38, CH_2Cl_2); ν_{max}/cm^{-1} (film) 1728 (C=O) and 2400–3600 (O–H); δ_H (400 MHz, $CDCl_3$) 1.07–1.15 (m, 1H, H-7 or H-8), 1.25–1.38 (m, 7H, 2×CH_3 and H-7 or H-8), 1.59–1.68 (m, 1H, H-7 or H-8), 2.01–2.09 (m, 1H, H-7 or H-8), 2.29 (ddt, 1H, *J* 19, 7, 2 Hz, H-3), 2.86–2.93 (m, 2H), 3.06–3.10 (m, 1H), 4.05–4.19 (m, 4H, 2×OCH_2), 6.18 ('t', 1H, *J* 7 Hz, H-5 or H-6), 6.44 ('t', *J* 7 Hz, H-6 or H-5); δ_P (162 MHz, $CDCl_3$) 32.4; *m/z* (ESI) found: $[M+H]^+$ 289.1202. $C_{13}H_{22}O_5P$ requires 289.1199.

4.4.2. (1*R*,2*S*)-2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carboxylic acid 16. A solution of (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4-methylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11** (142 mg, 0.257 mmol) in THF (1.4 mL) was stirred at 25 °C for 20 h with $LiOH\cdot H_2O$ (17.2 mg, 0.410 mmol) in H_2O (0.3 mL) and 35% aqueous H_2O_2 (0.1 mL). Addition of Na_2SO_3 (120 mg) and work up by analogy with the preceding experiment gave the *title compound* **16** (48.5 mg, 65%) as a colourless oil; $[\alpha]_D^{23}$ +78.2 (*c* 2.2, CH_2Cl_2); *m/z* (ESI) found: $[M+H]^+$ 291.1356. $C_{13}H_{24}O_5P$ requires 291.1356. Compound **16** was identical by ^1H NMR, ^{31}P NMR, IR and TLC (EtOAc) to the (1*S*,2*R*)-enantiomer *ent*-**16**, which is described below.

4.4.3. (1*S*,2*R*)-2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carboxylic acid *ent*-16. A solution of (4*S*,1′*S*,2′*R*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **12** (242 mg, 0.437 mmol) in THF (2.5 mL) was stirred at 0 °C for 5 h with water (0.6 mL), 35% aqueous hydrogen peroxide (0.2 mL) and $LiOH\cdot H_2O$ (29.5 mg, 0.704 mmol). Solid Na_2SO_3 (0.5 g) was added and the THF was removed by rotary evaporation. NaOH 1 M (5 mL) was added and the mixture was filtered. The white precipitate was washed with water (20 mL) and the combined filtrates were acidified with 2 M HCl to pH 2. Extraction with $CHCl_3$ (3×20 mL), then drying ($MgSO_4$) and evaporation, gave the title compound **16** (88.4 mg, 79%) as a colourless oil; $[\alpha]_D^{24}$ −78.8 (*c* 2.9, CH_2Cl_2); ν_{max}/cm^{-1} (film) 1728 (C=O) and 2400–3600 (O–H); δ_H (400 MHz, $CDCl_3$) 1.31 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$O), 1.61 (s, 3H, CH_3C=C), 1.63 (s, 3H, CH_3C=C), 2.20–2.28 (m, 4H, 2×CH_2C=C), 2.39–2.49 (m, 1H, H-2), 2.74 ('tt', 1H, *J* 10, 6 Hz, H-1), 4.08–4.17 (m, 4H, 2×OCH_2), 8.0 (br s, 1H, CO_2H), δ_P (162 MHz, $CDCl_3$) 30.9; δ_C (101 MHz, $CDCl_3$, assignments supported by HSQC) 14.95 (d, *J* 6 Hz, *C*H_3CH$_2$O), 17.24 (*C*H_3C=), 17.30 (*C*H_3C=), 28.57 (d, J_{C-P} 4 Hz, *C*H_2), 32.10 (d, $^1J_{C-P}$ 144 Hz, *C*H–P=O), 32.82 (d, $^3J_{C-P}$ 12 Hz, *C*H_2–CHC=O), 39.02 (d, $^2J_{C-P}$ 3 Hz, *C*H–C=O), 60.74 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 60.99 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 121.95 (d, $^3J_{C-P}$ 11 Hz, CH_3*C*=C), 122.26 (CH_3*C*=C), 176.48 (d, $^3J_{C-P}$ 7 Hz, CO_2H); *m/z* (ESI) found: $[M+H]^+$ 291.1357. $C_{13}H_{24}O_5P$ requires 291.1356.

4.5. X-ray diffraction data

4.5.1. X-ray diffraction data for (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 6. Chemical formula: $C_{30}H_{36}NO_6P$; formula weight 537.57; crystal system: orthorhombic; unit cell dimensions and volume with estimated standard deviations: *a*=10.5567(3) Å; *b*=12.0318(2) Å; *c*=21.8433(6) Å; α=90°; β=90°; γ=90°; *V*=2774.45(12) Å^3; temperature 120(2) K; space group $P2_12_12_1$; *Z*=4; λ=0.71073 Å; linear absorption coefficient (μ): 0.143 mm^{-1}; number of reflections measured: 24586; number of independent reflections: 6367 [R_{int}=0.0595]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0489, wR_2=0.1089; absolute structure parameter 0.25(10).

4.5.2. X-ray diffraction data for (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 10. Chemical formula: $C_{31}H_{38}NO_6P$; formula weight 551.59; crystal system: orthorhombic; unit cell dimensions and volume with estimated standard deviations: *a*=8.6007(4) Å; *b*=9.0921(4) Å; *c*=36.0268(16) Å; α=90°; β=90°; γ=90°; *V*=2817.2(2) Å^3; temperature 120(2) K; space group $P2_12_12_1$; *Z*=4; λ=0.71073 Å; μ=0.143 mm^{-1}; number of reflections measured: 19016; number of independent reflections: 6338 [R_{int}=0.0655]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0563, wR_2=0.1027; absolute structure parameter −0.08(13).

4.5.3. X-ray diffraction data for (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 11. Chemical formula: $C_{31}H_{40}NO_6P$; formula weight 553.61; crystal system: monoclinic; unit cell dimensions and volume with estimated standard deviations: *a*=9.7614(5) Å; *b*=14.9366(5) Å; *c*=10.2496(6) Å; α=90°; β=91.497(2)°; γ=90°; *V*=1493.90(13) Å^3; temperature 120(2) K; space group $P2_1$; *Z*=2; λ=0.71073 Å; μ=0.135 mm^{-1}; number of reflections measured: 14558; number of independent reflections: 6686 [R_{int}=0.0464]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0524, wR_2=0.0951; absolute structure parameter 0.11(9).

4.5.4. X-ray diffraction data for (4*S*,3′*S*)-3-[3-(diethoxyphosphinoyl)pentanoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 14. Chemical formula: $C_{27}H_{36}NO_6P$; formula weight 501.54; crystal system: orthorhombic; unit cell dimensions and volume with estimated standard deviations: *a*=9.2445(2) Å; *b*=15.3913(5) Å; *c*=18.2225(6) Å; α=90°; β=91.497(2)°; γ=90°; *V*=2600.7(18) Å^3; temperature 160(2) K; space group $P2_12_12_1$; *Z*=4; λ=0.71073 Å; μ=0.148 mm^{-1}; number of reflections measured: 19081; number of independent reflections: 5916 [R_{int}=0.0486]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0451, wR_2=0.0949; absolute structure parameter 0.12(9).

Crystallographic data (excluding structure factors) for compounds **6**, **10**, **11** and **14** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 617238, 605148, 605149 and 617237, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the EPSRC National Crystallography Service at Southampton for data collection. We are grateful to Mr. G. Coumbarides (NMR spectroscopy), Mrs. B. Stein (Mass Spectrometry at the EPSRC National Service Centre, Swansea) and to the late Mr. M. Cocksedge (FAB mass spectra at the ULIRS mass spectrometry service). We appreciate the contributions of Dr. Christine Bladon through her helpful suggestions and discussions.

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Tetrahedron 62 (2006) 12408–12414
Tetrahedron

Biphenyl- and terphenyl-based recyclable organic trivalent iodine reagents

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Received 30 August 2006; accepted 27 September 2006
Available online 2 November 2006

Abstract—Biphenyl- and terphenyl-based recyclable trivalent iodine reagents, such as 4-bromo-4′-(diacetoxyiodo)biphenyl, 4,4′-bis(diacetoxyiodo)biphenyl, 1,4-bis[4-(diacetoxyiodo)phenyl]benzene, 4-bromo-4′-[(hydroxy)(tosyloxy)iodo]biphenyl, 4,4′-bis[(hydroxy)(tosyloxy)iodo]biphenyl, were simply prepared and their reactivities for the oxidative rearrangement of ketones to esters, TEMPO-mediated oxidation of alcohols to aldehydes or ketones, oxidative dealkylation of *N*-alkylsulfonamides to sulfonamides, and α-tosyloxylation of ketones were compared with *p*-(diacetoxyiodo)toluene and *p*-[(hydroxy)(tosyloxy)iodo]toluene to show the same reactivities and, moreover, the biphenyl- and terphenyl-based iodoarenes formed were recovered by simple filtration of the reaction mixture in every reaction. Thus, these biphenyl- and terphenyl-based trivalent iodine reagents can be used as the recyclable reagents.

1. Introduction

Recently, synthetic use of hypervalent iodines for organic synthesis has been investigated widely because of their efficient oxidizing ability and less toxicity.[1] Especially, (diacetoxyiodo)benzene (DIB), iodosylbenzene, and [(hydroxy)(tosyloxy)iodo]benzene (HTIB) are well-known reagents and the oxidative reactions can be carried out under mild conditions with easy handling, high chemoselectivity, and low toxicity.[2] Based on the broad synthetic utility of these organohypervalent iodine compounds for organic synthesis, previously, we and others reported polymer-supported hypervalent iodine reagents such as poly[4-(diacetoxy)-iodo]styrene (PSDIB), poly[4-(hydroxy)(tosyloxy)iodo]-styrene (PSHTIB), etc.[3] The major advantages of the use of these polymer-supported hypervalent iodine reagents are as follows: reactions can be monitored by standard methods such as TLC, GC, HPLC, etc., reaction products can be obtained by simple filtration to remove the polymer-supported reagent, and regeneration and reuse of the recovered polymer-supported reagents are possible. Thus, polymer-supported hypervalent iodines are environmentally friendly reagents, and have wide applicability to organic synthesis in the chemical and pharmaceutical industries. However, the introduction of high loading rate of organic trivalent iodine groups onto polystyrene is not so easy and sometimes lowers the reactivities than those observed with DIB and HTIB. Recently, Kita et al. reported an elegant approach for recyclable trivalent iodine reagents, such as 1,3,5,7-tetrakis[(diacetoxyiodo)phenyl]adamantane[4a] and tetrakis[4-(diacetoxyiodo)phenyl]methane.[4b] Thus, these are not polymers, but they are recyclable trivalent iodine reagents. This approach impressed us, since we have experienced some limitations with polymer-supported trivalent iodine reagents, for example, oxidative dealkylation of *N*-alkylsulfonamides with PSDIB does not proceed effectively. Here, as a part of our study on environmentally benign organic synthesis with hypervalent iodines, we would like to report biphenyl- and terphenyl-based recyclable trivalent iodine reagents.

2. Results and discussion

Our approach is focused on biphenyl- and terphenyl-based trivalent iodines,[5] since the diiodination of biphenyl and terphenyl is easy and the solubility of these iodo compounds is not so high. Thus, the solubility of 4-bromo-4′-iodobiphenyl, 4,4′-diiodobiphenyl, and 1,4-bis(*p*-iodophenyl)benzene in hexane is 8.4 mg/ml, 2.2 mg/ml, and slightly soluble, respectively, and even in chloroform it is 114.9 mg/ml, 32.3 mg/ml, and 0.9 mg/ml, respectively. So, it is expected that 4,4′-diiodobiphenyl and 1,4-bis(*p*-iodophenyl)benzene are the core candidates in recyclable hypervalent iodines. The iodination of 4-bromobiphenyl, biphenyl, and terphenyl proceeded smoothly with molecular iodine and iodine pentoxide in nitrobenzene in the presence of a small amount of carbon tetrachloride and sulfuric acid, as in the preparation of PSDIB from polystyrene, as shown in Scheme 1. For

Keywords: 4-Bromo-4′-(diacetoxyiodo)biphenyl; 4,4′-Bis(diacetoxyiodo)-biphenyl; 1,4-Bis[4-(diacetoxyiodo)phenyl]benzene; 4-Bromo-4′-[(hydroxy)-(tosyloxy)iodo]biphenyl; 4,4′-Bis[(hydroxy)(tosyloxy)iodo]biphenyl; Oxidation; Aldehyde; Ketone; Ester; α-Tosyloxyketone; Sulfonamide.
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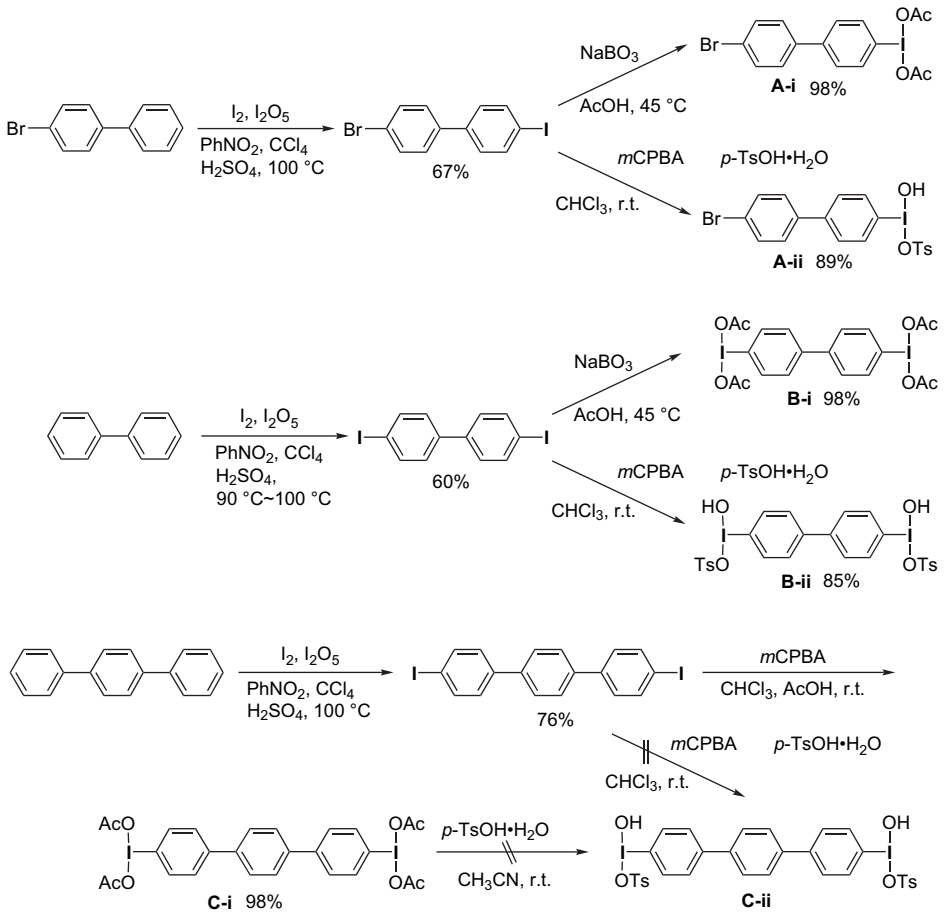
doi:10.1016/j.tet.2006.09.112



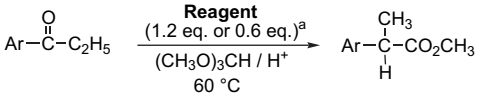
Scheme 1. Preparation of biphenyl- and terphenyl-based trivalent iodines.

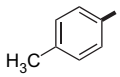
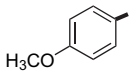
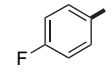
the preparation of 4-bromo-4′-(diacetoxyiodo)biphenyl (**A-i**), 4,4′-bis(diacetoxyiodo)biphenyl (**B-i**),[6] and 1,4-bis[4-(diacetoxyiodo)phenyl]benzene (**C-i**), there are two methods. The first method is the oxidation of iodo compounds with sodium peroxoborate in acetic acid as a standard method,[7] and the second one is the oxidation with *m*CPBA in a mixture of chloroform and acetic acid as shown in Scheme 1.[4] 4-Bromo-4′-[(hydroxy)(tosyloxy)iodo]biphenyl (**A-ii**) and 4,4′-bis[(hydroxy)(tosyloxy)iodo]biphenyl (**B-ii**) were directly prepared with *m*CPBA and *p*-toluenesulfonic acid monohydrate in chloroform, based on our previous report.[8] 1,4-Bis[4-(hydroxy)(tosyloxy)iodophenyl]benzene (**C-ii**) could not be prepared cleanly by the direct preparation of 1,4-bis(*p*-iodophenyl)benzene with *m*CPBA and *p*-toluenesulfonic acid monohydrate or by the exchange reaction of 1,4-bis[4-(diacetoxyiodo)phenyl]benzene (**C-i**) with *p*-toluenesulfonic acid monohydrate, as a traditional method.

2.1. Oxidative 1,2-aryl migration of alkyl aryl ketones

1,2-Aryl migration of propiophenones with the present trivalent iodine reagents **A-i**, **B-i**, and **C-i** in trimethyl orthoformate was carried out effectively, based on the previous report,[9] and the reactivities were compared with that of standard *p*-(diacetoxyiodo)toluene (**D-i**) as shown in Table 1. Since biphenyl- and terphenyl-based reagents **B-i** and **C-i** have two trivalent iodine groups, the mole amount used is reduced to a half-millimole amount of trivalent iodine reagents **A-i** and **D-i**. Thus, the results indicate that the present trivalent iodine

Table 1. Oxidative 1,2-aryl migration of alkyl aryl ketones to esters with reagents **A-i**–**D-i**



Reagent	Ar–	Time (h)	Yields (%)	
			Product	Recovery[b]
A-i		2	91	81
B-i			85	84
C-i			88	94
D-i			88	(—)
A-i		2	88	90
B-i			85	84
C-i			88	96
D-i			92	(—)
A-i		3	89	80
B-i			91	80
C-i			88	90
D-i			92	(—)
A-i		5[c]	86	81
B-i			84	84
C-i			87	94
D-i			82	(—)

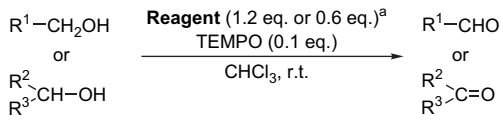
[a] For **B-i** and **C-i**: 0.6 equiv, and for **A-i** and **D-i**: 1.2 equiv.
[b] Yield of 4,4′-diiodobiphenyl, 4-bromo-4′-iodobiphenyl, or 1,4-bis(*p*-iodophenyl)benzene.
[c] Reaction was carried out at room temperature.

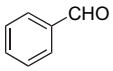
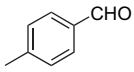
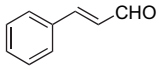
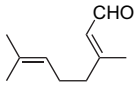
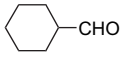
reagents **A-i**, **B-i**, and **C-i** showed the same reactivity to give the rearranged esters in high yields, as with the standard reagent **D-i**. Here, 4-bromo-4′-iodobiphenyl, 4,4′-diiodobiphenyl, and 1,4-bis(*p*-iodophenyl)benzene formed as byproducts could be recovered in high yields by simple filtration of the reaction mixture, though *p*-iodotoluene could not be recovered at all. Generally, the collecting ability is slightly decreased in the order of 1,4-bis(*p*-iodophenyl)benzene, 4,4′-diiodobiphenyl, and 4-bromo-4′-iodobiphenyl. Thus, after the reaction with 1,4-bis[4-(diacetoxyiodo)phenyl]benzene (**C-i**), 1,4-bis(*p*-iodophenyl)benzene was recovered quantitatively by simple filtration.

2.2. TEMPO-mediated oxidation of alcohols to aldehydes or ketones

TEMPO-mediated oxidation of primary alcohols and secondary alcohols[10] with the present trivalent iodine reagents **A-i**, **B-i**, and **C-i** in chloroform proceeded smoothly at room temperature to provide the corresponding aldehydes and ketone in good yields, and the reactivities were compared again with standard *p*-(diacetoxyiodo)toluene (**D-i**) as shown in Table 2. In trivalent iodine reagents **B-i** and **C-i**, a half-millimole amount of the reagents was used, based on that of trivalent iodine reagents **A-i** and **D-i**, and 10 mol % of TEMPO was used for effective oxidation. Again, the results indicate that trivalent iodine reagents **A-i**, **B-i**, and **C-i** showed the same reactivity as with the standard reagent **D-i**. Here, 4-bromo-4′-iodobiphenyl, 4,4′-diiodobiphenyl, and 1,4-bis(*p*-iodophenyl)benzene formed as byproducts could be recovered in high yields by simple filtration of the reaction mixture, though *p*-iodotoluene could not be recovered at all. TEMPO-mediated oxidation of cinnamyl alcohol with regenerated **C-i** provided cinnamaldehyde in high yields, together with high recovery of 1,4-bis(*p*-iodophenyl)benzene.

Table 2. TEMPO-mediated oxidation of alcohols to aldehydes or ketone with reagents **A-i**–**D-i**



Reagent	Product	Time (h)	Yields (%)	
			Product	Recovery[b]
A-i		2	98	93
B-i			93	89
C-i			99	96
D-i			97	(—)
A-i		2	93	75
B-i			90	89
C-i			90	96
D-i			94	(—)
A-i		2	71	86
B-i			73	83
C-i			95	94
			97[c]	93[c]
			97[d]	95[d]
D-i			99	(—)
A-i		2	81	84
B-i			79	90
C-i			79	92
D-i			89	(—)
A-i		24	95	93
B-i			95	89
C-i			97	95
D-i			100	(—)
A-i	$CH_3(CH_2)_{10}$–CHO	16	65	96
B-i			65	88
C-i			66	92
D-i			91	(—)
A-i		24	100	80
B-i			97	86
C-i			100	94
D-i			99	(—)

[a] For **B-i** and **C-i**: 0.6 equiv, and for **A-i** and **D-i**: 1.2 equiv.
[b] Yield of 4,4′-diiodobiphenyl, 4-bromo-4′-iodobiphenyl, or 1,4-bis(*p*-iodophenyl)benzene.
[c] Yield with the first regenerated **C-i**.
[d] Yield with the second regenerated **C-i**.

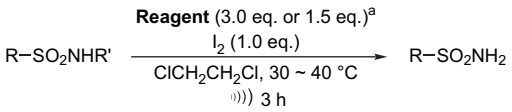
2.3. Sonochemical dealkylation of *N*-alkylsulfonamides

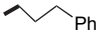
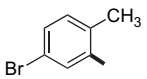
Previously, we reported sonochemical oxidative dealkylation of *N*-alkylsulfonamides with DIB in the presence of iodine to form the corresponding free sulfonamides and aldehydes.[11] Based on the report, *N*-alkylsulfonamides were treated with the present trivalent iodine reagents **A-i**, **B-i**, and **C-i** in the presence of iodine in 1,2-dichloroethane under ultrasonic irradiation conditions to generate the corresponding free sulfonamides in good yields as shown in Table 3. Again, the results indicate that trivalent iodine reagents **A-i**, **B-i**, and **C-i** have the same reactivity as that of standard reagent **D-i**. 4-Bromo-4′-iodobiphenyl, 4,4′-diiodobiphenyl, and 1,4-bis(*p*-iodophenyl)benzene formed as byproducts could be recovered in high yields by simple filtration of the reaction mixture, though *p*-iodotoluene could not be recovered at all.

2.4. α-Tosyloxylation of ketones

α-Tosyloxyketones are a very important strategic precursor for the direct construction of various heterocyclic

Table 3. Sonochemical dealkylation of *N*-alkyl-sulfonamides with reagents **A-i**–**D-i**

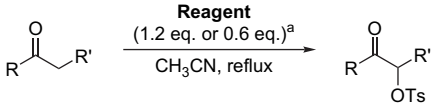


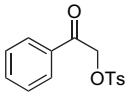
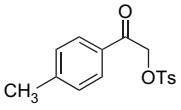
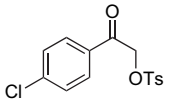
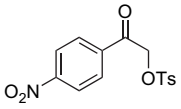
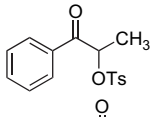
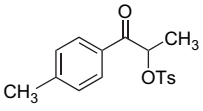
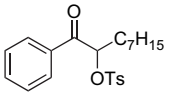
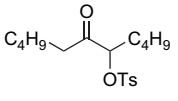
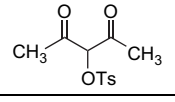
Reagent	R−	R'−	Yields (%)	
			Product	Recovery[b]
A-i		−CH_2CH_3	77	92
B-i			80	94
C-i			76	98
D-i			71	(—)
A-i			87	92
B-i			100	94
C-i			89	99
D-i			97	(—)
A-i[c]		−CH_2CH_3	66	90
B-i[c]			66	98
C-i[c]			58	98
D-i[c]			64	(—)

[a] For **B-i** and **C-i**: 1.5 equiv, and for **A-i** and **D-i**: 3.0 equiv.
[b] Yield of 4,4′-diiodobiphenyl, 4-bromo-4′-iodobiphenyl, or 1,4-bis(*p*-iodophenyl)benzene.
[c] Reaction was carried out for 6 h.

compounds such as thiazoles, oxazoles, selenazoles, imidazoles, pyrazoles, benzofurans, and lactones; and HTIB and PSHTIB are the sole reagents for the direct preparation of α-tosyloxyketones from ketones[2c,12] or alcohols.[13] Since biphenyl-based reagent **B-ii** has two trivalent iodine groups, a half-millimole amount of the reagent was used based on that of trivalent iodine reagents **A-ii** and **D-ii**. Here, various ketones were treated with the present trivalent iodine reagents **A-ii** and **B-ii** under refluxing conditions in acetonitrile to provide the corresponding α-tosyloxyketones in good yields as shown in Table 4. Again, the results indicate that the trivalent iodine reagents **A-ii** and **B-ii** have the same reactivity as that of the standard reagent **D-ii**. 4-Bromo-4′-iodobiphenyl and 4,4′-diiodobiphenyl formed as byproducts could be recovered in high yields by simple filtration of the reaction mixture, though *p*-iodotoluene could not be recovered at all.

Table 4. α-Tosyloxylation of ketones with reagents **A-ii**, **B-ii**, and **D-ii**



Reagent	Product	Time (h)	Yields (%)	
			Product	Recovery[b]
A-ii			85	88
B-ii		4	85	88
D-ii			87	(—)
A-ii			81	93
B-ii		8	84	81
D-ii			91	(—)
A-ii			92	84
B-ii		8	87	81
D-ii			95	(—)
A-ii			79	78
B-ii		8	88	81
D-ii			87	(—)
A-ii			81	93
B-ii		4	84	81
D-ii			91	(—)
A-ii			82	83
B-ii		4	86	74
D-ii			85	(—)
A-ii			81	81
B-ii		8	79	84
D-ii			80	(—)
A-ii[c]			77	87
B-ii[c]		8	72	82
D-ii[c]			65	(—)
A-ii			90	91
B-ii		4	83	84
D-ii			70	(—)

[a] For **B-ii**: 0.6 equiv and for **A-ii** and **D-ii**: 1.2 equiv.
[b] Yield of 4,4′-diiodobiphenyl and 4-bromo-4′-iodobiphenyl.
[c] Reaction was carried out at 60 °C.

3. Conclusion

4-Bromo-4′-(diacetoxyiodo)biphenyl (**A-i**), 4,4′-bis(diacetoxyiodo)biphenyl (**B-i**), and 1,4-bis[4-(diacetoxyiodo)-phenyl]benzene (**C-i**) could be used for the oxidative rearrangement of ketones to the esters, TEMPO-mediated oxidation of alcohols to the corresponding aldehydes or ketones, and oxidative dealkylation of *N*-alkylsulfonamides to sulfonamides, and 4-bromo-4′-[(hydroxy)(tosyloxy)-iodo]biphenyl (**A-ii**) and 4,4′-bis[(hydroxy)(tosyloxy)iodo]-biphenyl (**B-ii**) could be used for the α-tosyloxylation of ketones. These trivalent iodine reagents showed the same reactivity as that of *p*-(diacetoxyiodo)toluene (**D-i**) and *p*-[(hydroxy)(tosyloxy)iodo]toluene (**D-ii**). Moreover, after the reactions, the formed iodoarenes are recovered in high yields by simple filtration of the reaction mixture and they can be regenerated and reused for the same reaction. Thus, the present trivalent iodine reagents can be used as simple recyclable reagents, instead of polymer-supported trivalent iodine reagents such as PSDIB or PSHTIB.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained with JEOL-JNM-LA-400, JEOL-JNM-LA-400s, and JEOL-JNM-LA-500 spectrometers. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) in δ units. Mass spectra were recorded on JEOL-HX-110 and JEOL-JMS-ATII15 spectrometers. Melting points were determined on Yamato melting points apparatus Model MP-21. Silica gel 60 (Kanto Kagaku Co.) was used for column chromatography and Wakogel B-5F was used for preparative TLC. Sonication was performed by Tokyo Rika Kikai AC-70 CO (200 W; 28 kHz) ultrasonic cleaning device.

4.2. Typical procedure for the preparation of iodoarenes

A mixture of 5.2 g of biphenyl, 12.4 g of iodine, 4.7 g of diiodine pentoxide, 10 ml of carbon tetrachloride, and 15 ml of 50% sulfuric acid in 20 ml of nitrobenzene was kept at 90∼100 °C for 48 h. After the reaction, the reaction mixture was poured into methanol (350 ml). The precipitates were collected by filtration (8.1 g, 60% yield).

4.2.1. 4-Bromo-4′-iodobiphenyl. Mp 166–168 °C; IR (KBr) 1470, 1380, 1000, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.29 (2H, d, J=8.5 Hz), 7.41 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz), 7.76 (2H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ=93.43 (q), 121.99 (q), 128.44 (t), 128.72 (t), 132.02 (t), 137.99 (t), 138.96 (q), 139.49 (q).

4.2.2. 4,4′-Diiodobiphenyl. Mp 200–201 °C; IR (KBr) 2360, 1470, 1380, 1000, 800, 460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.28 (4H, d, J=8.5 Hz), 7.76 (4H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ=93.49 (q), 128.67 (t), 137.99 (t), 139.54 (q); elemental analysis calcd for $C_{12}H_8I_2$: C 35.50, H 1.99, I 62.51%; found: C 35.58, H 2.03, I 62.56%.

4.2.3. 4,4′-Bis(*p*-iodophenyl)benzene. Mp >280 °C; IR (KBr) 2600, 1480, 1400, 1000, 800, 460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.37 (4H, d, J=8.5 Hz), 7.63 (4H, s), 7.79

(4H, d, J=8.5 Hz); elemental analysis calcd for $C_{18}H_{12}I_2$: C 44.84, H 2.51, I 52.65%; found: C 44.25, H 2.61, I 52.55%.

4.3. Typical procedure for the preparation of (diacetoxyiodo)arenes

A mixture of 4,4′-diiodobiphenyl (1.02 g, 2.5 mmol) and sodium peroxoborate tetrahydrate (3.85 g, 25 mmol) in AcOH (150 ml) was kept at 40–50 °C for 1 h, and then sodium peroxoborate tetrahydrate (3.85 g, 25 mmol) was added again. The mixture was stirred for 24 h at 40–50 °C. After the reaction, water was added and the mixture was extracted with chloroform three times. The organic layer was dried over sodium sulfate. After filtration, removal of the solvent under reduced pressure gave 4,4′-bis(diacetoxyiodo)biphenyl (1.60 g, 99% yield).

4.3.1. 4-Bromo-4′-(diacetoxyiodo)biphenyl. Mp (decomp.) 171 °C; IR (KBr) 2400–2300, 1560, 1410, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.03 (6H, s), 7.45 (2H, d, J=8.5 Hz), 7.62 (2H, d, J=8.5 Hz), 7.65 (2H, d, J=8.5 Hz), 8.15 (2H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ=20.52 (p), 120.54 (q), 123.23 (q), 128.99 (t), 129.49 (t), 132.39 (t), 135.68 (t), 138.15 (q), 143.84 (q), 176.61 (q); elemental analysis calcd for $C_{16}H_{14}BrIO_4$: C 40.28, H 2.96%; found: C 40.25, H 3.06%.

4.3.2. 4,4′-Bis(diacetoxyiodo)biphenyl. Mp (decomp.) 176–177 °C; IR (KBr) 2360, 1580, 1410, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.04 (12H, s), 7.67 (4H, d, J=8.5 Hz), 8.20 (4H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ=20.52 (p), 121.42 (q), 129.89 (t), 135.76 (t), 142.90 (q), 176.65 (q); elemental analysis calcd for $C_{20}H_{20}I_2O_8\cdot H_2O$: C 36.39, H 3.36, I 38.44%; found: C 36.32, H 3.27, I 38.49%.

4.4. Preparation of 1,4-bis(4-diacetoxyiodophenyl)-benzene

To a stirred solution of 4,4′-bis(*p*-iodophenyl)benzene (0.96 g, 2 mmol) in a mixture of $CHCl_3$ (300 ml) and AcOH (40 ml) was added *m*CPBA (2.08 g, 12 mmol) at room temperature. The reaction mixture was stirred for 24 h under the same reaction conditions. The resultant slightly clouded solution was filtered to give a clear solution. Chloroform of the filtrate was removed under reduced pressure and then hexane was added to the residue and stirred for 8 h to precipitate 1,4-bis(4-diacetoxyiodophenyl)benzene. After filtration, the crude product was washed with hexane and Et_2O several times, and dried in vacuo to give 1,4-bis(4-diacetoxyiodophenyl)benzene (1.41 g, 98% yield).

4.4.1. 1,4-Bis(4-diacetoxyiodophenyl)benzene. Mp (decomp.) 214 °C; IR (KBr) 2360, 1560, 1390, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.04 (12H, s), 7.71 (4H, s), 7.73 (4H, d, J=8.5 Hz), 8.19 (4H, d, J=8.5 Hz); elemental analysis calcd for $C_{26}H_{24}I_2O_8\cdot 3CH_3COOH$: C 42.78, H 4.04, I 28.25%; found: C 42.67, H 4.24, I 28.30%.

4.5. Typical procedure for the preparation of [hydroxy(tosyloxy)iodo]arenes

To a mixture of 4,4′-diiodobiphenyl (2.03 g, 5 mmol) and *p*-toluenesulfonic acid monohydrate (2.00 g, 11 mmol) in chloroform (60 ml) was added *m*CPBA (2.10 g, 11 mmol). The obtained mixture was stirred for 4 h at room temperature under an argon atmosphere. After the reaction, diethyl ether (20 ml) was added to the reaction mixture, and the obtained mixture was filtered and the solids were washed with diethyl ether to provide 4,4′-bis[(hydroxy)(tosyloxy)iodo]biphenyl (3.32 g, 85% yield).

4.5.1. 4-Bromo-4′-[(hydroxy)(tosyloxy)iodo]biphenyl. Mp (decomp.) 98–100 °C; IR (KBr) 3700–3200, 1480, 1390, 1190, 1130, 1040, 1000, 800, 600 cm^{-1}; ^1H NMR ($CDCl_3$+3 drops of CF_3CO_2H) δ=2.45 (3H, s), 7.35 (2H, d, J=8.2 Hz), 7.48 (2H, d, J=8.7 Hz), 7.66 (2H, d, J=8.7 Hz), 7.73 (2H, d, J=8.2 Hz), 7.77 (2H, d, J=8.7 Hz), 8.29 (2H, d, J=8.7 Hz); elemental analysis calcd for $C_{19}H_{16}BrIO_4S$: C 41.70, H 2.95%; found: C 41.54, H 3.06%.

4.5.2. 4,4′-Bis[(hydroxy)(tosyloxy)iodo]biphenyl. Mp (decomp.) 104 °C; IR (KBr) 3700–3200, 1470, 1190, 1130, 1040, 800, 600 cm^{-1}; ^1H NMR ($CDCl_3$+3 drops of CF_3CO_2H) δ=2.45 (6H, s), 7.33 (4H, d, J=8.2 Hz), 7.72 (4H, d, J=8.2 Hz), 7.81 (4H, d, J=8.7 Hz), 8.37 (4H, d, J=8.7 Hz); elemental analysis calcd for $C_{26}H_{24}I_2O_8S_2\cdot H_2O$: C 39.01, H 3.27%; found: C 39.31, H 3.16%.

4.6. Typical procedure for the conversion of arylketones to esters

Sulfuric acid (2 mmol) was added dropwise to a solution of 4,4′-bis(diacetoxyiodo)biphenyl (0.6 mmol) and propiophenone (1.0 mmol) in 3 ml of trimethyl orthoformate at 0 °C. The reaction mixture was stirred for 2 h at 60 °C under an argon atmosphere. Hexane was then added to the solution, and the formed 4,4′-diiodobiphenyl was removed by filtration. The filtrate was poured into water (10 ml), extracted with ether, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was poured into methanol (5 ml). Once again 4,4′-diiodobiphenyl was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by preparative TLC on silica gel (85% yield).

4.6.1. Methyl 2-phenylpropanoate. Bp 65 °C/2.5 mmHg (lit.[14] 104–105 °C/18 mmHg); IR (neat) 2980, 1740, 1600, 1495, 1455, 1210, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.50 (3H, d, J=7.2 Hz), 3.66 (3H, s), 3.73 (1H, q, J=7.2 Hz), 7.23–7.35 (5H, m).

4.6.2. Methyl 2-(4-methylphenyl)propanoate. IR (neat) 2955, 1740, 1515, 1460, 1205, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (3H, d, J=7.2 Hz), 2.33 (3H, s), 3.65 (3H, s), 3.69 (1H, q, J=7.2 Hz), 7.13 (2H, d, J=8.1 Hz), 7.19 (2H, d, J=8.1 Hz).

4.6.3. Methyl 2-(4-methoxyphenyl)propanoate. IR (neat) 2980, 2960, 2840, 1740, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (3H, d, J=7.2 Hz), 3.65 (3H, s), 3.68 (1H, q, J=7.2 Hz), 3.79 (3H, s), 6.86 (2H, dt, J=8.7 and 2.0 Hz), 7.22 (2H, dt, J=8.7 and 2.0 Hz).

4.6.4. Methyl 2-(4-fluorophenyl)propanoate. IR (neat) 2980, 2960, 1740, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (3H, d, J=7.2 Hz), 3.66 (3H, s), 3.71 (1H, q, J=7.2 Hz),

7.00 (2H, tt, J=8.7 and 2.1 Hz), 7.26 (2H, ddt, J=8.7, 5.3, and 2.1 Hz).

4.7. Typical procedure for the oxidation of alcohols to aldehydes or ketones

4,4′-Bis(diacetoxyiodo)biphenyl (0.3 mmol) was added to a solution of cinnamyl alcohol (0.5 mmol) and TEMPO (7.8 mg, 0.05 mmol) in $CHCl_3$ (1 ml), and the mixture was stirred at room temperature for 2 h. Then, hexane was added and the mixture was filtered to remove the formed 4,4′-diiodobiphenyl. After removal of the solvent from the filtrate, the residue was poured into methanol (5 ml). Once again 4,4′-diiodobiphenyl was removed by filtration. After removal of the solvent from the filtrate, the corresponding carbonyl compound was obtained.

All aldehydes and ketones mentioned in this work are commercially available, and all compounds were identified with the authentic samples.

4.8. Typical procedure for the oxidative dealkylation of *N*-alkylsulfonamides

4,4′-Bis(diacetoxyiodo)biphenyl (0.75 mmol) and iodine (0.5 mmol) were added to a solution of *N*-ethyl-benzylsulfonamide (0.5 mmol) in 1,2-dichloroethane (7 ml). The mixture was stirred preliminarily for 10 min under dark conditions, and then irradiated with an ultrasonic cleaning bath (200 W; 28 kHz or 100 W; 28, 45, and 100 kHz) for 3 h under an argon atmosphere in the range of 30–40 °C. After the reaction, the mixture was poured into ethyl acetate and washed with aq sodium sulfite (Na_2SO_3) solution and subsequently washed with water. The organic layer was dried over sodium sulfate (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was poured into methanol (5 ml). The mixture was filtered to remove the formed 4,4′-diiodobiphenyl. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel preparative TLC using a mixture of hexane and ethyl acetate (2:1) as an eluant.

4.8.1. Benzylsulfonamide. Mp 99–100 °C (lit.[15] 101–102 °C); IR (KBr) 3380, 3320, 1325, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.30 (2H, s), 4.72 (2H, br s), 7.37–7.44 (5H, m); MS (EI) found: M^+=171.

4.8.2. 5-Bromo-2-methylbenzenesulfonamide. Mp 163.0–164.5 °C (lit.[16] 164.0–165.0 °C); IR (KBr) 3400, 3295, 1295, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.63 (3H, s), 4.92 (2H, br s), 7.21 (1H, d, J=8.0 Hz), 7.58 (1H, dd, J=8.2 and 2.2 Hz), 8.15 (1H, d, J=2.2 Hz); MS (EI) found: M^+= 249, 251.

Benzenesulfonamide was identified with commercially available authentic compound.

4.9. Typical procedure for the α-tosyloxylation of ketones

4,4′-Bis[(hydroxy)(tosyloxy)iodo]biphenyl (0.3 mmol) was added to a solution of acetophenone (0.5 mmol) in acetonitrile (3 ml). The mixture was refluxed for 4 h under an argon atmosphere, and then the reaction mixture was poured into methanol (5 ml). The mixture was filtered to remove 4,4′-diiodobiphenyl. After removal of the solvent under reduced pressure, the residue was poured into methanol (5 ml). The mixture was filtered to remove the formed 4,4′-diiodobiphenyl. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel by column chromatography.

4.9.1. α-Tosyloxyacetophenone. Mp 90 °C (lit.[13c] 90–91 °C); IR (KBr) 1715, 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.45 (3H, s), 5.27 (2H, s), 7.35 (2H, d, J=8.5 Hz), 7.47 (2H, t, J=8.2 Hz), 7.61 (1H, t, J=8.2 Hz), 7.85 (4H, m).

4.9.2. α-Tosyloxy-*p*-methylacetophenone. Mp 80 °C (lit.[13c] 82–83 °C); IR (KBr) 1700, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.41 (3H, s), 2.45 (3H, s), 5.24 (2H, s), 7.26 (2H, d, J=8.1 Hz), 7.35 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.1 Hz), 7.86 (2H, d, J=8.2 Hz).

4.9.3. α-Tosyloxy-*p*-chloroacetophenone. Mp 122 °C (lit.[13c] 125 °C); IR (KBr) 1710, 1360, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.46 (3H, s), 5.21 (3H, s), 7.35 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.6 Hz), 7.80 (2H, d, J= 8.6 Hz), 7.84 (2H, d, J=8.4 Hz).

4.9.4. α-Tosyloxy-*p*-nitroacetophenone. Mp 139–140 °C (lit.[13c] 139 °C); IR (KBr) 1710, 1340, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.47 (3H, s), 5.25 (2H, s), 7.37 (2H, d, J=8.3 Hz), 7.83 (2H, d, J=8.3 Hz), 8.02–8.05 (2H, m), 8.31–8.35 (2H, m).

4.9.5. α-Tosyloxypropiophenone. Mp 68 °C (lit.[13c] 68–69 °C); IR (KBr) 1700, 1370, 1170, 830, 760, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.60 (3H, d, J=7.0 Hz), 2.41 (3H, s), 5.79 (1H, q, J=7.0 Hz), 7.29 (2H, d, J=8.1 Hz), 7.46 (2H, t, J=7.2 Hz), 7.60 (1H, t, J=7.2 Hz), 7.75 (2H, d, J= 7.2 Hz), 7.88 (2H, d, J=8.1 Hz).

4.9.6. α-Tosyloxy-*p*-methylpropiophenone. Mp 88–89 °C; IR (KBr) 1690, 1360, 1180, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.56 (3H, d, J=7.0 Hz), 2.41 (3H, s), 2.42 (3H, s), 5.77 (1H, q, J=7.0 Hz), 7.23 (4H, m), 7.73 (4H, m); ^{13}C NMR ($CDCl_3$) δ=18.78 (p), 21.63 (p), 21.72 (p), 77.32 (t), 127.92 (t), 128.86 (t), 129.44 (t), 129.72 (t), 131.14 (q), 133.53 (q), 144.89 (q), 144.93 (q), 194.29 (q); HRMS (FAB) obsd: M+H=319.1004, calcd for $C_{10}H_{12}O$: M+H=319.1007.

4.9.7. α-Tosyloxyoctyl phenyl ketone. Mp 59–60 °C; IR (KBr) 1700, 1340, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.86 (3H, t, J=7.0 Hz), 1.20–1.43 (10H, m), 1.84–1.91 (2H, m), 2.40 (3H, s), 5.59 (1H, dd, J=8.2 and 4.8 Hz), 7.24 (2H, d, J=8.0 Hz), 7.43–7.47 (2H, m), 7.56–7.60 (1H, m), 7.73–7.77 (2H, m), 7.84–7.86 (2H, m); ^{13}C NMR ($CDCl_3$) δ=14.01 (p), 21.60 (p), 22.53 (s), 24.95 (s), 28.74 (s), 28.87 (s), 31.58 (s), 32.66 (s), 81.37 (t), 128.00 (t), 128.61 (t), 128.69 (t), 133.12 (q), 133.72 (t), 133.98 (q), 144.92 (q), 1955.02 (q); elemental analysis calcd for $C_{22}H_{28}O_4S$: C 68.01, H 7.43%; found: C 68.01, H 7.26%.

4.9.8. α-Tosyloxy-6-undecanone. Mp 72 °C; ^1H NMR ($CDCl_3$) δ=0.70–0.80 (3H, m), 0.86–0.89 (3H, m),

1.09–1.75 (14H, m), 2.46 (3H, s), 2.49–2.53 (2H, m), 4.64 (1H, dd, J=8.0 and 4.6 Hz), 7.36 (2H, d, J=8.0 Hz), 7.79–7.82 (2H, m); ^{13}C NMR ($CDCl_3$) δ=13.64 (p), 13.89 (p), 21.70 (p), 21.99 (s), 22.45 (s), 22.50 (s), 26.63 (s), 31.25 (s), 31.50 (s), 38.20 (s), 84.94 (t), 128.72 (t), 130.67 (t), 133.80 (q), 146.13 (q), 208.63 (q); elemental analysis calcd for $C_{18}H_{28}O_4S$: C 63.50, H 8.29% found: C 63.40, H 8.50%.

4.9.9. α-Tosyloxy-2,4-pentadione. Mainly enol tautomer; mp 82 °C (lit.[13b] 82–83 °C); IR (KBr) 3060, 1600, 1370, 1200, 1180, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.96 (6H, s), 2.49 (3H, s), 7.40 (2H, d, J=8.1 Hz), 7.83 (2H, d, J=8.1 Hz), 14.80 (1H, s).

Acknowledgements

Financial support by a Grant-in-Aid for Scientific Research (No. 16655012) from the Ministry of Education, Science, Sports, and Culture of Japan is gratefully acknowledged.

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Stereodynamics of Ar–CO rotation and conformational preferences of 2-amino-3-(2,4-difluorobenzoyl)-imidazo[1,2-*a*]pyridine

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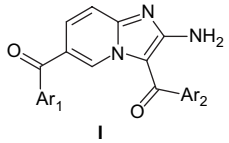
Received 4 August 2006; revised 20 September 2006; accepted 27 September 2006
Available online 27 October 2006

Abstract—The dynamic NMR analysis of **2**, a subunit of a new class of cyclic-dependent kinase inhibitors, reveals that the compound exists as two conformational isomers, *Z* and *E*, in acetone, as a consequence of the restricted rotation about the imidazopyridine–carbonyl bond. The less hindered *Z*-rotamer is the most abundant conformer (85:15 *Z*/*E* at 233 K) and the free energy of activation of the interconversion is 13.2 kcal mol^{-1}. The rotamer ratio and the interconversion barrier are similar in other solvents, such as CD_3OD and $CDCl_3$.

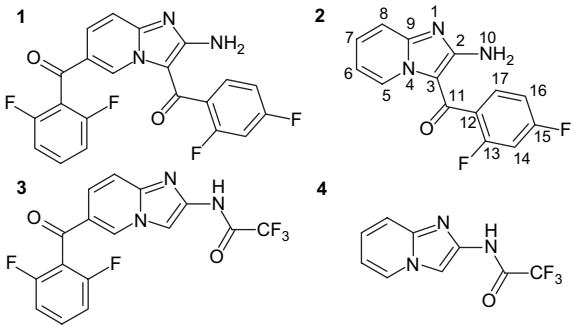
1. Introduction

Cyclic-dependent kinases (CDKs) are potential therapeutic targets for the treatment of cancer because they play a key role in initiating and coordinating the phases of the cell-division cycle.[1] In the context of a medicinal chemistry project aimed at the discovery of more efficient and selective CDK inhibitors, we have identified a new family of molecules comprising a 2-aminoimidazo[1,2-*a*]pyridine nucleus bearing benzoyl derivatives on positions 3 and 6.[2] Specifically, we have demonstrated that compounds of type **I** are potent and selective CDK2 inhibitors that compete with ATP for binding to a catalytic unit of the enzyme.[3] CDK2 is one of the most relevant members of the kinase family, since it is involved in two of the four phases of the basic cell-cycle.[4] Imidazopyridines have been shown to have significant potential as new drugs,[5] and they have been exploited to prepare antirhinovirus agents.[6]



I

In the course of the NMR analysis of **1**, the pronounced broadening of one of the aromatic signals in the ^{1}H spectrum suggested the existence of a slow conformational equilibrium in solution, which was confirmed by the splitting of some signals when the temperature was lowered. Variable-temperature NMR experiments performed for derivatives **2** and **3**, revealed a similar behaviour for **2**, whereas no line-broadening in the temperature range 233–313 K was detected for **3**. This finding indicates that the slow exchange is the result of the benzoyl substitution on position 3 of the imidazopyridine ring.



Here, we report on a dynamic NMR study of compound **2** to determine the most abundant conformer in solution, and to measure the value of the rotational barrier involved in the interconversion process. The final goal is to gain a better understanding of the conformational properties of this new

Keywords: Ar–CO rotation; Conformational analysis; Dynamic NMR; Imidazopyridine; CDK inhibitors.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.097

class of CDK2 inhibitors to aid the design of more potent derivatives.

2. Results and discussion

The conformational space available to compound **2** was explored by systematic rotation about the C3–C11 and C11–C12 bonds, optimization of the geometry obtained at each incremental step using the MMFF94 force field,[7] and energy calculation. The low-energy conformations were subjected to an energy minimization by the semi-empirical AM1 method[8] to obtain more refined structures. According to the AM1 calculations, the C3–C11–C12–C13 dihedral angle is close to 90°, similar to that of *ortho*-substituted diaryl or alkyl aryl ketones that adopt twisted conformations (dihedral angle in the range 60°–90°),[9] whereas the C2–C3–C11–CO dihedral angle is close to 0°, as described for benzaldehydes, even when *ortho*-substituted (Fig. 1).[9] As a consequence, rotation about C11–C12 interconverts two conformational enantiomers; the process is NMR-invisible, given the absence of substituents that can serve as prochiral probes. Conversely, rotation about C3–C11 interconverts two conformational isomers, *Z* and *E* (Fig. 1), and, provided that the rate of rotation is rendered sufficiently slow on the NMR time-scale, separated signals corresponding to each rotamer will be observed. Therefore, the conformational equilibrium detected for **2** must originate from slow rotation about the sp^2–sp^2 C3–C11 bond.

The ^{1}H spectrum of **2** in acetone at 303 K showed seven aromatic signals (Fig. 2a), three of them corresponding to the difluorobenzoyl protons, easily identified through the coupling to the ^{19}F nuclei, and the other four corresponding to the imidazopyridine protons: a doublet at 7.35 ppm, a triplet at 7.55 ppm, a broad triplet at 6.99 ppm and a very broad peak at 9.25 ppm. The broadening of the latter two signals was attributed to the proximity of the protons to the slow-rotating Ar–CO, and the signals assigned to H6 and H5, respectively. This assignment was confirmed through HMBC and COSY experiments (see Supplementary data). While the triplet at 7.55 ppm showed a long-range H,C correlation to a non-protonated carbon at 149.0 ppm (C9) in an HMBC experiment, such correlation was not detected for the triplet at 6.99 ppm, indicating that the former triplet corresponded to H7, three bonds away from C9, and the latter to H6. A coupling between H7 and H8, observed in a COSY experiment, led to the assignment of the doublet at 7.35 ppm to H8.

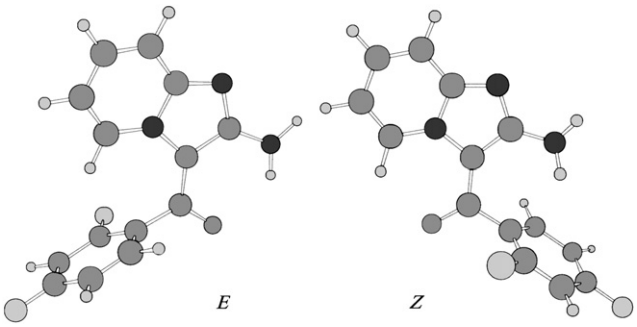


Figure 1. AM1-computed structures of the *E* and *Z* conformers of **2**.

The ^{1}H spectrum at 233 K showed two sets of signals in an 85:15 ratio; however, because of severe resonance overlapping, not all the minor peaks were identified (Fig. 2b). In particular, H5 major appeared at 9.69 ppm in a clean region of the spectrum; however, the position of the corresponding proton signal for the minor rotamer was unclear. The signal of H5 minor was detected through the selective inversion of H5 major in a 1D nuclear Overhauser effect spectroscopy (NOESY) experiment at 233 K, which gave rise to an exchange peak at 7.58 ppm (Fig. 2c). Two additional signals of opposite sign were present in the 1D NOESY spectrum, corresponding to NOEs between H5 and H6 for both rotamers. This result indicates that the rotamers, which are in slow exchange on the chemical shift time-scale, are in fast exchange on the T_1 time-scale.

The large chemical shift difference between H5 protons can be related to the conformational arrangement about the C3–C11 bond, allowing the assignment of the conformational isomers. H5 major is shifted to a higher frequency by 1.10 ppm, and H5 minor is shifted to a lower frequency by 1.01 ppm, with respect to the same proton in reference compound **4**. Because in the *Z*-rotamer H5 is in close proximity to the carbonylic oxygen atom (Fig. 1), the major species can be assigned to the *Z*-rotamer, where the deshielding experienced by H5 can be interpreted as a consequence of the through-space effect of the oxygen atom. Hence, the minor species would correspond to the *E*-rotamer, where H5 is shielded by the anisotropic effect of the benzoyl aromatic ring (Fig. 1). Consistently, the opposite trend was found for the NH_2 protons, which are shielded in the major rotamer by 1.54 ppm relative to the minor rotamer. The AM1 results suggest that the most abundant *Z*-rotamer is slightly more stable than the *E*-rotamer, by 0.14 kcal mol^{-1}.

Because the minor *E*-rotamer places the carbonylic oxygen atom within hydrogen bonding distance of the amine protons, the occurrence of intramolecular hydrogen bonding between these atoms can be envisaged. If this were the case, the population of this rotamer would be expected to show some dependence on the polarity of the solvent. This hypothesis was investigated by recording ^{1}H spectra of **2** in other solvents within the solubility limits of the compound ($CDCl_3$ and CD_3OD). The spectra also showed splitting of signals at 233 K, and the rotamer ratios were fairly similar to those in acetone (Table 1), demonstrating that the change of solvent polarity does not modify the conformational preferences. Thus, the existence of a hydrogen bond between the carbonylic oxygen atom and the amino protons cannot be inferred from NMR data.

Full line shape analysis of the ^{1}H spectra as a function of temperature led to the rate constants of the interconversion and to the barrier for rotation about the C3–C11 bond. The free-energy barrier of interconversion of the more stable into the less stable form in acetone is 13.2 kcal mol^{-1}. Similar line shape analysis was performed in $CDCl_3$ and CD_3OD, and yielded similar values (Table 1), indicating little influence of the solvent in the rate of interconversion, as those for the rotamer ratios.

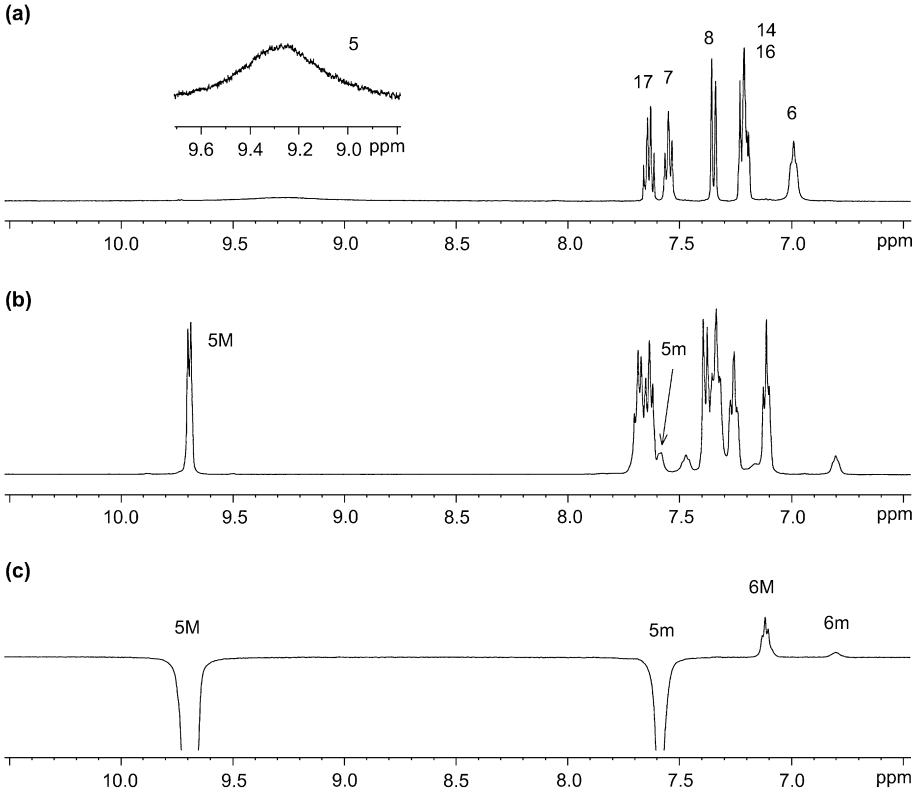
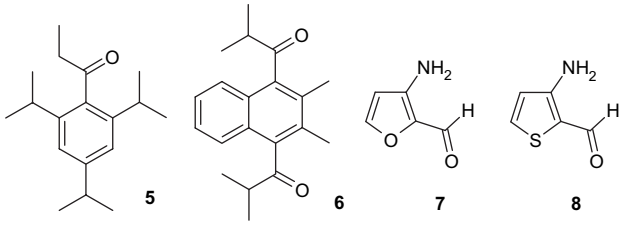
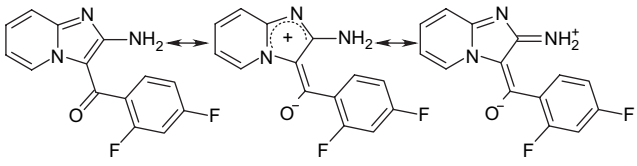


Figure 2. The 500 MHz spectra of **2** in acetone-d_6. (a) ^{1}H at 303 K; (b) ^{1}H at 233 K; (c) 1D NOESY at 233 K. The assignment of the resonances is shown. M, major; m, minor.

Rotation about the bond between an aromatic ring and a carbonyl group has been thoroughly studied by dynamic NMR spectroscopy. Interestingly, the energy barrier of the Ar–CO rotation measured in **2** is similar to those reported for some aromatic ketones bearing bulky substituents on *ortho*-positions such as **5** and **6** (Table 2).[10,11]



However, the root cause of the barrier to internal rotation differs in both types of structures. While the *ortho*-disubstituted ketones have the carbonyl group arranged essentially orthogonal to the aromatic ring and the rotation barrier is of a steric nature, the carbonyl group and the imidazopyridine are almost coplanar in **2**, and the barrier to rotation about the C3–C11 bond (π-barrier) originates from the stabilization of the carbonyl group brought about by the mesomeric effect of the aminoimidazopyridine ring (Scheme 1). In this respect, the energy barriers would be better compared with those measured in five-membered heteroaromatic *o*-aminoaldehydes such as **7** and **8**, which present the same type of conjugation (Table 2).[12] Interestingly, the value for the Ar–CO rotation in **2** is similar to that of **8**, indicating a similar degree of conjugation between the aromatic ring and the carbonyl group in the 2-aminoimidazopyridine and in the 3-aminothiophene.



Scheme 1.

Table 1. Interconversion barrier ($\Delta G^{\ddagger}$), conformer ratio at 233 K and chemical shift difference (Δd) of the monitored resonance (H6) at 233 K for **2**

Solvent	$\Delta G^{\ddagger}$ (kcal mol^{-1})	*Z*/*E* ratio	Δd (Hz, 500 MHz)
Acetone-d_6	13.2	85:15	154.4
$CDCl_3$	13.4	81:19	173.1
CD_3OD	13.0	82:18	165.5

Table 2. Free energies of activation ($\Delta G^{\ddagger}$) for Ar–CO rotation in several aromatic compounds

Compound	$\Delta G^{\ddagger}$ (kcal mol^{-1})	Solvent
2	13.2	Acetone-d_6
5	13.5	CD_2Cl_2
6	13.4	CD_2Cl_2
7	16.2	DMSO-d_6
8	13.7	CD_3CN

3. Conclusions

Variable-temperature NMR analysis of **2** demonstrates the coexistence of two conformational isomers in solution undergoing interconversion about the imidazopyridine–CO bond. In both rotamers, the carbonyl bond is coplanar to the imidazopyridine ring and orthogonal to the difluorobenzoyl ring. The *Z*-rotamer is the predominant conformation in solution, and the rotamer ratio is little affected by solvent changes. This finding indicates that the conformational preferences of **2** are intrinsic and not driven by interactions with the solvent molecules. Although the barriers to rotation about Ar–CO bonds have received considerable attention, to the best of our knowledge, this is the first time that the stereodynamics of the Ar–CO bond has been measured for an imidazopyridine ring, which is an important class of heterocyclic compounds. The results of further studies investigating the influence of the structure of the benzoyl ring on the rotamer ratio and on the rate of interconversion will be reported in due course.

4. Experimental

4.1. Materials

The title compound (**2**) was prepared following the general procedure described in Refs. 2 and 13. The assignment of the proton resonances is discussed in the text. ^{1}H NMR (500 MHz, acetone-d_6 at 30 °C): δ=9.25 (br s, 1H, H5), 7.63 (q, J=7.5 Hz, 1H, H17), 7.55 (t, J=7.6 Hz, 1H, H7), 7.35 (d, J=8.5 Hz, 1H, H8), 7.21 (m, 2H, H14 and H16), 6.99 (br t, 1H, H6), 5.39 (br s, 2H, NH_2). ^{13}C NMR (75 MHz, acetone-d_6 at 30 °C): δ=176.4 (C11), 164.9 (dd, J=250.3 Hz, 11.8 Hz, C15), 160.3 (dd, J=250.6 Hz, 12.6 Hz, C13), 160.1 (C2), 149.0 (C9), 131.7 (C7), 131.5 (dd, J=10.1 Hz, 5.2 Hz, C17), 129.3 (br s, C5), 126.4 (dd, J=17.5 Hz, 4.0 Hz, C12), 115.1 (C6), 113.7 (C8), 113.5 (dd, J=21.5 Hz, 3.7 Hz, C16), 109.3 (C3), 105.9 (t, J=25.9 Hz, C14). MS (EI): m/z 274 $[M+H]^+$.

4.2. NMR spectroscopy

The variable-temperature NMR spectra were acquired on a Bruker DRX 500 Avance spectrometer equipped with a 5-mm inverse probe. Proton and carbon chemical shifts were referenced to the residual solvent signals. Temperature calibration on the spectrometer was performed using a standard methanol sample. Proton spectra were acquired using 32K data points and zero-filled to 64K. The 1D NOESY experiments were carried out with the selective 1D double-pulse field gradient spin echo module[14] using a mixing time of 500 ms. Absolute value correlated spectroscopy (COSY), phase-sensitive heteronuclear single quantum coherence (HSQC) and heteronuclear multiple-bond correlation (HMBC) data were acquired using gradient selection techniques. Acquisition data matrices were defined by 1K×256 points in F_2 and F_1, respectively. The 2D data matrices were multiplied by the appropriate window functions and zero-filled to 2K×1K matrices. Linear prediction was applied before Fourier transformation, and polynomial baseline correction was used in both dimensions of the 2D spectra. Data were processed using the XWINNMR Bruker program on a Silicon Graphics computer. The energy barriers were determined by full line shape analysis of H6 resonance at various temperatures within the 223–313 K range (see Supplementary data). The corresponding free energies of activation were independent of temperature within the errors (±0.3 kcal mol^{-1}) and the average value was taken as the interconversion barrier. Similar values were obtained through line shape analysis of H5 resonance. The simulation was performed using a line-fitting program based on the Bloch equations in the presence of chemical exchange, and the best fit was judged visually by superimposing the predicted and experimental spectra.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.097.

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Chiral induction from solvents—lactic acid esters in the asymmetric hydroboration of ketones

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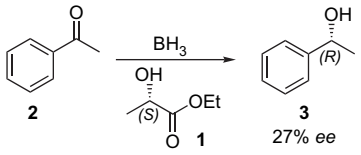
Received 13 July 2006; revised 20 September 2006; accepted 26 September 2006
Available online 27 October 2006

Abstract—The hydroboration of acetophenone in the chiral solvent (*S*)-methyl lactate exhibits moderate enantioselectivities. A six-membered transition state involving the ketone, the borane, and the lactate as the only chiral source is proposed. Molecular modeling explains the experimentally observed enantioselectivities. Calculated ee-values are in accordance with those experimentally observed. Improved ee-values (up to 60%) can be obtained in the presence of stoichiometric amounts of Lewis acid at lower reaction temperatures.

1. Introduction

Solvents can influence organic reactions and the respective product distribution in many ways.[1] In the case of chiral solvents as reaction medium, asymmetric induction can be observed and the products obtained can show enantiomeric excess (ee). The first successful experiments in this field were accomplished in 1975 by Seebach and Oei. They reported the synthesis of 2,3-diphenyl-2,3-butanediol from acetophenone by photolysis or electrolysis.[2] Using the amino ether (*S*,*S*)-(+)-1,4-bisdimethylamino-2,3-dimethoxybutane (DBB) as a chiral solvent the pinacol product could be isolated with 23% optical activity. A further example for the use of chiral solvents was reported by Furia et al., who used menthol in the asymmetric oxidation of sulphides and alkenes.[3] However, the enantioselectivities observed were only moderate (10% ee). Laarhoven and Cuppen irradiated 2-styrylbenzo-phenanthrene in various chiral solvents, such as ethyl lactate, ethyl mandelate, and their *O*-benzoyl-derivatives. The procedure afforded hexahelicenes with an optical yield of 0.2–2%.[4] As a consequence of the generally low enantioselection obtained the use of chiral solvents for asymmetric induction was neglected. However, recently asymmetric induction by chiral ionic liquids (CIL) has become an emerging field of research and impressive examples of highly enantioselective reactions have been described.[5,6] These include the asymmetric Baylis–Hillmann and aza-Baylis–Hillmann reactions developed by Vo-Thanh et al.[7] and Leitner et al.,[8] as well as the Michael addition of ketones to nitrostyrenes reported by Luo, Cheng and co-workers.[9] In the latter reaction, however, only 30 mol % of the task specific ionic liquid (TSIL) was employed.[10] Recently, we reported our first success in the enantioselective sodium borohydride reduction of acetophenone using chiral solvents for the asymmetric induction. Surprisingly, when we performed the reactions in (*S*)-lactic acid esters as solvent the (*R*)-enantiomer of phenylethanol was obtained in 27% ee (Scheme 1).[11]



Scheme 1. Solvent induced asymmetric borohydride reduction.

From a purely synthetic point of view, these results may so far have little value when compared to the Ru(II) based catalytic hydrogenations of Noyori and Ohkuma.[12] However, our interest lay in the development of solvent induced asymmetric reactions, at present an undoubtedly more multifaceted and complex research topic to address and to understand. Here, we report our further studies on the chiral solvent induced asymmetric reduction.

2. Results and discussion

Our continued studies of the solvent induced asymmetric borohydride reduction started by varying the ketone substrate.

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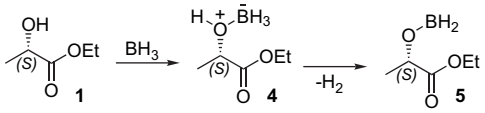
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.111

Table 1. Chiral solvent induced borane reduction of different ketones in (*S*)-lactic acid esters at 0 °C

Ketone	(*S*)-Ethyl lactate		(*S*)-Methyl lactate		Configuration of the product
	Conversion	ee	Conversion	ee	
Acetophenone	35	27	41	31	(*R*)
Butanone	75	6	70	8	(*R*)
3,3-Dimethylbutanone	80	14	87	19	(*R*)

Similarly to the hydroboration of acetophenone in (*S*)-ethyl lactate, the reduction of butanone and 3,3-dimethyl-2-butanone resulted in the corresponding products with increased conversion but the ee-values were considerably lower. However, by changing the chiral solvent from (*S*)-ethyl lactate to (*S*)-methyl lactate the enantioselectivities slightly increased (Table 1).

In order to gain a better understanding of the chiral (*S*)-lactate induction, we decided to prepare the *O*-methyl ether of lactic acid ethyl ester, ethyl 2-methoxypropionate. Performing the reaction using this chiral ether as solvent under otherwise same reaction conditions we observed insignificant enantioselectivities, indicating that the free hydroxyl group of (*S*)-ethyl lactate must be involved in the asymmetric induction. When BH_3 is added to lactic acid ester **1** a donor–acceptor adduct **4** is formed, which is presumably the active species in the hydroboration procedure (Scheme 2).



Scheme 2. Reaction of $BH_3 \cdot THF$ with ethyl lactate.

Subsequently, adduct **4** may undergo dehydrogenation to form the chiral borane **5**. In order to detect whether the chiral borane **5** is an intermediate in our solvent induced reduction, we prepared **5** by the addition of BH_3 to an equimolar amount of (*S*)-ethyl lactate and tested **5** in the reduction of acetophenone. When carrying out the reaction in THF, complete conversion was observed but no enantioselectivity could be detected; whereas performing the reaction in (*S*)-ethyl lactate as solvent only 3% conversion occurred but the product **3** was obtained with 7% ee. Hence, the borane **5** should be ruled out as the intermediate or chirality inducing reagent. From these results we can conclude that the presence of the free hydroxy group is crucial for the asymmetric induction. This is in agreement with previous findings of Vo-Thanh et al., Leitner et al., and Colonna et al.[7,8,13] However, the earlier reports on the mechanism of the hydroboration of carbonyl groups describe a four-membered transition state **TS 1** (Fig. 1a).[14] Applying this transition state model to our chiral solvent induced reduction would mean that the methyl lactate would not be sufficiently involved in the transition state and hence enantioselectivities should be low to zero, which is in contrast to the experimental observations. Consequently, (*S*)-methyl lactate, which is the only chiral source, must be involved in the transition state of asymmetric borohydride reduction of acetophenones.

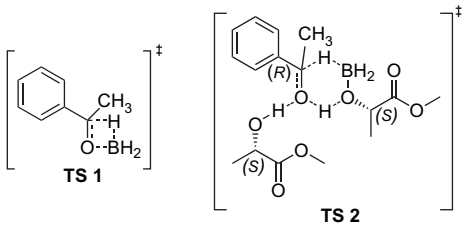


Figure 1. (a): Four-membered transition state.[14] (b) Six-membered transition state assumed for the chiral solvent induced hydroboration reaction of acetophenone.

A plausible transition state model **TS 2**, based on our observations, is given in Figure 1b. We assume a six-membered ring transition state for the investigated solvent induced borohydride reduction of acetophenone. In this transition state the borane acts as a Lewis acid and coordinates to the hydroxyl group of the (*S*)-methyl lactate causing the hydrogen of the O–H bond to become more acidic. This in turn allows the formation of a hydrogen bond to the oxygen atom of the acetophenone and as a consequence the carbonyl group is activated. Due to the ability of carbonyl groups to accept two hydrogen bonds, a second hydrogen bond from a different lactate molecules to the acetophenone acceptor is formed.[15] Through the coordination of the borane to the hydroxyl group of the methyl lactate, the B–H bond becomes activated: the electron density on the hydrogen atom increases, and it coordinates to the carbonyl C-atom of the acetophenone.

Molecular modeling was performed to explain the experimentally observed enantioselectivity. The calculations were carried out on the initial coordination state, which is assumed to be similar to the transition state. We used the parameterization of the Dreiding's force field,[16] which has been proven to give good results for organic compounds. Atomic charges were calculated by the semi-empirical method AM1[17] and all minimizations were performed with the Cerius[2] programs.[18] For calibration, initial test calculations on a set of lactate crystal structures and those of boranes were carried out and showed the applicability and reliability of the force field used. Hence, we started to analyze our system. At first the geometries of the involved molecules were optimized individually. Then the molecules were arranged in the six-membered ring (Fig. 1b). The molecular conformations and the possible arrangements in space were set up according to geometries found in crystal structures of similar compounds.[15] To assure close proximity of the reacting molecules the distance between the hydride of the BH_3 group and the carbonyl C-atom was restrained to a value of 270 pm, which corresponds to a close van der Waals contact.[15,19] Energy minimizations were carried out on various arrangements with the hydride attacking from both the *re*- and the *si*-faces of acetophenone. For the addition from the *si*-face the most favorable arrangement was found with a total energy of 88.53 kJ/mol (Fig. 2).

In contrast, the minimum total energy for the *re*-face attack amounted to 90.75 kJ/mol. Hence, an attack from the *si*-face yielding the (*R*)-alcohol is preferred by about 2.2 kJ/mol. As such, the (*R*)-alcohol should be the kinetically preferred product, which is in accordance with the experiment.

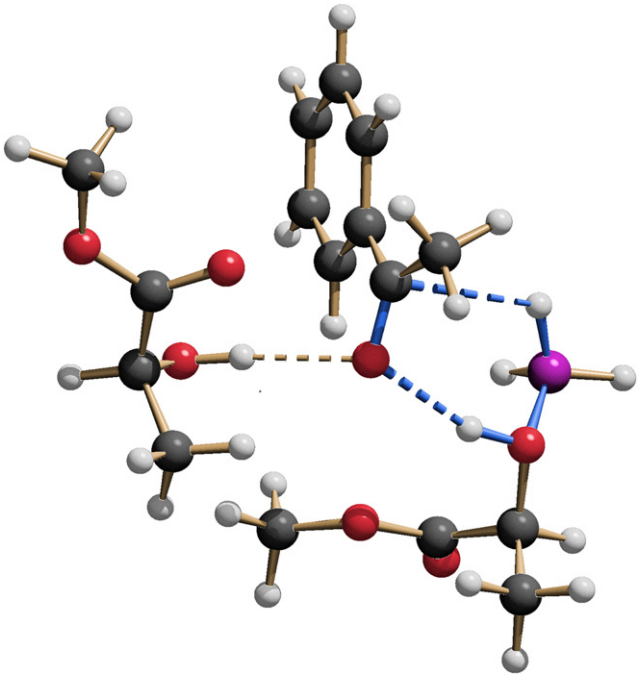


Figure 2. Calculated structure for the initial state for the enantioselective reduction of acetophenone with BH_3 in methyl lactate. The six-membered ring is shown in blue. The formation of the (*R*)-alcohol (as shown) is energetically preferred.

Applying the Boltzmann formula the calculated energy difference corresponds to an enantiomeric excess of 37% for the (*R*)-product at 0 °C, which is in striking accordance with the experimentally observed 31% ee. Within the limitation of theoretical methods and experimental errors, the accomplished calculations afforded astonishing conformity with the experimentally obtained enantioselectivities. As calculated, the experimentally determined ee increases with decreasing temperature down to −40 °C. For temperatures lower than −40 °C, calculations predicted a further increase in enantioselectivity, whereas the experimentally observed ees were reduced. This is probably due to the increasing viscosity of the reaction mixture, which eventually crystallized at temperatures below −60 °C. Hence, we performed the chiral solvent induced reductions by adding a solution of $BH_3 \cdot THF$ to acetophenone in methyl lactate at low temperatures. Addition of THF as a co-solvent lead to a considerable increase of reactivity most probably due to the better solubility and stirrability. However, with the dilution the enantioselectivity decreased significantly. This might be a consequence of weakening of the hydrogen-bond activation.

In the presence of a Lewis acid, closer interaction between the ketone and chiral solvent can be expected. Therefore, we added the $BH_3 \cdot THF$ solution to a mixture of acetophenone and $ZnCl_2$ in methyl lactate at −78 °C. This resulted in 78% conversion and the product was obtained with 50% ee. In comparison, an experiment without Lewis acid resulted in 44% conversion and 9% ee. Addition of an equivalent volume of the co-solvent THF to the methyl lactate at −78 °C improved the solubility and the conversion indeed becomes quantitative. Additionally, the enantioselectivity increased to 59% ee (Table 2).

Table 2. Conversion and enantiomeric excess observed in the reduction of acetophenone to (*R*)-phenylethanol in (*S*)-lactic acid methyl ester at −78 °C

Entry	Hydride source	Co-solvent	Lewis acid	Conversion (%)	ee (%)
1	BH_3	—	$ZnCl_2$	78	50
2	BH_3	THF	—	44	9
3	BH_3	THF	$ZnCl_2$	100	59
4	2/3 BH_3	THF	$ZnCl_2$	93	60
5	1/3 BH_3	THF	$ZnCl_2$	54	59

Conversion of the lactate induced reaction, however, was only quantitative when a threefold excess of hydride was added. Standard reaction conditions employing ketone to hydride ratios of 1:2 and 1:1 showed conversion of 93 and 54%, respectively, and the corresponding products were isolated in 60 and 59% ees. Presumably the reactivity of the three hydride equivalents of BH_3 is different due to the initially produced chiral borinic ester. A more detailed examination at −78 °C clearly displays a difference in the hydride transfer reactivity. Figure 3 shows the first-order kinetic plots with regard to the acetophenone concentration. In the case of equivalent amounts of ketone and BH_3 (a threefold excess of hydride) a clear slope for first-order kinetics is found. For the reactions with equal and twofold amount of hydride (2/3 BH_3 and 1/3 BH_3, respectively), it is not possible to determine which kinetics apply but each plot shows a clear two-slope behavior; the intersection points of the linear regression at about 4.2 and 3.5 indicate a change of the reaction kinetics at about 34 and 65% conversions, respectively.

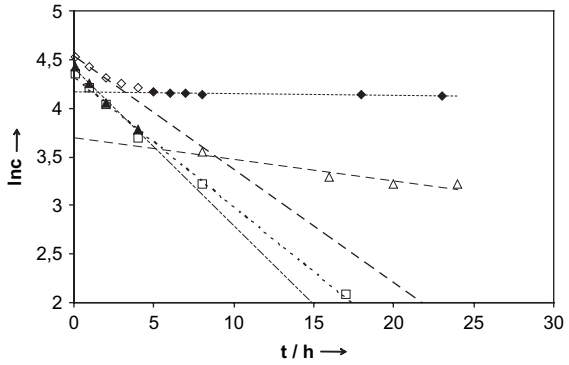


Figure 3. First-order plot of the reaction of acetophenone with different amounts of BH_3 in (*S*)-methyl lactate. BH_3 (1 equiv) (□), BH_3 (2/3 equiv) (△/▲), BH_3 (1/3 equiv) (◇/◆).

It can be concluded that the reaction rate of the first hydride is sufficiently high at −78 °C, whereas the rate of the second one is obviously slower. The rate slows down but by warming the reaction media up to ambient temperatures the second hydride's reactivity is increased. Presumably under these conditions it reacts at an appropriate rate with the ketone. Particularly noteworthy is the fact that this leads to the same enantioselectivity. This indicates that no detrimental effects on the enantioselection arise from the reaction of the primarily formed borinic ester. This is in contrast to the observations made without catalyst.

3. Conclusion

In summary, we here report a chiral solvent induced asymmetric hydroboration of ketones. Performing the borohydride reduction in (*S*)-lactic acid esters as the chiral solvent the resulting (*R*)-configured alcohol was obtained. The reaction outcome and enantioselectivity can be explained by a six-membered transition state **TS 2** (Figs. 1 and 2) which, in contrast to the earlier reported four-membered transition states **TS 1**, considers (*S*)-methyl lactate as the solvent and as the only possible chirality inducing source in the reaction medium. Addition of a Lewis acid to the chiral solvent even increased the enantioselectivities in the hydroboration procedure. Experiments to establish a more detailed mechanism of activation are currently in progress.

4. Experimental

In a three-necked flask, equipped with an adapter for N_2 and a pressure relief device, 10 mmol (1.3 g) $ZnCl_2$ were molten under N_2 and dissolved in 10 mL of the respective solvent or solvent mixture. The ketone (10 mmol) was added. The solution was cooled down to the reaction temperature. While stirring, 10 mL of a 1 M solution of BH_3 in THF were added dropwise via syringe to the mixture. The reaction mixture was kept at that temperature for at least 5 h and then allowed to slowly warm up to ambient temperature over night. In the case of the kinetic studies, the reaction was kept at −78 °C for the whole time. For the determination of conversion and enantiomeric excesses, 200 μL of the reaction mixture were hydrolyzed with 200 μL of water and the resulting clear solution was added onto a solid phase extraction tube Chromabond® XTR. Subsequent extraction using four times 1 mL of diethyl ether gave the samples, which were analyzed by GC. HP 5890 II/autosampler 6890 (250 °C); He 1 mL/min, Lipodex E, isotherm 100 °C, FID (300 °C).

Acknowledgements

We thank Norbert Schön for helpful discussions. S.H.H. is grateful for financial support from the ZFE Hochschule Darmstadt.

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Synthesis of bicyclic dioxetanes bearing a 2-hydroxy-1,1′-binaphthyl-5-yl moiety active toward intramolecular charge-transfer-induced chemiluminescent decomposition

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Received 24 August 2006; accepted 25 September 2006
Available online 27 October 2006

Abstract—Five pairs of diastereoisomeric dioxetanes, *cis*- and *trans*-**2a**–**2e**, were synthesized. These dioxetanes underwent intramolecular charge-transfer-induced decomposition with accompanying emission of orange light in TBAF in DMSO (*system **A***) as a complete homogeneous system and in [K⊂(18C6)]$^+$*t*-BuO$^-$ in PhH–THF (*system **B***) as a sterically anisotropic environment. Maximum wavelength (λ_{max}^{CTICL}) of chemiluminescence did not vary practically with the triggering system. The λ_{max}^{CTICL} was little affected also by substituents on the *upper-Nap* of dioxetanes **2**, nor by the difference in their stereochemistry, namely, *cis*- or *trans*-isomer. On the other hand, chemiluminescent efficiency was found to split up depending on stereochemistry of **2**. Dioxetane **2b** bearing a methoxycarbonyl group on the *upper-Nap* gave significantly weak light, while its free carboxylic acid analog **2c** afforded light effectively.

1. Introduction

A 2-substituted 1,1′-binaphthyl is a most promising functionality to construct optically active molecules and its fluorescence properties, which vary depending on the change of the dihedral angle between the two naphthyl groups is of much interest.[1] Such binaphthyl functionality should become a unique electron donor as well as the most influential part of an emitter, when introduced into a dioxetane active toward intramolecular charge-transfer-induced chemiluminescence (CTICL).[2–5] Thus, we attempted here to synthesize racemic dioxetanes bearing a 2-hydroxy-1,1′-binaphthyl-5-yl moiety and examined their CTICL decomposition as a fundamental investigation leading to studies of optically active dioxetanes.[6,7] Our design was based on an idea that a naphthyl group was introduced to the 2-hydroxynaphthyl moiety in a parent dioxetane, namely, 5-*tert*-butyl-1-(2-hydroxynaphthalen-5-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane **1**, which has very recently been found to exhibit chemiluminescence in high efficiency.[8] The thus-realized substrates were dioxetane **2a** bearing a rather simple 2-hydroxy-1,1′-binaphthyl-5-yl, dioxetane **2b** bearing a 2-hydroxy-2′-methoxy-3′-methoxycarbonyl-1,1′-binaphthyl, dioxetane **2c** bearing a 3′-carboxy-2-hydroxy-2′-methoxy-1,1′-binaphthyl moiety, and two 2′,3′-disubstituted 2-hydroxy-1,1′-binaphthyl analogs, **2d** and **2e**, which were synthesized from a precursor of **2b** (Fig. 1). The CTICL decomposition of these dioxetanes **2a**–**2e** was examined by the use of tetrabutylammonium fluoride (TBAF) in DMSO as a complete homogeneous system and by the use of a potassium *t*-butoxide complex of 18-crown-6 ether as a sterically anisotropic microenvironment in benzene (PhH)–THF.

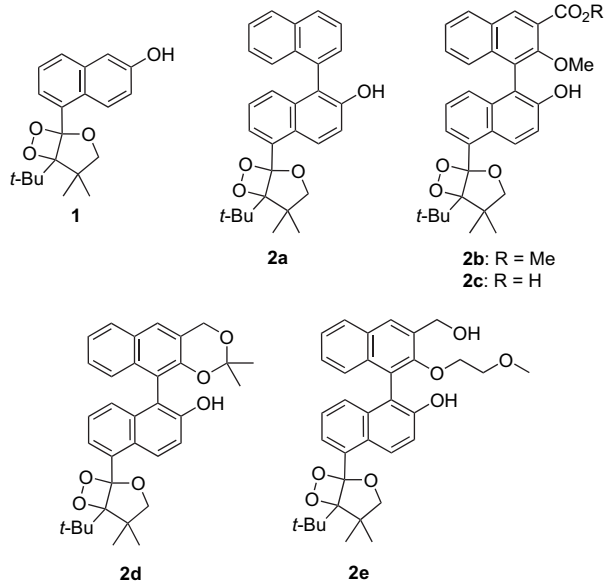

Figure 1.

Keywords: Dioxetane; Chemiluminescence; Binaphthyl; Crown ether.
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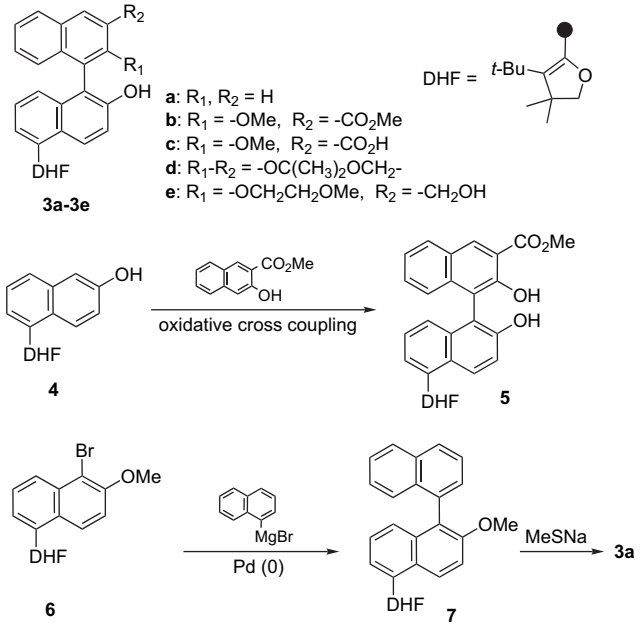
doi:10.1016/j.tet.2006.09.108

2. Results and discussion

2.1. Synthesis of bicyclic dioxetanes bearing a 2-hydroxy-1,1′-binaphthyl-5-yl moiety

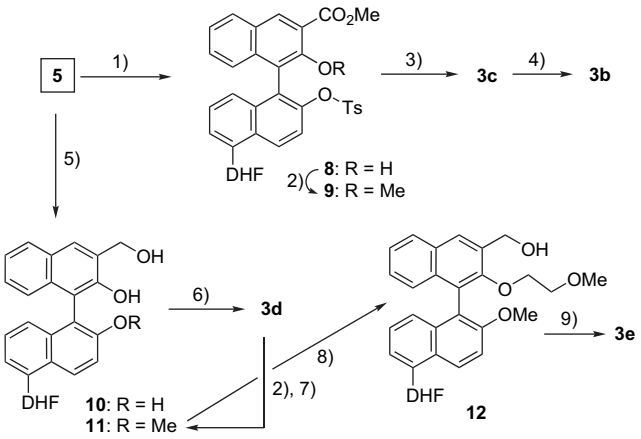
Synthesis of dioxetanes **2a–2e** was based on singlet oxygenation of the corresponding binaphthyl-substituted 4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofurans **3a–3e**. Since 5-aryl-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofurans have been known to undergo effectively 1,2-cycloaddition of singlet oxygen,[4,5] the synthesis of precursor dihydrofurans **3a–3e** was the step to be contrived carefully. Our synthetic strategy was to utilize dihydrofuran **5** bearing a 2,2′-dihydroxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-yl moiety as a key intermediate, since **5** has very recently been found to be effectively produced from 2-hydroxynaphthalen-5-yl-substituted dihydrofuran **4** by means of copper-catalyzed oxidative cross-coupling with methyl 3-hydroxynaphthalene-2-carboxylate (Scheme 1).[9] Thus, dihydrofurans **3b–3e** except **3a** were synthesized from **5** in several steps (vide infra).



Scheme 1.

Dihydrofuran **3a** substituted with a simple 2-hydroxy-1,1′-binaphthyl-5-yl group was synthesized by Pd-catalyzed cross-coupling[10] of dihydrofuran **6** bearing a 1-bromo-2-methoxynaphthalen-5-yl group with 1-naphthylmagnesium bromide giving dihydrofuran **7** bearing a 2-methoxy-1,1′-binaphthyl-5-yl group, and successive demethylation of the 2-methoxy group in **7** (Scheme 1).

The first step to synthesize **3b** bearing a 2-hydroxy-2′-methoxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-yl moiety from **5** was selective protection of the 2-hydroxy group into *p*-toluenesulfonate **8**. Next, the 2′-hydroxy group of **8** was methylated to give 2′-methoxy-derivative **9**, which was hydrolyzed into dihydrofuran **3c** bearing a 3′-carboxy-2-hydroxy-2′-methoxy-1,1′-binaphthyl-5-yl moiety. Finally, **3c** was esterified with methyl iodide and $NaHCO_3$ to afford **3b** (Scheme 2).



Scheme 2. Reagents and conditions: (1) TsCl/pyridine, (2) MeI/K_2CO_3, (3) NaOH, (4) MeI/$NaHCO_3$, (5) $LiAlH_4$, (6) $Me_2C(OMe)_2$/PPTS, (7) H_2O/TsOH/THF, (8) $MeOCH_2CH_2Br/K_2CO_3$, (9) MeSNa/DMF.

On the other hand, dihydrofuran **5** was reduced with $LiAlH_4$ to give dihydrofuran **10** bearing a 2,2′-dihydroxy-3′-hydroxymethyl-1,1′-binaphthyl-5-yl moiety, which was further treated with 2,2-dimethoxypropane to afford cyclic acetal **3d**. Williamson synthesis of **3d** with MeI followed by hydrolysis of acetal group gave dihydrofuran **11**, which was treated with 2-methoxyethyl bromide–K_2CO_3 to give dihydrofuran **12** bearing a 3′-hydroxymethyl-2-methoxy-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-yl moiety.[11] Demethylation of the 2-methoxy group with MeSNa gave dihydrofuran **3e** bearing a 2-hydroxy-3′-hydroxymethyl-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-yl moiety.

All dihydrofurans **3a–3e** synthesized here were obtained as a mixture of diastereomers, which could not be separated from each other. Therefore, 1,2-addition of singlet oxygen to **3** should afford the corresponding dioxetanes **2** also as a mixture of diastereomers, namely, *cis*-**2** in which both long wing of 1′-naphthyl (called *upper-Nap* for the sake of convenience) and O_7 of dioxetane O–O lie in the same side of the π-face of central hydroxynaphthyl ring, and *trans*-**2** in which the long wing of *upper-Nap* and the O_7 lie in the opposite side of the π-face to each other (Fig. 2). When a solution of dihydrofuran **3a** in CH_2Cl_2 was irradiated in the presence of a catalytic amount of tetraphenylporphin (TPP) with Na lamp under O_2 atmosphere at 0 °C for 1 h, dioxetane **2a** was selectively produced as a mixture of diastereomers (cis:trans=64:36), from which *cis*-**2a**, as the first fraction, and *trans*-**2a**, as the second fraction, were separated in pure form by column chromatography (SiO_2/hexane–AcOEt). Similar singlet oxygenation of dihydrofurans **3b–3e** gave the corresponding dioxetanes, **2b–2e** as a mixture of diastereomers (cis:trans=42:58 for **2b**, 48:52 for **2c**, 43:57 for **2d**, and 46:54 for **2e**). Chromatographic separation of the diastereomers afforded also *cis*-**2b–2e** and *trans*-**2b–2e** in pure form. The structures of these dioxetanes were determined by ^1H NMR, ^{13}C NMR, IR, mass spectral analyses and elemental analysis. Furthermore, X-ray single crystallographic analysis was successfully attained for *cis*-**2a**, *cis*-**2b**, *cis*-**2c**, *trans*-**2d**, and *cis*-**2e**. ORTEP views illustrated in Figure 3 show that two naphthyl rings lie in seriously twisted conformation for all these dioxetanes: dihedral angles θ (C_2–C_1–$C_{1'}$–$C_{2'}$) were 86.7° for *cis*-**2a**,

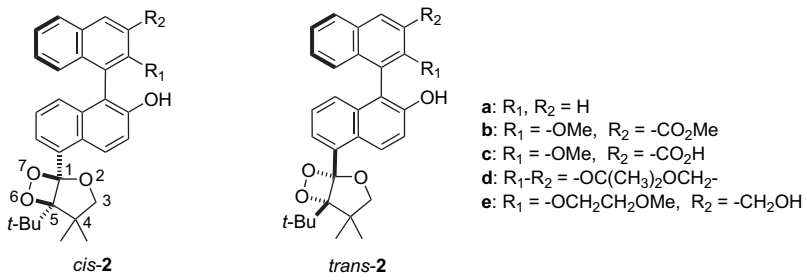


Figure 2.

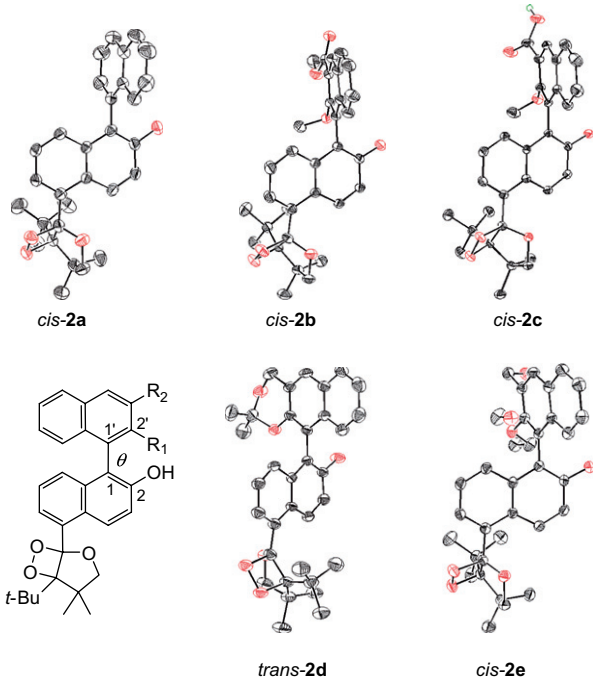


Figure 3. ORTEP views of dioxetane *cis*-**2a**, *cis*-**2b**, *cis*-**2c**, *trans*-**2d**, and *cis*-**2e**.

109.1° for *cis*-**2b**, 75.1° for *cis*-**2c**, 96.5° for *trans*-**2d**, and 76.5° for *cis*-**2e**.

2.2. Base-induced chemiluminescent decomposition of bicyclic dioxetanes bearing a 2-hydroxy-1,1′-binaphthyl-5-yl moiety

The parent dioxetane **1** bearing a 2-hydroxynaphthalen-5-yl moiety has been reported to undergo CTICL decomposition followed by a pseudo-first-order kinetics to give yellow light with maximum wavelength λ_{max}^{CTICL}=582 nm, when treated with a large excess of TBAF in DMSO.[8] Thus, we carried out first the CTICL decomposition of dioxetanes **2a**–**2e** in the TBAF in DMSO system (*system* ***A***) to evaluate their chemiluminescent properties in comparison with those of dioxetane **1**. When solutions of dioxetanes, *cis*-**2a** and *trans*-**2a** in DMSO (1.0×10^{-5} mol cm^{-3}, 1 mL) were added to solutions of TBAF in DMSO (1.0×10^{-2} mol cm^{-3}, 2 mL) at 25 °C, these diastereomeric dioxetanes decomposed rapidly to emit orange light with the same λ_{max}^{CTICL} (597 nm), though chemiluminescent efficiency (Φ^{CTICL}) and pseudo-first-order rate constant (k^{CTICL}) were somewhat different from each other. Then, the fluoride-induced chemiluminescent decomposition of dioxetanes, *cis*-**2b**–**2e** and *trans*-**2b**–**2e**, were carried out similarly. The results are summarized in Table 1, which reveals characteristic features for CTICL of **2** as follows. First, the introduction of the *upper-Nap* on the 2-hydroxynaphthyl ring of the parent dioxetane **1** caused a little red-shift of λ_{max}^{CTICL}s, which were observed at ca. 600 nm regardless of substituents on the *upper-Nap* ring. Secondly, Φ^{CTICL}s tended to decrease as substituent(s) was introduced into the *upper-Nap* ring of **2**, and the extreme was that for **2b**, Φ^{CTICL} of which was only 1/500–1/1000 of those for **1** and

Table 1. Base-induced chemiluminescent decomposition of bicyclic dioxetanes bearing a 2-hydroxy-1,1′-binaphthyl-5-yl moiety **2**[a]

Dioxetane		*System A*			*System B*		
		TBAF in DMSO			[K⊂(18C6)]$^+$*t*-BuO$^-$ in PhH–THF		
		λ_{max}^{CTICL}/nm	Φ^{CTICL} [b]	k^{CTICL}/s^{-1}	λ_{max}^{CTICL}/nm	Φ^{CTICL} [b]	k^{CTICL}/s^{-1}
2a	*cis*	597	1.6×10^{-2}	5.0×10^{-2}	594	9.2×10^{-3}	3.1×10^{-2}
	trans	597	1.8×10^{-2}	4.8×10^{-2}	594	8.8×10^{-3}	3.4×10^{-2}
2b	*cis*	600	2.0×10^{-5}	2.2×10^{-2}	600	9.7×10^{-3}	1.9×10^{-1}
	trans	600	1.8×10^{-5}	2.2×10^{-2}	600	7.5×10^{-3}	2.0×10^{-1}
2c	*cis*	609	8.5×10^{-3}	4.0×10^{-1}	600	9.4×10^{-3}	1.9×10^{-1}
	trans	609	9.3×10^{-3}	3.6×10^{-1}	600	7.4×10^{-3}	1.9×10^{-1}
2d	*cis*	600	9.2×10^{-3}	1.8×10^{-1}	595	6.9×10^{-3}	1.3×10^{-1}
	trans	600	1.1×10^{-2}	1.8×10^{-1}	595	6.2×10^{-3}	9.0×10^{-2}
2e	*cis*	600	1.7×10^{-2}	5.1×10^{-2}	595	7.2×10^{-3}	1.3×10^{-1}
	trans	600	1.2×10^{-2}	5.5×10^{-2}	595	5.5×10^{-3}	1.1×10^{-1}
1		582[c]	1.7×10^{-2}	3.7×10^{-2}	614	4.2×10^{-3}	4.5×10^{-2}

[a] Base-induced decompositions were carried out at 25 °C.
[b] Chemiluminescent efficiencies (Φ^{CTICL}) were based on the reported value for 3-(3-*tert*-butyldimethylsiloxyphenyl)-3-methoxy-4-(2′-spiroadamantane)-1,2-dioxetane (Φ^{CTICL}=0.29) (Ref. 12).
[c] Chemiluminescent properties for **1** in TBAF in DMSO summarized here are the values reported (Ref. 8).

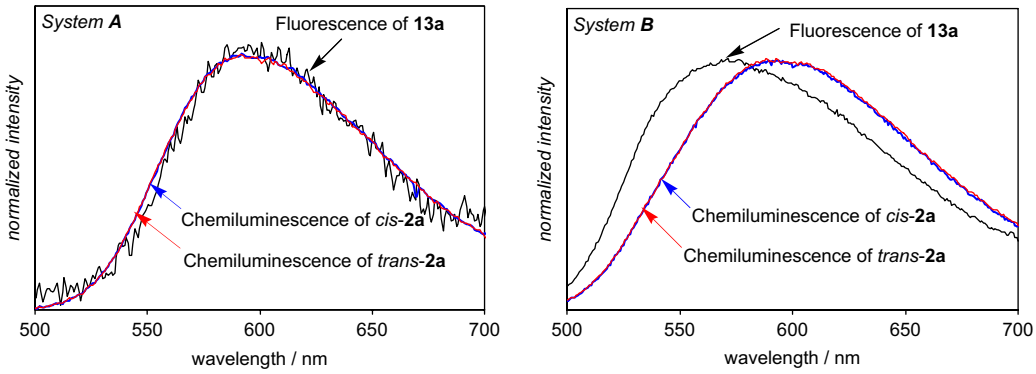
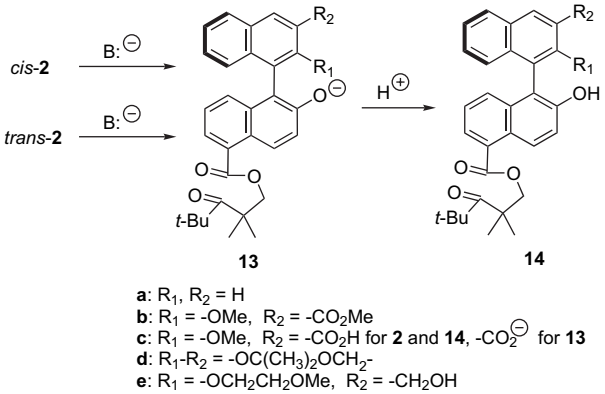


Figure 4. Chemiluminescent spectra of dioxetane **2a** and fluorescence spectra of keto ester **13a**.

the other dioxetanes **2a** and **2c**–**2e**. It should be noted that dioxetane **2c**, which is simply a carboxylic acid analog of **2b**, displayed chemiluminescence as effective as **2a**, **2d**, and **2e**. Thirdly, difference in configuration of the dioxetane, namely, cis- or trans-type, did not affect λ_{max}^{CTICL}, but caused apparently a split of Φ^{CTICL} and k^{CTICL} to some extent.

All spent mixtures of fluoride-induced decomposition of **2** in DMSO gave the corresponding keto esters of 1,1′-binaphthyl-5-carboxylic acid **14a**–**14e** in high isolated yields after neutralization; both *cis*-**2** and *trans*-**2** gave the same **14**. This fact shows that fluoride-induced decomposition of **2** produced undoubtedly oxido anion **13**. For instance, **13a** generated from the corresponding authentic keto esters, **14a** in TBAF in DMSO displayed fluorescence (efficiency $\Phi^{fl}=5.9\times10^{-2}$), the spectra of which coincided with the chemiluminescence spectra of the corresponding dioxetanes, *cis*-**2a** and *trans*-**2a** (Fig. 4). However, keto ester **14b** exhibited little observable fluorescence under similar conditions. This is a reason why Φ^{CTICL} was extremely low for **2b**, implying that Φ^{CTICL} is proportional to fluorescence efficiency of the emitter produced. On the other hand, keto ester **14c** would exist in TBAF in DMSO as a dianion form, and displayed fluorescence differently from **14b**. Conclusively, an electron-withdrawing ester function attached at the 3′-position of *upper-Nap* decreased fluorescence of **14b**, so that decreased significantly Φ^{CTICL} of **2b**, whereas its carboxylate anion did not deteriorate the fluorescence property of **13c** (Scheme 3).

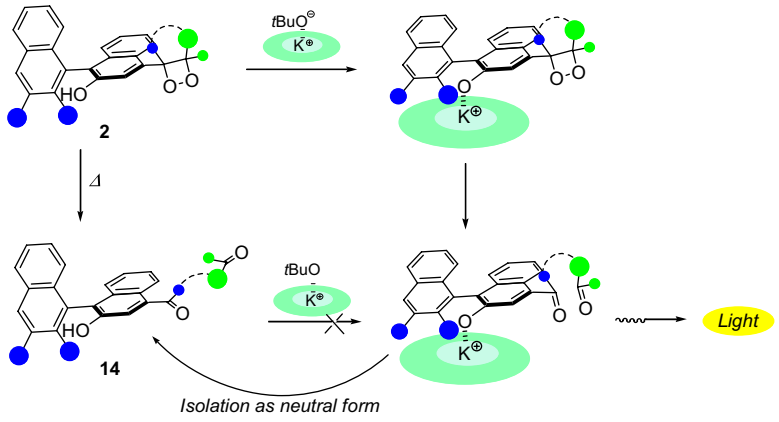


Scheme 3.

A complex of 18-crown-6 ether with *t*-BuOK, $[K\subset(18C6)]^{+}t\text{-}BuO^{-}$, provides a sterically anisotropic microenvironment to a ligand such as phenol and naphthol as they coordinate to it.[13–16] When dioxetane **1** was treated as a reference with a large excess of $[K\subset(18C6)]^{+}t\text{-}BuO^{-}$ in PhH–THF (1:1) (*system* ***B***) at 25 °C, **1** decomposed with accompanying emission of light with λ_{max}^{CTICL} at 614 nm, though Φ^{CTICL} decreased to 1/4 of the value in *system* ***A***. Chemiluminescent decomposition of **2a**–**2e** was examined similarly in *system* ***B***. The results are summarized in Table 1, which shows that the behavior of dioxetanes **2a**–**2e** in *system* ***B*** was considerably different from the case of **1**. Thus, λ_{max}^{CTICL}s did not change or rather shifted slightly to blue for **2**, whereas that for **1** shifted to red considerably as the base system changed from *system* ***A*** to *system* ***B***. Decrease of Φ^{CTICL}s was smaller for **2** than for **1** in *system* ***B***, and Φ^{CTICL}s were rather higher than that of **1**. Structural difference between diastereomers, *cis*-**2** and *trans*-**2**, caused difference in Φ^{CTICL} but not in λ_{max}^{CTICL} also for *system* ***B***. It should be noted here that difference in Φ^{CTICL} tended to expand in *system* ***B***, and its magnitude increased in the order of **2a**, **2c**≤**2d**<**2e**. Furthermore, weak diastereomeric recognition is apparently reflected in the singlet-chemiexcitation process for CTICL decomposition of **2**.

Table 1 shows that Φ^{CTICL} of **2b** appeared to increase surprisingly when the triggering system changed from *system* ***A*** to *system* ***B***. However, the spent reaction mixture after neutralization afforded free carboxylic acid **14c** but not ester **14b**. This fact suggests that hydrolysis of **2b** to dianion of **2c** took place far more rapidly than decomposition of **2b** into excited **13b**, and successive decomposition of **2c** occurred to emit light in *system* ***B***. The hydrolysis is presumably caused by a trace amount of water existing as hydroxide anion, which could hardly be excluded from *system* ***B*** in spite of careful experiment even under N_2 atmosphere, though such sensitivity was little observed for the other CTICLs.

Spent reaction mixtures from **2a**–**2e** except **2b** in *system* ***B*** gave the corresponding keto esters **14a** and **14c**–**14e** in high yields after neutralization. Therefore, emitters produced from dioxetanes were believed to be anionic keto esters **13** as in the case of *system* ***A***. However, all authentic anionic keto esters **13** generated from **14** displayed fluorescence spectra with λ_{max}^{fl}s at ca. 560 nm, which was considerably shorter than λ_{max}^{CTICL}s of chemiluminescent spectra from the corresponding dioxetanes **2** in *system* ***B***, as illustrated in Figure 4, where the case of **2a** and **13a** is shown as a



Scheme 4.

representative. The discrepancy between λ_{max}^{CTICL} and λ_{max}^{fl} suggests that excited keto ester **13** produced from dioxetane **2** lies presumably in conformation different from that of authentic **13** under the coordination to $[K\subset(18C6)]^+$. That is, dioxetane **2** produces most likely, in the coordination sphere, excited **13** retaining afterimage of stereochemistry of **2**, which could never be reproduced from authentic **14**, as illustrated in Scheme 4.

An AM1 MO calculation was indicative for the change of excitation energy depending on the conformational change of binaphthyl. Figure 5 illustrates the relationship of energy gap ($\Delta E=E_{LUMO}-E_{HOMO}$) with the dihedral angle (θ) for 2-oxido-1,1′-binaphthyl-5-carboxylic acid methyl ester as a model of **13a**. The calculation suggested for the model emitter that, as θ decreased from ca. 100°, ΔE increased so that emission shifted to blue more and more. Thus, the coordination to $[K\subset(18C6)]^+$ causes most likely decrease of θ larger for authentic **13** generated from **14** than for excited **13** produced from **2**.

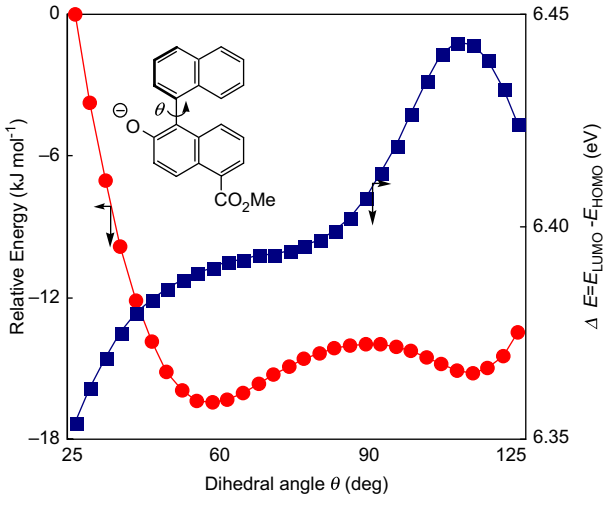


Figure 5. Relationship between ΔE and dihedral angle θ for 2-oxido-1,1′-binaphthyl-5-carboxylic acid methyl ester.

3. Conclusion

It was disclosed for CTICL decomposition of diastereoisomeric dioxetanes, *cis*-**2** and *trans*-**2**, in TBAF in DMSO (*system* ***A***) and in $[K\subset(18C6)]^+t$-BuO^- in PhH–THF (*system* ***B***) that λ_{max}^{CTICL} of chemiluminescence was little affected practically by the triggering system, the substituents on *upper-Nap*, nor their stereochemistry, whereas Φ^{CTICL} and k^{CTICL} split up depending on the stereochemistry of **2**. The bulk of substituents on *upper-Nap* was suggested to influence the magnitude of the split in Φ^{CTICL} between diastereoisomeric dioxetanes **2**. These findings provide a promising possibility that structural modification of dioxetanes **2d** and **2e** should lead to optically active dioxetanes that undergo CTICL decomposition responding to anisotropic microenvironment. The rather unexpected finding that very rapid hydrolysis of the ester function in **2b** into **2c** caused most likely significant increase of Φ^{CTICL} in *system* ***B*** may be useful to monitor hydrolysis of the ester function.

4. Experimental

4.1. General

Melting points were measured with a Yanako MP-S3 melting point apparatus and are uncorrected. IR spectra were taken on a JASCO FT/IR-300 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL EX-400 and JEOL EPC-500 spectrometers. Mass spectra were obtained by using JEOL JMS-AX-505H and JEOL JMS-T-100LC mass spectrometers. Elemental analysis was performed by means of Perkin–Elmer 2400II. Reagents were purchased from Aldrich, Tokyo Chemical Industries, Wako Pure Chemical Industries, and/or Kanto Chemical Industries. Column chromatography was carried out with silica gel, unless otherwise stated.

4.1.1. Synthesis of 4-*tert*-butyl-5-(2-methoxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (7). A solution of naphthalen-1-yl magnesium bromide, prepared from 1-bromonaphthalene (0.61 mL, 4.4 mmol) in dry THF (8 mL) was added dropwise to a suspension of 5-(5-bromo-6-methoxynaphthalen-1-yl)-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (**6**) (1.42 g, 3.65 mmol) and $Pd(PPh_3)_4$ (380 mg, 0.33 mmol) in dry THF (14 mL) under a nitrogen atmosphere for 20 min at refluxing temperature and then stirred for 7.5 h. The mixture was worked up as usual and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated

in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:40) to give dihydrofuran **7** (510 mg, 32.1%, conversion: 61.9%) as a colorless solid. Compound **7**: colorless plates melted at 137.0–137.5 °C (from AcOEt–hexane); (63:37 mixture of diastereomers) ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.07 (s, 9H×0.63), 1.08 (s, 9H×0.37), 1.43 (s, 3H), 1.51 (s, 3H), 3.72 (s, 3H), 4.01 (q_{AB}, J=6.4 Hz, 2H×0.37), 4.06 (q_{AB}, J=8.2 Hz, 2H×0.63), 7.09–7.16 (m, 2H), 7.20–7.46 (m, 6H), 7.56–7.61 (m, 1H), 7.89–7.93 (m, 2H), 8.10 (d with fine coupling, J=9.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3 and 27.4, 27.6 and 27.7, 32.1, 32.7, 47.4, 56.6, 83.3, 114.0 and 114.1, 123.2, 125.4 and 125.5, 125.6, 125.6 and 125.7, 125.8, 125.8 and 125.9, 126.2, 126.2 and 126.3, 127.4, 127.7, 127.7 and 127.8, 127.8 and 127.9, 128.1 and 128.2, 128.3 and 128.6, 132.9 and 133.0, 133.4 and 133.5, 133.6 and 133.7, 134.3 and 134.4, 134.5 and 134.6, 148.2, 154.5 ppm. IR (KBr): $\tilde{\nu}$ 2956, 2857, 1610, 1589, 1508, 1260, 1090, 1048 cm^{-1}. Mass (*m*/*z*, %): 436 (M^+, 80), 422 (36), 421 (100), 406 (16), 375 (19), 365 (17), 239 (10), 57 (19). HRMS (ESI): 459.2254, calcd for $C_{31}H_{32}O_2Na$ (M+Na$^+$) 459.2300. Anal. Calcd for $C_{31}H_{32}O_2$: C, 85.28; H, 7.39. Found: C, 84.90; H, 7.29.

4.1.2. Synthesis of 4-*tert*-butyl-5-(2-hydroxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (3a). Sodium methanethiolate (95%, 145 mg, 1.97 mmol) was added to a solution of 4-*tert*-butyl-5-(2-methoxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (**7**) (409 mg, 0.937 mmol) in dry DMF (4 mL) under a nitrogen atmosphere at room temperature and stirred for 1 h at 140 °C. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:4) to give dihydrofuran **3a** (363 mg, 91.7%) as a colorless solid. Compound **3a**: colorless granules melted at 199.5–200.0 °C (from AcOEt–hexane); (63:37 mixture of diastereomers) ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.06 (s, 9H×0.63), 1.08 (s, 9H×0.37), 1.44 (s, 3H), 1.52 (s, 3H), 4.01 (q_{AB}, J=7.8 Hz, 2H×0.37), 4.03 (q_{AB}, J=8.1 Hz, 2H×0.63), 4.86 (s, 1H×0.37), 4.90 (s, 1H×0.62), 7.04–7.08 (m, 1H), 7.15–7.20 (m, 1H), 7.26 (d with fine coupling, J=7.0 Hz, 1H), 7.30–7.41 (m, 3H), 7.47–7.55 (m, 1H), 7.58 (d with fine coupling, J=7.0 Hz, 1H), 7.63–7.68 (m, 1H), 7.96 (d, J=7.8 Hz, 1H), 7.98–8.03 (m, 1H), 8.02 (d, J=7.8 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3 and 27.4, 27.6 and 27.7, 32.1, 32.7, 47.4, 83.3, 117.7, 118.7 and 118.8, 125.6 and 125.7, 125.7, 125.7 and 125.9, 125.9 and 126.0, 126.4 and 126.5, 126.7 and 126.8, 127.6 and 127.7, 127.8, 127.8, 128.3 and 128.5, 129.1 and 129.2, 129.4 and 129.8, 131.5, 132.8, 132.9, 133.6 and 133.7, 133.9 and 134.0, 134.1, 148.1, 150.9 ppm. IR (KBr): $\tilde{\nu}$ 3512, 2955, 2865, 1614, 1590, 1469, 1386, 1300, 1197, 1050 cm^{-1}. Mass (*m*/*z*, %): 422 (M^+, 61), 408 (34), 407 (100), 392 (22), 377 (14), 351 (17), 239 (13), 57 (22). HRMS (ESI): 423.2334, calcd for $C_{30}H_{31}O_2$ (M+H$^+$) 423.2324. Anal. Calcd for $C_{30}H_{30}O_2$: C, 85.27; H, 7.16. Found: C, 85.06; H, 7.06.

4.1.3. Synthesis of 4-*tert*-butyl-5-[2′-hydroxy-3′-methoxycarbonyl-2-(4-methylphenylsulfonyloxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (8). *p*-Toluenesulfonyl chloride (944 mg, 4.95 mmol) was added to a solution of 4-*tert*-butyl-5-(2,2′-dihydroxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (**5**)[9] (2.03 g, 4.09 mmol) and triethylamine (2.9 mL, 21 mmol) in dry THF (10 mL) under a nitrogen atmosphere at room temperature and stirred for 25 h. The reaction mixture was added to satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2–hexane (1:1) to give dihydrofuran **8** (2.00 g, 75.1%) as a pale yellow solid. Compound **8**: pale yellow amorphous solid; (64:36 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.05 (s, 9H), 1.44 (s, 3H), 1.52 (s, 3H), 2.25 (s, 3H×0.64), 2.29 (s, 3H×0.36), 3.99 (d, J=7.8 Hz, 1H×0.36), 4.00 (d, J=7.8 Hz, 1H×0.64), 4.04–4.07 (m, 1H), 4.05 (s, 3H×0.36), 4.07 (s, 3H×0.64), 6.72 (d, J=8.7 Hz, 1H×0.64), 6.76–6.87 (m, 2H), 6.96 (d, J=7.8 Hz, 1H×0.36), 7.10–7.14 (m, 4H), 7.18–7.23 (m, 1H), 7.27–7.33 (m, 1H), 7.38–7.41 (m, 1H), 7.79–7.84 (m, 2H), 8.12 (s, 1H×0.64), 8.14 (s, 1H×0.36), 8.53 (s, 1H×0.36), 8.55 (s, 1H×0.64), 10.1 (s, 1H×0.36), 10.5 (s, 1H×0.64) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.5, 27.2 and 27.3, 27.5 and 27.6, 32.0 and 32.1, 32.7, 47.3 and 47.4, 52.5 and 52.6, 83.3, 113.4 and 113.5, 115.6 and 115.7, 121.9 and 122.0, 123.6 and 123.7, 124.6 and 124.7, 124.9 and 125.2, 125.9 and 126.0, 126.4 and 126.5, 126.9 and 127.0, 127.4 and 127.6, 127.9 and 128.0, 128.2 and 128.3, 128.5, 128.9 and 129.0, 129.1 and 129.3, 129.2 and 129.4, 130.9 and 131.1, 132.9 and 133.0, 133.1 and 133.2, 133.2, 133.9 and 134.0, 136.8 and 136.9, 144.1 and 144.2, 145.9 and 146.1, 147.4 and 147.6, 154.0 and 154.1, 170.0 and 170.1 ppm. IR (KBr): $\tilde{\nu}$ 3448, 2955, 2865, 1684, 1628, 1438, 1322, 1213, 1173, 1051 cm^{-1}. Mass (*m*/*z*, %): 650 (M^+, 69), 637 (13), 636 (49), 635 (100), 603 (28), 547 (31), 496 (21), 482 (19), 481 (51), 480 (25), 465 (30), 433 (19), 393 (18), 363 (14), 226 (19), 91 (45), 57 (29). HRMS (ESI): 673.2212, calcd for $C_{39}H_{38}O_7SNa$ (M+Na$^+$) 673.2236. Anal. Calcd for $C_{39}H_{38}O_7S$: C, 71.98; H, 5.89. Found: C, 71.77; H, 5.77.

4.1.4. Synthesis of 4-*tert*-butyl-5-[2′-methoxy-3′-methoxycarbonyl-2-(4-methyl-phenylsulfonyloxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (9). MeI (0.10 mL, 1.6 mmol) was added to a solution of 4-*tert*-butyl-5-[2′-hydroxy-3′-methoxycarbonyl-2-(4-methylphenylsulfonyloxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (**8**) (204 mg, 0.313 mmol) and K_2CO_3 (65 mg, 0.47 mmol) in dry DMF (2 mL) under a nitrogen atmosphere at room temperature and stirred for 1.5 h. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 to give dihydrofuran **9** (193 mg, 92.6%) as a pale yellow solid. Compound **9**: colorless plates melted at 189.0–189.5 °C (from EtOH–hexane); (64:36 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.02 (s, 9H×0.64), 1.08 (s, 9H×0.36), 1.44 (s, 3H), 1.53 (s, 3H), 2.23 (s, 3H×0.64), 2.26 (s, 3H×0.36), 3.32 (s, 3H×0.36), 3.41 (s, 3H×0.64), 3.99 (s, 3H×0.36), 4.00 (s, 3H×0.64), 4.01–4.09 (m, 2H), 6.71–6.91 (m, 3H), 7.02–7.25 (m, 5H), 7.35–7.43 (m, 2H), 7.83 (d, J=8.7 Hz, 1H), 7.87 (d, J=9.6 Hz, 1H), 8.16 (d, J=9.6 Hz, 1H), 8.39 (s, 1H×0.36), 8.41 (s, 1H×0.64) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.5, 27.3, 27.6, 31.9 and 32.1, 32.6 and 32.7,

47.5, 52.5, 61.8 and 61.9, 83.4 and 83.5, 121.8 and 121.9, 124.4 and 124.5, 124.6, 124.7 and 124.8, 125.2 and 125.3, 126.0 and 126.2, 126.3, 126.9 and 127.0, 127.1, 127.2, 128.2, 128.3 and 128.4, 128.5 and 128.6, 128.7, 129.0, 129.1 and 129.3, 130.7 and 130.8, 133.0 and 133.2, 133.4 and 133.5, 133.6, 134.0 and 134.1, 135.3, 144.2, 145.9 and 146.0, 147.3 and 147.4, 154.3 and 154.4, 166.8 ppm. IR (KBr): $\tilde{\nu}$ 2954, 2866, 1734, 1624, 1468, 1445, 1361, 1292, 1207, 1173, 1092 cm^{-1}. Mass (*m/z*, %): 664 (M^+, 79), 651 (17), 650 (43), 649 (100), 617 (21), 561 (19), 510 (19), 469 (12), 495 (32), 463 (19), 448 (13), 447 (33), 407 (13). HRMS (ESI): 687.2383, calcd for $C_{40}H_{40}O_7SNa$ (M+Na^+) 687.2392. Anal. Calcd for $C_{40}H_{40}O_7S$: C, 72.27; H, 6.06. Found: C, 72.23; H, 6.09.

4.1.5. Synthesis of 4-*tert*-butyl-5-(3′-carboxy-2-hydroxy-2′-methoxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (3c). NaOH (364 mg, 9.10 mmol) was added to a solution of 4-*tert*-butyl-5-[2′-methoxy-3′-methoxycarbonyl-2-(4-methylphenylsulfonyloxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (**9**) (840 mg, 1.26 mmol) in MeOH (5 mL) under a nitrogen atmosphere at room temperature and stirred at refluxing temperature for 4 h. The reaction mixture was poured into 1 N HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give dihydrofuran **3c** (577 mg, 92%) as a colorless solid. Compound **3c**: colorless granules melted at 235.5–236.5 °C (from AcOEt–hexane); (54:46 mixture of diastereomers) ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.03 (s, 9H×0.54), 1.07 (s, 9H×0.46), 1.44 (s, 3H), 1.52 (s, 3H), 3.45 (s, 3H×0.46), 3.46 (s, 3H×0.54), 4.00 (d, *J*=7.8 Hz, 1H×0.46), 4.01 (d, *J*=7.3 Hz, 1H×0.54), 4.05 (d, *J*=7.3 Hz, 1H×0.54), 4.06 (d, *J*=7.8 Hz, 1H×0.46), 5.66 (br s, 1H), 7.00–7.03 (m, 1H), 7.21–7.31 (m, 3H), 7.37–7.53 (m, 3H), 7.99 (br s, 1H), 8.09 (d, *J*=8.7 Hz, 1H), 8.81 (br s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3, 27.6 and 27.7, 31.9 and 32.0, 32.7, 47.4, 62.1 and 62.4, 83.3 and 83.4, 113.5, 118.3 and 118.4, 120.9, 123.3, 125.1, 125.3 and 125.6, 126.1 and 126.2, 126.5, 126.6 and 126.7, 127.9, 128.2 and 128.3, 129.0, 129.8, 129.9, 130.3 and 130.4, 133.6, 134.0, 136.4, 136.4, 147.7, 151.7, 154.1 and 154.2, 166.3 ppm. IR (KBr): $\tilde{\nu}$ 3357, 3181, 2957, 2864, 1729, 1687, 1620, 1449, 1298, 1230, 1044 cm^{-1}. Mass (*m/z*, %): 496 (M^+, 56), 495 (30), 482 (37), 481 (100), 466 (15), 453 (16), 407 (34), 371 (14), 277 (14), 266 (12), 57 (14). HRMS (ESI): 519.2166, calcd for $C_{32}H_{32}O_5Na$ (M+Na^+) 519.2147. Anal. Calcd for $C_{32}H_{32}O_5$: C, 77.40; H, 6.50. Found: C, 77.06; H, 6.41.

4.1.6. Synthesis of 4-*tert*-butyl-5-(2-hydroxy-2′-methoxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (3b). MeI (0.10 mL, 1.6 mmol) was added to a solution of 4-*tert*-butyl-5-(3′-carboxy-2-hydroxy-2′-methoxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (**3c**) (520 mg, 1.05 mmol) and $NaHCO_3$ (94 mg, 1.1 mmol) in dry DMF (5 mL) under a nitrogen atmosphere at room temperature and stirred overnight. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give dihydrofuran **3b** (486 mg, 90.8%) as a colorless solid. Compound **3b**: colorless needles melted at 178.5–179.5 °C (from EtOH–hexane); (58:42 mixture of diastereomers) ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.03 (s, 9H×0.58), 1.07 (s, 9H×0.42), 1.43 (s, 3H), 1.51 (s, 3H), 3.41 (s, 3H×0.42), 3.42 (s, 3H×0.58), 3.90 (s, 3H×0.42), 3.91 (s, 3H×0.58). 4.00 (d, *J*=8.2 Hz, 1H×0.42), 4.01 (d, *J*=7.8 Hz, 1H×0.58), 4.05 (d, *J*=7.8 Hz, 1H×0.58), 4.06 (d, *J*=8.2 Hz, 1H×0.42), 5.37 (s, 1H), 7.00–7.04 (m, 1H), 7.14–7.20 (m, 2H), 7.27 (d, *J*=6.9 Hz, 1H), 7.29–7.35 (m, 1H), 7.36 (d, *J*=9.2 Hz, 1H), 7.42–7.46 (m, 1H), 7.93 (d, *J*=8.2 Hz, 1H×0.58), 7.94 (d, *J*=7.8 Hz, 1H×0.42), 8.06 (d, *J*=9.2 Hz, 1H), 8.50 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.3, 27.5 and 27.6, 31.8 and 32.0, 32.6 and 32.7, 47.3, 52.4, 61.7 and 62.0, 83.2 and 83.3, 114.5, 118.3, 124.2 and 124.2, 125.1 and 125.3, 125.3, 125.4, 125.6 and 125.7, 125.8 and 125.9, 125.9 and 126.0, 127.8, 127.9 and 127.9, 128.3, 128.9, 129.1 and 129.2, 129.9 and 130.0, 133.7 and 133.8, 133.8, 133.9, 135.5 and 135.6, 147.9 and 148.0, 151.4, 155.0 and 155.1, 166.6 and 166.7 ppm. IR (KBr): $\tilde{\nu}$ 3427, 2954, 1678, 1618, 1452, 1365, 1307, 1237, 1052, 1006 cm^{-1}. Mass (*m/z*, %): 510 (M^+, 59), 496 (37), 495 (100), 480 (11), 407 (24). HRMS (ESI): 533.2292, calcd for $C_{33}H_{34}O_5Na$ (M+Na^+) 533.2304. Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.32; H, 6.71.

4.1.7. Synthesis of 4-*tert*-butyl-5-(2,2′-dihydroxy-3′-hydroxymethyl-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (10). A solution of 4-*tert*-butyl-5-(2,2′-dihydroxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (**5**) (501 mg, 1.01 mmol) in dry THF (2 mL) was added dropwise to a suspension of $LiAlH_4$ (61.3 mg, 1.62 mmol) in dry THF (5 mL) under a nitrogen atmosphere at 0 °C and stirred for 2 h at room temperature. The reaction mixture was poured into 2 N HCl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–CH_2Cl_2 (20:1) to give dihydrofuran **10** (411 mg, 86.9%) as a colorless solid. Compound **10**: colorless granules melted at 233.0–233.5 °C (from AcOEt); (55:45 mixture of diastereomers) ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.06 (s, 9H), 1.43 (s, 3H×0.55), 1.44 (s, 3H×0.45), 1.50 (s, 3H×0.55), 1.52 (s, 3H×0.45), 2.52 (m, 1H), 3.92 (d, *J*=8.0 Hz, 1H×0.55), 3.97 (d, *J*=8.0 Hz, 1H×0.55), 4.00 (d, *J*=7.8 Hz, 1H×0.45), 4.05 (d, *J*=7.8 Hz, 1H×0.45), 4.84 (dd, *J*=13.3 and 6.0 Hz, 1H×0.45), 4.89 (d, *J*=10.1 Hz, 1H×0.55), 4.90 (d, *J*=10.1 Hz, 1H×0.55), 4.94 (dd, *J*=13.3 and 5.3 Hz, 1H×0.45), 5.16 (s, 1H×0.55), 5.19 (s, 1H×0.45), 7.04 (m, 2H), 7.21–7.24 (m, 2H), 7.28–7.38 (m, 2H), 7.38 (d, *J*=9.2 Hz, 1H×0.55), 7.39 (d, *J*=9.2 Hz, 1H×0.45), 7.82–7.85 (m, 1H), 7.86 (s, 1H×0.45), 7.88 (s, 1H×0.55), 8.08 (d, *J*=9.2 Hz, 1H×0.55), 8.08 (d, *J*=9.2 Hz, 1H×0.45) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3, 27.6 and 27.7, 32.0 and 32.1, 32.7, 47.4, 62.6 and 62.9, 83.2 and 83.3, 111.2 and 111.4, 111.6 and 112.0, 118.1 and 118.2, 124.1 and 124.3, 124.4 and 124.5, 124.9 and 125.0, 126.3 and 126.4, 126.6 and 126.7, 127.3, 128.1, 128.1 and 128.3, 128.2 and 128.4, 128.5, 129.0, 129.1 and 129.2, 129.3, 133.0 and 133.3, 133.5 and 133.6, 134.1 and 134.1, 147.6 and 147.8, 151.2 and 151.4, 152.5 and 152.6 ppm. IR (KBr): $\tilde{\nu}$ 3405, 2957, 1618, 1391, 1208, 1047 cm^{-1}. Mass (*m/z*, %): 468 (M^+, 60), 454 (36), 453 (100), 451 (13), 420 (14), 403 (14), 379 (26). HRMS (ESI): 491.2185, calcd for

$C_{31}H_{32}O_4Na$ ($M+Na^+$) 491.2198. Anal. Calcd for $C_{31}H_{32}O_4$: C, 79.46; H, 6.88. Found: C, 79.27; H, 6.75.

4.1.8. Synthesis of 4-*tert*-butyl-5-[2-hydroxy-1-(2,2,-dimethyl-1,3-dioxa-1,2,3,4-tetrahydroanthracen-9-yl)-naphthalen-5-yl]-3,3-dimethyl-2,3-dihydrofuran (3d). Pyridinium *p*-toluenesulfonate (PPTS) (54.1 mg, 0.215 mmol) was added to a solution of 4-*tert*-butyl-5-(2,2′-dihydroxy-3′-hydroxymethyl-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (**10**) (1.01 g, 2.16 mmol) and acetone dimethyl acetal (0.32 mL, 2.6 mmol) in acetone (10 mL) under a nitrogen atmosphere at 0 °C and stirred for 1 h at refluxing temperature. The reaction mixture was poured into satd aq $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–CH_2Cl_2 (1:30) to give dihydrofuran **3d** (1.03 g, 93.5%) as a colorless solid. Compound **3d**: yellow plates melted at 182.5–183.0 °C (from AcOEt–hexane); (55:45 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.04 (s, 9H×0.45), 1.07 (s, 9H×0.55), 1.35 (s, 3H), 6.38 (s, 3H×0.45), 1.40 (s, 3H×0.55), 1.43 (s, 3H), 1.51 (s, 3H), 4.00 (d, J=8.2 Hz, 1H×0.45), 4.00 (d, J=7.8 Hz, 1H×0.55), 4.05 (d, J=7.8 Hz, 1H×0.55), 4.06 (d, J=8.2 Hz, 1H×0.45), 4.97 (s, 1H), 5.10 (q_{AB}, J=15.8 Hz, 2H×0.55), 5.10 (q_{AB}, J=15.1 Hz, 2H×0.45), 7.02–7.05 (m, 1H), 7.11–7.17 (m, 2H), 7.19–7.23 (m, 1H), 7.24 (d, J=6.9 Hz, 1H), 7.30–7.32 (m, 1H), 7.34 (d, J=9.2 Hz, 1H), 7.61 (s, 1H), 7.76 (d, J=8.2 Hz, 1H×0.45), 7.77 (d, J=8.2 Hz, 1H×0.55), 8.01 (d, J=9.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.1 and 24.3, 25.2 and 25.3, 27.3 and 27.4, 27.5 and 27.6, 31.9 and 32.0, 32.7, 47.3 and 47.3, 61.1 and 61.2, 83.2 and 83.3, 100.2 and 100.3, 114.3 and 114.4, 114.8 and 115.0, 117.8 and 117.8, 121.3 and 121.3, 124.2 and 124.3, 124.6 and 124.7, 124.8 and 124.8, 125.3 and 125.4, 125.5, 125.5 and 125.7, 126.7, 127.6 and 127.6, 127.7 and 127.7, 127.7, 127.9 and 127.9, 128.6, 133.1 and 133.2, 133.5, 133.8, 148.2 and 148.2, 148.7 and 148.8, 151.2 and 151.3 ppm. IR (KBr): $\tilde{\nu}$ 2955, 1614, 1371, 1275, 1051 cm^{-1}. Mass (*m*/*z*, %): 508 (M^+, 33), 451 (42), 450 (100), 436 (29), 435 (63), 420 (16), 403 (20), 379 (14). HRMS (ESI): 531.256, calcd for $C_{34}H_{36}O_4Na$ ($M+Na^+$) 531.2511. Anal. Calcd for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13. Found: C, 79.94; H, 7.10.

4.1.9. Synthesis of 4-*tert*-butyl-5-(2′-hydroxy-3′-hydroxymethyl-2-methoxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (11). MeI (0.60 mL, 9.6 mmol) was added to a solution of 4-*tert*-butyl-5-[2-hydroxy-1-(2,2,-dimethyl-1,3-dioxa-1,2,3,4-tetrahydroanthracen-9-yl)naphthalen-5-yl]-3,3-dimethyl-2,3-dihydrofuran (**3d**) (4.03 g, 7.92 mmol) and K_2CO_3 (1.64 g, 11.9 mmol) in dry DMF (40 mL) under a nitrogen atmosphere at room temperature and stirred for 9 h. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give 4.13 g of 4-*tert*-butyl-5-[2-methoxy-1-(2,2,-dimethyl-1,3-dioxa-1,2,3,4-tetrahydroanthracen-9-yl)naphthalen-5-yl]-3,3-dimethyl-2,3-dihydrofuran as a colorless solid. The solid (4.13 g), ethylene glycol (5.0 mL, 90 mmol), and $TsOH\cdot H_2O$ (150 mg, 0.789 mmol) was dissolved in dry THF (40 mL) under a nitrogen atmosphere at room temperature and refluxed for 3 h. The reaction mixture was poured into satd aq $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give dihydrofuran **11** (3.54 g, 92.8%) as a colorless solid. Compound **11**: pale yellow granules melted at 206.0–207.0 °C (from MeOH–CH_2Cl_2); (52:48 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.06 (s, 9H×0.48), 1.07 (s, 9H×0.52), 1.43 (s, 3H×0.48), 1.44 (s, 3H×0.52), 1.50 (s, 3H×0.48), 1.52 (s, 3H×0.52), 2.65 (br s, 1H), 3.74 (s, 3H×0.48), 3.75 (s, 3H×0.52), 3.95 (q_{AB}, J=8.0 Hz, 2H×0.48), 4.02 (q_{AB}, J=8.4 Hz, 2H×0.52), 4.86 (q_{AB}, J=13.3 Hz, 1H×0.52), 4.89 (q_{AB}, J=12.8 Hz, 1H×0.48), 5.70 (br s, 1H×0.48), 5.84 (br s, 1H×0.52), 6.95 (d, J=8.2 Hz, 1H×0.48), 7.10 (d, J=8.7 Hz, 1H×0.52), 7.10–7.23 (m, 3H), 7.25–7.31 (m, 2H), 7.48 (d, J=9.2 Hz, 1H×0.48), 7.49 (d, J=9.6 Hz, 1H×0.52), 7.77–7.81 (m, 2H), 8.17 (d, J=9.2 Hz, 1H×0.48), 8.18 (d, J=9.6 Hz, 1H×0.52) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3 and 27.3, 27.6 and 27.7, 32.0 and 32.1, 32.7, 47.4, 56.5 and 56.6, 62.9 and 63.1, 83.2 and 83.3, 114.1, 115.5 and 115.6, 115.8, 123.4 and 123.5, 124.5 and 124.9, 125.5 and 125.7, 126.2 and 126.3, 126.4, 126.4 and 126.5, 127.6, 127.9 and 128.1, 128.1 and 128.2, 128.2 and 128.3, 128.6 and 128.7, 128.8 and 128.9, 133.4 and 133.5, 133.8, 133.8, 134.0 and 134.1, 147.8 and 147.9, 149.9 and 150.0, 155.7 and 155.8 ppm. IR (KBr): $\tilde{\nu}$ 3364, 2954, 2866, 1613, 1508, 1395, 1264, 1215, 1085, 1049 cm^{-1}. Mass (*m*/*z*, %): 482 (M^+, 97), 481 (11), 480 (13), 468 (37), 467 (100), 466 (12), 465 (21), 452 (10), 449 (12), 434 (11), 403 (20), 394 (12), 393 (30), 374 (15), 370 (11), 279 (13), 239 (11), 57 (21). HRMS (ESI): 505.2330, calcd for $C_{32}H_{34}O_4Na$ ($M+Na^+$) 505.2355. Anal. Calcd for $C_{32}H_{34}O_4$: C, 79.64; H, 7.10. Found: C, 79.39; H, 7.07.

4.1.10. Synthesis of 4-*tert*-butyl-5-[3′-hydroxymethyl-2-methoxy-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (12). 2-Methoxyethyl bromide (0.65 mL, 6.9 mmol) was added to a solution of 4-*tert*-butyl-5-(2′-hydroxy-3′-hydroxymethyl-2-methoxy-1,1′-binaphthyl-5-yl)-3,3-dimethyl-2,3-dihydrofuran (**11**) (2.78 g, 5.76 mmol) and K_2CO_3 (1.30 g, 9.41 mmol) in dry DMF (30 mL) under a nitrogen atmosphere at room temperature and stirred for 12 h. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give dihydrofuran **12** (2.87 g, 92.2%) as a colorless solid. Compound **12**: colorless granules melted at 150.5–151.0 °C (from AcOEt–hexane); (52:48 mixture of diastereomers) ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.02 (s, 9H×0.52), 1.06 (s, 9H×0.48), 1.44 (s, 3H), 1.51 (s, 3H×0.52), 1.52 (s, 3H×0.42), 3.12–3.30 (m, 2H), 3.23 (s, 3H×0.52), 3.27 (s, 3H×0.48), 3.34–3.43 (m, 1H), 3.48–3.56 (m, 1H), 3.75 (s, 3H), 4.03 (q_{AB}, J=8.0 Hz, 2H×0.52), 4.04 (q_{AB}, J=7.3 Hz, 2H×0.48), 4.36 (t, J=7.1 Hz, 1H×0.48), 4.67 (t, J=7.1 Hz, 1H×0.52), 4.81–4.90 (m, 2H), 7.04–7.22 (m, 4H), 7.27 (d, J=6.4 Hz, 1H), 7.32–7.35 (m, 1H), 7.46 (d, J=9.6 Hz, 1H), 7.82 (d, J=8.2 Hz, 1H), 7.84 (s, 1H×0.48), 7.85 (s, 1H×0.52), 8.14 (d, J=9.2 Hz,

1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.2, 27.6 and 27.7, 31.8 and 31.9, 32.6 and 32.6, 47.3, 56.4 and 56.5, 58.5 and 58.6, 62.6 and 62.7, 71.3, 71.7 and 71.9, 83.3 and 83.3, 113.7 and 113.9, 119.3 and 119.4, 123.1 and 123.4, 124.5 and 124.6, 124.9 and 125.2, 126.0, 126.0, 126.0, 126.1 and 126.1, 127.8, 127.8 and 127.9, 128.0 and 128.1, 128.1, 128.9 and 129.1, 133.4 and 133.4, 133.9, 133.9 and 133.9, 134.0 and 134.2, 148.0 and 148.0, 154.3 and 154.8, 154.9, 154.9 ppm. IR (KBr): $\tilde{\nu}$ 3488, 2955, 2865, 1648, 1611, 1509, 1361, 1263, 1104, 1050 cm^{-1}. Mass (*m*/*z*, %): 540 (M^+, 100), 526 (16), 525 (37), 492 (15), 462 (10), 403 (18), 59 (16), 57 (12). HRMS (ESI): 563.2753, calcd for $C_{35}H_{40}O_5Na$ (M+Na^+) 563.2773. Anal. Calcd for $C_{35}H_{40}O_5$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.38.

4.1.11. Synthesis of 4-*tert*-butyl-5-[2-hydroxy-3′-hydroxymethyl-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (3e). Sodium methanethiolate (95%, 750 mg, 10.2 mmol) was added to a solution of 4-*tert*-butyl-5-[3′-hydroxymethyl-2-methoxy-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-yl]-3,3-dimethyl-2,3-dihydrofuran (**12**) (2.87 g, 5.33 mmol) in dry DMF (30 mL) under a nitrogen atmosphere at room temperature and stirred at 135 °C for 1 h. The reaction mixture was poured into satd aq $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1:1) to give dihydrofuran **3e** (1.65 g, 58.8%) as a colorless solid. Compound **3e**: colorless granules melted at 178.0–179.0 °C (from MeOH–CH_2Cl_2); (50:50 mixture of diastereomers) ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.00 (s, 9H×0.50), 1.05 (s, 9H×0.50), 1.43 (s, 3H), 1.51 (s, 3H×0.50), 1.52 (s, 3H×0.50), 3.11–3.15 (m, 1H×0.50), 3.20–3.27 (m, 1H×0.50), 3.21 (s, 3H×0.50), 3.24 (s, 3H×0.50), 3.29–3.39 (m, 1H), 3.42–3.52 (m, 2H), 4.03 (q_{AB}, J=7.8 Hz, 2H×0.5), 4.04 (q_{AB}, J=7.8 Hz, 2H×0.50), 4.50 (t, J=7.1 Hz, 1H×0.50), 4.75 (t, J=7.1 Hz, 1H×0.50), 4.78–4.84 (m, 2H), 5.64 (s, 1H×0.50), 5.65 (s, 1H×0.50), 7.09–7.28 (m, 5H), 7.34 (d, J=9.2 Hz, 1H), 7.37–7.40 (m, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.86 (d, J=2.7 Hz, 1H), 8.04 (d, J=9.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3, 27.6 and 27.7, 31.8 and 31.9, 32.6 and 32.7, 47.3, 58.6 and 58.7, 62.3 and 62.4, 71.5 and 71.6, 71.7 and 71.8, 83.3 and 83.4, 115.0 and 115.2, 118.0 and 118.1, 121.0 and 120.3, 124.6 and 125.0, 125.2 and 125.3, 125.6, 125.8 and 125.9, 126.1 and 126.2, 126.8 and 126.9, 127.7 and 127.8, 128.0 and 128.2, 128.1, 128.3 and 128.4, 130.2 and 130.5, 130.7 and 130.8, 133.6, 133.7, 133.8, 134.3 and 134.5, 147.9 and 148.0, 151.5 and 151.6, 155.5 and 155.9 ppm. IR (KBr): $\tilde{\nu}$ 3379, 3284, 2955, 2865, 1647, 1617, 1468, 1396, 1300, 1237, 1129, 1105 cm^{-1}. Mass (*m*/*z*, %): 526 (M^+, 100), 512 (26), 511 (66), 493 (10), 478 (17), 448 (10), 435 (11), 420 (16), 419 (12), 405 (14), 403 (19), 239 (10), 59 (36), 57 (17). HRMS (ESI): 549.2612, calcd for $C_{34}H_{38}O_5Na$ (M+Na^+) 549.2617. Anal. Calcd for $C_{34}H_{38}O_5$: C, 77.54; H, 7.27. Found: C, 77.83; H, 7.44.

4.2. Synthesis of bicyclic dioxetanes 2: general procedure

A solution of 5-(1,1′-binaphthyl-5-yl)-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran **3** (50–200 mg) and TPP (ca. 1 mg) in CH_2Cl_2 (3–10 mL) was irradiated externally with 940 W Na lamp under an oxygen atmosphere at 0 °C for 1–4 h. The photolysate was concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 to give a stereoisomeric mixture of 1-(1,1′-binaphthyl-5-yl)-5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane *cis*-**2** and *trans*-**2** as a colorless solid (cis:trans=64:36 for **2a**, 42:58 for **2b**, 48:52 for **2c**, 43:57 for **2d**, and 46:54 for **2e**) in 90–96% yields. The mixture was further separated into pure *cis*-**2** and pure *trans*-**2** by means of column chromatography (SiO_2).

4.2.1. 5-*tert*-Butyl-1-(2-hydroxy-1,1′-binaphthyl-5-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (2a). Compound *cis*-**2a**: colorless granules melted at 163.5–164.0 °C (from THF–AcOEt). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.96 (s, 9H), 1.33 (s, 3H), 1.69 (s, 3H), 4.13 (d, J=8.2 Hz, 1H), 4.73 (d, J=8.2 Hz, 1H), 4.90 (s, 1H), 7.17 (d, J=8.7 Hz, 1H), 7.23–7.33 (m, 3H), 7.35 (d, J=8.5 Hz, 1H), 7.51 (dd with fine coupling, J=8.3 and 6.9 Hz, 1H), 7.57 (d, J=6.9 Hz, 1H), 7.66 (dd, J=8.3 and 6.9 Hz, 1H), 7.97 (d, J=8.3 Hz, 1H), 8.03 (d, J=8.3 Hz, 1H), 8.06–8.07 (m, 1H), 8.67 (br d, J=8.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.1, 26.3, 26.8, 36.9, 45.7, 80.6, 106.0, 117.2, 117.7, 119.5, 125.2, 125.8, 125.9, 126.6, 127.0, 127.4, 128.0, 128.2, 128.4, 129.4, 129.6, 131.5, 131.5, 132.9, 134.2, 134.9, 150.5 ppm. IR (KBr): $\tilde{\nu}$ 3512, 2978, 2893, 1613, 1473, 1385, 1264, 1203, 1038, 994 cm^{-1}. Mass (*m*/*z*, %): 454 (M^+, 44), 398 (30), 314 (33), 298 (22), 297 (100), 269 (23), 268 (15), 252 (12), 251 (13). HRMS (ESI): 477.2032, calcd for $C_{30}H_{30}O_4Na$ (M+Na^+) 477.2042. Anal. Calcd for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.00; H, 6.66. Compound *trans*-**2a**: colorless granules melted at 163.0–164.0 °C (from THF–AcOEt). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.98 (s, 9H), 1.32 (s, 3H), 1.69 (s, 3H), 4.11 (d, J=8.3 Hz, 1H), 4.73 (d, J=8.3 Hz, 1H), 4.87 (s, 1H), 7.18 (d, J=8.3 Hz, 1H), 7.25 (dd, J=8.3 and 7.3 Hz, 1H), 7.31–7.39 (m, 3H), 7.50 (d, J=6.7 Hz, 1H), 7.54 (dd, J=7.8 and 7.3 Hz, 1H), 7.66 (dd, J=8.3 and 6.7 Hz, 1H), 7.99 (d, J=8.3 Hz, 1H), 8.04 (d, J=7.8 Hz, 1H), 8.04–8.06 (m, 1H), 8.68–8.70 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.1, 26.2, 26.8, 36.9, 45.7, 80.6, 106.0, 117.2, 118.7, 119.4, 125.2, 125.6, 126.1, 126.6, 126.7, 127.0, 127.4, 127.9, 128.2, 128.6, 129.4, 129.8, 131.5, 131.5, 132.8, 134.2, 135.0, 150.5 ppm. IR (KBr): $\tilde{\nu}$ 3412, 2979, 2902, 1616, 1599, 1473, 1387, 1211, 1038 cm^{-1}. Mass (*m*/*z*, %): 454 (M^+, 35), 398 (26), 314 (31), 298 (24), 297 (100), 269 (24), 268 (13), 251 (12), 250 (13), 239 (23), 57 (22). HRMS (ESI): 509.2339, calcd for $C_{31}H_{34}O_5Na$ (M+Na^++MeOH) 509.2304. Anal. Calcd for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 78.98; H, 6.60.

4.2.2. 5-*tert*-Butyl-1-(2-hydroxy-2′-methoxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (2b). Compound *cis*-**2b**: colorless plate melted at 170.0–171.0 °C (from AcOEt–hexane). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.91 (s, 9H), 1.32 (s, 3H), 1.68 (s, 3H), 3.42 (s, 3H), 3.96 (s, 3H), 4.14 (d, J=8.2 Hz, 1H), 4.75 (d, J=8.2 Hz, 1H), 5.14 (s, 1H), 7.13–7.17 (m, 2H), 7.25 (m, 1H), 7.36 (dd with fine coupling, J=9.6 and 6.9 Hz, 1H), 7.38 (d, J=9.6 Hz, 1H), 7.48 (dd with fine

coupling, J=8.3 and 6.9 Hz, 1H), 7.97 (d, J=8.3 Hz, 1H), 8.06–8.09 (m, 1H), 8.54 (s, 1H), 8.74–8.76 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.0, 26.1, 26.7, 36.8, 45.7, 52.5, 61.7, 80.6, 106.0, 115.1, 117.7, 117.7, 124.1, 125.2, 125.4, 125.5, 126.2, 126.8, 127.6, 127.7, 128.6, 129.1, 129.2, 130.0, 131.5, 134.1, 134.8, 135.5, 151.0, 155.1, 166.6 ppm. IR (KBr): $\tilde{\nu}$ 3406, 2960, 1704, 1620, 1269, 1224, 1003 cm^{-1}. Mass (*m*/*z*, %): 542 (M^+, 56), 510 (M^+-32, trace), 486 (12), 454 (13), 386 (28), 385 (100), 370 (23), 326 (19), 294 (15), 266 (24), 239 (13), 226 (12). HRMS (ESI): 565.2182, calcd for $C_{33}H_{34}O_7Na$ (M+Na^+) 565.2202. Anal. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32. Found: C, 72.76; H, 6.31. Compound *trans*-**2b**: colorless granules melted at 163.5–164.0 °C (from CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.97 (s, 9H), 1.33 (s, 3H), 1.69 (s, 3H), 3.43 (s, 3H), 3.98 (s, 3H), 4.13 (d, J=8.7 Hz, 1H), 4.74 (d, J=8.7 Hz, 1H), 5.10 (s, 1H), 7.12 (d, J=8.2 Hz, 1H), 7.16 (d, J=8.5 Hz, 1H), 7.20 (dd, J=8.5 and 7.0 Hz, 1H), 7.38 (d, J=9.6 Hz, 1H), 7.39 (dd, J=8.2 and 6.9 Hz, 1H), 7.50 (dd, J=8.2 and 6.9 Hz, 1H), 7.99 (d, J=8.2 Hz, 1H), 8.05–8.08 (m, 1H), 8.55 (s, 1H), 8.71–8.75 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.0, 26.2, 26.8, 36.9, 45.7, 52.5, 62.0, 80.6, 106.0, 115.1, 117.7, 124.0, 125.2, 125.4, 125.5, 126.1, 126.9, 127.6, 127.7, 128.7, 129.1, 129.3, 130.1, 131.6, 134.1, 134.8, 135.5, 151.0, 155.2, 166.6 ppm. IR (KBr): $\tilde{\nu}$ 3406, 2960, 1704, 1621, 1224, 1003 cm^{-1}. Mass (*m*/*z*, %): 542 (M^+, 45), 510 (M^+-32, trace), 486 (13), 454 (14), 386 (26), 385 (100), 326 (21), 297 (13), 294 (14), 278 (13), 266 (29), 239 (18), 226 (17), 57 (66). HRMS (ESI): 565.2199, calcd for $C_{33}H_{34}O_7Na$ (M+Na^+) 565.2202. Anal. Calcd for $C_{33}H_{34}O_7$+CH_2Cl_2 (3.0% w/w): C, 71.26; H, 6.20. Found: C, 70.97; H, 6.50.

4.2.3. 5-*tert*-Butyl-1-(3′-carboxy-2-hydroxy-2′-methoxy-1,1′-binaphthyl-5-yl)-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (2c). Compound *cis*-**2c**: colorless granules melted at 179.5–180.5 °C (from THF–hexane). ^{1}H NMR (400 MHz, acetone-d_6): δ_H 0.93 (s, 9H), 1.31 (s, 3H), 1.72 (s, 3H), 3.50 (s, 3H), 4.21 (d, J=8.2 Hz, 1H), 4.65 (d, J=8.2 Hz, 1H), 7.16–7.20 (m, 2H), 7.34 (dd, J=8.5 and 7.3 Hz, 1H), 7.42 (dd with fine coupling, J=8.3 and 6.8 Hz, 1H), 7.46 (d, J=9.3 Hz, 1H), 7.52 (dd with fine coupling, J=8.1 and 6.8 Hz, 1H), 7.99–8.02 (m, 1H), 8.12 (d, J=8.1 Hz, 1H), 8.61 (s, 1H), 8.79 (br d, J=9.3 Hz, 1H) ppm. ^{13}C NMR (125 MHz, acetone-d_6): δ_C 20.2, 26.2, 27.1, 37.5, 46.3, 61.7, 81.1, 106.6, 116.3, 118.4, 119.0, 125.8, 126.1, 126.2, 126.5, 126.9, 127.3, 127.6, 128.4, 129.2, 129.3, 130.0, 130.9, 132.6, 133.9, 136.2, 136.7, 153.5, 155.8, 167.3 ppm. IR (KBr): $\tilde{\nu}$ 3412, 3126, 2976, 2911, 1735, 1619, 1590, 1446, 1355, 1224, 1038 cm^{-1}. Mass (*m*/*z*, %): 528 (M^+, 25), 500 (14), 472 (14), 386 (15), 385 (42), 372 (28), 371 (100), 370 (19), 356 (15), 343 (26), 327 (18), 326 (28), 294 (17), 267 (20), 266 (27), 255 (16), 239 (26), 226 (23), 57 (55). HRMS (ESI): 551.2059, calcd for $C_{32}H_{32}O_7Na$ (M+Na^+) 551.2046. Anal. Calcd for $C_{32}H_{32}O_7$: C, 72.71; H, 6.10. Found: C, 72.32; H, 6.50. Compound *trans*-**2c**: colorless granules melted at 175.0–175.5 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, acetone-d_6): δ_H 0.96 (s, 9H), 1.31 (s, 3H), 1.73 (s, 3H), 3.54 (s, 3H), 4.18 (d, J=8.2 Hz, 1H), 4.63 (d, J=8.2 Hz, 1H), 7.15 (d, J=8.7 Hz, 1H), 7.19 (d, J=8.7 Hz, 1H), 7.33 (dd, J=8.7 and 7.3 Hz, 1H), 7.40 (dd with fine coupling, J=8.7 and 6.7 Hz, 1H), 7.46 (d, J=9.6 Hz, 1H), 7.52 (dd, J=7.8 and 6.7 Hz, 1H), 7.98–8.01 (m, 1H), 8.12 (d, J=7.8 Hz, 1H), 8.60 (s, 1H), 8.76–8.79 (m, 1H) ppm. ^{13}C NMR (125 MHz, acetone-d_6): δ_C 20.2, 26.3, 27.1, 37.5, 46.4, 61.9, 81.1, 106.7, 116.4, 117.3, 119.0, 125.8, 125.9, 126.3, 126.5, 127.0, 127.3, 127.6, 128.4, 129.2, 129.4, 130.1, 131.0, 132.8, 133.9, 136.2, 136.8, 153.5, 155.8, 167.3 ppm. IR (KBr): $\tilde{\nu}$ 3421, 3200, 2976, 2892, 1717, 1620, 1591, 1447, 1400, 1370, 1274, 1225, 1038 cm^{-1}. Mass (*m*/*z*, %): 528 (M^+, 37), 500 (23), 472 (17), 444 (15), 386 (23), 385 (68), 372 (26), 371 (100), 370 (31), 356 (14), 343 (46), 327 (23), 326 (34), 294 (22), 267 (19), 266 (40), 255 (21), 239 (30), 226 (30), 57 (95). HRMS (ESI): 551.2039, calcd for $C_{32}H_{32}O_7Na$ (M+Na^+) 551.2046. Anal. Calcd for $C_{32}H_{32}O_7$+H_2O (1.7% w/w): C, 71.49; H, 6.19. Found: C, 71.17; H, 6.30.

4.2.4. 5-*tert*-Butyl-1-[2-hydroxy-1-(2,2-dimethyl-1,3-dioxa-1,2,3,4-tetrahydro-anthracen-9-yl)naphthalen-5-yl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (2d). Compound *cis*-**2d**: colorless needles melted at 145.0–146.0 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.91 (s, 9H), 1.32 (s, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.67 (s, 3H). 4.13 (d, J=8.5 Hz, 1H), 4.75 (d, J=8.5 Hz, 1H), 4.84 (s, 1H), 5.16 (q_{AB} with fine coupling, J=15.1 Hz, 2H), 7.14–7.19 (m, 2H), 7.21–7.28 (m, 2H), 7.34 (d, J=9.3 Hz, 1H), 7.36 (dd with fine coupling, J=8.1 and 6.8 Hz, 1H), 7.69 (s, 1H), 7.82 (d, J=8.1 Hz, 1H), 8.02–8.05 (m, 1H), 8.69–8.73 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.0, 24.3, 25.2, 26.1, 26.7, 36.8, 45.7, 61.2, 80.6, 100.2, 106.0, 114.9, 115.0, 117.3, 117.8, 121.3, 124.4, 124.6, 124.8, 124.9, 126.8, 127.0, 127.3, 127.8, 127.9, 127.9, 128.6, 131.1, 133.0, 134.8, 148.8, 150.8 ppm. IR (KBr): $\tilde{\nu}$ 3500, 2993, 1617, 1371, 1135, 1039 cm^{-1}. Mass (*m*/*z*, %): 540 (M^+, 10), 539 (27), 482 (35), 481 (100), 425 (17), 382 (13), 341 (19), 326 (23), 325 (91), 324 (31), 297 (11), 296 (11), 239 (11), 57 (22). HRMS (ESI): 563.2413, calcd for $C_{34}H_{36}O_6Na$ (M+Na^+) 563.2410. Anal. Calcd for $C_{34}H_{36}O_4$+H_2O (2.5% w/w): C, 73.62; H, 6.82. Found: C, 73.26; H, 6.91. Compound *cis*-**2d**: colorless granules melted at 165.0–165.5 °C (from AcOEt–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (s, 9H), 1.33 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.70 (s, 3H), 4.13 (d, J=8.3 Hz, 1H), 4.74 (d, J=8.3 Hz, 1H), 4.88 (s, 1H), 5.16 (q_{AB} with fine coupling, J=15.4 Hz, 2H), 7.09 (d, J=8.3 Hz, 1H), 7.15 (d, J=8.4 Hz, 1H), 7.24 (dd, J=8.3 and 7.3 Hz, 1H), 7.26 (dd with fine coupling, J=8.4 and 7.3 Hz, 1H), 7.34 (d, J=9.5 Hz, 1H), 7.36 (dd with fine coupling, J=8.1 and 6.8 Hz, 1H), 7.69 (s, 1H), 7.82 (d, J=8.1 Hz, 1H), 8.00–8.04 (m, 1H), 8.66–8.68 (br d, J=9.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.1, 24.2, 25.3, 26.2, 26.8, 36.9, 45.7, 61.4, 80.6, 100.4, 105.9, 114.7, 115.1, 117.3, 117.8, 121.4, 124.3, 124.4, 124.9, 125.0, 126.8, 127.3, 127.8, 127.9, 128.0, 128.7, 131.3, 133.2, 134.8, 148.9, 150.8 ppm. IR (KBr): $\tilde{\nu}$ 3416, 2979, 1617, 1371, 1268, 1133, 1046 cm^{-1}. Mass (*m*/*z*, %): 540 (M^+, 9), 539 (24), 507 (10), 482 (34), 481 (95), 449 (35), 434 (23), 425 (17), 382 (14), 341 (20), 325 (27), 324 (100), 323 (35), 298 (10), 297 (15), 295 (11), 239 (12), 162 (12), 57 (33). HRMS (ESI): 595.2686, calcd for $C_{35}H_{40}O_7Na$ (M+Na^++MeOH) 595.2672. Anal. Calcd for $C_{34}H_{36}O_4$+AcOEt (2.0% w/w): C, 75.11; H, 6.76. Found: C, 74.81; H, 6.75.

4.2.5. 5-*tert*-Butyl-1-[2-hydroxy-3′-hydroxymethyl-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-yl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (2e). Compound *cis*-**2e**: colorless granules melted at 165.5–166.0 °C (from THF–MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (s, 9H), 1.32 (s, 3H), 1.67 (s, 3H), 3.20 (ddd, *J*=10.8, 6.2, and 2.3 Hz, 1H), 3.05 (s, 3H), 3.30 (ddd, *J*=10.8, 6.0, and 2.3 Hz, 1H), 3.37 (ddd, *J*=10.8, 6.2, and 2.3 Hz, 1H), 3.45 (ddd, *J*=10.8, 6.0, and 2.3 Hz, 1H), 4.15 (br d, *J*=8.2 Hz, 1H), 4.48 (br s, 1H), 4.75 (d, *J*=8.2 Hz, 1H), 4.87 (m, 2H), 5.11 (s, 1H), 7.17 (d, *J*=8.2 Hz, 1H), 7.25 (dd, *J*=8.2 and 6.9 Hz, 1H), 7.30 (dd, *J*=8.2 and 6.9 Hz, 1H), 7.32 (d, *J*=8.2 Hz, 1H), 7.36 (d, *J*=9.6 Hz, 1H), 7.44 (dd with fine coupling, *J*=8.2 and 6.9 Hz, 1H), 7.90 (d, *J*=8.2 Hz, 1H), 7.95 (s, 1H), 8.08–8.10 (m, 1H), 8.75–8.78 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.0, 26.1, 26.8, 36.8, 45.7, 58.8, 62.5, 71.6, 71.7, 80.7, 105.9, 115.8, 117.5, 120.0, 124.8, 125.6, 125.8, 126.8, 127.2, 127.7, 127.9, 128.3, 128.7, 128.8, 130.7, 130.8, 131.4, 133.5, 134.6, 134.7, 151.1, 155.7 ppm. IR (KBr): $\tilde{\nu}$ 3307, 2961, 1618, 1516, 1400, 1335, 1234, 1104, 1040, 1020 cm^{-1}. Mass (*m*/*z*, %): 558 (M^+, 68), 540 (15), 402 (18), 401 (71), 339 (14), 372 (14), 342 (19), 325 (33), 324 (31), 297 (16), 296 (17), 269 (19), 239 (31), 59 (100), 57 (58). HRMS (ESI): 581.2503, calcd for $C_{34}H_{38}O_7Na$ (M+Na^+) 581.2515. Anal. Calcd for $C_{34}H_{38}O_7$: C, 73.10; H, 6.86. Found: C, 72.91; H, 6.70. Compound *trans*-**2e**: colorless granules melted at 165.0–166.0 °C (from THF–MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.96 (s, 9H), 1.33 (s, 3H), 1.69 (s, 3H), 3.25 (ddd, *J*=10.8, 5.8, and 2.3 Hz, 1H), 3.31 (s, 3H), 3.34 (ddd, *J*=10.8, 6.4, and 2.3 Hz, 1H), 3.27 (ddd, *J*=10.8, 6.4, and 2.3 Hz, 1H), 3.48 (ddd, *J*=10.8, 5.8, and 2.3 Hz, 1H), 4.13 (d, *J*=8.5 Hz, 1H), 4.69 (br s, 1H), 4.75 (d, *J*=8.5 Hz, 1H), 4.86 (s, 2H), 5.11 (s, 1H), 7.90 (d, *J*=8.7 Hz, 1H), 7.25–7.32 (m, 3H), 7.36 (d, *J*=9.6 Hz, 1H), 7.43 (dd with fine coupling, *J*=7.8 and 7.3 Hz, 1H), 7.90 (d, *J*=7.8 Hz, 1H), 7.95 (s, 1H), 8.07–8.10 (m, 1H), 8.73–8.75 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.0, 26.1, 26.8, 36.9, 45.7, 58.8, 62.5, 71.7, 71.8, 80.6, 106.0, 115.8, 117.5, 117.7, 119.9, 124.6, 125.4, 125.7, 126.8, 127.1, 127.7, 128.0, 128.3, 128.7, 130.8, 130.9, 131.5, 133.6, 134.7, 134.7, 151.1, 155.9 ppm. IR (KBr): $\tilde{\nu}$ 3421, 2976, 1618, 1474, 1400, 1370, 1234, 1106, 1038 cm^{-1}. Mass (*m*/*z*, %): 558 (M^+, 50), 402 (18), 401 (56), 339 (17), 372 (13), 342 (18), 325 (28), 324 (26), 298 (13), 297 (20), 296 (12), 269 (19), 252 (12), 239 (31), 141 (13), 59 (100). HRMS (ESI): 581.2511, calcd for $C_{34}H_{38}O_7Na$ (M+Na^+) 581.2515. Anal. Calcd for $C_{34}H_{38}O_7$+CH_3OH (2.1% w/w): C, 72.35; H, 6.98. Found: C, 72.02; H, 7.07.

4.3. Chemiluminescence measurement: general procedure

Chemiluminescence were measured using a Hamamatsu Photonics PMA-11 multi-channel detector and/or JASCO FP-750 spectrometer.

TBAF in DMSO (*system* ***A***): freshly prepared solution (2 mL) of TBAF (1.0×10^{-2} mol cm^{-3}) in DMSO was transferred to a quartz cell (10×10×50 mm) and the latter placed in the spectrometer, which was thermostated with stirring at 25 °C. After 3–5 min, a solution of the dioxetane in DMSO (1.0×10^{-5} mol cm^{-3}, 1 mL) was added by means of a syringe with immediate starting of measurement. The intensity of the light emission time-course was recorded and processed according to first-order kinetics. The total light emission was estimated by comparing it with that of an adamantylidene dioxetane, whose chemiluminescent efficiency Φ^{CTICL} has been reported to be 0.29 and was used here as a standard.[12]

[K⊂(18C6)]$^+$*t*-BuO$^-$ in PhH–THF (1:1) (*system* ***B***): *t*-BuOK (1.0 mol cm^{-3} in THF, 2 mL, 2 mmol) was added to a solution of 18-crown-6 ether (555 mg, 2.10 mmol) in dry benzene (10 mL) and dry THF (8 mL) at room temperature under a nitrogen atmosphere and stirred for 10 min. Chemiluminescence measurement using the solution of 18-crown–ether complex of *t*-BuOK in PhH–THF was carried out similarly to the case of *system* ***A***.

4.4. Isolation of keto esters 14 from the spent reaction mixture after chemiluminescent decomposition of dioxetanes 2: general procedure

A solution of the dioxetane **2** (20–30 mg) in DMSO (3 mL) was added to a solution of TBAF (1 M in THF, 0.1 mL) in DMSO (0.9 mL) at room temperature under nitrogen atmosphere. After stirring for 1 h, the reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. ^{1}H NMR spectral analysis showed that the residue was comprised of keto ester **14** without detectable amount of other products. The residue was purified by column chromatography on silica gel with AcOEt–hexane to give the corresponding keto ester **14**.

4.4.1. 2,2,4,4-Tetramethyl-3-oxopentyl 2-hydroxy-1,1′-binaphthyl-5-carboxylate (14a). Colorless granules melted at 174.0–174.5 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.43 (s, 6H), 4.50 (s, 2H), 5.06 (br s, 1H), 7.19–7.22 (m, 1H), 7.25–7.35 (m, 3H), 7.43 (d, *J*=9.6 Hz, 1H), 7.49–7.52 (m, 2H), 7.61–7.65 (m, 1H), 7.89 (d with fine coupling, *J*=6.9 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 8.01 (d, *J*=8.2 Hz, 1H), 8.95 (d, *J*=9.6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 28.2, 45.9, 49.2, 72.3, 119.0, 119.1, 125.2, 125.6, 126.0, 126.6, 126.7, 126.9, 127.2, 127.3, 127.7, 128.5, 129.4, 129.6, 130.1, 131.2, 132.8, 134.1, 134.5, 151.1, 167.5, 216.1 ppm. IR (KBr): $\tilde{\nu}$ 3411, 2974, 1719, 1685, 1668, 1512, 1366, 1262, 1136 cm^{-1}. Mass (*m*/*z*, %): 454 (M^+, 56), 399 (10), 398 (33), 314 (39), 298 (33), 297 (100), 269 (27), 268 (16), 252 (13), 251 (14), 250 (18), 239 (29), 57 (39). HRMS (ESI): 509.2292, calcd for $C_{31}H_{34}O_5Na$ (M+Na^++MeOH) 509.2304. Anal. Calcd for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 78.86; H, 6.59.

4.4.2. 2,2,4,4-Tetramethyl-3-oxopentyl 2-hydroxy-2′-methoxy-3′-methoxycarbonyl-1,1′-binaphthyl-5-carboxylate (14b). Colorless granules melted at 149.0–149.5 °C (from AcOEt–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.30 (s, 9H), 1.44 (s, 6H), 3.46 (s, 3H), 3.96 (s, 3H), 4.50 (q_{AB}, *J*=11.0 Hz, 2H), 5.31 (br s, 1H), 7.15 (d, *J*=8.7 Hz, 1H), 7.21–7.26 (m, 2H), 7.36 (dd with fine coupling, *J*=7.8 and 7.7 Hz, 1H), 7.47 (d, *J*=9.2 Hz, 1H), 7.48 (dd, *J*=7.7 and 6.9 Hz, 1H), 7.90 (d with fine coupling,

J=6.9 Hz, 1H), 7.97 (d, J=7.8 Hz, 1H), 8.55 (s, 1H), 8.78 (d, J=9.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 23.8, 28.2, 45.9, 49.2, 52.5, 62.0, 72.3, 114.9, 119.5, 123.8, 125.2, 125.2, 125.5, 126.2, 126.9, 127.5, 127.5, 128.2, 129.1, 129.3, 129.8, 130.0, 134.2, 134.3, 135.5, 151.6, 155.2, 166.6, 167.4, 216.1 ppm. IR (KBr): $\tilde{\nu}$ 3431, 2955, 1716, 1687, 1620, 1446, 1365, 1308, 1251, 1136, 1061 cm^{-1}. Mass (*m*/*z*, %): 542 (M^+, 63), 486 (11), 454 (10), 386 (28), 385 (100), 370 (19), 326 (16), 294 (12), 266 (16), 57 (31). HRMS (ESI): 565.2186, calcd for $C_{33}H_{34}O_7Na$ (M+Na^+) 565.2202. Anal. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32. Found: C, 72.97; H, 6.30.

4.4.3. 2,2,4,4-Tetramethyl-3-oxopentyl 3′-carboxy-2-hydroxy-2′-methoxy-1,1′-binaphthyl-5-carboxylate (14c). Colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.30 (s, 9H), 1.45 (s, 6H), 3.50 (s, 3H), 4.51 (s, 2H), 5.32 (br s, 1H), 7.22 (d, J=8.5 Hz, 1H), 7.25–7.31 (m, 2H), 7.45 (dd, J=8.1 and 6.8 Hz, 1H), 7.47 (d, J=9.5 Hz, 1H), 7.56 (dd, J=8.1 and 6.8 Hz, 1H), 7.93 (d with fine coupling, J=6.8 Hz, 1H), 8.05 (d, J=8.1 Hz, 1H), 8.93 (s, 1H), 9.04 (d, J=9.5 Hz, 1H), 11.2 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 23.7, 23.7, 28.2, 45.9, 49.2, 62.5, 72.5, 113.8, 119.5, 121.0, 122.8, 125.2, 126.0, 126.9, 127.0, 127.7, 127.8, 129.0, 129.4, 130.1, 130.2, 130.5, 134.0, 136.2, 136.7, 151.7, 154.2, 165.6, 167.3, 216.1 ppm. IR (KBr): $\tilde{\nu}$ 3422, 3293, 2983, 1711, 1686, 1624, 1516, 1458, 1366, 1259, 1219, 1105 cm^{-1}. Mass (*m*/*z*, %): 528 (M^+, 39), 500 (25), 472 (17), 444 (14), 385 (79), 372 (25), 371 (100), 370 (25), 360 (17), 356 (14), 344 (23), 343 (47), 327 (29), 326 (32), 294 (20), 267 (20), 266 (34), 255 (26), 239 (22), 226 (34), 57 (82). HRMS (ESI): 551.2037, calcd for $C_{32}H_{32}O_7Na$ (M+Na^+) 551.2046. Anal. Calcd for $C_{32}H_{32}O_7$: C, 72.71; H, 6.10. Found: C, 72.39; H, 6.29.

4.4.4. 2,2,4,4-Tetramethyl-3-oxopentyl 6-hydroxy-5-(2,2-dimethyl-1,3-dioxa-1,2,3,4-tetrahydroanthracen-9-yl)-naphthalene-1-carboxylate (14d). Pale yellow amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.30 (s, 9H), 1.37 (s, 3H), 1.42 (s, 3H), 1.44 (s, 6H), 4.50 (q_{AB}, J=10.5 Hz, 2H), 5.05–5.06 (m, 1H), 5.12 (q_{AB}, J=15.3 Hz, 2H), 7.09 (d, J=8.5 Hz, 1H), 7.19 (dd, J=8.5 and 7.0 Hz, 1H), 7.21 (d with fine coupling, J=7.9 Hz, 1H), 7.26 (dd, J=8.2 and 7.0 Hz, 1H), 7.33 (dd, J=7.9 and 7.1 Hz, 1H), 7.44 (d, J=9.4 Hz, 1H), 7.65 (s, 1H), 7.79 (d, J=8.2 Hz, 1H), 7.88 (d with fine coupling, J=7.1 Hz, 1H), 8.94 (d, J=9.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 23.7, 24.4, 25.1, 28.2, 45.9, 49.2, 61.1, 72.2, 100.4, 114.4, 114.7, 119.1, 121.3, 124.4, 124.5, 124.9, 125.0, 126.8, 127.0, 127.2, 127.3, 127.5, 127.8, 128.6, 130.0, 133.2, 134.4, 148.8, 151.5, 167.6, 216.0 ppm. IR (KBr): $\tilde{\nu}$ 3448, 2983, 2865, 1715, 1685, 1612, 1438, 1259, 1178, 1138, 1115 cm^{-1}. Mass (*m*/*z*, %): 540 (M^+, 20), 483 (34), 482 (88), 426 (21), 383 (12), 343 (20), 326 (26), 325 (100), 324 (33), 297 (14), 269 (12), 239 (13), 57 (15). HRMS (ESI): 563.2379, calcd for $C_{34}H_{36}O_6Na$ (M+Na^+) 563.2409. Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.21; H, 6.64.

4.4.5. 2,2,4,4-Tetramethyl-3-oxopentyl 2-hydroxy-3′-hydroxymethyl-2′-(2-methoxyethoxy)-1,1′-binaphthyl-5-carboxylate (14e). Colorless amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.30 (s, 9H), 1.44 (s, 3H), 1.45 (s, 3H), 3.23–3.28 (m, 1H), 3.25–3.26 (m, 3H), 3.33 (ddd, J=11.0, 6.0, and 2.3 Hz, 1H), 4.43 (ddd, J=11.0, 6.0, and 1.8 Hz, 1H), 3.51 (ddd, J=11.0, 6.4, and 2.3 Hz, 1H), 4.50 (s, 2H), 4.64 (dd, J=7.3 and 6.9 Hz, 1H), 4.79 (dd with fine coupling, J=12.4 and 7.3 Hz, 1H), 4.84 (dd, J=12.4 and 6.9 Hz, 1H), 5.7 (br s, 1H), 7.11 (d, J=8.2 Hz, 1H), 7.22–7.27 (m, 2H), 7.32 (d, J=8.7 Hz, 1H), 7.39–7.46 (m, 1H), 7.45 (d, J=9.6 Hz, 1H), 7.89 (d, J=8.2 Hz, 1H), 7.89–7.90 (m, 1H), 7.91 (s, 1H), 8.97 (d, J=9.6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 23.8, 28.2, 45.9, 49.2, 58.7, 62.4, 71.8, 71.8, 72.3, 115.5, 119.4, 119.9, 124.7, 125.4, 125.6, 126.9, 127.1, 127.4, 127.5, 128.2, 128.3, 130.1, 130.7, 130.8, 133.6, 134.3, 134.5, 151.8, 155.9, 167.5, 216.1 ppm. IR (KBr): $\tilde{\nu}$ 3422, 2958, 2874, 1716, 1685, 1514, 1475, 1254, 1198, 1254, 1143, 1107, 1047 cm^{-1}. Mass (*m*/*z*, %): 558 (M^+, 61), 540 (12), 402 (19), 401 (61), 372 (12), 343 (10), 342 (15), 326 (13), 325 (29), 324 (27), 297 (10), 296 (11), 269 (11), 268 (11), 239 (18), 59 (100), 57 (45). HRMS (ESI): 581.2480, calcd for $C_{34}H_{38}O_7Na$ (M+Na^+) 581.2515. Anal. Calcd for $C_{34}H_{38}O_7$: C, 73.10; H, 6.86. Found: C, 73.17; H, 6.63.

4.5. Fluorescence measurement: general procedure

Freshly prepared solution of 2.05–2.10×10^{-5} mol dm^{-3} of **14a**–**14e** and of 1.0×10^{-2} mol dm^{-3} of TBAF in DMSO was transferred to a quartz cell (10×10×50 mm) and the latter placed in the spectrometer, which was thermostated with stirring at 25 °C. Thus, the fluorescence spectra of **14a**–**14e** were measured by means of JASCO FP-750. The fluorescence of **14a**–**14e** in 18-crown- ether complex of *t*-BuOK in PhH–THF system was measured similarly to the case of TBAF in DMSO.

4.6. X-ray single crystallographic analysis of dioxetanes

X-ray diffraction data were collected on a Rigaku Mercury CCD diffractometer with graphite monochromated Mo Kα (λ=0.71070 Å) radiation. Data were processed using CrystalClear.[†] The structure was solved by direct method (SHELX97)[‡] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 6532 observed reflections and 390 variable parameters (for **2a**), on 6312 observed reflections and 395 variable parameters (for **2b**), on 7001 observed reflections and 446 variable parameters (for **2c**), on 13,200 observed reflections and 846 variable parameters (for **2d**), and on 7345 observed reflections and 461 variable parameters (for **2e**). All calculations were performed using the CrystalStructure crystallographic software package.[§,¶]

[†] Rigaku Corporation, 1999.
[‡] Sheldrick, G. M. University of Gottingen, Gottingen, Germany, 1997.
[§] CrystalStructure 3.6.0: Crystal Structure Analysis Package, Rigaku and Rigaku/MSC(2000–2003). 9009 New Trails Dr. The Woodlands, TX 77381, USA.
[¶] CRYSTALS Issue 10: Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W. Chemical Crystallography Laboratory, Oxford, UK, 1996.

Crystal data for compound *cis*-**2a**: $C_{30}H_{30}O_4 \cdot C_4H_8O$ (M_r=526.67), colorless platelet (recrystallized from THF), 0.30×0.20×0.08 mm, orthorhombic, space group *Pccn* (#56), a=23.64(3) Å, b=22.72(1) Å, c=10.635(8) Å, V=5712.5(89) Å^3, Z=8, ρ_{calcd}=1.225 g cm^{-3}, T=150 K, $2\theta_{max}$=55.0°, F(000)=2256.00, reflections collected/unique 58,346/6532 (R_{int}=0.083), μ(Mo Kα)=0.81 cm^{-1}. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.8818 to 1.0000. The data were corrected for Lorentz and polarization effects. Final R indices $R1$=0.093 [$I>2\sigma(I)$], $wR2$=0.208 (all data), GOF on F^2=0.768, and residual electron density 0.35/−0.32 eÅ^{-3}.

Crystal data for compound *cis*-**2b**: $C_{33}H_{34}O_7$ (M_r=542.63), colorless platelet (recrystallized from dioxane), 0.30×0.20×0.15 mm, monoclinic, space group $C2/c$ (#15), a=29.96(2) Å, b=12.904(6) Å, c=14.57(2) Å, β=96.138(8)°, V=5601.5(76) Å^3, Z=8, ρ_{calcd}=1.287 g cm^{-3}, T=150 K, $2\theta_{max}$=55.0°, F(000)=2304.00, reflections collected/unique 29,440/6312 (R_{int}=0.038), μ(Mo Kα)=0.90 cm^{-1}. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.8452 to 1.0000. The data were corrected for Lorentz and polarization effects. Final R indices $R1$=0.063 [$I>2\sigma(I)$], $wR2$=0.196 (all data), GOF on F^2=1.002, and residual electron density 0.40/−0.39 eÅ^{-3}.

Crystal data for compound *cis*-**2c**: $C_{32}H_{32}O_7 \cdot C_4H_8O_2$ (M_r=616.71), colorless prism (recrystallized from dioxane), 0.20×0.10×0.10 mm, triclinic, space group P-1 (#2), a=8.12(2) Å, b=13.40(2) Å, c=15.06(2) Å, α=89.43(9)°, β=77.95(8)°, γ=82.12(8)°, V=1587.1(46) Å^3, Z=2, ρ_{calcd}=1.290 g cm^{-3}, T=120 K, $2\theta_{max}$=55.0°, F(000)=656.00, reflections collected/unique 16,809/7001 (R_{int}=0.046), μ(Mo Kα)=0.92 cm^{-1}. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.8462 to 1.0000. The data were corrected for Lorentz and polarization effects. Final R indices $R1$=0.059 [$I>2\sigma(I)$], $wR2$=0.151 (all data), GOF on F^2=1.003, and residual electron density 0.62/−0.70 eÅ^{-3}.

Crystal data for compound *trans*-**2d**: $C_{34}H_{36}O_6 \cdot 0.5(C_4H_8O)$ (M_r=576.71), colorless prism (recrystallized from THF), 0.30×0.25×0.10 mm, triclinic, space group P-1 (#2), a=10.930(11) Å, b=16.31(2) Å, c=18.60(3) Å, α=107.22(3)°, β=98.74(3)°, γ=102.62(3)°, V=3004.5(66) Å^3, Z=4, ρ_{calcd}=1.275 g cm^{-3}, T=150 K, $2\theta_{max}$=55.0°, F(000)=1232.00, reflections collected/unique 31,765/13,200 (R_{int}=0.039), μ(Mo Kα)=0.86 cm^{-1}. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.8740 to 1.0000. The data were corrected for Lorentz and polarization effects. Final R indices $R1$=0.065 [$I>2\sigma(I)$], $wR2$=0.162 (all data), GOF on F^2=1.017, and residual electron density 0.38/−0.30 eÅ^{-3}.

Crystal data for compound *cis*-**2e**: $C_{34}H_{38}O_7 \cdot C_4H_8O$ (M_r=630.78), colorless prism (recrystallized from THF), 0.20×0.10×0.10 mm, triclinic, space group P-1 (#2), a=10.193(5) Å, b=11.647(12) Å, c=14.59(2) Å, α=88.59(8)°, β=77.07(7)°, γ=85.02(8)°, V=1681.9(31) Å^3, Z=2, ρ_{calcd}=1.245 g cm^{-3}, T=150 K, $2\theta_{max}$=55.0°, F(000)=676.00, reflections collected/unique 17,692/7345 (R_{int}=0.038), μ(Mo Kα)=0.86 cm^{-1}. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.8324 to 1.0000. The data were corrected for Lorentz and polarization effects. Final R indices $R1$=0.067 [$I>2\sigma(I)$], $wR2$=0.173 (all data), GOF on F^2=1.013, and residual electron density 0.51/−0.46 eÅ^{-3}.

Crystallographic data for the structural analysis of compounds *cis*-**2a**, *cis*-**2b**, *cis*-**2c**, *trans*-**2d**, and *cis*-**2e** have been deposited at the Cambridge Crystallographic Data Center, CCDC-617817 (for *cis*-**2a**), −617818 (for *cis*-**2b**), −620734 (for *cis*-**2c**), −617819 (for *trans*-**2d**), and −617820 (for *cis*-**2e**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033 or deposit@ccdc.cam.au.uk).

Acknowledgements

The authors gratefully acknowledge financial assistance provided by a Grant-in aid (No. 13640546 and No. 14540506) for Scientific Research by the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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