ELSEVIER

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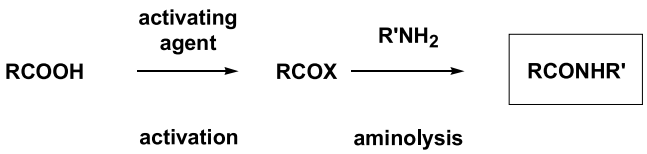
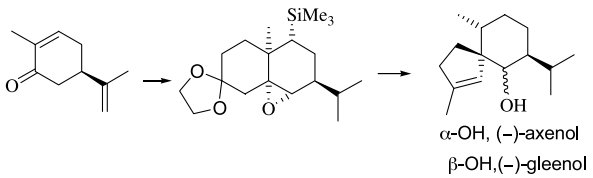
Contents

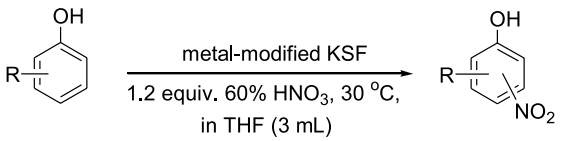
REPORT



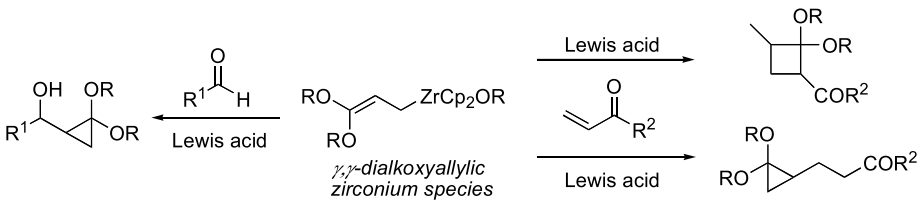
A review of methods and strategies available to the organic chemists to form amide bonds.

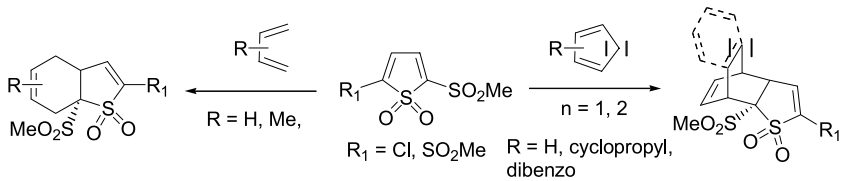
ARTICLES

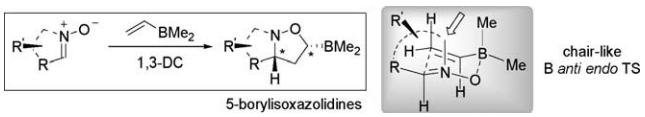


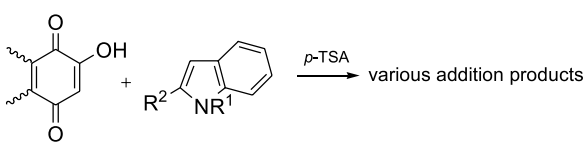


Nitration of phenolic compounds has been investigated by metal-modified montmorillonite KSF catalysts such as Yb–Mo–HKSF or Eu–Mo–HKSF.

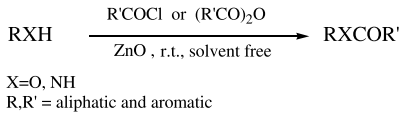


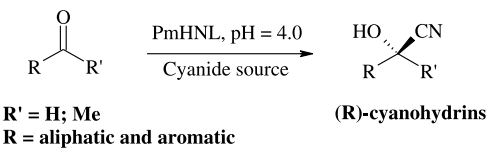




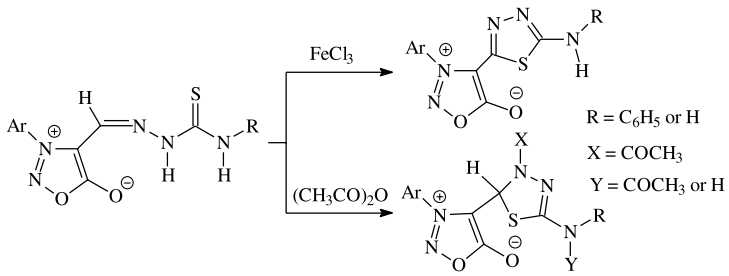


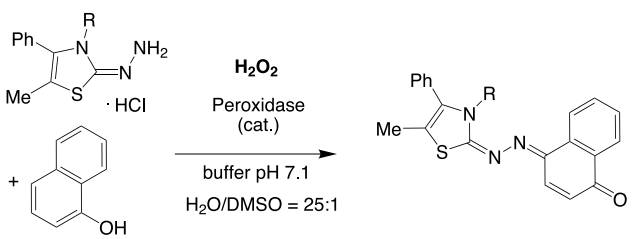
The *p*-toluenesulfonic acid-catalyzed reaction of indoles with hydroxyquinones affords a variety of addition products depending on the nature of the quinone ring and the indole derivative.

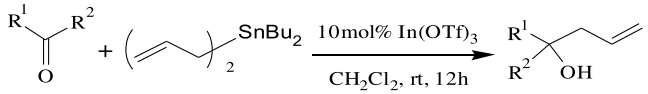


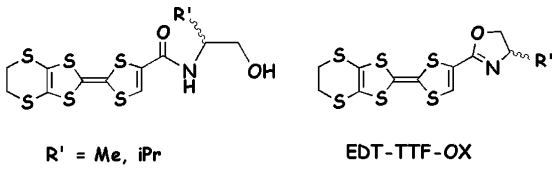


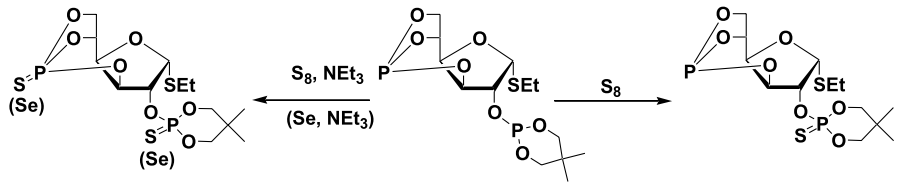
Asymmetric synthesis of (*R*)-cyanohydrins by a new HNL is described.



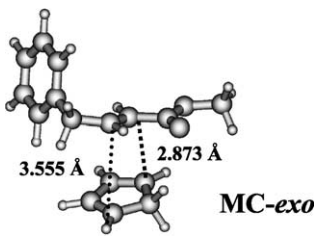


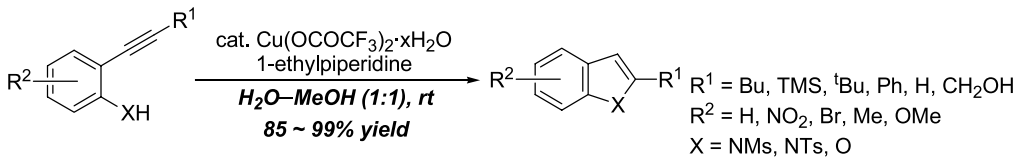


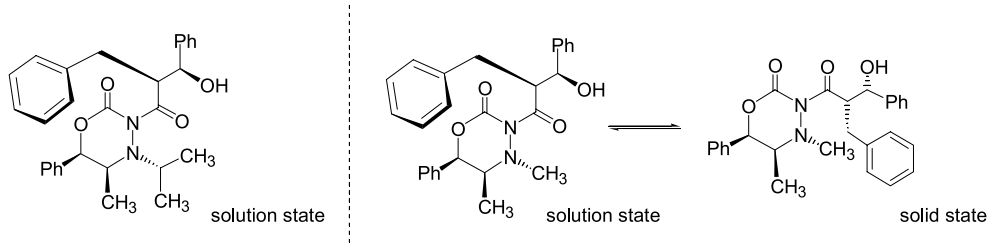


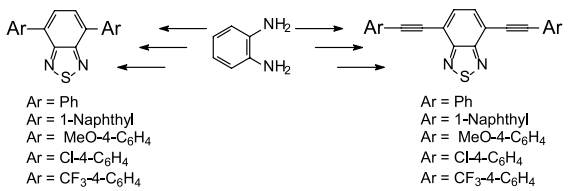


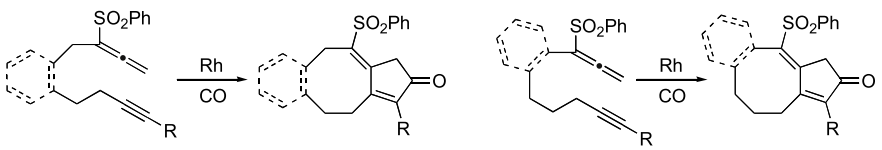
A theoretical study was carried out at the B3LYP/6-31G(d) level of calculation in order to predict and interpret the *exo*/*endo* ratio of adducts obtained by Diels–Alder cycloaddition of *N*-benzyl imine of methyl glyoxylate to cyclopentadiene. The theoretical predictions are in good agreement with the experimental study based on NMR spectroscopy.

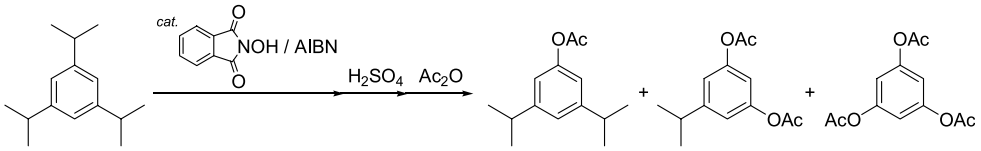


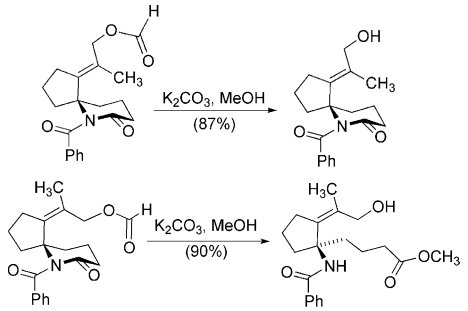


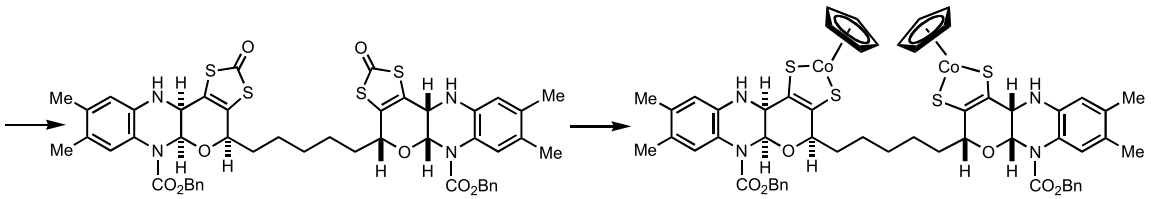


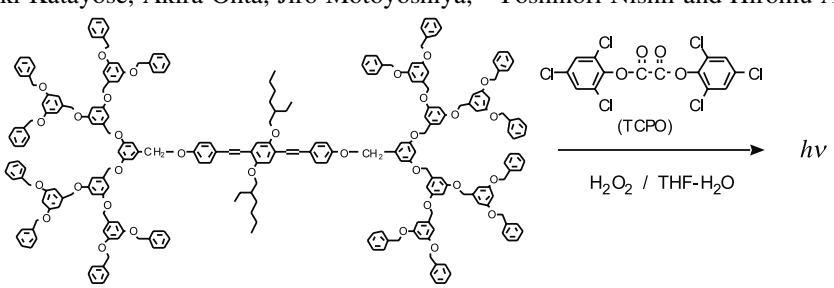


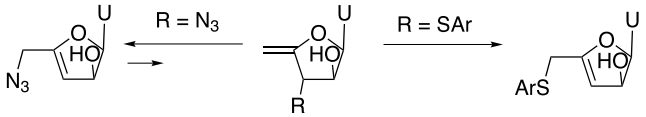


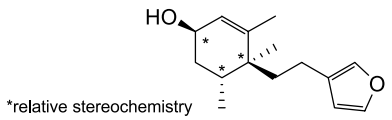








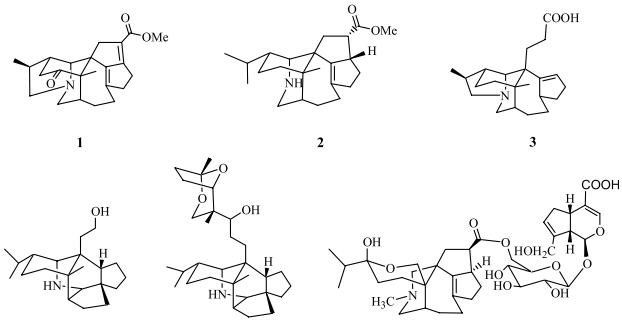




pelseneeriol-1 (**1**)

Pelseneeriols (e.g., **1**) were isolated along with known drimane and *ent*-pallescensin A-like compounds from both mantle and mucus of the mollusc.

Six new *Daphniphyllum* alkaloids, namely caldaphnidines A–F (**1**–**6**), were isolated from the leaves and the seeds of *Daphniphyllum calycinum*. The structure of **1** was determined by a single-crystal X-ray diffraction, and the structure of **2**–**6** was established by spectroscopic methods, especially 2D NMR techniques (^{1}H–^{1}H COSY, HMQC, HMBC, and NOESY).



OTHER CONTENTS

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Amide bond formation and peptide coupling

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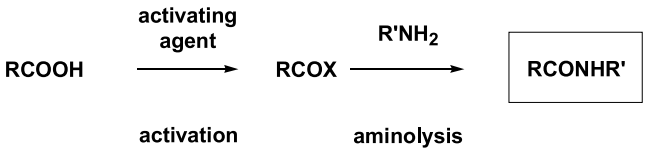
1. Introduction

The amide functionality is a common feature in small or complex synthetic or natural molecules. For example, it is ubiquitous in life, as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis (nearly all known enzymes are proteins), transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen). Amides also play a key role for medicinal chemists. An in-depth analysis of the Comprehensive Medicinal Chemistry database revealed that the carboxamide group appears in more than 25% of known drugs.[1] This can be expected, since carboxamides are neutral, are stable and have both hydrogen-bond accepting and donating properties.

In nature, protein synthesis involving a sequence of peptide coupling reactions (amide bond formation between two α-amino acids or peptides) is very complex, probably to safeguard the unique and precisely defined amino acid sequence of every protein. This barrier is overcome in vivo by a selective activation process catalysed by enzymes, where the required amino acid is transformed into an intermediate amino ester. This intermediate is then involved in a process mediated by the coordinated interplay of more than a hundred macromolecules, including mRNAs, tRNAs, activating enzymes and protein factors, in addition to ribosomes.[2]

Amide or ester bond formation between an acid and, respectively, an amine or an alcohol are formally condensations. The usual esterifications are an equilibrium reaction, whereas, on mixing an amine with a carboxylic acid, an acid–base reaction occurs first to form a stable salt. In other words, the amide bond formation has to fight against adverse thermodynamics as the equilibrium shown in Scheme 1 and lies on the side of hydrolysis rather than synthesis.[3]

The direct condensation of the salt can be achieved at high temperature (160–180 °C),[4] which is usually quite incompatible with the presence of other functionalities (see also Section 2.6.3). Therefore, activation of the acid, attachment of a leaving group to the acyl carbon of the acid, to allow attack by the amino group is necessary (Scheme 2).



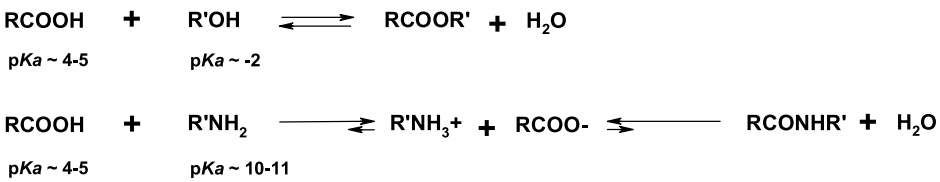
Scheme 2. Acid activation and aminolysis steps.

Hence, a plethora of methods and strategies have been developed and these are now available for the synthetic, medicinal or combinatorial chemist. Relevant examples of these methods are indicated in this report. The chemist might have to screen a variety of such conditions to find the method best adapted to his situation. For example, due to poor reactivity or steric constraints in some extreme cases, the challenge will be to get the amide formed at all. In other situations, the chemist will require the reaction to avoid racemisation. In general, the aim could also be to optimise the yield, to reduce the amount of by-products, to improve selectivity, to facilitate the final purification, to define a scalable process or to exploit more economical reagents. In the last two decades, the combined rapid development of solid-phase technologies and coupling methods has enabled parallel synthesis to become a tool of choice to produce vast amounts of diverse compounds for early discovery in the pharmaceutical industry.

2. Amide bond formation: methods and strategies

Carboxy components can be activated as acyl halides, acyl azides, acylimidazoles, anhydrides, esters etc. There are different ways of coupling reactive carboxy derivatives with an amine:

- an intermediate acylating agent is formed and isolated then subjected to aminolysis



Scheme 1. Ester bond versus amide bond formation.

- a reactive acylating agent is formed from the acid in a separate step(s), followed by immediate treatment with the amine
- the acylating agent is generated in situ from the acid in the presence of the amine, by the addition of an activating or coupling agent.

As illustrated in the Section 1, amide bond formation can often present difficulties such as low yields, racemisation, degradation, difficult purification etc. To face these challenges, numerous mild coupling reagents and methods have been developed that not only are high yielding, but that potentially help to prevent racemisation of neighbouring chiral centres. A classical example of racemisation is encountered in peptide synthesis when the terminal acid peptide is activated, leading to the formation of the corresponding oxazolone **1a**. Under mild basic conditions, the oxazolone undergoes racemisation via the formation of conjugated anionic intermediate **2**. The resulting oxazolone **1a**, **1b** mixture reacts then with a nucleophile, explaining the loss of chiral integrity of the coupled material **3a**, **3b** (Scheme 3). Therefore, peptides are usually grown at the *N*-terminus and mild activation conditions are needed. In this latter approach, the activation is advantageously performed on an *N*-protected α-amino acid, thus avoiding the oxazolone formation.

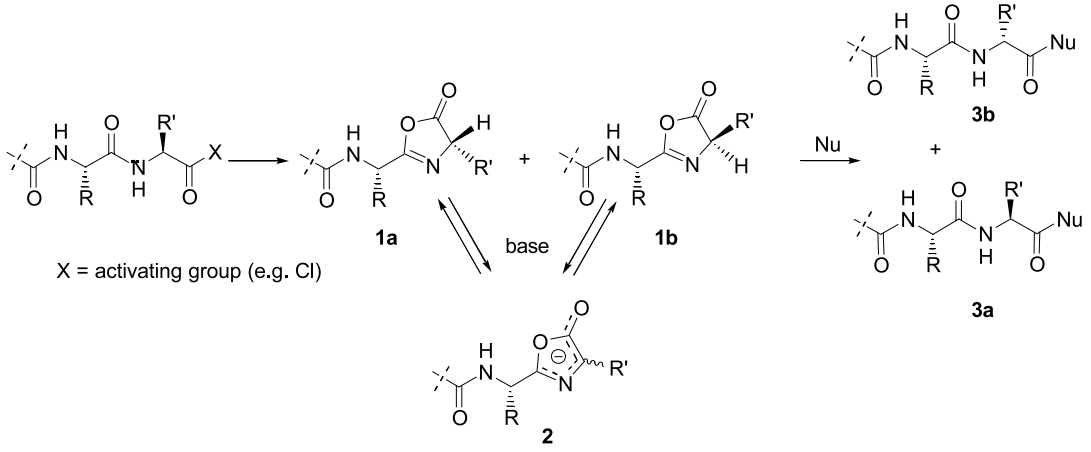
2.1. Acyl halides

2.1.1. Acyl chlorides. Acyl chlorides (also called acid chlorides) are one of the easiest methods to activate an acid and numerous acyl chlorides are commercially available. This is usually a two-step process, involving first the conversion of the acid into the acyl halide followed by the coupling itself.

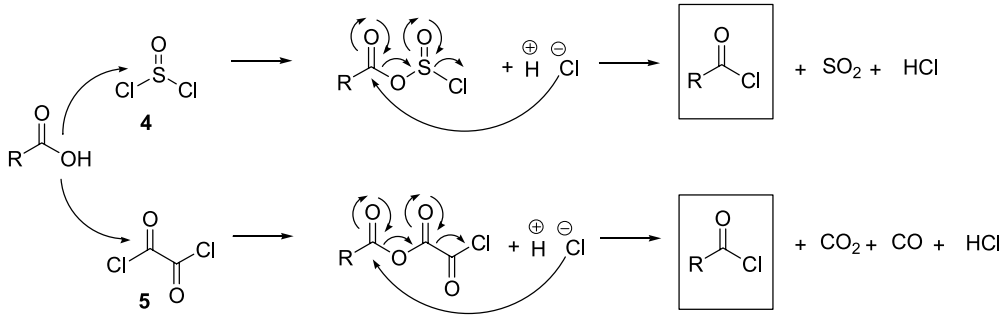
2.1.1.1. Acyl chloride formation. Thionyl chloride $SOCl_2$ **4**,[5] oxalyl chloride $(COCl)_2$ **5**,[6,7] phosphorus trichloride PCl_3,[8] phosphorus oxychloride $POCl_3$[9] and phosphorus pentachloride PCl_5[10] are commonly used to generate acyl chlorides from their corresponding acids. Phoshonium pentachloride is generally used for aromatic acids, which contains electron-withdrawing substituents and which do not react readily with thionyl chloride **4**.[11] The mechanism of acid chloride formation using thionyl chloride **4** or oxalyl chloride **5** is illustrated in Scheme 4. **Caution**: it is important to note that the use of oxalyl chloride **5** is accompanied by the stoichiometric production of two molecules of gas, one of which is carbon monoxide.[12] The generated volume of gas and resulting chemical or safety hazards should always be taken into consideration before setting up these reactions.[13]

These reactions are often promoted by the addition of a drop of dimethylformamide (DMF).[14] The catalytic role of DMF is described in Scheme 5.

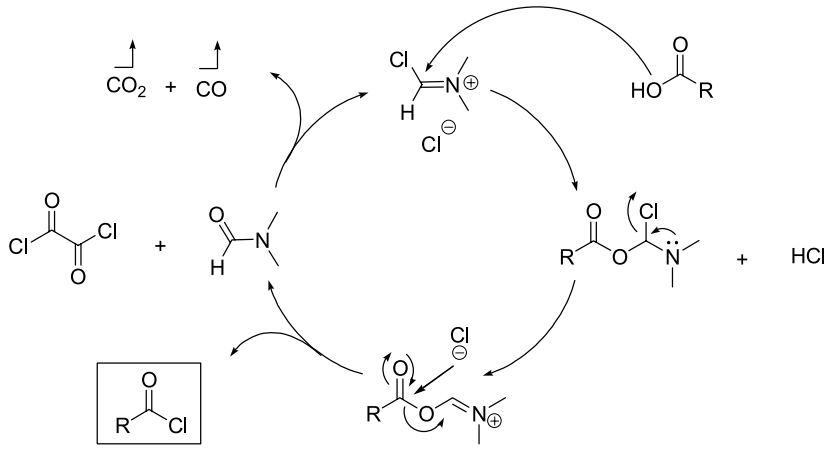
One of the major disadvantages of the previously cited chlorinating agents is the production of HCl. Some substrates (e.g., those containing Boc-protected amines)



Scheme 3. Oxazolone-mediated racemisation occurring during peptide coupling.



Scheme 4. Mechanism for acyl chloride formation using oxalyl chloride **5** or thionyl chloride **4**.



Scheme 5. Activation with DMF: catalytic cycle.

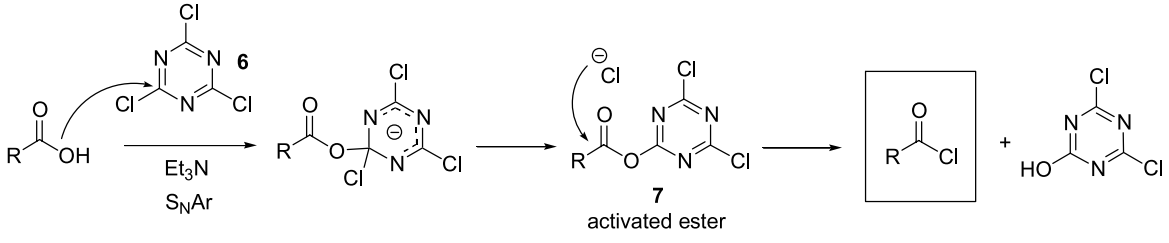
are acid sensitive and require non-acidic conditions. For example, cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) **6** is used to carry out acyl chloride formation in the presence of triethylamine.[15] The presence of this organic base maintains the basic pH conditions throughout the reaction. The proposed mechanism involves an initial aromatic nucleophilic substitution that generates the corresponding activated aromatic ester **7** and the chlorine anion. The following step is the nucleophilic attack of the chlorine anion on the activated ester to generate the desired acyl chloride (Scheme 6).

Cyanuric chloride **6** is a suitable activating agent for the large-scale manufacture of amides.[16] The process presents many advantages. It involves only 0.33 equiv of triazine promoter, which minimises reagent utilisation and by-product generation. Inexpensive inorganic bases may be used instead of amine bases and the reaction tolerates water. The resulting cyanuric acid by-product can be easily removed by filtration and with a basic wash.

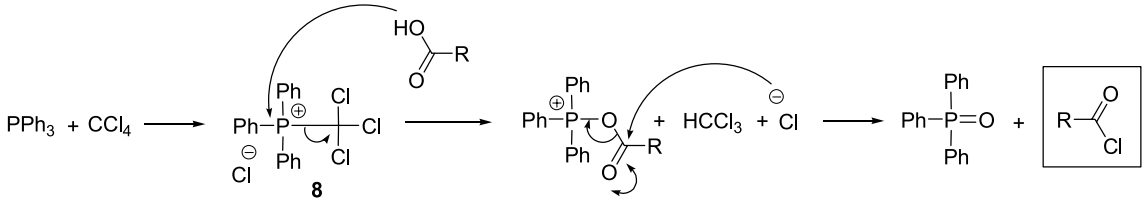
Neutral conditions have also been developed and provide mild conversion of carboxylic acid into acyl chloride. For example, triphenylphosphine (TPP) and a source of chloride have been studied. Carboxylic acids are converted by TPP and carbon tetrachloride into the corresponding acyl chloride,[17] analogous to the conversion of alkyl alcohols into alkyl chlorides.[18] It is suggested that initial formation of triphenyltrichloromethylphosphonium chloride **8** occurs with further reaction yielding chloroform and triphenyl-acyloxyphosphonium chloride (Scheme 7).

Difficulties to separate the product from the phosphorus-containing by products can be avoided by the use of polymer-supported phosphine–carbon tetrachloride reagent. **Caution**: the toxicity and environmental risks[19] associated with carbon tetrachloride render this procedure less attractive. Carbon tetrachloride can be substituted by hexachloroacetone.[20] Villeneuve has demonstrated that carboxylic acids could be converted by hexachloroacetone and TPP at low temperature into the corresponding acyl chloride. This method was also applied to generate highly reactive formyl chloride. Alternatively, trichloroacetonitrile and TPP also provide mild and efficient conditions.[21]

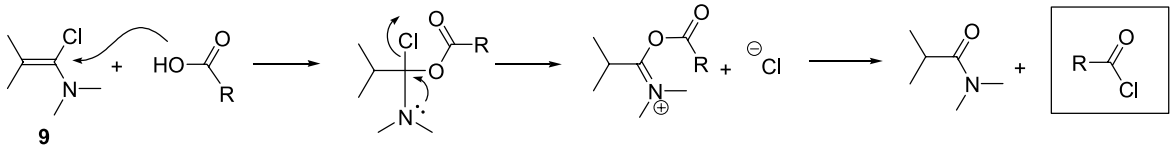
Other neutral conditions are described by Ghosez et al. using tetramethyl-α-chloroenamine **9**.[22] During this process, the formation of hydrogen halides is avoided. Thus,



Scheme 6. Acyl chloride formation using cyanuric chloride **6**.



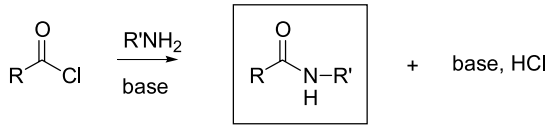
Scheme 7. Acyl chloride formation using TPP and carbon tetrachloride.



Scheme 8. Use of Ghosez chlorination agent **9**.

this method is extremely useful when acid-labile protecting groups are present (Scheme 8).

2.1.1.2. Coupling reactions with acyl chlorides. The amide bond is formed by reacting the acyl chloride with the desired amine (Scheme 9). An additional base is usually required to trap the formed HCl and to avoid the conversion of the amine into its unreactive HCl salt. Couplings are usually performed in inert dry solvents, in the presence of a non-nucleophilic tertiary amine (NEt_3,[23] iPr_2NEt [also called Hünig's base], or *N*-methylmorpholine). Having said that, acyl chlorides are often robust enough to be coupled to amines under aqueous conditions, for example, in the presence of NaOH[24] (Schotten–Baumann conditions).



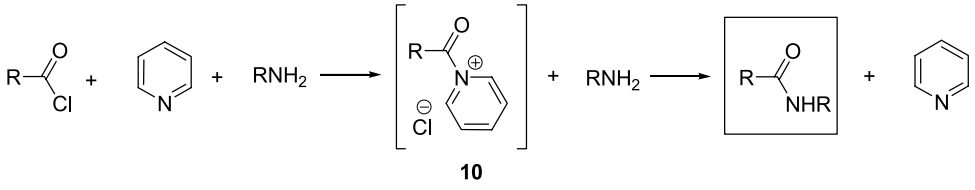
Scheme 9. Aminolysis.

These reactions can be accelerated with a catalytic amount of pyridine or *N*,*N*-dimethylaminopyridine (DMAP).[25] In some cases, pyridine is used as the solvent. The formation of an intermediate acylpyridinum salt **10** is stipulated (Scheme 10).

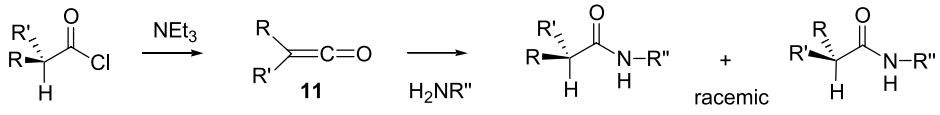
The use of metallic zinc can also accelerate the coupling at room temperature. The method is applicable to alkyl, aryl, heterocycles, carbohydrates and amino acids and leads to high yields.[26]

2.1.1.3. Limitations of acyl chlorides. Nevertheless, acyl chlorides have limited value in peptide coupling because of the danger of hydrolysis, racemisation, cleavage of protecting groups and other side reactions (e.g., *N*-carboxy anhydride formation, see Section 2.4.2.3). The tendency of acyl chlorides to racemise under basic conditions can be illustrated by the standard synthesis of ketenes.[27] Ketenes **11** are formed by reacting an acyl chloride containing an α proton with NEt_3. The ketene **11** can further react with a nucleophile such as an amine to yield the corresponding addition product with an obvious loss of chiral integrity (Scheme 11).

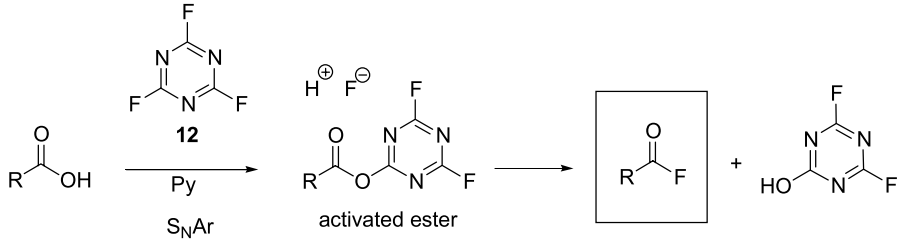
2.1.2. Acyl fluorides. Racemisation and side reaction problems can sometimes be avoided by using acyl fluorides as active intermediates.[28] Acyl fluorides are, indeed, less moisture sensitive than acyl chlorides and more reactive towards amines. Another advantage is that they are compatible with Fmoc or Cbz *N*-protections and even with *t*Bu esters or other acid-labile ester groups, and thus they are useful in peptide chemistry.[29] They react in the same way as acyl chlorides.



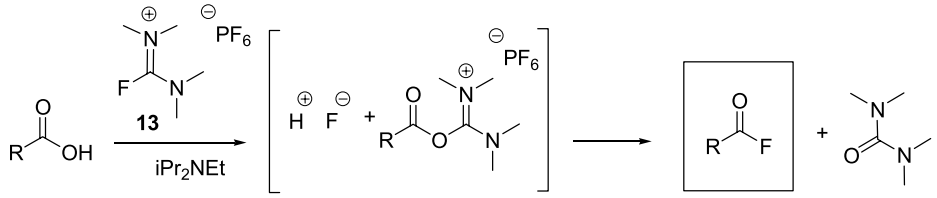
Scheme 10. Catalytic role of pyridine.



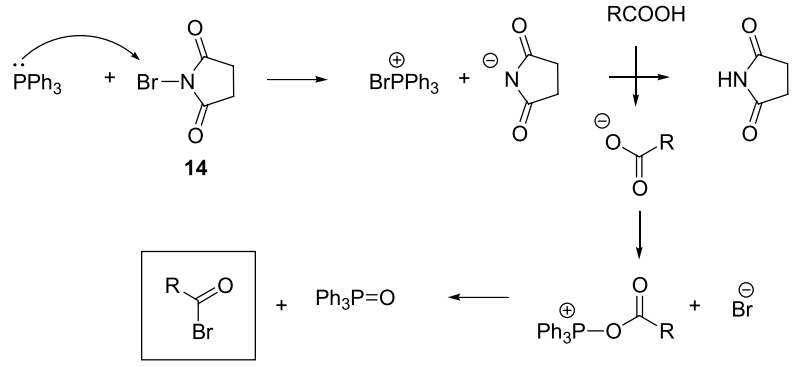
Scheme 11. Potential racemisation via ketene formation.



Scheme 12. Acyl fluoride formation using cyanuric fluoride **12**.



Scheme 13. Acyl fluoride formation using TFFH **13**.



Scheme 14. Acyl bromide formation using TPP and NBS **14**.

Acyl fluorides are commonly formed using cyanuric fluoride **12**[30] in the presence of pyridine and react in a similar way to cyanuric chloride **6** (Scheme 12).

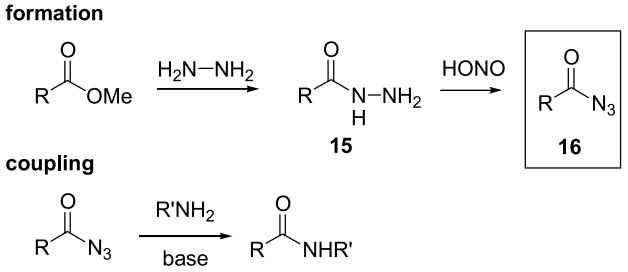
Alternatively, *N*,*N*-tetramethylfluoroformamidinium hexafluorophosphate (TFFH) **13** can be used in the presence of Hünig's base.[31] This salt is advantageous in being non-hygroscopic and stable to handling under ordinary conditions. The postulated two-step mechanism is described in Scheme 13. The TFFH **13** activation uses the urea formation as the driving force. Very similar reagents are used as one-pot coupling reagents and do not require the isolation of the intermediate acyl chloride.[32]

Diethylaminosulphur trifluoride (DAST) Et_2NSF_3[33,34] and deoxofluor $(MeOEt)_2NSF_3$[35] have been used to convert carboxylic acid or acyl chloride into carbonyl fluoride. These fluorinating agents have the advantage of reacting in the absence of a base. Differential scanning calorimetry (DSC) studies suggest that deoxofluor is safer to use on a large scale than DAST, as its exotherm is gradual over a wider temperature range and easier to control.

2.1.3. Acyl bromides. Acyl bromides are used on some rare occasions to generate amide bonds. α-Bromoacetyl bromide is one of the most common examples. Acid bromides prepared with phosphorus pentabromide usually also undergo α-bromination.[36] Other ways to prepare acyl bromides in situ are to use Ph_3P/*N*-bromosuccinimide NBS **14**[37] (see Scheme 14 and Section 2.5.2.2.1), PPh_3/Br_2,[38] $SOBr_2$,[39] BBr_3/Al_2O_3[40] or even $(BrCO)_2$[41] (see Section 2.1.1). More recently, they have also been prepared under mild conditions using 1-bromo-*N*,*N*-2-trimethyl-1-propenylamine.[42,43]

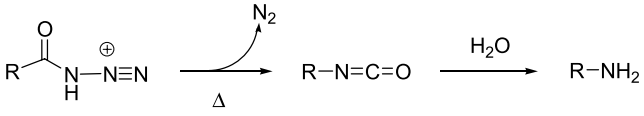
2.2. Acyl azides

The acyl azide[44] route is one of the first developed for peptide coupling by Curtius.[45] Acyl azides can be prepared from the corresponding methyl esters via a two-step synthesis. The methoxy group is displaced with hydrazine to generate the acyl hydrazide **15**, which then undergoes a nitrosation reaction to yield the final acyl azide **16** (Scheme 15).

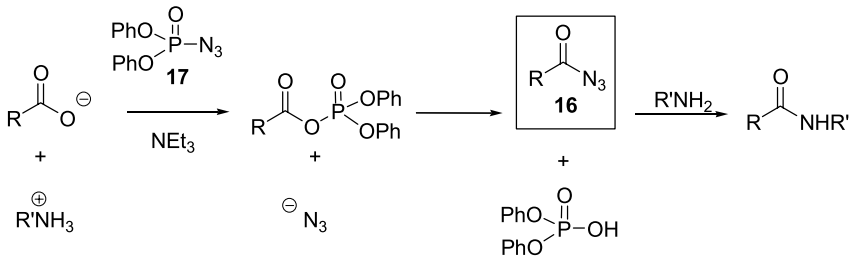


Scheme 15. Historical mutistep amide synthesis via acyl azide preparation.

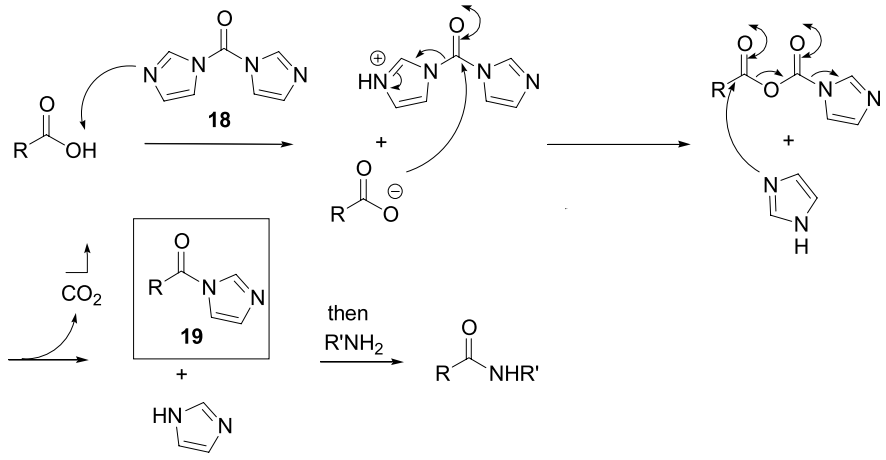
This is usually an efficient coupling method with almost no racemisation, but an occasional side reaction is a Curtius rearrangement, leading to the formation of the unwanted corresponding isocyanate (Scheme 16).[46]



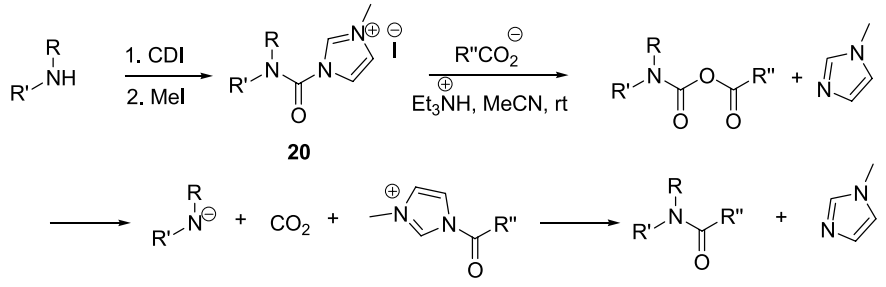
Scheme 16. Possible side reaction: Curtius rearrangement.



Scheme 17. One-pot amide preparation using DPPA **17**.



Scheme 18. One-pot amide preparation using CDI **18**.



Scheme 19. Multistep carbamoylimidazolium salt **20** strategy.

A more convenient one-pot process has been developed using diphenylphosphonic azide (DPPA) **17**[47] (see Section 2.5.2.2.1). If no nucleophile is present, the acyl azide **16** can rearrange to yield the corresponding isocyanate (Scheme 17).

2.3. Acylimidazoles using CDI

Carbonyl diimidazole (CDI) **18**[48] is a useful coupling reagent that allows one-pot amide formation. Acyl carboxy imidazole and imidazole are initially formed but readily react together to yield the activated species as the acylimidazole **19** (Scheme 18). Practically, the acylimidazole is preformed for 1 h and then the amine is added. This reaction, which generates imidazole in situ, does not need an additional base and is even compatible with HCl salts of the amine.[49,50] This reagent is commonly used on a large scale[51] in peptide chemistry and its use can be extended to the formation of esters and thioesters.

Carbamoylimidazolium salts **20**[52] obtained from the reaction of secondary amines with *N*,*N*′-carbonyldiimidazole, followed by methylation with methyl iodide, have also been used for the preparation of tertiary amides and proved to be efficient. A proposed mechanism has been described. The carbamoylimidazolium salt serves as both the source of the amine donor and as the activation reagent for the carboxylic acid acceptor (Scheme 19).

With a similar activation step to that in the use of CDI **18**, *N*,*N*′-carbonylbis(3-methylimidazolium) triflate (CBMIT) **21** has been described as an efficient aminoacylating reagent for peptide synthesis (Fig. 1).[53]

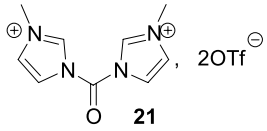


Figure 1. CBMIT **21** coupling reagent.

2.4. Anhydrides

Anhydrides are species that readily react with a vast range of nucleophiles such as alcohols, thiols and, of course, amines. This strategy ranges from the use of simple symmetric anhydrides to rather refined mixed anhydrides involving, for example, isoureas or phosphoric acid-derived species.

2.4.1. Symmetric anhydrides. The diversity of commercially available anhydrides is rather limited and, quite often, the desired anhydride has to be prepared beforehand.

Symmetric anhydrides are formed either by heating the corresponding acid or, in milder conditions, by reacting two molecules of acid in the presence of one equivalent of dicyclohexyl carbodiimide (DCC) **22**,[54] following the mechanism described in Scheme 20. The driving force of this reaction is the formation of the urea by-product.

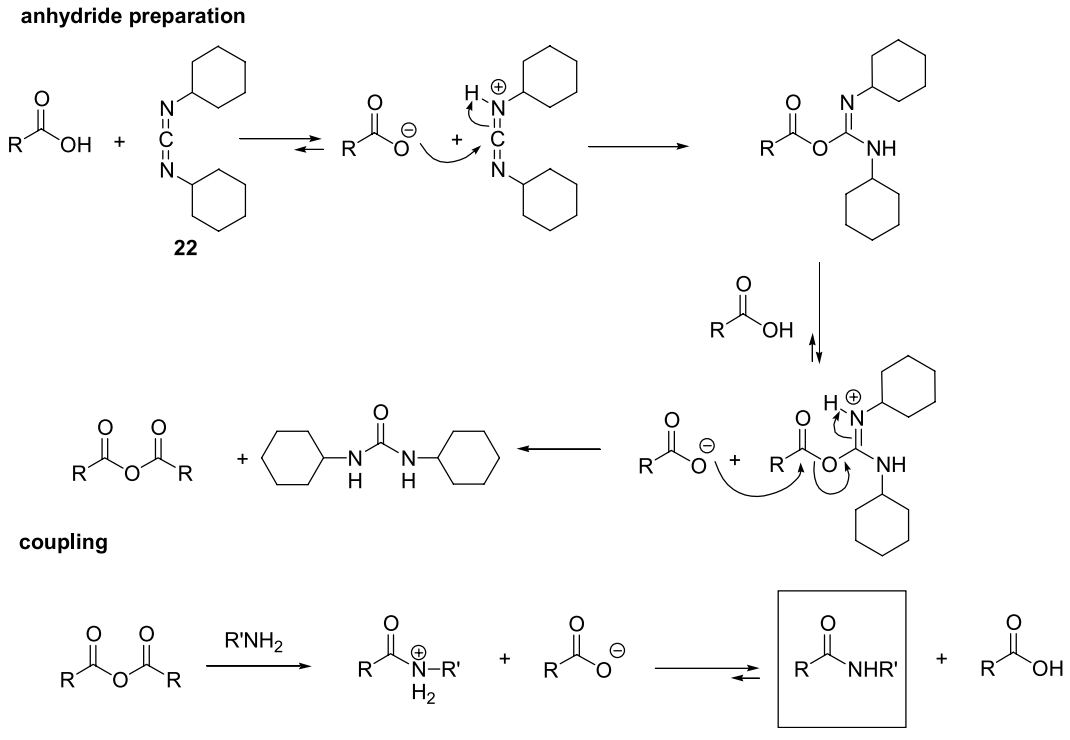
The anhydride is then reacted in a second step with the selected amine. In theory, no additional base is required as the addition generates a carboxylate anion in situ. This mild and efficient coupling method is compatible with peptide formation. The main limitation is that only half of the acid is effectively coupled and the other half is wasted. This could be a problem if the acid is valuable.

2.4.2. Mixed anhydrides.

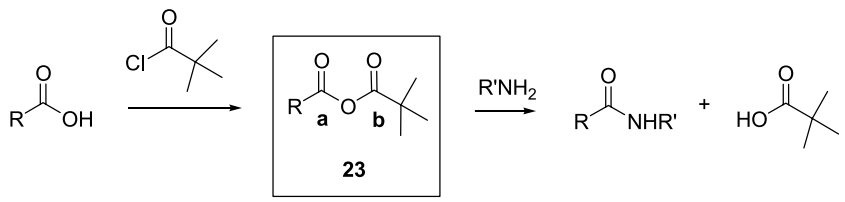
2.4.2.1. Mixed carboxylic anhydrides. To overcome this waste problem, mixed anhydride methods have been developed where the second carboxylic moiety is cheap and easy to couple onto the acid. The difficulty is to get regioselectivity in the nucleophilic addition for position **a** over position **b** (Scheme 21). Mixed pivalic anhydrides **23**[55] are one of the rare examples in this series. The desired aminolysis selectivity is believed to be due to the steric hindrance of the *t*Bu group.

2.4.2.2. Mixed carbonic anhydrides. Another strategy is to differentiate both reactive centres by their chemical nature. Excellent selectivity is observed with mixed carbonic anhydrides **24**. The carbonate electrophilic centre **a** is more reactive than the carboxylic site **b** as the reactive centre **a** is less stabilised by resonance (Scheme 22).

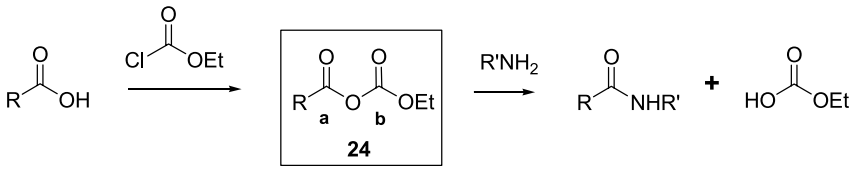
Ethoxycarbonyl anhydrides **24** can be generated using ethyl chloroformate[56] (Scheme 22) or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EDDQ) **25** (Scheme 23).[57]



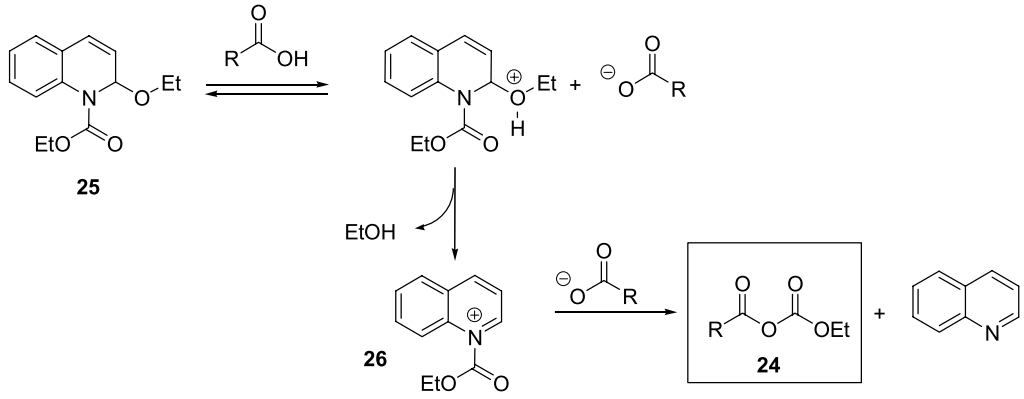
Scheme 20. Anhydride preparation and consecutive coupling with amines.



Scheme 21. Two-step coupling procedure via pivalic anhydride **23**.



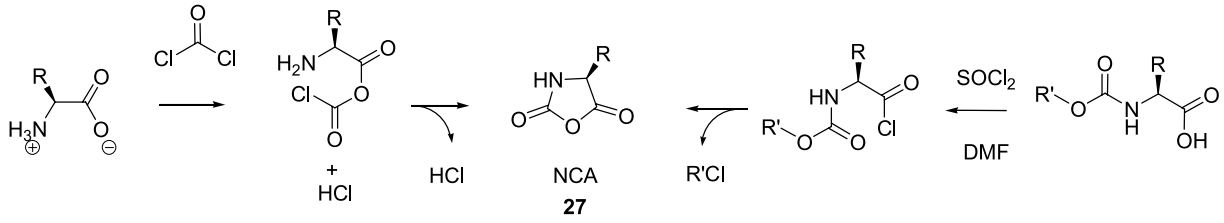
Scheme 22. Two-step coupling via ethyl carbonic anhydride **24**.



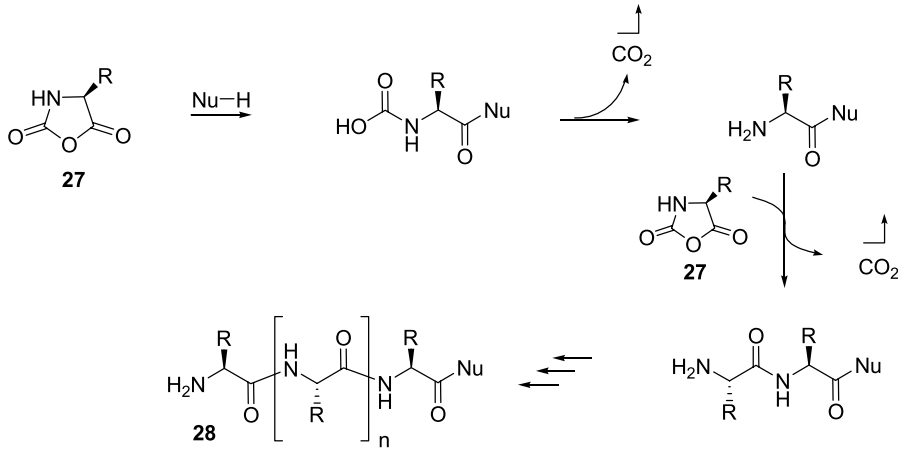
Scheme 23. Ethoxycarbonyl anhydride **24** preparation using EDDQ **25**.

Under acidic conditions, ethanol is eliminated from EDDQ **25**, generating a reactive ethyl formate quinolinium salt **26**. This intermediate has a similar reactivity to the pyridinium salts described in the acyl chloride section and readily reacts with the desired carboxylate to form the required ethoxycarbonyl anhydride. The driving force of this reaction is the generation of the aromatic quinoline.

2.4.2.3. *N*-Carboxy anhydrides or Leuch's anhydrides. The anhydride strategy has been explored and expanded further by Leuch in the domain of peptide synthesis. Cyclic anhydrides can be readily prepared from unprotected amino acids and phosgene. An alternative procedure consists of reacting *N*-protected (Boc, Cbz, Fmoc) amino acids with thionyl chloride and DMF (Scheme 24). In this case, the acid chloride reacts with the carbonyl of the neighbouring carbamate to yield the corresponding *N*-carboxy anhydride (NCA) **27**. Such reactivity, once more, illustrates why acyl chlorides are best avoided in peptide synthesis.[58,59]



Scheme 24. NCA **27** preparation.



Scheme 25. Uncontrolled homopolyamino acid **28** formation.

NCAs **27** can react in different ways. A catalytic amount of a nucleophile (e.g., primary or secondary amine) will initiate a chain reaction that leads to the formation of homopolyamino acids **28**. The ring opening followed by decarboxylation yields a new nucleophile that reacts on the next molecule of NCA **27** and so on (Scheme 25).

Under more carefully controlled conditions, however, NCAs **27** can be mono-coupled to the nitrogen of an unprotected amino acid in high optical purity. The NCA **27** has to be added to a basic aqueous solution of the selected amino acid at 0 °C (Scheme 26).

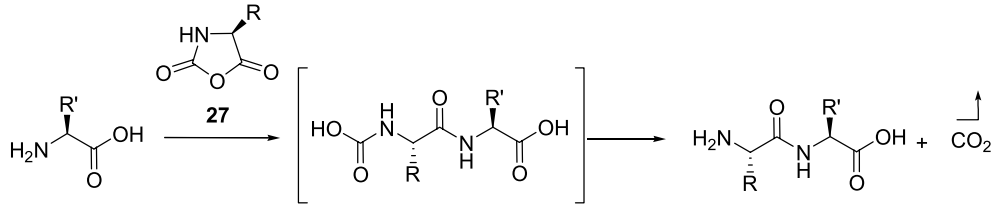
The key factor is the relative stability/instability of the intermediate carbamic acid that prevents the formation of the free aminodipeptide while NCA **27** is still present in the reaction mixture. This process can be repeated several times to form small oligopeptides in solution. The over coupling is the principal limitation of this method. The thio-analogues can also be used. The higher stability of the corresponding thiocarbamic acid (TCA) **29** avoids any over-reaction, but they are prone to racemisation (Scheme 27).

More recently Fuller[60] has introduced Boc or Cbz *N*-protected NCAs **30** (also called UNCAs) (Scheme 28). The U stands for urethane (synonym of carbamate) describing the nature of the *N*-Boc and *N*-Cbz protection. These compounds are stable crystalline solids (in the absence of water). The obvious advantage of the *N*-protection is to avoid over-reaction. On the one hand, UNCAs represent an ideal peptide reagent as the only by-product of the coupling is CO_2, but, on the other hand, they are obtained from a time-consuming preparation. Their synthesis first requires preparation of the intermediate NCA, followed by the *N*-protection by acylation in the presence of a non-nucleophilic base such as *N*-methylmorpholine **6**.

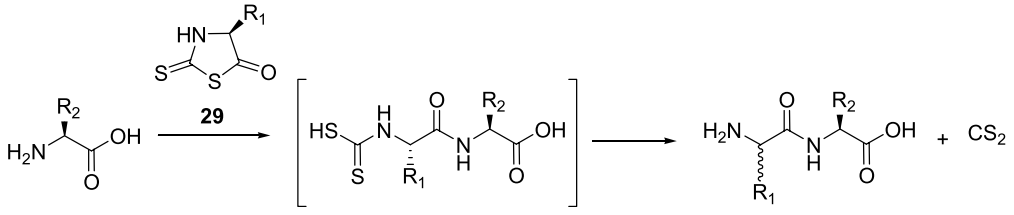
2.4.2.4. Broadened concept of mixed anhydrides. The notion of mixed anhydrides can be extended to other activated species resulting from the condensation or addition of the carboxylic acid with phosphoric acid-derived species, boronic acid derivatives, carbodiimides or even ethoxyacetylene. The case of phosphorous-containing coupling reagents is treated separately.

2.4.2.4.1. Ethoxyacetylene. Ethoxyacetylene **31** has been used as a mild dehydrating agent and reported in peptide synthesis.[61] It enables the conversion of sensitive acids into their masked anhydrides **32**.[62] The activated acid then undergoes the classical aminolysis (Scheme 29).

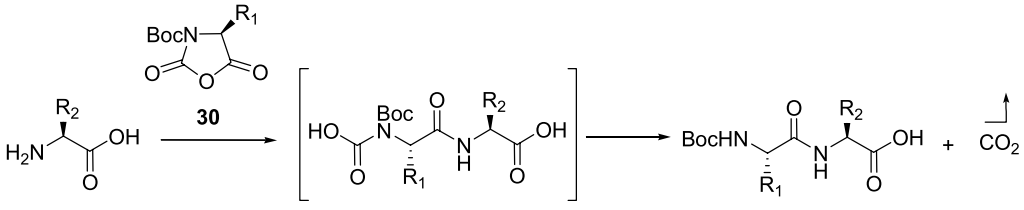
2.4.2.4.2. Acyloxyboron intermediates. Acyloxyboron species generated from carboxylic acids and boron reagents often react with amines to give amides. Boron reagents such as BR_3 (R=C_8H_{17} or OMe),[63] $ClB(OMe)_2$, $HB(OR)_2$ (R=*i*Pr or *t*Am), $BH_3\cdot R_3N$ (R=Me or Bu),[64] or $BF_3\cdot Et_2O$[65] readily react with carboxylic acids to yield acyloxyboron intermediates, which are coupled to amines in moderate yields. The main drawback of this procedure is the low conversion rate usually observed during the aminolysis step. Mechanistic studies suggest the leaving group ejected in this process fragments to liberate 1 equiv of alkyl alcohol, which competitively destroys the active intermediate by attack at the boron centre.[66] This difficulty



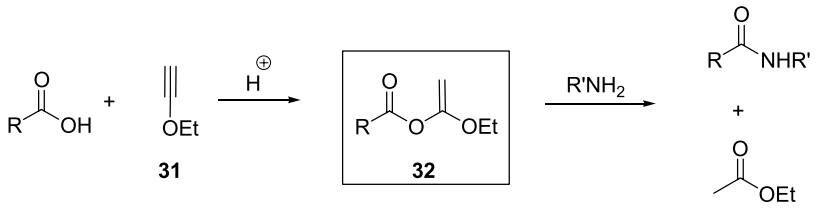
Scheme 26. Controlled peptide synthesis using NCAs **27**.



Scheme 27. Peptide coupling using TCAs **29**.



Scheme 28. Peptide coupling using UNCAs **30**.

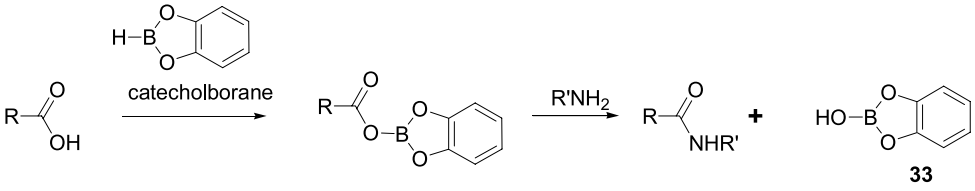


Scheme 29. Two-step amide formation using ethoxyacetylene **31**.

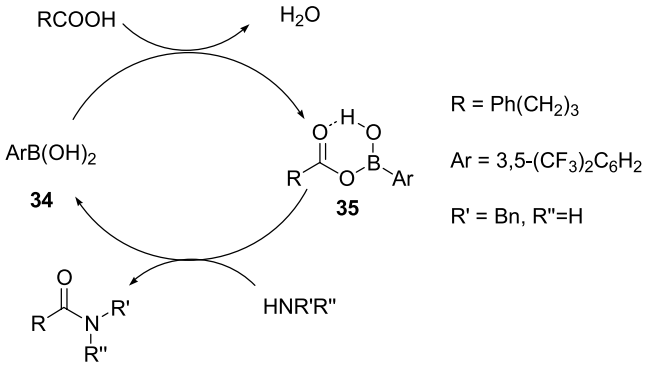
has been overcome by using arylboronic species as leaving groups. For example, good yields have been described using catecholborane for the synthesis of lactones.[67] Once released during the aminolysis, the resulting *o*-phenylene borate **33** is, indeed, less prone to degradation. Furthermore, if any hydrolysis did occur, the leaving group **33** would generate a rather poorly nucleophilic phenolic derivative (Scheme 30).

Arylboronic acids with electron-withdrawing groups such as 3,4,5-trifluorophenylboronic acid, 3,5-bis-(trifluoromethyl)phenylboronic acid[68] and 3,4,5-trifluorophenylboronic acid[69] can efficiently act as amidation catalysts. A simplified mechanism is depicted in Scheme 31. The carboxylic acid is activated in the presence of arylboronic acid **34** as monoacyloxyboronic acid **35** with loss of a molecule of water. Then the activated acid undergoes aminolysis, yielding the desired amide and regenerating the arylboronic acid **34**.

2.4.2.4.3. *O*-Acylisourea using carbodiimides as coupling reagents. Dicyclohexyl carbodiimide (DCC) **22**,[70] diisopropyl carbodiimide (DIC) **36** and 1-ethyl-3-(3′-dimethylamino)carbodiimide HCl salt (EDC or WSC·HCl) **37** (Fig. 2) are frequently used for amide bond formation (this method can also be used to synthesise anhydrides and esters).[71] No additional amine is theoretically required during this one-pot procedure. The carbodiimide reacts with the carboxylic acid to form the *O*-acylisourea mixed anhydride **38** (Scheme 32, see Section 2.4.1). This intermediate can then directly react with the amine to yield the desired amide and the urea by-product **39**. The isolation of the symmetric carboxylic anhydride from the reaction mixture, however, suggests that a more complex



Scheme 30. Acylboronate formation and aminolysis.



Scheme 31. Catalytic use of boronic species in amide couplings.

mechanism might co-exist.[72–74] The driving force of this reaction is the formation of the urea by-product **39**.

Often racemisation and acetyl transfer forming the unreactive *N*-acylurea **40** are observed (Scheme 33). This side reaction can be considerably diminished by reacting the acid and the coupling reagent at 0 °C before adding the amine. Furthermore, adding a selected nucleophile that reacts faster than the competing acyl transfer and generates an intermediate still active enough to couple with the amine also prevents the side reactions. Such nucleophiles are DMAP (see Section 2.1.1) and hydroxybenzotriazole (HOBt) **41** (see Section 2.5.2).[75]

Different carbodiimides are commercially available (Fig. 2).

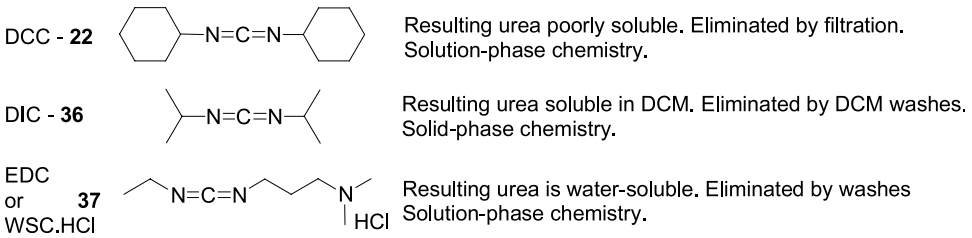
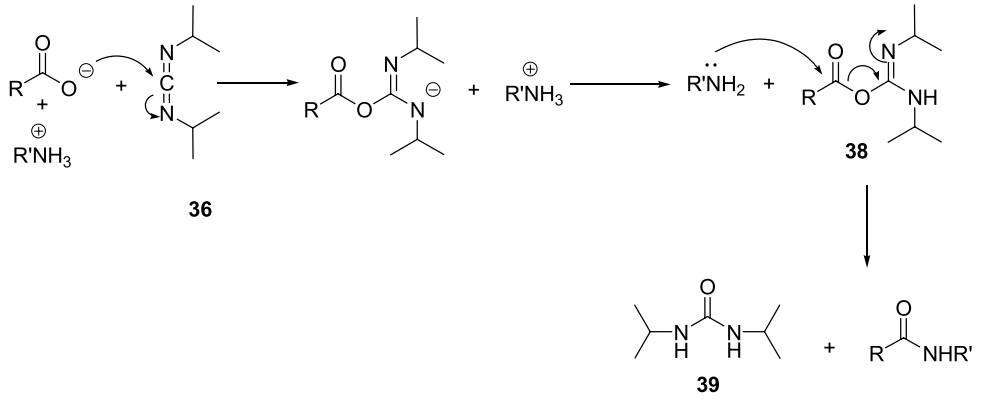
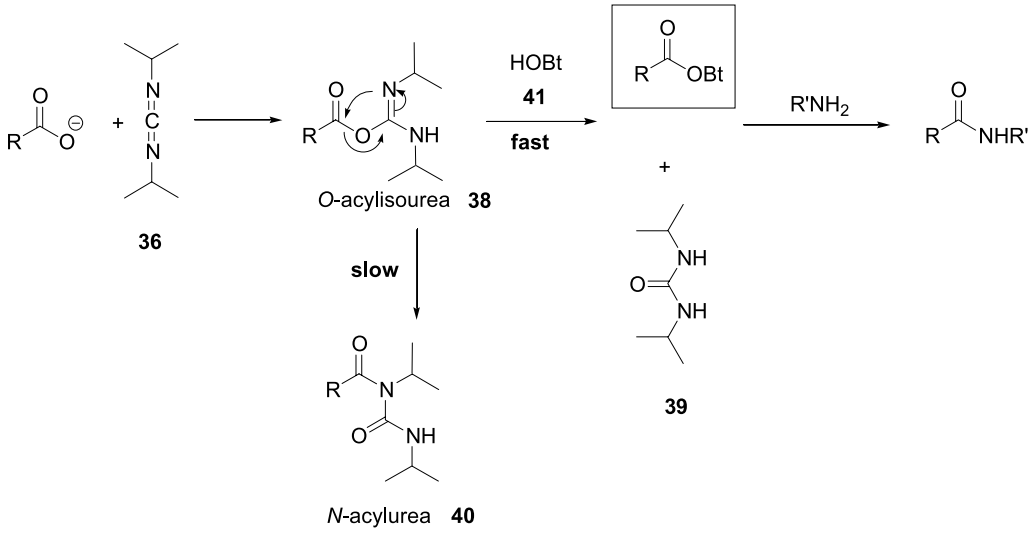


Figure 2. Commonly used carbodiimides.



Scheme 32. One-pot carbodiimide amide coupling.



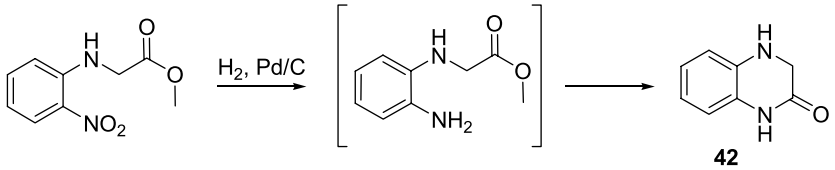
Scheme 33. Use of HOBt **41** to minimise the formation of unreactive *N*-acylurea **40**.

Caution: all of them are sensitisers and should be handled with care. The difference in solubility of their urea by-products can be advantageously used during the purification. For example, dicyclohexyl urea DHU is rather insoluble and can be eliminated by filtration. On the contrary, dimethylaminopropyl-3-ethylurea is extremely water soluble and can be eliminated by aqueous workup. When used in solid-phase chemistry the solid DHU is extremely difficult to separate from the resin. Diisopropyl urea **39** is slightly more soluble in dichloromethane than DHU, which therefore, renders it easier to wash off from the solid support.

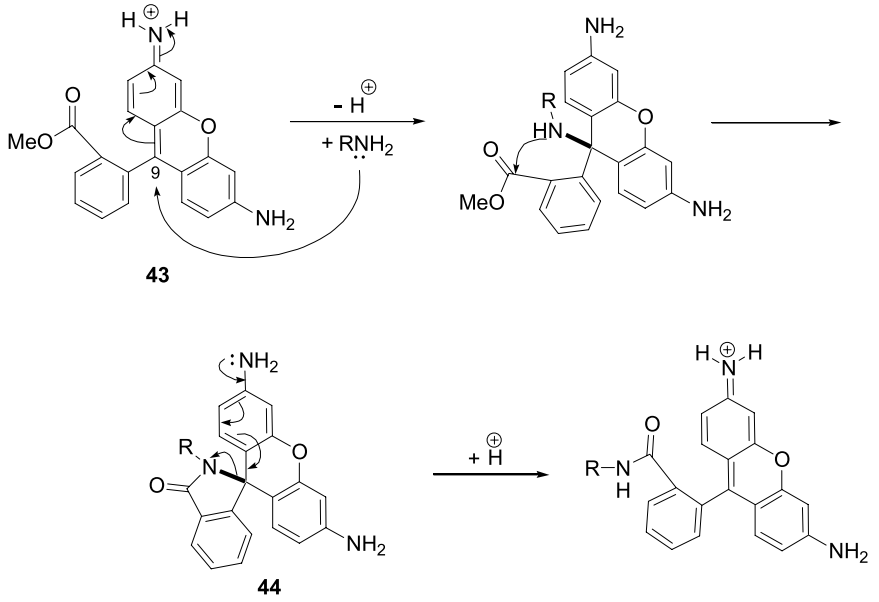
2.5. Esters

2.5.1. Alkyl esters. Alkyl esters (e.g., methyl, ethyl, benzyl esters) cannot be considered as activated species and are commonly used as protecting groups in peptide synthesis. Alkyl esters can, however, be displaced occasionally by amines under forcing conditions such as the use of high temperatures or the addition of a Lewis acid (e.g., $TiCl_4$).[76] Ring formation can also bring about the required assistance. For example, in the synthesis of benzopiperazinone **42** the intramolecular amide is spontaneously formed from the methyl or ethyl ester upon reduction of the nitro group (Scheme 34).[77] Most of the time, alkyl esters are stable under usual coupling conditions and such examples remain anecdotic.

Another interesting example of condensation between an amine and a methyl ester has been described recently in the chemistry of rhodamines, which are used as standard fluorescent probes (Scheme 35). Fluorescent probes have long been used to study complex biological systems.



Scheme 34. Benzopiperazinone ring formation under reductive conditions.



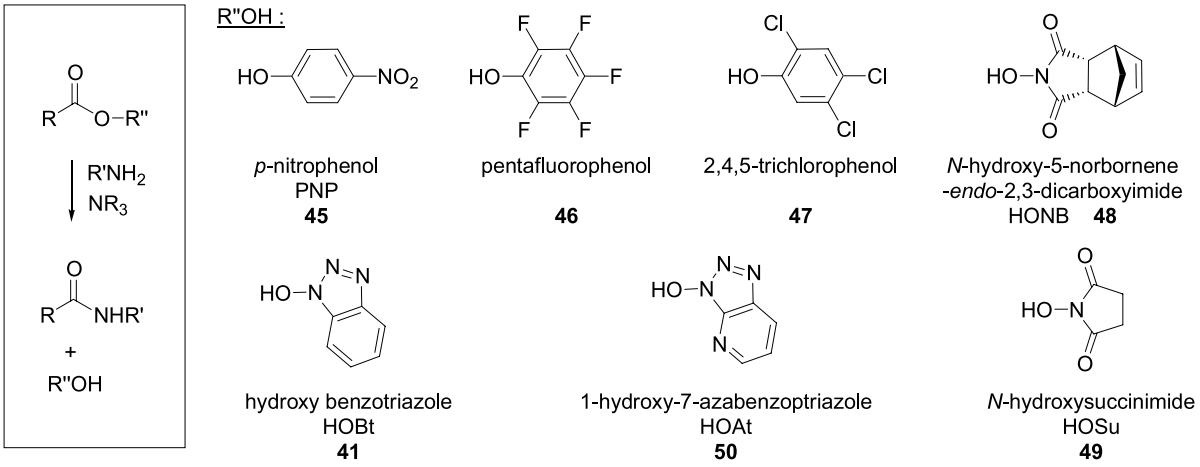
Scheme 35. Rhodamine methyl ester **42** coupling to amines.

Rhodamines are usually 'conjugated' to the molecule of interest via an amide bond. There are numerous publications describing such coupling reactions between the acid residue of rhodamine and diverse amines, but Adamczyk et al. described a direct coupling of rhodamine methyl ester **43** with amines.[78] He theorised that the nucleophile could undergo reversible addition at the 9-position of the quinone like structure of the rhodamine. This is followed by intramolecular trapping of the amine by the proximal methyl ester. The final amide is then generated by ring opening of the intermediate spiro-lactam **44**, which also allows the regeneration of the conjugated fluorescent moiety.

2.5.2. Active esters. Activated esters such as aromatic esters are usually easier to hydrolyse than alkyl esters and are prone to react with a wide range of nucleophiles. More importantly, they cleanly react with amines under mild conditions with usually reduced racemisation. Scheme 36 gives a selection of different alcohols that are commonly used. The increased electrophilicity of the carbonyl centre, compared to alkyl esters, results from the electron-withdrawing character of the selected alcohols.

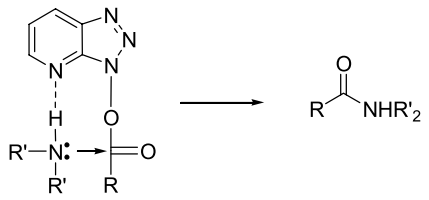
The choice of the alcohol depends on the type of application. In peptide synthesis, for example, the most commonly used are HOBt **41**, *p*-nitrophenol (PNP) **45**[79] and the pentafuorophenol moiety (PFP) **46**.[80] PFP esters have been recommended for the preparation of heterocyclic acids, where DCC **22** or DIC **36** on its own had failed.[81] They are also known to lead to a very rapid coupling with Fmoc-protected amino acids.[82] 2,4,5-Trichlorophenol **47** derived esters are reported to be more reactive than both PNP esters[83] and *N*-hydroxy-5-norbornene-endo-2,3-dicarboxyimide (HONB) esters **48**.[84,85] 2,4,5-Trichlorophenyl esters are also superior to *N*-hydroxysuccinimide (HOSu) **49** as a racemisation suppressant in peptide synthesis. HOSu esters still, however, offer an interesting alternative, as they are water soluble and therefore, easy to eliminate at the purification stage.

Hydroxy-7-azabenzotriazole (HOAt) **50** has been reported

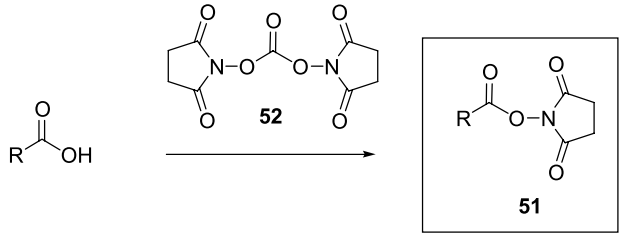


Scheme 36. Commonly used alcohols in amide coupling.

to be more efficient than HOBt **41** in some difficult cases such as coupling with hindered bases. The increased efficiency might be due to the additional chelation or to the neighbouring effect provided by the pyridine nitrogen during the aminolysis step (Scheme 37).[86]



Scheme 37. Additional chelation with HOAt **50**.



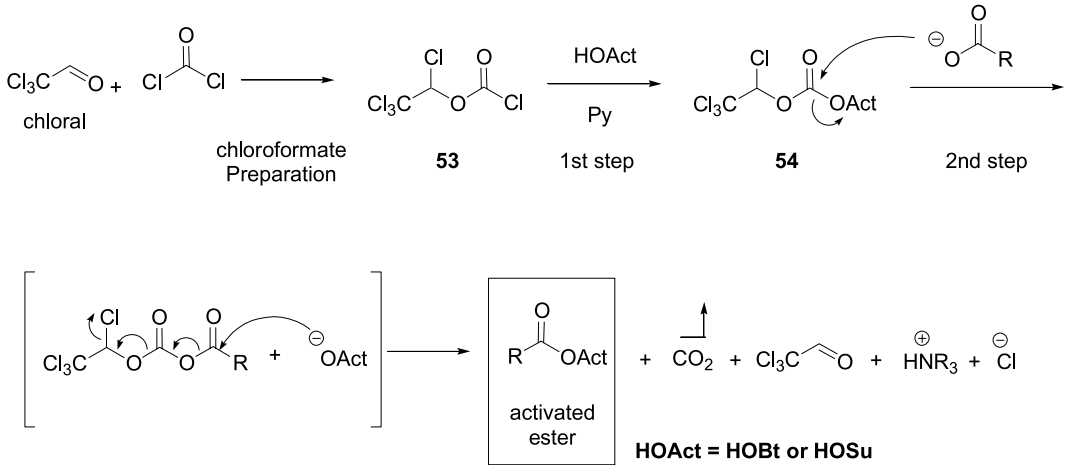
Scheme 38. Succinimidyl ester preparation.

2.5.2.1. Multistep procedures. Active esters can be prepared in advance, purified and stored over time. Some amino acids are even commercially available as their benzotriazole (Bt) esters. Activated esters are usually synthesised using standard ester-formation methods such as DCC **22** (see Section 2.4.1 and Section 2.4.2.4.3), but some other more exotic procedures can be found in the literature.

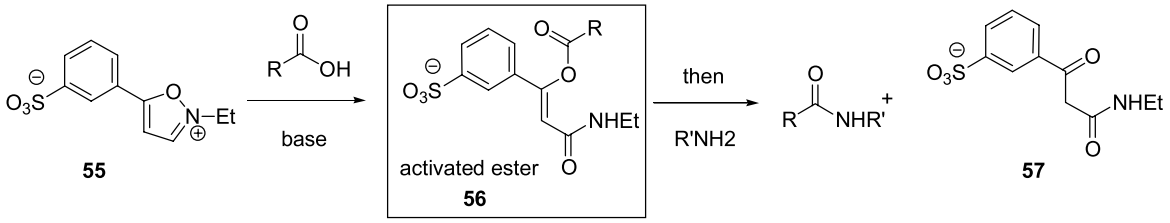
2.5.2.1.1. Succinimidyl esters. Succinimidyl esters **51** can be generated by reacting the corresponding acid and *N*,*N*′-disuccinimidyl carbonate (DSC) **52**.[87] The mechanism is similar to the CDI **18** mechanism (Scheme 38).

2.5.2.1.2. Use of 1,2,2,2-tetrachloroethyl chloroformate as intermediate. Activated esters have been prepared using 1,2,2,2-tetrachloroethyl chloroformate **53**, which is readily synthesised from chloral and phosgene. This reactive species can advantageously be reacted with an alcohol (e.g., HOBt **41** and HOSu **49**) to yield the corresponding 1,2,2,2-tetrachloroethyl carbonate **54**, which can be further reacted with an acid under basic conditions to generate the activated ester (Scheme 39).[88]

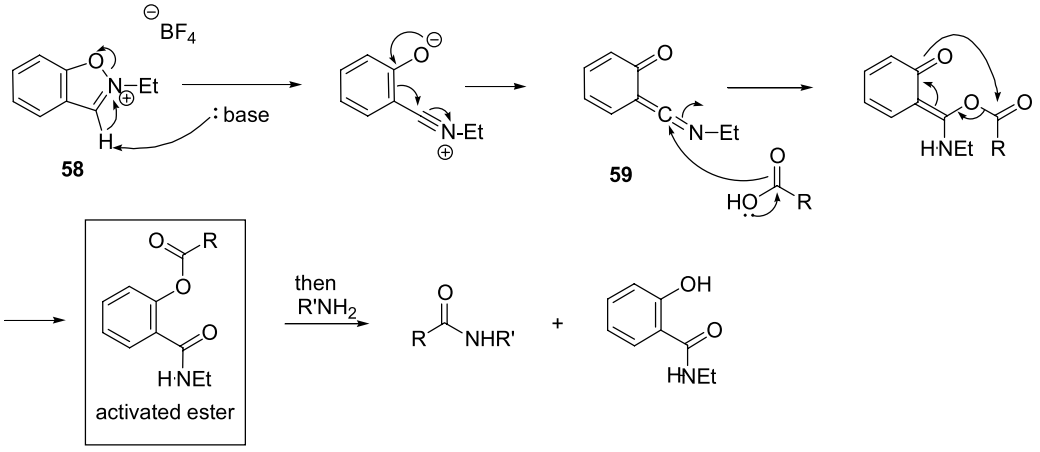
2.5.2.1.3. Isoxazolium salts. In the 1960s, Woodward developed a method using *N*-ethyl-5-phenylisoxazolium-3′-sulfonate, also called Woodward's reagent K or NEPIS **55** (Scheme 40).[89] This zwitterion reacts with *N*-protected amino acids in the presence of triethylamine to generate an enol ester **56**. This activated ester does not require purification and readily reacts and undergoes aminolysis to yield the peptide derivative, accompanied by the enol that tautomerises to the ketone **57**. The sulfonate by-product can easily be eliminated by aqueous washing. Unfortunately, the ionic nature of this reagent makes it difficult to use on solid-phase.



Scheme 39. Multistep preparation of activated esters using 1,2,2,2-tetrachloroethyl chloroformate **53**.



Scheme 40. Coupling procedure using reagent K **55**.



Scheme 41. Two-step coupling procedure using *N*-ethylbenzisoxazolium tetrafluoroborate **58**.

Another example is *N*-ethylbenzisoxazolium tetrafluoroborate **58** (Scheme 41). Mechanistic studies show that the *N*-ethylbenzisoxazolium cation readily undergoes base-catalysed ring opening to form the transitory *N*-ethylbenzoketoketenimine **59**.[90] In the presence of carboxylic acids, the addition product rapidly rearranges to form the active phenol ester. The major limitation of this method is the slowness of the aminolysis step (four times slower than with *p*-nitrophenol) that enables side reactions to take place and therefore make this reagent less popular.

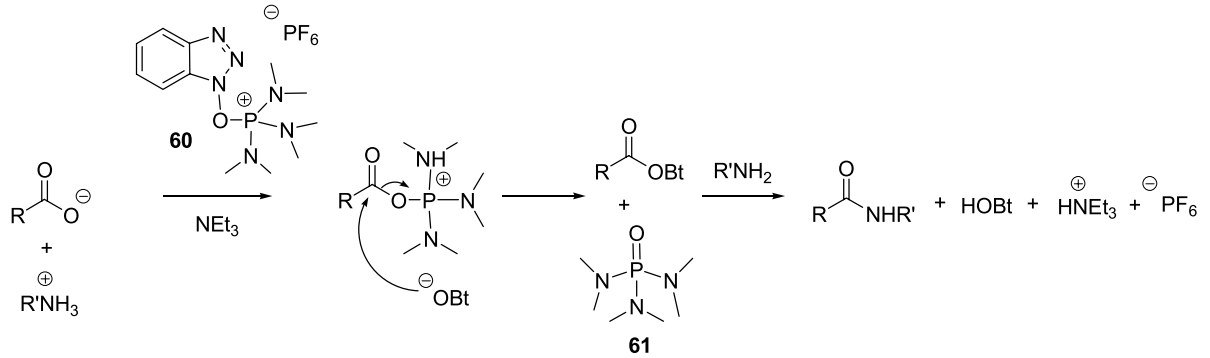
2.5.2.2. One-pot solutions. One-pot coupling conditions have been developed for peptide synthesis where the active ester is prepared in situ as an intermediate and subsequently reacts with the desired amine. As described in Section 2.4.2.4.3, this can be simply achieved by adding catalytic or stoichiometric amounts of HOBt **41** to standard DCC **22** coupling conditions.

More recently, efficient catalysts, which already incorporate the phenol have been proposed as elegant solutions for peptide couplings. Most coupling reagents are nowadays commercially available. They can be sorted according to their nature, that is, uronium, phosphonium and immonium salts. Among them, HOBt- and HOAt-based onium salts and halogenated coupling reagents have been designed. Some other examples of one-pot amide formation will be discussed at the end of this Section.

2.5.2.2.1. Phosphonium salts. Benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) **60**, also called Castro's reagent,[91] is the first published example of these HOBt-based onium salt reagents. The one-pot coupling is performed mixing the desired acid and amine in the presence of BOP **60** and triethylamine or Hünig's base. The deprotonated acid first reacts with BOP **60** to generate both an activated acyl-phosphonium species and HOBt **41**. HOBt **41** readily reacts with the activated acid to produce a reactive Bt ester, which finally undergoes aminolysis. The driving force of this phosphonium-based reaction is to generate the corresponding oxide **61** (Scheme 42).[92]

Caution: Castro's reagent is very effective, but generates hexamethylphosphoric triamide (HMPA) **61**, which is extremely toxic. Benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBop®) **62** has therefore been developed.[93] It is equally efficient, but generates a less toxic by-product, 1,1′,1″-phosphoryltripyrrolidine **63** (Fig. 3).

N-Methyl-α-amino acids are very difficult to couple even with PyBop® **62** or BOP **60**. The couplings are slow, low yielding and racemisation starts to take place. One explanation could be that the HOBt ester intermediate (that is so effective with primary amines) is too bulky to readily react with the secondary amine, hence enabling degradation to take place. Some effective reagents have been developed where HOBt **41** has been banned. For example, bromotri(pyrrolidino)phosphonium hexafluorophosphate



Scheme 42. One-pot coupling procedure using BOP **60**.

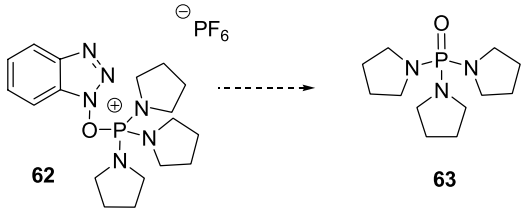
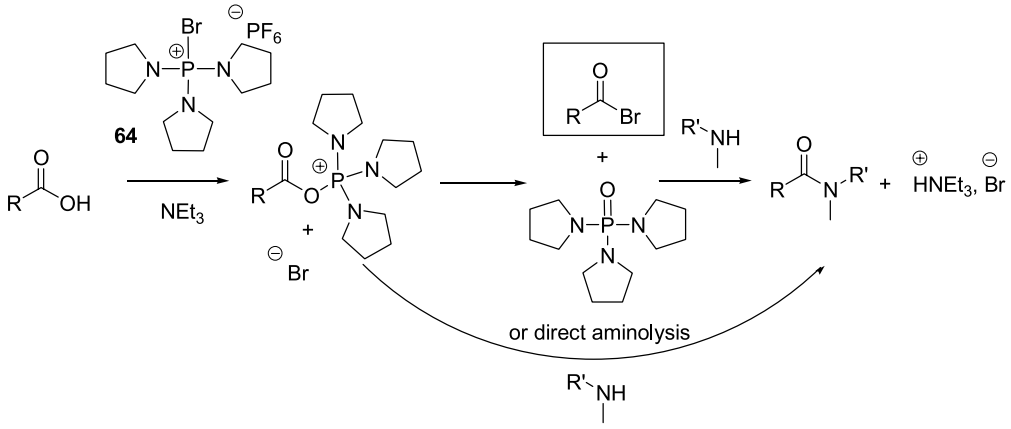


Figure 3. PyBop® **62** and its phosphoric amide by-product **63**.

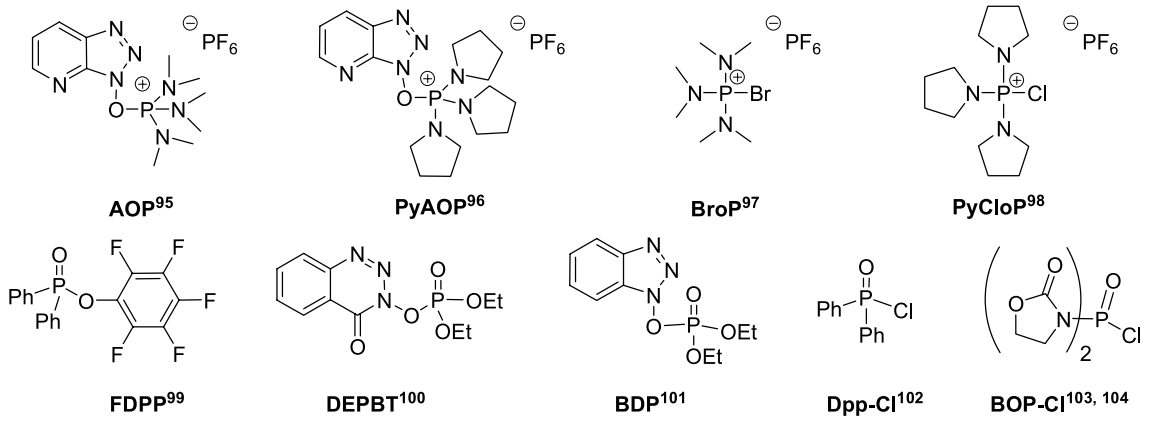
(PyBrop) **64** (Scheme 43) is an efficient peptide coupling reagent for *N*-methylated amino esters.[94] The deterrent effect of HOBt **41** can be further confirmed by the fact that the addition of HOBt **41** to the coupling mixture enhances degradation and racemisation.

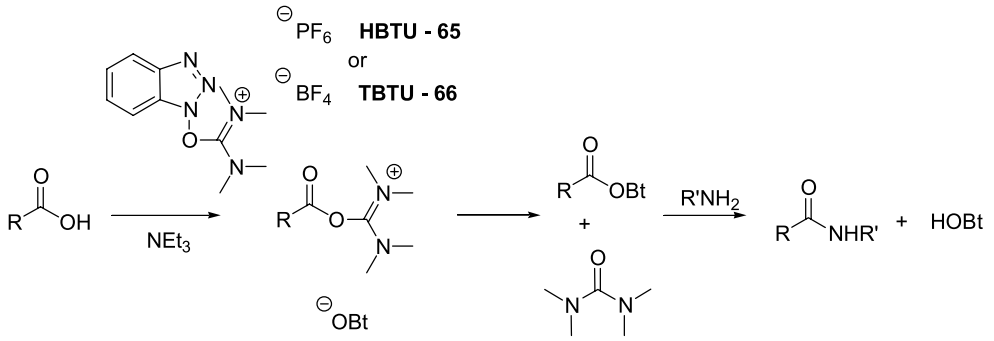
Different mechanistic pathways have been suggested (Scheme 43), one of which speculates the in situ formation of the acyl bromide (see TFFH **13** activation in the Section 2.1.2).



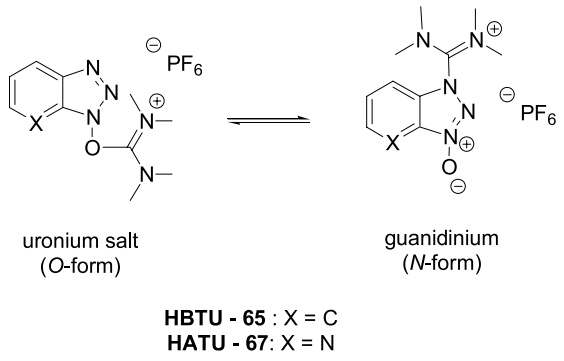
Scheme 43. One-pot coupling procedure using PyBrop **64**.

Table 1. Phosphonium-based coupling reagents

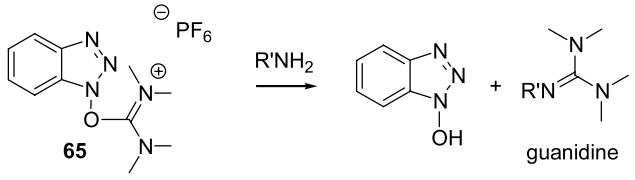




Scheme 44. One-pot coupling procedure using HBTU **65** or TBTU **66**.



Scheme 45. Equilibrium between uronium and guanidinium species.

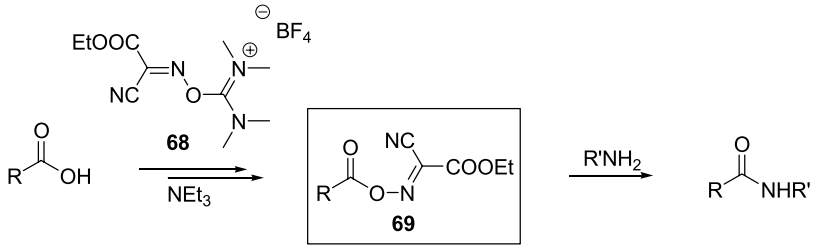


Scheme 46. Potential guanidine by-product formation when using HBTU **65**.

2.5.2.2.2. Uronium salts. Another family of reagents has been developed around uronium species such as *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) **65**[105] or its tetrafluoroborate equivalent TBTU **66**.[106] The counterion has no influence on the reactivity. The coupling is performed in a similar way to that using the phosphonium species. In this case, the driving force is the generation of the urea by-product (Scheme 44).

In solution, benzotriazole uronium species (*O*-form) are in equilibrium with the guanidinium species (*N*-form). The guanidinium *N*-form is usually reported as the crystalline form (Scheme 45).[107] HATU **67** has been proven to be very efficient in difficult sterically hindered couplings and usually gives a minimal level of racemisation.[108,109] It involves the formation of 7-azabenzotriazol-1-yl esters, very highly reactive species towards amines, probably because of intramolecular general base catalysis.

Uronium species are also known to be guanidylation agents (Scheme 46). This side reaction can be diminished by adding HOBt **41** to the reaction (a similar concept to the use of DCC **22** and HOBt **41**).



Scheme 47. One-pot coupling procedure using TOTU **68**.

Table 1 gives a non exhaustive list of other literature phosphonium-based coupling agents,[95–104] and their mechanisms can be easily deduced by comparison with the reagents previously described.

As explained for the phosphonium salts (see PyBrop **64**), one of the limitations of the activated esters (HOBt etc.) is the steric hindrance during the aminolysis step (e.g., α,α-dialkyl-amino acids or *N*-alkyl-amino acids). Some novel

Table 2. Uronium/Guanidinum-based coupling reagents

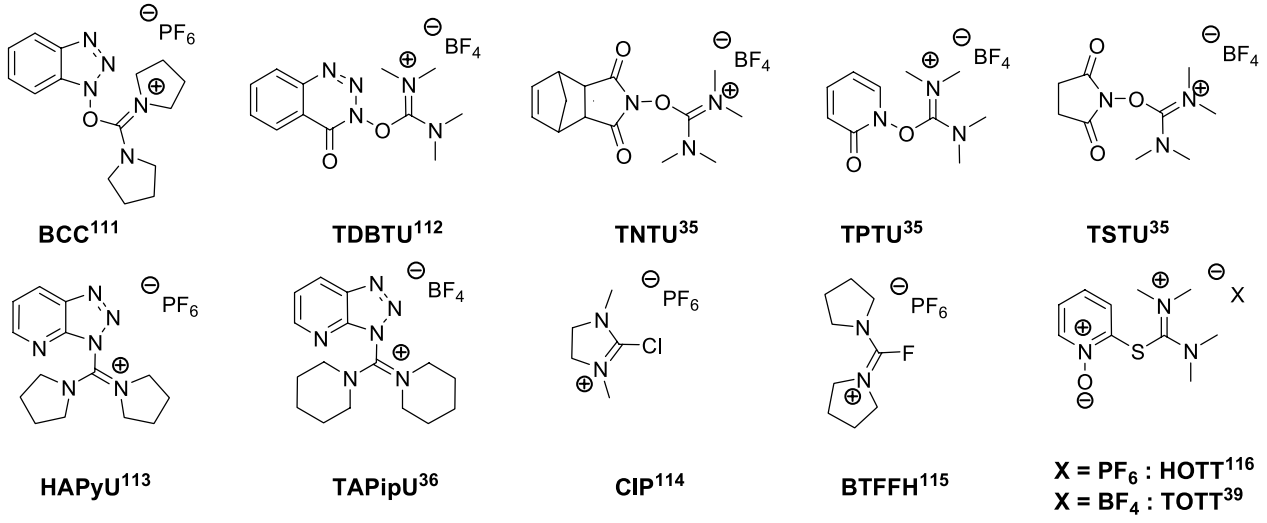
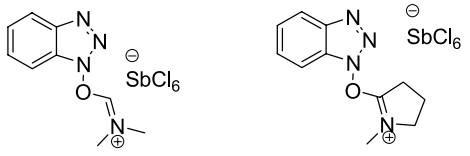


Table 3. Iminium-based coupling reagents



BOMI[117] **BDMP**[118]

coupling reagents have been designed to offer alternative activation intermediates. For example, *O*-((ethoxycarbonyl)cyanomethylene amino)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TOTU) **68** generates an activated acyl oxime **69** and low-racemisation peptide couplings have been described (Scheme 47).[110]

Tables 2 and 3 give a non-exhaustive list of, respectively, other literature uronium- and iminium-based coupling agents.[35,36,39,111–118] Iminium-based reagents can be considered as an extension of their uronium-based counterparts and analogous mechanisms can be applied. These reagents are used either on their own or in combination with HOBt **41**.

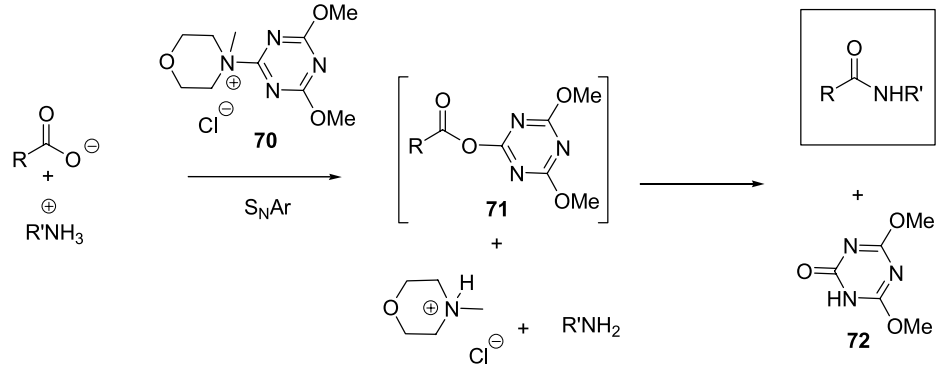
2.5.2.2.3. Ammonium salts.

2.5.2.2.3.1. Triazinyl esters. Recently, Kunishima and co-workers[119,120] have described the use of 4-(4,6-dimethoxy-(1,3,5)triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM) **70** as an effective activating agent not only for ester coupling, but also for amide bond formation and peptide synthesis (Scheme 48).[121] This reagent initially undergoes similar S_NAr reactions as in the case of cyanuric fluoride (see Section 2.1.2). The activated ester **71** is then displaced by the amine. The advantage of this one-pot procedure is that no additional base is required as *N*-methylmorpholine is liberated during the first step. The triazinone by-product **72** is easily eliminated by aqueous washing.

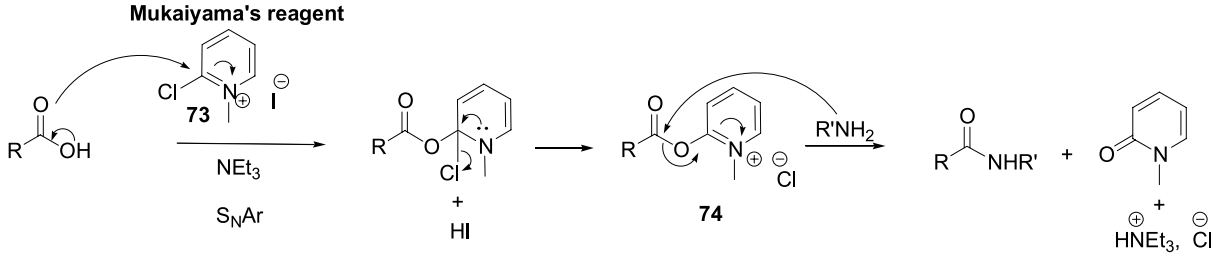
2-Chloro-4,6-dimethoxy-1,3,5-triazine has also been utilised. It is a commercially available and very cheap reagent. As mentioned previously for DMTMM **70**, a similar mechanism occurs. The insoluble hydroxytriazine by-product is formed and can be removed by filtration.[122]

2.5.2.2.3.2. Mukaiyama's reagent. Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide **73**, gives, in the presence of a carboxylic acid and a tertiary amine, an activated pyridinium ester **74** that reacts with a range of nucleophiles. Some of the applications include the conversion of β-amino acids into β-lactams, the formation of esters (e.g., activated Bt ester) and amides (Scheme 49).[123] This reagent is not often used in peptide synthesis and, due to the poor solubility of the pyridinium iodides in conventional solvents, the reaction has to be performed under reflux in methylene chloride.

Recently, Xu et al. have published alternatives to Mukaiyama's reagent **73**. In order to improve the solubility of the pyridinium compounds, the tetrafluoroborate and hexachloroantimonate counterions were adopted (Fig. 4). 2-Bromo-3-ethyl-4-methylthiazolium tetrafluoroborate (BEMT) **75** was successfully applied to the synthesis of oligopeptides containing *N*-alkyl or α-*C*-dialkyl amino acids,[124] and, later, they developed other 2-halopyridinium salts such as 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) **76**, 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP) **77**, 2-bromo-1-ethylpyridinium hexachloroantimonate (BEPH) **78**, and 2-fluoro-1-ethylpyridinium hexachloroantimonate (FEPH) **79**.[125] These α-halopyridinium-type coupling reagents were also used in solid-phase peptide



Scheme 48. One-pot coupling procedure using DMTMM **70**.



Scheme 49. One-pot coupling procedure using Mukaiyama's reagent **73**.

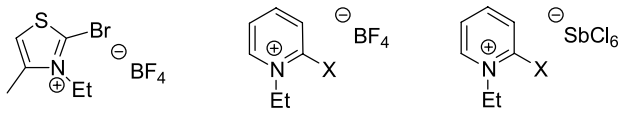


Figure 4. Alternative Mukaiyama-type reagent with improved solubility.

synthesis, especially for the synthesis of peptides containing *N*-methyl amino acid residues.

2.6. Other coupling methods

This section will review some original strategies and alternative methods to generate an amide bond, as well as providing a brief overview on the use of solid-supported strategies for the formation of amides.

2.6.1. Staudinger ligation. The Staudinger ligation[126] of peptides with a *C*-terminal phosphinothioester **80** and an *N*-terminal azide **81** is an emerging method in protein synthesis from peptide fragments (Scheme 50).

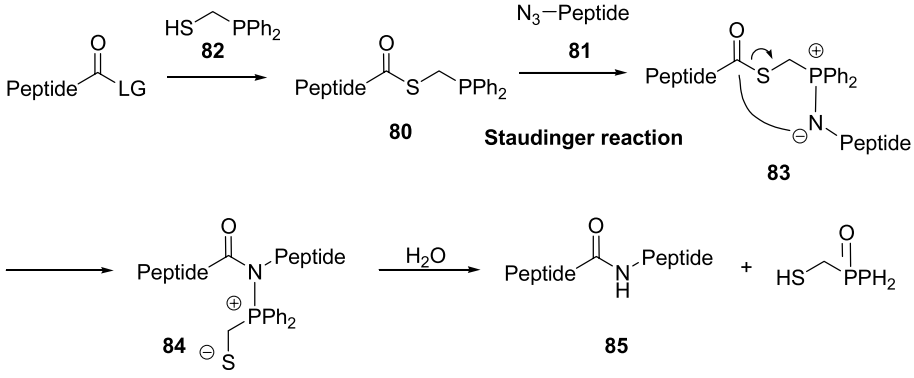
The first stage is to prepare the two peptides. The *C*-terminal part of the first peptide is coupled with the phosphinomethyl thiol **82** and the *N*-terminal part of the second peptide is converted into the corresponding azide **81**. The two fragments are then reacted together and undergo a Staudinger type of reaction, detailed in Scheme 51, to lead to the iminophosphorane **83**. This intermediate readily undergoes an *S*- to *N*-acyl transfer to produce the corresponding amidophosphonium salt **84**. Hydrolysis generates the desired amide **85**.

2.6.2. Using proteases and amidases. Although proteases and amidases naturally hydrolyse amide bonds, there are examples in the literature, which show their use to form amide bonds. Two different methods are used, namely thermodynamic and kinetic control.

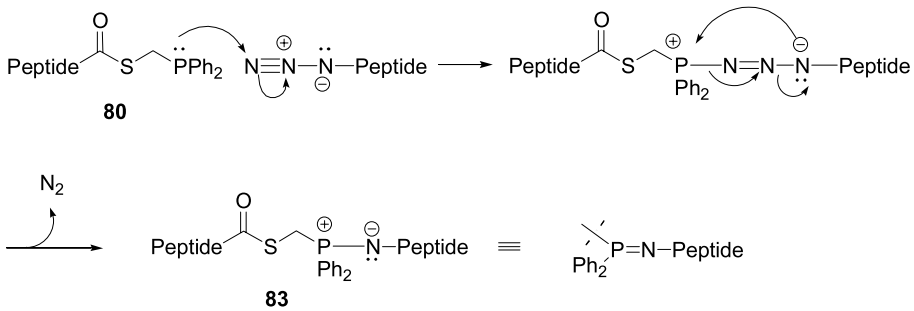
Under thermodynamic control, the reaction conditions are modified to drive the equilibrium to the synthesis of the amides, instead of their hydrolysis. For example, replacing the water by organic solvents to suppress the ionisation of the starting material, or increasing the concentration of the starting materials, or choosing protective groups to promote precipitation of the product, can tilt the equilibrium towards amide bond formation.[127]

Under kinetic control, the carboxylic compound is usually activated as an ester, which forms with the enzyme an acyl enzyme intermediate, which subsequently reacts with the amine to give the desired amide. Kinetically controlled syntheses are more common and generally faster than those which are thermodynamically controlled.

Enzymes belonging to the following families are routinely used as catalysts: proteases,[128] subtilisin,[129] acylases, amidases and lipases.[130] One of the main disadvantages of biocatalysis is that enzymes only feature limited substrate compatibility. Therefore, the enzymatic approach is often neglected at the discovery stages, because it frequently requires a time-consuming screening process, even to establish the feasibility, whereas it is strongly considered



Scheme 50. Staudinger ligation.



Scheme 51. Mechanism of Staudinger reaction.

at the process development stage where the optimisation efforts are worthwhile, considering the following potential synthetic and economic advantages of biocatalysis:

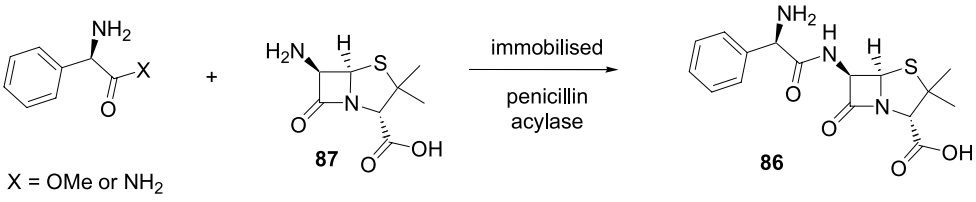
- reaction temperatures are significantly reduced to near-ambient conditions and, as a result, its applications can be extended to thermally labile compounds.
- reactions are frequently performed in aqueous media, which considerably reduces the problem of production waste management and enables the implementation of environmentally friendly chemistry (Green Chemistry).
- use of immobilised enzyme reactors or enzyme membrane reactors facilitates the purification and allows an easy recycling of the enzymatic catalyst.
- with enzymes, enantioselectivity of over 99% ee can be achieved routinely (although by no means in every case), allowing the manufacture of enantiomerically pure drugs or advanced pharmaceutical intermediates.

Kyotorphin (Tyr-Arg),[131] a potent analgesic, was produced on a kilogram scale using α-chymotrypsin, a peptidase isolated from bovine pancreas, as catalyst. Unprotected tyrosine and arginine were selectively coupled to form only one out of the two possible dipeptides. Another industrial example is the 100 tons-per-year production of ampicillin **86** (penicillin-derived antibiotic) from 6-aminopenicillanic acid (6-APA) **87**. 6-APA is subjected to an enzymatic acylation reaction in the presence of immobilised penicillin acylase with phenylglycine methyl ester or amide (Scheme 52).[132]

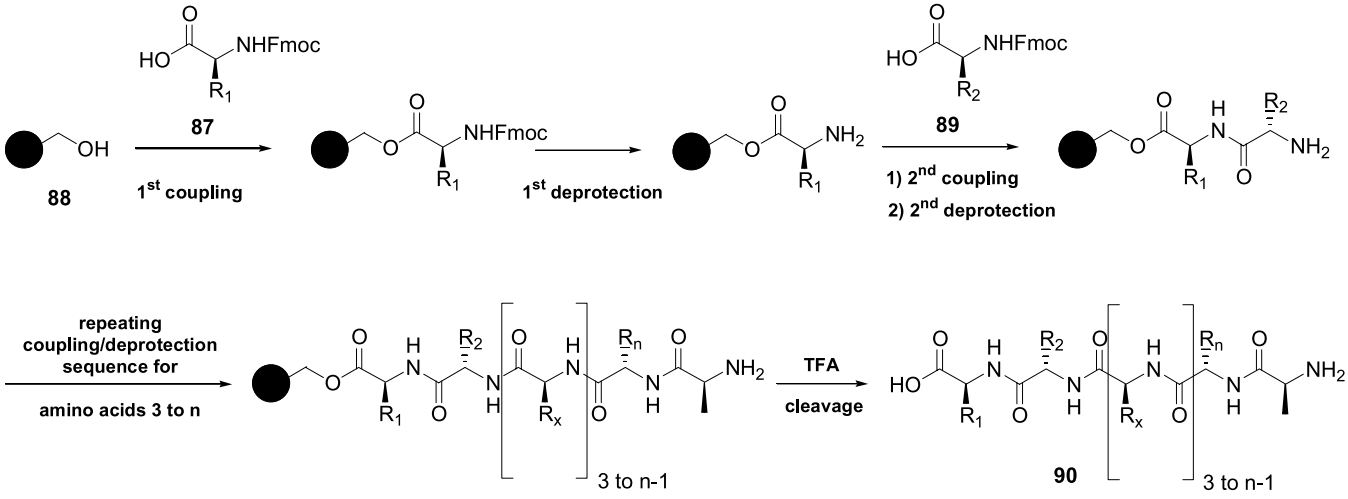
Gotor et al. reported *Candida antartica* lipase (CAL)- and *Pseudomonas cepacia* lipase-catalysed amidation reactions of β-hydroxyesters,[133] β-aryl esters,[134] α,β-unsaturated esters,[135] α-haloesters[136] or diesters using different types of methyl and ethyl esters.

2.6.3. Microwave activation. In several cases, microwave irradiation has been a successful alternative to conventional high temperatures to perform direct condensation of amines to carboxylic acids without prior activation. The use of direct microwave heating is reported to reduce the chemical reaction time, reduce side reactions, increase yields and improve reproducibility.[137] The microwave irradiation may be run with or without catalyst.[138] Different kinds of catalysts such as K-10 montmorillonite,[139] imidazole,[140] zeolite-HY,[141] polyphosphoric acid,[142] *p*-toluenesulfonic acid,[143] $TaCl_5$-silica gel,[144] KF-alumina and -silica gel[145] have been used.

2.6.4. Solid-phase strategy. No attempt is made here to provide an exhaustive catalogue of solid-phase coupling conditions, but merely to demonstrate that solid-supported strategies can advantageously be used to synthesise amides. Methods involving solid-phase have been initially developed to facilitate the synthesis of peptides.[146] This process is now performed on automated synthesisers that can assemble sequences of up to 50 amino acids in a few days. During the last two decades, solid-supported chemistry has yielded numerous applications, especially in the field of parallel and combinatorial chemistry.[147] Amides are a convenient way of introducing a point of diversity on a template as numerous amines and acids are commercially available. Using such parallel techniques, libraries of more than 20,000 compounds have been produced. Three different strategies are used in solid-supported synthesis:



Scheme 52. Industrial multi-ton process for production of ampicillin **86**.

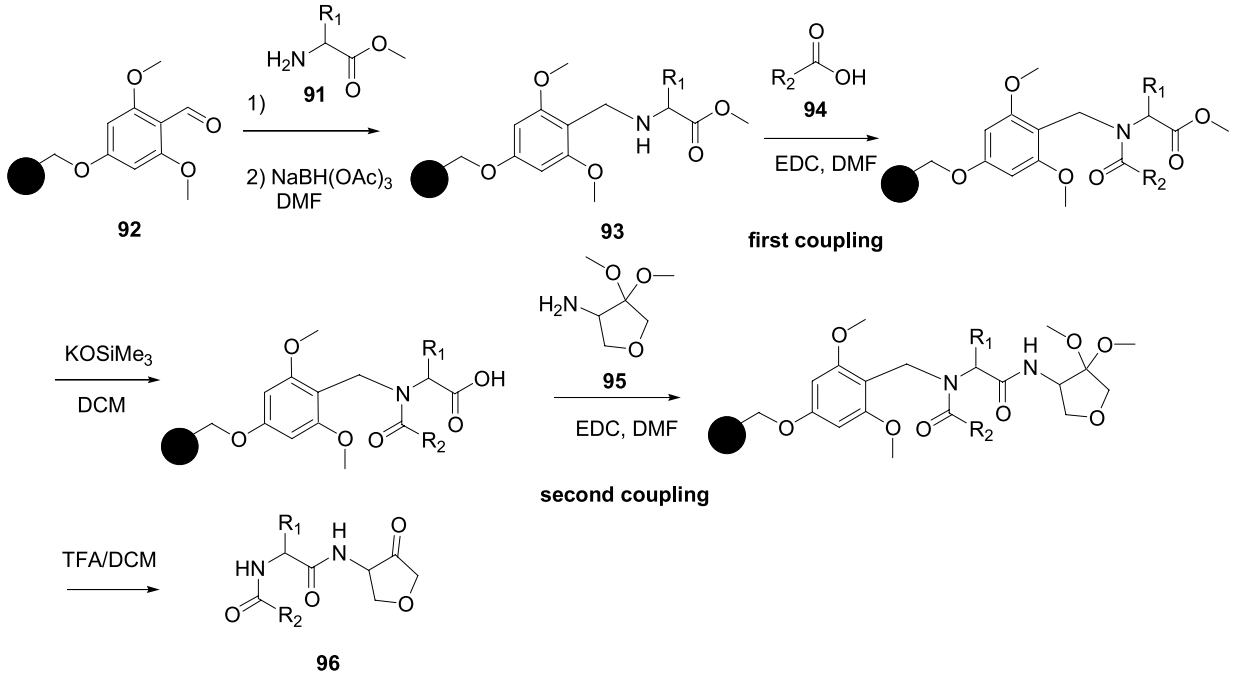


Scheme 53. Solid-supported peptide synthesis.

- classical polymer-supported synthesis
- polymer-supported reagents
- catch and release strategy.

2.6.4.1. Classical polymer-supported synthesis. One of the best examples of amide bond formation on solid-phase is encountered in peptide synthesis.[148] The principle of polymer-supported peptide synthesis is illustrated in Scheme 53. The first *N*-protected amino acid **87** is loaded onto the resin **88** using standard coupling reagents. After removal of the protecting group, the second *N*-protected amino acid **89** is coupled to the first. This sequence is repeated until all desired amino acids are loaded. The last step is the cleavage of the final peptide **90** from the polymer support. The choice of the resin and the *N*-protecting group is crucial as the conditions of the repeated coupling/deprotection sequences should not trigger a premature cleavage of the unfinished peptide or induce alteration of the polymer-supported peptide. For example, hydroxybenzyl-based resins such as Wang resin are stable under basic conditions and are advantageously used in conjunction with fluorenemethyloxycarbonyl (Fmoc) *N*-protected amino acids. The peptide is cleaved off the resin under acidic conditions using trifluoroacetic acid (TFA). Fmoc is readily removed under basic conditions with a piperidine solution wash and is stable in the presence of standard uronium/phosphonium coupling reagents such as PyBop® **62**, PyBrop **64**, TBTU **66** etc.

The amide functionality is often used as a convenient way of introducing diversity in parallel synthesis as numerous acids/acyl chlorides and amides are commercially available. Both the amine or the acid can be polymer-supported, as illustrated in Scheme 54.[149] In this example an α-amino methyl ester **91** is loaded via reductive amination on an aldehyde resin **92**.[150] The resulting secondary amine **93** is then coupled to a selection of acids **94**. After saponification of the polymer-supported amino acid, a functionalised amine **95** is coupled. Both coupling were performed using



Scheme 54. Solid-phase multistep synthesis.

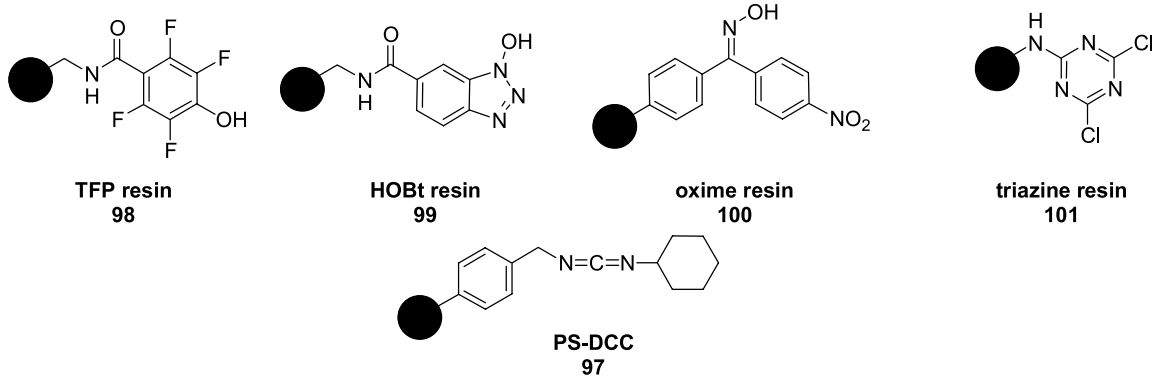


Figure 5. Resins for solid-phase-assisted amide synthesis.

3 equivalents of EDC **37** and an excess of acid or amine. The final release of the final compound **96** is performed under acidic cleavage conditions.

This method presents the usual advantages of solid-phase chemistry. The reagents can be used in a large excess to push the reaction to completion and the final excess of reagent and by-products can be washed off. The full range of coupling reagents and methods are potentially applicable and the choice has to be case based.

2.6.4.2. Polymer-supported reagents. The second strategy consists of using polymer-supported activating agents such as PS-DCC **97** (Fig. 5). The main advantage is that the coupling reagent-related by-products are polymer bound and easy to eliminate by filtration.

2.6.4.3. Catch and release strategy. The final strategy entails immobilising the acid on a polymer-support as an active ester. When reacted with a nucleophile such as an amine, the amide is cleaved off the resin. The main difference between this and the previous strategy is that this latter method usually tolerates the performance of some chemistry on the polymer-supported ester, provided that strong nucleophiles are avoided. During the cleavage, a limiting amount of amine can be used to avoid the presence of excess amine in the final mixture. The acid is loaded onto the resin using classic ester condensations methods for tetrafluorophenol (TFP) resin **98**,[151] HOBt resin **99**[152] and oxime resin **100**.[153] The triazine resin **101** is loaded via an aromatic nucleophilic substitution in the presence of the acid (Fig. 5).[154]

3. Conclusions

Methodologies to form an amide bond have been described since the beginning of organic chemistry, but, in the past two decades, the design and the synthesis of innovating coupling reagents has been an area of intense investigation. Most of these new developments were originally aimed towards the highly demanding and specialised field of peptide synthesis. Indeed, many of these reagents have been developed on purpose, to enable the coupling of specific amino acids, or to work in conjunction with a precise protecting group (e.g., Fmoc, Boc etc.). The main difficulties to overcome were to synthesise hindered peptides, to avoid racemisation or to be robust enough for solid-phase synthesis. Today, peptides are routinely synthesised on solid support using automated systems. Furthermore, a significant number of the coupling reagents described in this review are commercially available and have significantly expanded the arsenal of the synthetic chemist for the formation of any type of amide bonds.

The predominance of carbodiimide and active ester techniques has been gradually replaced with the so-called ‘onium salts’. Among these reagents, HOBt- and HOAt-based uronium, phosphonium and immonium salts are proving to be very efficient. Many other reagents, however, could be more adapted to a specific case, since they might be cheaper or facilitate the final purification. For example, robust and classical methods involving acyl halides, anhydrides, acylimidazoles and enzymes are still largely used and should be considered.

Therefore, depending on the demands of the specific synthesis, the chemist will have a choice between many different conditions and strategies, as widely enumerated in this review.

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References and notes

1. Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55–68.
2. Stryer, L. In *Biochemistry* 4th ed.; W. H. Freeman: New York, 1995; Chapter 2, pp 17–25.
3. Ulijn, R. V.; Moore, B. D.; Janssen, A. E. M.; Halling, P. J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1024–1028.
4. (a) Jursic, B. S.; Zdravkovski, Z. *Synth. Commun.* **1993**, *23*, 2761–2770. (b) Beckwith, A. L. J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Synthesis of Amides; Interscience: London, 1970; pp 105–109.
5. (a) *Synthetic Reagents*; Pizey, J. S., Ed.; Wiley: New York, 1974; Vol. 1, pp 321–357. (b) *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: New York, 1999; pp 370–373. (c) Chu, W.; Tu, Z.; McElveen, E.; Xu, J.; Taylor, M.; Luedtke, R. R.; Mach, R. H. *Bioorg. Med. Chem.* **2005**, *13*, 77–87.
6. (a) Adams, R.; Ulrich, L. H. *J. Am. Chem. Soc.* **1920**, *42*, 599–611. (b) Kuwajima, I.; Urabe, H. In *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 486–489.
7. Knapp, S.; Gibson, F. S. In *Organic Syntheses*; Wiley: New York, 1998, Collect. Vol. IX, pp 516–521.
8. *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: New York, 1999; p 333.
9. Klosa, J. *J. Prakt. Chem. (Leipzig)* **1962**, *19* (No. 1–2), 45–55.
10. (a) Antell, M. F. In *The Chemistry of Acyl Halides*; Patai, S., Ed.; Interscience: London, 1972; pp 40–44. (b) *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: New York, 1999; pp 335–338.
11. Vogel, A. I.; Tatchell, A. R.; Furnis, B. S.; Hannaford, A. J.; Smith, P. W. G. *Vogel’s Textbook of Practical Organic Chemistry,* 5th ed.; Prentice Hall: Harlow, 1996; p 1073.
12. Bruckner, R. *Advanced Organic Chemistry, Reaction Mechanisms*; Harcourt/Academic: San Diego, 2002; p 238.
13. Urben, P. G. *Bretherick’s Handbook of Reactive Chemicals Hazards*, 6th ed.; Butterworth–Heinemann: Oxford, 1999; p 230.
14. (a) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653–1658. (b) Bruckner, R. *Advanced Organic Chemistry, Reaction Mechanisms*; Harcourt/Academic: San Diego, 2002; p 239.

15. Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, *32*, 3037–3040.
16. Rayle, H. L.; Fellmeth, L. *Org. Process Res. Dev.* **1999**, *3*, 172–176.
17. (a) Lee, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3440. (b) Crofts, P. C.; Downie, I. M. *J. Chem. Soc., Abstr.* **1963**, 2559–2560. (c) Downie, I. M.; Lee, J. B.; Matough, M. F. S. *Chem. Commun.* **1968**, 1350–1351.
18. Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *12*, 801–811.
19. Carbon tetrachloride is ozone depleting chemical and is toxic to aquatic organisms.
20. Villeneuve, G. B.; Chan, T. H. *Tetrahedron Lett.* **1997**, *38*, 6489–6492.
21. Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323–5326.
22. Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180–1181.
23. Sānchez-Sancho, F.; Mann, E.; Herradōn, B. *Synlett* **2000**, *4*, 509–513.
24. Bouron, E.; Goussard, G.; Marchand, C.; Bonin, M.; Pannecoucke, X.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 7227–7230.
25. Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494–501.
26. Meshram, H. M.; Reddy, G. S.; Reddy, M. M.; Yadav, J. S. *Tetrahedron Lett.* **1998**, *39*, 4103–4106.
27. Luknitskii;, F. I.; Vovsi, B. A. *Usp. Khim.* **1969**, *38*, 1072–1088.
28. For a review on peptide coupling using acyl halides: Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268–274.
29. Carpino, L. A.; Sadar-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651–9652.
30. (a) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487. (b) Savrda, J.; Chertanova, L.; Wakselman, M. *Tetrahedron* **1994**, *50*, 5309–5322.
31. Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401–5402.
32. El-Faham, A. *Chem. Lett.* **1998**, 671–672.
33. Badu, S. V. V.; Gopi, H. N.; Ananda, K. *Indian J. Chem. Sect. B* **2000**, *39*, 384–386.
34. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.
35. LaI, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem.Commun.* **1999**, 215–216.
36. Pryor, K. E.; Shipps, G. W., Jr.; Skyler, D. A.; Rebek, J., Jr. *Tetrahedron* **1998**, *54*, 4107–4124.
37. Froeyen, P. *Synth. Commun.* **1995**, *25*, 959–968.
38. Bestmann, H. J.; Kunstmann, R.; Schulz, H. *Justus Liebigs Ann. Chem.* **1966**, *699*, 33–39.
39. Saraf, S. D.; Zaki, M. *Synthesis* **1973**, 612.
40. Bains, S.; Green, J.; Tan, L. C.; Pagni, R. M.; Kabalka, G. W. *Tetrahedron Lett.* **1992**, *33*, 7475–7476.
41. Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039–4040.
42. DalPozzo, A.; Ni, M.; Muzi, L.; Caporale, A.; de Castiglione, R.; Kaptein, B.; Broxterman, Q. B.; Formaggio, F. *J. Org. Chem.* **2002**, *67*, 6372–6375.
43. Devos, A.; Remion, J.; Frisque-Hesbain, A. M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, *24*, 1180–1181.
44. Klausner, Y.; Bodansky, M. *Synthesis* **1974**, 549–559.
45. Curtius, Th. *Berichte der Deutschen Chemischen Gesellschaft* **1902**, *35*, 3226–3228.
46. (a) Curtius, T. *Ber.* **1890**, *23*, 3023. (b) Curtius, T. *J. Prakt. Chem. [2]* **1894**, *50*, 275. (c) Smith, P. A. S. *Org. React.* **1946**, *3*, 337–449.
47. Shioiri, T.; Ninomiya, K.; Yamada, S. Y. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
48. Paul, R.; Anderson, W. *J. Am. Chem. Soc.* **1960**, *82*, 4596–4600.
49. Staab, H. A. *Justus Liebigs Ann. Chem.* **1957**, *609*, 75–83.
50. Staab, H. A.; Lueking, M.; Duerr, F. H. *Chem. Ber.* **1962**, *95*, 1275–1283.
51. Dale, D. J.; Draper, J.; Dunn, P. J.; Hughes, M. L.; Hussain, F.; Levett, P. C.; Ward, G. B.; Wood, A. S. *Org. Process Res. Dev.* **2002**, *6*, 767–772.
52. Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7485–7488.
53. (a) Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856. (b) Gibson, F. S.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2615–2617.
54. Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233–284.
55. Wittenberger, S. J.; McLaughlin, M. A. *Tetrahedron Lett.* **1999**, *40*, 7175–7178.
56. Chu, W.; Tu, Z.; McElveen, E.; Xu, J.; Taylor, M.; Luedtke, R. R.; Mach, R. H. *Bioorg. Med. Chem.* **2005**, *13*, 77–87.
57. Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651–1652.
58. Leuchs, H. *Berichte der Deutschen Chemischen Gesellschaft* **1906**, *39*, 857–861.
59. Poduska, K.; Gross, H. *Chem. Ber.* **1961**, *49*, 527–537.
60. Fuller, W. D.; Cohen, M. P.; Shabankareh, M.; Blair, R. K. *J. Am. Chem. Soc.* **1990**, *112*, 7414–7416.
61. (a) Broekema, R.; Van Der Werf, S.; Arens, J. F. *Recl. Trav. Chim.* **1958**, *77*, 258–266. (b) Sheehan, J. C.; Hlavka, J. J. *J. Org. Chem.* **1958**, *23*, 635–636.
62. Simmons, H.; Erdman, J. R. *J. Org. Chem.* **1968**, *33*, 3808–3816.
63. Pelter, A.; Levitt, T. E.; Nelsoni, P. *Tetrahedron* **1970**, *26*, 1539–1544.
64. Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, *12*, 1013.
65. Tani, J.; Oine, T.; Junichi, I. *Synthesis* **1975**, 714–716.
66. Pelter, A.; Levitt, T. E. *Tetrahedron* **1970**, *26*, 1545–1553.
67. Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393–4394.
68. Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196–4197.
69. Ishihara, K.; Ohara, S.; Yamamoto, H. *Macromolecules* **2000**, *33*, 3511–3513.
70. Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068.
71. Sheehan, J.; Cruickshank, P. A. *J. Org. Chem.* **1961**, *26*, 2525–2528.
72. Smith, M. B.; March, J. In *March's Advanced Organic Chemistry, Reactions, Mechanisms, and Structure*, 5th ed.; Wiley-Interscience: New York, 2001.
73. Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1973**, *95*, 4052–4053.
74. (a) Schuessler, H.; Zahn, H. *Chem. Ber.* **1962**, *95*, 1076–1080. (b) Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1974**, *96*, 1606–1607.
75. Windridge, G. C.; Jorgensen, E. C. *J. Am. Chem. Soc.* **1971**, *17*, 6318–6319.

76. Chakrabarti, J. K.; Hotten, T. M.; Pullar, I. A.; Tye, N. C. *J. Med. Chem.* **1989**, *32*, 2573–2582.
77. Chicharro, R.; Castro, S.; Reino, J. L.; Aran, V. J. *Eur. J. Org. Chem.* **2003**, *12*, 2314–2326.
78. Adamczyk, M.; Grote, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1539–1541.
79. Gangwar, G. M.; Pauletti, T.; Siahaan, J.; Stella, V. J.; Borchardt, R. T. *J. Org. Chem.* **1997**, *62*, 1356–1362.
80. Kisfaludy, L.; Schón, I.; Szirtes, T.; Nyéki, O.; Lów, M. *Tetrahedron Lett.* **1974**, *19*, 1785–1786.
81. Rajappan, V. P.; Hosmane, R. S. *Synth. Commun.* **1998**, *28*, 753–764.
82. Kisfaludy, L.; Schon, I. *Synthesis* **1983**, 325–326.
83. Bentley, P. H.; Gregory, H.; Laird, A. H.; Morley, J. S. *J. Chem. Soc., Suppl.* **1964**, 6130–6138.
84. Fujino, M.; Kobayashi, S.; Obayashi, M.; Fukuda, T.; Shinagawa, S.; Nishimura, O. *Chem. Pharm. Bull.* **1974**, *22*, 1857–1863.
85. Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 585–590.
86. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.
87. Ogura, H.; Kobayashi, T.; Shimizu, K.; Kawabe, K.; Takeda, K. *Tetrahedron lett.* **1979**, *20*, 4745–4746.
88. Jaoudai, M.; Martinez, J.; Castro, B.; Barcelo, G.; Sennyey, G.; Senet, J.-P. *J. Org. Chem.* **1987**, *52*, 2364–2367.
89. Woodward, R.; Olofson, R. A.; Mayer, M. *J. Am. Chem. Soc.* **1961**, *83*, 1010–1012.
90. *Heterocyclic Chemistry*, 3rd ed.; Gilchrist, T. L., Ed.; Addison Wesley Longman: Harlow, 1997; p 333.
91. Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219–1222.
92. Castro, B.; Dormoy, J.-R.; Dourtoglou, B.; Evin, G.; Selve, C.; Ziegler, J.-C. *Synthesis* **1976**, 751.
93. (a) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron. Lett.* **1990**, *31*, 205–208. (b) Wang, W.; McMurray, J. S. *Tetrahedron Lett.* **1999**, *40*, 2501–2504.
94. (a) Coste, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967–1970.(b) Coste, J.; Castro, B. Fr. Patent 89-02-361
95. Carpino, L. A.; El-Faham, A.; Albericio, F. *Tetrahedron Lett.* **1994**, *35*, 2279–2282.
96. Albericio, F.; Cases, M.; Alsina, J.; Triolo, S. A.; Carpino, L. A.; Kates, S. A. *Tetrahedron Lett.* **1997**, *38*, 4853–4856.
97. Coste, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669–672.
98. Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967–1970.
99. Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711–6714.
100. Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91–93.
101. Kim, S.; Chang, H.; Ko, Y. K. *Tetrahedron Lett.* **1985**, *26*, 1341–1342.
102. Ramage, R.; Hopton, D.; Parrott, M. J.; Richardon, R. S.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, *3*, 461–470.
103. Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernàndez-Lizarde, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.
104. Pettit, G. R.; Taylor, S. R. *J. Org. Chem.* **1996**, *61*, 2322–2325.
105. (a) Dourtoglou, V.; Ziegler, J.-C.; Gross, B. *Tetrahedron Lett.* **1978**, *15*, 1269–1272. (b) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927–1930.
106. Pettit, G. R.; Taylor, S. R. *J. Org. Chem.* **1996**, *61*, 2322–2325.
107. Abdelmoty, I.; Albericio, F.; Carpino, L. A.; Foxman, B. M.; Kates, S. A. *Lett. Pept. Sci.* **1994**, *1*, 57–67.
108. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.
109. Carpino, L. A.; El-Faham, A.; Albericio, F. *Tetrahedron Lett.* **1994**, *35*, 2279–2282.
110. Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625–6628.
111. Chen, S.; Xu, J. *Tetrahedron Lett.* **1992**, *33*, 647–650.
112. Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927–1930.
113. (a) Albericio, F.; Cases, M.; Alsina, J.; Triolo, S. A.; Carpino, L. A.; Kates, S. A. *Tetrahedron Lett.* **1997**, *38*, 4853–4856. (b) Ehrlich, A.; Rothemund, S.; Brudel, M.; Beyermann, M.; Carpino, L. A.; Bienert, M. *Tetrahedron Lett.* **1993**, *34*, 4781–4784.
114. (a) Akaji, K.; Kuriyama, N.; Kiso, Y. *Tetrahedron Lett.* **1994**, *35*, 3315–3318. (b) Akaji, K.; Kuriyama, N.; Kiso, Y. *J. Org. Chem.* **1996**, *61*, 3350–3357.
115. El-Faham, A. *Chem. Lett.* **1998**, 671–672.
116. Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *J. Org. Chem.* **1999**, *64*, 8936–8939.
117. (a) Li, P.; Xu, J. C. *Tetrahedron Lett.* **1999**, *40*, 3605–3608. (b) Li, P.; Xu, J. C. *Tetrahedron Lett.* **2000**, *41*, 721–724.
118. Li, P.; Xu, J.-C. *Chem. Lett.* **1999**, 1163–1164.
119. Kunishima, M.; Kawachi, C.; Iwasaki, F.; Terao, K.; Tani, S. *Tetrahedron Lett.* **1999**, *40*, 5327–5330.
120. Kunishima, C.; Kawashi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **1999**, *55*, 13159–13170.
121. Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275–277.
122. Taylor, E. C.; Schrader, T. H.; Walensky, L. D. *Tetrahedron* **1992**, *48*, 19–32.
123. (a) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1164. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707–721. (c) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465–1466.
124. Xu, J. C.; Li, P. *Tetrahedron Lett.* **1999**, *40*, 8301–8304.
125. Li, P.; Xu, J.-C. *Tetrahedron* **2000**, *56*, 8119–8131.
126. Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Org. Chem.* **2002**, *67*, 4993–4996.
127. Oyama, K. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: Chichester, 1992; pp 237–247.
128. Morihara, K.; Oka, T. Enzymic Semisynthesis of Human Insulin by Transpeptidation Method with Achromobacter Protease: Comparison with the Coupling Method, 20th ed. In *Peptide Chemistry* 1983. Volume Date 1982, pp 231–236.
129. Moree, W. J.; Sears, P.; Kawashiro, K.; Witte, K.; Wong, C. H. *J. Am. Chem.* **1997**, *119*, 3942–3947.
130. Garcia, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1994**, *23*, 6935–6940.
131. Fischer, A.; Bommarius, A. S.; Drauz, K.; Wandrey, C. *Biocatalysis* **1994**, *8*, 289–307.
132. (a) WO9856946. (b) Schmid, A.; Hollmann, F.; Park, J. B.; Buhler, B. *Curr. Opin. Biotechnol.* **2002**, *13*, 359–366.
133. Garcia, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1993**, *4*, 2199–2210.
134. Gotor, V.; Menendez, E.; Mouloungui, Z.; Gaset, A. *J. Chem. Soc., Perkin Trans 1* **1993**, *20*, 2453–2456.
135. Sánchez, V.; Rebolledo, F.; Gotor, V. *Synlett* **1994**, 529–530.
136. Astorga, C.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1994**, *7*, 829–832.

137. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
138. (a) Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155–2162. (b) Vázquez-Tato, M. P. *Synlett* **1993**, 506. (c) Marrero-Terrero, A. L.; Loupy, A. *Synlett* **1996**, 245–246. (d) Seijas, J. A.; Vázquez-Tato, M. P.; Martinez, M. M.; Nunez-Corredoira, G. *J. Chem. Res., Synop.* **1999**, *7*, 420–421.
139. Ruault, P.; Pilard, J.-F.; Touaux, B.; Texier-Boullet, F.; Hamelin, J. *Synlett* **1994**, 935–936.
140. (a) Baldwin, B. W.; Hirose, T.; Wang, Z.-H. *Chem. Commun. (Cambridge)* **1996**, *23*, 2669–2670. (b) Hirose, T.; Baldwin, B. W.; Wang, Z. H. *Jpn. Kokai Tokkyo Koho* **1998**, 4.
141. Gadhwal, S.; Dutta, M. P.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Indian J. Chem., Sect. B* **1998**, *37*, 725–727.
142. El'tsov, A. V.; Martynova, V. P.; Sokolova, N. B.; Dmitrieva, N. M.; Brykov, A. S. *Zh. Obshch. Khim.* **1995**, *65*, 511–513.
143. Hajipour, A. R.; Ghasemi, M. *Indian J. Chem., Sect. B* **2001**, *40*, 504–507.
144. Chandrasekhar, S.; Takhi, M.; Uma, G. *Tetrahedron Lett.* **1997**, *38*, 8089–8092.
145. Marquez, H.; Plutin, A.; Rodriguez, Y.; Perez, E.; Loupy, A. *Synth. Commun.* **2000**, *30*, 1067–1073.
146. (a) *Chemical Approaches to the Synthesis of Peptides and Proteins*; Llyod-Williams, P., Albericio, F., Eds.; CRC: New York, 1997. (b) Stewart, J.; Young, J. In *Solid-phase Peptide Synthesis: A Practical Approach*; Atherton, E., Sheppard, R. A., Eds.; IRL: Oxford, 1989.
147. (a) Bunin, B. A., *The Combinatorial Index*; Academic: London, 1998. (b) Novabiochem catalogue 2004/5
148. Cammish, L. E.; Kates, S. A. In *Fmoc Solid-phase Peptide Synthesis: A Practical Approach*; Chan, W. C., White, P. D., Eds.; Oxford University Press: Oxford, 2000; p 227.
149. Fenwick, A. E.; Garnier, B.; Gribble, A. D.; Ife, R. J.; Rawlings, A. D.; Witherington, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 195–198.
150. Fivush, A. M.; Wilson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151–7154.
151. Salvino, J. M.; Kumar, N. V.; Orton, E.; Airey, J.; Kiesow, T.; Crawford, K.; Mathew, R.; Krolikowski, P.; Drew, M.; Engers, D.; Krolikowski, D.; Herpin, T.; Gardyan, M.; McGeehan, G.; Labaudiniere, R. *J. Comb. Chem.* **2000**, *2*, 691–697.
152. Baxendale, I. R.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1983–1986.
153. Scialdone, M. A. *Tetrahedron Lett.* **1996**, *37*, 8141–8144.
154. Masala, S.; Taddei, M. *Org. Lett.* **1999**, *1*, 1355–1357.

Biographical sketch

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Silicon guided rearrangement of epoxydecalines to spirocyclic compounds. Synthesis of gleenol and axenol from carvone

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Abstract—The synthesis of the spirocyclic sesquiterpenes (−)-gleenol and (−)-axenol in enantiomerically pure form has been achieved starting from *R*-(−)-carvone. The key step is the silicon guided acid-promoted rearrangement of a 9-trimethylsilyl-5,6-epoxy-noreudesmane prepared from 3-trimethylsilyldihydrocarvone in several steps involving Robinson annulation, enone deconjugation and epoxidation. Acid treatment of the epoxy-noreudesmane gave a norspiroaxane as the main product, which was used as intermediate for the synthesis of two naturally occurring sesquiterpenes gleenol and axenol.

1. Introduction

It is generally accepted that many biogenetic pathways leading to natural products involve the Wagner–Meerwein rearrangement of carbocationic intermediates. In the early past century, Robinson suggested that eremophilanes were formed in nature from C-5 cationic eudesmanoid precursors via a route involving methyl migration (Fig. 1, path a, X=Y=H).[1] A similar intermediate has been proposed as biogenetic precursor of sesquiterpenes bearing the spiro[4,5]decane framework, that is, spirovetivanes (path b, X=Y=H) and spiroaxanes (path c, X=Y=H, R=Me and R′=H, or R=H and R′=Me), via processes involving migration of C-1 or C-9 methylenes with concomitant contraction of the A or B ring, respectively.[2] Following our research on the synthesis of bioactive sesquiterpenes[3] we became interested in the use of such rearrangements in the laboratory as a synthetic route toward naturally occurring compounds. In particular, we were interested in the rearrangement of 4,5-epoxydecalins as a way to obtain 5-methyldecalin or spiro[4,5]decane-based compounds functionalized at C-4. Although such biomimetic approach has received some attention in the past,[4] the task, however, has been shown to be difficult and only very few successful examples have been described in the literature. Among them, we can mention the photochemical rearrangement of dienones leading to 1,2-methylene or 1,2-methyl migration products,[5] the thermal or acid-catalyzed rearrangements of eudesmanes with special structural features such as hydroxy enones to spirovetivanes,[6] and α,β-epoxy ketones to spirovetivanes or eremophilanes,[7] and the rearrangement of an epoxy eudesmanolide to an eremophilanolide.[8]

This fact may be due to one or more of these reasons: (a) lack of selectivity of the migrating group; (b) 1,2-elimination of the hydroxyl group before rearrangement[9] and; (c) a Grob-type rearrangement of the 1,3-hydroxy-carbocations that result after the initial rearrangement in the case of epoxides.[10] In previous articles, we have shown that some of these drawbacks can be overcome and selectivity during migration can be gained by introducing a TMS group in the vicinity of the migrating group, so methylene migration is preferred if the epoxide and the TMS group are on the same ring while methyl migration is the main pathway if they are on diferent rings of the decalin system.[11] For instance we have used the rearrangement of a 1-trimethylsilyl-4,5-epoxyeudesmane in a synthesis of spirovetivanes from santonin[12] and a similar strategy was used by Hwu[13] in a synthesis of solavetivone from carvone (Fig. 1, path b, X=Me_3Si, Y=H). In these cases the TMS group at C-1 promoted the migration of the methylene group C-9 toward the C-5 carbocation by stabilizing the forming carbocation at C-10 (β-effect), at the time it prevented further rearrangements in the resulting carbocation by rapidly eliminating the TMS group to form a double bond between C-1 and C-10 (super proton behavior).[14] According to these results it was envisaged that a similar rearrangement directed by a TMS group located at C-9 in the eudesmane framework should favor migration of methylene C-1, therefore, permitting the synthesis of spiroaxane type

Keywords: Spiroaxane sesquiterpenes; Wagner–Merweein rearrangement; Epoxides; Silicon; Carbocation.
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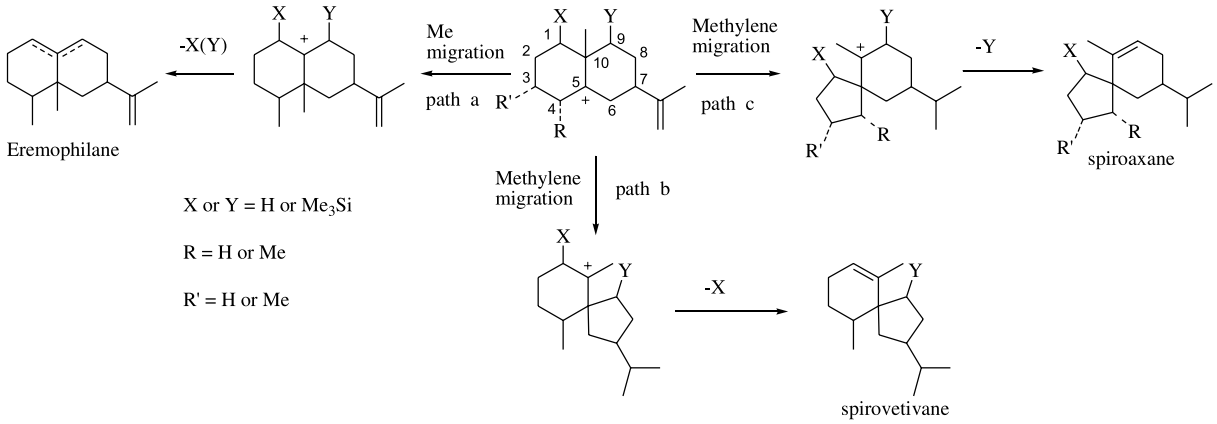
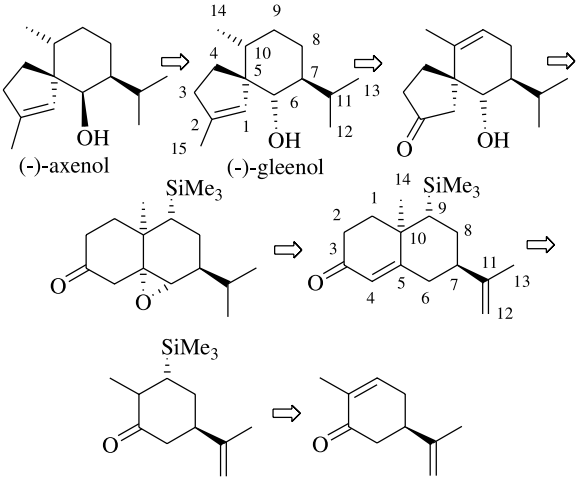


Figure 1. Cationic rearrangement of eudesmanes to eremophilanes and spirocyclic sesquiterpenes.

sesquiterpenes (Fig. 1, path c, X=H, Y=Me_3Si). In this article, we present our results in this subject and its application to the synthesis of (−)-gleenol and its C-6 epimer, (−)-axenol, which is the enantiomer of the naturally occurring (+)-axenol. (−)-Gleenol has been isolated from *Picea glehni*,[15] *Picea koraiensis*,[16] *Cryptomeria japonica*,[17] *Juniperus oxycedrus*,[18] and the brown alga *Taonia atomaria*.[19] Its enantiomer (+)-gleenol and the C-6 epimer of this, (+)-axenol, have been isolated from New Zealand *Eurypon* sp. sponges.[20] (+)-Gleenol shows termiticidal and antihelmintic activities,[21] and growth regulation effects on plant seeds. In recent years, some syntheses of gleenol and its C-6 epimer have been reported.[22]

2. Results and discussion

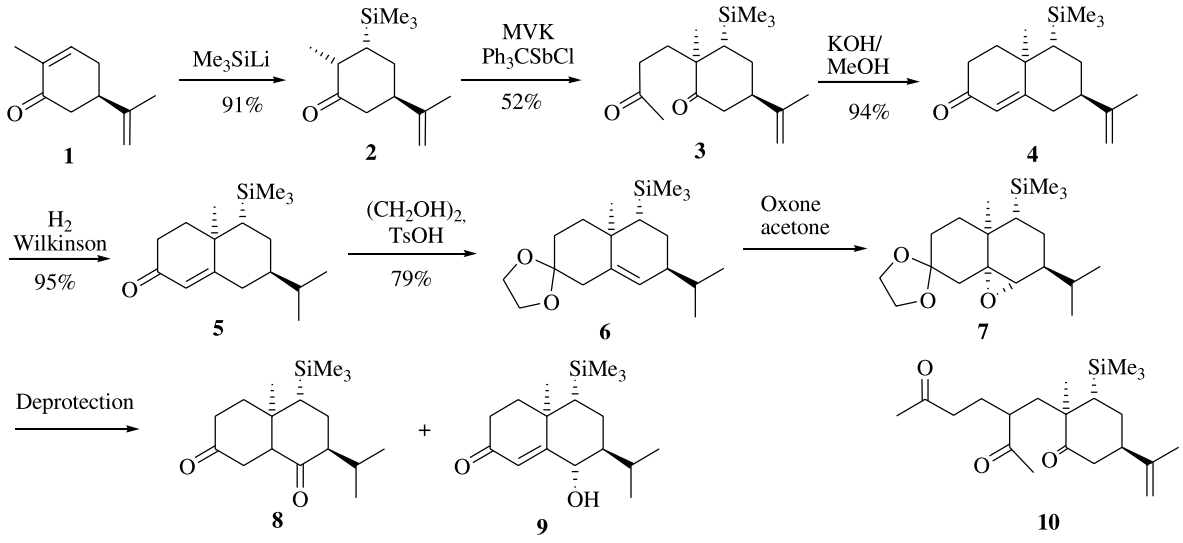
Our synthetic strategy was based on the rearrangement of a C-5 cationic decalinic intermediate guided by a silicon group located at C-9 of the decalin skeleton. Accordingly, the retrosynthetic analysis outlined in Scheme 1 was designed. *R*-(−)-carvone (**1**) was chosen as starting material, which would provide the B ring of the decalin system. Treatment of this compound with Me_3SiLi in THF at −78 °C in the conditions described by Still[23] gave



Scheme 1. Retrosynthetic analysis for axenol and gleenol and numbering system.

3-trimethylsilyldihydrocarvone **2** in 91% yield. The stereochemistry of C-3 in this compound was initially assigned according to the preference of the reagent for axial addition to cyclic enones, and was ascertained in further steps of the synthetic sequence (see below). In the next steps, the decalin system was built up via a Robinson annulation. Treatment of **2** with methyl vinyl ketone (MVK) in the presence of Ph_3CSbCl[24] gave a mixture from which compound **3** was isolated in 52% yield besides 27% of unreacted starting material. The reaction could not be extended until total consumption of **2** because of the formation of by-products resulting from Michael reaction between the formed compound **3** and MVK (compound **10**). Cyclization to the decalin was achieved by treatment of **3** with methanolic KOH in 94% yield.[25] The stereochemistry of compound **4** was established by NOE experiments. Thus, a NOE was observed between the signal at δ 0.91, corresponding to H-9, and the signal at δ 4.73 corresponding to the one of the olefinic protons of the isopropylidene chain. Furthermore, irradiation at the frequency of the methyl group signal (δ 1.28) gave NOEs with the signals corresponding to H-6α (δ 2.65) and H-7 (δ 2.57–2.46) proton, therefore, indicating the cis disposition of the TMS group and the trans disposition of the isopropylidene side chain relative to the bridgehead methyl, respectively. This result is similar to the one obtained with other Robinson annulation with 3-substituted dihydrocarvone.[26] Once the decalin system was obtained, the double bond in the side chain was selectively hydrogenated with the Wilkinson catalyst to give noreudesmane **5** (Scheme 2).

In order to achieve the cationic rearrangement of the decalin and to leave a functional group at C-6 we needed an epoxide in the C(5)–C(6) position, which means that deconjugation of the enone double bond was required. A first attempt to do so by treatment of **5** with strong base (potassium *tert*-butoxide) and reduction of the ketone[27] gave a complex reaction mixture. Therefore, deconjugation was achieved via acetal **6**, which was obtained by treatment of **5** with ethyleneglycol and *p*-toluenesulfonic acid (TsOH). Epoxidation of **6** with acetone–oxone gave only the α-epoxide **7** in 89% yield. However, all attempts to deprotect the acetal (HCl–acetone or montmorillonite KSF) were unsuccessful as they gave rise to the cleavage of the oxirane ring providing the 3,6-diketone **8** or the corresponding γ-hydroxyenone **9**. Therefore, we decided to carry out the

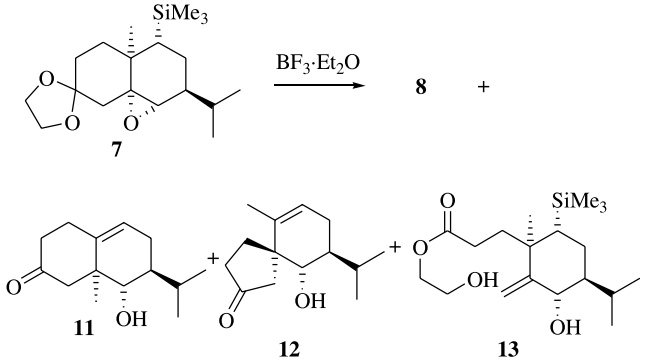


Scheme 2. Synthesis of epoxydecaline **7**.

cationic rearrangement to the spiroscyclic skeleton with compound **7**.

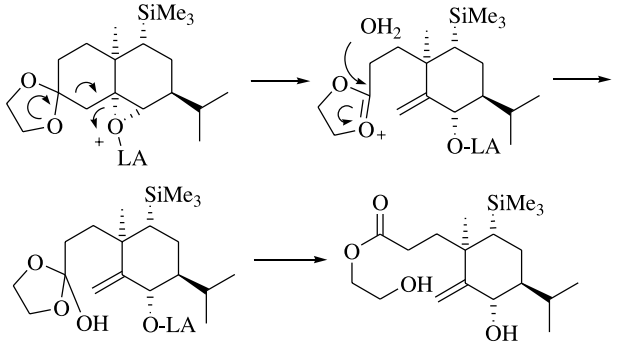
According to our previous findings,[11,12] we expected that rearrangement catalyzed by a Lewis acid and directed by the silicon group at C-9 would take place with preferential migration of the C-1 methylene group. Treatment of compound **7** with $BF_3{\cdot}Et_2O$ in different solvents gave product mixtures in which rearrangement via the C-5 carbocation was the main reaction pathway (Scheme 3). As we expected, the presence of the silicon group on the same ring of the epoxide favored the migration of methylene C-1 to give spirocompound **12** in a 4–5:1 ratio towards the methyl migration product **11**. Cleavage of the epoxide could not be completely avoided and compound **8** was also obtained after acidic treatment. Besides, a compound **13** resulting from cleavage of the acetal moiety was obtained. A possible mechanism for the formation of this compound is given in Scheme 4.

Compound **12**, obtained in this way was used as a synthetic intermediate for the synthesis of (−)-gleenol (**23**) and (−)-axenol (**21**). Hydrogenation of the double bond on Pd/C (5%) quantitatively gave two epimeric compounds **14** and **15** in 7:5 ratio, respectively. The stereochemistry of the new stereogenic center was assigned by NOE experiments. Thus, upon irradiation on the signal of the axial H-6 proton (δ 3.63, d, $J=10.0$ Hz) in compound **14**, NOE was observed with the isopropyl group (δ 0.80, d, $J=7.0$ Hz) and with the H-14 methyl group indicating that both H-6 and methyl H-14 are in the β-side of the molecule. A similar irradiation of H-6 (δ 3.24, d, $J=10.5$ Hz) in compound **15** did not give NOE with H-14 (δ 0.89, d, $J=6.8$ Hz). Although compounds **14** and **15** were difficult to separate, upon protection of the hydroxyl groups as trimethylsilyl (TMS) ethers in the hydrogenation mixture both compounds could be very easily separated affording compound **16** (50%) and **17** (30%). Introduction of the methyl group at C-2 required the use of cerium reagents[28] since MeMgBr and MeLi brought about quantitative enolization of the ketone. Treatment of compound **17** with MeLi in the presence of $CeCl_3$ gave a 1:1.5 mixture of two alcohols in 96% yield. Subsequent dehydration of the mixture with mesyl chloride and triethylamine afforded a mixture of alkenes, which were separated by chromatography. The ^{1}H NMR of compound **18** showed an AB system composed by two broad doublets at δ 2.22 and δ 1.78 with a geminal coupling of 16.4 Hz corresponding to the two H-1 allylic protons, as well as an ABX system formed by a signal at δ 2.36 (ddd, $J=16.4$, 4.8, 2.4 Hz) and a broad doublet at δ 2.03 ($J=16.4$ Hz)

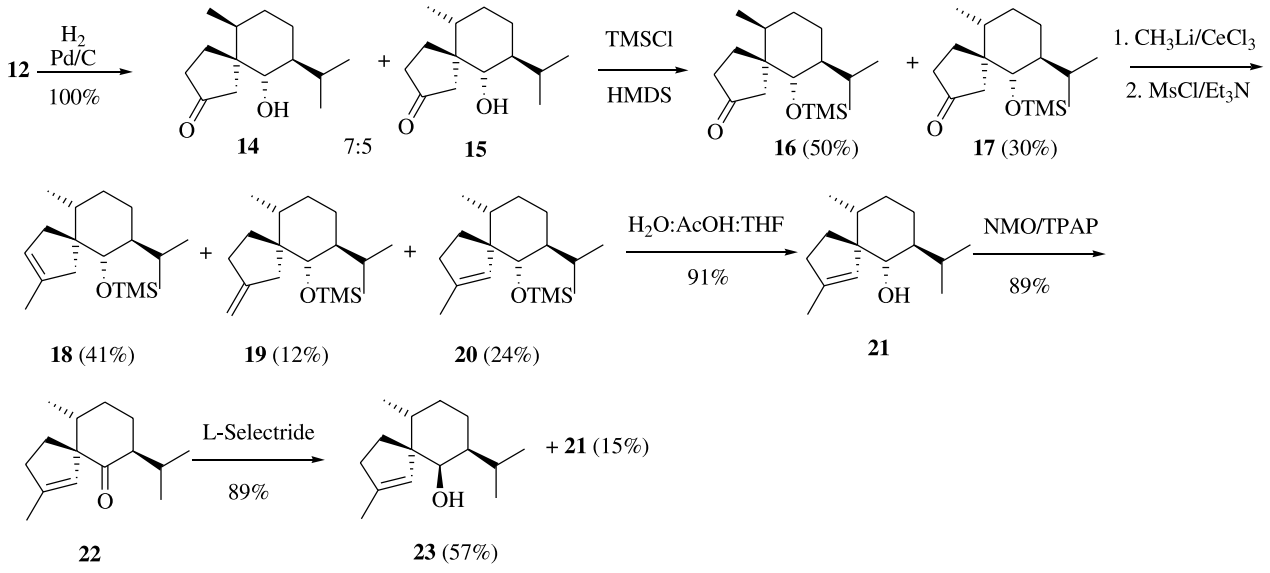


Solvent	8	11	12	13
CH_3CN	11%	8%	21%	15%
CH_2Cl_2	20%	9%	33%	2%
acetone	15%	6%	30%	7%

Scheme 3. Rearrangement of compound **7**.



Scheme 4. Proposed mechanism for the formation of compound **13**.



Scheme 5. Synthesis of (−)-axenol (**21**) and (−)-gleenol (**23**) from compound **12**.

corresponding to two H-4 allylic protons, and the olefinic H-3 signal at 5.07 (br s). Accordingly, the $\Delta^{2,3}$ structure was assigned to this compound. Alkene **19** showed two doublets at δ 4.69 (J=1.9 Hz) and δ 4.64 (J=1.9 Hz) characteristics of an exomethylene group. Finally, compound **20** showed a triplet at δ 2.15 (J=7.4 Hz) corresponding to the two H-3 allylic protons, therefore, the $\Delta^{1,2}$ structure was assigned (Scheme 5).

Treatment of compound **20** with aqueous acid brought about deprotection of the hydroxyl group to give compound **21**, which showed spectral features coincident with those described for natural (+)-axenol and opposite optical rotation sign. Compound **21** has been also described by Caine as an intermediate for the synthesis of axisonitrile 3.[22a] For the synthesis of **23**, the inversion of C-6 was required. Initial attempts using the Mitsunobu protocol failed, probably because of the steric hindrance in the proximity of the hydroxyl group. Therefore, inversion was carried in two steps. Oxidation of the hydroxyl group with NMO-TPAP in compound **21** gave the corresponding ketone **22** in 89% yield. Finally, the ketone was reduced with L-selectride affording compound **23** in 75% yield together with 15% of the previous alcohol **21**. Compound **23** had spectral features coincident with natural (−)-gleenol.

In summary, we have presented here the first cationic rearrangement of a 5,6-epoxy-noreudesmane into a norspiroaxane with concomitant contraction of ring B in the decalin system. This rearrangement is guided by a silicon group at C-9, which allows a selective migration of the C-1 methylene group towards migration of the bridgehead methyl group in a 5:1 ratio. The synthetic utility of this rearrangement is illustrated by the synthesis of two spiroaxanes, the naturally occurring (−)-gleenol, and (−)-axenol, which is the enantiomer of natural (+)-axenol, which have been prepared from carvone in ca. 0.5% overall yield.

3. Experimental

3.1. General

All melting points are uncorrected. Column chromatography was performed on silica gel (SDS, silica gel 60, 0.035–0.070 mm particle size). Commercial reagents and solvents were analytical grade or were purified by standard procedures, prior to use.[29] All reactions involving air or moisture sensitive materials were carried out under argon atmosphere. Specific rotations were measured in $CHCl_3$. IR were recorded as liquid film in NaCl for oils and as KBr discs for solids. NMR were run in $CDCl_3$ at 400 MHz for ^{1}H and at 75 MHz for ^{13}C NMR, and referenced to the solvent as internal standard. The carbon type was determined by DEPT experiments. EIMS were run at 70 eV.

3.1.1. (3*R*,5*S*)-5-Isopropenyl-2-methyl-3-trimethylsilylcyclohexanone (2). A solution obtained from 1.6 M MeLi in diethyl ether (32.6 mL, 53.3 mmol) and dry THF (100 mL) was added to a frozen solution of hexamethyldisilane (13.6 mL, 66.6 mmol) in HMPA (20 mL) at −78 °C under argon. Then, the reaction flask was introduced in an ice bath and the frozen solution left to melt. After 15 min of stirring at 0 °C, the reaction mixture was cooled at −78 °C and a solution of *R*-(−)-carvone (4.0 g, 26.6 mmol) in THF (25 mL) was added dropwise. After 1 h at this temperature, water (30 mL) was added, the mixture was left to reach room temperature, THF was removed under reduced pressure and the aqueous solution was extracted with diethyl ether (3×100 mL). The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography eluting with hexane/diethyl ether 9:1 afforded 5.41 g (91%) of compound **2**: an oil; $[\alpha]_D^{19}$+7.8 (*c* 1.3); MS *m*/*z* 224 (M^+, 12), 209 (50), 195 (22), 181 (30), 73 (100); HRMS 224.1589 (M^+), $C_{13}H_{24}OSi$ required 224.1596; IR (NaCl) 3076, 1708, 1441, 1252, 847 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.80 (1H, br s), 4.70 (1H, br s), 2.57 (1H, m), 2.49 (1H, dd, J= 1.6, 6.8 Hz), 2.34 (1H, ddd, J=1.1, 8.1, 14.0 Hz), 2.01 (1H,

dddd, J=1.1, 4.1, 7.8, 14.0 Hz), 1.74 (1H, m), 1.68 (3H, s), 1.40 (1H, ddd, J=4.0, 6.0, 8.1 Hz), 1.12 (3H, d, J=7.3 Hz), 0.00 (9H, s); ^{13}C NMR δ 213.4 (s), 146.7 (s), 110.9 (t), 46.6 (d), 44.0 (d), 43.8 (t), 28.8 (t), 27.8 (d), 21.0 (q), 14.7 (q), −1.0 (q).

3.1.2. (2*R*,3*R*,5*S*)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)-3-(trimethylsilyl)cyclohexanone (3). A mixture of compound **2** (2.04 g, 9.1 mmol), MVK (1.5 mL, 18.2 mmol) and Ph_3CSbCl_3 (264 mg, 0.46 mmol) was stirred at 0 °C, under argon in the dark. After 24 h, the reaction mixture was diluted with EtOAc and the solvent removed under reduced pressure. Column chromatography eluting with hexane/EtOAc (10:0–7:3) allowed to obtain 556 mg (27%) of starting material, 1.40 g (52%) of compound **3**:[30] an oil; $[\alpha]_D^{21}$ +39.5 (*c* 1.8); MS *m*/*z* 294 (M^+, 2), 237 (36), 236 (49), 223 (32), 143 (38), 131 (16), 130 (100), 115 (38), 73 (86); HRMS 294.2011, $C_{17}H_{30}O_2Si$ required 294.2015; IR (NaCl) 3085, 1705, 1426, 1377, 1252, 837 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.79 (1H, s), 4.66 (1H, s), 2.52–2.38 (4H, m), 2.10 (3H, s), 2.01–1.84 (4H, m), 1.70 (3H, s), 1.23 (1H, dd, J=4.4, 7.1 Hz), 1.08 (3H, s), 0.04 (9H, s); ^{13}C NMR δ 215.2 (s), 208.2 (s), 146.9 (s), 110.8 (s), 49.8 (s), 43.6 (d), 42.5 (t), 38.2 (t), 32.0 (t), 31.6 (d), 29.9 (q), 27.1 (t), 22.3 (q), 20.9 (q), 0.5 (q).

3.1.3. (7*S*,9*R*,10*R*)-3-Oxo-9-trimethylsilyl-15-nor-4,11-eudesmadiene (4). A 1 M solution of KOH in MeOH (17 mL) was added to compound **3** (1.25 g, 4.3 mmol) and the mixture stirred for 8 h at room temperature, under argon in the dark. After this time, satd aqueous NH_4Cl was added and the mixture extracted with EtOAc, washed with brine and dried over $MgSO_4$. Column chromatography eluting with hexane/EtOAc 9:1 gave 1.11 g (94%) of compound **4**: mp 62–63 °C (hexane/EtOAc); $[\alpha]_D^{21}$ −119.8 (*c* 1.5); MS *m*/*z* 276 (M^+, 8), 233 (11), 208 (11), 176 (14), 132 (25), 73 (100); HRMS 276.1911, $C_{17}H_{28}OSi$ required 276.1909; IR (NaCl) 1674, 1443, 1250, 871, 834 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.73 (1H, d, J=0.9 Hz), 4.88 (1H, s), 4.75 (1H, s), 2.65 (1H, ddd, J=2.1, 6.3, 9.0 Hz), 2.57–2.46 (2H, m), 2.36–2.33 (1H, m), 2.30–2.28 (1H, m), 2.03 (1H, ddq, J=2.7, 5.1, 13.3 Hz), 1.85–1.84, (2H, m), 1.78 (1H, dt, J=4.5, 14.0 Hz), 1.67 (3H, s), 1.28 (3H, s), 0.91 (1H, dd, J=4.1, 12.5 Hz), 0.08 (9H, s); ^{13}C NMR δ 199.0 (s), 171.6 (s), 145.9 (s), 124.9 (d), 112.9 (t), 40.9 (d), 39.1 (s), 38.0 (t), 36.6 (t), 34.0 (t), 32.2 (d), 26. (t), 22.5 (q), 20.6 (q), 0.4 (q).

3.1.4. (7*S*,9*R*,10*R*)-3-Oxo-9-trimethylsilyl-15-nor-4-eudesmene (5). A solution of Wilkinson's catalyst (150 mg) in benzene (4 mL) was added to a solution of compound **4** (1.04 g, 3.8 mmol) in benzene (6 mL) under H_2 at atmospheric pressure. The mixture was stirred for 3.5 h and the solvent removed under reduced pressure. The residue was chromatographed eluting with hexane/EtOAC 9:1 to give 1.0 g (95%) of compound **5**: mp 121–122 °C (hexane/EtOAc); $[\alpha]_D^{22}$ −129.2 (*c* 1.3); MS *m*/*z* 278 (M^+, 19), 264 (22), 263 (100), 235 (19), 208 (25), 145 (15), 73 (65); HRMS 278.2063, $C_{17}H_{30}OSi$ required 278.2066; IR (NaCl) 1674, 1609, 1459, 1250, 871, 834 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.64 (1H, s), 2.51–2.24 (4H, m), 2.04 (1H, ddd, J=2.9, 5.0, 13.4 Hz), 1.77 (1H, dt, J=3.6, 12.9 Hz), 1.60–1.40 (2H, m), 1.26 (3H, s), 0.86 (3H, d, J=6.3 Hz), 0.81 (3H, d, J=6.6 Hz), 0.07 (9H, s); ^{13}C NMR δ 199.0 (s), 171.1 (s), 124.9 (s), 43.0 (d), 38.9 (s), 38.1 (t), 36.8 (t), 34.0 (t), 33.3 (d), 26.7 (t), 26.0 (d), 20.7 (q), 20.7 (q), 20.4 (q), 0.3 (q).

3.1.5. (7*S*,9*R*,10*R*)-3,3-Ethylenedioxy-9-trimethylsilyl-15-nor-5-eudesmene (6). A solution containing compound **5** (3.07 g, 11.0 mmol), ethyleneglycol (6.5 mL, 117 mmol) and TsOH (1.06 g, 3.3 mmol) in benzene (110 mL) was heated at reflux temperature overnight using a Dean–Stark system. The reaction mixture was washed with cold satd aqueous $NaHCO_3$ and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated under reduced pressure. Column chromatography eluting with hexane/EtOAc 9:1–7:3 afforded 2.82 g (79%) of acetal **6** and 558 mg (18%) of starting material.

Compound **6**. Mp 95–97 °C; $[\alpha]_D^{21}$ +67.0 (*c* 1.1); MS *m*/*z* 322 (M^+, 7), 279 (22), 117 (14), 107 (14), 99 (100), 73 (87); HRMS 322.2318, $C_{19}H_{34}O_2Si$ required 322.2328; IR (KBr) 1362, 1247, 1103, 865, 831 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.39 (1H, br s), 3.90 (4H, m), 2.47 (1H, td, J=2.1, 14.0 Hz), 2.04 (1H, dd, J=3.0, 14.0 Hz), 1.78 (1H, br s), 1.74 (1H, t, J=3.6 Hz), 1.61–1.51 (5H, m), 1.28 (1H, m), 1.05 (3H, s), 0.93 (3H, d, J=6.3 Hz), 0.85 (3H, d, J=6.3 Hz), 0.02 (9H, s); ^{13}C NMR δ 141.0 (s), 126.7 (d), 109.3 (s), 64.1 (t), 42.1 (t), 41.4 (d), 38.1 (t), 37.5 (s), 31.7 (d), 31.6 (d), 31.2 (t), 23.8 (t), 21.3 (q), 21.2 (q), 20.7 (q), −0.0 (q).

3.1.6. (5*R*,6*S*,7*S*,9*R*,10*R*)-5,6-Epoxy-3,3-ethylenedioxy-9-trimethylsilyl-15-noreudesmane (7). A solution of $NaHCO_3$ (6.0 g, 71.1 mmol) in water (55 mL) was added to a solution of acetal **6** (2.08 g, 6.2 mmol) in 1:1 CH_2Cl_2/acetone (110 mL). The mixture was cooled at 0 °C and 18-crown-6 (100 mg, 0.37 mmol) and oxone® (7.08 g, 11.5 mmol) were added. After stirring for 2 h, the mixture was diluted with CH_2Cl_2 and washed with satd aqueous $NaHCO_3$, 10% aqueous Na_2SO_3 and again with satd aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and chromatographed using hexane/EtOAc 9:1–6:4 to give 1.94 g (89%) of epoxide **7**: an oil; $[\alpha]_D^{25}$ +20.2 (*c* 1.2); MS *m*/*z* 338 (M^+, 2), 239 (11), 180 (33), 143 (34), 107 (23), 99 (96), 86 (46), 73 (100); HRMS 338.2267, $C_{19}H_{34}O_3Si$ required 338.2277; IR (NaCl) 1249, 1101, 865, 834 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.89 (4H, m), 2.79 (1H, br s), 2.25 (1H, d, J=13.6 Hz), 1.80–1.65 (3H, m), 1.63–1.50 (4H, m), 1.35–1.24 (1H, m), 1.15–1.12 (1H, m), 1.14 (3H, s), 1.03 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.6 Hz), 0.58 (1H, dd, J=2.8, 10.9 Hz), 0.02 (9H, s); ^{13}C NMR δ 109.2 (s), 66.3 (d), 64.2; 64.1 (t), 63.2 (s), 41.5 (t), 41.0 (d), 36.8 (t), 35.0 (s), 30.9 (t), 30.8 (d), 28.0 (d), 21.1 (q), 20.9 (q), 20.8 (t), 20.5 (q), 0.5 (q).

3.1.7. Rearrangement of compound 7. (5*S*,6*S*,7*S*)-6-Hydroxy-3-oxo-15-nor-9-eremophilene (11) and (5*R*,6*S*,7*S*)-6-hydroxy-7-isopropyl-10-methylspiro[4.5]dec-9-en-2-one (12). $BF_3{\cdot}Et_2O$ (0.8 mL) was added dropwise to a solution of compound **7** (1.78 g, 5.2 mmol) in CH_2Cl_2 (100 mL) at −78 °C under argon. The resulting solution was stirred at this temperature for 5 min and at 0 °C for additional 35 min. Then acetone (30 mL) and 2 M HCl (1.6 mL) were added and stirring continued for 30 min at room temperature. Satd

aqueous $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2, washed with brine and dried. After removal of the solvent under reduced pressure, chromatography with CH_2Cl_2/isopropanol 99:1 eluted in this order, 305 mg (20%) of diketone **8**, 99 mg (9%) of compound **11**, 378 mg (33%) of spirocompound **12** and 35 mg (2%) of ester **13**.

Diketone **8**. Mp 124–126 °C (hexane/EtOAc); $[\alpha]_D^{25}$ −79.5 (*c* 1.6); IR (KBr) 1705, 1247, 864, 836 cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (3H, s), 0.94 (3H, d, J=5.7 Hz), 0.72 (3H, J=5.7 Hz), 0.09 (9H); ^{13}C NMR δ 213.0 (s), 211.5 (s), 58.1 (d), 55.7 (d), 43.7 (s), 40.9 (t), 37.6 (t), 37.4 (t), 33.6 (d), 28.2 (d), 27.8 (t), 20.8 (q), 20.7 (q), 14.8 (q), 0.3 (q).

Compound **11**. An oil; $[\alpha]_D^{26}$ −72.5 (*c* 1.5); MS *m*/*z* 222 (M^+, 28), 137 (25), 136 (100), 123 (12), 94 (18); HRMS 222.1629, $C_{14}H_{22}O_2$ required 222.1620; IR (NaCl) 3445, 1661, 1056 cm^{-1}; ^1H NMR (300 MHz) δ 5.46 (1H, t, J= 2.4 Hz), 3.45 (1H, d, J=11.3 Hz), 2.58 (1H, d, J=13.4 Hz), 2.56 (1H, m), 2.37–2.31 (2H, m), 2.23 (1H, d, J=13.4 Hz), 2.12 (1H, sext, J=3.4 Hz), 1.94–1.86 (2H, m), 1.72–1.65 (2H, m), 1.01 (3H, s), 0.90 (3H, d, J=7.2 Hz), 0.83 (3H, d, J=6.8 Hz); ^{13}C NMR δ 211.5 (s), 137.4 (s), 121.3 (d), 78.0 (d), 52.8 (t), 44.5 (s), 41.3 (t), 39.4 (d), 31.5 (t), 25.7 (d), 24.0 (t), 20.6 (q), 18.9 (q), 15.2 (q).

Spirocompound **12**. Mp 90–91 °C (hexane/EtOAc); $[\alpha]_D^{21}$ − 115.2 (*c* 1.3); MS *m*/*z* 222 (M^+, 14), 194 (19), 136 (100), 121 (22), 105 (32), 93 (51), 79 (24); HRMS 222.1616, $C_{14}H_{22}O_2$ required 222.1620; IR (KBr) 3434, 1725, 1181 cm^{-1}; ^1H NMR (300 MHz) δ 5.37 (1H, d, J= 5.1 Hz), 3.58 (1H, d, J=11.3 Hz), 2.59–2.49 (1H, m), 2.48 (1H, d, J=17.3 Hz), 2.35–2.11 (2H, m), 2.10–2.02 (3H, m), 1.95–1.83 (2H, m), 1.78 (1H, td, J=2.5, 11.1 Hz), 1.65 (3H, br s), 1.53 (1H, m), 0.89 (3H, d, J=7.0 Hz), 0.81 (3H, d, J= 6.8 Hz); ^{13}C NMR δ 220.3 (s), 136.4 (s), 122.9 (d), 77.8 (d), 49.1 (s), 44.7 (t), 41.5 (d), 38.0 (t), 30.8 (t), 25.5 (d), 23.6 (t), 20.6 (q), 19.3 (q), 15.2 (q).

Compound **13**. An oil; $[\alpha]_D^{25}$ +5.9 (*c* 0.6); IR (NaCl) 3549–3104, 1733, 1716, 1464, 1250, 851, 835 cm^{-1}; ^1H NMR (300 MHz) δ 5.23 (1H, s), 4.78 (1H, s), 4.16 (2H, q, J= 4.1 Hz), 4.01 (1H, d, J=10.6 Hz), 3.79 (2H, t, J=4.6 Hz), 2.22–2.05 (4H, m), 1.70–1.45 (3H. m), 1.15 (3H, s), 0.93 (3H, d, J=7.0 Hz), 0.85 (3H, d, J=7.0 Hz), 0.02 (9H, s); ^{13}C NMR δ 174.6 (s), 154.9 (s), 106.2 (t), 71.1 (d), 66.1 (t), 61.2 (t), 49.6 (d), 42.5 (s), 34.8 (t), 34.7 (d), 29.3 (t), 27.0 (d), 25.2 (q), 21.1 (t), 21.0 (q), 15.9 (q), 1.3 (q).

3.1.8. (5*R*,6*S*,7*S*,10*S*)-6-Hydroxy-7-isopropyl-10-methylspiro[4.5]decan-2-one (14) and (5*R*,6*S*,7*S*,10*R*)-6-hydroxy-7-isopropyl-10-methylspiro[4.5]decan-2-one (15). Compound **12** (1.36 g, 6.1 mmol) dissolved in acetone (50 mL) was hydrogenated over 5% Pd/C (415 mg) for 2 h. The reaction mixture was filtered though a pad of silica gel to remove the catalyst and the filtrate concentrated under reduced pressure to give 1.37 g (100%) of a ca. 7:5 mixture of two epimeric compounds **14** and **15**. For analytical purposes, compounds **14** and **15** were separated in an independent run after repeated chromatography eluting with hexane/EtOAc 9:1–6:4.

Compound **15**. Mp 68–70 °C; $[\alpha]_D^{23}$ −15.6 (*c* 1.3); MS *m*/*z* 224 (M^+, 14), 181 (22), 142 (22), 123 (30), 83 (100), 81 (22), 69 (20), 55 (27); HRMS 224.1773, $C_{14}H_{24}O_2$ required 224.1776; IR (KBr) 3415, 1729, 1460, 1398, 1177 cm^{-1}; ^1H NMR (300 MHz) δ 3.24 (1H, d, J=10.5 Hz), 2.42 (1H, dddd, J=1.7, 7.7, 12.1, 20.0 Hz), 2.31–2.11 (3H, m), 2.05–1.97 (2H, m), 1.93–1.80 (2H, m), 1.55–1.34 (3H, m), 1.18 (1H, m), 1.05–0.94 (2H, m), 0.89 (3H, d, J=6.8 Hz), 0.84 (3H, d, J=6.6 Hz), 0.78 (3H, d, J=7.0 Hz); ^{13}C NMR δ 221.0 (s), 78.9 (d), 53.4 (s), 45.6 (d), 40.0 (d), 38.5 (t), 37.9 (t), 31.2 (t), 31.1 (t), 25.9 (d), 22.5 (t), 21.0 (q), 16.4 (q), 15.5 (q).

Compound **14**. Mp 115–116 °C; $[\alpha]_D^{23}$ −40.7 (*c* 1.2); MS *m*/*z* 224 (M^+, 38), 181 (16), 142 (38), 123 (43), 83 (100), 81 (16), 55 (19); HRMS 224.1777, $C_{14}H_{24}O_2$ required 224.1776; IR (KBr) 3427, 1729, 1398, 1187 cm^{-1}; ^1H NMR (300 MHz) δ 3.63 (1H, d, J=10.0 Hz), 2.59 (1H, d, J=18.3 Hz), 2.43 (1H, dq, J=1.5, 8.7 Hz), 2.19–2.10 (2H, m), 1.99 (1H, d quint, J=2.3, 7.0 Hz), 1.90 (1H, d, J= 18.3 Hz), 1.95–1.80 (1H, m), 1.75–1.65 (1H, m), 1.67 (1H, s), 1.47–1.40 (3H, m), 1.30–1.20 (2H, m), 0.95 (3H, d, J= 7.1 Hz), 0.90 (3H, d, J=7.0 Hz), 0.80 (3H, d, J=7.0 Hz); ^{13}C NMR δ 220.7 (s), 74.2 (d), 48.1 (s), 46.6 (t), 46.1 (d), 39.7 (d), 37.5 (t), 33.1 (t), 29.1 (t), 25.7 (d), 21.1 (q), 17.6 (t), 15.7 (q), 14.0 (q).

3.1.9. (5*R*,6*S*,7*S*,10*R*)-7-Isopropyl-10-methyl-6-trimethylsilyloxyspiro[4.5]decan-2-one (17) and (5*R*,6*S*,7*S*,10*S*)-7-isopropyl-10-methyl-6-trimethylsilyloxyspiro[4.5]decan-2-one (16). The above hydrogenation mixture was dissolved in pyridine (50 mL) and treated with hexamethyldisilazane (6.7 mL, 31.8 mmol) and TMSCl (3.2 mL, 25.1 mmol). After 1 h, the solvent was removed under reduced pressure and the resulting oil chromatographed eluting with hexane/EtOAc 1:0–7:3 to give in this order 536 mg (30%) of compound **17** and 896 mg (50%) of **16**.

Compound **17**. Mp 46–47 °C; $[\alpha]_D^{25}$ +13.2 (*c* 1.4); MS *m*/*z* 296 (M^+, 69), 281 (27), 184 (34), 171 (45), 157 (35), 111 (32) 97 (53), 85 (61), 71 (74), 69 (57), 57 (100), 55 (52); HRMS 296.2178, $C_{17}H_{32}O_2Si$ required 296.2172; IR (KBr) 1742, 1251, 1086, 838 cm^{-1}; ^1H NMR (300 MHz) δ 3.24 (1H, d, J=10.2 Hz), 2.43 (1H, d, J=18.5 Hz), 2.27 (1H, m), 2.23 (1H, d, J=7.5 Hz), 2.15–1.98 (2H, m), 2.01 (1H, d, J=18.5 Hz), 1.72 (1H, m), 1.57–1.35 (3H, m), 1.10–0.90 (3H, m), 0.85 (3H, d, J=7.2 Hz), 0.81 (3H, d, J=6.8 Hz), 0.71 (3H, d, J=7.0 Hz), 0.11 (9H, s); ^{13}C NMR δ 221.0 (s), 79.8 (d), 50.2 (s), 46.7 (d), 41.6 (d), 38.9 (t), 37.7 (t), 30.8 (t), 30.7 (t), 25.3 (d), 22.1 (t), 21.4 (q), 16.8 (q), 15.4 (q), 1.0 (q).

Compound **16**. Mp 52–53 °C; $[\alpha]_D^{26}$ +55.0 (*c* 1.2); MS *m*/*z* 296 (M^+, 100), 171 (96), 157 (54), 75 (26), 73 (67); HRMS 296.2177, $C_{17}H_{32}O_2Si$ required 296.2172; IR (KBr) 1744, 1251, 1083, 839 cm^{-1}; ^1H NMR (300 MHz) δ 3.60 (1H, d, J=10.0 Hz), 2.51 (1H, dd, J=1.0, 17.9 Hz), 2.35–2.13 (2H, m), 2.06–1.91 (3H, m), 1.90–1.80 (1H, m), 1.40–1.32 (2H, m), 1.23–1.16 (2H, m), 0.95 (3H, d, J=7.1 Hz), 0.86 (3H, d, J=7.0 Hz), 0.72 (3H, d, J=6.8 Hz), 0.10 (9H, s); ^{13}C NMR δ 219.9 (s), 74.2 (d), 49.3 (s), 47.2 (d), 45.6 (t), 36.1 (t), 36.0 (d), 29.7 (t), 28.4 (t), 25.1 (d), 21.4 (q), 17.4 (t), 15.6 (q), 14.6 (q), 1.0 (q).

3.1.10. (5*S*,6*S*,7*S*,10*R*)-7-Isopropyl-2,10-dimethyl-6-trimethylsilyloxyspiro[4.5]dec-1-ene (20). A suspension of anhydrous $CeCl_3$ (300 mg, 1.2 mmol) in dry THF (6 mL) was stirred overnight under argon and in an ultrasound bath for 3 h (additional) until the obtention of an homogeneous suspension of finely divided $CeCl_3$. A solution of compound **17** (98 mg, 0.33 mmol) in THF (1 mL) was added, the mixture was cooled at 0 °C followed by the addition of a 1.6 M solution of MeLi in diethyl ether (0.65 mL, 1.0 mmol). After 20 min, the reaction was quenched with satd aqueous NH_4Cl, extracted with diethyl ether, washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure to give 100 mg (96%) of an oil composed of a ca. 2:3 of two epimeric alcohols. For analytical purposes both epimers were separated in an independent run by chromatography with hexane/EtOAc 9:1–5:5.

Minor isomer. An oil; $[\alpha]_D^{25}-28.7$ (*c* 1.4); IR (NaCl) 3500, 1252, 839 cm^{-1}; ^1H NMR (300 MHz) δ 4.04 (1H, s), 3.22 (1H, d, $J=10.5$ Hz), 2.04–1.94 (2H, m), 1.62–1.57 (2H, m), 1.50–1.39 (4H, m), 1.28 (3H, s), 0.85 (3H, d, $J=7.0$ Hz), 0.81 (3H, d, $J=6.7$ Hz), 0.71 (3H, d, $J=6.9$ Hz), 0.19 (9H, s); ^{13}C NMR δ 81.4 (d), 78.7 (s), 53.2 (s), 46.4 (d), 41.8 (d), 41.7 (t), 41.6 (t), 33.5 (t), 30.5 (t), 25.8 (q), 25.1 (d), 22.7 (t), 21.6 (q), 16.3 (q), 16.1 (q), 1.1 (q).

Major isomer. An oil; $[\alpha]_D^{25}-26.5$ (*c* 1.4); MS *m/z* 312 (M^+, 37), 295 (28), 294 (100), 211 (28), 204 (41), 117 (76), 161 (62), 157 (38), 121 (50), 73 (36); HRMS 312.2474, $C_{18}H_{36}O_2Si$ requiere 312.2485; IR (NaCl) 3400, 1251, 1078, 837 cm^{-1}; ^1H RMN (300 MHz) δ 3.20 (1H, d, $J=$ 10.4 Hz), 2.00 (1H, d quint, $J=2.2$, 6.9 Hz), 1.83–1.70 (3H, m), 1.61–1.55 (2H, m), 1.49–1.37 (2H, m), 1.32 (3H, s), 0.95 (3H, d, $J=6.8$ Hz), 0.84 (3H, d, $J=7.0$ Hz), 0.68 (3H, d, $J=6.9$ Hz), 0.12 (9H, s); ^{13}C RMN δ 82.5 (d), 80.6 (s), 53.5 (s), 46.2 (d), 42.0 (t), 41.2 (t), 40.0 (d), 34.5 (t), 32.0 (t), 29.1 (q), 24.8 (d), 22.5 (t), 21.6 (q), 17.7 (q), 16.0 (q), 1.4 (q).

The resulting alcohol mixture (100 mg, 0.32 mmol) was dissolved in THF (5 mL) and treated with Et_3N (0.23 mL, 1.6 mmol) and MsCl (48 μL, 0.61 mmol) at room temperature. After 1.5 h, water was added and the mixture extracted with ether, washed with brine and dried. Column chromatography eluting with hexane/EtOAc 1:0–9:1 allowed to obtain 38 mg (41%) of **18**, 11 mg (12%) of **19** and 22 mg (23%) of **20**.

Compound **18**. An oil; $[\alpha]_D^{25}-18.3$ (*c* 1.4); MS *m/z* 294 (M^+, 38), 204 (100), 161 (52), 123 (26), 121 (53), 120 (50), 119 (44), 105 (33), 80 (45), 75 (26), 73 (52); HRMS 294.2368, $C_{18}H_{34}OSi$ required 294.2379; IR (NaCl) 1250, 1099, 897, 837 cm^{-1}; ^1H NMR (300 MHz) δ 5.07 (1H, br s), 3.23 (1H, d, $J=10.4$ Hz), 2.36 (1H, dq, $J=2.4$, 16.3 Hz), 2.22 (1H, d, $J=16.4$ Hz), 2.03 (2H, m), 1.78 (1H, d, $J=$ 16.3 Hz), 1.81 (3H, s), 1.48 (1H, dq, $J=3.2$, 12.6 Hz), 1.36 (1H, dq, $J=3.2$, 12.6 Hz), 1.26–1.05 (3H, m), 0.86 (3H, d, $J=$ 7.0 Hz), 0.73 (3H, d, $J=6.5$ Hz), 0.70 (3H, d, $J=6.9$ Hz), 0.07 (9H, s); ^{13}C NMR δ 140.2 (s), 122.2 (d), 80.3 (d), 52.1 (s), 46.5 (d), 43.9 (t), 41.1 (d), 36.9 (t), 30.3 (t), 25.4 (d), 22.3 (t), 21.5 (q), 16.5 (q), 15.9 (q), 15.4 (q), 1.0 (q).

Compound **19**. An oil; $[\alpha]_D^{25}-13.2$ (*c* 0.5); ^1H NMR (300 MHz) δ 4.69 (1H, d, $J=1.9$ Hz), 4.64 (1H, d, $J=$ 1.9 Hz), 3.20 (1H, d, $J=10.4$ Hz), 2.37 (1H, d, $J=16.4$ Hz), 2.25 (2H, s, m), 2.03 (2H, m), 1.84 (1H, m), 1.32–1.01 (4H, m), 0.85 (3H, d, $J=7.2$ Hz), 0.82 (3H, d, $J=6.8$ Hz), 0.69 (3H, d, $J=7.0$ Hz), 0.10 (9H, s).

Compound **20**. An oil; $[\alpha]_D^{25}-35.0$ (*c* 1.2); MS *m/z* 294 (M^+, 56), 161 (40), 134 (53), 121 (100), 108 (44), 81 (33), 73 (68), 69 (28), 57 (37); HRMS 294.2376, $C_{18}H_{34}OSi$ required 294.2379; IR (NaCl) 1249, 1114, 836 cm^{-1}; ^1H NMR (300 MHz) δ 5.23 (1H, s), 3.23 (1H, d, $J=10.6$ Hz), 2.15 (2H, t, $J=7.4$ Hz), 2.08 (1H, dq, $J=2.4$, 7.0 Hz), 1.97–1.87 (1H, m), 1.72 (3H, s), 1.64–1.56 (2H, m), 1.43–1.25 (3H, m), 0.87 (3H, d, $J=7.0$ Hz), 0.75 (3H, d, $J=6.5$ Hz), 0.71 (3H, d, $J=7.0$ Hz), 0.11 (9H, s); ^{13}C NMR δ 142.9 (s), 123.2 (d), 80.8 (d), 61.4 (s), 46.5 (d), 41.9 (d), 36.6 (t), 32.8 (t), 31.4 (t), 25.5 (d), 22.7 (t), 21.4 (q), 17.1 (q), 16.7 (q), 15.2 (q), 1.1 (q).

3.1.11. (−)-Axenol (21). Trimethylsilyl ether **20** (35 mg, 0.12 mmol) was stirred in 3:5:10 H_2O/AcOH/THF (2.5 mL) for 45 min at room temperature. The mixture was diluted with CH_2Cl_2, washed with satd aqueous $NaHCO_3$ and brine, and dried. Column chromatography eluting with hexane/EtOAc 95:5 gave 24 mg (91%) of compound **21**: an oil; $[\alpha]_D^{25}-35.0$ (*c* 1.2); MS *m/z* 222 (M^+, 27), 204 (32), 121 (100), 108 (38), 97 (30), 93 (37), 81 (93), 71 (39), 69 (53), 57 (68), 55 (54); HRMS 222.1988, $C_{15}H_{26}O$ required 222.1984; IR (NaCl) 3561, 3474, 1464, 1374, 989 cm^{-1}; ^1H NMR (300 MHz) δ 5.12 (1H, d, $J=1.7$ Hz), 3.04 (1H, t, $J=$ 10.4 Hz), 2.21–2.05 (4H, m), 1.76 (3H, br s), 1.51 (2H, m), 1.20–0.98 (4H, m), 0.87 (3H, d, $J=7.1$ Hz), 0.77 (3H, d, $J=$ 7.0 Hz), 0.76 (3H, d, $J=6.6$ Hz); ^{13}C NMR δ 147.3 (s), 121.7 (d), 78.3 (d), 61.2 (s), 47.1 (d), 40.7 (d), 36.8 (t), 33.1 (t), 31.8 (t), 26.1 (d), 23.1 (t), 21.1 (q), 17.2 (q), 16.9 (q), 15.7 (q).

3.1.12. (5*S*,7*S*,10*R*)-(+)-7-Isopropyl-2,10-dimethylspiro[4.5]dec-1-en-6-one (22). Tetrapropylammonium perruthenate (TPAP) (2.7 mg, 0.008 mmol) was added to a solution of compound **21** (19 mg, 0.076 mmol) and NMO (22 mg, 0.19 mmol) in CH_2Cl_2 (0.6 mL). After 1.5 h the reaction mixture was chromatographed eluting with hexane/EtOAC 8:2 to give 15 mg (89%) of compound **22**: mp 44–46 °C; $[\alpha]_D^{25}+56.8$ (*c* 0.8); MS *m/z* 220 (M^+, 28), 121 (99), 108 (62), 107 (34), 97 (29), 93 (39), 85 (39), 83 (33), 81 (41), 71 (63), 69 (56), 57 (100), 55 (71); HRMS 220.1826, $C_{15}H_{24}O$ required 220.1827; IR (KBr) 1705, 1458, 1448, 871 cm^{-1}; ^1H NMR (300 MHz) δ 5.28 (1H, d, $J=1.5$ Hz), 2.77 (1H, ddd, $J=4.5$, 8.7, 14.4 Hz), 2.19–1.97 (5H, m), 1.70 (3H, d, $J=1.3$ Hz), 1.69–1.45 (4H, m), 1.33–1.23 (1H, m), 0.85 (3H, d, $J=7.0$ Hz), 0.85 (3H, d, $J=5.8$ Hz), 0.82, (3H, d, $J=6.8$ Hz); ^{13}C NMR δ 212.6 (s), 144.8 (s), 123.0 (d), 69.6 (s), 53.3 (d), 43.5 (d), 36.0 (t), 31.7 (t), 28.5 (t), 28.1 (t), 26.2 (d), 21.4 (q), 18.7 (q), 17.0 (q), 16.6 (q).

3.1.13. (−)-Gleenol (23). A solution of compound **22** (14 mg, 0.064 mmol) in THF (0.75 mL) was treated with a 1 M solution of L-Selectride in THF (0.32 mL, 0.32 mmol) at room temperature. After 24 h, a solution of H_2O (0.3 mL) in EtOH (1 mL) was added, the reaction was stirred for 20 min followed by the addition of a mixture of 4 M

aqueous NaOH (0.32 mL) and 30% H_2O_2 (0.65 mL). After stirring for 2 h, water was added and the mixture extracted with EtOAc, washed with brine and dried. Column chromatography eluting with hexane/EtOAc 9:1 gave 2.1 mg (15%) and 9.5 mg (67%) of (−)-gleenol **23**: an oil; $[\alpha]_D^{25}-22.9$ (*c* 0.4) [lit.[18] $[\alpha]_D^{20}-15.02$ (*c* 0.5)]; MS *m/z* 222 (M^+, 16), 204 (28), 121 (100), 108 (38), 107 (28), 93 (30), 81 (80), 69 (31); HRMS 222.1992, $C_{15}H_{26}O$ required 222.1984; IR (NaCl) 3502, 1463, 1376 cm^{-1}; ^1H NMR (300 MHz) δ 5.15 (1H, d, $J=1.5$ Hz), 3.51 (1H, s), 2.20 (1H, m), 1.94–1.74 (1H, m), 1.72 (3H, d, $J=1.3$ Hz), 1.80–1.60 (1H, m), 1.70–1.60 (1H, m), 1.41–1.60 (1H, m), 1.50–1.40 (1H, m), 1.30–1.20 (1H, m), 1.20–1.10 (1H, m), 1.14–1.00 (1H, m), 0.90 (3H, d, $J=6.6$ Hz), 0.89 (3H, d, $J=6.6$ Hz), 0.73 (3H, d, $J=6.8$ Hz); ^{13}C NMR δ 142.8 (s), 125.5 (d), 76.4 (d), 58.8 (s), 45.3 (d), 36.3 (t), 34.0 (d), 34.0 (t), 31.7 (t), 29.3 (d), 24.4 (t), 21.2 (q), 20.7 (q), 17.0 (q), 16.2 (q).

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References and notes

1. (a) Dewick, P. M. *Nat. Prod. Rep.* **2002**, *19*, 181–222 and previous reviews in this series. (b) Marshall, J. A.; Brady, S. F.; Andersen, N. H. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 283–285. (c) Robinson, R. *The Structural Relations of Natural Products*; Clarendon: Oxford, 1955; p 12.
2. Eggers, M. D.; Sinnwell, V.; Stahl-Biskup, E. *Phytochemistry* **1999**, *51*, 987–990.
3. (a) Bargues, V.; Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *Tetrahedron* **1998**, *54*, 1845–1852. (b) Bargues, V.; Blay, G.; Cardona, L.; Collado, A.; García, B.; Muñoz, M. C.; Pedro, J. R. *J. Org. Chem.* **2000**, *65*, 2138–2144. (c) Blay, G.; Cardona, L.; García, B.; Lahoz, L.; Pedro, J. R. *Eur. J. Org. Chem.* **2000**, 2145–2151. (d) Blay, G.; Cardona, L.; García, B.; Lahoz, L.; Monje, B.; Pedro, J. R. *Tetrahedron* **2000**, *56*, 6331–6338. (e) Blay, G.; Bargues, V.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **2000**, *65*, 6703–6707. (f) Blay, G.; Cardona, L.; García, B.; Lahoz, L.; Pedro, J. R. *J. Org. Chem.* **2001**, *66*, 7700–7705. (g) Blay, G.; Bargues, V.; Cardona, L.; García, B.; Pedro, J. R. *Tetrahedron* **2001**, *57*, 9719–9725.
4. Coates, R. M. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 73–230.
5. Caine, D.; Graham, S. L. *J. Org. Chem.* **1980**, *45*, 3790–3797.
6. Andersen, N. H.; Falcone, M. S.; Syrdal, D. D. *Tetrahedron Lett.* **1970**, *21*, 1759–1762.
7. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1989**, *45*, 3809–3818.
8. Kitagawa, I.; Yamazoe, Y.; Takeda, R.; Yosioka, I. *Tetrahderon Lett.* **1972**, *48*, 4843–4846.
9. Coxon, J. M.; Lindley, N. B. *Aust. J. Chem.* **1976**, *29*, 2207–2217.
10. (a) Hikino, H.; Kohama, T.; Takemoto, T. *Tetrahedron* **1969**, *25*, 1037–1045. (b) Mehta, G.; Chetty, G. L.; Nayak, U. R.; Dev, S. *Tetrahedron* **1968**, *24*, 3775–3786.
11. Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Pedro, J. R. *Tetrahedron Lett.* **2003**, *44*, 8117–8119.
12. Blay, G.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294–7302.
13. Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1992**, *57*, 922–928.
14. Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic: London, 1988.
15. Kurvyakov, P. I.; Gatilov, Y. V.; Yu, V.; Khan, V. A.; Dubovenko, Zh. V.; Pentegova, V. A. *Khim. Prir. Soedin.* **1979**, 164–168.
16. Khan, V. A.; Dubovenko, Zh. V.; Pentegova, V. A. *Khim. Prir. Soedin.* **1983**, 109–110.
17. Nagahama, S.; Tazaki, M.; Nomura, H.; Nishimura, K.; Tajima, M.; Iwasita, Y. *Mokuzai Gakkaishi* **1996**, *42*, 1127–1133.
18. Barrero, A. F.; Sánchez, J. F.; Oltra, J. E.; Altarejos, J.; Ferrol, N.; Barragan, A. *Phytochemistry* **1991**, *30*, 1551–1554.
19. de Rosa, S.; de Giulio, A.; Iodice, C.; Zavodink, N. *Phytochemistry* **1994**, *37*, 1327–1330.
20. Barrow, C. J.; Blunt, J. W.; Munro, M. H. G. *Aust. J. Chem.* **1988**, *41*, 1755–1761.
21. Bozan, B.; Ozek, T.; Kurkcuoglu, M.; Kirimer, N.; Baser, K.; Husnu, C. *Planta Med.* **1999**, *65*, 781–782.
22. (a) Caine, D.; Deutsch, H. *J. Am. Chem. Soc.* **1978**, *100*, 8030–8031. (b) Ohira, S.; Yoshihara, N.; Hasegawa, T. *Chem. Lett.* **1998**, 739–740. (c) Oesterreich, K.; Spitzner, D. *Tetrahedron* **2002**, *58*, 4331–4334. (d) Oesterreich, K.; Klein, I.; Spitzner, D. *Synlett* **2002**, 1712–1714.
23. Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063–3064.
24. Baranovsky, A. V.; Jansen, B. J. M.; Meulemans, T. M.; de Groot, A. *Tetrahedron* **1998**, *54*, 5623–5634.
25. Jansen, B. J. M.; Kreuger, J. A.; de Groot, A. *Tetrahedron* **1989**, *45*, 1447–1452.
26. Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073–10082.
27. (a) Zhabinskii, V. N.; Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4022–4027. (b) Krieg, R.; Schönecker, B. *Liebigs Ann. Chem.* **1994**, 1025–1032.
28. Imamoto, T.; Takiyama, N.; Nakamura, N.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.
29. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.
30. Besides, 108 mg (3%) and 103 mg (3%) of two epimer products of structure **10** were obtained. *Compound* **10a**. An oil; ^1H NMR (300 MHz) δ 4.75 (1H, s), 4.64 (1H, s), 2.52–2.20 (6H, m), 2.07 (3H, d, $J=1.2$ Hz), 2.04 (3H, d, $J=1.5$ Hz), 1.66 (3H, s), 1.32 (1H, d, $J=14.1$ Hz), 1.02 (3H, s), 0.00 (9H, s); ^{13}C NMR δ 216.0 (s), 211.3 (s), 207.5 (s), 146.9 (s), 110.9 (t), 50.3 (s), 46.6 (d), 43.1 (d), 42.3 (t), 39.9 (t), 39.4 (t), 33.0 (d), 29.8 (q), 29.7 (q), 27.3 (t), 27.0 (t), 22.2 (q), 20.7 (q), 0.3 (q). *Compound* **10b**. An oil; ^1H NMR (300 MHz) δ 4.75 (1H, s), 4.64 (1H, s), 2.49–2.22 (6H, m), 2.12 (3H, s), 2.04 (3H, s), 1.67 (3H, s), 0.93 (3H, s), 0.00 (9H); ^{13}C NMR δ 215.3 (s), 211.4 (s), 207.3 (s), 146.8 (s), 110.5 (t), 50.6 (s), 47.1 (d), 43.6 (d), 42.3 (t), 40.0 (t), 39.3 (t), 33.2 (d), 29.8 (q), 29.2 (q), 27.3 (t), 26.8 (t), 21.8 (q), 20.8 (q), 0.2 (q).

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Nitration of phenolic compounds by metal-modified montmorillonite KSF

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Abstract—The nitration of phenolic compounds with 60% nitric acid (1.2 equiv) has been carried out in the presence of metal-modified montmorillonite KSF, prepared from different metals (V, Mo, W; Sc, La, Yb, Eu, In, Bi, Ti, Zr, Hf) and KSF or nitric acid treated HKSF, as catalysts. These catalysts showed good stabilities and high catalytic activities in nitration process. In addition, these catalysts can be recovered easily and reused for many times in nitration. This process is an eco-safer and environment-benign way for clean synthesis of nitrated phenolic compounds.

1. Introduction

The replacement of current chemical processing with more environmentally benign alternatives is an increasingly attractive subject.[1] Nitration of aromatic compounds is one of the most important industrial processes[2–9] and is the subject of a large body of literature.[10–13] Especially, nitrated phenolic compounds are very useful intermediates in the preparation of fine chemicals.[13–16] In general, nitration of aromatic compounds typically requires a mixture of concentrated or fuming nitric acid with sulfuric acids leading to excessive acid waste streams and added expense.[17] The obvious disadvantages of the commercial manufacturing process currently used has led to a substantial effort to develop viable alternatives, by using solid acid catalysts, other sources of NO_2^+, organic nitrating agents, other acids replacing sulfuric acid, etc.[18,19] But, none of them thus far have practical value in industrial use. Recently, it was found that metal salts or metal complexes could be used as catalysts for the nitration of phenolic compounds, although the loss of catalyst occurred during the recovery of the employed catalyst in above nitration processes.[20–23] Enlightened by these findings, we attempted to seek out a more practical process for the nitration of phenolic compounds using stoichiometric or a small excess of nitric acid under mild conditions because the development of environmentally friendly practical procedures for the nitration of aromatic compounds is highly desirable. So far, we have reported that $Ln(OPf)_3$ (Ln = Sc, Yb, La, Pf = $C_8F_{17}SO_3$), $Bi(NO_3)_3$/montmorillonite KSF and Zr or Hf oxychloride complex/montmorillonite KSF are effective catalysts for nitration of aromatic or phenolic compounds with a small excess of 60–65% nitric acid under mild conditions.[24–28] However, in these nitration processes, 500 mg of KSF for 1.0 mmol of phenolic compounds are required to give the nitrated products in good yields. Obviously, the large amount of KSF will cause the inconvenience for the practical nitration process. Therefore, we attempted to reduce the amount of KSF in this nitration process. The problem is that if the nitration is carried out with less amount of KSF, the loss of active components in KSF will hamper the catalytic ability of these catalysts because the nitration was carried out in a strong nitric acid solution. Therefore, the modification of KSF to achieve higher catalytic ability is desirable.

In fact, considerable attention has been given to the development of new functionally active supports, and a new class of catalysts based on layered aluminosilicates modified by the introduction of the hydroxo complexes of polyvalent metals into the interlayer space has been reported.[29–31] These materials possess unique structural and catalytic properties, which depend on both the chemical properties of the introduced compounds and modification procedures and conditions.[32,33] Montmorillonites are silicates of aluminum with layered structure that present a wide use in organic synthesis[33] and exhibit specific features.[34] In the recent years, metal-modified

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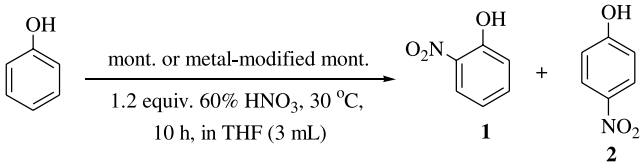
montmorillonites were reported widely, and many metals, such as Zn, Mn, Fe, Cu, Cr, V, Mo Ti, etc.,[35–39] were commonly used to improve the catalytic abilities of montmorillonites. In these catalysts, the metal complexes are doped into the layered structure of montmorillonites and exist in more stable states. In any sense, these catalysts could keep excellent catalytic activity even after recycling and can be reused for many times. We thought that these metal-modified montmorillonite catalysts might be more efficient for the catalytic nitration of phenolic compounds in a similar way. Moreover, by adopting metals to modify montmorillonite, the montmorillonite's catalytic ability can be improved and the employed amount of KSF in these catalysts could be reduced to some extent. Herein, we wish to report a new catalytic system for the nitration of phenolic compounds to give the corresponding nitrated products in good yields in a heterogeneous phase under mild conditions. By this protocol, the amount of KSF in the corresponding mixed catalyst was reduced to 250 mg for 1.0 mmol of phenolic compounds, and the catalysts could be recycled and reused easily.

2. Results and discussion

Montmorillonite K10, montmorillonite KSF and nitric acid treated montmorillonite KSF (denoted as HKSF) were used as base catalysts and carriers. The preparation of metal-modified montmorillonite catalysts was carried out by the similar methods as those described in previous literature.[35–39] The procedure is shown below. Single-metal-modified montmorillonite catalysts were first prepared by wet impregnation method. Montmorillonite was impregnated with V, Mo, W, respectively, by mixing calculated amounts (10 wt% calculated by metal oxides) of the ammonium salt of V, Mo and W with the clay and refluxing either in acetone or in the mixed solvent of acetone and water with magnetic stirring. Acetone was dried off from the catalyst sample at room temperature. The resulting catalyst sample was further dried at 120 °C by an oven for 2 h and calcined by muffle furnace at 600 °C for 4 h. The catalyst samples prepared are denoted either as M_1–HKSF or as M_1–KSF in which M_1 represents the first incorporated metal. These M_1–HKSF and M_1–KSF sample were used as carriers and then modified with second metal such as In, Bi, Ti, Zr, Hf, Sc, Yb, Eu by the similar method. The resulting sample was dried at 120 °C by an oven for 2 h and calcined by muffle furnace at 400 °C for 4 h. The catalyst samples prepared are denoted as M_2–M_1–HKSF or M_2–M_1–KSF where M_1 and M_2 are the incorporated metals.

We examined montmorillonite clays (250 mg) and single-metal-modified KSF (250 mg) in the nitration of phenol (1.0 mmol) with 1.2 equiv of 60% nitric acid in THF (3 mL). The results are summarized in Table 1. Montmorillonite K10 and montmorillonite KSF (250 mg) could be used as nitration catalysts of phenol in 3 mL of THF (Table 1, entries 1 and 2). However, when KSF was washed by water (denoted as HKSF) or by nitric acid, or was calcined at 600 °C by a muffle furnace (denoted as CKSF) for 4 h, no reaction occurred under the same conditions (Table 1, entries 3–5). These results suggest that when the employed amount of KSF was reduced to 250 mg for 1.0 mmol of phenol, the loss of active component by nitric acid solution will cause serious deactivation of the catalyst in nitration process. Metal Mo and V modified HKSF or KSF gave the good results in the nitration of phenol although metal W modified HKSF or KSF did not catalyze the nitration of phenolic compounds under the same conditions (Table 1, entries 6–11). These results suggest that Mo and V modified HKSF or KSF can be used in nitration even with reduced amount of KSF.

Table 1. Nitration of phenol catalyzed by montmorillonite or metal-modified montmorillonite (250 mg)

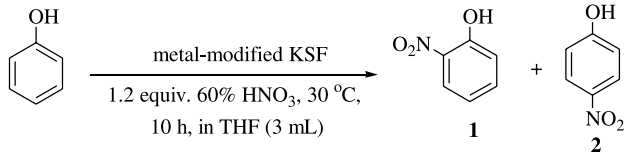


Entry	Catalyst	Yield (%)[a]	
		1	**2**
1	Mont. K10	38	42
2	Mont. KSF	39	45
3	CKSF[b]	nr	
4	WKSF[c]	nr	
5	HKSF[d]	nr	
6	Mo–HKSF[e]	39	47
7	Mo–KSF[f]	37	45
8	V–HKSF[f]	35	45
9	V–KSF[f]	39	46
10	W–HKSF[g]	nr	
11	W–KSF[g]	nr	

[a] Isolated yield.
[b] KSF was calcined at 600 °C for 4 h.
[c] KSF was washed by water.
[d] KSF was washed by 10% HNO_3.
[e] Metal Mo modified KSF or HKSF.
[f] Metal V modified KSF or HKSF.
[g] Metal W modified KSF or HKSF.

Next using these double-metal-modified KSF catalysts (M_2–M_1–HKSF or M_2–M_1–KSF), in which the second doped metal is In (M_2 = In, M_1 = Mo, V, W), we examined their catalytic abilities in this nitration reaction. The results are summarized in Table 2. We found that metal W modified KSF did not have the catalytic ability in this nitration either even doped with second metal In and the metal V or Mo modified KSF with second metal In gave the good results in the same reaction (Table 2, entries 1–6). Thus, metal V and

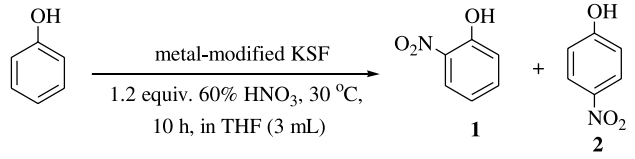
Table 2. Nitration of phenol catalyzed by metal-modified KSF (250 mg)



Entry	Catalyst	Yield (%)[a]	
		1	**2**
1	In–Mo–KSF	41	47
2	In–Mo–HKSF	43	44
3	In–V–KSF	41	47
4	In–V–HKSF	37	48
5	In–W–KSF	nr	
6	In–W–HKSF	nr	

[a] Isolated yield.

Table 3. Nitration of phenol catalyzed by metal-modified KSF (250 mg)



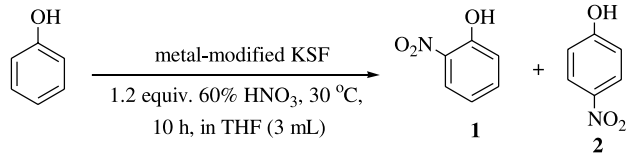
Entry	Catalyst	Yield (%)[a]	
		1	**2**
1	Ti–Mo–HKSF	nr	
2	Zr–Mo–HKSF	38	45
3	Hf–Mo–HKSF	41	48
4	Sc–Mo–HKSF	41	46
5	La–Mo–HKSF	41	44
6	Yb–Mo–HKSF	42	45
7	Eu–Mo–HKSF	37	43
8	Bi–Mo–HKSF	39	42
9	Zr–Mo-KSF	39	43
10	Eu–Mo–KSF	37	45

[a] Isolated yield.

Mo modified KSF are suitable for the doping of the second metal.

Therefore, metal V and Mo modified KSF were utilized as carriers, respectively, and were modified with other metal salts such as $TiCl_4$, $ZrCl_4$, $HfCl_4$, $Sc(NO_3)_3$, $La(NO_3)_3$, $Yb(NO_3)_3$, $Eu(NO_3)_3$, and $Bi(NO_3)_3$ in a similar way as that described above. We examined these catalysts in the nitration reaction and the results are summarized in Tables 3 and 4, respectively. Except metal Ti modified catalysts (Ti–Mo–HKSF and Ti–V–HKSF) all these catalysts gave good results in this nitration under the same conditions (Table 3, entries 1–10 and Table 4, entries 1–8). It should be noted that when M_2–V–KSF or M_2–V–HKSF was used as the catalyst, the corresponding nitrated products **1** and **2** were obtained as slightly red colorized solid presumably due to the oxidation ability of metal V.

Table 4. Nitration of phenol catalyzed by metal-modified KSF (250 mg)

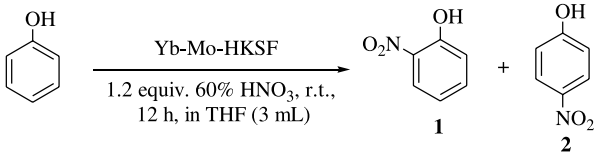


Entry	Catalyst	Yield (%)[a]	
		1	**2**
1	Ti–V–HKSF	nr	
2	Zr–V–HKSF	38	45
3	Hf–V–HKSF	41	48
4	Sc–V–HKSF	41	46
5	La–V–HKSF	41	44
6	Yb–V–HKSF	42	45
7	Eu–V–HKSF	37	43
8	Bi–V–HKSF	39	42

[a] Isolated yield.

Moreover, it should be emphasized here that this catalytic nitration is a heterogeneous catalytic process and these catalysts could be easily recovered from reaction mixture just by filtration. These catalysts can be reused for many times without degradation after them have been reactivated by heating at 120 °C with an oven. In our experiment, we chose one of these catalysts, and reused this catalyst for six times and it still has good catalytic activity. The results are summarized in Table 5.

Table 5. Nitration of phonol catalyzed by recovered catalyst



Run	Mass of catalyst/mg recovered catalyst[a]	Yield (%)[b]	
		1	**2**
1	286[c]	45	46
2	276 (96)	40	45
3	270 (94)	42	44
4	249 (87)	40	50
5	228 (80)	41	50
6	209 (73)	43	47

[a] Mass of catalyst recovered from each run and the data in parantheses indicate the percentage of recovery.
[b] Isolated yield.
[c] Recovered catalyst was used.

All these carriers and catalysts were characterized by powder X-ray diffraction (XRD). XRD patterns of KSF,

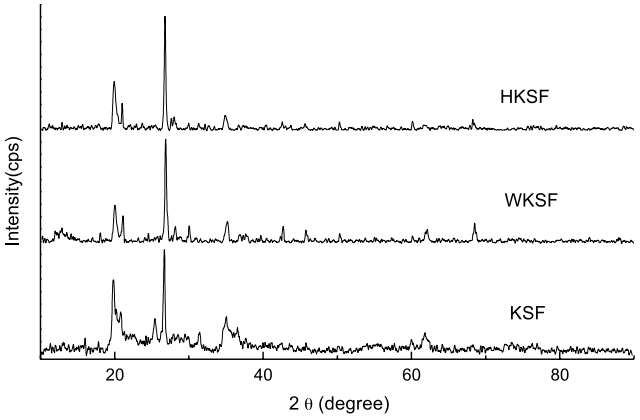


Figure 1. XRD patterns of KSF, KSF washed by water and KSF washed by 10% HNO_3.

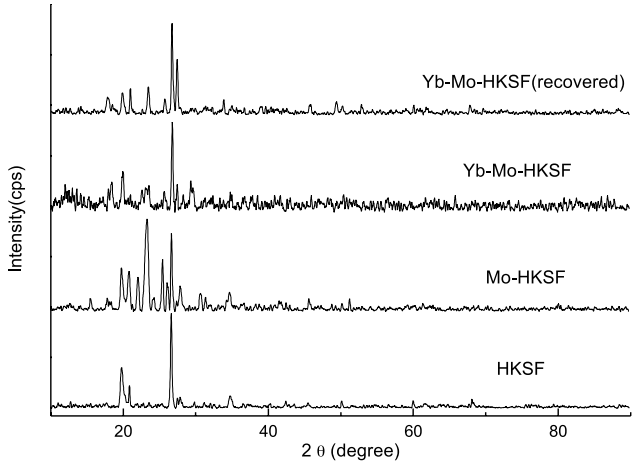


Figure 2. XRD patterns of HKSF, metal modified HKSF catalysts and recycled catalyst.

WKSF (washed by water) and HKSF (washed by 10% HNO_3) are presented in Figure 1. All these clays showed intense lines in their fine structure. As it has been pointed out, when KSF was washed by nitric acid solution, the active components lost into water. The XRD pattern has indeed showed some changes in fine structure although the basal structure of KSF was kept. XRD patterns of HKSF and its metal modified structure are presented in Figures 2 and 3, respectively. When HKSF was modified by metal Mo or by double metals Yb–Mo, the composition of the clays was changed and these differences have been indicated in their XRD which lead to different catalytic activities in nitration. The doping of metal did not effect the basal supporting structure of HKSF as shown in Figures 2 and 3. The XRD analysis of the recovered catalyst indicated no alteration with the original catalyst even Yb–Mo–HKSF catalyst was reused for six times. Metal V or double metals Yb–V modified catalysts showed similar characters as with that of metal Mo or double metals Yb–Mo modified catalysts.

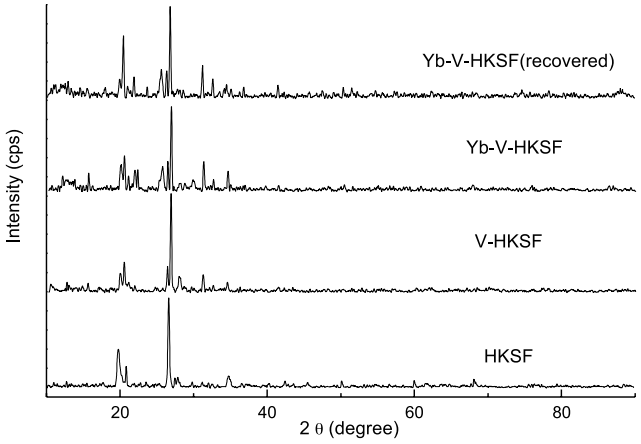


Figure 3. XRD patterns of HKSF, metal modified HKSF catalysts and recycled catalyst.

These catalytic systems were more effective and reusable in the nitration of phenolic compounds because of its stability against strong hydrolytic reaction conditions in nitration. Based on above investigation, we turned out to use Yb–Mo–HKSF or Eu–Mo–HKSF as catalysts to nitrate a variety of other phenolic substrates with 1.2 equiv of 60% nitric acid in THF. This electrophilic aromatic nitration reaction proceeded smoothly for many phenolic substrates. The results are shown in Table 6. 4-Fluorophenol, 4-chlorophenol, 4-isopropylphenol, 4-*tert*-butylphenol, reacted smoothly to afford a mono-nitrated product in excellent yields (Table 6, entries 1, 2, 4, and 5). For the nitration of 4-bromophenol, four nitrated products, 4-bromo-2-nitrophenol, 2-bromo-4-nitrophenol, 2,4-dibromo-6-nitrophenol and 4-nitrophenol, were obtained in total 99% yield (Table 6, entry 3 and Fig. 4). This nitration behavior has been described in previous literature.[40] In the case of the activated phenolic aromatic compound, 4-methoxyphenol, mono-nitrated product and dinitrated product were obtained in total 76% yield (mono/di = 66:34, when 1.2 equiv HNO_3 was used) or in total 66% yield (mono/di = 6:94, when 2.0 equiv HNO_3 was used) (Table 6, entries 6 and 7).

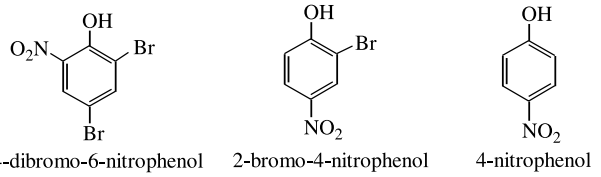
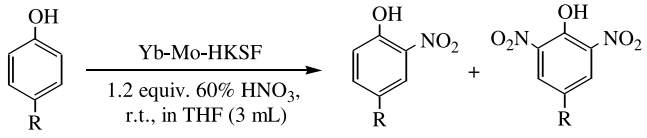


Figure 4.

In addition, we also examined the nitration reaction of 2-cresol, 3-cresol and 4-cresol by 1.2 equiv of 60% nitric acid in the presence of Yb–Mo–HKSF or Eu–Mo–HKSF. In the case of 3-cresol, three mono-nitrated phenolic products were obtained in total 91% yield (Table 7, entry 2). However, in the nitration of 4-cresol and 2-cresol, both mono-nitrated and dinitrated products were obtained in good total yields, respectively, at the same time under identical conditions (Table 7, entries 1 and 3).

We further investigated the nitration of 2-chlorophenol, 1,2-diethoxybenzene, 2-ethoxyphenol and resorcinol with

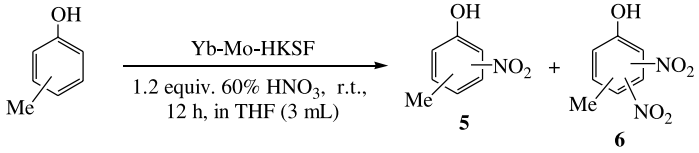
Table 6. Nitration of phenolic compounds catalyzed by Yb–Mo–HKSF or Eu–Mo–HKSF (250 mg)

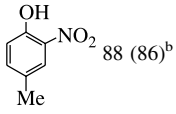
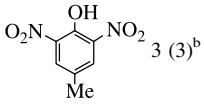
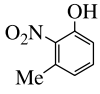
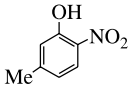
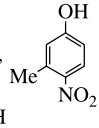
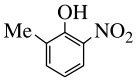
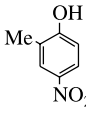
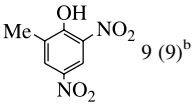


Entry	R	Time (h)	Yield (%)[a]	
			3	**4**
1	F	12	87 (90)[b]	—
2	Cl	4	88 (78)[b]	—
3	Br	4	63 (65)[b], other products 36 (29)[b,c]	—
4	*i*-Pr	12	74 (87)[b]	—
5	*t*-Bu	12	88 (93)[b]	—
6	OMe	4	50 (48)[b]	26 (24)[b]
7[d]	OMe	1	4 (4)[b]	62 (63)[b]

[a] Isolated yields.
[b] Eu–Mo–HKSF was used as catalyst.
[c] The products include 2,4-dibromo-6-nitrophenol, 2-bromo-4-nitrophenol and 4-nitrophenol (Fig. 4).
[d] The quantity of nitric acid is 2.0 equiv.

Table 7. Nitration of cresol catalyzed by Yb–Mo–HKSF or Eu–Mo–HKSF (250 mg)



Entry	Cresol	Yield (%)[a]	
		5	**6**
1	4-MeC_6H_4OH	 88 (86)[b]	 3 (3)[b]
2	3-MeC_6H_4OH	 13 (9)[b],  26 (25)[b],  52 (53)[b]	
3	2-MeC_6H_4OH	 39 (40)[b],  45 (42)[b]	 9 (9)[b]

[a] Isolated yields.
[b] Eu–Mo–KHSF was used as the catalyst.

60% HNO_3 (1.2 equiv) in the presence of Yb–Mo–HKSF or Eu–Mo–HKSF under identical conditions. The results are summarized in Table 8. We found that nitration of 2-chlorophenol proceeded smoothly within 4 h to give the mono-nitrated products in high yields (Table 8, entry 1). For 2-ethoxyphenol, a similar good result was obtained under identical conditions (Table 8, entry 2). For nitration of 1,2-diethoxybenzene, mono-nitrated product was obtained in 66% yield with 60% HNO_3 (1.2 equiv) at 60 °C (Table 8, entry 3). For resorcinol, mono-nitrated product was obtained in 66% yield under identical conditions (Table 8, entry 4).

In conclusion, we have found an environmentally conscious practical procedure for the nitration of phenolic compounds under mild conditions. In the presence of metal-modified montmorillonite catalysts, less amount of catalysts (250 mg catalyst for 1.0 mmol of phenolic substrate) and 1.2 equiv, of 60% nitric acid can be used in nitration of a variety of phenolic compounds to give the nitrated products in good to high yields. The use of a large excess amount of concentrated or fumed nitric acid can be avoided by this catalytic system. Moreover, these catalysts can be easily recovered from the reaction mixture and can be reused for many times. This nitration method was carried out in THF, an environmentally safer solvent without sulfuric acids. Overall, this method is an eco-safer and environment-benign way for nitration of phenolic compounds.

3. Experimental

3.1. General remarks

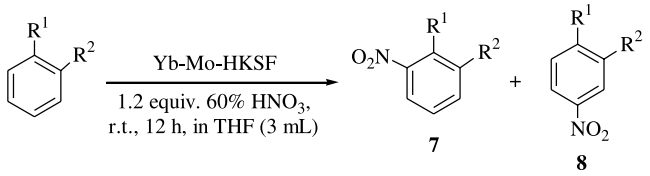
MPs were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. All of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA^+ mass spectrometer. The XRD patterns of the catalyst samples oriented on glass slides were recorded on a Philips semiautomatic diffractometer with Ni-filtered Cu Kα radiation ($\lambda = 1.54178$ Å). A scan rate of 0.02° min^{-1} was used on the samples over the 2θ range of 10–90°. Organic solvents were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. The orientation of nitration was determined by NMR analysis. Flash column chromatography was carried out using 300–400 mesh silica gel. The spectroscopic and analytic data of the most nitrated products have been disclosed in the previous literature.[26,27]

3.2. Preparation of metal catalysts used in the nitration of phenolic compounds

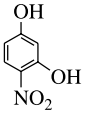
Preparation of modified carrier: montmorillonite KSF (20 g) and 10% of nitric acid (50 mL) were put into a 250 mL beaker and the mixture was stirred for 12 h at room temperature. Then, the mixture was filtrated and washed by water until the filtrate showed pH ≈ 7. The residue was dried at 120 °C by an oven for 2 h, which was used as carrier (HKSF).

Preparation of single-metal-modified catalysts (Mo-HKSF): $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.83 g) was dissolved in 20 mL of mixed solution of acetone and water (3:1), then the above 13.5 g of HKSF was added into the solution and the resulting mixtures were refluxed with magnetic stirring for 2 h. Next, the solvent was removed under reduced pressure upon heating at 80 °C and the residue was further dried at 120 °C by an oven for 2 h and then calcined by a muffle furnace at 600 °C for 4 h to obtain the single metal Mo modified catalyst (Mo–HKSF). In addition, V–HKSF and W–HKSF were prepared in the similar procedure.

Table 8. Nitration aromatic compounds catalyzed by Yb–Mo–HKSF or Eu–Mo–HKSF (250 mg)



7 8

Entry	R^1	R^2	Time (h)	Yield (%)[a]	
				7	**8**
1	OH	Cl	4	43 (48)[b]	54 (44)[b]
2	OH	OE*t*	4	35 (33)[b]	54 (53)[b]
3[c]	OE*t*	OE*t*	24	—	66 (64)[b]
4			1		67 (69)[b]

[a] Isolated yield.
[b] Eu–Mo-HKSF was used as the catalyst.
[c] The reaction temperature is 60 °C.

Preparation of double-metals-modified catalysts (Yb–Mo–HKSF)/ 1.82 g of $Yb(NO_3)_3$ was dissolved in 20 mL of mixed solution of acetone and water (3:1), then 9.0 g of Mo–HKSF was added into the solution and the mixtures were refluxed with magnetic stirring for 2 h. Next, the solvent was removed under reduced pressure upon heating at 80 °C and the residue was further dried at 120 °C by an oven for 2 h and then calcined by a muffle furnace at 400 °C for 4 h to obtain the double-metals Yb–Mo modified catalyst (Yb–Mo–HKSF). In addition, M–Mo–HKSF, M–V–HKSF and M–W–HKSF (M=In, Bi, Ti, Zr, Hf, Sc, Yb, Eu, herein, $TiCl_4$, $ZrCl_4$, $HfCl_4$, $Sc(NO_3)_3$, $La(NO_3)_3$, $Yb(NO_3)_3$, $Eu(NO_3)_3$, $In(NO_3)_3$ and $Bi(NO_3)_3$ were used as mental salts) were prepared in the similar procedures as those described above.

3.3. General procedure for the nitration of phenolic compounds

Catalyst (250 mg) was put into a glass vessel, and then phenol (94 mg, 1.0 mmol) and THF (3 mL) was added into the glass vessel. Nitric acid (60%, 0.095 mL, $d=1.3667$, 1.2 mmol) was added dropwise into the vessel and the mixtures were stirred for 12 h at room temperature. The catalyst was recovered by filtration, and the filtrate was extracted with dichloromethane (CH_2Cl_2). The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatograph (eluent: petroleum ether/EtOAc=10:1) to give 2-nitrophenol (59 mg) and 4-nitrophenol (62 mg) in total 87% yield.

3.4. The recovery of the catalysts and the reusing procedure

The catalyst can be easily recovered from the reaction mixture just by filtration and reused for many times after it is activated by heating in an oven at 120 °C for 2 h. The recycled catalyst was used for the nitration of phenol. After filtration, the catalyst was recovered and the reaction mixture was extracted with dichloromethane (CH_2Cl_2). The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatograph (eluent:petroleum ether/EtOAc=10:1) to give 2-nitrophenol (62 mg) and 4-nitro-phenol (63 mg), total yield 90%.

3.4.1. 2,4-Dibromo-6-nitrophenol. A yellow solid: 26 mg, yield 9%, mp 114–116 °C, IR (KBr) ν 1531, 1392 cm^{-1} (NO_2), 3070, 1242 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 8.00 (1H, d, $J=2.4$ Hz, Ar), 8.25 (1H, d, $J=2.4$ Hz, Ar), 11.05 (1H, s, ArOH); MS (EI) *m/z* 297 (M^+, 100), 267 (M^+-30, 18.37), 239 (M^+-58, 19.23), 223 (M^+-74, 12.92). Anal. Calcd for $C_6H_3Br_2NO_3$ (%): requires C, 24.27; H, 1.02; N, 4.72%. Found: C, 24.55; H, 1.11; N, 4.54%.

3.4.2. 2-Bromo-4-nitrophenol. A yellow solid: 17 mg, yield 8%, mp 115–118 °C, IR (KBr) ν 1515, 1337 cm^{-1} (NO_2), 3390, 1249 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 6.21 (1H, s, ArOH), 7.13 (1H, d, $J=9.0$ Hz, Ar), 8.16 (1H, dd, $J=9.0$, 3.0 Hz, Ar), 8.44 (1H, d, $J=3.0$ Hz, Ar); MS (EI) *m/z* 219 (M^+, 100), 189 (M^+-30, 85.62), 171 (M^+-46, 12.50), 145 (M^+-74, 31.51), 119 (M^+-100, 8.76). Anal. Calcd for $C_6H_4BrNO_3$ (%): requires C, 33.06; H, 1.85; N, 6.42%. Found: C, 33.09; H, 1.92; N, 6.6 8%.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.027

References and notes

1. Clark, J. H. *Green Chem.* **1999**, *1*, 1–8.
2. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1999.
3. Olah, G. A.; Malhotra, R.; Narang, S. C. In *Nitration: Methods and Mechanism*; Feuer, H., Ed.; VCH: New York, 1989.
4. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University: Ithaca, New York, 1969.
5. Olah, G. A.; Kuhn, S. J. In Olah, G. A., Ed.; *Friedel-Crafts and Related Reactions*; Wiley: New York, 1964; Vol. 2.
6. Olah, G. A.; Narang, S. C.; Olah, J. A.; Lammertsma, K. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, 4487–4491.
7. Thompson, M. J.; Zeeger, P. J. *Tetrahedron* **1991**, *47*, 8787–8790.
8. Bisarya, S. C.; Joshi, S. K.; Holker, A. G. *Synth. Commun.* **1993**, *8*, 1125–1137.
9. Robrgues, J. A. R.; Oliveira, A. P.; Moran, P. J. S.; Custodio, R. *Tetrahedron* **1999**, *55*, 6733–6738.
10. Olah, G. A.; Albright, F., Ed.; ACS Symposium Series, Vol. 22; American Chemical Society: Washington DC, 1967; p 1.
11. Hoggett, J. G.; Moodie, R. B.; Penton, J. R.; Schofield, K. *Nitration and Aromatic Reactivity*; Cambridge University Press: London, 1971.
12. Schofield, K. *Aromatic Nitration*; Cambridge University Press: London, 1980.
13. Malysheva, L. V.; Paukshtis, E. A.; Ione, K. G. *Catal. Rev. Sci. Eng.* **1995**, *37*, 179.
14. Stewart, J. T.; Janicki, C. A. *Anal. Profiles Drug Subst.* **1987**, *16*, 119.
15. Desai, M. N. *Indian J. Appl. Chem.* **1970**, *33*, 277–282.
16. Mottier, M. *Arch. Sci. Phys. Nat.* **1934**, *16*, 301.
17. Lunar, L.; Sicilia, D.; Rubio, S.; Perez-Bendito, D.; Nickel, U. *Water Res.* **2000**, *34*, 1791–1802.
18. Firouzabadi, H.; Iranpoor, N.; Zolfigol, M. A. *Synth. Commun.* **1997**, *19*, 3301–3311.
19. Iranpoor, N.; Firouzabadi, H.; Zolfigol, M. A. *Synth. Commun.* **1993**, *15*, 2773–2781.
20. Ouertani, M.; Girard, P.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 4315–4318.
21. Cornelis, A.; Laszlo, P.; Pennetreau, P. *Bull. Soc. Chim. Belg.* **1984**, 961–972.
22. Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909–917.
23. Laszlo, P.; Cornelis, A. *Aldrichmica Acta* **1988**, 97–103.
24. Shi, M.; Cui, S. C. *J. Fluorine Chem.* **2002**, *113*, 207–209.
25. Shi, M.; Cui, S. C. *Chem. Commun.* **2002**, 994–995.
26. Cui, S. C.; Shi, M. *Adv. Synth. Catal.* **2003**, *345*, 1197–1202.
27. Shi, M.; Cui, S.-C.; Yin, W.-P. *Eur. J. Org. Chem.* **2005**, 2379–2384.
28. Shi, M.; Cui, S.-C. *Adv. Synth. Catal.* **2003**, *345*, 1329–1333.
29. Gandia, L. M.; Vicente, M. A.; Gil, A. *Appl. Catal., A* **2000**, *196*, 281–292.
30. Prinetto, F.; Tichit, D.; Teissier, R.; Coq, B. *Catal. Today* **2000**, *55*, 103–116.
31. Pinnavaia, T. J. *Science* **1983**, *220*, 365–371.
32. Narkynan, S.; Deshpande, K. *Appl. Catal., A* **2000**, *193*, 17–27.
33. Varma, R. S. *Tetrahedron* **2002**, *58*, 1235–1255.
34. Vaccari, A. V. *Appl. Clay Sci.* **1999**, *14*, 161–198.
35. Clark, P. D.; Mesher, S. T. E.; Primak, A. *Phosphorus, Sulfur and Sillicon* **1996**, *114*, 99–108.
36. Clark, P. D.; Mesher, S. T. E.; Primak, A.; Yao, H. *Catal. Lett.* **1997**, *43*, 79–82.
37. Shinde, A. B.; Shrigadi, N. B.; Samant, S. D. *Appl. Catal., A* **2004**, *276*, 5–8.
38. Castillo, H. L.; Gil, A.; Grange, P. *Catal. Lett.* **1997**, *43*, 133–137.
39. Kurian, M.; Sankaran, S. *React. Kinet. Catal. Lett.* **2004**, *81*, 57–64.
40. Clewley, R. G.; Fischer, A.; Henderson, G. N. *Can. J. Chem.* **1989**, 1472–1479.

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Lewis acid promoted reactions of γ,γ-dialkoxyallylic zirconium species with various carbonyl compounds

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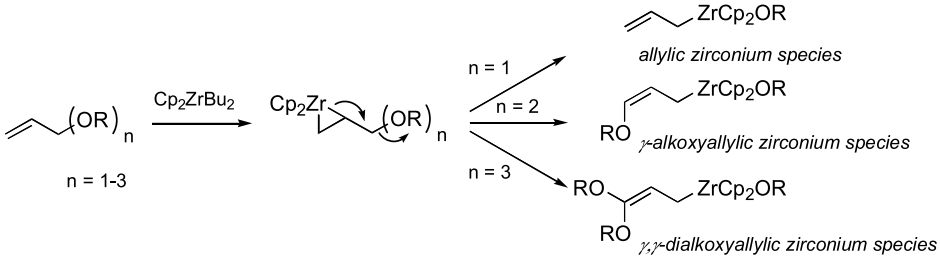
Abstract—The reactions of γ,γ-dialkoxyallylic zirconium species with carbonyl compounds in the presence of Lewis acid are reported. The reactivity of γ,γ-dialkoxyallylic zirconium species and reaction pathway were strongly dependent on the structure and electrostatic nature of the carbonyl compounds.

1. Introduction

Although many kinds of allylic organometallics have been reported during the last three decades, development of novel preparative methods and their useful reactions is an important subject due to the importance of the carbon–carbon bond formation in the organic synthesis.[1] We have developed the preparative method for the allylic and related zirconium species from allyl ether derivatives with zirconocene–butene complex through β-elimination of alkoxyl group.[2–5] Our method for the generation of allylic zirconiums has some characteristic features: (1) zirconium species attack initially to the double bond of the allyl ether and the subsequent elimination of alkoxyl group provides the allylic zirconium.[6,7] Mechanism of this process is different from that of the reaction of low valent metal with allyl halide involving the direct oxidative insertion of metal to carbon–halogen bond. (2) Relatively stable allylic ether can be used as a precursor for the allylic organometallics. (3) A variety type of substrates can be used as a precursor (acrolein acetal and acrylic acid *ortho* ester etc.). Along with this line, we have reported the preparative method for the allylic zirconium,[2] alkoxyallylic zirconium,[3] and dialkoxyallylic zirconium species[4,5] from the corresponding allylic ethers (Scheme 1).

Among the reactions of allylic zirconium species with carbonyl compounds, we found interesting reactivities of γ,γ-dialkoxyallylic zirconium species and the detail of the reaction as α,β-unsaturated acyl anion equivalent have been reported.[4] γ,γ-Dialkoxyallylic zirconium species **1** react with aldehyde at the γ-position of zirconium in the absence or presence of 0.2–0.3 equiv of Lewis acid (Eq. 1 in Scheme 2). Therefore, this zirconium species **1** work as acryloyl anion equivalent.[10] On the other hand, in the presence of more than a stoichiometric amount of Lewis acid, *gem*-dialkoxycyclopropane derivatives **3** are formed in the reaction of **1** with aldehyde, in which **1** serves as



Scheme 1.

Keywords: Lewis acid; Zirconium species; Cyclopropane derivatives.
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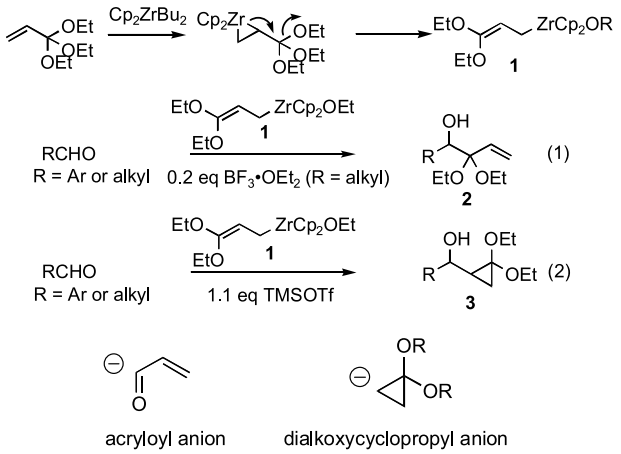


Scheme 2.

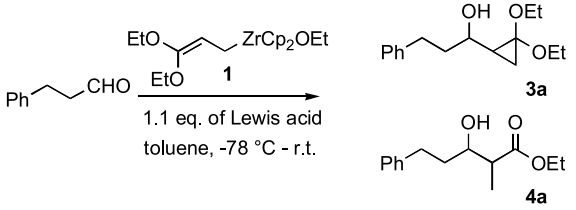
dialkoxycyclopropyl anion equivalent (Eq. 2 in Scheme 2). We report here the detail of the Lewis acid promoted reactions of γ,γ-dialkoxyallylic zirconium species with carbonyl compounds.[5]

2. Results and discussions

2.1. Reaction of γ,γ-diethoxyallylic zirconium species 1 with carbonyl compounds (1,2-addition)

γ,γ-Dialkoxyallylic zirconium species **1** can be prepared from triethyl orthoacrylate[8] with zirconocene–butene complex[9] by our reported procedure as shown in Scheme 2. Examination of Lewis acid for the preparation of *gem*-dialkoxycyclopropane derivatives by the reaction of the zirconium species **1** with aldehyde is summarized in Table 1. In the presence of stoichiometric amount of Lewis acid, the zirconium species **1** smoothly reacted with aldehydes to give the *gem*-diethoxycyclopropane derivatives **3** as a diastereomeric mixture. Regarding the Lewis acid, when $BF_3 \cdot OEt_2$ or $TiCl_4$ was employed, the reaction of **1** with 3-phenylpropionaldehyde gave **3a** in 75 and 57% yield, respectively, along with a small amount of uncyclized product **4a**[11] (entries 1 and 2). This result may support the following discussion for the mechanism of this reaction (vide infra). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) smoothly promoted the reaction of **1** to give **3a** in 88% yield without the formation of **4a** (entry 3).

Table 1. Examination of Lewis acid for the reaction of **1**

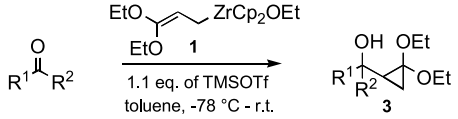


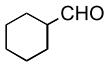
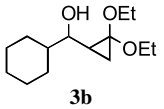
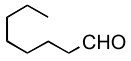
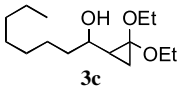
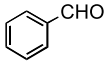
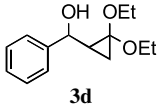
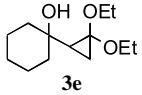
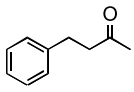
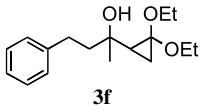
Entry	Lewis acid	Yield of **3a** (%)[a,b]
1	$BF_3 \cdot OEt_2$	75
2	$TiCl_4$	57
3	TMSOTf	88

[a] Isolated yield. Yield was based on **1**.
[b] Diastereomeric mixture (1:1–2:1).

Using TMSOTf, the reaction of **1** with other carbonyl compounds was examined (Table 2). The zirconium species **1** reacted with not only aliphatic aldehydes but also aromatic aldehydes to give the cyclopropane derivatives (**3b**, **3c**, and **3d**) in good yields (entries 1–3). Ketones also reacted with **1** to afford the adducts (**3e**, **3f**). Although the isolation yield was satisfactoly in the case of ketone, small amount of elimination product was obtained because of the adducts were relatively unstable due to the facile elimination of the hydroxyl group during silica gel column chromatography (entries 4, 5).

Table 2. TMSOTf-promoted reaction of **1** with carbonyl compounds



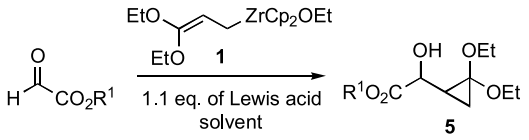
Entry	Carbonyl compound	Product	Yield (%)[a,b]
1		 **3b**	87
2		 **3c**	75
3		 **3d**	81
4		 **3e**	83
5		 **3f**	76

[a] Isolated yield. Yield was based on **1**.
[b] Diastereomeric mixture (1:1–2:1).

The reaction of γ,γ-diethoxyallylic zirconium species **1** with glyoxylate derivatives[12] was examined. Under the reaction conditions using TMSOTf (see Table 2), the desired product could not be obtained (Table 3, entry 1). In toluene, $Cu(OTf)_2$ or $Zn(OTf)_2$ which can be coordinated by two carbonyl groups also did not work well resulting in a complex mixture along with a significant amount of starting glyoxylate (entries 2 and 3). We found that the reaction proceeded smoothly in dichloromethane solvent. Thus, after the generation of **1** in toluene, the solvent was changed to dichloromethane for the reaction with glyoxylate and the best result was obtained in the case of $Cu(OTf)_2$ (entry 5).

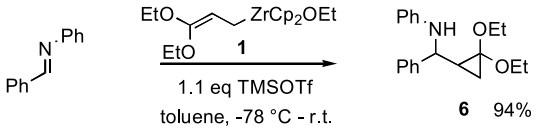
The reaction of the zirconium species **1** with imine derivatives was also examined (Scheme 3). Although **1** reacted with benzylideneaniline to give cyclopropane adduct **6** in 94% yield, unfortunately with other structurally similar imine derivatives such as naphthylideneaniline or benzylidene-*p*-methoxyaniline, clean reaction was not realized.

Table 3. Reaction of **1** with glyoxylate in the presence of Lewis acid



Entry	R^1	Lewis acid	Solvent	Product	Yield (%)[a,b]
1	*i*-Pr	TMSOTf	Toluene	—[c]	
2	*i*-Pr	$Cu(OTf)_2$	Toluene	—[c]	
3	*i*-Pr	$Zn(OTf)_2$	Toluene	—[c]	
4	*i*-Pr	TMSOTf	CH_2Cl_2	**5a**	52
5	*i*-Pr	$Cu(OTf)_2$	CH_2Cl_2	**5a**	85
6	*i*-Pr	$Zn(OTf)_2$	CH_2Cl_2	**5a**	55
7	Me	$Cu(OTf)_2$	CH_2Cl_2	**5b**	60
8	Et	$Cu(OTf)_2$	CH_2Cl_2	**5c**	78
9	Bn	$Cu(OTf)_2$	CH_2Cl_2	**5d**	60

[a] Isolated yield. Yield was based on **1**.
[b] Diastereomeric mixture (1:1–2:1).
[c] Complex mixture along with the recovery of glyoxylate.



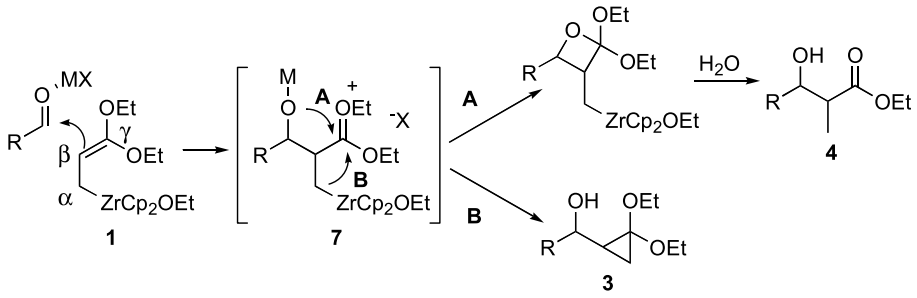
Scheme 3.

in the formation of the oxetane derivative, which after hydrolysis gave uncyclized product **4** as a by-product. The formation of cyclopropane derivatives in the reaction of alkoxyallylic tin derivatives with carbonyl compounds has also been reported.[13]

2.2. Reaction of γ,γ-diethoxyallylic zirconium species 1 with unsaturated carbonyl compounds

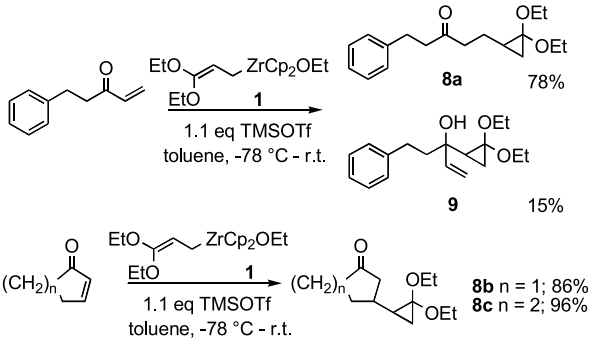
The reaction of γ,γ-diethoxyallylic zirconium species **1** with α,β-unsaturated ketone derivatives was examined. Under the TMSOTf-promoted conditions, with acyclic vinyl ketone, 5-phenylpent-1-en-3-one, the 1,4-addition reaction at the β-position of **1** proceeded predominantly to afford the cyclopropane **8a** in good yield (Scheme 5). With cycloalkenones, 1,4-adduct **8b** and **8c** were selectively obtained.

TMSOTf promoted reaction of **1** with benzyl acrylate as a typical model substrate of α,β-unsaturated ester was conducted (Scheme 6). Two products, diethoxycyclopropane **11** and diethoxycyclobutane **12** were obtained, although the yield was not good as a synthetic reaction. The reaction pathway to these products is possibly explained by considering the intermediate **10** derived through the 1,4-addition of the β-position of the zirconium species **1**. In the intermediate **10**, both nucleophilic centers competitively react to the carbenium ion site, that is, attack by ketene silyl acetal moiety provides the cyclobutane **12** (path B),[14]

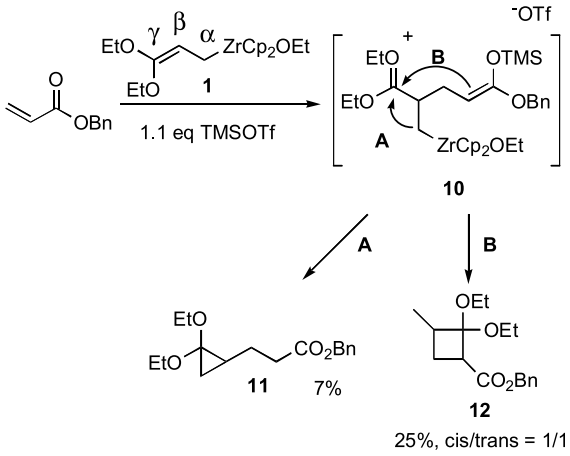


Scheme 4.

The reaction mechanism for the 1,2-addition of γ,γ-diethoxyallylic zirconium species **1** to the carbonyl compound is shown in Scheme 4. When less than a stoichiometric amount of Lewis acid is employed, the zirconium species **1** react at the γ-position with carbonyl compound through six-membered transition state, in which the activation of carbonyl group can be achieved by the coordination to the zirconium.[4] However, two geminal γ-ethoxy substituents of the zirconium species **1** makes the γ-position sterically hindered site and due to the ketene acetal structure the β-position should be electron rich site compared with allylic and γ-alkoxyallylic zirconium species. Therefore, in the presence of stoichiometric amount of Lewis acid, this zirconium species **1** react with activated carbonyl compound at the β-position as a ketene diethyl acetal leading to the formation of intermediate **7**. Subsequently, in the case of TMSOTf as Lewis acid, alkylzirconium part attacks to oxocarbenium ion moiety intramolecularly to give cyclopropane derivative **3** (path B). In the case of $BF_3 \cdot OEt_2$, competitive attack of the alkoxyl group in the intermediate **7** to the oxocarbenium ion resulted while the cyclopropane **11** is formed by the attack of alkylzirconium moiety (path A). To control the reaction pathway and to improve the product yield further reactions were conducted using various α,β-unsaturated carbonyl compounds such as lactone, amide, and *N*-acyloxazolidinone derivatives as described below.

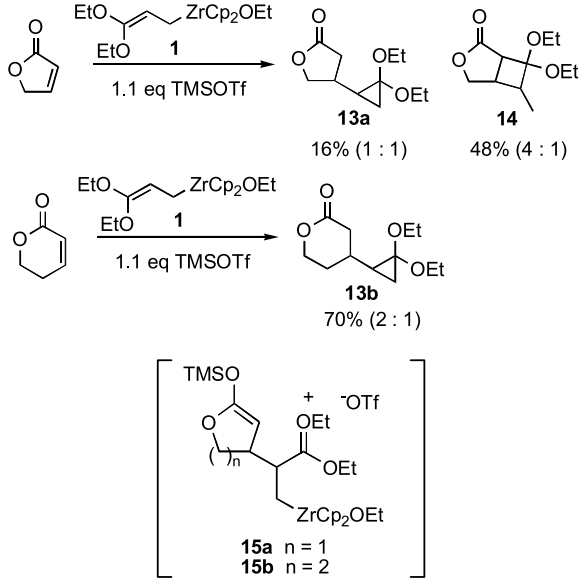


Scheme 5.



Scheme 6.

With α,β-unsaturated lactone derivatives the reaction proceeded smoothly. In the reaction of the zirconium species **1** with five-membered ring lactone, a mixture of the cyclopropane **13a** and the cyclobutane **14** were obtained in 16 and 48% yield, respectively. On the other hand, cyclopropane derivative **13b** was selectively obtained in the case of six-membered ring lactone. These results should be explained as follows. In both cases, 1,4-addition reaction at the β-position of the zirconium species **1** to the α,β-unsaturated lactone afforded the intermediate (**15a** or **15b**) having oxonium ion and silyl enol ether parts in the same molecule. In the case of six-membered ring lactone, it should be difficult to form the cyclobutane ring, because the oxonium ion and silyl enol ether are not close enough to react due to the equatorial oriented oxonium ion part on the pseudo chair like conformation of six-membered ring silyl enol ether (Scheme 7).

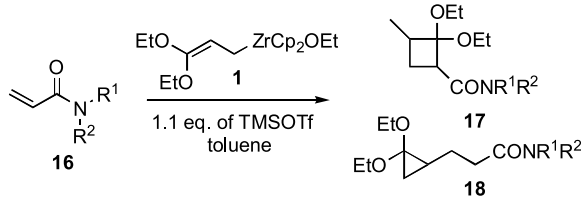


Scheme 7.

For the development of a highly selective method for the preparation of either cyclopropane or cyclobutane derivatives, we paid attention to the electron density of the ketene acetal moiety in the intermediate. Thus, an increase in the electron density of the ketene acetal moiety in the intermediate **10** by replacing one oxygen atom with electron-donating nitrogen atom would make path B favorable (Scheme 6). Therefore, as the substrate we adopted the acryl amide instead of ester for the selective construction of cyclobutane derivatives.

Results of the reaction of **1** with acryl amide derivatives **16** in the presence of TMSOTf are shown in Table 4. As expected, the reaction of **1** with *N*,*N*-dimethyl acrylamide smoothly proceeded to give cyclobutane derivative **17** exclusively (entry 1). In this reaction, the cis isomer was predominantly obtained. Improvement of the diastereoselectivity could be achieved by employing a more bulky substituent on the nitrogen atom ($R^1=R^2=$Bn or *i*-Pr, entries 2,3). The ratio of cyclobutane **17** and cyclopropane **18** was found to be affected by the electron density on the nitrogen atom. That is, when the electron density of the nitrogen atom was lowered by connecting to an aromatic ring, as in the case of *N*,*N*-diphenyl acrylamide, cyclopropane derivative **18** was obtained as a major product (entry 5). Under these conditions, the reaction did not proceed by introducing a substituent on the acryloyl moiety (crotonamide and methacrylamide) under these conditions.

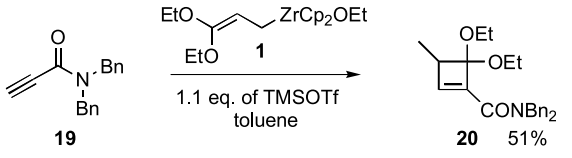
Table 4. Reaction of **1** with acrylamie derivatives



Entry	Amide		Yield (%)[a]	**17**/**18**[b]	**17**: cis/trans[b]
1	$R^1=R^2=$Me	**16a**	54	>95:5	82:18
2	$R^1=R^2=$Bn	**16b**	83	>95:5	>95:5
3	$R^1=R^2=$*i*-Pr	**16c**	56	>95:5	>95:5
4	$R^1=$Me, $R^2=$Ph	**16d**	85	>95:5	83:17
5	$R^1=R^2=$Ph	**16e**	61	25:75	85:15

[a] Isolated yield. Yield was based on **1**.
[b] Ration was determined by crude ^{1}H NMR.

The reaction of the zirconium species **1** with *N*,*N*-dibenzyl propiolamide (**19**) also proceeded to give the cyclobutene derivative **20** in 51% yield (Scheme 8).

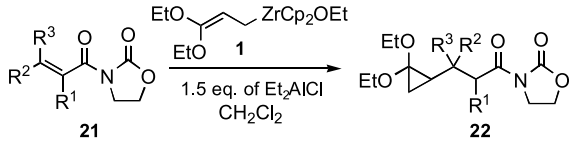


Scheme 8.

The selective construction of cyclopropane derivatives through path A in Scheme 6 was surveyed. To suppress the formation of cyclobutane derivatives through path B, α,β-unsaturated *N*-acyloxazolidinone derivatives **21**, which have oxazolidinone instead of dialkyl amine as the amide moiety, was used with the expectation of lowered nucleophilicity of ketene acetal moiety in the intermediate

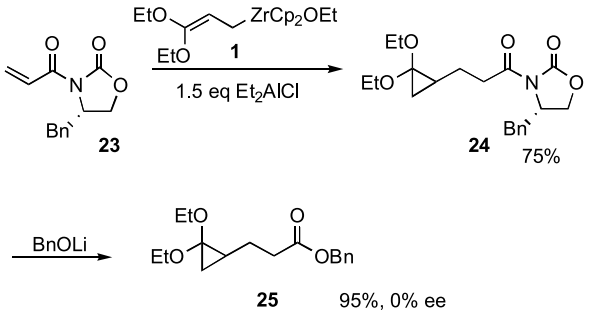
due to the decrease in the electron density as compared with *N*,*N*-dialkylamide. The results are summarized in Table 5.

Table 5. The reaction of **1** with acryloyl oxazolidinone derivatives



Entry	Substrate	Product	Yield (%)[a,b]
1	**21a**	**22a**	83
2	**21b**	**22b**	90 (1:1)
3	**21c**	**22c**	72 (7:3)
4	**21d**	**22d**	39

[a] Isolated yield. Yield was based on **1**.
[b] Ration was determined by crude ^{1}H NMR.



Scheme 9.

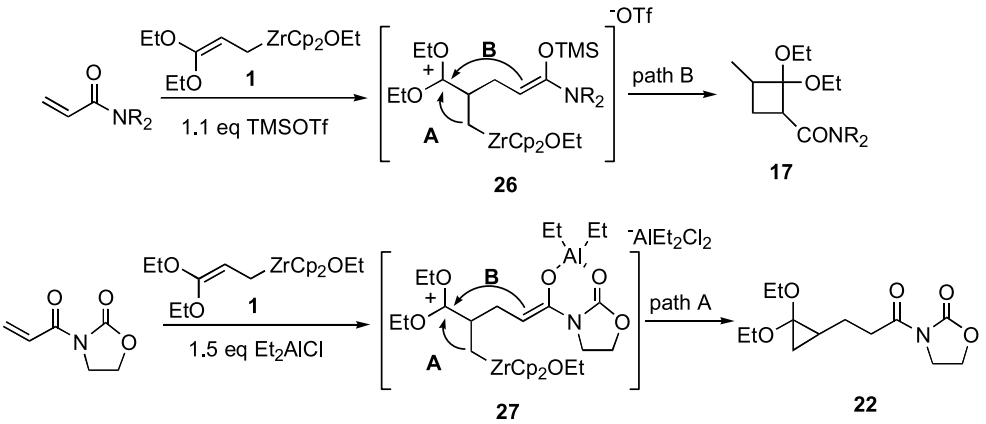
For the reaction to proceed, choice of solvent and Lewis acid was crucial. That is, since the 1,4-addition of **1** did not occur in toluene in which **1** was prepared, it was needed to change the solvent to dichloromethane before **1** was reacted with *N*-acyloxazolidinones. As a Lewis acid, diethylaluminum chloride worked nicely as compared with other Lewis acid such as trimethylsilyl triflate or titanium chloride. Thus, in the presence of 1.5 equiv of diethylaluminum chloride in dichloromethane, reaction of **1** with *N*-acryloyloxazolidinone **21a** gave the cyclopropane derivative **22a** as a sole product (entry 1). Under the similar conditions, **21b** or **21c**, which has substitent on the α,β-unsaturated carbonyl moiety, also reacted with **1** to give the cyclopropane **22** selectively in good yield, but the diastereoselectivity was low (entries 2 and 3). Surprisingly, sterically demanding β,β-disubstituted compound **21d** also reacted with **1** under these conditions to afford cyclopropane derivative **22d** in moderate yield.

The asymmetric reaction of **1** with chiral substrate **23** was also examined, but any chiral induction was not observed (Scheme 9).

The high selectivity for the formation of cyclopropane derivative **22** should be explained by the relatively lower electron density of the *N*,*O*-acetal moiety in the intermediate **27** as compared with that of the acrylamide which produced cyclobutane derivatives **17**. Thus, by changing the electronic nature of the residual group of the enoyl compound, selective formation of the *gem*-dialkoxycyclopropane **22** or cyclobutane **17** can be controlled through the 1,4-addition of **1** to an α,β-unsaturated carboxylic acid derivative (Scheme 10).

3. Conclusion

The addition reactions of γ,γ-dialkoxyallylic zirconium species **1** with various carbonyl compounds in the presence of Lewis acid were described. In the case of the reaction with aldehyde and ketones, 1,2-addition of the zirconium species **1** proceeded as dialkoxycyclopropyl anion equivalent. On the other hand, the reaction of **1** with α,β-unsaturated ester and amide derivatives gave cyclopropane and cyclobutane derivatives through 1,4-addition reaction. These compounds



Scheme 10.

could be obtained selectively by the appropriate choice of the substrate and reaction conditions.

4. Experimental

Zirconocene dichloride was purchased from Tokyo Kasei Kogyo. All reactions were conducted under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H NMR and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as an internal standard, respectively. Mass spectra and HRMS were recorded by electron impact ionization at 70 eV. Column chromatography was performed on neutral silica gel (75–150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30×2.2 cm i.d. prepacked column (silica gel, 10 μm) with a UV or RI detector.

4.1. General procedure for generation of 1 and its reaction with aldehyde (ketone) or α,β-unsaturated carbonyl compounds in the presence of Lewis acid

Under argon atmosphere, to a solution of zirconocene dichloride (1.05 g, 3.6 mmol) in toluene (18 mL) was added *n*-butyllithium (1.46 M in hexane, 4.9 mL, 7.2 mmol) at −78 °C and the mixture was stirred at the same temperature for 1 h. A solution of triethyl orthoacrylate (522 mg, 3 mmol) in toluene (5 mL) was added to the reaction mixture at −78 °C and then the temperature was raised to ambient temperature. After being stirred for 3 h, were successively added a solution of carbonyl compound (3.6 mmol) in toluene (3 mL) at −78 °C and trimethylsilyl trifluoromethanesulfonate (0.6 mL, 3.3 mmol), and the whole was stirred at the same temperature for 10 min. The reaction temperature was raised to ambient temperature and the stirring was continued for 4.5 h. After addition of saturated aqueous ammonium chloride, the reaction mixture was extracted with ether for three times. Organic layer was washed with brine, dried with magnesium sulfate, and concentrated under vacuum. The residue was purified by neutral silica gel column chromatography to afford product. If the trimethylsilyl group could not be completely cleaved under the above mentioned procedure, the organic layer was washed several times with 1 N HCl. Although compound **3** is relatively stable under acid treatment in workup stage, it is labile during the purification by acidic silica gel column chromatography.

4.1.1. γ,γ-Diethoxyallylic zirconium species (1). ^{1}H NMR (300 MHz, benzene-d_6) δ 6.00–5.92 (10H, m), 4.50 (1H, t, J=8.7 Hz), 4.04 (2H, q, J=7.2 Hz), 3.91 (2H, q, J=7.0 Hz), 3.80 (2H, q, J=6.9 Hz), 1.97 (2H, d, J=8.7 Hz), 1.33 (3H, t, J=7.2 Hz), 1.25 (3H, t, J=6.9 Hz), 1.08 (3H, t, J=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.6, 110.7, 93.9, 68.8, 64.2, 64.0, 34.3, 20.1, 15.6, 15.1.

4.1.2. 1-(2,2-Diethoxycyclopropyl)-3-phenyl-1-propanol (3a). *Compound* **3a**-*less polar*. Colorless oil; IR (neat) 3468 ν cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (5H, m), 3.88 (1H, dq, J=9.5, 7.1 Hz), 3.81 (1H, dq, J=9.3, 7.1 Hz), 3.64–3.54 (2H, m), 3.42 (1H, m), 2.86 (1H, ddd, J=14.2, 9.7, 6.3 Hz), 2.74 (1H, ddd, J=14.2, 9.5, 7.0 Hz), 2.45 (1H, br s), 1.99–1.91 (2H, m), 1.36 (1H, ddd, J=9.9, 8.2, 6.5 Hz), 1.23 (6H, t, J=7.1 Hz), 1.10 (1H, dd, J=9.9, 5.8 Hz), 0.81 (1H, dd, J=6.5, 5.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 128.3, 128.2, 125.7, 91.3, 72.1, 62.4, 61.9, 38.2, 32.1, 30.9, 17.3, 15.4, 15.3. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.54; H, 9.02.

Compound **3a**-*more polar*. Colorless oil; IR (neat) 3443 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m), 3.82–3.71 (3H, m), 3.60 (1H, dq, J=9.5, 7.0 Hz), 3.54 (1H, dq, J=9.3, 7.0 Hz), 2.87 (1H, ddd, J=14.1, 7.5, 7.5 Hz), 2.75 (1H, ddd, J=14.1, 8.4, 8.4 Hz), 2.35 (1H, br s), 1.94–1.88 (2H, m), 1.34 (1H, ddd, J=10.0, 6.8, 5.8 Hz), 1.22 (3H, t, J=7.0 Hz), 1.20 (3H, t, J=7.0 Hz), 1.04 (1H, dd, J=10.0, 5.8 Hz), 1.00 (1H, dd, J=6.8, 5.8 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 142.2, 128.5, 128.3, 125.7, 91.3, 68.6, 62.2, 61.8, 38.8, 31.7, 30.5, 15.3, 15.2, 14.6. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.47; H, 9.22.

4.1.3. Cyclohexyl(2,2-diethoxycyclopropyl)methanol (3b). *Compound* **3b**-*less polar*. Colorless oil; IR (neat) 3476 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (1H, dq, J=9.5, 7.1 Hz), 3.78 (1H, dq, J=9.3, 7.1 Hz), 3.62–3.53 (2H, m), 3.06 (1H, br t, J=7.8 Hz), 2.35 (1H, br s), 1.97 (1H, br d, J=12.8 Hz), 1.84–1.72 (3H, m), 1.67 (1H, br d, J=11.0 Hz), 1.54–1.46 (1H, m), 1.34 (1H, ddd, J=9.6, 9.0, 6.4 Hz), 1.30–1.00 (5H, m), 1.22 (3H, t, J=7.2 Hz), 1.21 (3H, t, J=7.1 Hz), 1.10 (1H, dd, J=9.6, 5.7 Hz), 0.77 (1H, dd, J=6.4, 5.7 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 91.1, 77.4, 62.4, 61.8, 43.7, 29.3, 29.2, 29.1, 26.6, 26.2, 26.1, 18.3, 15.4, 15.3. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.38; H, 10.97.

Compound **3b**-*more polar*. Colorless oil; IR (neat) 3443 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (1H, dq, J=9.5, 7.1 Hz), 3.77 (1H, dq, J=9.3, 7.1 Hz), 3.64–3.52 (3H, m), 1.89 (1H, br d, J=12.7 Hz), 1.81–1.72 (4H, m), 1.68 (1H, br d, J=12.0 Hz), 1.51–1.44 (1H, m), 1.37 (1H, ddd, J=9.6, 7.7, 5.0 Hz), 1.30–1.08 (5H, m), 1.22 (3H, t, J=7.1 Hz), 1.21 (3H, t, J=7.1 Hz), 1.02–0.98 (2H, m). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 91.3, 72.6, 62.3, 61.6, 44.0, 29.1, 29.0, 28.0, 26.6, 26.4, 26.3, 15.4, 15.3, 14.2. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.10; H, 10.90.

4.1.4. 1-(2,2-Diethoxycyclopropyl)-1-octanol (3c). *Compound* **3c**-*less polar*. Colorless oil; IR (neat) 3471 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (1H, dq, J=9.5, 7.1 Hz), 3.77 (1H, dq, J=9.3, 7.1 Hz), 3.61–3.49 (2H, m), 3.31 (1H, m), 2.30 (1H, br s), 1.70–1.23 (13H, m), 1.21 (3H, t, J=7.1 Hz), 1.19 (3H, t, J=7.1 Hz), 1.06 (1H, dd, J=10.0, 5.7 Hz), 0.87 (3H, t, J=7.1 Hz), 0.76 (1H, dd, J=6.1, 6.0 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 91.4, 72.9, 62.4, 61.9, 36.5, 31.8, 31.1, 29.7, 29.3, 25.8, 22.7, 17.5, 15.4, 15.3, 14.1. Anal. Calcd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.87; H, 11.98.

Compound **3c**-*more polar*. Colorless oil; IR (neat) 3435 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82–3.65 (3H, m), 3.58 (1H, dq, J=9.5, 7.1 Hz), 3.52 (1H, dq, J=9.3, 7.1 Hz), 2.25 (1H, br s), 1.60–1.23 (13H, m), 1.20 (6H, t, J=7.1 Hz), 1.01–0.93 (2H, m), 0.87 (3H, t, J=7.1 Hz). ^{13}C NMR

(125.7 MHz, $CDCl_3$) δ 91.4, 69.2, 62.2, 61.7, 37.2, 31.8, 30.5, 29.6, 29.3, 25.4, 22.7, 15.4, 15.3, 14.5, 14.1. Anal. Calcd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.45; H, 11.84.

4.1.5. (2,2-Diethoxycyclopropyl)-phenylmethanol (3d). *Compound* **3d**-*less polar*. Colorless oil; IR (neat) 3420 ν cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.28 (5H, m), 4.45 (1H, dd, J=8.3, 1.2 Hz), 3.95 (1H, dq, J=9.5, 7.1 Hz), 3.82 (1H, dq, J=9.5, 7.1 Hz), 3.70 (1H, dq, J=9.5, 7.1 Hz), 3.59 (1H, dq, J=9.5, 7.1 Hz), 2.76 (1H, br s), 1.63 (1H, ddd, J=9.9, 8.5, 6.5 Hz), 1.31 (3H, t, J=7.1 Hz), 1.23 (3H, t, J=7.1 Hz), 1.16 (1H, dd, J=9.9, 5.9 Hz), 0.98 (1H, dd, J=6.5, 5.9 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.3, 128.4, 127.4, 125.9, 91.7, 74.5, 62.6, 62.1, 32.5, 17.8, 15.5, 15.3. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.99; H, 8.55.

Compound **3d**-*more polar*. White crystal; mp 40–41 °C. IR (KBr) 3235 $\nu$$cm^{-1}$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.28 (5H, m), 4.76 (1H, d, J=6.7 Hz), 3.83 (1H, dq, J=9.5, 7.1 Hz), 3.71–3.62 (2H, m), 3.37 (1H, dq, J=9.5, 7.1 Hz), 2.65 (1H, br s), 1.57 (1H, ddd, J=9.9, 6.8, 6.8 Hz), 1.28 (3H, t, J=7.1 Hz), 1.19–1.12 (2H, m), 1.14 (3H, t, J=7.1 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.9, 128.2, 127.3, 125.8, 91.4, 71.6, 62.3, 61.8, 32.5, 15.7, 15.3, 15.2. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.04; H, 8.46.

4.1.6. 1-(2,2-Diethoxycyclopropyl)cyclohexanol (3e). Colorless oil; IR (neat) 3438 ν cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (1H, dq, J=9.5, 7.1 Hz), 3.81 (1H, dq, J=9.5, 7.1 Hz), 3.59 (1H, dq, J=9.5, 7.1 Hz), 3.49 (1H, dq, J=9.5, 7.1 Hz), 2.98 (1H, s), 1.76–1.45 (8H, m), 1.41–1.25 (2H, m), 1.27 (1H, dd, J=10.4, 7.3 Hz), 1.23 (3H, t, J=7.1 Hz), 1.22 (3H, t, J=7.1 Hz), 1.17 (1H, dd, J=7.3, 5.7 Hz), 0.94 (1H, dd, J=10.4, 5.7 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 92.0, 68.4, 62.4, 62.2, 39.7, 37.1, 33.1, 25.8, 22.2, 21.9, 15.4, 15.3, 13.2. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.22; H, 10.81.

4.1.7. 2-(2,2-Diethoxycyclopropyl)-4-phenyl-2-butanol (3f). *Compound* **3f**-*less polar*. Colorless oil; IR (neat) 3518 ν cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.17 (5H, m), 3.89 (1H, dq, J=9.5, 7.1 Hz), 3.83 (1H, dq, J=9.5, 7.1 Hz), 3.61 (1H, dq, J=9.5, 7.1 Hz), 3.51 (1H, dq, J=9.5, 7.1 Hz), 3.16 (1H, br s), 2.80–2.70 (2H, m), 1.90–1.76 (2H, m), 1.41 (3H, s), 1.29–1.20 (2H, m), 1.25 (3H, t, J=7.1 Hz), 1.23 (3H, t, J=7.1 Hz), 1.01 (1H, dd, J=10.2, 5.6 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 143.0, 128.4, 128.3, 125.6, 91.1, 69.2, 62.4, 62.2, 44.4, 33.0, 30.3, 29.3, 15.4, 15.3, 14.0. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.26; H, 9.52.

Compound **3f**-*more polar*. Colorless oil; IR (neat) 3509 ν cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.17 (5H, m), 3.88 (1H, dq, J=9.5, 7.1 Hz), 3.82 (1H, dq, J=9.5, 7.1 Hz), 3.61 (1H, dq, J=9.5, 7.1 Hz), 3.49 (1H, dq, J=9.5, 7.1 Hz), 3.14 (1H, br s), 2.90–2.69 (2H, m), 1.97–1.87 (2H, m), 1.31 (1H, dd, J=10.5, 7.3 Hz), 1.26 (3H, s), 1.24 (3H, t, J=7.1 Hz), 1.21 (3H, t, J=7.1 Hz), 1.18 (1H, dd, J=7.3, 5.6 Hz), 0.99 (1H, dd, J=10.5, 5.6 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 142.9, 128.3, 128.3, 125.6, 92.1, 69.8, 62.5, 62.1, 46.0, 33.6, 30.5, 25.9, 15.4, 15.3, 13.5. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.21; H, 9.47.

4.1.8. Isopropyl 2-(2,2-diethoxycyclopropyl)-2-hydroxyacetate (5a). *Compound* **5a**-*less polar*. Colorless oil; IR (neat) $\nu$$cm^{-1}$; 3478, 2979, 2934, 1731, 1452, 1376, 1255, 1195, 1108, 1054, 953. ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, dq, J=6.0, 6.0 Hz), 3.89–3.80 (2H, m), 3.72 (1H, dq, J=9.2, 6.8 Hz), 3.63 (1H, dq, J=9.2, 7.2 Hz), 3.57 (1H, dq, J=9.2, 7.2 Hz), 2.97 (1H, d, J=6.8 Hz), 1.43 (1H, ddd, J=10.0, 8.4, 6.4 Hz), 1.26 (3H, d, J=6.0 Hz), 1.25 (3H, d, J=6.0 Hz), 1.22 (3H, t, J=7.2 Hz), 1.18 (3H, t, J=7.2 Hz), 1.10 (1H, dd, J=10.0, 6.4 Hz), 1.02 (1H, t, J=6.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.8, 90.5, 70.1, 69.2, 62.4, 62.1, 28.5, 21.8, 21.7, 16.1, 15.4, 15.2. ESI-MS *m/z*: 247 (M^++1). HRMS Calcd for $C_{12}H_{23}O_5$: 247.1545 (M^++1), found: 247.1556.

Compound **5a**-*more polar*. Colorless oil; IR (neat) $\nu$$cm^{-1}$; 3466, 2979, 2934, 1736, 1455, 1376, 1261, 1200, 1108, 1057, 959. ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, dq, J=6.0, 6.0 Hz), 4.07 (1H, dd, J=7.6, 4.0 Hz), 3.80 (1H, dq, J=9.6, 7.2 Hz), 3.76 (1H, dq, J=9.2, 7.2 Hz), 3.58 (1H, dq, J=9.2, 7.2 Hz), 3.56 (1H, dq, J=9.6, 7.2 Hz), 3.00 (1H, d, J=4.0 Hz), 1.50 (1H, ddd, J=10.0, 7.6, 6.4 Hz), 1.27 (6H, d, J=6.0 Hz), 1.19 (3H, t, J=7.2 Hz), 1.17 (3H, t, J=7.2 Hz), 1.11 (1H, dd, J=10.0, 6.4 Hz), 1.04 (1H, t, J=6.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3, 90.9, 69.4, 68.9, 62.3, 61.8, 28.2, 21.8, 21.7, 16.0, 15.3. ESI-MS *m/z*: 247 (M^++1). HRMS Calcd for $C_{12}H_{23}O_5$: 247.1545 (M^++1), found: 247.1561. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.29; H, 8.60.

4.1.9. Methyl 2-(2,2-diethoxyxyclopropyl)-2-hydroxyacetate (5b). *Compound* **5b**-*less polar*. Colorless oil; IR (neat) $\nu$$cm^{-1}$; 3478, 2978, 1741, 1443, 1256, 1197, 1093, 1054, 940. ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (1H, dd, J=8.4, 5.2 Hz), 3.86–3.68 (2H, m), 3.77 (3H, s), 3.61 (1H, dq, J=9.2, 7.2 Hz), 3.55 (1H, dq, J=9.2, 7.2 Hz), 3.00 (1H, d, J=5.2 Hz), 1.46 (1H, ddd, J=10.4, 8.4, 6.4 Hz), 1.21 (3H, t, J=7.2 Hz), 1.18 (3H, t, J=7.2 Hz), 1.12 (1H, dd, J=10.4, 6.4 Hz), 1.01 (1H, t, J=6.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.5, 90.6, 70.2, 62.5, 62.1, 52.3, 28.3, 16.2, 15.3, 15.2. ESI-MS *m/z*: 219 (M^++1). HRMS Calcd for $C_{10}H_{19}O_5$: 219.1232 (M^++1), found: 219.1235.

Compound **5b**-*more polar*. Colorless oil; IR (neat) $\nu$$cm^{-1}$; 3460, 2977, 1742, 1445, 1380, 1255, 1200, 1056, 979, 939. ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (1H, d, J=7.6 Hz), 3.82–3.69 (2H, m), 3.78 (3H, s), 3.57 (1H, dq, J=9.6, 7.2 Hz), 3.53 (1H, dq, J=9.6, 7.2 Hz), 3.07 (1H, br s), 1.53 (1H, ddd, J=11.2, 7.6, 6.0 Hz), 1.18 (3H, t, J=7.2 Hz), 1.16 (3H, t, J=7.2 Hz), 1.10 (1H, dd, J=11.2, 6.0 Hz), 1.05 (1H, t, J=6.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3, 91.1, 69.1, 62.7, 62.1, 52.6, 28.4, 16.1, 15.5, 15.4. ESI-MS *m/z*: 219 (M^++1). HRMS Calcd for $C_{10}H_{19}O_5$: 219.1232 (M^++1), found: 219.1237. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.61; H, 8.11.

4.1.10. Ethyl 2-(2,2-diethoxycyclopropyl)-2-hydroxyacetate (5c). *Compound* **5c**-*less polar*. Colorless oil; IR (neat) $\nu$$cm^{-1}$; 3480, 2978, 1937, 1738, 1449, 1369, 1255,

1195, 1093, 1053, 945. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (2H, q, J=7.2 Hz), 3.93 (1H, dd, J=8.4, 7.2 Hz), 3.85 (1H, dq, J=9.2, 7.2 Hz), 3.73 (1H, dq, J=9.6, 7.2 Hz), 3.64 (1H, dq, J=9.2, 7.2 Hz), 3.57 (1H, dq, J=9.6, 7.2 Hz), 2.93 (1H, d, J=7.2 Hz), 1.46 (1H, ddd, J=10.4, 8.4, 6.4 Hz), 1.30 (3H, t, J=7.2 Hz), 1.24 (3H, t, J=7.2 Hz), 1.19 (3H, t, J=7.2 Hz), 1.13 (1H, dd, J=10.4, 6.4 Hz), 1.04 (1H, t, J=6.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2, 90.6, 70.1, 62.5, 62.1, 61.5, 28.4, 16.2, 15.4, 15.2, 14.2. ESI-MS m/z: 233 (M^++1). HRMS Calcd for $C_{11}H_{21}O_5$: 233.1389 (M^++1), found: 233.1389.

Compound **5c**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 3464, 2978, 2930, 1738, 1449, 1370, 1255, 1200, 1056, 944. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32–4.21 (2H, m), 4.15 (1H, dd, J=7.6, 2.0 Hz), 3.86–3.72 (2H, m), 3.64–3.52 (2H, m), 1.58–1.51 (1H, m), 2.96 (1H, br s), 1.30 (3H, td, J=7.2, 2.0 Hz), 1.20 (3H, td, J=7.2, 2.0 Hz), 1.19 (3H, td, J=7.2, 2.0 Hz), 1.13 (1H, ddd, J=10.4, 6.4, 2.0 Hz), 1.07 (1H, td, J=6.4, 2.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.7, 90.9, 68.8, 62.4, 61.9, 61.6, 28.2, 16.0, 15.3, 15.2, 14.2. ESI-MS m/z: 233 (M^++1). HRMS Calcd for $C_{11}H_{21}O_5$: 233.1389 (M^++1), found: 233.1381.

4.1.11. Benzyl 2-(2,2-diethoxycyclopropyl)-2-hydroxyacetate (5d). *Compound* **5d**-*less polar*. Colorless oil; IR (neat) νcm^{-1}; 3465, 2977, 2930, 1739, 1455, 1376, 1256, 1196, 1092, 1054, 993. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (5H, m), 5.26 (1H, d, J=12.4 Hz), 5.21 (1H, d, J=12.4 Hz), 4.02 (1H, dd, J=8.0, 7.2 Hz), 3.84 (1H, dq, J=9.6, 7.2 Hz), 3.67 (1H, dq, J=9.6, 7.2 Hz), 3.62 (1H, dq, J=9.6, 7.2 Hz), 3.48 (1H, dq, J=9.6, 7.2 Hz), 2.97 (1H, d, J=7.2 Hz), 1.48 (1H, ddd, J=10.4, 8.0, 6.0 Hz), 1.22 (3H, t, J=7.2 Hz), 1.15 (3H, t, J=7.2 Hz), 1.12 (1H, dd, J=10.4, 6.0 Hz), 1.06 (1H, t, J=6.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.0, 135.4, 128.6, 128.4, 128.3, 90.5, 70.1, 67.1, 62.5, 62.1, 28.2, 16.2, 15.4, 15.2. ESI-MS m/z: 295 (M^++1). HRMS Calcd for $C_{16}H_{22}O_5Na$: 317.1365 (M^++Na), found: 317.1396.

Compound **5d**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 3455, 2976, 2930, 1742, 1455, 1379, 1258, 1201, 1120, 1056, 981. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (5H, m), 5.27 (1H, d, J=12.0 Hz), 5.20 (1H, d, J=12.0 Hz), 4.20 (1H, dd, J=8.0, 4.0 Hz), 3.79 (1H, dq, J=10.0, 7.2 Hz), 3.62 (1H, dq, J=9.6, 7.2 Hz), 3.56 (1H, dq, J=9.6, 7.2 Hz), 3.37 (1H, dq, J=10.0, 7.2 Hz), 2.98 (1H, d, J=4.8 Hz), 1.53 (1H, ddd, J=10.4, 8.0, 6.8 Hz), 1.19 (3H, t, J=7.2 Hz), 1.13 (1H, dd, J=10.4, 6.8 Hz), 1.08 (3H, t, J=7.2 Hz), 1.06 (1H, t, J=6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6, 135.2, 128.6, 128.5, 128.4, 90.8, 69.1, 67.2, 62.3, 61.8, 28.2, 16.2, 15.3, 15.2. ESI-MS m/z: 295 (M^++1). HRMS Calcd for $C_{16}H_{22}O_5Na$: 317.1365 (M^++Na), found: 317.1381.

4.1.12. *N*-[(2,2-Diethoxycyclopropyl)(phenyl)methyl]-aniline (6). *Compound* **6**-*less polar*. Colorless oil; IR (neat) νcm^{-1}; 3402, 2975, 1707, 1603, 1507, 1264, 1054, 750. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.22 (5H, m), 7.06 (2H, t, J=7.5 Hz), 6.63 (1H, t, J=7.5 Hz), 6.52 (2H, d, J=7.5 Hz), 4.49 (1H, br s), 4.11 (1H, d, J=8.6 Hz), 3.86–3.53 (4H, m), 1.57 (1H, ddd, J=10.3, 8.6, 6.7 Hz), 1.22 (3H, t, J=7.1 Hz), 1.20 (3H, t, J=7.1 Hz), 1.07 (1H, dd, J=10.3, 5.9 Hz), 0.92 (1H, dd, J=6.7, 5.9 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 147.8, 143.8, 129.0, 128.4, 126.7, 126.3, 117.2, 113.4, 91.5, 62.4, 61.8, 57.1, 34.0, 18.0, 15.4, 15.1. EI-MS m/z: 311 (M^+), 266 (M^+−OEt). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.99; H, 8.11; N, 4.46.

Compound **6**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 3382, 2882, 1603, 1513, 1296, 1121, 1052, 747. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.23 (5H, m), 7.10 (2H, t, J=7.5 Hz), 6.66 (1H, t, J=7.5 Hz), 6.51 (2H, d, J=7.5 Hz), 4.35 (1H, br s), 4.17 (1H, d, J=9.7 Hz), 3.90 (1H, dq, J=9.4, 7.1 Hz), 3.65–3.58 (2H, m), 3.11 (1H, dq, J=9.4, 7.1 Hz), 1.52 (1H, ddd, J=9.7, 9.7, 6.7 Hz), 1.32 (3H, t, J=7.1 Hz), 1.20 (1H, dd, J=9.7, 5.6 Hz), 1.08 (3H, t, J=7.1 Hz), 0.96 (1H, dd, J=6.7, 5.9 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 147.8, 143.8, 129.0, 128.4, 126.7, 126.3, 117.2, 113.4, 91.5, 62.4, 61.8, 57.1, 34.0, 18.0, 15.4, 15.1. EI-MS m/z: 311 (M^+), 266 (M^+−OEt). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.99; H, 8.11; N, 4.46.

4.1.13. 4-(2,2-Diethoxycyclopropyl)-1-phenyl-2-butanone (8a). Colorless oil; IR (neat) 1715 νcm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.16 (5H, m), 3.73–3.48 (4H, m), 2.90 (2H, t, J=7.8 Hz), 2.74 (2H, t, J=7.8 Hz), 2.55–2.41 (2H, m), 1.77–1.54 (2H, m), 1.20 (3H, t, J=7.1 Hz), 1.18 (3H, t, J=7.1 Hz), 1.11 (1H, dq, J=10.0, 7.0 Hz), 0.94 (1H, dd, J=10.0, 5.4 Hz), 0.43 (1H, dd, J=7.0, 5.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.9, 141.1, 128.5, 128.3, 126.0, 91.9, 62.2, 61.4, 44.2, 42.7, 29.8, 24.7, 22.7, 18.0, 15.4, 15.3. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.40; H, 9.08.

4.1.14. 3-(2,2-Diethoxycyclopropyl)-5-phenyl-1-penten-3-ol (9). *Compound* **9**-*less polar*. Colorless oil; IR (neat) 3496 νcm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.16 (5H, m), 5.83 (1H, dd, J=17.3, 10.7 Hz), 5.31 (1H, dd, J=17.3, 1.7 Hz), 5.15 (1H, dd, J=10.7, 1.7 Hz), 3.88 (1H, dq, J=9.5, 7.1 Hz), 3.82 (1H, dq, J=9.5, 7.1 Hz), 3.62 (1H, dq, J=9.5, 7.1 Hz), 3.50 (1H, dq, J=9.5, 7.1 Hz), 3.35 (1H, s), 2.81 (1H, ddd, J=13.8, 9.9, 7.5 Hz), 2.66 (1H, ddd, J=13.8, 9.6, 7.8 Hz), 2.02–1.93 (2H, m), 1.37 (1H, dd, J=10.5, 7.3 Hz), 1.25 (3H, t, J=7.1 Hz), 1.20 (3H, t, J=7.1 Hz), 1.14 (1H, dd, J=7.3, 5.9 Hz), 0.95 (1H, dd, J=10.5, 5.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9, 141.9, 128.4, 128.3, 125.6, 113.0, 92.2, 72.3, 62.6, 62.2, 44.8, 32.4, 30.2, 15.4, 15.3, 13.8. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.38; H, 9.09.

Compound **9**-*more polar*. Colorless oil; IR (neat) 3494 νcm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.15 (5H, m), 6.05 (1H, dd, J=17.3, 10.7 Hz), 5.34 (1H, dd, J=17.3, 1.3 Hz), 5.16 (1H, dd, J=10.7, 1.3 Hz), 3.86 (1H, dq, J=9.5, 7.1 Hz), 3.76 (1H, dq, J=9.5, 7.1 Hz), 3.60 (1H, dq, J=9.5, 7.1 Hz), 3.48 (1H, dq, J=9.5, 7.1 Hz), 3.45 (1H, br s), 2.74 (1H, ddd, J=13.6, 12.4, 5.2 Hz), 2.66 (1H, ddd, J=13.6, 12.1, 4.9 Hz), 1.97 (1H, ddd, J=13.6, 12.1, 5.2 Hz), 1.80 (1H, ddd, J=13.6, 12.4, 4.9 Hz), 1.36 (1H, dd, J=10.4, 7.4 Hz), 1.24 (3H, t, J=7.1 Hz), 1.25–1.21 (1H, m), 1.20 (3H, t, J=7.1 Hz), 1.02 (1H, dd, J=10.4, 5.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.5, 142.9, 128.4, 128.3, 125.6, 112.2, 91.2, 72.1, 62.5, 62.3, 42.7, 32.4, 29.8, 15.3,

15.2, 13.6. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.50; H, 9.12.

4.1.15. 3-(2,2-Diethoxycyclopropyl)cyclopentanone (8b). Colorless oil; IR (neat) 1742 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70–3.37 (4H, m), 2.40–1.99 (4H, m), 1.97–1.81 (2H, m), 1.68–1.56 (1H, m), 1.13–1.06 (6H, m), 1.04–0.90 (2H, m), 0.51 (0.5H, t, J=5.7 Hz), 0.47 (0.5H, t, J=5.7 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 219.11, 219.00, 91.47, 91.35, 61.92, 61.86, 61.38, 61.30, 45.12, 44.09, 38.18, 38.01, 36.13, 29.70, 29.66, 29.59, 28.68, 17.24, 17.05, 15.24, 15.20, 15.11, 15.08. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.89.

4.1.16. 3-(2,2-Diethoxycyclopropyl)cyclohexanone (8c). *Compound* **8c**-*less polar*. Colorless oil; IR (neat) 1714 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76–3.66 (2H, m), 3.73 (1H, dq, J=9.5, 7.1 Hz), 3.69 (1H, dq, J=9.5, 7.1 Hz), 2.58 (1H, br d, J=14.0 Hz), 2.34 (1H, br d, J=14.3 Hz), 2.25 (1H, ddd, J=14.2, 11.5, 6.0 Hz), 2.16 (1H, dd, J=14.0, 10.5 Hz), 2.06–2.00 (1H, m), 1.93–1.88 (1H, m), 1.71–1.43 (3H, m), 1.17 (3H, t, J=7.1 Hz), 1.16 (3H, t, J=7.1 Hz), 1.02–0.95 (2H, m), 0.54–0.48 (1H, m). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 211.5, 91.5, 62.1, 61.6, 48.2, 41.3, 38.3, 30.5, 30.3, 24.9, 17.3, 15.4, 15.3. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.89.

Compound **8c**-*more polar*. Colorless oil; IR (neat) 1716 ν cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78–3.69 (2H, m), 3.53 (1H, dq, J=9.5, 7.1 Hz), 3.48 (1H, dq, J=9.5, 7.1 Hz), 2.42 (1H, br d, J=13.1 Hz), 2.34 (1H, br d, J=14.2 Hz), 2.26 (1H, ddd, J=13.8, 12.1, 5.6 Hz), 2.17–2.11 (1H, m), 2.07–2.00 (2H, m), 1.70–1.45 (3H, m), 1.18 (3H, t, J=7.1 Hz), 1.17 (3H, t, J=7.1 Hz), 1.01 (1H, ddd, J=9.8, 9.8, 6.2 Hz), 0.97 (1H, dd, J=9.8, 5.1 Hz), 0.48 (1H, dd, J=6.2, 5.1 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 211.7, 91.7, 62.3, 61.6, 47.3, 41.4, 38.6, 31.7, 30.7, 25.2, 17.1, 15.4, 15.3. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.71; H, 9.83.

4.1.17. Benzyl 3-(2,2-diethoxycyclopropyl)propanoate (11). Colorless oil; IR (neat) νcm^{-1}; 2975, 1737, 1455, 1263, 1166, 1054, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (5H, m), 5.12 (2H, s), 3.74–3.49 (4H, m), 2.46 (2H, td, J=7.2, 4.3 Hz), 1.82 (1H, sext, J=7.2 Hz), 1.66 (1H, sext, J=7.2 Hz), 1.21–1.11 (1H, m), 1.20 (3H, t, J=7.1 Hz), 1.17 (3H, t, J=7.1 Hz), 0.97 (1H, dd, J=10.0, 5.5 Hz), 0.47 (1H, t, J=5.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3, 136.1, 128.5, 128.2, 91.8, 66.1, 62.2, 61.4, 34.1, 24.6, 23.9, 18.0, 15.4, 15.3. EI-MS *m*/*z*: 292 (M^+), 263 (M^+-Et), 247 (M^+-OEt), 201 (M^+-Bn). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.64; H, 8.41.

4.1.18. Benzyl 2,2-diethoxy-3-methylcyclobutanecarboxylate (12). *Compound trans*-**12**. Colorless oil; IR (neat) νcm^{-1}; 2975, 1738, 1455, 1329, 1226, 1188, 1132, 1051, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (5H, m), 5.25 (1H, d, J=12.6 Hz), 5.09 (1H, d, J=12.6 Hz), 3.64–3.50 (2H, m), 3.37 (2H, q, J=7.1 Hz), 3.30 (1H, dd, J=9.2, 5.3 Hz), 2.73–2.62 (1H, m), 2.32 (1H, ddd, J=11.2, 10.0, 5.3 Hz), 1.41 (1H, ddd, J=11.2, 9.2, 7.3 Hz), 1.18 (3H, t, J=7.1 Hz), 1.10 (3H, t, J=7.1 Hz), 1.07 (3H, d, J=5.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.4, 136.6, 128.3, 127.9, 127.8, 102.3, 66.0, 56.8, 56.1, 40.7, 37.8, 22.9, 15.2, 15.1. EI-MS *m*/*z*: 292 (M^+). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.78; H, 8.24.

Compound cis-**12**. Colorless oil; IR (neat) νcm^{-1}; 2977, 1737, 1455, 1197, 1054, 975. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (5H, m), 5.20 (1H, d, J=12.5 Hz), 5.10 (1H, d, J=12.5 Hz), 3.61 (2H, dq, J=9.7, 7.1 Hz), 3.52–3.43 (2H, m), 3.38 (1H, dq, J=9.7, 7.0 Hz), 3.21 (1H, t, J=8.8 Hz), 2.53–2.43 (1H, m), 1.97 (1H, dt, J=11.3, 8.8 Hz), 1.79 (1H, dt, J=11.3, 8.8 Hz), 1.19 (3H, t, J=7.1 Hz), 1.11 (3H, t, J=7.0 Hz), 1.07 (3H, d, J=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0, 136.3, 128.4, 128.1, 127.9, 103.9, 66.2, 57.7, 57.6, 47.5, 39.9, 22.3, 15.2, 15.1, 15.0. EI-MS *m*/*z*: 292 (M^+). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.78; H, 8.24.

4.1.19. 7,7-Diethoxy-6-methyl-4-oxabicyclo[3.2.0]heptan-2-one (14a). *Compound* **14a**-*less polar*. Colorless crystals; mp 60.5–62.0 °C. IR (KBr) νcm^{-1}; 2980, 1779, 1732, 1457, 1373, 1189, 1097, 1012. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (1H, dd, J=9.9, 2.2 Hz), 4.26 (1H, dd, J=9.9, 7.7 Hz), 3.74 (1H, dq, J=9.4, 7.0 Hz), 3.51–3.42 (3H, m), 3.36 (1H, dd, J=7.7, 2.3 Hz), 2.96 (1H, qd, J=7.7, 2.2 Hz), 2.86–2.78 (1H, m), 1.21 (3H, t, J=7.0 Hz), 1.15 (3H, t, J=7.0 Hz), 1.10 (3H, d, J=7.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.32, 100.8, 67.6, 58.3, 56.8, 49.5, 41.3, 30.1, 15.0, 14.9, 10.0. EI-MS *m*/*z*: 214 (M^+). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.85; H, 8.34.

Compound **14a**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 2977, 2930, 1775, 1455, 1371, 1259, 1164, 1052, 928. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (1H, dd, J=9.4, 7.1 Hz), 4.22 (1H, dd, J=9.4, 2.1 Hz), 3.58 (1H, dq, J=9.8, 7.1 Hz), 3.54–3.41 (2H, m), 3.37 (1H, dq, J=9.4, 7.1 Hz), 3.28 (1H, d, J=8.1 Hz), 2.51–2.36 (2H, m), 1.19 (3H, t, J=7.1 Hz), 1.16 (3H, t, J=7.1 Hz), 1.15 (3H, d, J=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7, 99.4, 73.3, 57.2, 56.7, 45.9, 46.1, 34.5, 15.0, 14.9, 14.2. EI-MS *m*/*z*: 214 (M^+). HRMS Calcd for $C_{11}H_{18}O_4$: 214.1205 (M^+), found: 214.1206.

4.1.20. 4-(2,2-Diethoxycyclopropyl)dihydro-2(3*H*)-furanone (13a). IR (neat) νcm^{-1}; 2977, 1779, 1458, 1372, 1267, 1166, 1054, 1018. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (1H, dd, J=8.8, 7.0 Hz), 4.09 (1H, dd, J=8.8, 6.7 Hz), 3.76–3.66 (2H, m), 3.58 (1H, dq, J=9.5, 7.1 Hz), 3.15 (1H, dq, J=9.3, 7.1 Hz), 2.71 (1H, dd, J=19.6, 10.7 Hz), 2.41–2.30 (2H, m), 1.23–1.16 (1H, m), 1.20 (3H, t, J=7.1 Hz), 1.19 (3H, t, J=7.1 Hz), 1.07 (1H, dd, J=9.9, 6.0 Hz), 0.61 (1H, t, J=6.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.0, 90.7, 72.7, 62.3, 61.8, 35.3, 35.0, 27.4, 17.1, 15.3, 15.2. EI-MS *m*/*z*: 215 (M^++1), 169 (M^+-OEt). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.64; H, 8.30.

4.1.21. 4-(2,2-Diethoxycyclopropyl)tetrahydro-2*H*-pyran-2-one (13b). *Compound* **13b**-*less polar*. Colorless oil; IR (neat) νcm^{-1}; 2976, 1739, 1446, 1399, 1285, 1252, 1221, 1196, 1060. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (1H, dt, J=11.3, 4.1 Hz), 4.25 (1H, td, J=11.3, 4.1 Hz), 3.75 (1H, dq, J=9.4, 7.1 Hz), 3.72 (1H, dq, J=9.4, 7.1 Hz), 3.53 (1H, dq, J=9.4, 7.1 Hz), 3.44 (1H, dq, J=9.4, 7.1 Hz), 2.84 (1H, dd, J=17.5, 5.9 Hz), 2.31 (1H, dd, J=17.5, 9.4 Hz), 1.99–1.93 (1H, m), 1.76–1.65 (2H, m), 1.19 (3H, t, J=

7.1 Hz), 1.18 (3H, t, J=7.1 Hz), 1.05 (1H, dd, J=9.8, 5.5 Hz), 1.00 (1H, td, J=9.8, 5.5 Hz), 0.57 (1H, t, J=5.5 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.0, 91.2, 68.6, 62.2, 61.8, 36.7, 31.6, 30.0, 28.2, 17.3, 15.4, 15.3. HRMS Calcd for $C_{12}H_{20}O_4$: 228.1362 (M^+), found: 228.1340.

Compound **13b**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 2976, 1741, 1454, 1398, 1307, 1254, 1223, 1196, 1063. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (1H, dt, J=11.4, 4.2 Hz), 4.25 (1H, ddd, J=11.4, 10.1, 4.0 Hz), 3.80–3.68 (2H, m), 3.56 (1H, dq, J=9.5, 7.0 Hz), 3.47 (1H, dq, J=9.5, 7.0 Hz), 2.69 (1H, ddd, J=17.2, 7.1, 1.2 Hz), 2.31 (1H, dd, J=17.2, 9.9 Hz), 2.11–2.04 (1H, m), 1.80–1.65 (2H, m), 1.20 (3H, t, J=7.0 Hz), 1.19 (3H, t, J=7.0 Hz), 1.08–0.98 (2H, m), 0.60–0.52 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.3, 91.3, 68.6, 62.3, 61.8, 35.7, 31.3, 30.2, 29.3, 17.1, 15.4, 15.3. EI-MS *m*/*z*: 229 (M^++1), 183 (M^+−OEt). HRMS Calcd for $C_{12}H_{20}O_4$: 228.1362 (M^+), found: 228.1368.

4.1.22. *N*,*N*-Dimethyl-2,2-diethoxy-3-methylcyclobutanecarboxamide (17a). *Compound* **17a**-*less polar*. Colorless oil; IR (neat) νcm^{-1}; 2977, 1650, 1398, 1263, 1192, 1054, 968, 659. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46–3.42 (3H, m), 3.27–3.20 (2H, m), 3.10 (3H, s), 2.87 (3H, s), 2.32 (1H, ddq, J=9.8, 8.8, 6.8 Hz), 1.90 (1H, q, J=10.2 Hz), 1.75 (1H, dt, J=10.2, 8.8 Hz), 1.14 (3H, t, J=7.1 Hz), 1.07 (3H, t, J=7.0 Hz), 1.02 (3H, d, J=6.8 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.5, 104.2, 56.9, 56.2, 46.6, 38.1, 36.9, 35.4, 22.9, 15.4, 15.2, 14.3. EI-MS *m*/*z*: 229 (M^+), 200 (M^+−Et), 184 (M^+−OEt). HRMS Calcd for $C_{12}H_{23}NO_3$: 229.1678 (M^+), found: 229.1674.

Compound **17a**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 2975, 1649, 1393, 1226, 1134, 1060, 985. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59–3.48 (2H, m), 3.39 (1H, dd, J=8.3, 3.3 Hz), 3.34 (2H, q, J=7.1 Hz), 3.02 (3H, s), 2.93 (3H, s), 2.68–2.59 (1H, m), 2.33 (1H, ddd, J=10.0, 9.4, 3.3 Hz), 1.27 (1H, dt, J=10.0, 8.3 Hz), 1.21 (3H, t, J=7.1 Hz), 1.06 (3H, t, J=7.1 Hz), 1.02 (3H, d, J=5.9 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.2, 102.8, 56.6, 56.4, 44.4, 39.3, 37.3, 35.9, 24.2, 15.2, 15.1 14.5. EI-MS *m*/*z*: 229 (M^+), 184 (M^+−OEt). HRMS Calcd for $C_{12}H_{23}NO_3$: 229.1678 (M^+), found: 229.1664.

4.1.23. *N*,*N*-Dibenzyl-2,2-diethoxy-3-methylcyclobutanecarboxamide (17b). Colorless oil; IR (neat) νcm^{-1}; 2977, 1650, 1443, 1424, 1218, 1198, 1064, 702. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (2H, t, J=7.6 Hz), 7.32–7.22 (6H, m), 7.18 (2H, d, J=7.4 Hz), 5.41 (1H, d, J=14.1 Hz), 5.26 (1H, d, J=17.3 Hz), 5.15 (1H, d, J=17.3 Hz), 4.65 (1H, d, J=14.1 Hz), 3.39–3.32 (2H, m), 3.30–3.20 (2H, m), 3.11 (1H, dq, J=9.2, 7.0 Hz), 2.36–2.26 (1H, m), 2.03 (1H, dt, J=13.2, 10.2 Hz), 1.84 (1H, dt, J=10.2, 8.6 Hz), 1.09 (3H, t, J=7.1 Hz), 1.07 (3H, d, J=6.9 Hz), 1.01 (3H, t, J=7.0 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.0, 137.1, 137.0, 129.4, 128.9, 128.3, 127.4, 127.3, 126.5, 104.2, 57.1, 57.0, 48.8, 48.4, 46.9, 38.1, 23.3, 15.2, 14.4. EI-MS *m*/*z*: 381 (M^+), 336 (M^+−OEt), 290 (M^+−Bn). Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.37; H, 8.10; N, 3.75.

4.1.24. 2,2-Diethoxy-*N*,*N*-diisopropyl-3-methylcyclobutanecarboxamide (17c). Colorless oil; IR (neat) νcm^{-1}; 2970, 1643, 1442, 1374, 1291, 1191, 1134, 1058. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57–4.46 (1H, m), 3.50–3.39 (4H, m), 3.42–3.31 (1H, m), 3.14 (1H, dd, J=10.0, 8.5 Hz), 2.35–2.24 (1H, m), 1.92 (1H, q, J=10.0 Hz), 1.75 (1H, dt, J=10.0, 8.5 Hz), 1.38 (3H, d, J=6.7 Hz), 1.36 (3H, d, J=6.8 Hz), 1.19 (3H, d, J=6.5 Hz), 1.17 (3H, t, J=7.0 Hz), 1.12 (3H, t, J=7.0 Hz), 1.12 (3H, d, J=6.4 Hz), 1.05 (3H, d, J=6.8 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.2, 103.9, 57.1, 56.9, 47.9, 47.8, 45.5, 38.0, 23.3, 20.9, 20.0, 19.5, 15.3, 15.2, 14.3. EI-MS *m*/*z*: 285 (M^+). Anal. Calcd for $C_{16}H_{31}NO_3$: C, 67.33; H, 10.95; N, 4.91. Found: C, 67.13; H, 10.87; N, 4.89.

4.1.25. 2,2-Diethoxy-*N*,3-dimethyl-*N*-phenylcyclobutanecarboxamide (17d). *Compound cis*-**17d**. Colorless oil; IR (neat) νcm^{-1}; 2975, 1657, 1496, 1387, 1190, 1054, 699. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, t, J=7.2 Hz), 7.32–7.22 (3H, m), 3.53–3.41 (2H, m), 3.27 (3H, s), 3.13–3.04 (2H, m), 3.01–2.93 (1H, m), 2.29–2.19 (1H, m), 1.92–1.85 (1H, m), 1.79–1.69 (1H, m), 1.20 (3H, t, J=7.0 Hz), 1.09 (3H, d, J=6.9 Hz), 1.00 (3H, t, J=6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.6, 144.0, 129.2, 128.0, 127.3, 103.6, 57.1, 56.3, 45.4, 38.8, 37.9, 23.5, 15.4, 15.0, 14.4. EI-MS *m*/*z*: 292 (M^++1), 262 (M^+−Et). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.78; H, 8.67; N, 4.75.

Compound trans-**17d**. Colorless oil; IR (neat) νcm^{-1}; 2974, 1657, 1496, 1380, 1053, 701. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, t, J=7.2 Hz), 7.29–7.21 (3H, m), 3.38–3.29 (2H, m), 3.28 (3H, s), 3.22 (1H, d, J=8.0 Hz), 2.83–2.72 (2H, m), 2.29–2.14 (2H, m), 1.26–1.25 (1H, m), 1.15 (3H, t, J=7.0 Hz), 0.95 (3H, d, J=6.9 Hz), 0.83 (3H, t, J=6.9 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.2, 144.2, 129.2, 128.8, 127.4, 102.3, 56.4, 55.7, 44.3, 39.5, 38.0, 24.8, 15.2, 15.1, 14.3. EI-MS *m*/*z*: 292 (M^++1), 262 (M^+−Et), 246 (M^+−OEt). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.17; H, 8.68; N, 4.77.

4.1.26. 2,2-Diethoxy-3-methyl-*N*,*N*-diphenylcyclobutanecarboxamide (17e). White crystal; mp 87.5–88.4 °C. IR (KBr) νcm^{-1}; 2972, 1660, 1479, 1365, 1134, 1055, 982. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.13 (10H, m), 3.53–3.33 (3H, m), 2.93–2.82 (2H, m), 2.33 (1H, td, J=9.8, 1.8 Hz), 2.25 (1H, dq, J=2.8, 7.0 Hz), 1.29–1.21 (1H, m), 1.25 (3H, t, J=7.0 Hz), 0.99 (3H, d, J=6.8 Hz), 0.87 (3H, t, J=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5, 143.2, 129.9, 128.8, 126.9, 125.8 103.0, 56.4, 55.9, 45.1, 39.4, 24.3, 15.3, 15.11, 14.4. EI-MS *m*/*z*: 353 (M^+). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.78; H, 7.46; N, 4.15.

4.1.27. 3-(2,2-Diethoxycyclopropyl)-*N*,*N*-diphenylpropanamide (18e). Colorless oil; IR (neat) νcm^{-1}; 2975, 1732, 1675, 1593, 1492, 1369, 1273, 1054. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.22 (10H, m), 3.68–3.48 (4H, m), 2.39–2.32 (2H, m), 1.96–1.83 (1H, m), 1.68–1.57 (1H, m), 1.18 (3H, t, J=7.1 Hz), 1.16 (3H, t, J=7.1 Hz), 1.16–1.08 (1H, m), 0.91 (1H, dd, J=9.9, 5.4 Hz), 0.38 (1H, t, J=5.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9, 142.9, 130.0–125.0 (aromatic), 92.0, 62.1, 61.4, 35.0, 25.0, 24.3, 17.9, 15.4, 15.3. EI-MS *m*/*z*: 353 (M^+), 324 (M^+−Et).

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.43; H, 7.69; N, 4.07.

4.1.28. *N,N*-Dibenzyl-4,4-diethoxy-3-methyl-1-cyclobutene-1-carboxamide (20). Colorless oil; IR (neat) νcm^{-1}; 2975, 1639, 1611, 1421, 1219, 1188, 1048, 979. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.17 (10H, m), 6.44 (1H, s), 4.67 (1H, s), 4.65 (1H, s), 4.63 (1H, d, J=14.6 Hz), 4.50 (1H, d, J=14.6 Hz), 3.74 (1H, dq, J=9.4, 7.1 Hz), 3.72–3.64 (2H, m), 3.56 (1H, dq, J=9.4, 7.1 Hz), 2.98 (1H, q, J=7.0 Hz), 1.18 (6H, t, J=7.1 Hz), 1.12 (3H, d, J=7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.5, 143.7, 142.3, 137.0, 136.9, 128.8, 128.7, 128.5, 128.4, 127.4, 127.3, 127.1, 105.0, 59.4, 59.3, 50.3, 47.9, 46.8, 15.4, 15.3, 13.8. EI-MS *m/z*: 379 (M^+). HRMS Calcd for $C_{24}H_{29}NO_3$: 379.2147 (M^+), found: 379.2134.

4.2. General procedure for the reaction of 1 with acryloyl oxazolidinone derivatives in the presence of Lewis acid

A solution of triethyl orthoacrylate (174 mg, 1 mmol) in toluene (2 mL) was added to a solution of 'Cp_2Zr' (1.2 mmol), prepared from Cp_2ZrCl_2 with *n*-BuLi at −78 °C. After being stirred for 3 h at room temperature, the solvent was removed in vacuo and CH_2Cl_2 (8 mL) was added to the residue. A solution of acryloyl oxazolidinone derivative (1.2 mmol) shown in Table 4 in CH_2Cl_2 (2 mL) and diethylaluminum chloride (1.0 M *n*-hexane solution, 1.5 mL, 1.5 mmol) were added to the mixture at −78 °C and then the mixture was stirred at room temperature for 3 h. The reaction mixture was extracted with diethyl ether after addition of NH_4Cl aq and the extract was washed with brine, dried over $MgSO_4$. Purification of the residue, obtained by evaporation of the solvent, by neutral silica gel column chromatography (hexane–AcOEt) gave the product **22** shown in Table 5.

4.2.1. 3-[3-(2,2-Diethoxycyclopropyl)propanoyl]-1,3-oxazolidin-2-one (22a). Colorless oil; IR (neat) νcm^{-1}; 2976, 1782, 1700, 1389, 1212, 1053, 761. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (2H, t, J=8.1 Hz), 4.01 (2H, t, J=8.1 Hz), 3.74–3.53 (4H, m), 3.09–2.94 (2H, m), 1.93–1.82 (1H, m), 1.70–1.59 (1H, m), 1.27–1.20 (1H, m), 1.19 (3H, t, J=7.0 Hz), 1.18 (3H, t, J=7.0 Hz), 0.97 (1H, dd, J=9.9, 5.6 Hz), 0.48 (1H, t, J=5.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2, 153.5, 91.9, 62.1, 62.0, 61.4, 42.5, 34.9, 24.6, 23.1, 18.0, 15.4, 15.3. EI-MS *m/z*: 271 (M^+). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.44; H, 7.83; N, 5.19.

4.2.2. 3-[3-(2,2-Diethoxycyclopropyl)-2-methylpropanoyl]-1,3-oxazolidin-2-one (22b). *Compound* **22b**-*less polar*. Colorless oil; IR (neat) νcm^{-1}; 2976, 1780, 1699, 1388, 1267, 1200, 1055. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42–4.36 (2H, m), 4.08–3.95 (2H, m), 3.82 (1H, tq, J=6.7, 6.7 Hz), 3.74–3.49 (4H, m), 1.79–1.61 (2H, m), 1.24–1.14 (10H, m), 0.95 (1H, dd, J=9.9, 5.4 Hz), 0.54 (1H, t, J=5.4 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 177.1, 153.1, 91.8, 62.6, 61.8, 61.3, 42.8, 37.2, 32.0, 22.9, 17.9, 16.5, 15.4. EI-MS *m/z*: 285 (M^+). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.85; H, 8.17; N, 4.93.

Compound **22b**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 2976, 1781, 1698, 1453, 1388, 1262, 1199, 1054, 1001, 954. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (2H, t, J=8.1 Hz), 4.02 (2H, t, J=8.1 Hz), 3.84 (1H, sext, J=6.9 Hz), 3.74–3.54 (4H, m), 2.09 (1H, ddd, J=13.9, 6.9, 4.9 Hz), 1.32 (1H, ddd, J=13.6, 9.4, 6.9 Hz), 1.22 (3H, d, J=6.9 Hz), 1.20 (3H, t, J=7.1 Hz), 1.18 (3H, t, J=7.1 Hz), 1.18–1.10 (1H, m), 0.99 (1H, dd, J=9.9, 5.5 Hz), 0.48 (1H, t, J=5.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.1, 153.1, 91.3, 62.1, 61.8, 61.4, 42.8, 37.4, 31.9, 23.3, 18.4, 17.3, 15.4, 15.3. EI-MS *m/z*: 285 (M^+), 256 (M^+−Et), 240 (M^+−OEt). HRMS Calcd for $C_{14}H_{23}NO_5$: 285.1576 (M^+), found: 285.1561.

4.2.3. 3-[3-(2,2-Diethoxycyclopropyl)butanoyl]-1,3-oxazolidin-2-one (22c). *Compound* **22c**-*less polar*. Colorless oil; IR (neat) νcm^{-1}; 2976, 1782, 1699, 1388, 1295, 1220, 1060. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (2H, t, J=8.0 Hz), 4.02 (2H, td, J=8.0, 3.4 Hz), 3.80–3.64 (2H, m), 3.55–3.40 (2H, m), 3.16 (1H, dd, J=15.5, 7.6 Hz), 2.75 (1H, dd, J=15.5, 6.2 Hz), 1.87–1.74 (1H, m), 1.17 (3H, t, J=7.1 Hz), 1.16 (3H, t, J=7.1 Hz), 1.07 (1H, td, J=10.0, 6.4 Hz), 1.06 (3H, d, J=6.9 Hz), 0.98 (1H, dd, J=10.0, 6.3 Hz), 0.48 (1H, t, J=6.3 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.3, 153.5, 92.3, 62.6, 61.4, 42.5, 42.4, 31.4, 30.1, 19.8, 17.8, 15.4. EI-MS *m/z*: 285 (M^+). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.66; H, 8.14; N, 4.91.

Compound **22c**-*more polar*. Colorless oil; IR (neat) νcm^{-1}; 2975, 1782, 1700, 1388, 1222, 1059, 761. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (2H, t, J=8.1 Hz), 4.01 (2H, td, J=8.1, 2.4 Hz), 3.82–3.68 (2H, m), 3.58–3.42 (2H, m), 3.11 (1H, dd, J=15.4, 5.3 Hz), 2.83 (1H, dd, J=15.4, 8.7 Hz), 1.87–1.75 (1H, m), 1.19 (3H, t, J=7.1 Hz), 1.18 (3H, t, J=7.1 Hz), 1.10 (3H, d, J=6.6 Hz), 1.04 (1H, td, J=10.0, 6.5 Hz), 0.94 (1H, dd, J=9.9, 6.5 Hz), 0.57 (1H, t, J=6.5 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.8, 153.5, 91.9, 62.6, 61.9, 61.5, 42.6, 41.3, 31.6, 30.4, 20.5, 17.7, 15.5, 15.3. EI-MS *m/z*: 285 (M^+). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.63; H, 8.10; N, 4.88.

4.2.4. 3-[3-(2,2-Diethoxycyclopropyl)-3-methylbutanoyl]-1,3-oxazolidin-2-one (22d). Colorless oil; IR (neat) νcm^{-1}; 2976, 1780, 1698, 1391, 1361, 1219, 1052, 761. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (2H, t, J=7.1 Hz), 4.07–3.98 (2H, m), 3.76 (1H, dq, J=9.5, 7.1 Hz), 3.74 (1H, dq, J=9.5, 7.1 Hz), 3.52–3.44 (2H, m), 3.16 (1H, d, J=15.3 Hz), 2.92 (1H, d, J=15.3 Hz), 1.28 (1H, dd, J=10.3, 8.0 Hz), 1.18 (3H, t, J=7.1 Hz), 1.17 (3H, t, J=7.1 Hz), 1.11 (3H, s), 1.07 (3H, s), 0.88–0.83 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1, 153.6, 91.5, 62.2, 61.6, 61.3, 45.3, 42.7, 35.0, 33.0, 26.6, 25.4, 15.5, 15.4, 14.3. EI-MS *m/z*: 299 (M^+), 270 (M^+−Et), 254 (M^+−OEt). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.98; H, 8.31; N, 4.66.

4.2.5. (4*S*)-4-benzyl-3-[3-(2,2-diethoxycyclopropyl)propanoyl]-1,3-oxazolidin-2-one (24). Colorless oil; IR (neat) νcm^{-1}; 2975, 1784, 1700, 1388, 1269, 1211, 1054, 703. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (2H, t, J=7.1 Hz), 7.27 (1H, t, J=7.1 Hz), 7.21 (2H, d, J=7.6 Hz), 4.70–4.64 (1H, m), 4.20 (1H, dd, J=8.9, 7.7 Hz), 4.16 (1H, dd, J=8.9,

3.0 Hz), 3.80–3.51 (4H, m), 3.31 (1H, dt, $J=13.4$, 2.4 Hz), 3.11–2.95 (2H, m), 2.77 (1H, dt, $J=13.4$, 9.0 Hz), 1.97–1.88 (1H, m), 1.72–1.63 (1H, m), 1.30–1.24 (1H, m), 1.22 (3H, t, $J=7.1$ Hz), 1.19 (3H, t, $J=7.0$ Hz), 1.01 (1H, dd, $J=9.9$, 5.4 Hz), {0.53 (t, $J=5.4$ Hz), 0.51 (t, $J=5.4$ Hz) 1H}. ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.0, 153.4, 135.3, 129.4, 128.9, 127.3, 92.0, 66.2, 62.2, 61.5, 55.2, 37.9, 35.4, 24.7, 23.1, 18.0, 15.4, 15.3. EI-MS *m/z*: 361 (M^+), 316 (M^+-OEt). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.21; H, 7.37; N, 3.89.

4.3. 3-(2,2-Diethoxycyclopropyl)-propionic acid benzyl ester (25). Under an argon atmosphere, to a solution of benzyl alcohol (19.1 mg, 0.18 mmol) in THF (1.5 mL) was added *n*-butyllithium (1.46 M in hexane, 0.09 mL, 0.13 mmol) at −78 °C and the mixture was stirred at 0 °C for 15 min. A solution of **24** (32 mg, 0.09 mmol) in THF (1 mL) was added to the reaction mixture at −78 °C and then the temperature was raised to ambient temperature. After being stirred for 1 h, saturated aqueous ammonium chloride was added to the mixture and the reaction mixture was extracted with ether for three times. Organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. The residue was purified by neutral silica gel column chromatography to afford product **25** (25 mg, 0.084 mmol, 95%). Spectral data of **25** was identified with those of compound **11**.

References and notes

1. For reviews on preparation and reactions of allylic organometallic reagents, see: (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (d) Roush, W. R. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 2. (e) Yamamoto, Y. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 2. (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
2. (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295. (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507. (c) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. (d) Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 5469. (e) Ito, H.; Hanzawa, Y.; Taguchi, T. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 217. (f) Ito, H. *Chemistry and Chemical Industry* **1995**, *48*, 155. (g) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299–305.
3. Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 7873.
4. (a) Ito, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 5829. (b) Sato, A.; Ito, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 918. (c) Sato, A.; Ito, H.; Yamaguchi, Y.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 10239.
5. (a) Ito, H.; Kuroi, H.; Ding, H.; Taguchi, T. *J. Am. Chem. Soc.* **1998**, *120*, 6623. (b) Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3217. (c) Ito, H.; Sato, A.; Kusanagi, T.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3397.
6. *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; See also Ref. 1f.
7. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.
8. Stetter, H.; Uerdingen, W. *Synthesis* **1973**, 207.
9. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
10. Reviews of α,β-unsaturated acyl anion equivalent based on the heteroatom stabilized allylic and allenic anions; (a) Yamamoto, Y. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 2. (b) Yamamoto, H. In Trost, B. M., Fleming, I., Eds.; Comprehensive organic synthesis; Pergamon: Oxford, 1991; Vol. 2. Addition of α,β-unsaturated acyl zirconiums as unmasked acyl anions with aldehyde and ketone; (c) Harada, S.; Taguchi, T.; Tabuchi, N.; Narita, K.; Hanzawa, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1696 and references cited. See also; (d) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 8141. (e) Hanzawa, Y. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002.
11. Hena, M. A.; Terauchi, S.; Kim, C.; Horiike, M.; Kiyooka, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1883.
12. (a) Schuda, P. F.; Ebner, C. B.; Potlock, S. J. *Synthesis* **1987**, *12*, 1055. (b) Trova, M. P.; Gauuan, P. J. F.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crapoc, J. D.; Dayc, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695.
13. Examples for the cyclopropanation reaction of monoalkoxyallylic metals with carbonyl compounds. (a) Hoffmann, R. W.; Metternich, R. *Liebigs Ann. Chem.* **1985**, 2390. (b) Barrett, A. G. M.; Seefeld, M. A. *Tetrahedron* **1993**, *49*, 7857. (c) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1991**, *56*, 483. (d) Marshall, J. A.; Jablonowski, J. A.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 7825.
14. For reviews on the [2+2]-cycloaddition of ketene acetal with α,β-unsaturated carbonyl compound, see: (a) *Carbocyclic four-membered ring compounds*; de Meijere, A., Ed.; Houben-Weyl Methods of Organic Chemistry; Thieme: Stuttgart, 1997; Vol. 17e/f. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (c) Fruhauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (d) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297. (e) Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 940.

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Chemo-, regio- and stereoselective Diels–Alder reactions of EWG bearing thiophene-1,1-dioxides

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Abstract—EWG-containing thiophene-1,1-dioxides were found to be very active dienophiles in reactions with 1,3-dienes to afford corresponding cycloadducts in mild conditions. A chemo-, regio- and stereoselective cycloaddition was observed. Reaction resulted in formation of derivatives of tetrahydrobenzothiophene-1,1-dioxides in high yields.

1. Introduction

The Diels–Alder reaction of thiophene-1,1-dioxides ranks as extensively researched topic in organic chemistry.[1–8] It is a very powerful tool in synthesis but only a limited number of such reactions for thiophenedioxides with dienes have been reported until now.[2,7,8b]

In the most cases thiophene-1,1-dioxides behave as cyclic 1,3-dienes.[1–8] Dimerization in which one molecule acts as a diene and another as a dienophile take place for unsubstituted thiophenedioxide,[3,4] and for a few halogenated ones.[2,7] There are a few examples of [2+4]-cycloadditions in which thiophenedioxides react as dienophiles to give cycloadducts in low yield.[2,7,8] Moreover all known thiophene-1,1-dioxides appeared to have low reactivity toward cycloaddition with a large variety of dienophiles. In many cases higher reaction temperatures are needed.[1,6–8] This is especially true for the low reactive thiophene-1,1-dioxides bearing alkyl substitutions.

2. Results and discussion

We have recently reported a convenient synthesis of a number of thiophene-1,1-dioxides bearing electron withdrawing groups.[9] Most of them are extremely electron deficient systems that have not yet been investigated. It could be assumed that the activity of thiophene-1,1-dioxides bearing EWG in cycloaddition reactions would differ significantly from the reactivity of thiophenedioxides known before. It might be expected that properties of these substances as electrophiles and dienophiles would change considerably. Now we report the investigation of the reactivity of thiophene-1,1-dioxides bearing EWG-groups in reaction with 1,3-dienes.

Two thiophene-1,1-dioxides (2-chloro-5-methylsulfonyl-thiophene-1,1-dioxide **1** and 2,5-bis(methylsulfonyl-thiophene)-1,1-dioxide **2**) have been studied as model compounds. Both reagents can be easily prepared in high yields.[9] Compound **2** has a symmetrical structure, but thiophene-1,1-dioxide **1** has two differently activated double bonds, therefore, chemoselectivity of the Diels–Alder reaction should be investigated.

We found these substances to be very active reagents in the Diels–Alder reaction with 2,3-dimethylbutadiene. The highly exothermic reactions take place spontaneously at room temperature in THF, and gave corresponding cycloadducts **1a** and **2a** in 56 and 31% yields, respectively. It should be noted that both thiophene-1,1-dioxides react as dienophiles exclusively in contrast to the reactivity of previously described thiophene-1,1-dioxides. This new type of reactivity of thiophene-1,1-dioxides is important both from fundamental point of view and also for synthetic reasons. Diels–Alder adducts formed in this way contain activated double bond and can be used for subsequent functionalization in reaction with various dienes, dipoles and nucleophiles. These reactions would open broad synthetic possibilities for the synthesis of new complex carbo- and heterocyclic molecules.

Keywords: Diels–Alder reaction; Thiophene-1,1-dioxides; EWG-groups; endo-Selectivity; Tetrahydrobenzothiophene-1,1-dioxide derivates; DFT PBE calculations.
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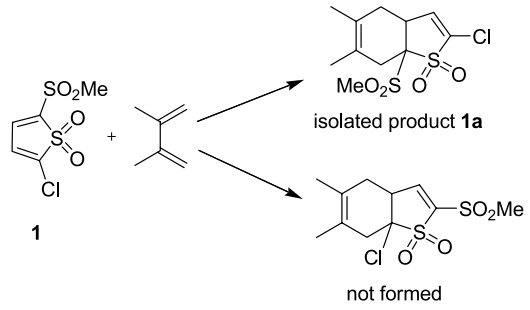
Excellent chemoselectivity was observed for the reaction of thiophenedioxide **1**. The corresponding Diels–Alder adduct was formed during the reaction by the most activated double bond. The double bond bearing the Cl-functional group did not participate in the reaction (Scheme 1).



Scheme 1.

Table 1. Reaction of thiophene-1,1-dioxed **1** with dienes

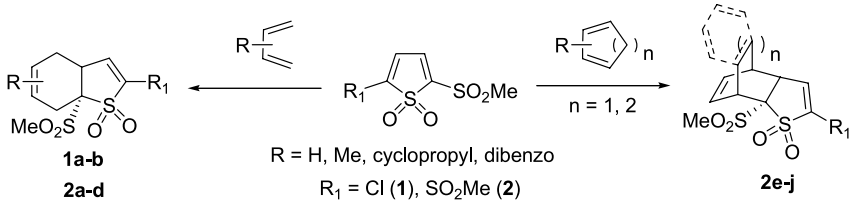
Diene	Product	Yield (%)	Method
	1a	91	A
	1b	96	A

The reaction proceeds in THF at −10 °C within 1–2 h or in CH_2Cl_2 during 3–4 h at 0–5 °C to give products **1a** and **2a** in excellent yield (91 and 97%, respectively) (Tables 1 and 2). Having found the optimal reaction condition we have investigated the regioselectivity and stereoselectivity of cycloaddition with isoprene and piperylene.

The formation corresponding cycloadduct were attempted in three ways (see Section 5). The first method 'A' reaction was carried out in CH_2Cl_2 at −5–0 °C during 3–4 h, the second method 'B' reaction was carried out in THF at −10 °C within 1 h. The third method 'C' was developed for 9,10-dimethylanthracene. Suspension of the thiophene-dioxide and 9,10-dimethylanthracene in trifluoroacetic acid was agitated at room temperature for 24 h.

It is known that the Diels–Alder reaction with isoprene is used to study the regioselectivity of cycloaddition.[10] In fact only one *para*-regioisomer was isolated from the reaction with both dienophiles (products **1b**, **2b**) (Tables 1 and 2). Structures of these adducts was established by HMBC experiments (Fig. 2).

Encouraged by these results, we submitted compound **2** into the reaction with 1-methylbutadiene (piperylene) to test stereoselectivity of the cycloaddition. Well known 1,3-pentadienes react with dienophiles to form *ortho*-adducts predominantly.[10] Moreover, cyclic sulfonyl-bearing dienophiles have also been investigated in the reaction with piperylene where *ortho*-cycloaddition was also demonstrated.[11] The reaction of **2** with piperylene gave an exclusive formation of the one isomer **2d**. The structure and stereochemical peculiarities of **2d** were established unambiguously by the single-crystal X-ray analysis. The X-ray structure of cycloadduct **2d** is shown in Figure 1. It is



Scheme 2. Diels–Alder reaction of thiophene-1,1-dioxides with dienes.

A significant difference in the ^1H NMR spectra of the two cycloadducts **1a** and **2a** for the signal of the olefin proton is observed. For compound **2a** this signal is shifted 1 ppm downfield (7.68 ppm for **2a** compared to 6.47 ppm for cycloadduct **1a**). This difference shows that the double bond in **1a** bears a chlorine atom. In the ^{13}C NMR spectra this difference is more significant (19 ppm).

Extreme reactivity of thiophene-1,1-dioxides bearing EWG leads to an exothermic reaction, and as a result, the formation of byproducts and lower yields of target cycloadducts. Therefore, some optimization of the reaction conditions was necessary. Thiophene-1,1-dioxides **1** and **2** are soluble to some extent in THF, but this only leads to low yields of cycloadducts. We found that better yields could be obtained at a lower temperature, or by using CH_2Cl_2 in which thiophene-1,1-dioxides **1** and **2** are almost insoluble.

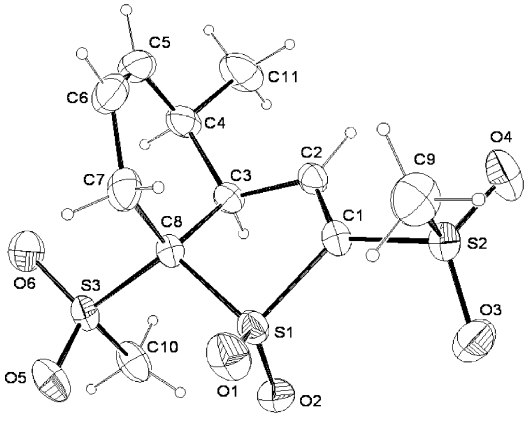
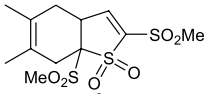
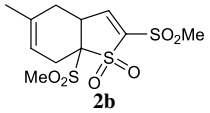
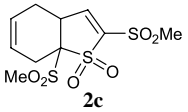
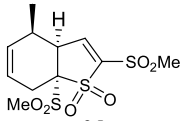
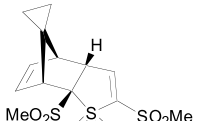
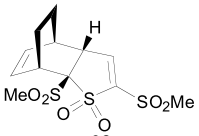
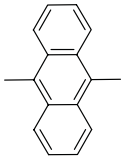
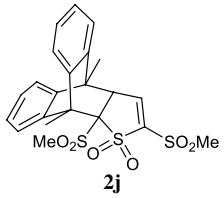


Figure 1. ORTEP structure of cycloadduct **2d**.

Table 2. Diels–Alder reaction thiophene-1,1-dioxide **2** with various dienes

Dienes	Product	Yield (%)	Method
	 **2a**	97	A
	 **2b**	89	A
	 **2c**	98	A
	 **2d**	82	A
	 **2e**	74	B
	 **2f**	93	B
	 **2j**	68	C

worth mentioning that the unexpected regioisomer was formed. In fact **2d** contains the 'piperylene methyl' arranged in the opposite position to the $NeSO_2$– group. The product **2d** is formed as a result of *meta–endo* Diels–Alder reaction (relative to the thiophene-1,1-dioxide ring) (Table 2).[10]

Generalizing of the scope and limitation of thiophenedioxide cycloaddition, we have investigated this reaction with a number of alicyclic and cyclic dienes to prepare various novel cycloadducts (Scheme 2).[12] Usually the Diels–Alder reaction proceed very well to give derivatives of tetrahydrobenzothiophene-1,1-dioxide in high yield as single diastereomers (Table 2).

Structures of compounds **2e–f** have been assigned by comparison of their ^1H and ^{13}C NMR data with **2d**. All the cycloadducts are *exo*-products. The *exo* stereochemistry was deduced from the value of coupling constant $J_{3a,4}$, which is in the range 2.9–4.0 Hz for all adducts. Full assignment of the structures of **1b**, **2b** was made by ^1H, ^{13}C NMR, COSY, NOESY and HMBC measurements. Moreover, NOESY experiments allowed definative assignment of stereochemistry to the structures **2f** and **2e**. Figure 2 shows important connectivities found in the HMBC spectra of cycloadducts **1b** and **2c** and enhancements from NOESY experiment of **2f**. Adduct **2e** also has the *exo*-stereochemistry. The coupling constant $J_{3a,4}=4.0$ Hz from **2f** was found as well in **2e** (Fig. 2).

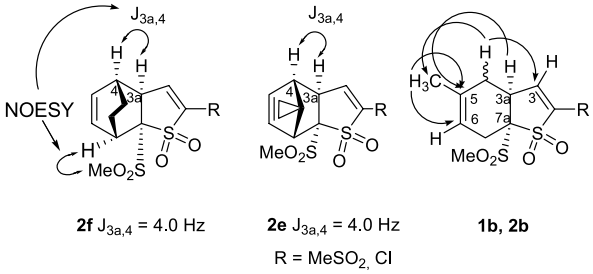


Figure 2. Coupling constants $J_{3a,4}$ for **2f**, **2e**, NOESY correlation in **2f** and HMBC spectra connectivities in **1b**, **2b**.

3. Computational studies

Having obtained unusual results in the reaction with piperylene, we decided to investigate the reaction of **1** and **2** with dienes by density-functional calculations (DFT). DFT calculations were performed within Perdew–Burke–Ernzerhof (PBE) generalized gradient approximation, using extended basis sets of Gaussian functions of TZ2p quality, as implemented in a recent version of the original computer code.[13] All structures were verified by vibrational analysis.

The observed regioselectivity of reactions between thiophene-1,1-dioxides **1**, **2** and appropriate dienes can be explained using the results of our DFT PBE calculations. The computer plots and energies of transition states and reaction of *trans*-piperylene are presented in Table 3. Despite a our mixture of *cis*- and *trans*-piperylenes being used in experiment, it is well known that *cis*-piperylene is almost unreactive towards dienophiles under moderate temperatures.[11] So *cis*-piperylene give an energetically very unfavorable transition states, therefore, this data is not presented here.

We found that results of calculations are in very good agreement with our experimental data. In fact, the activation energy of reaction for the *meta–endo*-transition state (5.0 kcal/mol) is the lowest. Reaction energy for this case (−43.0 kcal/mol) is also most more favorable.

All other possible transition states and products have more higher energies compared with *meta–endo*-transition state. The reaction between **2** and piperylene gave the product favorable both for kinetic and thermodynamic control of cycloaddition. In such a way the Me-group in six-membered cycle of **2d** obviously should located in only direction confirmed by X-ray analysis.

DFT PBE calculations of the reactions between thiophene-1,1-dioxides **1**, **2** and appropriate dienes also confirms *endo*-stereoselectivity of the reaction. Usually *endo* transition states are more stable than the *exo* one (Table 4). In the case of Diels–Alder reaction of thiophenedioxides with isoprene the difference in calculated energies is not significant. Nevertheless, both the energy of transition state and the reaction energy are also favorable for the experimentally

Table 3. Calculated activation (E_{ts}) and reaction (E_{rxn}) energies (kcal mol^{-1}) for *endo* and *exo* cycloaddition of **2** and *trans*-piperylene

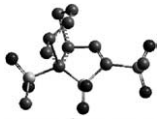
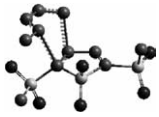
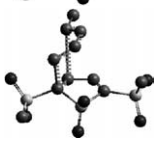
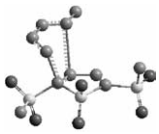
2d *endo*-TS	E_{ts}	E_{rxn}	**2d** *exo*-TS	E_{ts}	E_{rxn}
	7.9	−38.7		17.7	−38.2
	5.0	−43.0		13.8	−40.5

Table 4. Calculated activation (E_{ts}) and reaction (E_{rxn}) energies (kkal mol^{-1})

Adduct	*Endo*-cycloaddition		*Exo*-cycloaddition	
	E_{ts}	E_{rxn}	E_{ts}	E_{rxn}
1a	8.8	−46.1	10.2	−45.3
meta	8.8	−46.2	11.1	−45.5
1b				
para	8.5	−45.8	10.3	−45.1
2a	7.2	−48.0	8.2	−46.6
meta	6.9	−48.0	8.7	−46.8
2b				
para	6.3	−47.7	8.4	−46.4
2c	6.3	−46.8	8.9	−45.5
2e	6.3	−17.7	13.1	−18.5
2f	11.8	−33.2	15.7	−30.2
2j	17.7	−14.9		

observed regiochemistry to form the *para*-cycloadduct. Reaction energies (Table 4) showing that the **1b** and **2b** adducts have about 1 kcal/mol gain from the alternative isomer.

4. Conclusion

In summary, EWG-containing thiophene-1,1-dioxides were found to be very active dienophiles in reactions with 1,3-dienes to afford the corresponding cycloadducts in mild conditions. A chemo-, regio- and stereoselective cycloaddition was observed. Reaction resulted in the formation of derivatives of tetrahydrobenzothiophene-1,1-dioxides in high yields. The experimental results are in very good agreement with DFT-calculations.

5. Experimental

All starting materials unless otherwise noted were commercially available. All products unless otherwise noted were identified by comparison of NMR spectral and physical data with the data reported in the literature. Melting points are uncorrected. Silica gel 230–400 mesh was used for column chromatography; all solvents were dried and purified by standard methods. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-400 MHz spectrometer in $CDCl_3$, CD_3CN and CD_3COCD_3.

5.1. Typical procedure for the cycloaddition in CH_2Cl_2 (method A)

5.1.1. 2-Chloro-5,6-dimethyl-1,1-dioxido-4,7-dihydro-1-benzothien-7a(3a*H*)-yl methyl sulfone (1a). To a suspension of 2-chloro-5-methylsulfonylthiophene-1,1-dioxide **1** (272 mg, 1 mmol) in dry CH_2Cl_2 (10 ml) was added freshly distilled dimethylbutadiene (1 ml, 8.8 mmol) at 0–5 °C. The reaction mixture was stirred for 3 h at 0 °C. After removal of the solvent in vacuo, the residue was chromatographed on silica gel to give **1a** as colorless crystals (282 mg, 91%). *Compound* **1a**. Mp 141–142 °C (from $CHCl_3$). IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.79 (s, 3H), 2.10 (d, J=3.0 Hz, 1H), 2.44 (d, J=16.4 Hz, 1H), 2.90 (m, 2H), 3.22 (s, 3H), 3.78 (m, 1H), 6.62 (d, J=3.0 Hz, 1H). ^{13}C (CD_3CN, 100 MHz): δ 18.5, 19.3, 30.8, 33.9, 38.5, 40.0, 82.7, 124.3, 126.1, 133.2, 135.1. Calcd for $C_{11}H_{15}ClO_4S_2$, C, 42.51; H, 4.86; found C, 42.49; H, 4.89.

5.1.2. 2-Chloro-5-methyl-1,1-dioxido-4,7-dihydro-1-benzothien-7a(3a*H*)-yl methyl sulfone (1b). *Compound* **1b**. Mp 145–146 °C (from $CHCl_3$), 284 mg, 96%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (s 3H), 2.14 (dd, J=16.0, 3.8 Hz, 1H), 2.49 (dd, J=16.0, 6.15 Hz, 1H), 2.87 (dd, J=16.0, 3.8 Hz, 1H), 3.07 (dd, J=16.0, 5.4 Hz, 1H), 3.23 (s, 3H), 3.85 (ddd, J=13.5, 6.8, 3.5 Hz, 1H), 5.60 (m, 1H), 6.52 (d, J=3.5 Hz, 1H). ^{13}C NMR (CD_3CN, 100 MHz): δ 18.3, 23.0, 29.1, 33.2, 49.2, 81.1, 113.9, 135.1, 140.0, 145.4. Calcd for $C_{10}H_{13}ClO_4S_2$, C, 40.47; H, 4.41; found C, 40.74; H, 4.75.

5.1.3. 5,6-Dimethyl-2,7a-bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-1-benzothiophene 1,1-dioxide (2a). *Compound* **2a**. Mp 174–176 °C (from CH_2Cl_2), 344 mg, 97%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.79 (s, 3H), 2.12 (dd, J=12.0, 3.3 Hz, 1H), 2.45 (dd, J=9.3, 4.0 Hz, 1H), 2.92 (d, J=16.5 Hz, 2H), 3.23 (s, 6H), 3.83 (ddd, J=12.0, 4.0, 3.3 Hz, 1H), 6.46 (d, J=4.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN): δ 18.5, 18.9, 30.5, 33.2, 39.2, 41.7, 87.0, 101.3, 124.7, 127.3, 145.3, 154.1. Calcd for $C_{12}H_{18}O_6S_3$, C, 40.66; H, 5.12; found C, 40.37; H, 5.01.

5.1.4. 5-Methyl-2,7a-bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-1-benzothiophene 1,1-dioxide (2b). *Compound* **2b**. Mp 170–171 °C (from $CHCl_3$), 333 mg, 98%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, CD_3CN): δ 2.16 (s, 3H), 2.26 (dd, J=9.0, 4.0 Hz, 1H), 2.52 (dd, J=9.0, 4.0 Hz, 1H), 2.88 (m, 1H), 3.00 (dd, J=17.6, 5.3 Hz, 1H), 3.19 (s,

3H), 3.24 (s, 3H), 3.94 (m, 1H), 5.57 (m, 1H), 7.68 (d, J= 4.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN): δ 18.1, 23.9, 29.7, 30.1, 39.5, 41.3, 85.4, 119.1, 139.6, 145.9, 153.3. Calcd for $C_{11}H_{16}O_6S_3$, C, 38.81; H, 4.74; found C, 38.74; H, 4.71.

5.1.5. 2,7a-Bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-1-benzothiophene 1,1-dioxide (2c). *Compound* **2c**. Mp 152–154 °C (from CH_2Cl_2), 290 mg, 89%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22–2.28 (m, 1H), 2.61–2.67 (m, 1H), 2.87–2.93 (m, 1H), 3.10–3.15 (m, 1H), 3.23 (s, 3H), 3.27 (s, 3H), 3.83 (ddd, J=12.0, 4.0, 3.3 Hz, 1H), 6.46 (m, 2H), 7.55 (d, J=4.1 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN): δ 19.8, 18.9, 30.5, 33.2, 39.2, 41.7, 87.0, 101.3, 124.8, 127.3, 145.3, 154.1. Calcd for $C_{10}H_{14}O_6S_3$, C, 36.80; H, 4.32; found C, 36.41; H, 4.30.

5.1.6. 4-Methyl-2,7a-bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-1-benzothiophene 1,1-dioxide (2d). *Compound* **2d**. Mp 170–171 °C (from $CHCl_3$), 279 mg, 82%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, CD_3CN): δ 1.35 (d, J=7.3 Hz, 3H), 2.75–2.87 (m, 2H), 2.88–2.95 (ddd, J=8.2, 5.3, 2.9 Hz, 1H), 3.22 (s, 3H), 3.28 (s, 3H), 4.00 (dd, J=6.2, 2.9 Hz, 1H), 5.70–5.77 (m, 1H), 5.92–6.02 (ddd, J=9.1, 6.2, 2.9 Hz, 1H), 7.60 (d, J=2.9 Hz, 1H). ^{13}C NMR (CD_3CN, 100 MHz): δ 16.5, 24.9, 31.7, 38.6, 44.8, 45.5, 86.8, 124.8, 132.9, 146.3, 148.9. Calcd for $C_{11}H_{16}O_6S_3$, C, 38.81; H, 4.74; found C, 38.76; H, 4.70.

5.2. Typical procedure for the cycloaddition in THF (method B)

5.2.1. 2′,7a′-Bis(methylsulfonyl)-3a′,4′,7′,7a′-tetrahydrospiro[cyclopropane-1,8′-[1]thia [4,7]metano[1] benzothiophene] 1′,1′-dioxide (2e). To a solution of 2,5-bismethylsulfonylthiophene-1,1-dioxide **2** (272 mg, 1 mmol) in dry THF (10 ml) was added freshly distilled spiro[2.4]hepta-4,6-diene (1 ml, 10.0 mmol) at −10 °C and agitated for 1 h at this temperature. After removal of the solvent in vacuo, the residue was chromatographed on silica gel to give **2e** as colorless crystals (269 mg, 74%). **2e**: mp 212 °C (from MeCN). IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, CD_3COCD_3): δ 0.46–1.45 (m, 4H), 2.96 (m, 3H), 3.43 (s, 3H), 3.47 (m, 1H), 3.83 (m, 1H), 4.33 (ddd, J=7.1, 4.0 Hz, 1H), 6.34 (dd, J=8.5, 3.2 Hz, 1H), 6.49 (dd, J=8.5, 3.2 Hz, 1H), 7.66 (d, J=3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.6, 10.0, 34.2, 42.1, 44.8, 45.6, 125.4, 128.2, 131.3, 145.2, 145.9, 146.4. Calcd for $C_{13}H_{16}O_6S_3$, C, 42.84; H, 4.42; found C, 42.71; H, 4.39.

5.2.2. 2,7a-Bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1-benzothiophene 1,1-dioxide (2f). *Compound* **2f**. Mp 191–192 °C (from MeCN), 327 mg, 93%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, CD_3CN): δ 1.35 (d, J=7.3 Hz, 3H), 2.75–2.87 (m, 2H), 2.88–2.95 (ddd, J=8.2, 5.3, 2.9 Hz, 1H), 3.22 (s, 3H), 3.28 (s, 3H), 4.00 (dd, J=6.2, 4.0 Hz, 1H), 5.70–5.77 (m, 1H), 5.92–6.02 (ddd, J=9.1, 6.2, 4.0 Hz, 1H), 7.60 (d, J=4 Hz, 1H). ^{13}C NMR (CD_3CN, 100 MHz,): δ 21.7, 22.0, 35.5, 41.5, 42.9, 44.9, 47.7, 89.5, 122.3, 131.5, 135.9, 152.0. Calcd for $C_{12}H_{16}O_6S_3$, C, 40.89; H, 4.58; found C, 40.82; H, 4.45.

5.3. Preparation of 9,10-dimethylanthracene adduct (method C)

A mixture of 2,5-bis(methylsulfonyl)thiophene-1,1-dioxide **2** (272 mg, 1 mmol) and 9,10-dimethylanthracene (227 mg, 1.1 mmol) in anhydrous trifluoroacetic acid (10 ml) was stirred vigorously for 24 h. Then product was filtered and washed with 10 ml of toluene three times. Following desiccation in vacuo, pure adduct as yellowish crystals was isolated.

5.3.1. Compound 2j. *Compound* **2j**. Mp 311 °C (dec), 326 mg, 68%. IR (υ, cm^{-1}): 1330, 1100 (SO_2). ^{1}H NMR (400 MHz, CD_3CN): δ 2.09 (s, 3H), 2.18 (s, 3H), 2.57 (s, 3H), 2.72 (s, 3H), 4.01 (d, J=3.3 Hz, 1H), 7.17–7.26 (m, 4H), 7.43–7.53 (m, 4H), 7.67 (d, J=3.3 Hz, 1H). ^{13}C NMR (CD_3COCD_3, 100 MHz,): δ 13.8, 14.4, 23.5, 36.5, 44.7, 56.4, 76.4, 121.4, 126.1, 126.4, 126.5, 128.5, 149.1, 178.8. Calcd for $C_{22}H_{22}O_6S_3$, C, 55.21; H, 4.63; found C, 55.35; H, 4.55.

5.4. X-ray crystallographic analysis of 2d

$C_{11}H_{16}O_6S_3$, M=340.42, monoclinic, space group $P2_1/c$, a=13.413(3) Å, b=9.843(2) Å, c=11.121(2) Å, β=91.94(2)°, V=1467.4(5) Å^3, Z=4, D_c=1.541 g/cm^3, monochromated Mo K$_\alpha$ radiation, λ=0.71073 Å. A colorless prism of compound **2d** (from approximate dimensions 0.52×0.22×0.18 mm), mounted on a glass fiber in random orientation, was used for X-ray data collection. Data were collected on Enraf-Nonius CAD-4 diffractometer using $\theta/2\theta$ at a temperature of 20±1 °C. A total of 2813 reflections were collected of which 2576 were unique. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 calculations to give R=0.0502, R_w=0.0709 for 2576 observed independent reflections [$|F_o^2| > 3\sigma(F_o)^2$, $2° < \Theta < 65°$]. All non-hydrogen atoms were located in succeeding difference Fourier syntheses and anisotropically treated. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. All calculations were performed on an IBM RISC System/6000 380 computer using SHELX-93.

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References and notes

1. Melles, J. L. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 869–874.
2. Bluestone, H.; Bimber, R.; Berkey, R.; Mandel, Z. *J. Org. Chem.* **1961**, *26*, 346–351.
3. Bailey, W. J.; Cummins, E. W. *J. Am. Chem. Soc.* **1954**, *76*, 1936–1939.
4. Nagasawa, H.; Sugihara, Y.; Ishii, A.; Nakayama, J. *Bull. Soc. Chem. Jpn.* **1999**, *72*, 1919–1926.
5. Nakayama, J. *Bull. Soc. Chem. Jpn.* **2000**, *73*, 1–17.

6. (a) Nakayama, J.; Nagasawa, H.; Sugihara, Y.; Ishii, A. *Heterocycles* **2000**, *52*, 365–382. (b) Nakayama, J.; Hasemi, R.; Yoshimura, K.; Sugihara, Y.; Yamaoka, S.; Nakamura, N. *J. Org. Chem.* **1998**, *63*, 4912–4924. (c) Nakayama, J.; Nagasawa, H.; Sugihara, Y.; Ishii, A. *J. Am. Chem. Soc.* **1997**, *119*, 9077–9078. (d) Nakayama, J.; Hirashima, A. *J. Am. Chem. Soc.* **1990**, *112*, 7648–7653.
7. Dmowski, W.; Manko, V. A.; Nowak, I. *J. Fluorine Chem.* **1998**, *88*, 143–151.
8. (a) Gronowitz, S. Thiophene and its Derivatives: part 1 In *The Chemistry of Heterocyclic Compounds: a Series of Monographs*, *Vol. 44*; Wiley: New York, 1985; pp 571–628. (b) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856–867.
9. (a) Nenajdenko, V. G.; Gavryushin, A. E.; Balenkova, E. S. *Tetrahedron Lett.* **2001**, *42*, 4397–4399. (b) Nenajdenko, V. G.; Moiseev, A. M.; Balenkova, E. S. *Russ. Chem. Bull.* **2004**, *10*, 2241–2247.
10. (a) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; Wiley: New York, 2002; pp 2–28. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley: New York, 1990; pp 2–17. (c) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.
11. (a) Malcolm, J. B.; Lloyd-Williams, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2878. (b) Scribner, R. M. *J. Org. Chem.* **1966**, *31*, 3671–3682.
12. Cyclopentadiene undergoes cycloaddition in two ways and the reaction soon will be reported separately.
13. (a) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868. (b) Laikov, D. N. *Chem. Phys. Lett.* **1997**, *281*, 151–156. (c) Trifonova, O. I.; Ochertyanova, E. A.; Akhmedov, N. G.; Roznyatovsky, V. A.; Laikov, D. N.; Ustynyuk, N. A.; Ustynyuk, Yu. A. *Inorg. Chim. Acta* **1998**, *280*, 328–338. (d) Ustynyuk, Yu. A.; Ustynyuk, L. Yu.; Laikov, D. N.; Lunin, V. V. *J. Organomet. Chem.* **2000**, *597*, 182–189. (e) Shutov, P. L.; Karlov, S. S.; Harms, K.; Tyurin, D. A.; Churakov, A. V.; Lorberth, J.; Zaitseva, G. S. *Inorg. Chem.* **2002**, *41*, 6147–6152. (f) Nuzhdin, K. B.; Nesterov, S. V.; Tyurin, D. A.; Feldman, V. I.; Wei, L.; Lund, A. *J. Phys. Chem. A* **2005**, *109*, 6166–6173.

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Computer-assisted design of asymmetric 1,3-dipolar cycloadditions between dimethylvinylborane and chiral nitrones

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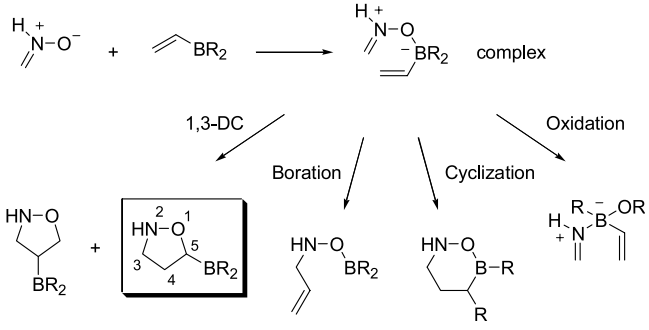
Abstract—This report describes a theoretical study of the 1,3-dipolar cycloadditions between dimethylvinylborane and different chiral nitrones, aimed at identifying the requisite structural features to achieve high levels of selectivity. Excellent regioselectivities towards the formation of the 5-borylisoxazolidines are computed in all cases due to the presence of a strong secondary orbital interaction between the boron of the vinylborane and the oxygen of the nitrones. While these transition structures show [3+3] character, 4-boryl regioisomeric structures have classical [3+2] character with weak carbon–boron secondary orbital interactions. *Endo* transition structures leading to the favoured products adopt chair-like conformations only, unlike their *exo* counterparts, which exhibit either boat or twist-boat structures. Placing a stereocentre adjacent to the nitrone nitrogen appears to be an effective strategy to stereodiscriminate the *anti* and *syn* approaches of the dipolarophile.

1. Introduction

The 1,3-dipolar cycloaddition (1,3-DC) is a valuable reaction for the synthesis of five-membered heterocycles in organic chemistry. The asymmetric version of this transformation offers remarkable synthetic potential for the ultimate construction of acyclic, carbocyclic and heterocyclic systems in a stereocontrolled fashion.[1] Nitrones are important 1,3-dipoles because they display great reactivity and the isoxazolidine products arise with three possible new stereogenic centres.[2] These products are key intermediates to form 1,3-aminoalcohols, which, in turn, are extremely useful reagents as chiral building blocks and ligands.

In the past years, Singleton and others described a wide range of Diels–Alder reactions using vinylboranes as dienophiles of exceptional reactivity, regioselectivity and *endo*-stereoselectivity.[3] This noteworthy reactivity is based on the trivalent valence of the boron atom of the vinylborane that can generate important secondary orbital interactions (SOIs) with other atoms involved in the reaction.

Recently, Rastelli et al. reported a theoretical study on the 1,3-DC of nitrone with vinylboranes and their competition with boration, cyclization and oxidation reactions (Scheme 1).[4,5] They suggested that the boron of the vinylborane initially coordinates to the nitrone oxygen forming a complex, which then can lead to several transition structures (TSs) through different reaction pathways. For vinylborane, they predicted that the 1,3-DC reaction was highly favoured kinetically and the energy of the TSs corresponding to



Scheme 1. Competitive reactions of nitrone with vinylboranes.

Keywords: Chiral nitrones; Vinylboranes; 1,3-Dipolar cycloadditions; Theoretical study; Selectivity.
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the other pathways increased in the following order: organoboration $<$[3+3] cyclization $\ll$oxidation.

Furthermore, these 1,3-dipolar cycloadditions were predicted to have very high reaction rates and complete *endo*-stereoselectivity and regioselectivity towards the formation of the 5-borylisoxazolidine products. They also studied the effect of the substituents on the boron atom in the vinylborane (CH_2=CH–BR_2; R=H, Cl, Me). For dimethylvinylborane and dichlorovinylborane they were not able to find the TSs for the cyclization reactions.

Based on this foundation, we decided to investigate whether it would be possible to exploit the striking properties of vinylboranes in asymmetric 1,3-dipolar cycloadditions with chiral nitrones. In the present paper, we describe a theoretical study of the reactivity of dimethylvinylborane with chiral nitrones **1**–**4** (Chart 1). In particular, we have analyzed how the structural features of the chiral nitrones would affect the outcome of the 1,3-DC reactions both in terms of reactivity and selectivity. We have also inspected the competitive pathways that are possible for these systems. Nitrones **1**–**4** were selected because they were previously prepared from readily available enantiopure materials and underwent 1,3-dipolar cycloadditions easily, paving the way to important natural products.

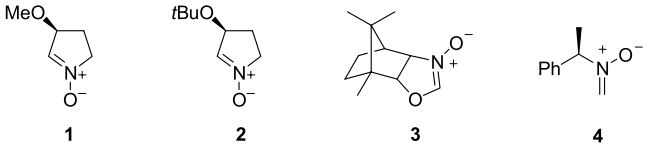


Chart 1.

Nitrones **1** and **2** were synthesized by Cicchi, Brandi and coworkers in a five-step procedure from diethyl L-malate.[6] The 1,3-DC of nitrone **2** with various olefins followed by reductive cleavage of the N–O bond of the isoxazolidines lead directly to a range of enantiomerically pure 1,3-aminoalcohols, which were tested as catalysts in the alkylation of benzaldehyde by diethylzinc. In most cases, the cycloadditions of nitrone **2** proceeded with high regio- and *exo*-selectivity, but the *anti*:*syn* ratios were variable.

The camphor-derived oxazoline *N*-oxide **3**, readily prepared by Langlois et al. from (+)-3-(hydroxyamino)borneol hydrochloride, underwent asymmetric cycloadditions with different alkenes, leading to the selective formation of aldol-type adducts, which were used in the synthesis of β-lactones,[7] (+)-carbovir[8] and (−)-frontalin.[9] They also performed semiempirical FMO calculations in an attempt to rationalize the observed selectivities.

The open-chain nitrone **4** was obtained by Tice and Ganem, who relied on an asymmetric 1,3-DC to carry out the synthesis of (+)-hypusine.[10] Although the key reaction took place with complete control of the regioselectivity, a 1:1 mixture of diastereomeric cycloadducts was formed.

Due to the versatility of the carbon–boron bond and the high regio- and stereoselectivity predicted by theoretical calculations, we believe the asymmetric 1,3-DC of chiral nitrones with vinylboranes could be an extremely useful reaction in organic synthesis, so working towards this goal should be worth the effort. At this stage we focused on the theoretical aspects of these reactions in order to identify the requisite structural features of the chiral nitrones that would ensure the success of the cycloaddition process.

2. Computational methods

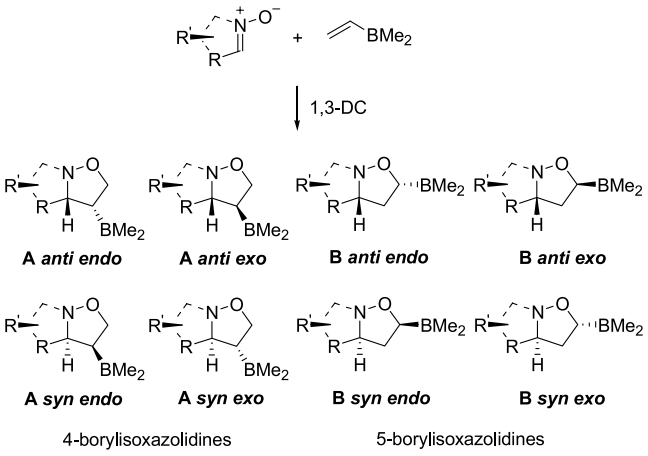
Geometry optimizations of reactants and transition structures were carried out with density functional theory (DFT) using the B3LYP functional[11] and the 6-31G* basis set.[12] Frequency calculations were used to confirm the nature of the stationary points. All transition structures had only one imaginary frequency corresponding to the formation of the expected bonds. Quick reaction coordinate (QRC)[13] calculations were performed to determine the connections of the boration TSs with the reactants and the products. Natural bond orders (NBO)[14] were calculated to analyze the interactions between the atoms of the dipolarophile and the nitrones in the TSs. Thermochemical properties include zero-point energies (ZPE) without scaling and were calculated at 1 atm and 298.15 K. All calculations were performed using Jaguar version 4.2.[15]

3. Results and discussion

As Rastelli et al. found for the parent nitrone, the reactants may form a complex by coordination of the electrophilic boron atom of the vinylborane to the oxygen of the nitrone.[4] This strong boron–oxygen interaction influences the rate and the selectivity of the reaction to a great extent. Starting from the different conformations adopted by the complex, several processes can take place, namely 1,3-DC, vinylboration, [3+3] atom cyclization and oxidation. We have studied the competition between all the plausible pathways for the systems under study. We have not investigated the oxidation reaction because the energy of the corresponding TS was shown to be much higher than the ones corresponding to the 1,3-dipolar cycloaddition and boration pathways. In agreement with previous results for dimethylvinylborane,[4] we were not able to locate the [3+3] cyclization TSs because all the attempts systematically lead to the cycloaddition counterparts.[16]

The 1,3-DC reaction of a chiral nitrone with dimethylvinylborane leads to eight diastereoisomeric TSs, corresponding to the *endo* and *exo* approaches of the dipolarophile to both faces (*anti* and *syn*) of the chiral nitrone with the two regiochemistries (A and B) (Scheme 2).[17] When the nitrone carbon is not prochiral (R=H), such as in nitrone **4**, then the *endo* and *exo* approaches from opposite faces give rise to the same adduct, so only four products can result.

We have first analyzed the geometries and energies of the transition structures for the reactions of nitrones **1** and **2** with dimethylvinylborane (Figs. 1–3 and Table 1). The 1,3-DC TSs for **1** and **2** are asynchronous like the structures previously found for the parent nitrone[4] (see Supplementary material for full details of geometries and NBOs). However,



Scheme 2. Possible cycloadducts arising from the 1,3-DC of a chiral nitrone and dimethylvinylborane.

for these systems only B-TSs have [3+3] character (distances O1–B<O1–C5) while A-TSs adopt classical [3+2] character (distances C3–C4<C3–B). Moreover, the boron–carbon and boron–oxygen distances in A- and B-TSs, respectively, are significantly longer than those for the TSs of nitrone. For instance, for **1** the distances range from 2.825 to 3.063 Å for B–C3 in A-TSs and from 1.679 to 1.820 Å for

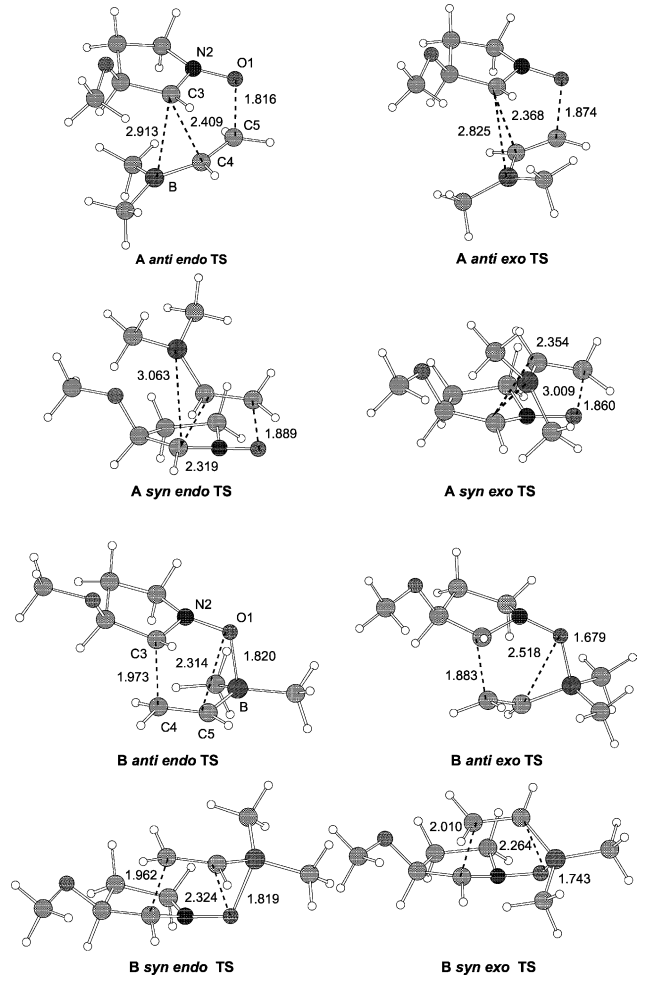


Figure 1. Transition structures for the 1,3-DC between dimethylvinylborane and nitrone **1** (distances in Å).

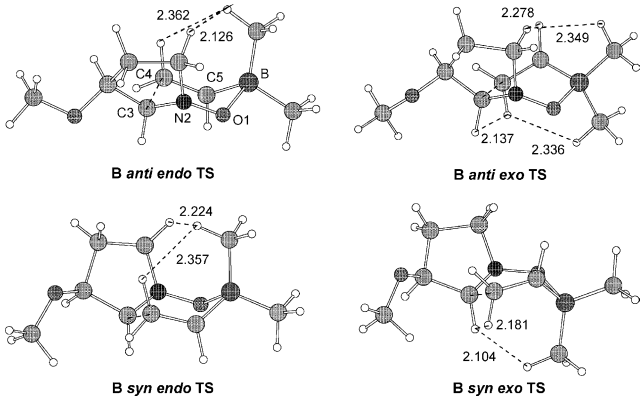


Figure 2. Top views of the B–TSs for the 1,3-DC reaction between dimethylvinylborane and nitrone **1**, including close contacts (distances in Å).

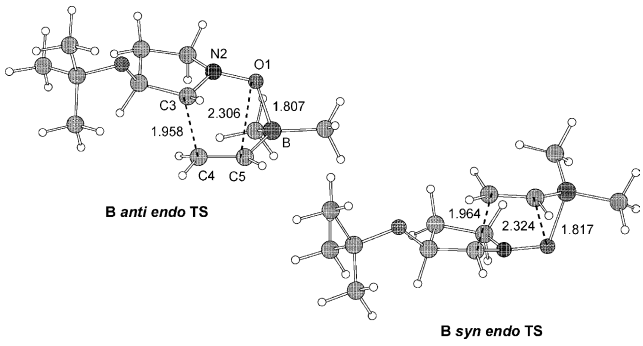


Figure 3. B *anti endo* and B *syn endo* TSs for the 1,3-DC between dimethylvinylborane and nitrone **2** (distances in Å).

B–O1 in B–TSs, while for the parent nitrone they are 2.218 and 2.692 Å and 1.613 and 1.630 Å, respectively. These values suggest non-classical B–O [3+3] SOIs would be weaker for substituted nitrones.[18] Consequently, the activation energies are calculated to increase, but the reaction rates for these 1,3-dipolar cycloadditions are still predicted to be very high (Table 1). The calculated activation energies show that the most stable transition structures for nitrones **1** and **2** are the B *anti endo* and B *syn*

Table 1. B3LYP/6-31G* activation energies (relative values in parentheses) including zero-point energy (ZPE) corrections (in kcal mol^{-1}) and calculated ratios for the 1,3-DC of dimethylvinylborane and nitrones **1** and **2**

Nitrone	TS	$\Delta E_0^{\ddagger}$ (kcal/mol)	Calcd ratios (%)[a]
1	A *anti endo*	12.89 (3.35)	0.2
	A *anti exo*	12.74 (3.20)	0.3
	A *syn endo*	14.95 (5.42)	0.0
	A *syn exo*	15.87 (6.33)	0.0
	B *anti endo*	9.54 (0.00)	62.3
	B *anti exo*	15.64 (6.10)	0.0
	B *syn endo*	9.86 (0.32)	36.4
	B *syn exo*	12.16 (2.62)	0.8
2	A *anti endo*	12.34 (3.49)	0.2
	A *anti exo*	12.59 (3.74)	0.1
	A *syn endo*	15.06 (6.21)	0.0
	A *syn exo*	15.46 (6.61)	0.0
	B *anti endo*	8.85 (0.00)	57.1
	B *anti exo*	15.17 (6.32)	0.0
	B *syn endo*	9.04 (0.18)	42.0
	B *syn exo*	11.51 (2.66)	0.7

[a] Approximate ratios were computed from the Boltzmann factors.

endo TSs, where the nitrone oxygen is strongly coordinated to the boron atom of dimethylvinylborane (B–O1 distances: 1.807–1.820 Å). NBO analysis indicates that these TSs present very similar interactions. The boron–oxygen NBOs are very important (ca. 0.42) and so are the values corresponding to the forming carbon–carbon and carbon–oxygen bonds (ca. 0.52 and 0.20, respectively). In contrast, in the TSs corresponding to the A regiochemistry the boron atom has a less relevant role because the C3–B NBOs are much smaller (0.04–0.07), although they display similar C–C and O–C primary interactions. This analysis supports the computed preference for the oxygen of the nitrone to attack adjacent to the boron could be justified by the presence of strong boron–oxygen stabilizing SOIs in B–TSs. In addition, the comparison of the *exo* and *endo* modes of addition for the B regiochemistry reveals that the *exo* approaches present lower B–O1 distances (1.7 vs 1.8 Å, approximately) in the TSs of both nitrones **1** and **2**. While the same situation was described for nitrone before, the difference was smaller and, moreover, the Wiberg bond indices were the same for both TSs. Interestingly, for nitrones **1** and **2**, the B–O NBOs are considerably higher for *exo* TSs (e.g., 0.53 vs 0.41 for B *anti exo* and B *anti endo* TSs of **1**).

This finding seemed unusual to us because, in general, the Diels–Alder reactions of vinylboranes present *endo* TSs with stronger SOIs than their *exo* counterparts, which explains their higher stabilization.[19] Rastelli made use of NBO analysis to rationalize the lower energy of the B *endo* TS for the reaction between nitrone and vinylborane, stating that the B *exo* TS was less supported by the B–O interaction because it presented higher repulsive terms.[4] A closer inspection of the B transition structures reveals that in all *endo* TSs the atoms involved in the 1,3-DC process can be accommodated into strain-free chair-like arrangements, whereas *exo* TSs can only be attained by adopting more energetic boat-like structures. This may lead to the higher stabilization of the *endo* TSs. The top views of the TSs for the 1,3-DC reactions corresponding to the B regiochemistry clearly depict this situation. As an example, Figure 2 shows the top views of the B–TSs for the 1,3-DC reaction between nitrone **1** and dimethylvinylborane. The higher energy of the boat-like B *anti exo* TS can be rationalized by considering the eclipsing of bonds. In addition, there are four close contacts between hydrogen atoms that contribute to raise its energy. The B *syn exo* TS looks more like a twist-boat, so some torsional strain is relieved, and also presents two H–H close contacts. *endo* TSs have repulsive van der Waals interactions between the chair substituents in a 1,3-diaxial relationship; however, the lack of eclipsed bonds accounts for their higher stabilization. Thus, the strong preference for the oxygen of the nitrone to attack adjacent to the boron is governed by a strong boron–oxygen SOI, and the strong *endo* preference is controlled by the preference for a chair-like rather than a boat-like [3+3] transition state.

The calculated energy difference between the highly favoured B *anti endo* and B *syn endo* TSs is very small (0.32 and 0.18 kcal/mol for nitrones **1** and **2**, respectively, see Table 1). As a result, the computed ratios for the products derived from these diastereomeric TSs are low (62:36 for **1** and 57:42 for **2**). Although we expected that the *t*-butoxy group in **2** would induce higher facial diastereoselectivity in these reactions, the calculated ratio was slightly lower than the one computed for the less bulky nitrone **1**.

A possible explanation for this observation could be related to the fact that the substituents in the five-membered ring of both nitrones are not close enough to the reaction centres in the TSs, so the methoxy and *t*-butoxy groups are too distant to the atoms of the approaching dipolarophile to destabilize the *syn* TSs relative to their *anti* counterparts (Figs. 1 and 3). The poor facial selectivity calculated for **1** and **2** suggests that it would be more beneficial to place the stereogenic centre of the nitrone adjacent to the nitrogen rather than to the carbon of the 1,3-dipole moiety. In this way, the substituents in the nitrone would stereodifferentiate the *anti* and *syn* approaches of the dipolarophile by experiencing different interactions with the ligands on the boron atom in the preferred B-TSs.

We then searched the chemical literature to find chiral nitrones that fulfilled this structural requirement and came across nitrones **3** and **4** (Chart 1). The cyclic compound **3** looked ideal in terms of structural rigidity. On the other hand, the conformational flexibility of the open-chain analogue could be detrimental. However, one of the practical advantages of employing nitrone **4** relies on the fact that the 1-phenylethyl group attached to the nitrogen can be easily removed by hydrogenolysis. Therefore, we decided to study the reactions of both systems in an attempt to investigate the effect of the conformational flexibility of the nitrone on the selectivity of the cycloaddition process.

The transition structures located for the 1,3-DC reaction of **3** are gathered in Figure 4. In general terms, the geometries and NBOs of the TSs of nitrone **3** were comparable to the ones previously found for analogues **1** and **2**. A-TSs displayed [3+2] character, while their B analogues adopted chair- or boat-like [3+3] structures for the *endo* and *exo* pathways, respectively. In this case, all the *anti* TSs were more favourable than the *syn* TSs, which contrasted with the results obtained for nitrones **1** and **2** (Table 2). As can be observed from Figure 4, in the *syn* TSs the vinylborane lies close to one of the methyl groups attached to the bridge carbon of the bicyclic framework, which explains the higher energy of these structures. We were pleased to compute an excellent selectivity for nitrone **3**.

The B *anti endo* product was predicted to be highly favoured kinetically (98%). This TS displays a [3+3] chair-like structure with strong primary (C3–C4 and O1–C5 NBOs: 0.50 and 0.20, respectively) and secondary orbital interactions (O1–B NBO: 0.47). It is interesting to note that the energy barrier for the B *anti endo* mode of addition is extremely low, much lower than the values calculated for **1** and **2**. We believe there are electronic and steric reasons for this result. Firstly, the attachment of an oxygen atom to the nitrone carbon increases the energy of the HOMO of the 1,3-dipole, lowering the $HOMO_{nitrone}$–$LUMO_{vinylborane}$ gap, thus making the 1,3-DC reaction more favourable (see Supplementary material). For instance, the energy of the HOMO for **1** is −0.22 eV, while the corresponding value for **3** is −0.19 eV. The analysis of the HOMO coefficients for nitrone **3** clearly suggests the presence of an extra

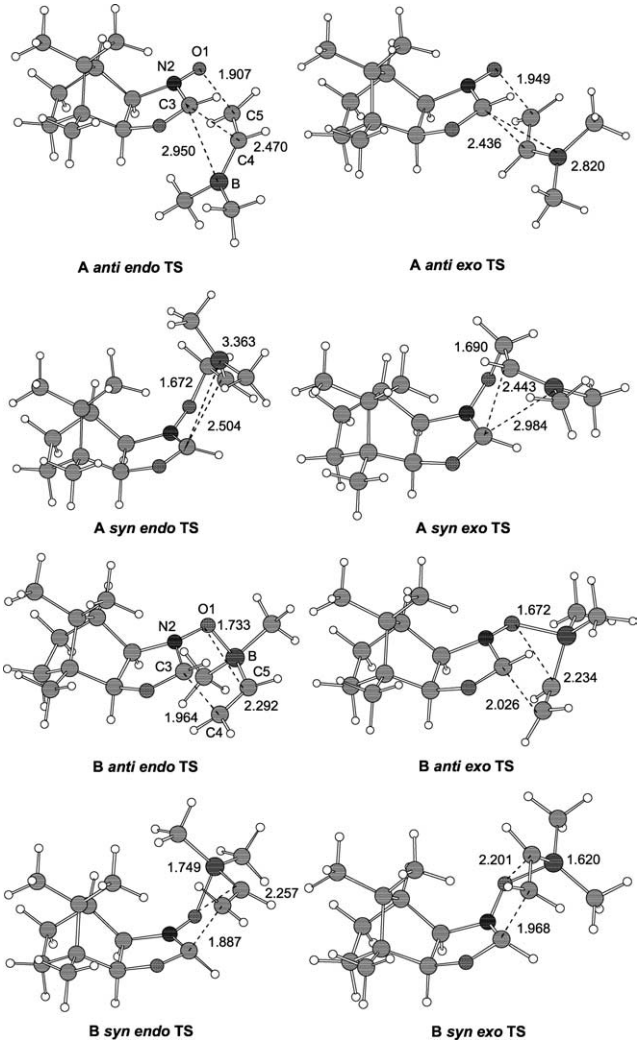


Figure 4. Transition structures for the 1,3-DC between dimethylvinylborane and nitrone **3** (distances in Å).

oxygen atom contributes to raise the energy of this frontier orbital. In addition, as a consequence of the replacement of a sp^3 carbon (such as in **1** and **2**) by an oxygen, the steric hindrance decreases, resulting in a higher reaction rate for **3**.

Owing to the flexible nature of the open-chain nitrone **4**, the study of its cycloaddition reaction was far more complicated. In this case, there are two single carbon–carbon bonds in the side chain that can be rotated, so different conformers are possible for the transition structures. The corresponding dihedral angles, ϕ_1 and ϕ_2, are shown for the A *anti endo* TS presented in Figure 5. We obtained the initial geometries of the TSs by manually stretching the O1–C5 and C3–C4 bonds of the optimized products to 2.2 Å. After that, we performed systematic conformational searches for each approximation by varying the dihedral angles under consideration. The generated input structures were optimized using AM1 and then reoptimized with RHF/3-21G and B3LYP/6-31G* to find the conformers of minimum energy. This analysis yielded TSs with reasonable values for the dihedral angles studied (Fig. 5). For instance, all TSs display ϕ_1 around 60°, so that the nitrogen atom and the methyl group adopt gauche orientations relative to one of the aromatic carbons. In this way, van der Waals interactions are minimized since the smallest atom bonded to the stereogenic centre (hydrogen) is eclipsed with another aromatic carbon. In addition, in each *anti* TS O1 has an *anti* orientation relative to the substituted aromatic carbon (ϕ_2 = 170–178°). If this torsion angle is set to 60 or −60° the atoms of the incoming vinylborane experience severe repulsive steric interactions with either the phenyl or the methyl groups attached to the stereocentre, so the

Table 2. B3LYP/6-31G* activation energies (relative values in parentheses) including zero-point energy (ZPE) corrections (in kcal mol^{-1}) and calculated ratios for the 1,3-DC of dimethylvinylborane and nitrone **3**

TS	$\Delta E_0^{\ddagger}$ (kcal/mol)	Calcd ratios (%)[a]
A *anti endo*	6.74 (5.10)	0.0
A *anti exo*	6.84 (5.20)	0.0
A *syn endo*	20.56 (18.92)	0.0
A *syn exo*	18.99 (17.35)	0.0
B *anti endo*	1.64 (0.00)	98.2
B *anti exo*	4.05 (2.41)	1.8
B *syn endo*	17.71 (16.07)	0.0
B *syn exo*	16.13 (14.49)	0.0

[a] Approximate ratios were computed from the Boltzmann factors.

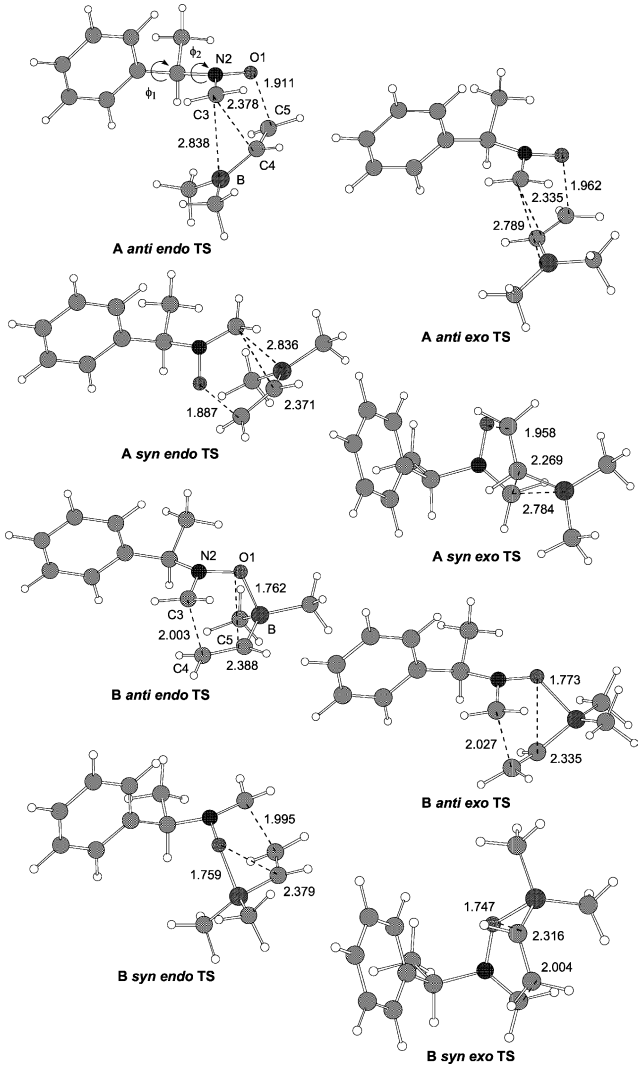


Figure 5. Transition structures for the 1,3-DC between dimethylvinylborane and nitrone **4** (distances in Å). ϕ_1 = N2–C*–C–C and ϕ_2 = O1–N2–C*–C.

corresponding conformations are highly disfavoured. For the same reason, in *syn* TSs, ϕ_2 is close to 60° for *endo* pathways and to −60° for their *exo* counterparts.[20] The TSs corresponding to the B regiochemistry exhibit other interesting features. Unlike the results obtained for nitrones **1**–**3**, for this open-chain compound all the *endo* TSs display stronger B–O SOIs than *exo* TSs as suggested by the calculated NBOs (see Supplementary material). As an example, the O1–B NBO is 0.60 for the B *anti endo* TS and 0.55 for the B *anti exo* TS. Also, despite B–TSs still have [3+3] character, the primary carbon–carbon interactions are less important than the boron–oxygen SOIs, which adopt outstandingly high values of NBOs.

For instance, for the B *anti endo* TS, NBOs decrease in the following order: 0.60 for O1–B, 0.51 for C3–C4 and 0.10 for O1–C5. This structure has the optimal geometry in terms of steric and electronic interactions: ϕ_1 and ϕ_2 present the most favourable values, the atoms involved in the TS are arranged in a strain-free chair-like structure and the O1–B and C3–C4 interactions are very strong. As a consequence, the B *anti endo* TS is computed to be highly favoured (Table 3). To calculate the product distribution for nitrone **4** one has to keep in mind that only one stereogenic centre is created in the 1,3-DC reaction, so only four diastereomeric adducts can be formed. For example, both the *anti endo* and *syn exo* B–TSs contribute to generate to the (5*R*)-borylisoxazolidine product. Therefore, the 5-boryl isomers are predicted to be formed exclusively with a very high diastereomeric *R*/*S* ratio (ca. 91:9). These results suggest it might not be essential that the chiral nitrones posses a cyclic structure for obtaining high stereoselectivities.

Table 3. B3LYP/6-31G* activation energies (relative values in parentheses) including zero-point energy (ZPE) corrections (in kcal mol^{-1}) and calculated ratios for the 1,3-DC of dimethylvinylborane and nitrone **4**

TS	$\Delta E_0^{\ddagger}$ (kcal/mol)	Calcd ratios (%)[a]
A *anti endo*	11.89 (4.48)	0.1
A *anti exo*	11.92 (4.51)	0.0
A *syn endo*	14.16 (6.75)	0.0
A *syn exo*	13.22 (5.81)	0.0
B *anti endo*	7.41 (0.00)	91.1
B *anti exo*	8.94 (1.53)	7.1
B *syn endo*	9.89 (2.48)	1.4
B *syn exo*	10.90 (3.50)	0.3

[a] Approximate ratios were computed from the Boltzmann factors.

The highly favoured B transition structures for the 1,3-dipolar cycloaddition reactions of nitrones **1**–**4** with dimethylvinylborane are similar to the cyclic transition structures proposed by Zimmerman and Traxler for the aldol reactions of metal enolates with carbonyl compounds (Fig. 6).[21] The *endo* transition structures leading to the favoured 5-borylisoxazolidines adopt chair-like conformations whereas their *exo* counterparts exhibit either boat or twist-boat structures. Our observations on systems **1**–**4**, combined with experimental data from the literature, suggest that, in general, the chair-like *endo* transition structures should be highly favoured.

In addition, the computed facial selectivity for nitrones **3** and **4** were much higher than those for **1** and **2**, supporting our premise that the facial diastereoselectivity would be

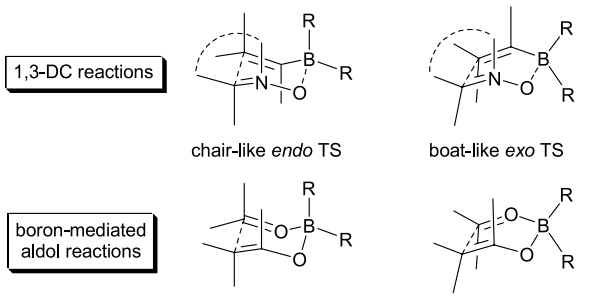


Figure 6. Chair- and boat-like transition structures for 1,3-DC and boron-mediated aldol reactions.

optimized by placing the stereocentre adjacent to the nitrogen rather than to the carbon of the 1,3-dipole (Fig. 7). In such situation, the B–TS corresponding to the *syn* approach should be destabilized due to the repulsive van der Waals interactions experienced between the substituent on the stereocentre of the dipolarophile and the ligands on the boron atom.

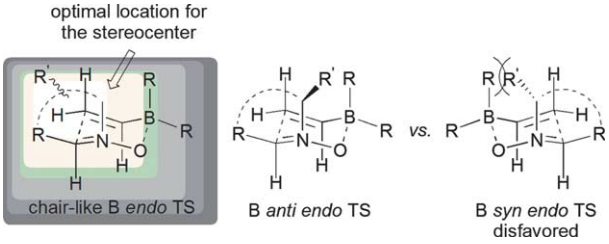


Figure 7. *anti* and *syn* transition structures for the preferred B *endo* pathways for the 1,3-DC reactions of chiral nitrones with vinylboranes.

We finally studied the vinylboration processes for all the systems under investigation in order to check that their TSs had higher energy than the structures for the cycloadditions. Figure 8 shows some selected *anti* and *syn* transition structures corresponding to the boration of the chiral nitrones with dimethylvinylborane (see Supplementary material for the geometries of all the boration TSs).

The oxygen–boron distances were exceptionally short, ranging from 1.498 to 1.553 Å, while the carbon–carbon distances were between 1.948 and 1.997 Å. These values are similar to the ones reported for the reaction between nitrone and vinylborane.[4] QRC calculations confirmed that these highly asynchronous TSs were connected to the reactants and the products via concerted pathways.

As expected from the theoretical results of the 1,3-DC reactions, the *anti* TSs have lower energy than their *syn* counterparts (Table 4). In addition, the computed activation energies predict that the vinylboration process should be less favoured than the 1,3-dipolar cycloaddition, agreeing with previous results obtained by Rastelli for the parent nitrone.[4] Although the calculated energy difference between these two competing reaction pathways is slightly lower for nitrones **1**–**4**, these results suggest the reactions between the chosen nitrones and dimethylvinylborane should yield the cycloadducts without the formation of secondary products.

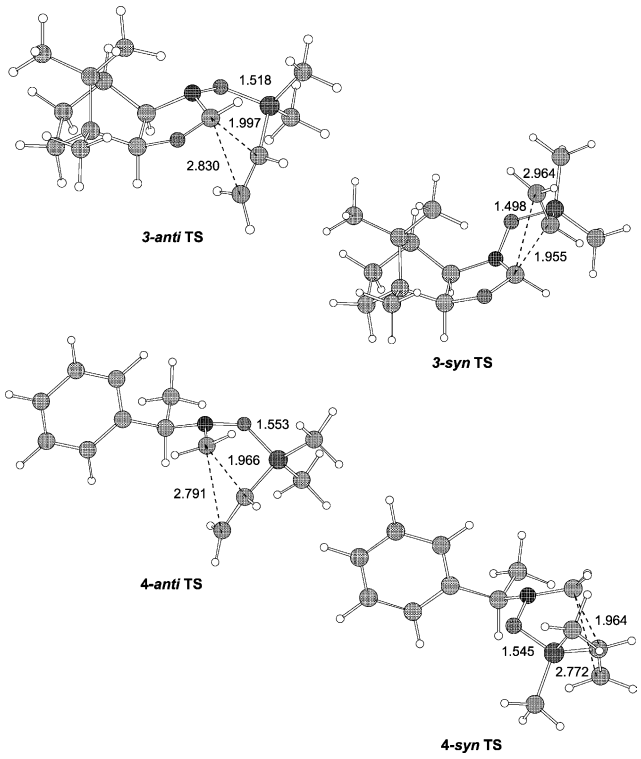


Figure 8. Transition structures for the boration of nitrones **3** and **4** with dimethylvinylborane (distances in Å).

Table 4. B3LYP/6-31G* activation energies including zero-point energy (ZPE) corrections (in kcal mol^{-1}) for the boration of nitrones **1**–**4** with dimethylvinylborane

Nitrone	TS	$\Delta E_0^{\ddagger}$
1	*anti*	13.06
	syn	15.47
2	*anti*	12.34
	syn	15.38
3	*anti*	3.73
	syn	17.25
4	*anti*	11.37
	syn	14.04

4. Conclusions

The results of our calculations for the 1,3-dipolar cycloadditions of nitrones **1**–**4** with dimethylvinylborane predict that the B *anti endo* transition structure would be the major one in all cases, although the B *syn endo* TS would be also significant for the simplest nitrones **1** and **2**. The complete B regioselectivity predicted by this study can be rationalized by considering the strong [3+3] boron–oxygen secondary orbital interaction observed in the six-membered ring transition structures corresponding to these pathways. While these transition structures show [3+3] character, 4-boryl regioisomeric structures have classical [3+2] character with weak carbon–boron secondary orbital interactions. The *endo* transition structures leading to the favoured 5-borylisoxazolidines adopt chair-like conformations whereas their *exo* counterparts exhibit boat or twist-boat structures. This investigation also indicates that either cyclic or acyclic nitrones with the appropriate substitution pattern could display complete *anti* facial diastereoselectivity. Nitrones having the stereogenic centre adjacent to the nitrogen of the 1,3-dipole moiety, such as **3** and **4**, should be more selective than those with the stereodifferentiating element attached to the sp^2 carbon.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.004. Selected distances (in Å) and bond orders for the transition structures studied in the paper. Thermochemical Data (kcal/mol) for all the transition structures studied in the paper. Cartesian coordinates and absolute energies (in hartrees), including ZPE, and number of imaginary frequencies of all stationary points reported in the paper; values of imaginary frequencies of all transition structures. B3LYP/6-31G* optimized geometries for all the transition structures studied in the paper. Energies and atomic coefficients of the frontier molecular orbitals of the reactants.

References and notes

1. For a recent review see: Gothelf, K. V.; Jørgensen, A. *Chem. Rev.* **1998**, *98*, 863–909.
2. Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
3. (a) Singleton, D. A.; Martínez, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 7423–7424. (b) Singleton, D. A.; Martínez, J. P. *Tetrahedron Lett.* **1991**, *32*, 7365–7368. (c) Singleton, D. A.; Martínez, J. P.; Watson, J. V. *Tetrahedron Lett.* **1992**, *33*, 1017–1020. (d) Singleton, D. A.; Martínez, J. P.; Watson, J. V.; Ndip, G. M. *Tetrahedron* **1992**, *48*, 5831–5838. (e) Singleton, D. A.; Leung, S.-W. *J. Org. Chem.* **1992**, *57*, 4796–4797. (f) Singleton, D. A.; Martinez, J. P.; Ndip, G. M. *J. Org. Chem.* **1992**, *57*, 5768–5771. (g) Noiret, N.; Youssofi, A.; Carboni, B.; Vaultier, M. *J. Chem. Soc., Chem. Commun.* **1992**, *16*, 1105–1107. (h) Singleton, D. A.; Kim, K.; Martinez, J. P. *Tetrahedron Lett.* **1993**, *34*, 3071–3074. (i) Singleton, D. A.; Redman, A. M. *Tetrahedron Lett.* **1994**, *35*, 509–512. (j) Singleton, D. A.; Lee, Y.-K. *Tetrahedron Lett.* **1995**, *36*, 3473–3476. (k) Lee, Y.-K.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 2255–2258. (l) Singleton, D. A.; Leung, S.-W.; Martínez, J. P.; Lee, Y.-K. *Tetrahedron Lett.* **1997**, *38*, 3163–3166. (m) Batey, R. A.; Lin, D.; Wong, A.; Hayhoe, C. L. S. *Tetrahedron Lett.* **1997**, *38*, 3699–3702. (n) Singleton, D. A.; Leung, S.-W. *J. Organomet. Chem.* **1997**, *544*, 157–161. (o) Zaidlewicz, M.; Binkul, J. R.; Sokol, W. *J. Organomet. Chem.* **1999**, *580*, 354–362.

4. Rastelli, A.; Gandolfi, R.; Sarzi-Amadé, M.; Carboni, B. *J. Org. Chem.* **2001**, *66*, 2249–2458.
5. Alkynyl- and vinylboronates have been used as dipolarophiles in the 1,3-dipolar cycloaddition reactions of nitrones and nitrile *N*-oxides. However, it has been shown that the reactivity and selectivity pattern of these boron-activated dipolarophiles is significantly influenced by the oxygen atoms attached to the boron. Preliminary DFT calculations performed in our group suggest the lower electrophilic character of the boron atom relative to their dialkyl counterparts affects the potential energy surfaces to a great extent, making these cycloadditions become classical [3+2] processes. For a related DFT study see: (a) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Tetrahedron* **2003**, *59*, 9167–9171. For 1,3-DC with nitrones see: (b) Carboni, B.; Ollivault, M.; Le Bouguenec, F.; Carrié, R.; Jazouli, M. *Tetrahedron Lett.* **1997**, *38*, 6665–6668. For 1,3-DC with nitrile *N*-oxides see: (c) Wallace, R. H.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941–6944. (d) Wallace, R. H.; Liu, J. *Tetrahedron Lett.* **1994**, *35*, 7493–7496. (e) Jazouli, M.; Baba, S.; Carboni, B.; Carrie, R.; Soufiaoui, M. *J. Organomet. Chem.* **1995**, *498*, 229–235. (f) Wallace, R. H.; Liu, J.; Zong, K. K.; Eddings, A. *Tetrahedron Lett.* **1997**, *38*, 6791–6794. (g) Liu, J.; Eddings, A.; Wallace, R. H. *Tetrahedron Lett.* **1997**, *38*, 6795–6798. (h) Wallace, R. H.; Zong, K. K. *J. Organomet. Chem.* **1999**, *581*, 87–91. (i) Zhang, A.; Kan, Y.; Zhao, G.-L.; Jiang, B. *Tetrahedron* **2000**, *56*, 965–970.
6. (a) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748. (b) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293–301.
7. Dirat, O.; Berranger, T.; Langlois, Y. *Synlett* **1995**, 935–937.
8. Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523–5526.
9. Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran-Huu-Dau, M. E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123–5128.
10. Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048–5050.
11. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785–789.
12. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.
13. Silva, M. A.; Goodman, J. M. *Tetrahedron Lett.* **2003**, *44*, 8233–8236.
14. (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.
15. Jaguar 4.2, Schrodinger, Inc., Portland, Oregon, 2002.
16. We have come across similar findings when studying the Diels–Alder reactions of alkynylboranes, which makes us believe this behavior could be related to a bifurcation in the potential energy surface. (a) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2002**, *67*, 8203–8209. (b) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2003**, *68*, 4059–4066.
17. We followed Rastelli's nomenclature for the regiochemistry (A and B pathways generate 4- and 5-borylisoxazolidines, respectively).
18. This observation suggests the conclusions drawn with prototype compounds may not be completely valid for real systems and highlights the importance of the model chosen for performing computational studies.
19. (a) Singleton, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 6563–6564. (b) Pellegrinet, S. C.; Silva, M. A.; Goodman, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 8832–8837. (c) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *ARKIVOC* **2003**, *X*, 556–565. (d) Pellegrinet, S. C.; Silva, M. A.; Goodman, J. M. *J. Comput. Aided Mol. Des.* **2004**, *18*, 209–214.
20. Several conformational switches in transition structures have been described for other cycloaddition reactions. For example, see: Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064–1073.
21. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

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Acid-catalyzed addition of indoles to hydroxyquinones

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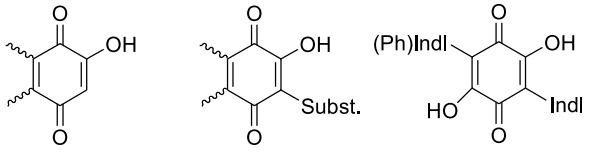
Abstract—Hydroxyquinones react smoothly with substituted indoles in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford a variety of addition products. The main products are either the corresponding *p*-quinone or the corresponding hydroquinone, resorcinol and benzenetriol mono- and diindolyl derivatives, depending on the nature of the hydroxyquinone and the substituents on the indole ring.

1. Introduction

Hydroxyquinones, quinones with hydroxy groups on the quinone ring **1**, comprise an interesting class of organic compounds. A great variety of hydroxyquinones are found in nature and the fact that most of them exhibit interesting biological activity[1] makes them attractive synthetic targets.[2] The presence of the hydroxy group enriches the chemical behaviour of the quinone ring and for this reason hydroxyquinones can be used as versatile building blocks for the construction of more complex compounds.[2]

Since most of the biologically active hydroxyquinones bear substituents at the position next to the hydroxy group, one of the interesting features of their chemistry is the functionalization of this position in the unsubstituted compounds.[2] Indeed, hydroxyquinones of type **2** present some unique properties depending on the nature of the substituent.



The combination of the hydroxyquinone moiety with the indole ring gives rise to the interesting classes of indolo quinones[3] and indolyl quinones, asterriquinones being the most known representatives of the latter. Asterriquinones, 3,6-diindolyl-2,5-dihydroxy-1,4-benzoquinones, **3**, have been used as insulin mimetics, with obvious pharmacological consequences. It was also found that analogous compounds in which an indolyl group has been replaced by a phenyl group exhibit the same activity.[4]

Indolyl quinones have generally been prepared by the addition of indole derivatives to quinones in acetic acid,[5a] and more recently, by the $Bi(OTf)_3$[5b] and $InBr_3$[5c] catalyzed conjugate addition of indoles to *p*-quinones.

An elegant method for the preparation of asterriquinones by acid-catalyzed insertion of indole units into 2,5-dihalogen-1,4-benzoquinones and subsequent alkaline hydrolysis to the hydroxy analogues has also been reported.[6]

The reaction of hydroxyquinones with indole derivatives has not been studied. Since hydroxyquinones exhibit different reactivity patterns from quinones, such a reaction might lead to interesting products. For this reason we investigated the acid-catalyzed reaction of hydroxyquinones with indole derivatives and report the results of our study in this paper.

2. Results and discussion

Six different hydroxyquinones, namely 2-hydroxy-1,4-naphthoquinone or lawsone (**4**), 2-hydroxy-5,6-dimethyl-1,4-benzoquinone (**5**), 2-hydroxy-1,4-triptycenequinone (**6**), 2-hydroxy-5-methyl-1,4-benzoquinone (**7**), 2-hydroxy-5-phenyl-1,4-benzoquinone (**8**) and 2,5-dihydroxy-1,4-benzoquinone (**9**) (Fig. 1) were selected for this study.

In order to find the optimum reaction conditions the addition of *N*-methylindole (**10**) to lawsone (**4**) was tried using three different acidic catalysts. The reaction with boron trifluoride etherate afforded the bis-indolyl-1,3-naphtalenediol

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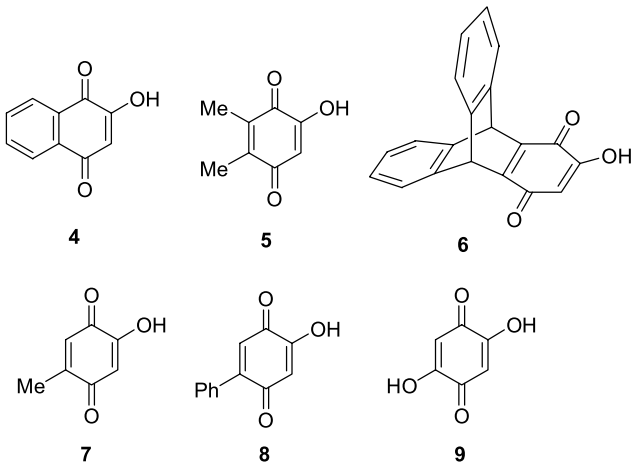
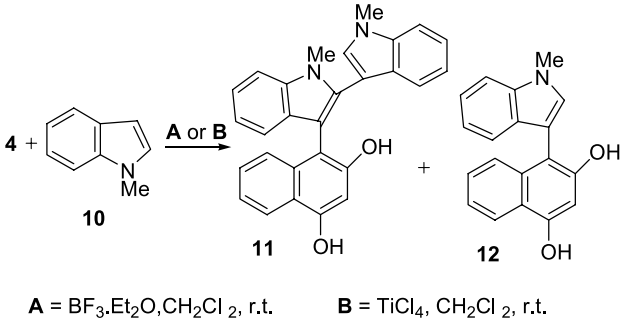


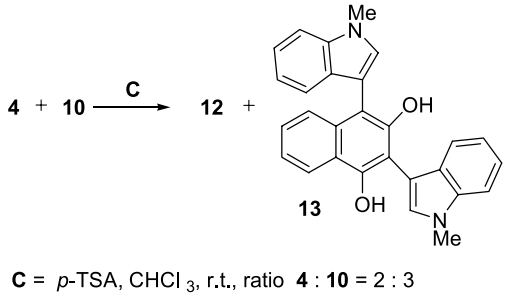
Figure 1. Hydroxyquinones used.

derivative **11** and the corresponding 4-indolyl anlogue **12** in yields ranging between 10–20% for **11** and 5–10% for **12**, depending on the solvent (toluene, CH_2Cl_2) and the quinone/indole ratio (1:1, 2:3 or 1:2). Similar results were obtained when titanium tetrachloride was used as a Lewis acid catalyst (Scheme 1). Unreacted lawsone was also recovered from the reaction mixture, as well as unidentified oligomers of indole. The latter are resulting from the well-known oligomerization of indole under Lewis acidic conditions.[7]



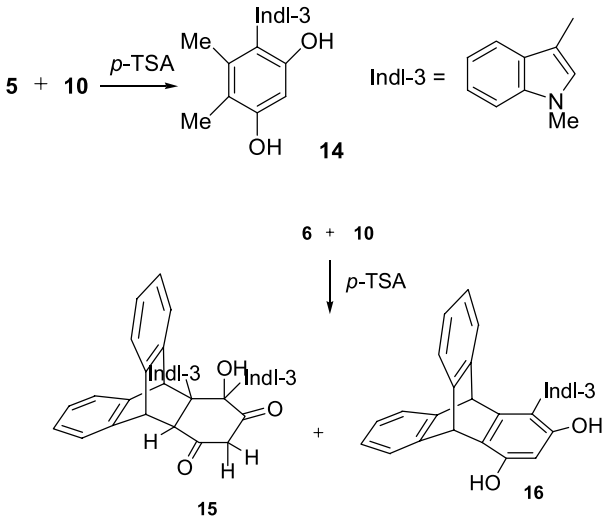
Scheme 1. Reaction of lawsone (**4**) with *N*-methylindole (**10**) and $BF_3 \cdot Et_2O$ or $TiCl_4$ as catalysts.

Better results were obtained when *p*-toluenesulfonic acid (*p*-TSA) was used as catalyst. In this case the reaction was a clean one and the 4-indolyl-1,3-naphthalenediol derivative **12** and the 2,4-diindolyl analogue **13** were the two main products (Scheme 2). Best yields (35% for **12** and 50% for **13**) were obtained in $CHCl_3$, with a ratio of quinone/indole 2:3 after 24 h at room temperature. These reaction conditions were applied to the other hydroxyquinones.



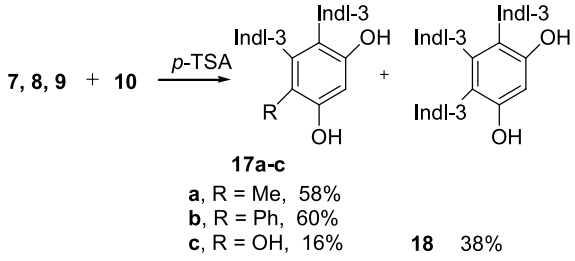
Scheme 2. Reaction of lawsone (**4**) with *N*-methylindole (**10**) and *p*-toluenesulfonic acid as catalyst.

Analogous results were obtained from the reaction of *N*-methylindole (**10**) with the 5,6-disubstituted-hydroxyquinones **5** and **6**. In the case of dimethylhydroxyquinone **5** the indolyl resorcinol derivative **14** was the only isolable product in 58% yield. Hydroxytriptycenequinone **6** afforded, in addition to the expected resorcinol analogue **16** (23% yield), the diindolyl derivative **15**, a Michael addition product, in 15% yield (Scheme 3).



Scheme 3. Reaction of hydroxyquinones **5** and **6** with *N*-methylindole (**10**).

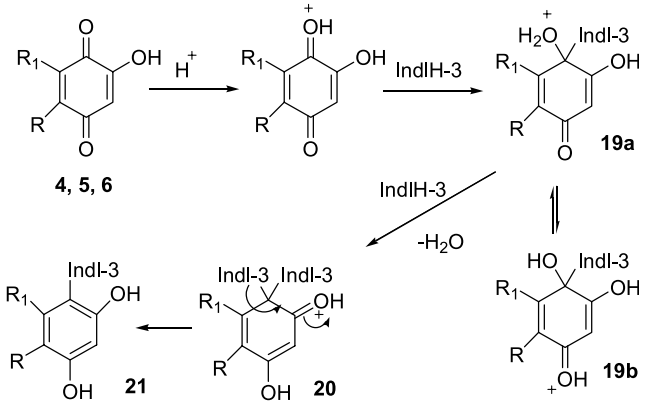
The reaction of **10** with hydroxyquinones **7**, **8** and **9** gave different results. All three quinones, having unsubstituted position 6, afforded the diindolyl resorcinol derivatives **17a–c** (Scheme 4). In the case of dihydroxybenzoquinone **9** the triindolyl resorcinol derivative **18** was the main product of the reaction in 38% yield. Yields reported on the scheme are referred to quinone/indole ratio 1:2.



Scheme 4. Reaction of monosubstituted hydroxyquinones **7**, **8** and **9** with *N*-methylindole (**10**).

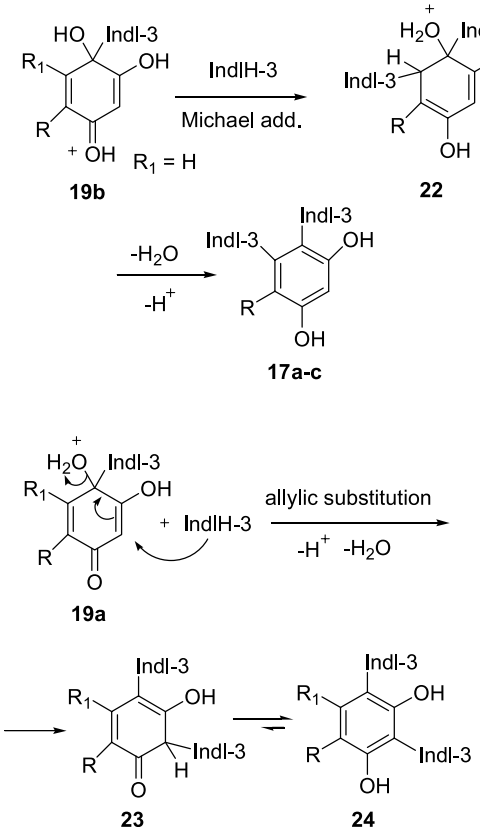
From the above results it becomes obvious that the acid-catalyzed reaction of 5,6-disubstituted hydroxyquinones **4**, **5** and **6** with *N*-methylindole leads mainly to 4-mono or 2,4-diindolyl resorcinol derivatives. A plausible reaction pathway explaining these products involves the initial addition of indole to the protonated carbonyl of the hydroxyquinone, to form **19a**. The latter reacts with a second indole molecule to afford the *gem*-diindolyl derivative **20**, which is

transformed to the isolated 4-indolyl resorcinol derivatives **21** with the expulsion of an indole unit (Scheme 5). It must be noted that the formation of *gem*-diindolyl derivatives, analogous to **20**, has been reported recently[8] from the reaction of carbonyl or quinonoid compounds and indoles under acidic conditions.



Scheme 5. Proposed reaction pathway for the formation of indolyl resorcinol derivatives **21**.

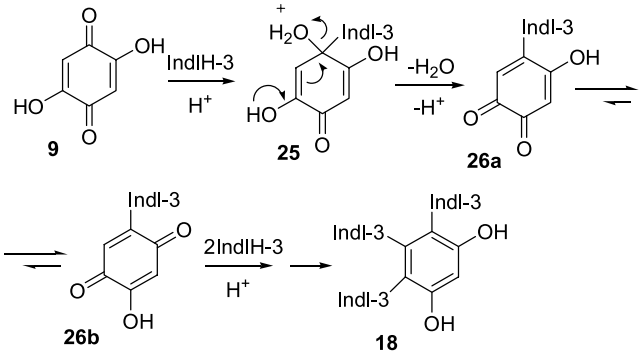
The other two types of products, diindolyl resorcinol derivatives **13** and **17**, arise from the tautomeric forms **19a** and **19b**, respectively. In the case of hydroxyquinones **7**, **8** and **9** the lack of substituent at position 6 ($R_1=H$) facilitates the Michael addition of a second indole molecule. The initially formed Michael adduct **22** loses H_2O to afford the diindolyl derivatives **17a–c** (Scheme 6).



Scheme 6. Proposed reaction pathway for the formation of indolyl resorcinol derivatives **17a–c** and **24**.

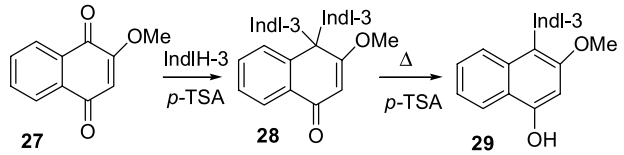
Another possible parallel route is the indole-allylic substitution at carbon-3 of **19a**, leading to 2,4-diindolyl resorcinol derivatives **24** (Scheme 6). This route predominates in the reaction of lawsone (**4**) with *N*-methylindole and hence the isolation of **13** as the main product.

The formation of the triindolyl derivative **18** can be explained by the same reaction pattern. The initially formed **25**, analogous to **19a**, with the participation of the hydroxy group expels H_2O to afford the indolyl-hydroxy-*o*-benzoquinone **26a**. The latter, most probably through the predominant *p*-benzoquinone form **26b**, reacts with indole and affords **18** with the insertion of two more indole units (Scheme 7). The intermediate 5-indolyl-hydroxy-benzoquinone **26b** is completely analogous to 5-methyl and 5-phenyl substituted hydroxyquinones **7** and **8** and hence displays the same type of reactivity.



Scheme 7. Proposed reaction pathway for the formation of triindolyl resorcinol derivative **18**.

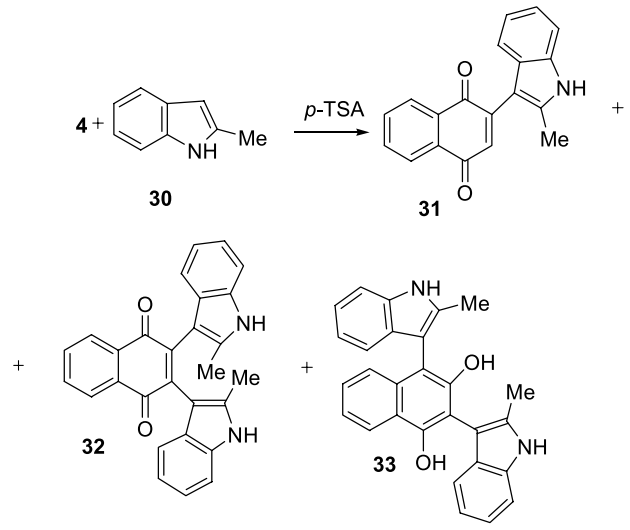
In order to verify the proposed reaction pathway the reaction of lawsone methyl ether **27** with *N*-methylindole in the presence of *p*-TSA was investigated. In this case the *gem*-diindolyl derivative **28** was isolated in 21% yield, proving thus that compounds such as **20** are possible intermediates in the initial reaction. Moreover, **28** was transformed to derivative **29**, analogous to **21**, upon reflux in toluene with the addition of *p*-TSA (Scheme 8). This transformation indicates that the proposed analogous pathway from **20** to **21** is most possible.



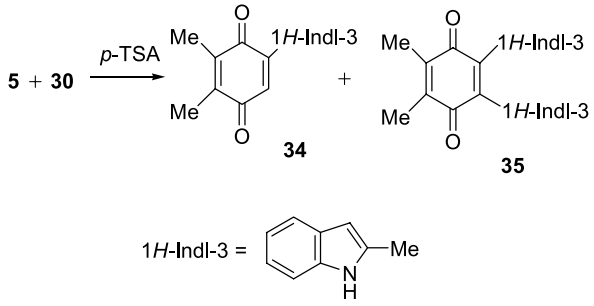
Scheme 8. Reaction of lawsone methyl ether **27** with *N*-methylindole (**10**).

Different results were obtained from the reaction of hydroxyquinones with 2-methylindole (**30**). Again the quinone/indole ratio was 2:3 for quinones **4**, **5** and **6**. Lawsone (**4**) afforded the 2-indolyl and 2,3-diindolyl-1,4-naphthoquinone derivatives **31** and **32** (15 and 28% yields respectively), along with a small amount (20%) of 2,4-diindolyl-1,3-naphthalenediol **33** (Scheme 9).

The mono- and diindolylquinones **34** and **35** were also the products of the reaction of dimethyl hydroxybenzoquinone (**5**) with **30** in 19 and 28% yields, respectively (Scheme 10).

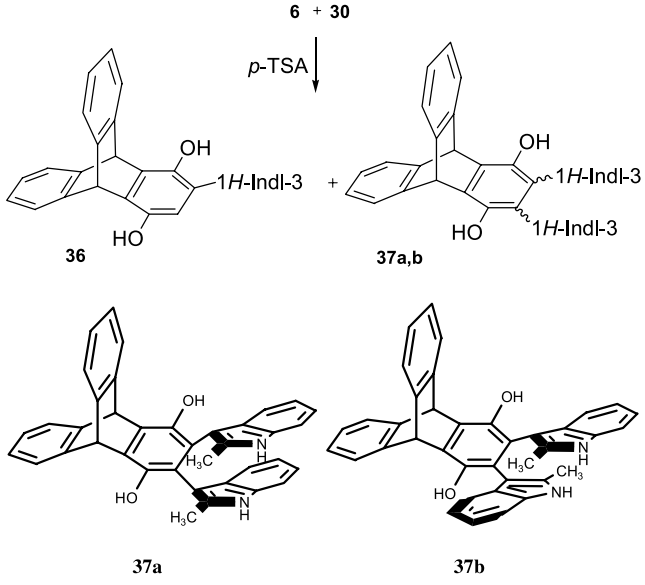


Scheme 9. Reaction of lawsone (**4**) with 2-methylindole (**30**).



Scheme 10. Reaction of hydroxyquinone **5** with 2-methylindole (**30**).

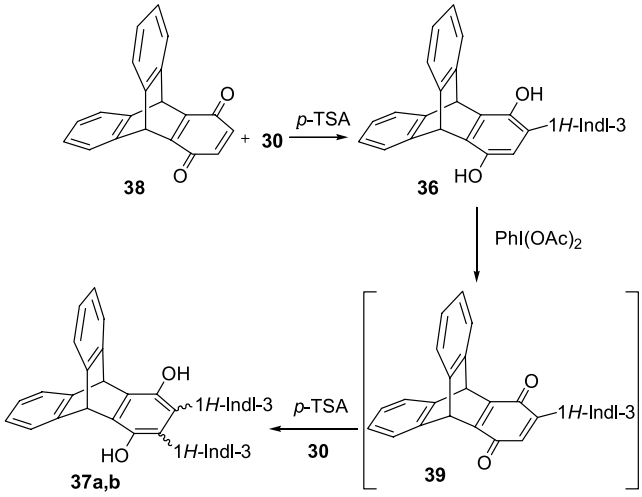
Hydroxytriptycenequinone **6** afforded analogous products but in the reduced hydroquinonic form. The mono indolyl derivative **36** was isolated in 35% yield and, interestingly enough, two rotational isomers of the diindolyl analogue, **37a** and **37b**, were separated in 11 and 18% yields, respectively (Scheme 11). Distinction between the two rotamers **37a** and **37b** is based on the shift of the methyl



Scheme 11. Reaction of hydroxytriptycenequinone **6** with 2-methylindole (**30**).

groups of the indole rings in their ^{1}H NMR spectra. Indeed, in *anti* isomer **37b** the methyl groups appear an upfield shift at 1.40 δ, due to the magnetic shielding of the benzene ring, compared to 1.96 δ of the methyl groups in the corresponding *syn* isomer **37a**.

In order to verify the structures of **37a**,**b** another approach to these interesting rotamers was attempted. *p*-TSA-catalysed addition of 2-methylindole (**30**) to hydroxytriptycenequinone **38** afforded the indolyl hydroquinone **36**, which was oxidized to the corresponding quinone **39** by $PhI(OAc)_2$. The latter, without isolation, subjected to *p*-TSA-catalyzed reaction with 2-methylindole to afford, among other products, a separable mixture of rotamers **37a**,**b**, both isomers in all respects identical to those isolated previously (Scheme 12).



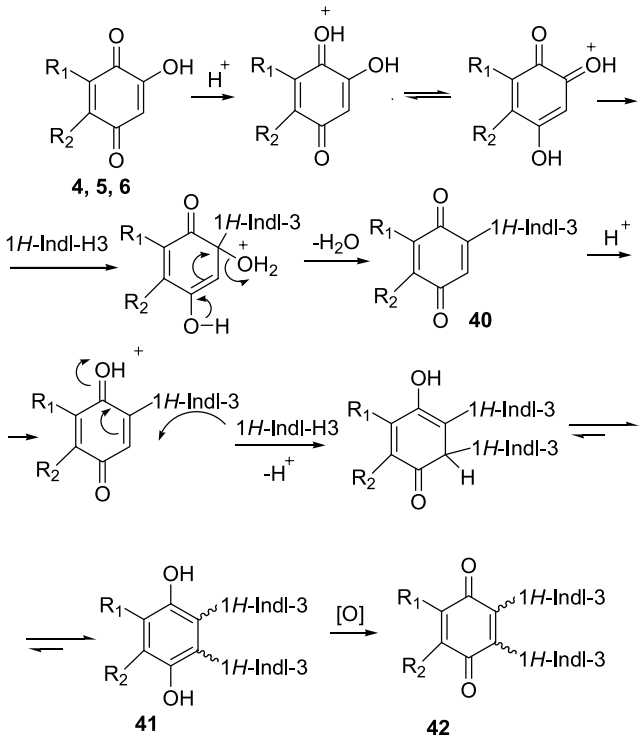
Scheme 12. Alternative preparation of rotamers **37a**,**b**.

This difference in reactivity between 1-methyl and 2-methylindole towards 5,6-disubstituted hydroxyquinones can be explained in terms of greater steric hindrance of 2-methylindole. This is probably the reason that initial 2-methylindole attack takes place at carbon-2 instead of carbon-1 to afford the isolated compounds **40** (Scheme 13).

The reaction can proceed further with the Michael addition of a second indole molecule to the protonated form of **40** to afford the diindolyl hydroquinone derivative **41**. The latter is not isolated, except in the case of hydroxytriptycenequinone **6**, but is further oxidized to the corresponding diindolylquinone **42**. This oxidation can take place either by some quinonoid species or by air, during column chromatography. A more complicated pathway, involving possibly the addition of a second indole molecule followed by its elimination in a next step, could explain the formation of the indolyl hydroquinone derivative **36**.

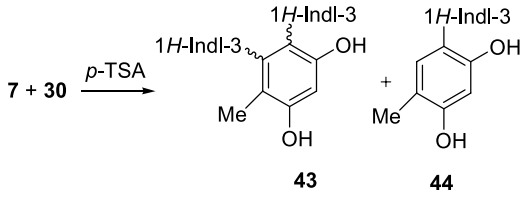
The steric hindrance mentioned above for the 5,6-disubstituted hydroxyquinones **4**, **5**, **6** is lesser in 5-monosubstituted ones **7**, **8**, **9** and hence the different products in their acid-catalyzed reaction with 2-methylindole (**30**).

The reactions of hydroxyquinones **7**, **8**, **9** with **30** were carried out with hydroxyquinone/indole ratio 1: 2. The



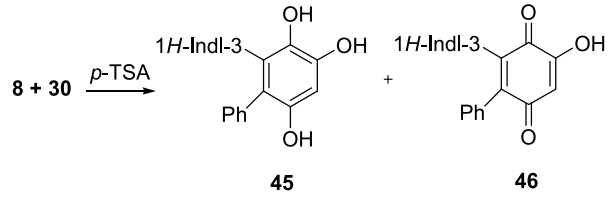
Scheme 13. Proposed reaction pathway for the reaction of 5,6-disubstituted hydroxyquinones **4**, **5** and **6** with 2-methylindole (**30**).

reaction of 5-methyl-2-hydroxy-1,4-benzoquinone (**7**) afforded after column chromatography the di- and mono-indolyl resorcinol derivatives **43** and **44**, in 25 and 28% yields, respectively (Scheme 14). The former consisted of an inseparable mixture of rotamers (most possibly *syn* and *anti*) in a ratio of ~1:1. This conclusion is based on the fact that, although ^{1}H and ^{13}C NMR spectra are too complicated in the aromatic region, peaks for four methyl indole substituents (and a fifth for the methyl in the resorcinol ring) are distinct in both spectra.



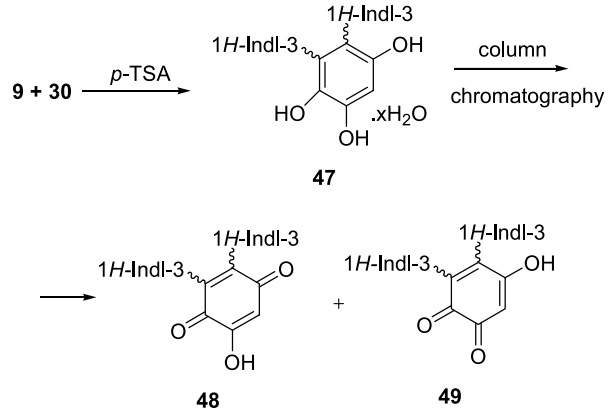
Scheme 14. Reaction of methyl hydroxybenzoquinone **7** with 2-methylindole (**30**).

Somehow different results were obtained from the reaction of phenyl hydroxybenzoquinone **8** with 2-methylindole. The trihydroxy phenyl indolyl derivative **45** was isolated from the reaction mixture by filtration, in 83% yield. Column chromatography of the filtrate afforded the hydroxyquinone analogue **46** in 5% yield (Scheme 15). On attempted purification by column chromatography, **45** was partly oxidized on the column to the corresponding quinone derivative **46** and the same was observed in an independent oxidation of **45** by $FeCl_3$. The formation of **45** as practically the sole reaction product can be attributed to the steric effects of the phenyl substituent on the quinonoid ring.



Scheme 15. Reaction of phenyl hydroxybenzoquinone **8** with 2-methylindole (**30**).

Finally, the reaction of 2,5-dihydroxybenzoquinone (**9**) proved more difficult to investigate. The solid resulting from this reaction was isolated by filtration. Spectroscopic evidence showed that it consisted mainly of 1,2-diindolyl trihydroxy derivative **47** as a mixture of rotamers, which crystallized with water (Scheme 16). As **47** could not be purified further, the whole reaction mixture was chromatographed on a column to afford the corresponding *p*- and *o*-hydroxyquinone derivatives **48** and **49**.



Scheme 16. Reaction of dihydroxybenzoquinone **9** with 2-methylindole (**30**).

These oxidation products of **47** were isolated in 23 (**48**) and 42% (**49**) yields and both of them consisted of 1:1 mixture of rotamers, thus exhibiting complicated spectroscopic data, especially in the aromatic region. Both *p*- and *o*-quinone isomers have the same molecular formula, calculated by exact mass measurements, and distinction between them is based mainly on the shift of the quinonoid carbonyls in the ^{13}C NMR. Indeed, these carbonyls appear for **48** at δ 187.2 and 183.3, whereas for **49** at δ 179.5 and 177.5. This upfield shift is in agreement with the reported values for the very few cases of hydroxyquinones existing in *o*-tautomeric form.[9,10]

3. Conclusions

The above results suggest that the acid-catalyzed addition of indoles to hydroxyquinones is best effected by *p*-TSA and depends mainly on the structure of the hydroxyquinone. In most cases the reaction starts with the addition of indole to the most activated position, carbonyl-1 in its protonated form. If there is strong steric hindrance (both from hydroxyquinone and indole) initial attack takes place at position 2, with characteristic example the reaction of

5,6-disubstituted hydroxyquinones **4**, **5** and **6** with 2-methylindole. The addition of a second indole molecule is controlled by the type of the first adduct and the nature of the substituents on the quinone ring.

From the synthetic point of view the acid-catalyzed addition of indoles to hydroxyquinones leads to some interesting indolyl mono and disubstituted hydroquinone, resorcinol and trihydroxybenzene derivatives. The isolation of the second group of products, quinones or hydroxyquinones with indole substituents, is also significant, as generally these type of compounds exhibit interesting biological activity.[6c]

4. Experimental

4.1. General

Lawsone (**4**) and 2,5-dihydroxy-1,4-benzoquinone (**9**) were commercially available. 2-Hydroxy-5,6-dimethyl-1,4-benzoquinone[11] (**5**), 2-hydroxy-1,4-triptycenequinone[12] (**6**), 2-hydroxy-5-methyl-1,4-benzoquinone[13] (**7**) and 2-hydroxy-5-phenyl-1,4-benzoquinone[14] (**8**) were prepared according to published literature methods.

4.2. Reactions of lawsone with *N*-methylindole and $BF_3 \cdot Et_2O$ or $TiCl_4$ as acidic catalysts

To a solution (or suspension) of lawsone (1 mmol) and *N*-methylindole (1, 1.5 or 2 mmol) in dichloromethane or toluene (10 mL) a catalytic amount of $BF_3 \cdot Et_2O$ or $TiCl_4$ was added and the resulting mixture was stirred at room temperature for 24–48 h. Solvent was removed in vacuo and column chromatography of the residue (silica gel, hexanes/ethyl acetate 10:1 gradually increasing to pure ethyl acetate) afforded, except unreactant indole, oligomers of indole and unreactant lawsone, *4-[2-(1-methyl-1H-indol-3-yl)-1-methyl-1H-indol-3-yl]-1,3-naphthalenediol* (**11**). Yields 10–20%: mp 266–269 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11–8.05 (m, 1H), 7.55–7.42 (m, 3H), 7.33 (t, $J=8$ Hz, 1H), 7.27–7.17 (m, 4H), 7.15–7.07 (m, 3H), 6.85 (s, 1H), 6.52 (s, 1H), 5.89 (br s, 1H), 5.52 (br s, 1H), 3.81 (s, 3H), 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 153.2, 153.0, 137.4, 136.1, 135.2, 134.5, 129.3, 128.7, 127.2, 125.5, 124.5, 121.6, 121.2, 120.9, 120.6, 120.0, 119.3, 119.1, 118.8, 109.1, 108.9, 106.6, 104.9, 100.0, 32.3, 30.9; MS *m/z* (%) 418 (M^+, 78), 287 (83), 260 (50), 131 (100). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 79.93; H, 5.13; N, 6.25 and *4-(1-methyl-1H-indol-3-yl)-1,3-naphthalenediol* (**12**). Yields 5–10%: mp 222–224 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (dd, $J_1=2$ Hz, $J_2=6$ Hz, 1H), 7.51 (m, 1H), 7.46 (d, $J=8$ Hz, 1H), 7.38–7.25 (m, 4H), 7.11 (t, $J=7$ Hz, 1H), 7.19 (s, 1H), 6.70, (s, 1H), 5.56 (br s, 1H), 5.45 (br s, 1H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 152.8, 152.3, 136.2, 134.4, 128.7, 127.8, 125.2, 124.0, 121.3, 120.6, 120.3, 119.6, 119.4, 118.1, 108.5, 107.3, 103.8, 99.7, 31.9; MS *m/z* (%) 289 (M^+, 100), 261 (22), 131 (16). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.26; N, 4.84. Found: C, 78.41; H, 5.39; N, 4.44.

4.3. Reactions of 5,6-disubstituted hydroxyquinones 4, 5 and 6 with *N*-methylindole in the presence of *p*-TSA

The proper hydroxyquinone **4**, **5** or **6** (2 mmol), *N*-methylindole (3 mmol) and a catalytic amount of *p*-TSA were added to $CHCl_3$ (10 mL) and the resulting mixture was stirred at room temperature for 24 h. Removal of the solvent and column chromatography (silica gel, hexanes/ethyl acetate 10:1 gradually increasing to pure ethyl acetate) afforded the products.

4.3.1. Reaction of lawsone 4. Isolated compounds: naphthalenediol derivative **12** in 35% yield and *2,4-bis(1-methyl-1H-indol-3-yl)-1,3-naphthalenediol* (**13**). Yield 50%: mp 257–260 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24–8.17 (m, 1H), 7.49–7.42 (m, 2H), 7.33–7.17 (m, 7H), 7.07–7.01 (m, 2H), 6.98–6.81 (m, 2H), 6.37 (br s, 2H), 3.64 (s, 6H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 144.2, 136.1, 129.1, 128.9, 128.7, 128.5, 127.3, 125.4, 125.3, 122.9, 120.5, 120.1, 119.6., 118.0, 117.5, 117.4, 115.4, 108.4, 108.1, 100.5, 31.4; MS *m/z* (%) 418 (M^+, 32), 390 (100), 260 (96), 131 (18). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.11; H, 5.30; N, 6.35.

4.3.2. Reaction of 5,6-dimethyl hydroxyquinone 5. The only isolable product was *4,5-dimethyl-6-(1-methyl-1H-indol-3-yl)-1,3-benzenediol* (**14**). Yield 58%: mp 179–182 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.24 (m, 3H), 7.10 (t, $J=4$ Hz, 1H), 6.99 (s, 1H), 6.38 (s, 1H), 5.72 (s, 1H, OH), 5.24 (s, 1H, OH), 3.81 (s, 3H), 2.14 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 152.4, 138.8, 137.3, 128.9, 128.0, 122.3, 120.1, 119.8, 114.7, 112.5, 109.5, 108.3, 99.2, 32.9, 17.7, 11.6; MS *m/z* (%) 267 (M^+, 100), 252 (21), 138 (57), 131 (20). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.11; H, 6.36; N, 5.07.

4.3.3. Reaction of hydroxytriptycenequinone 6. From this reaction the following compounds were isolated in order of eluance: *4-hydroxy-4,5-bis(1-methyl-1H-indol-3-yl)-triptyceno-1,3-cyclohexanedione* (**15**). Yield 15%: mp 283–286 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, $J=6$ Hz, 1H), 7.74–7.62 (m, 2H), 7.53 (d, $J=8$ Hz, 1H), 7.45–7.33 (m, 3H), 7.29–7.13 (m, 4H), 7.10 (s, 1H), 7.06–6.97 (m, 2H), 6.90 (d, $J=8$ Hz, 1H), 6.77 (t, $J=7$ Hz, 1H), 6.68 (d, $J=8$ Hz, 1H), 6.55 (s, 1H), 5.63 (s, 1H), 5.54 (s, 1H), 3.93 (s, 3H), 3.46 (s, 3H), 3.37 (d, $J=20$ Hz, 1H), 3.05 (d, $J=20$ Hz, 1H), 2.17 (br s, 1H, OH), 1.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.6, 195.8, 158.3, 142.4, 141.6, 141.1, 139.2, 137.3, 137.0, 130.5, 130.0, 129.2, 128.5, 127.6, 127.0, 126.7, 126.6, 126.2, 125.7, 125.3, 125.1, 124.7, 123.5, 123.1, 122.2, 122.1, 120.1, 120.0, 119.9, 119.5, 115.4, 110.1, 109.6, 107.2, 62.2, 54.6, 52.0, 49.8, 49.7, 33.2, 32.8, 30.9; MS *m/z* (%) 544 ($M^+ - H_2O$, 100), 516 (10), 178 (82), 131 (33). Anal. Calcd for $C_{38}H_{30}N_2O_3$: C, 81.12; H, 5.37; N, 4.98. Found: C, 81.37; H, 5.02; N, 4.65 and *4-(1-Methyl-1H-indol-3-yl)-1,3-triptycenediol* (**16**). Yield 23%: mp 277–280 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 8.98, (s, 1H, OH), 7.65–7.22 (m, 6H), 7.18–7.08 (m, 4H), 7.03–6.83 (m, 4H), 6.24 (s, 1H), 5.85 (s, 1H), 5.29 (s, 1H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 152.5, 151.0, 146.9, 146.2, 145.9, 145.6, 145.4, 136.5, 128.4, 128.1, 124.3, 124.2, 123.9, 123.5, 122.8,

122.7, 122.1, 121.1, 120.0, 118.5, 108.8, 108.7, 107.8, 99.0, 50.9, 46.0, 32.4; MS *m/z* (%) 415 (M^+, 60), 284 (100), 131 (86). Anal. Calcd for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.09; N, 3.37. Found: C, 83.38; H, 4.99; N, 3.12.

4.4. Reactions of 5-substituted hydroxybenzoquinones 7, 8 and 9 with *N*-methylindole in the presence of *p*-TSA

4.4.1. Reaction of 5-methyl-hydroxybenzoquinone 7. The reaction was carried out under the conditions described previously, with quinone/indole ratio 1:2. Column chromatography afforded *4-methyl-5,6-bis(1-methyl-1H-indol-3-yl)-1,3-benzenediol* (**17a**) in 58% yield: oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.08 (m, 8H), 6.98 (s, 2H), 6.27 (s, 1H), 5.18 (br, 2H, OH), 3.68 (s, 3H), 3.67 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 152.5, 137.8, 136.9, 133.5, 133.2, 129.9, 128.1, 127.5, 123.2, 122.0, 120.3, 120.0, 119.9, 119.4, 115.4, 113.4, 109.7, 109.5, 108.8, 104.7, 102.0, 32.9, 31.3, 15.0; MS *m/z* (%) 383 ($M^+ + 1$, 100), 252 (53), 130 (10). ESI-HRMS *m/z* calcd for $C_{25}H_{22}N_2O_2 + Na$ (MNa^+) 405.15735, found 405.15739.

4.4.2. Reaction of 5-phenyl-hydroxybenzoquinone 8. The reaction was carried out under the conditions described previously. The precipitated solid was *4-phenyl-5,6-bis(1-methyl-1H-indol-3-yl)-1,3-benzenediol* (**17b**) in 60% yield: mp 171–173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J=7.3 Hz, 1H), 7.48–7.33 (m, 5H), 7.32–7.09 (m, 8H), 7.06 (s, 1H), 6.51 (s, 1H), 5.29 (br, 2H, OH), 3.80 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.5, 152.5, 137.9, 137.2, 137.0, 133.4, 133.1, 129.9, 129.1, 129.0, 127.8, 127.7, 127.2, 122.3, 122.2, 120.5, 120.4, 120.2, 120.0, 119.4, 114.3, 109.7, 109.6, 108.6, 104.7, 102.4, 33.1, 31.4; MS *m/z* (%) 444 (M^+, 100), 131 (10), 130 (11), 77 (11). Anal. Calcd for $C_{30}H_{24}N_2O_2$: C, 81.06; H, 5.44; N, 6.30. Found: C, 80.88; H, 5.55; N, 6.03.

4.4.3. Reaction of 2,5-dihydroxybenzoquinone 9. The reaction was carried out under the conditions described previously. Isolated from the column: *5,6-bis(1-methyl-1H-indol-3-yl)-1,2,4-benzenetriol* (**17c**). Yield 16%: mp 170–172 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 11.00 (br, 2H, OH), 7.47–7.31 (m, 4H), 7.24–7.17 (m, 4H), 7.10–7.01 (m, 2H), 6.54 (s, 1H), 6.40 (s, 1H), 3.83 (s, 3H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 147.2, 143.5, 136.3, 135.6, 131.5, 128.9, 127.2, 126.8, 120.7, 120.2, 119.0, 118.7, 118.6, 118.0, 117.5, 111.3, 110.1, 108.5, 108.2, 103.8, 102.5, 31.9, 30.0; MS *m/z* (%) 384 (M^+, 14), 131 (10). ESI-HRMS *m/z* calcd for $C_{24}H_{20}N_2O_3 + H$ (MH^+) 385.15467, found 385.15481 and *4,5,6-tris(1-methyl-1H-indol-3-yl)-1,3-benzenediol* (**18**). Yield 38%: mp 95–100 °C; mixture of rotamers, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63–7.54 (m, 2H), 7.44–6.89 (m, 13H), 6.60 (br s, 1H), 5.41 (br, 2H, OH), 3.75 (br s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.0 (br), 153.3 (br), 137.8, 137.3, 137.2, 137.0, 134.3, 133.6, 133.3 (br), 130.4, 129.9, 129.8, 128.7, 127.7, 127.6, 127.5, 126.3, 122.4, 122.2, 122.0, 120.4, 120.1, 120.0, 119.7, 119.4, 119.0, 110.1, 109.8, 109.3, 108.7, 104.9, 102.0 (br), 33.1, 32.8, 31.3; MS *m/z* (%) 497 (M^+, 15), 368 (100), 130 (11). ESI-HRMS *m/z* calcd for $C_{33}H_{27}N_3O_2 + Na$ (MNa^+) 520.19955, found 520.19960.

4.4.4. Reaction of lawsone methyl ether 27 with *N*-methylindole in the presence of *p*-TSA. Lawsone methyl ether[15] **27** (1 mmol), *N*-methylindole (1 mmol) and a catalytic amount of *p*-TSA were added to $CHCl_3$ (10 mL) and the resulting mixture was stirred at room temperature for 24 h. Removal of the solvent and column chromatography (silica gel, hexanes/ethyl acetate) afforded as main product *3-methoxy-4,4-bis(1-methyl-1H-indol-3-yl)-1(4H)-naphthalenone* (**28**) in 21% yield. Mp > 280 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J=7.1 Hz, 1H), 7.44–7.35 (m, 3H), 7.33–7.21 (m, 4H), 7.20–7.11 (m, 2H), 6.98–6.87 (m, 2H), 6.57 (s, 2H), 5.86 (s, 1H), 3.67 (s, 6H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.8, 180.1, 146.2, 137.4, 131.9, 130.9, 130.1, 129.9, 127.0, 126.6, 125.7, 122.1, 121.7, 121.5, 119.0, 118.7, 117.0, 109.3, 100.7, 64.9, 56.0, 32.8; MS *m/z* (%) 432 (M^+, 20), 431 (33), 401 (27), 158 (100). Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.45; H, 5.83; N, 6.15. To a solution of naphthalenone **28** (0.2 mmol) in $CHCl_3$ (10 mL) a catalytic amount of *p*-TSA was added and the resulting solution was refluxed for 3 h. As no reaction was observed, the solvent was replaced by toluene (10 mL) and the suspension was refluxed for 8 h. After removal of the solvent and column chromatography *3-methoxy-4-(1-methyl-1H-indol-3-yl)-1-naphthol* (**29**) was isolated in 86% yield, oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12–8.09 (m, 1H), 7.74–7.67 (m, 1H), 7.39 (d, J=7.9 Hz, 1H), 7.18–7.32 (m, 5H), 7.11 (br s, 1H, OH), 7.04 (appt. t, J=7.4 Hz, 1H), 6.80 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2, 152.4, 136.9, 129.3, 128.9, 126.7, 126.1, 122.8, 121.4, 121.3, 120.7, 120.1, 119.1, 109.3, 98.3, 56.8, 32.9; MS *m/z* (%) 303 (M^+, 100), 260 (85), 131 (78). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.32; H, 5.84; N, 4.63.

4.5. Reactions of 5,6-disubstituted hydroxyquinones 4, 5 and 6 with 2-methylindole in the presence of *p*-TSA

The reactions were carried out under the conditions described for the reactions of the same hydroxyquinones with *N*-methylindole.

4.5.1. Reaction of lawsone 4. Isolated compounds: *2-(2-methyl-1H-indol-3-yl)naphtho-1,4-quinone* (**31**). Yield 15%: mp 180–183 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (br s, 1H, NH), 8.22–8.09 (m, 2H), 7.80–7.69 (m, 2H), 7.57–7.49 (m, 1H), 7.32–7.25 (m, 1H), 7.19–7.02 (m, 2H), 7.09 (s, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.3, 184.7, 144.5, 137.0, 135.5, 134.8, 133.7, 133.5, 132.9, 132.3, 127.7, 127.0, 125.9, 122.2, 120.9, 119.3, 110.7, 107.3, 29.7; MS *m/z* (%) 287 (M^+, 91), 270 (100), 230 (41), 154 (37), 130 (13). Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.11; H, 4.82; N, 4.42, *2,3-bis(2-methyl-1H-indol-3-yl)naphtho-1,4-quinone* (**32**). Yield 28%: mp >300 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20–8.12 (m, 2H), 7.81–7.64 (m, 4H), 7.17 (d, J=7 Hz, 1H), 7.03–6.64 (m, 6H), 6.59 (d, J=7 Hz, 1H), 1.67 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 184.0, 140.9, 140.6, 135.8, 135.1, 134.9, 132.7, 132.3, 127.7, 127.0, 125.9, 119.9, 118.7, 109.9, 109.7, 107.1, 12.9; MS *m/z* (%) 416 (M^+, 100), 401 (32), 372 (11), 285 (12), 130 (19). Anal. Calcd for $C_{28}H_{20}N_2O_2$: C, 80.15; H, 4.84; N, 6.73. Found: C, 79.73; H, 4.89; N, 6.45, *2,4-bis(2-methyl-1H-indol-3-yl)-1,3-naphthalenediol* (**33**). Yield 20%: oil; ^{1}H

NMR ($CDCl_3$, 300 MHz) 8.40 (d, $J=8$ Hz, 1H), 8.15 (br s, 1H, NH), 8.03 (br s, 1H, NH), 7.76 (d, $J=8$ Hz, 1H), 7.57–7.00 (m, 11H), 5.75 (s, 1H, OH), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 147.7, 135.4, 134.8, 133.6, 132.5, 132.4, 131.2, 128.7, 127.5, 125.9, 124.5, 123.8, 123.5, 121.9, 120.2, 119.8, 118.6, 118.1, 117.8, 110.1, 109.8, 107.2, 11.9, 11.8; MS *m/z* (%) 418 (M^+, 16), 402 (55), 401 (88), 387 (17), 130 (37). ESI-HRMS *m/z* (MNa^+) calcd for $C_{28}H_{22}N_2O_2+Na$ 441.15735, found 441.15795.

4.5.2. Reaction of 5,6-dimethyl hydroxyquinone 5. Isolated (after column chromatography) compounds: *2,3-dimethyl-5-(2-methyl-1H-indol-3-yl)benzo-1,4-quinone* (**34**). Yield 19%: mp 192–195 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.24 (br s, 1H, NH), 7.45 (d, $J=7$ Hz, 1H), 7.27 (d, $J=7$ Hz, 1H), 7.20–7.09 (m, 2H), 6.80 (s, 1H), 2.39 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.7, 186.9, 141.9, 141.2, 140.7, 136.3, 135.4, 132.4, 127.8, 122.2, 120.8, 119.3, 110.6, 107.3, 13.8, 12.8, 12.2; MS *m/z* (%) 265 (M^+, 100), 250 (96), 194 (60), 154 (94), 130 (49). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.54; H, 5.71; N, 5.26 and *5,6-dimethyl-2,3-bis(2-methyl-1H-indol-3-yl)benzo-1,4-quinone* (**35**). Yield 28%: mp >280 °C; ^1H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 10.03, (s, 2H, NH), 7.15–7.01 (m, 3H), 6.94–6.78 (m, 4H), 6.69–6.62 (m, 1H), 2.15 (s, 6H), 1.98 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.3, 140.2, 138.2, 137.6, 135.4, 134.8, 127.6, 127.0, 119.8, 118.7, 118.6, 118.3, 109.8, 109.6, 106.7, 106.5, 12.7, 12.2; MS *m/z* (%) 394 (M^+, 100), 379 (39), 131 (11). Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.82; H, 5.63; N, 6.86.

4.5.3. Reaction of 2-hydroxytriptycenequinone 6. Isolated (after column chromatography) compounds: 2-(2-methyl-1H-indol-3-yl)-1,4-triptycenediol (**36**). Yield 35%: mp >265 °C, dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06, (br s, 1H, NH), 7.52–7.41 (m, 4H), 7.38–7.26 (m, 2H), 7.16 (t, $J=7.0$ Hz, 1H), 7.10–6.98 (m, 5H), 6.37 (s, 1H), 5.92 (s, 1H), 5.84 (s, 1H), 4.90 (br s, 1H, OH), 4.52 (br, 1H, OH), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.8, 145.7, 145.6, 143.6, 143.2, 135.4, 133.6, 132.6, 132.3, 127.7, 125.0, 124.0, 123.8, 121.9, 120.3, 119.0, 118.4, 115.2, 110.5, 107.7, 47.8, 47.5, 12.1; MS *m/z* (%) 415 (M^+, 100), 202 (17), 178 (14), 131 (15). Anal. Calcd for $C_{29}H_{21}NO_2$: C, 83.80; H, 5.09; N, 3.37. Found: C, 83.87; H, 5.29; N, 3.09, *syn-2,3-bis(2-methyl-1H-indol-3-yl)-1,4-triptycenediol* (**37a**). Yield 11%: mp 225–227 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (br, 2H, NH), 7.57–7.48 (m, 4H), 7.17–7.04 (m, 4H), 7.00–6.87 (m, 6H), 6.69–6.62 (m, 2H), 5.98 (s, 2H), 4.97 (br s, 2H, OH), 1.95 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2, 142.9, 135.4, 135.0, 131.3, 124.9, 124.0, 123.9, 121.4, 119.9, 119.0, 118.5, 109.9, 107.4, 48.0, 12.5; MS *m/z* (%) 544 (M^+, 11), 202 (9), 178 (100). Anal. Calcd for $C_{38}H_{28}N_2O_2$: C, 83.80; H, 5.18; N, 5.14. Found: C, 83.89; H, 5.44; N, 4.70 and *anti-2,3-bis(2-methyl-1H-indol-3-yl)-1,4-triptycenediol* (**37b**). Yield 18%: mp 261–263 °C; ^1H NMR ($CDCl_3$, 300 MHz) 7.51 (br s, 2H, NH), 7.50–7.40 (m, 4H), 7.19 (d, $J=7$ Hz, 2H), 7.03–6.95 (m, 10H), 5.97 (s, 2H), 4.89 (br s, 2H, OH), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1, 143.2, 135.0, 134.9, 131.2, 124.9, 124.0, 123.9, 121.2, 119.8, 118.9, 118.7, 110.3, 106.3, 47.8, 12.4; MS *m/z* (%) 544 (M^+, 12), 178 (100), 131 (32), 130 (34). ESI-HRMS *m/z* calcd for $C_{38}H_{28}N_2O_2+Na$ (MNa^+) 567.20430, found 567.20421.

4.6. Alternative preparation of rotamers 37a and 37b

To a solution of triptycene-1,4-quinone[12] (**38**) (1 mmol) and 2-methylindole (**30**) (1 mmol) in $CHCl_3$ (10 mL) a catalytic amount of *p*-TSA was added and the resulting solution was stirred overnight. Column chromatography under the previously described conditions afforded *2-(2-methyl-1H-indol-3-yl)-1,4-triptycenediol* (**36**) in 85% yield. 1 mmol of **36** was oxidized by 0.7 mmol of $PhI(OAc)_2$ in CH_2Cl_2 at room temperature to afford after column chromatography (silica gel, hexanes/ethyl acetate 3:1) *2-(2-methyl-1H-indol-3-yl)-1,4-triptycenedione* (**38**) in 58% yield. Triptycenequinone **38** (0.5 mmol) was dissolved in $CHCl_3$ (10 mL), 2-methylindole (**30**) (0.5 mmol) and a catalytic amount of *p*-TSA were added and the resulting solution was stirred for 4 h. Column chromatography (silica gel, hexanes/ethyl acetate 10:1 gradually increasing to pure ethyl acetate) afforded *syn-2,3-bis(2-methyl-1H-indol-3-yl)-1,4-triptycenediol* (**37a**) in 7% yield and and *anti-2,3-bis(2-methyl-1H-indol-3-yl)-1,4-triptycenediol* (**37b**) in 17% yield. Both rotamers were in all respects identical to those prepared from the reaction of 2-hydroxytriptycenequinone **6**.

4.7. Reactions of 5-substituted hydroxybenzoquinones 7, 8 and 9 with 2-methylindole in the presence of *p*-TSA

The reactions were carried out by dissolving the appropriate hydroxyquinone (1 mmol), 2-methylindole (2 mmol) and a catalytic amount of *p*-TSA in $CHCl_3$ (15 mL) and overnight stirring at room temperature.

4.7.1. Reaction of 5-methyl-hydroxybenzoquinone, 7. Column chromatography (silica gel, hexanes/ethyl acetate 10:1 gradually increasing to pure ethyl acetate) afforded *4-methyl-5,6-bis(2-methyl-1H-indol-3-yl)-1,3-benzenediol* (**43**) (1:1 mixture of rotamers) in 25% yield: mp 144–148 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (br s, 2H, NH), 7.27–6.96 (m, 12H), 6.87–6.63 (m, 6H), 6.55 (d, $J=8.9$ Hz, 1H), 6.32 (d, $J=6.9$ Hz, 2H), 6.24 (d, $J=7.9$ Hz, 1H), 4.85 (br s, 2H), 2.13 (s, 3H), 2.09 (s, 3H), 1.82 (s, 3H), 1.69 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ complicate at the aromatic region with characteristic peaks at 155.1, 154.9, 97.3, 26.7, 15.8, 15.7, 13.9, 13.2; MS *m/z* 382 (M^+). ESI-HRMS *m/z* calcd for $C_{25}H_{22}N_2O_2+H$ (MH^+) 383.17540, found 383.17492 and *4-methyl-6-bis(2-methyl-1H-indol-3-yl)-1,3-benzenediol* (**44**) in 28% yield: oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (br s, 1H, NH), 7.36 (d, $J=7.9$ Hz, 1H), 7.30 (d, $J=7.9$ Hz, 1H), 7.17 (appt. t, $J=8.8$ Hz, 1H), 7.09 (appt. t, $J=7.4$ Hz, 1H), 6.97 (s, 1H), 6.50, (s, 1H), 5.36 (br s, 1H), 5.16 (br s, 1H), 2.33 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 152.6, 135.5, 133.5, 133.3, 128.2, 121.7, 120.1, 118.8, 115.9, 112.5, 110.5, 107.5, 102.1, 15.0, 12.0; MS *m/z* (%) 253 (M^+, 100), 130 (24). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.57; H, 5.78; N, 5.19.

4.7.2. Reaction of 5-phenyl-hydroxybenzoquinone 8. The reaction was carried out under the conditions described

previously. The precipitated solid was *5-phenyl-6-(2-methyl-1H-indol-3-yl)-1,2,4-benzenetriol* (**45**) in 83% yield: mp 215–217 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 9.87 (s, 1H, NH), 7.27–7.17 (m, 2H), 7.05–6.88 (m, 8H, aromatic + OH), 6.66 (s, 1H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 146.4, 143.5, 137.1, 135.7, 134.9, 133.4, 130.1, 128.1, 126.5, 124.9, 120.5, 120.4, 119.7, 118.2, 118.1, 109.8, 106.2, 102.4, 11.6; MS *m/z* (%) 331 (M^+, 100), 130 (26). Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.03; H, 5.10; N, 3.94.

The reaction mixture, after the filtration of **45** was chromatographed on column to afford *5-hydroxy-2-(2-methyl-1H-indol-3-yl)-3-phenyl-1,4-benzoquinone* (**46**) in 5% yield: mp 94–96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (br s, 1H, NH), 7.21–7.00 (m, 10H, aromatic + OH), 6.30 (s, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.2, 183.8, 154.5, 145.7, 135.3, 135.1, 134.4, 133.4, 130.9, 130.5, 128.4, 128.3, 121.7, 120.2, 119.1, 110.5, 108.1, 105.4, 12.9; MS *m/z* (%) 329 (M^+, 96), 315 (59), 202 (24), 130 (100). ESI-HRMS *m/z* calcd for $C_{21}H_{15}NO_3$ + Na (MNa^+) 352.09441, found 352.09504.

4.7.3. Reaction of 2,5-dihydroxybenzoquinone 9. The reaction was carried out under the conditions described previously. The precipitated solid was filtered and estimated to be *5,6-bis(2-methyl-1H-indol-3-yl)-1,2,4-benzenetriol* (**47**) and most possibly mixture of rotamers, ^{1}H and ^{13}C NMR are too complicate and show the existence of a substantial quantity of water. ESI-HRMS is in agreement with the proposed structure as it gives for $C_{24}H_{20}N_2O_3$ + H *m/z* (MH^+) 385.15467, calcd 385.15407. In another run the whole reaction mixture was chromatographed on column (silica gel, hexanes/ethyl acetate 10:1 gradually increasing to pure ethyl acetate) to afford *5-hydroxy-2,3-bis(2-methyl-1H-indol-3-yl)-benzo-1,4-quinone* (**48**) (1:1 mixture of rotamers) in 23% yield: mp >280 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91–7.79 (br, 4H, NH), 7.34 (br, 2H, OH), 7.16–6.66 (m, 16H), 6.30 (s, 2H), 1.96 (s, 3H), 1.87 (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.2, 183.2, 154.6, 141.6, 141.4, 136.9, 136.1, 135.1, 134.9, 128.1, 127.2, 121.4, 120.0, 119.9, 119.8, 119.4, 119.0, 110.4, 110.3, 110.2, 110.1, 108.2, 108.1, 13.7, 13.6, 13.4, 13.3; MS *m/z* (%) 382 (M^+, 25), 131 (100). ESI-HRMS *m/z* calcd for $C_{24}H_{18}N_2O_3$ + Na (MNa^+) 405.12096, found 405.12077 and *5-hydroxy-3,4-bis(2-methyl-1H-indol-3-yl)-benzo-1,2-quinone* (**49**) (1:1 mixture of rotamers) in 42% yield: mp >280 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 10.68 (br s, 2H), 7.36–6.75 (m, 10H), 6.34 (s, 1H), 5.78 (s, 1H), 1.57 (s, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 179.5, 177.5, 168.8, 156.3, 147.1 MHz, 136.1, 135.2, 135.0, 132.8, 129.7, 128.2, 127.2, 126.3, 125.7, 125.5, 125.2, 123.1, 122.7, 120.2, 120.0, 119.3, 118.5, 117.0, 110.7, 110.3, 109.1, 108.9, 103.2, 99.4, 21.4 (br), 15.6, 12.0. ESI-HRMS *m/z* calcd for $C_{24}H_{18}N_2O_3$ + H *m/z* (MH^+) 383.13957, found 383.13898 and $C_{24}H_{18}N_2O_3$ + Na (MNa^+) 405.12096, found 405.12091.

References and notes

1. Thomson, R. H. *Naturally occurring quinones IV*; Blackie Academic & Professional: London, 1997.
2. Spyroudis, S. *Molecules* **2000**, *5*, 1291–1330.
3. Tišler, M. In Katrizky, A. R., Ed.; Advances in heterocyclic chemistry; Academic: London, 1989; Vol. 45, p 37.
4. Liu, K.; Xu, L.; Szalkowski, D.; Li, Z.; Ding, V.; Kwei, G.; Huskey, S.; Moller, D. E.; Heck, J. V.; Zhang, B. B.; Jones, A. B. *J. Med. Chem.* **2000**, *43*, 3487–3494.
5. (a) Henrion, J.-C.; Jacquet, B.; Hocquaux, M.; Lion, C.; Hedayatullah, M. *Bull. Soc. Chim. Belg.* **1996**, *105*, 403–407. (b) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 9121–9124. (c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Synthesis* **2004**, 106–110.
6. (a) Pirrung, M. C.; Park, K.; Li, Z. *Org. Lett.* **2001**, *3*, 365–367. (b) Pirrung, M. C.; Li, Z.; Park, K.; Zhu, J. *J. Org. Chem.* **2002**, *67*, 7919–7926. (c) Pirrung, M. C.; Deng, L.; Li, Z.; Park, K. *J. Org. Chem.* **2002**, *67*, 8374–8378.
7. (a) Ottoni, O.; Neder, A.; deV, F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005–1007. (b) Tajima, N.; Hayashi, T.; Nakatsuka, S.-i. *Tetrahedron Lett.* **2001**, *41*, 1059–1062.
8. (a) Yadav, J. S.; Subba Reddy, B. V.; Murthy, Ch.V.S.R.; Majesh Kumar, G.; Madan, Ch. *Synthesis* **2001**, 783–787. (b) Lion, C.; Henrion, J.-C.; Jacquet, B.; Hocquaux, M.; Maignan, J.; Barre, G.; Baudry, R. *Bull. Soc. Chim. Belg.* **1997**, *106*, 835–836.
9. Itokawa, H.; Qiao, Y.; Takeya, K. *Phytochemistry* **1991**, *30*, 637–640.
10. Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M. *J. Org. Chem.* **2003**, *68*, 5627–5631.
11. Fieser, L. F.; Ardao, M. L. *J. Am. Chem. Soc.* **1956**, *78*, 774–781.
12. Spyroudis, S.; Xanthopoulou, N. *J. Org. Chem.* **2002**, *67*, 4612–4614.
13. Woodward, R. B.; Sondheimer, F.; Toup, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.
14. Fieser, L. *J. Am. Chem. Soc.* **1948**, *70*, 3165–3173.
15. Fieser, L. *J. Am. Chem. Soc.* **1926**, *48*, 2922–2937.

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Zinc oxide (ZnO) as a new, highly efficient, and reusable catalyst for acylation of alcohols, phenols and amines under solvent free conditions

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Abstract—Zinc oxide (ZnO) is a highly efficient catalyst for the acylation of a variety of alcohols, phenols and amines with acid chlorides or acid anhydrides under solvent free conditions. Primary, secondary, tertiary, allylic and benzylic alcohols, diols and phenols with electron donating or withdrawing substituents can be easily acylated in good to excellent yield.

1. Introduction

The acylation of alcohols, phenols and amines is an important transformation in organic synthesis.[1] Acylation of such functional groups is often necessary during the course of various transformation in a synthetic sequence, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products. Various catalysts developed for acylation include DMAP,[2] $CoCl_2$,[3] Bu_3P,[4] Triflates,[5–10] $TaCl_5$,[11] zeolite,[12] clays,[13] Nafion-H,[14] Yttria-zirconia,[15] $LiClO_4$,[16] $Mg(ClO_4)_2$,[17] ionic liquids,[18] $InCl_3$,[19] $ZrCl_4$,[20] $Cu(BF_4)\cdot xH_2O$,[21] $RuCl_3$,[22] P_2O_5/SiO_2,[23] $ZrOCl_2\cdot 8H_2O$,[24] and alumina.[25] However, the reported methodologies suffer from various disadvantages, such as potential hazard associated with handling of the catalyst [e.g., the LD_{50} (intravenous in rat) value of 56 mg kg^{-1} of DMAP makes it highly toxic[26] and Bu_3P is flammable with a flash point of 37 °C and undergoes aerial oxidation],[27] expensive or commercially unavailable reagents, requirement of longer reaction times, harsh reaction conditions, use of halogenated solvents and excess acylating agents. Triflates are costly and moisture sensitive, and special efforts are required to prepare the catalyst [e.g., $Bi(OTf)_3$, Nafion-H, and yttria-zirconia]. In most of the cases the reported methods work well on primary or secondary alcohols only and failed to protect tertiary alcohols or less reactive phenols. A few of these methods also suffer from side reactions such as dehydration and rearrangement and might not be fully compatible for the acylation reactions with substrates bearing acid-sensitive groups.

Synthetic chemists continue to explore new methods to carry out chemical transformations. One of these new methods is to run reactions on the surface of solids. As the surfaces have properties that are not duplicated in the solution or gas phase, entirely new chemistry may occur. Even in the absence of new chemistry, a surface reaction may be more desirable than a solution counterpart, because the reaction is more convenient to run, or a high yield of product is attained. For these reasons, synthetic surface organic chemistry is a rapidly growing field of study. Experiments using these solid phase catalysts generally have the following features: (i) it is often easy to isolate the products and to separate the catalyst; (ii) comparing the reaction conditions with those of related homogeneous reactions, they are so mild that a high yield of specific products and suppression of by-product formation are expected; (iii) selectivity and activity of the catalysts are often comparable to those of enzymes.[28] Several classes of solids have commonly been used for surface organic chemistry including aluminas, silica gels, and clays. Zinc oxide (ZnO) is certainly one of the most interesting of these solids because it has surface properties that suggest that a very rich organic chemistry may occur there.[29,30d]

Although numerous methods to achieve acylation reactions are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. In continuation of our systematic evaluation of the efficacy of metal

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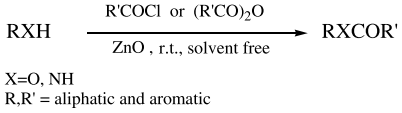
Table 1. Acetylation of phenol (1 mmol) based on ZnO and AcCl (1 mmol) in different reaction conditions

Entry	Equiv of ZnO	Solvent	Time	Yield (%)
1	0.5	CH_3CN	6 h	30
2	0.5	$PhCH_3$	10 h	10
3	0.5	CH_2Cl_2	5 h	30
4	0.5	No solvent	15 min	94
5	1	No solvent	20 min	87
6	0.1	No solvent	40 min	83
7	No catalyst	No solvent	10 h	Trace

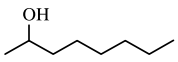
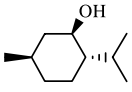
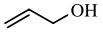
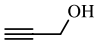
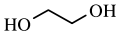
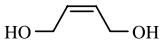
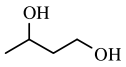
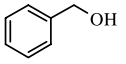
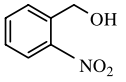
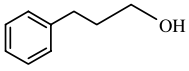
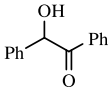
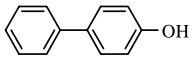
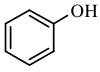
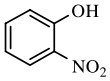
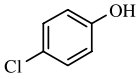
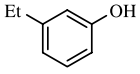
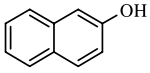
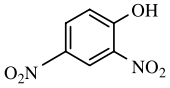
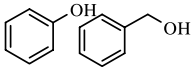
oxysalts as catalysts,[30] we report, herein, our results on acylation of alcohols, phenols, aliphatic and aromatic amines using ZnO at room temperature under solvent free conditions (Scheme 1, Tables 2 and 3). To the best of our knowledge, this is the first demonstration of the ZnO based acylation.



Scheme 1.

The reaction conditions were standardized after conducting the acylation of phenol in different reaction conditions using varying amounts of ZnO (Table 1). Thus, under optimum conditions, phenol (1 equiv) was acetylated at room temperature almost quantitatively with acetyl chloride (1 equiv) in the presence of 0.5 equiv ZnO without use of any solvents (Table 1, entry 4). Attempted acetylation of phenol with acetic anhydride in the presence of ZnO failed.

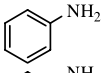
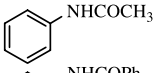
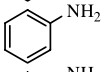
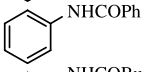
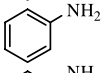
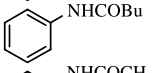
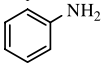
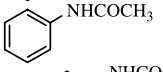
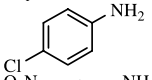
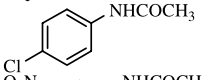
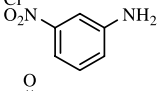
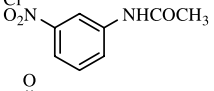
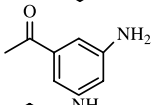
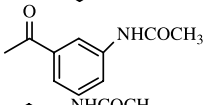
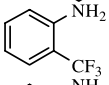
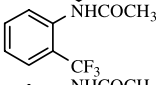
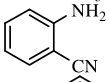
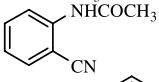
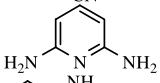
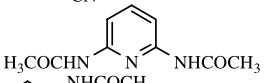
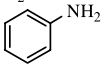
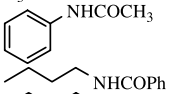
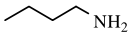
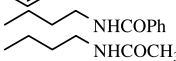
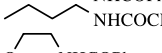
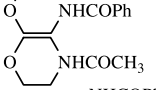
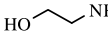
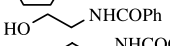
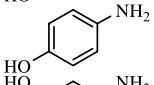
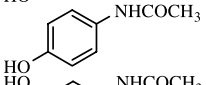
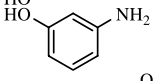
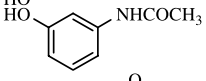
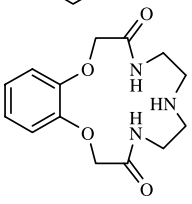
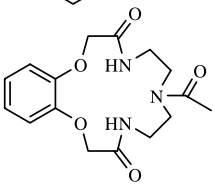
Table 2. ZnO (0.5 mmol) catalyzed acylation of alcohols and phenols (1 mmol) using acid chlorides (1 mmol)

Entry	Substrate	Acylation reagent[a]	Time (min)	Yield (%)[b]
1	CH_3CH_2OH	PhCOCl	15	91
		CH_3COCl	10	95
		Ac_2O	180	—
		$(PhCO)_2O$	180	—
2	$CH_3(CH_2)_5CH_2OH$	PhCOCl	15	87
		CH_3COCl	10	90
3	$CH_3(CH_2)_2CH_2OH$	PhCOCl	15	84
		CH_3COCl	10	86
4	$CH_3(CH_2)_6CH_2OH$	PhCOCl	15	86
		CH_3COCl	10	78
5		PhCOCl	240	78
		CH_3COCl	30	80
6		PhCOCl	240	81
		CH_3COCl	30	70
7		PhCOCl	60	84
		CH_3COCl	20	86
8		PhCOCl	15	73
		CH_3COCl	8	70
9		PhCOCl	20	53
		CH_3COCl	8	58
10		PhCOCl	15	85[c]
		CH_3COCl	8	91[c]
11		PhCOCl	15	78[c]
		CH_3COCl	8	80[c]
12		PhCOCl	300	83[c]
		CH_3COCl	20	87[c]
13		PhCOCl	15	92
		CH_3COCl	10	90
14		PhCOCl	20	89
		CH_3COCl	10	92
15		PhCOCl	15	85
		CH_3COCl	10	90
16		PhCOCl	30	91[d]
		CH_3COCl	20	82[d]
17		PhCOCl	90	67[e]
		CH_3COCl	30	65[e]
18		PhCOCl	30	82[d]
		CH_3COCl	15	85[d]
19		PhCOCl	30	95
		CH_3COCl	15	94
20		PhCOCl	40	94
		CH_3COCl	20	90
21		PhCOCl	20	93
		CH_3COCl	15	90
22		PhCOCl	20	85
		CH_3COCl	15	92
23		PhCOCl	30	91
		CH_3COCl	20	90
24		PhCOCl	40	82[f]
		CH_3COCl	20	87[f]
25		PhCOCl	30	92[g]
26	CH_3CH_2OH	PhCOCl	30	90[h]

[a] Acylation reagent (1 equiv) for every OH function was used.
[b] Isolated yields.
[c] The corresponding dibenzoate and diacetate was prepared.
[d] The reaction was carried out in CH_2Cl_2.
[e] The reaction was carried out at <0 °C.
[f] The reaction was carried out at 90 °C.
[g] Only the aliphatic alcohol was benzoylated with the use of 1 equiv of acylating agent.
[h] The reaction was carried out on 100 mmol scale.

The results of the reactions of a diverse range of alcohols and phenols are summarized in Table 2. An acid chloride was preferred over the corresponding acid anhydride. The reaction with acid anhydride was too slow to have practical application. Both primary and secondary alcohols react very

Table 3. ZnO (0.5 mmol) catalyzed acylation of amines (1 mmol) using acid anhydrides (1 mmol)

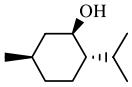
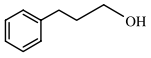
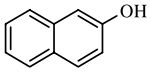
Entry	Substrate	Acylation reagent[a]	Products	Time (min)	Yield (%)[b]
1		$(CH_3CO)_2O$		10	96
2		$(PhCO)_2O$		10	92
3		$(BuCO)_2O$		15	94
4		CH_3COCl		15	94
5		$(CH_3CO)_2O$		15	95
6		$(CH_3CO)_2O$		20	95
7		$(CH_3CO)_2O$		15	95
8		$(CH_3CO)_2O$		20	87
9		$(CH_3CO)_2O$		20	82
10		$(CH_3CO)_2O$		40	58
11		$(CH_3CO)_2O$		40	96[c]
12		$(PhCO)_2O$ $(CH_3CO)_2O$	 	20 10	93 95
13		$(PhCO)_2O$ $(CH_3CO)_2O$	 	20 10	67 84
14		$(PhCO)_2O$		40	64
15		$(CH_3CO)_2O$		10	90
16		$(CH_3CO)_2O$		10	87
17		$(CH_3CO)_2O$		20	83

[a] Acylation agent (1 equiv) for every NH_2 function was used.
[b] Isolated yields.
[c] The reaction was carried out on 100 mmol scale.

well (entries 1–16) and tertiary alcohol (entry 17) is also acylated smoothly without any side products observed. The conversion of ethanol into ethyl benzoate on a 100 mmol scale (entry 26) proceeded just as well as the 1 mmol reaction. Acylation of optically active substrate resulted in excellent yield (entry 7). Allyl and propargyl alcohols were also satisfactorily acylated under similar reaction conditions and no rearrangement was observed (entries 8 and 9). To extend the scope and generality of the use of the ZnO for this type process we have also investigated the acylation of diols. No selectivity between primary and secondary hydroxyl groups was observed.

Phenolic compounds containing both electron-withdrawing and donating groups (entries 18–24) reacted equally efficiently under the standard reaction conditions. Acylation of 2,4-dinitrophenol at room temperature was, however, sluggish; it could be completely acylated in an oil bath at 90 °C (entry 24). According to Table 2, the reaction of phenols with acid chlorides was slow in comparison to those aliphatic alcohols. Indeed, a mixture of benzyl alcohol and phenol furnished only the expected benzyl benzoate on reaction with 1 equiv of PhCOCl (entry 25). Finally, the reaction of benzoin and 4-hydroxybiphenyl (entries 16 and 18) were very slow under similar conditions. Even after

Table 4. Comparison of protocols for the acylation of alcohols and phenols

Entry	Substrate	Reagent/catalyst	Acylating agent	Time	Temperature (°C)	Yield (%)	References
1		ZnO	PhCOCl	60 min	25	84	[a]
		Al_2O_3	PhCOCl	120 min	25	96	25
		$Bi(OTf)_3$	$(PhCO)_2O$	60 min	Reflux	95	9e
		$ZrOCl_2 \cdot 8H_2O$	CH_3COCl	1.5 day	25	93	24
2		ZnO	PhCOCl	15 min	25	85	[a]
		Al_2O_3	PhCOCl	90 min	25	99	25
3		ZnO	PhCOCl	90 min	25	67	[a]
		Al_2O_3	PhCOCl	No reaction			25
		$Bi(OTf)_3$	$(PhCO)_2O$	80 min	Reflux	45	9e
		$ZrOCl_2 \cdot 8H_2O$	PhCOCl	No report			24
4		ZnO	PhCOCl	30 min	25	91	[a]
		Al_2O_3	PhCOCl	No reaction			25
		$Bi(OTf)_3$	$(PhCO)_2O$	45 min	Reflux	95	9e
		$ZrOCl_2 \cdot 8H_2O$	PhCOCl	21 h	25	98	24

[a] Present work.

vigorous stirring for 4 h at 25 °C, the reactions were incomplete. However, acylation was achived in 91 and 82% yields with benzoin and 4-hydroxybiphenyl, respectively, at 25 °C for 30 min in the presence of dichloromethane (CH_2Cl_2).

The experimental results of the acylation of amines are summarized in Table 3. It is significant to note that acid anhydrides were preferred to the acid chlorides. All the amines reacted very rapidly within 10–40 min The conversion of aniline into acetanilide on a 100 mmol scale (entry 11) proceeded just as well as the 1 mmol reaction. Other functional groups such as keto and cyano remained unaffected during the acylation reaction (entries 7 and 9).

The reactions of amines with Ac_2O were so fast in comparison to those of the aliphatic alcohols that the selective protection of an amine in the presence of aliphatic alcohols appeared to be a distinct possibility (entry 14). Also, the amino group in aminophenol was selectivity acylated (entries 15 and 16). It is noteworthy that, entry 17 can survive in the present method indicating mildness of reaction conditions.

A comparison of the catalytic efficiency of ZnO with selected previously known catalysts is collected in Table 4 to demonstrate that the present protocol is indeed superior to several of the other protocols. Menthol is completely benzoylated in less than 60 min at 25 °C in 84% isolated yield using the present protocol. Most of the other protocols listed take either longer time for completion or use high temperature. Benzoylation of *t*-butanol with 1 equiv of PhCOCl afforded 67% yields in 270 min under solvent free conditions in the presence of ZnO but Al_2O_3 and $ZrOCl_2.\cdot 8H_2O$ did not catalyze the same reaction. The ZnO catalyzed benzoylation of 2-naphthol with stoichiometric amount of PhCOCl afforded 94% yield at room temperature for 30 min while the 2-naphthol and other phenols did not react at all in the presence of Al_2O_3. The use of $ZrOCl_2 \cdot 8H_2O$ is equally effective, however, it requires long times to completion. This is in contrast to the use of ZnO that was very effective for acylation of phenols.

Another interesting behaviour of zinc oxide (ZnO) lies in the fact that it can be re-used after simple washing with CH_2Cl_2, rendering thus process more economic. The yields of acetanilide (a model compound for amines) and phenyl benzoate (a model compound for phenols) in the 2nd, 3rd, 4th and 5th uses of the ZnO were almost as high as in the first use.

In conclusion, we have presented a simple, solvent free, and efficient protocol for the acylation of alcohols, phenols, and amines. Furthermore, an alcohol can be acylated in the presence of phenols with very high selectivity. No competitive Fries rearrangement was observed for phenolic substrates. Secondary and tertiary alcohols did not experience any competitive dehydration. Also, the advantages include the low cost of the catalyst, operation at room temperature, large scale treatment, high yields, and excellent chemoselectivity.

2. Experimental

2.1. General procedure

To a mixture of ZnO (dry powder, 0.04 g, 0.5 mmol) and an acid chloride or anhydride (1 mmol), alcohol, phenol or amine (1 mmol) was added. The reaction mixture was stirred with a mechanical stirrer for a certain period of time (Tables 2 and 3) as required to complete the reaction (monitored by TLC) at room temperature. The solid mass (ZnO) was then eluted with CH_2Cl_2 (20 mL), and the CH_2Cl_2 extract was then washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of solvent furnished, practically pure, the corresponding product. The identity of these compounds was easily established by comparison of their ^1H NMR spectra with those of authentic samples.[31]

2.1.1. 7-Acetyl-5,6,7,8,9,10-hexahydro-2*H*,1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (entry 17, Table 3). To a mixture of ZnO (dry powder, 0.04 g, 0.5 mmol) and an acetic anhydride (1 mmol, 0.094 mL), 5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (1 mmol

0.29 g) was added. The reaction mixture was stirred with a mechanical stirrer for 20 min as required to complete the reaction (monitored by TLC) at room temperature. The solid mass (ZnO) was then eluted with CH_2Cl_2 (20 mL), and the CH_2Cl_2 extract was then washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of solvent furnished practically pure the corresponding product. This was further purified by recrystallization with suitable solvent (ether or $CHCl_3$) gave the title compound as a white solid, mp 218–220 °C. [Found: C 57.21; H, 6.22. $C_{16}H_{21}N_3O_5$ requires C, 57.30; H, 6.31%]; δ_H (250 MHz, $CDCl_3$) 7.85 (2H, s, –N*H*), 7.00–7.08 (4H, m, Ph), 4.50 (4H, s, CH_2CO), 3.53 (8H, s, NHCH_2-CH_2N), 3.00 (3H, s, *Me*CO); δ_C (62.9 MHz, $CDCl_3$) 16.2, 41.1, 45.7, 77.6, 112.1, 120.8, 147.9, 165.8, 169.3; *m*/*z* 335 (100 MH^+).

Acknowledgements

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References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999.
2. Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
3. (a) Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *2001*, 57. (b) Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* **1986**, *27*, 3791.
4. Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358.
5. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.
6. Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265.
7. Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342.
8. Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743.
9. (a) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926. (b) Carrigan, M. D.; Freiberg, D. A.; Smith, R. C.; Zerth, H. M.; Mohan, R. S. *Synthesis* **2001**, 2091. (c) Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851. (d) Chakraborti, A. K.; Shivani, R. G. *Synlett* **2003**, 1805. (e) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartol, G.; Romeo, R. *Tetrahedron Lett.* **2003**, *59*, 5621. (f) Karimi, B.; Maleki, J. *J. Org. Chem.* **2003**, *68*, 4951.
10. Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369.
11. Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263.
12. Ballini, R.; Bosica, G.; Carloni, S.; Ciaralli, L.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1998**, *39*, 6049.
13. Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215.
14. Kumareswaran, R.; Pachamuthu, K.; Vankar, Y. D. *Synlett* **2000**, 1652.
15. Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dongare, M. K. *Synlett* **2001**, 206.
16. Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* **2001**, 1584.
17. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synlett* **2003**, 39.
18. Lee, S. G.; Park, J. H. *J. Mol. Catal. A: Chem.* **2003**, *194*, 49.
19. Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 3521.
20. Chakraborti, A. K.; Gulhan, R. *Synlett* **2004**, 627.
21. Chakraborti, A. K.; Shivani, R. G. *Synthesis* **2004**, 111.
22. Kanta De, S. *Tetrahedron Lett.* **2004**, *45*, 2919.
23. Eshghi, H.; Shafieyoon, P. *J. Chem. Res. (S)* **2004**, 802.
24. Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* **2005**, *46*, 147.
25. Yadav, V. K.; Babu, K. G. *J. Org. Chem.* **2004**, *69*, 577.
26. Sweet, D. V. In *Registry of Toxic Effects of Chemical Substances*, *Vol. 1985–1986*; U.S. Government Printing Office: Washington, DC, 1988; p 3336.
27. Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093.
28. Pagni, R. M.; Kabalka, G. W.; Boothe, R.; Gaetano, K.; Stewart, L. J.; Conaway, R.; Dial, C.; Gray, D.; Larson, S.; Luidhart, T. *J. Org. Chem.* **1998**, *53*, 4477.
29. Kim, Y. J.; Varma, R. S. *Tetrahedron Lett.* **2004**, 7205.
30. (a) Hosseini Sarvari, M.; Shargh, H. *J. Org. Chem.* **2004**, *69*, 6953. (b) Hosseini Sarvari, M. *Synthesis* **2005**, 787. (c) Sharghi, H.; Hosseini Sarvari, M. *J. Chem. Res. (S)* **2003**, *3*, 176. (d) Sharghi, H.; Hosseini Sarvari, M. *Synthesis* **2002**, 1057. (e) Sharghi, H.; Hosseini Sarvari, M. *Tetrahedron* **2002**, *58*, 10323.
31. CRC, *Handbook of Tables for Organic Compound Identification*, 3rd and 54th ed.

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A new (*R*)-hydroxynitrile lyase from *Prunus mume*: asymmetric synthesis of cyanohydrins

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Abstract—A new hydroxynitrile lyase (HNL) was isolated from the seed of Japanese apricot (*Prunus mume*). The enzyme has similar properties with HNL isolated from other *Prunus* species and is FAD containing enzyme. It accepts a large number of unnatural substrates (benzaldehyde and its variant) for the addition of HCN to produce the corresponding cyanohydrins in excellent optical and chemical yields. A new HPLC based enantioselective assay technique was developed for the enzyme, which promotes the addition of KCN to benzaldehyde in a buffered solution (pH=4.5).

1. Introduction

Hydroxynitrile lyases (HNLs) are widely distributed in nature and believed mainly to be a plant enzyme. There are four classes of HNL reported in the literature till now,[1] among them mandelonitrile lyase (EC 4.1.2.10) has been extensively studied in the area of enzymology and organic synthesis. Hydroxynitrile lyases (HNLs) are one of the key enzymes in cyanogenic plants,[2] catalyzing the final step in the biodegradation pathway of cyanogenic glycosides releasing HCN and the corresponding carbonyl components. HCN released by HNL can serve as a repellent factor to predators or as susceptibility component of plants to fungal attack when produced at high local concentrations.[3] Mandelonitrile lyase, one of the most well studied HNLs, are mainly found in Rosaceae species (Genus: *Prunus*), catalyzes the formation of benzaldehyde and HCN from (*R*)-mandelonitrile.[4] Whereas formation of the cyanohydrin from aldehyde and HCN should also be catalyzed by the same enzyme. Pioneering work by Effenberger, Griengl and others opened a new era in the area of asymmetric cyanohydrin synthesis by HNLs.[5] For example, crude meals from the kernels of almond, apple, cherry, apricots, and plums serve as source of HNLs. To detect new HNLs, it has proved not sufficient simply to screen for the presence of carbonyl compounds or HCN, since the breakdown of cyanohydrins may be catalyzed by enzymes other than HNLs: instead, the catalysis of cyanohydrin formation is a more reliable indicator of the presence of a HNL.[6]

Optically active cyanohydrins are excellent building blocks for the total synthesis of several biologically active natural products.[7] Both the alcohol and the nitrile parts of the cyanohydrin functionality can undergo transformation to a range of groups.[8] There are general methods that proceed without racemization, so that the optical purity is retained. In our previous communication we had reported a few cyanogenic plant species capable of showing mandelonitrile lyase activity[9] from a rich biodiversity of plant kingdom available in Japan. Japanese flowering apricot may be the longest lived of the flowering fruit trees eventually forming a picturesque 20-ft tall tree. It produces Ume fruit round in shape and 1–3 inches in diameter. The ripened fruit is yellowish red in color and have a fleshy covering. In this article, we would like to report our research on a new HNL from the seed of Japanese apricot.

2. Results and discussion

2.1. Enzyme assay

The enzyme was isolated from the seeds of ripened Ume fruit. Crude preparation of enzyme serves the purpose of our study, but we have partially purified the enzyme by 30% $(NH_4)_2SO_4$ precipitation to obtain a homogeneous solution

Keywords: Hydroxynitrile-lyase; *Prunus mume*; Cyanohydrins; Asymmetric synthesis.
Abbreviations: HNL, hydroxynitrile lyase; PmHNL, *Prunus mume* hydroxynitrile lyase; PaHNL, *Prunus amygdalus* hydroxynitrile lyase; DIPE, diisopropyl ether; TBME, *tert*-butyl methyl ether; DBE, di-*n*-butyl ether; DME, 1,2-dimethoxyethane.
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Table 1. Monosubstituted benzaldehydes screened with crude PmHNL

Substrate	Conversion (%)[a]	ee (%)[b]	Configuration[c]
Benzaldehyde	13	93	*R*
2-Chlorobenzaldehyde	37	56	*R*
3-Chlorobenzaldehyde	38	92	*R*
4-Chlorobenzaldehyde	21	99	*R*
4-Bromobenzaldehyde	22	99	*R*
4-Fluorobenzaldehyde	28	84	*R*
2-Methylbenzaldehyde	6.0	61	*R*
3-Methylbenzaldehyde	7.5	87	*R*
4-Methylbenzaldehyde	7.0	95	*R*
2-Methoxybenzaldehyde	6.0	41	*R*
3-Methoxybenzaldehyde	31	92	*R*
4-Methoxybenzaldehyde	17	97	*R*
2-Trifluoromethylbenzaldehyde	72	5	*R*
3-Trifluoromethylbenzaldehyde	91	68	*R*
4-Trifluoromethylbenzaldehyde	90	76	*R*
3-Nitrobenzaldehyde	87	65	*R*
4-Nitrobenzaldehyde	89	71	*R*
4-Benzyloxybenzaldehyde	5.8	98	*R*
4-*N*,*N*-Dimethylaminobenzaldehyde	nd	0	
4-Hydroxybenzaldehyde	nd	5	*R*
3-Phenoxybenzaldehyde	42	>99	*R*
4-Allyloxybenzaldehyde	6.4	98	*R*
4-*tert*-Butyldimethylsilyloxybenzaldehyde	4.8	97	*R*

[a] Conversion (%) was calculated after 30 min of reaction time.[15]
[b] Determined by chiral HPLC.
[c] Confirmed by comparing the retention time with that of optically active standard compounds.

of enzyme. Previously reported HNL assay method[10] mainly involved the decomposition of mandelonitrile in a buffered solution and the formation of benzaldehyde was measured spectrophotometrically. We have developed a new HPLC based assay technique, in which the formation of (*R*)-mandelonitrile from benzaldehyde in citrate buffer (pH=4.5) was monitored by chiral HPLC. At different time intervals aliquots were withdrawn and analyzed by chiral HPLC. It was assumed that at low pH, corresponding chemical reaction was suppressed, so the overall mandelonitrile production only comes from HNL catalyzed addition. However, to obtain accurate results, a blank reaction was performed side by side without enzyme, and the amount of mandelonitrile obtained was deducted from the biocatalyzed reaction product. The HPLC based HNL assay technique has several advantages over the other traditional assay technique. Sensitivity and reproducibility are very high in the HPLC based assay method. Using different dilution of enzyme and varying substrate concentration yields almost similar results in all case. Moreover, cyanohydrins itself are well separated in a chiral column, hence avoiding further derivatization method. Finally, configurational assignment of the product cyanohydrins is also possible with comparing standard compounds (synthesized by chemical methods).

2.2. Reaction condition for substrate screening

Next, our focus is to test a large number of different aldehydes and ketones for possible substrate of PmHNL (*Prunus mume* hydroxynitrile lyase). Generally similar reaction condition as the PmHNL assay was employed for the substrate screening methods. In a typical screening methods substrates were taken in aq buffer (pH 4.5) followed by addition of KCN (1.25 equiv) and enzyme solution (see Section 4 for detailed description). After certain time (see Tables 1–6), reaction mixtures were taken and the formation of products were analyzed with chiral HPLC/GC. The main intention of the study was to test a large number of substrates and find the substrates, which provide better enantioselection. We have attempted an enzymatic transcyanation with acetone cyanohydrin as the cyanide source, but the slow reaction (decomposition of acetone cyanohydrin is slow at lower pH e.g., 4–4.5) rate

Table 2. Heteroaromatic and polycyclic aldehydes screened with crude PmHNL

Substrate	Conversion (%)[a]	ee (%)[b]	Configuration[c]
2-Furancarboxaldehyde	1.2	98	*S*
2-Thiophenecarboxaldehyde	31	88	*S*
2-Pyridinecarboxaldehyde	89	22	*S*
3-Pyridinecarboxaldehyde	90	75	*R*
4-Pyridinecarboxaldehyde	65	41	*R*
2-Quinolinecarboxaldehyde	38	21	*S*
4-Quinolinecarboxaldehyde	73	28	*R*
1-Napthalenecarboxaldehyde	60	93	*R*
2-Napthalenecarboxaldehyde	58	98	*R*
9-Anthral	16	0	

[a] Conversion (%) was calculated after 30 min of reaction time.[15]
[b] Determined by chiral HPLC.
[c] Confirmed by comparing the retention time with that of optically active standard compounds.

Table 3. Disubstituted benzaldehydes screened with crude PmHNL

Substrate	Conversion (%)[a]	ee (%)[b]	Configuration[c]
2,3-Dichlorobenzaldehyde	11	22	*R*
2,4-Dichlorobenzaldehyde	13	78	*R*
2,5-Dichlorobenzaldehyde	8.8	57	*R*
2,6-Dichlorobenzaldehyde	10	12	*R*
3,4-Dichlorobenzaldehyde	7.9	94	*R*
3,5-Dichlorobenzaldehyde	21	92	*R*
2,3-Dimethoxybenzaldehyde	7.0	37	*R*
2,4-Dimethoxybenzaldehyde	11	48	*R*
2,5-Dimethoxybenzaldehyde	9.0	63	*R*
2,6-Dimethoxybenzaldehyde	6.5	32	*R*
3,4-Dimethoxybenzaldehyde	13	78	*R*
3,5-Dimethoxybenzaldehyde	17	97	*R*
Piperonal	34	98	*R*
2,4-Dimethylbenzaldehyde	5.8	86	*R*

[a] Conversion (%) was calculated after 30 min of reaction time.[15]
[b] Determined by chiral HPLC.
[c] Confirmed by comparing the retention time with that of optically active standard compounds.

Table 4. Polysubstituted benzaldehydes screened with crude PmHNL

Substrate	Conversion (%)[a]	ee (%)[b]	Configuration[c]
2,3,4-Trimethoxybenzaldehyde	14	11	*R*
2,4,5-Trimethoxybenzaldehyde	16	28	*R*
3,4,5-Trimethoxybenzaldehyde	24	31	*R*
2,3,4,5-Tetrafluorobenzaldehyde	26	23	*R*
2,3,5,6-Tetrafluorobenzaldehyde	21	12	*R*
2,3,4,5,6-Pentafluorobenzaldehyde	31	0	
2,3,4,5,6-Pentabromobenzaldehyde	18	0	

[a] Conversion (%) was calculated after 1 h of reaction time.[15]
[b] Determined by chiral HPLC.
[c] Confirmed by comparing the retention time with that of optically active standard compounds.

Table 5. Aliphatic methylketones screened with crude PmHNL

Substrate	Conversion (%)[a]	ee (%)[b]	Configuration[c]
2-Butanone[d]	48	72	*R*
2-Pentanone	46	81	*R*
3-Methyl-2-butanone	39	42	*R*
2-Hexanone[d]	48	80	*R*
4-Methyl-2-pentanone[d]	40	88	*R*
3,3-Dimethyl-2-butanone	28	38	*R*
2-Heptanone	39	74	*R*
5-Methyl-2-hexanone	30	76	*R*
2-Octanone	22	67	*R*
2-Nonanone	20	65	*R*
2-Decanone	18	52	*R*
2-Undecanone	21	31	*R*
2-Dodecanone	14	0	
Cyclopropylmethylketone	58	0	
Trimethylsilylmethylketone	62	72	*R*

[a] Conversion (%) was calculated after 3 h by analyzing ^{1}H NMR of the crude reaction mixture.
[b] Determined by chiral GC (β-Dex120).
[c] Confirmed by comparing the retention time with that of optically active standard compounds.
[d] These cyanohydrins are not resolved in chiral GC column, hence ee was determined by preparing the corresponding TMS–ether derivative.

Table 6. Aliphatic aldehydes screened with crude PmHNL

Substrate	Conversion (%)[a]	ee (%)[b]	Configuration[c]
Propanal	48	78	*R*
Butanal[d]	51	84	*R*
Isobutyraldehyde	43	88	*R*
Pivaladehyde	29	92	*R*
Pentanal[d]	36	85	*R*
Hexanal[d]	38	81	*R*
Cyclopentanecarboxaldehyde	51	91	*R*
Cyclohexanecarboxaldehyde	54	94	*R*

[a] Conversion (%) was calculated after 3 h by analyzing ^{1}H NMR of the crude reaction mixture.
[b] Determined by chiral GC (β-Dex325).
[c] Confirmed by comparing the retention time with that of optically active standard compounds.
[d] These cyanohydrins are not resolved in chiral GC column, hence ee was determined by preparing the corresponding TMS–ether derivative.

makes the process not applicable for screening purpose, whereas the use of HCN was avoided due to difficulties in handling. The pH profile of the reaction was investigated and it was found that the enzyme is active mainly at lower pH. Increasing the pH (pH of the final reaction mixture) higher than 5.5 led to yielding products of low optical purity due to the corresponding chemical reaction. At pH 6.5 activities was totally lost, and the product was completely racemic (Fig. 1).

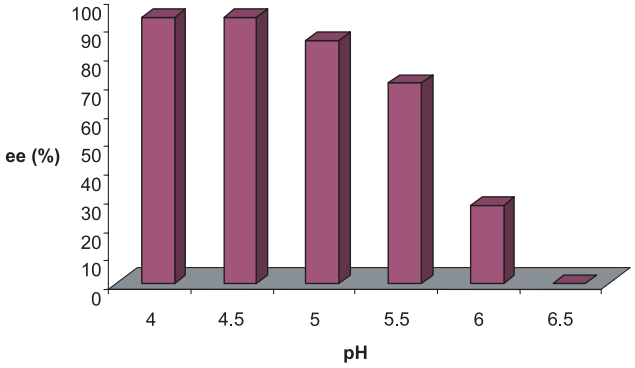

Figure 1. pH effect on ee of PmHNL catalyzed (*R*)-mandelonitrile formation.

The enzyme works nicely in a wide temperature range varying from −10 to 40 °C. The best temperature for the enzymic reaction was found to be 15–25 °C, using benzaldehyde as a substrate. Above 40 °C, the enzymic activity decreased significantly and it produces racemic cyanohydrin (Fig. 2).

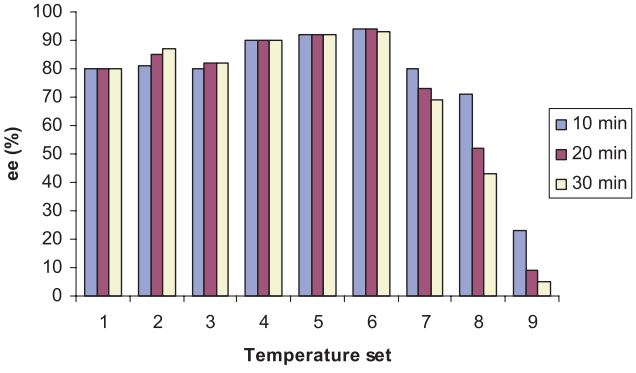

Figure 2. Temperature dependence of ee for (*R*)-mandelonitrile synthesis by PmHNL three sets of data were measured after 10, 20, and 30 min reaction time. Temperature of the reaction was −10 °C (1), 0 °C (2), 5 °C (3), 10–12 °C (4), 18–20 °C (5), 25 °C, (6), 40 °C (7), 50 °C (8), 70 °C (9).

Next, we have screened different organic solvents for the PmHNL activity. It has been reported by several researchers that, defatted powdered HNL meal (almond, apple, cherry) are active in polar but aprotic organic solvents and produces cyanohydrin with high enantioselectivity.[11] Whereas immobilization of HNLs on some support also allowed its use in organic solvent.[12] We have tested PmHNL's activity in several organic solvents by taking the partially purified homogeneous enzyme solution. A biphasic reaction condition (organic solvent/buffer, 10:1) allows us to detect the product by HPLC. The best solvent was diisopropylether (DIPE), *tert*-butylmethylether (TBME) and di-*n*-butylether (DBE). With all the three solvents more than 95% enantioselectivity was observed. However, the rate of the reaction was very slow and it takes 24–36 h to obtain appreciable amount of conversion. HCN in organic solvent and acetonecyanohydrin was used as the cyanating agent (Fig. 3).

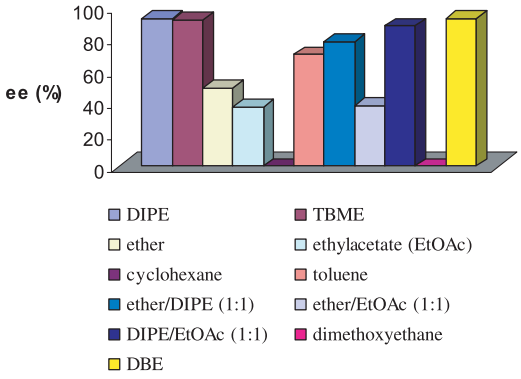

Figure 3. Solvent effect on ee of PmHNL catalyzed (*R*)-mandelonitrile synthesis.

2.3. Substrate specificity

A large number of substrates including aliphatic, aromatic, and heteroaromatic aldehydes as well as aliphatic ketones were tested for PmHNL activity.

2.3.1. Aromatic aldehydes. Aromatic aldehydes (mono, di, and polysubstituted), heteroaromatic aldehydes as well as polycyclic aromatic aldehydes were employed as PmHNL substrates. The results were summarized in Tables 1–5.

It was observed that substrates having *ortho* substituent (irrespective of its electronic nature) are poor substrates in terms of enantioselectivity of the resulting cyanohydrins. We have taken a series of substituted chlorobenzaldehydes and compared their enantioselectivity with PmHNL (Fig. 4).

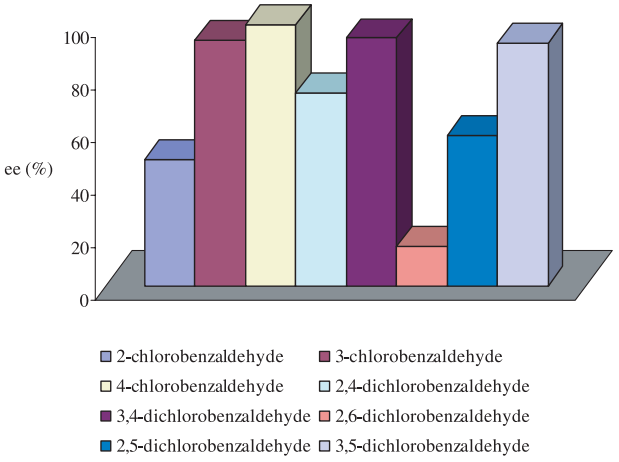

Figure 4. ee comparison of chlorosubstituted benzaldehydes (showing an *ortho* effect).

2.3.2. Aliphatic ketones. Mainly methyl ketones were tested for PmHNL activity. In a typical reaction ketones were taken in citrate buffer (pH 4.0, reaction pH 4.5),

followed by addition of enzyme and aq KCN solution. Generally it takes 3 h for appreciable amount of conversion (detected by TLC). Longer reaction time allows complete conversion but also leads to product having poor optical purity due to the corresponding chemical cyanation. The chemical yield of the obtained cyanohydrins was determined from ^{1}H NMR of crude samples. By comparing the integral values of Me-signals (singlet, at δ 2.2 ppm in the ketone and δ 1.5–1.6 ppm in the cyanohydrin) the relative ratios hence the chemical yield was determined.

The optical purity of the ketone cyanohydrins were measured efficiently by chiral GC (β-cyclodextrin stationary phase). Only three of the synthesized cyanhohydrins need to be derivatized (ethylmethylketone, *n*-butylmethylketone and isobutylmethylketone, as their TMS ether) in order to determine the ee. Remaining all cyanohydrins is well separated by β-cyclodextrin stationary phase, hence eliminating the derivatization protocol as often used by many researchers. The optical purity of the synthesized cyanohydrins is lower when compared with similar HNL from almonds. Methyl ketones having no branching at α-position are good substrates, for example, ethyl, *n*-propyl, *n*-butyl, and *n*-amyl methyl ketones provide cyanohydrin with 72–88% ee. Whereas substrates having branching at α-position give poor ee, for example, *i*-propyl and *t*-butyl methylketone yields cyanohydrin with 42 and 38% ee only. Increasing the chain length has a mild but definite effect on optical purity of the synthesized cyanohydrins. Undecanone (having C9 unit at one end) is the limiting substrate in the series accepted by PmHNL, although ee is low (31%, Table 5), where as dodecanone yields racemic cyanohydrin.

2.3.3. Aliphatic aldehydes. Aliphatic aldehydes were screened for PmHNL activity by similar methods as described earlier for corresponding methyl ketones. Reaction was monitored by TLC and chemical yield was determined with the help of ^{1}H NMR. It seems that aliphatic aldehydes are better substrates than their methyl ketone counterparts. Their reactivities are high probably due to the high reactivity of aldehyde functionality than those of the ketones. It is important to mention that all the aliphatic aldehydes tested so far, provides excellent enantioselection. Thus, it is quite evident that aliphatic aldehydes are better substrates for PmHNL than the corresponding methyl ketones. From the previous discussion we have also noticed, with the branching at α-position in the methyl ketone leads with poor enantioselection (*t*-butylmethyl ketone and isopropylmethyl ketone), whereas the corresponding aldehyde partners, for example, pivaladehyde and isobutyraldehyde both are excellent substrates for PmHNL (Table 6). Thus, presence of methyl moiety in the methyl ketones must play a decisive role for poor enantioselectivity. The optical purity of the product cyanohydrins was determined directly by chiral GC cyclodextrin columns and in some cases cyanohydrins were derivatized to the corresponding trimethylsilylether (OTMS).

2.3.4. Preparative scale asymmetric synthesis of cyanohydrins by PmHNL. Owing to their broad synthetic potential, cyanohydrins have attracted attention as starting materials for the preparation of several important classes of compounds, and it is probable that the use of enantiomerically pure cyanohydrins as building blocks for the production of chiral industrial chemicals will continue to grow. The pioneering work of Becker and Pfeil demonstrated for the first time that the HNL isolated from almond can be employed successfully for the production of (*R*)-cyanohydrins from aldehyde and HCN on a kilogram scale. One should consider four major points in a large scale HNL catalyzed synthesis of cyanohydrins, for example, reaction media, cyanating source, physical state of enzyme

Table 7a. Preparative scale cyanohydrin a synthesis by PmHNL with selected aromatic aldehydes

Substrate[a]	Yield (%)	Time (h)[b]	ee (%)[c]
Benzaldehyde	65	24	95
para-Tolualdehyde	68	42	96
para-Anisaldehyde	78	20	98
4-Fluorobenzaldehyde	60	16	86
4-Chlorobenzaldehyde	78	16	99
4-Bromobenzaldehyde	82	26	99
4-Nitrobenzaldehyde	93	6	71
3-Nitrobenzaldehyde	96	9	64
4-Trifluoromethylbenzaldehyde	88	8	72
2-Furan carboxaldehyde	65	78	96
2-Thiophene carboxaldehyde	82	24	88
3-Pyridine carboxaldehyde	80	12	65
2-Quinlonine carboxaldehyde	78	14	14
4-Quinlonine carboxaldehyde	82	15	21
Piperonal	88	30	97
3-Phenoxybenzaldehyde	68	36	98
3,4-Dichlorobenzaldehyde	52	52	94
3,5-Dichlorobenzaldehyde	58	60	95
3,4-Dimethoxybenzaldehyde	65	48	92
3,5-Dimethoxybenzaldehyde	48	50	93
4-Benzyloxybenzaldehyde	60	72	98
Napthalene-1-carboxaldehyde	70	32	90
Napthalene-2-carboxaldehyde	78	40	96

[a] All reactions were performed with 5 g of substrate, 1.5 equiv of acetonecyanohydrin in biphasic reaction media (total reaction volume is 50 mL, DIPE/aq buffer, 10:1).
[b] The reaction was monitored by TLC.
[c] ee's were determined by chiral HPLC analysis at 254 nm (by applying same condition as described earlier).

and external conditions (temperature and pH). We generally apply a vigorously stirred biphasic (citrate buffer, pH 4.0, and organic solvent) reaction media using transcyanation reaction with acetonecyanohydrin and PmHNL as the biocatalyst. We generally employed DIPE, TBME, and DBE as the organic media for transcyanation reaction. By applying the above reaction condition we are able to synthesize a large number of cyanohydrins with excellent enantioselection from several aromatic aldehydes (Table 7a). It was observed that substrates, which showed poor enantioselectivity in aq media, (e.g., 3-NO_2, 4-NO_2, 3-pyr, 4-CF_3, 2 and 4 quinolinecarboxaldehyde) do not markedly change their activity with change in the reaction media (Table 7a). Moderate to low enantioselectivity was observed in the synthesized cyanohydrins from those highly reactive aldehydes. As all those aldehydes are highly activated due to their structural feature, chemical yield of the corresponding cyanohydrins is very high. The possible reason for the low enantioselectivity can be attributed due to the corresponding chemical cyanation, which occurs side by side with the enzymatic cyanation. Though it was thought that by changing the reaction media from aq to organic solvent, the corresponding chemical reaction may be suppressed.

By employing the above reaction condition, aliphatic methylketones and aliphatic aldehydes were subjected to PmHNL catalyzed cyanohydrin synthesis. The detailed results are shown in Table 7b. In case of aliphatic carbonyl compounds, those compounds were tested only which provides good enantioselection in the earlier screening method (Tables 5 and 6).

It is clear from the above discussion that by applying a vigorously stirred biphasic reaction media (aq buffer/polar aprotic solvent like DIPE), the yield and optical purity of the synthesized cyanohydrins can be enhanced markedly. This method is also applicable for obtaining a large quantity of chiral cyanohydrins for industrial purposes. Further focus will be on the reuse of this new enzyme PmHNL by immobilization methods as reported by other researchers with different HNLs. And currently we are working on those aspects to find out an effective PmHNL system, which allows us to overcome all the associated problems as discussed earlier.

2.4. Structure–activity relationships

Though hydroxynitrile lyase research was widely explored by the researchers, no suitable model except one rough model by Ognyanov et al.[13] was known from which one can predict structure–activity relationship of a given sets of substrate. The model reported by Ognyanov and co-workers is based on computer assisted modeling, and one can have a rough idea of predicting the steric limits of modified substrate for PaHNL (*Prunus amygdalus* Batsch. *Syn*: *Prunus dulcis*) catalyzed cyanohydrin formation. Though one can explain the minimum steric requirements needed to be a perfect HNL substrate by using this model, but one cannot explain the minimum electronic parameters needed to be an ideal HNL substrate. The following structure–activity relationship can be predicted from the above discussion as well as previous results reported by other researchers, although the prediction is purely hypothetical, as no theoretical calculations were performed. The prediction is entirely based on the results obtained by us and several previous researchers. When we compare our enzyme PmHNL with the most widely known (*R*)-HNL, PaHNL (almond); we found that PmHNL is better enzyme than PaHNL with regard to the aromatic substrates. With aliphatic aldehydes PmHNL gives similar results as PaHNL. However, PaHNL is superior when aliphaticmethyl ketones were used as substrate. The following points are predicted based on our research on PmHNL and previous results with PaHNL.

(a) presence of substituents in *ortho* position (irrespective of its electronic nature) always lead to sluggish reaction (poor ee) compared to *meta* and *para* substituents.
(b) electron donating groups such as −Me, reduced the reactivity of the aldehyde, thereby affording lower yields compared to that of the parent compound benzaldehyde. Whereas presence of group having −I (inductive) effect and +R (resonance) effect, for example, halogen, OMe are more reactive than the parent benzaldehyde.

Table 7b. Preparative scale cyanohydrin synthesis by PmHNL with selected aliphatic aldehydes and methyl ketones

Substrate[a]	Yield (%)	Time (h)[b]	ee (%)[c]
Propanal	68	11	94
Butanal	58	14	90
Isobutanal	62	10	94
Pivalaldehyde	52	6	96
Pentanal	57	16	88
Hexanal	60	22	90
Cyclopentanecarboxaldehyde	70	14	94
Cyclohexanecarboxaldehyde	72	12	93
2-Pentanone	60	42	72
2-Hexanone	65	58	83
4-Methyl-2-pentanone	56	48	88
5-Methyl-2-hexanone	49	60	65
Trimethylsilylmethylketone	52	18	78

[a] All reactions were performed with 5 g of substrate, 1.5 equiv of acetonecyanohydrin in biphasic reaction media (total reaction volume is 50 mL, DIPE/aq buffer, 10:1).
[b] The reaction was monitored by TLC.
[c] ee's were determined by chiral GC analysis (by applying same condition as described earlier).

(c) presence of strong electron withdrawing substituents such as $-NO_2$, CF_3 activated the aldehyde so much, that almost in all cases complete conversion was observed within a short time. High reactivity of these aldehydes also caused the low ee due to non-enzymatic cyanation reaction. It was reported by Han et al.[5e] that *para*-trifluoromethylbenzaldehyde when treated with PaHNL, produced cyanohydrin with no enantioselectivity; but the same substrate provides 75% ee when reacted with PmHNL. Where as *meta*-trifluoromethyl benzaldehyde provides 70–80% ee with both the enzyme. The reason for *para*-selectivity of PmHNL for this particular substrate is unclear.

(d) 4-hydroxybenzaldehyde acted as poor substrate for PmHNL. But when the hydroxyl group was protected as ether functionality (–OBn, –Oallyl, –OTBS), the respective aldehydes are excellent substrates for PmHNL in terms of enantioselection.

(e) *N*-containing heteroaryl carboxaldehydes turned out to be poor substrates from an enantioselective point of view, as observed in the case of pyridine and quinoline series aldehydes. Whereas O and S-containing heterocyclic carboxaldehydes are excellent substrates for PmHNL as well as PaHNL.

(f) in the polycyclic aromatic aldehyde series, poor reactivity of 9-anthral suggested that maximum two rings can be accommodated in the PmHNL active site (both of the substrates 1 and 2-napthal provides good selectivity with PmHNL compared to PaHNL as reported by Riva et al.[5f]).

(g) increasing the number of substituents in the aromatic ring often lead to poor enantioselection. Tri, tetra, and penta substituted aromatic aldehydes always provides poor or no enantioselectivity.

(h) both PmHNL and PaHNL accept a broad range of aliphatic aldehydes (acyclic and cyclic) as their substrates, and overall good selectivity was observed. It was observed that, aliphatic cyclic aldehydes, for example, cyclopentane and cyclohecxane carboxaldehyde are excellent substrate compared to their linear counterpart, as both of the aldehydes react fast and provides the corresponding cyanohydrin in good chemical and optical yield.

(i) aliphatic methylketones are also accepted as substrate, but compared to their aldehyde counterpart less enantioselectivity was observed. It is also important to mention that PaHNL is little superior than PmHNL, when aliphatic methyl ketones are used as substrates (in terms of ee).

3. Conclusion

In conclusion, we have found a new (*R*) hydroxynitrile lyase from Japanese apricot (*P. mume*). The new enzyme accepts a broad array of substrates ranging from aromatic, heteroaromatic, bicyclic as well as aliphatic carbonyl compounds and yields the corresponding cyanohydrins with excellent enantioselection. Studies directed towards finding new substrates for PmHNL and predicting an effective model, which can explain the minimum requirements needed to be an efficient HNL substrate are in progress. We are also investigating the enzymological properties of PmHNL in detail.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. Ripened Ume fruit (*P. mume*) was obtained from local fruit market and stored at 4 °C. All aldehydes used in the experiment are freshly distilled or washed with aq $NaHCO_3$ solution to minimize the amount of free acid, which are supposed to inhibit HNL activity. Mandelonitrile and acetone cyanohydrins were freshly distilled prior to use. Reactions were monitored by TLC, carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic vanillin, and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 400 MHz spectrometer at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Chiral HPLC was performed using chiral OJ-H column (0.46×25 cm, Daicel industries) with water 717 autosampler and UV–vis detector (254 nm). Eluting solvent used was different ratio of hexane and 2-propanol. Chiral GC analysis was performed in a Schimadzu autosampler with cyclodextrins columns as chiral stationary phase (Fused silica capillary column, 30 m×0.25 mm×0.25 μm thickness, β-Dex-120 and β-Dex-325 from SUPELCO, USA) using He as a carrier gas (Detector temperature: 230 °C and injection temperature 220 °C).

4.2. Enzyme extraction from *P. mume*

Ripened Ume fruit was taken and the fleshy cover was removed to obtain the seeds. The upper layer of the seeds was cracked with hammer to give the soft kernels inside. Those kernels were collected and homogenized in a homogenizer at 4 °C, with aq potassium phosphate buffer (10 mM, pH=6.0), to give a milky suspension. The suspension was filtered through four layers of cheese cloth to remove the insoluble part. After that it was centrifuged (18,800 g, 30 min), removal of the residue gives a crude preparation of PmHNL. The crude preparation was fractionated with $(NH_4)_2SO_4$. Proteins precipitating with 30% saturation were collected by centrifugation (18,800 g, 20 min), dissolved in minimum volume of phosphate buffer and dialyzed against the same buffer with three changes. After that the dialyzed solution was centrifuged and the supernatant was stored at 4 °C and assayed for HNL activity.

4.3. PmHNL assay

In a typical assay reaction 1.0 M of benzaldehyde solution (in DMSO, 40 μL) was dissolved in 400 mM citrate buffer (760 μL, pH=4.0), followed by addition of 100 μL of enzyme solution and 100 μL of 1.0 M KCN solution (total

reaction volume 1 mL). After 5 min, the 100 μL of the reaction mixture was taken out and extracted with 900 μL hexane–2-propanol (9/1), the organic layer was analyzed with chiral HPLC for the formation of (*R*)-mandelonitrile. A blank reaction was also performed without enzyme, and the amount of mandelonitrile obtained was deducted from the biocatalyzed reaction product. One unit of the enzyme is defined as the amount of the enzyme that produces 1 μmol of (*R*)-mandelonitrile under reaction condition in 1 min.

The protein content in PmHNL was measured by Bradford method using Bio-Rad protein assay kit using BSA as the standard.[14] The protein content in a crude extract of PmHNL was found to roughly 10 mg/mL and activity was 120 U/mL as determined by the above method. The enzyme is a flavoprotein (FAD containing), as evident by the yellow color. Absorption spectroscopy also reveals the fact.

4.4. Substrate screening condition using PmHNL

In an Eppendrof tube, 1.0 M solution (40 μL, in DMSO) of the respective carbonyl compound was taken. Citrate buffer (400 mM, pH=4.0), 760 μL was added to it, followed by addition of 100 μL PmHNL and 1.25 M, solution of KCN (dissolved in citrate buffer, pH=4.0). The reaction was monitored by taking a small aliquot of reaction mixture (every 5 min interval, 25 μL). The sample was extracted with ethyl acetate and the organic layer was analyzed with HPLC. The course of the reaction was followed until appreciable amount of conversion was achieved (30 min to 1 h, depending on structural features of the aromatic aldehydes). For the case of aliphatic aldehydes and ketones, the above procedure was little modified, as substantial more amount of sample is needed to analyze the product formation by GC. Aliphatic carbonyl compounds (100 mg) were dissolved in 5 mL of citrate buffer, followed by addition of PmHNL solution (200 U/mmol of substrate) and 1.0 M of KCN solution (2 equiv). For those cyanohydrins, which are well resolved in chiral GC column (comparing from standard synthesized compounds), the course of the reaction was followed by extraction and analyzing the product formation by GC. In other cases, the reaction was followed by TLC, and after appreciable amount of conversation was achieved, the cyanohydrins are derivatized as the corresponding silyl ether (OTMS) and analyzed by chiral GC. It was assumed that in all the cases corresponding chemical cyanation caused by KCN is minimum due to low pH of the reaction medium. Using KCN as a cyanating source, within 1–3 h (depending on the structural features of the carbonyl compounds), appreciable amount of conversion was achieved, hence large number of substrates (approx. 20) can be analyzed in a single day operation.

4.5. Generation of HCN solution in organic solvent

All reaction equipment in which cyanides are used or produced was placed in a well ventilated hood. Proper gloves were worn in when handling cyanides, splash proof goggles and proper mask were also used when dealing with HCN. The solution of HCN in organic solvent (DIPE, TBME, DBE) can be generated as follows. In an aq solution of NaCN/KCN, concd HCl (35%) was dropped at 0 °C, until pH=4.0. The mixture was stirred for 20 min and then extracted with an appropriate organic solvent. The HCN solution was stored in a dark bottle at 0 °C, with little addition of citrate buffer (pH=4.0). The HCN concentration of the obtained solution was determined as reported by Sheldon et al.[12a]

4.6. Preparative scale biphasic synthesis of cyanohydrins using PmHNL

Carbonyl compounds (5 g) were taken in appropriate solvent (DIPE, TBME or DBE, 50 mL) saturated with 5 mL of citrate buffer (pH=4.0). Solution of PmHNL (50 U/mmol of substrate) followed by acetonecyanohydrin (1.5 equiv) was added to the reaction mixture. The reaction was vigorously stirred until the desired conversion was achieved (by TLC). Usual extractive work-up afforded the cyanohydrins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.105. Spectral (^{1}H and ^{13}C NMR) data for selected compounds and GC/HPLC retention time are available.

References and notes

1. (a) Smitskamp-Wilms, E.; Brussee, J.; Van der Gen, A.; van Scharrenburg, G. J. M.; Sloothaak, J. B. *Recl. Trav. Chim. Pay-Bas.* **1991**, *110*, 209–215. (b) Gerstner, E.; Kiel, U. Z. *Physiol. Chem.* **1975**, *356*, 1853–1857. (c) Xu, L.-L.; Singh, B. K.; Conn, E. E. *Arch. Biochem. Biophys.* **1986**, *250*, 322–328. (d) Yemm, R. S.; Poulton, J. E. *Arch. Biochim. Biophys.* **1986**, *247*, 440–445. (e) Albrecht, J.; Jansen, I.; Kula, M.-R. *Biotechnol. Appl. Biochem.* **1993**, *17*, 191–203. (f) Wajant, H.; Förster, S.; Selmar, D.; Effenberger, F.; Pfizenmaier, K. *Plant Physiol.* **1995**, *109*, 1231–1238. (g) Wajant, H.; Mundry, K.-W. *Plant Sci.* **1993**, *89*, 127–133. (h) Bove, C.; Conn, E. E. *J. Biol. Chem.* **1961**, *236*, 207–210. (i) Kuroki, G. W.; Conn, E. E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 6978–6981. (j) Wajant, H.; Förster, S.; Bottinger, H.; Effenberger, F.; Pfizenmaier, K. *Plant Sci.* **1995**, *108*, 1–11. (k) Hughes, J.; Lakey, J. H.; Hughes, M. A. *Arch. Biochim. Biophys.* **1994**, *311*, 496–502.
2. (a) Hickel, A.; Hasslacher, M.; Griengl, H. *Physiol. Plant* **1996**, *98*, 891–898. (b) Wajant, H.; Effenberger, F. *Biol. Chem.* **1996**, *377*, 611–617. (c) Seigler, D. S. Cyanide and

Cyanogenic Glycosides. In *The Chemical Participants*, 2nd ed.; Rosenthal, G. A., Berenbaum, M. R., Eds.; Herbivores: Their Interactions with Secondary Metabolites; Academic: New York; Vol. 1, pp 35–77. (d) Conn, E. E. *Ann. Rev. Plant. Physiol.* **1980**, *31*, 433–451.

3. (a) Nahrstedt, A. *Plant Syst. Evol.* **1985**, *150*, 35–47. (b) Lieberei, R.; Selmar, D.; Biehl, B. *Plant Syst. Evol.* **1985**, *150*, 49–63. (c) Okolie, P. N.; Obasi, B. N. *Phytochemistry* **1993**, *33*, 775–778. (d) Kakes, P.; Hakvoort, H. *Phytochemistry* **1992**, *31*, 1501–1505. (e) Wajant, H.; Riedel, D.; Benz, S.; Mundry, K.-W. *Plant Sci.* **1994**, *103*, 145–154. (f) Poulton, J. E. Enzymology of Cyanogenesis in Rosaceous Stone Fruits. In *β-Glucosidases: Biochemistry and Molecular Biology*; Esen, A., Ed.; ACS Symposium Series 533; Oxford University Press: New York, 1993; pp 170–190. (g) Wu, H. C.; Poulton, J. E. *Plant Physiol.* **1991**, *96*, 1329–1337.
4. (a) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682. (c) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176. (d) Griengl, H.; Schwab, H.; Fechter, M. *Trends Biotechnol.* **2000**, *18*, 252–256. (e) Effenberger, F. *Chimia* **1999**, *53*, 3–10. (f) Johnson, D. V.; Griengl, H. *Adv. Biochem. Eng./Biotechnol.* **1999**, *63*, 32–55.
5. Few recent references on HNL catalyzed cyanohydrin synthesis and screening for new HNL. A detailed referencing can be found in the previous reviews (4a–4e). (a) Kobler, C.; Bohrer, A.; Effenberger, F. *Tetrahedron* **2004**, *60*, 10397–10410. (b) Solís, A.; Luna, H.; Manjarrez, N.; Pérez, H. I. *Tetrahedron* **2004**, *60*, 10427–10431. (c) Avi, M.; Fechter, M. H.; Belaj, F.; Pöchlauer, P.; Griengl, H. *Tetrahedron* **2004**, *60*, 10411–10418. (d) Kobler, C.; Effenberger, F. *Tetrahedron: Asymmetry* **2004**, *15*, 3731–3742. (e) Han, S.; Chen, P.; Lin, G.; Huang, H.; Li, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 843–846. (f) Cruz Silva, M. M.; Melo, M. L.; Parolin, M.; Tessaro, D.; Riva, S.; Danieli, B. *Tetrahedron: Asymmetry* **2004**, *15*, 21–27. (g) Li, N.; Zong, M.-H.; Peng, H.-S.; Wu, H.-C.; Liu, C. *J. Mol. Catal. B: Enzym.* **2003**, *22*, 7–12. (h) Li, N.; Zong, M.-H.; Liu, C.; Peng, H.-S.; Wu, H.-C. *Biotechnol. Lett.* **2003**, *25*, 219–222. (i) Fröhlich, R. F. G.; Zabelinskaja-Mackova, A. A.; Fechter, M. H.; Griengl, H. *Tetrahedron: Asymmetry* **2003**, *14*, 355–362. (j) Hernández, L.; Luna, H.; Ruíz-Terán, F.; Vázquez, A. *J. Mol. Catal. B: Enzym.* **2004**, *30*, 105–108.
6. Hickel, A.; Heinrich, G.; Schwab, H.; Griengl, H. *Biotechnol. Tech.* **1997**, *11*, 55–58.
7. Kruse, C. G. Chiral Cyanohydrins — Their Manufacture and Utility as Chiral Building Blocks. In *The Commercial Manufacture and Applications of Optically Active Compounds*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Chirality in industry; Wiley: Chichester, UK, 1992; Chapter 14, pp 279–299.
8. (a) Schmidt, M.; Herve, S.; Klempier, N.; Griengl, H. *Tetrahedron* **1996**, *52*, 7833–7840. (b) Brussee, J.; Loos, W. T.; Kruse, C. G.; van der Gen, A. *Tetrahedron.* **1990**, *46*, 979–986. (c) Menendez, E.; Brieva, R.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1995**, 989–990.(d) A list of reactions on both the hydroxyl (protected and unprotected) and nitrile functionality and corresponding literature references can be found at Ref. 4b
9. (a) Asano, Y.; Tamura, K.; Doi, N.; Ohmiya, T., *Biosci. Biotech. Biochem.* **2005**, in press. (b) Tamura, K.; Asano, Y. Studies on mandelonitrile lyases from plants. Masters thesis, Toyama Prefectural University, 2003.
10. Hanefeld, U.; Straathof, A. J. J.; Heijnen, J. J. *Biochim. Biophys. Acta* **1999**, *1432*, 185–193.
11. (a) Zandergen, P.; Van der Linden, J.; Brussee, J.; Van der Gen, A. *Synth. Commun.* **1991**, *21*, 1387–1391. (b) Lin, G.; Han, S.; Li, Z. *Tetrahedron* **1999**, *55*, 3531–3540. (c) Kiljunen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, *8*, 1225–1234.
12. (a) van Langen, L. M.; Selassa, R.; Rantwijk, F.; Sheldon, R. A. *Org. Lett.* **2005**, *7*, 327–329. (b) Veum, L.; Hanefeld, U.; Pierre, A. *Tetrahedron* **2004**, *60*, 10419–10425. (c) Effenberger, F.; Ziegler, T.; Förster, S. Degussa. Eur. Patent 276,375, 1987. (d) Kula, M, R.; Stürtz, I, M.; Wandrey, C.; Kragl, U. Forschungszentrum Jülich. Eur. Patent 446,826, 1991. (e) Becker, W.; Pfeil, E. Boehringer. Ger. Patent 1,593,260, 1966. (f) Wehtje, E.; Adlercreutz, P.; Mattiason, B. *Appl. Microbiol. Biotechnol.* **1988**, *29*, 419. (g) Westman, T, L. Monsanto, U.S. Patent 3,649,457, 1968.
13. Ognyanov, V. I.; Datcheva, V. K.; Kyler, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 6992–6995.
14. Bradford, M. *Anal. Biochem.* **1976**, *72*, 248–254.
15. Gerrits, P. J.; Zumbrägel, F.; Marcus, J. *Tetrahedron* **2001**, *57*, 8691–8698.

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Efficient syntheses of thiadiazoline and thiadiazole derivatives by the cyclization of 3-aryl-4-formylsydnone thiosemicarbazones with acetic anhydride and ferric chloride

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Abstract—3-Aryl-4-formylsydnone 4′-phenylthiosemicarbazones **3a–d** and 3-aryl-4-formylsydnone thiosemicarbazones **3e–h** are effective precursors of sydnonyl-substituted heterocycles. The thiosemicarbazones **3a–d** reacted with acetic anhydride (**4a**) to give 4-acetyl-2-phenylamino-5-(3-arylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles **5a–d** and 4-acetyl-2-(*N*-phenylacetamido)-5-(3-arylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles **6a–d**. However, under similar method, thiosemicarbazones **3e–h** produced only 4-acetyl-2-acetamido-5-(3-arylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles **6e–h** in high yield. The sydnonyl-substituted thiadiazole derivatives **7a–h** were also obtained successfully by the cyclization of 3-aryl-4-formylsydnone thiosemicarbazones **3a–h** with ferric chloride (**4b**). In the cyclization, the thiosemicarbazones **3a–d** are more reactive than the thiosemicarbazones **3e–h**.

1. Introduction

Several sydnone compounds exhibit pharmacological activities, including antimicrobial, anti-inflammatory, analgesic and antipyretic activities.[1–6] Various substituted thiadiazoles and thiadiazolines also exhibit biological behavior.[7–12] Therefore, interest in the syntheses of thiadiazole and thiadiazoline derivatives is significant. Thus, synthesis of sydnones with a thiadiazolyl or thiadiazolinyl group substituted at a suitable position by a convenient method is an important part of developing new and potentially biological active compounds. In view of the continued interest in the development of simpler and more convenient synthetic routes for preparing heterocyclic systems,[13–20] an efficient and useful method is reported herein to synthesize some novel sydnonyl-substituted thiadiazolines **5a–6h** and thiadiazoles **7a–h** by the reaction of 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones **3a–d** or 3-aryl-4-formylsydnone thiosemicarbazones **3e–h** with cyclization reagents, such as acetic anhydride (**4a**) and ferric chloride (**4b**).

2. Results and discussion

Thiosemicarbazones exhibit various biological activities and are extensively applied in medicine—particularly in the treatment of tuberculosis.[21,22] Numerous compounds with a thiosemicarbazone moiety also exhibit biological activity.[23,24] Accordingly, 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones **3a–d** and 3-aryl-4-formylsydnone thiosemicarbazones **3e–h** were synthesized in good yields by the reactions of 3-aryl-4-formylsydnones **1a–d** with 4′-phenylthiosemicarbazide (**2a**) and thiosemicarbazide (**2b**), respectively.[19]

In our previous work, thiosemicarbazones **3** reacted with cyclization reagents, such as ethyl chloroacetate, ethyl 2-chloroacetoacetate and 2-bromoacetophenone to yield sydnonyl-substituted thiazolidinone and thiazoline derivatives.[19] Aldehyde thiosemicarbazones are also appropriate substrates for the preparation of five- or six-membered heterocyclic rings that contain three heteroatoms by reacting them with oxidizing reagents or other cyclization reagents.[25–27] Hence, this study addresses on the reactions of 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones **3a–d** or 3-aryl-4-formylsydnone thiosemicarbazones **3e–h** with acetic anhydride (**4a**) to produce sydnonyl-substituted thiadiazoline derivatives. The treatment of 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones **3a–d** with acetic anhydride in dichloromethane solution, following by heating at 75 °C in an oil bath for 18–20 h, produced the

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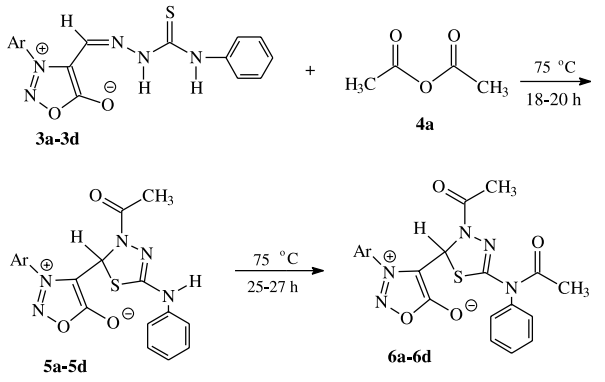
desired products **5a–d** with favorable yields (Scheme 1). Among these new products, the yellow crystals **5a**, and **5d** were analytically pure and suitable for X-ray structural determination. Figures 1 and 2 present the ORTEP drawings of 4-acetyl-2-phenylamino-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (**5a**) and 4-acetyl-2-phenylamino-5-[3-(4-ethoxyphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (**5d**), respectively.



Scheme 1. Compounds **3a**, **5a**, **6a**: Ar=C_6H_5; **3b**, **5b**, **6b**: Ar=*p*-$CH_3C_6H_4$; **3c**, **5c**, **6c**: Ar=*p*-$CH_3OC_6H_4$; **3d**, **5d**, **6d**: Ar=*p*-$C_2H_5OC_6H_4$.

When the reactions of compounds **3a–d** with acetic anhydride were heated for a longer period, 43–47 h, the initial products, monoacetyl-substituted thiadiazolines **5a–d** were completely converted to diacetyl-substituted thiadiazolines **6a–d** by TLC survey (Scheme 1). Of these new products, the yellow crystals **6a** were analytically pure and suitable for X-ray structural determination. Figure 3 shows the ORTEP drawing of 4-acetyl-2-(*N*-phenylacetamido)-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (**6a**). Table 1 presents all of the crystal data on compounds **5a**, **5d**, and **6a**. However, treating 3-aryl-4-formylsydnone 4′-thiosemicarbazones **3e–h** with acetic anhydride without any other solvent, and heating the mixed solution at 60 °C for 7–9 h directly produced the diacetyl-substituted thiadiazolines **6e–h** in good yields (Scheme 2). Figure 4 displays the ORTEP drawing of 4-acetyl-2-acetamido-5-[3-(4-methoxyphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (**6g**). In the treatment of **3e–h** with acetic anhydride, there are no monoacetyl-substituted thiadazolines **5e–h** that can be possibly detected by TLC even in the lower reaction temperature. Accordingly, we can conclude that compounds **3e–h** were more reactive than compounds **3a–d**.

The reaction time, the reaction temperature and the reaction yields of thiosemicarbazones **3a–h** with acetic anhydride reveal that compounds **3e–h** are more reactive than compounds **3a–d**. In the reaction of compounds **3a–d** with acetic anhydride, the resonance effect between NH and the phenyl group may reduce the nucleophilicity of NH, and the steric effect of phenyl group on the NH retards nucleophilic substitution with acetic anhydride. Therefore, the initial monoacetyl-substituted products **5a–d** are gradually

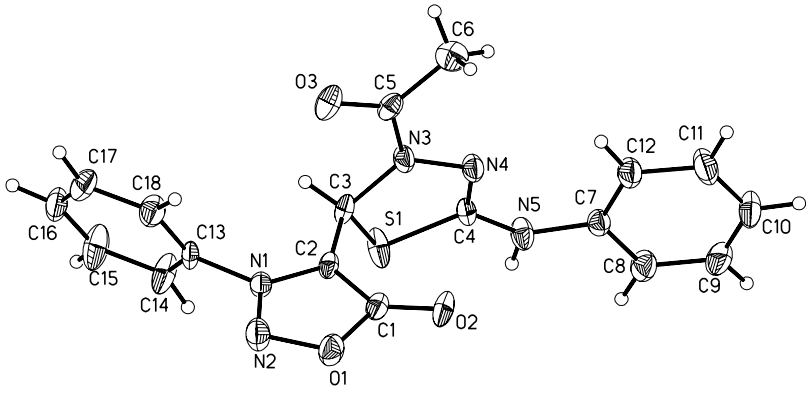


Figure 1. Crystal structure of compound **5a**.

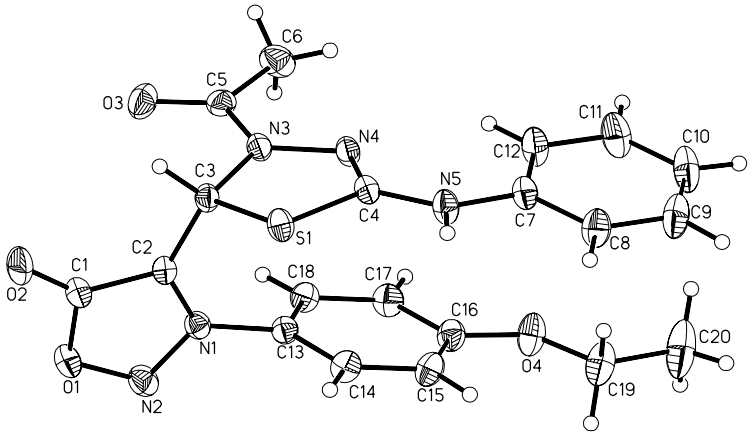


Figure 2. Crystal structure of compound **5d**.

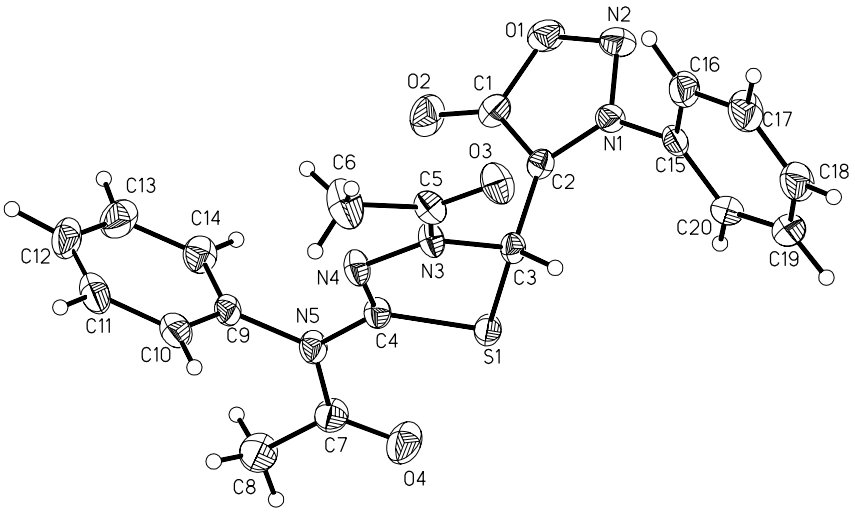
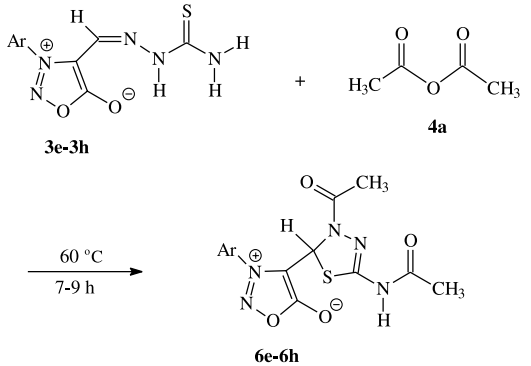


Figure 3. Crystal structure of compound **6a**.

Table 1. Crystal data of compounds **5a**, **5d**, and **6a**

Compound	**5a**	**5d**	**6a**
Diffractometer	Bruker Smart Apex CCD	Bruker Smart Apex CCD	Bruker Smart Apex CCD
Formula	$C_{18}H_{15}N_5O_3S$	$C_{20}H_{19}N_5O_4S$	$C_{20}H_{17}N_5O_4S$
Formula weight	381.41	425.47	423.46
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	*P bca*	*P*21/*n*	*P*21/*c*
a (Å)	16.7333(18)	16.0618(15)	9.8673(7)
b (Å)	11.3458(12)	7.6630(7)	17.2563(12)
c (Å)	18.584(2)	17.8528(16)	11.9236(8)
α (°)	90.00	90.00	90.00
β (°)	90.00	106.182(2)	104.3800(10)
γ (°)	90.00	90.00	90.00
V (Å^3)	3528.2(7)	2110.3(3)	1966.7(2)
Z	8	4	4
D_{calcd} (g cm^{-3})	1.436	1.396	1.430
F_{000}	1584.00	928.00	880.00
μ (Mo K_α) (cm^{-1})	2.14	1.96	2.04
Crystal size (mm)	0.11×0.12×0.26	0.27×0.27×0.28	0.14×0.15×0.20
Temperature (K)	298	298	298
Scan type	Phi-omega scan	Phi-omega scan	Phi-omega scan
θ_{max}, (°)	28.33	28.32	28.29
Reflections measured	Total: 4305	Total: 5079	Total: 4758
No. observations ($I>2.00\sigma(I)$)	3285	4297	3606
No. variables	304	364	339
Residuals: R; R_w	0.1191; 0.2046	0.0438; 0.1127	0.0617; 0.1263
GoF	1.350	1.028	1.136



Scheme 2. Compounds **3e**, **6e**: Ar=C_6H_5; **3f**, **6f**: Ar=*p*-$CH_3C_6H_4$; **3g**, **6g**: Ar=*p*-$CH_3OC_6H_4$; **3h**, **6h**: Ar=*p*-$C_2H_5OC_6H_4$.

converted to diacetyl-substituted thiadiazolines **6a–d** by further heating. In the case of compounds **3e–h**, nucleophilicity of thioamide is low like that of amide. The reaction of **3e–h** with acetic anhydride should proceed through the intermediates **5e–h** like the reaction of **3a–d** as shown in Scheme 1. The NH_2 at the 2-position of intermediates **5e–h** with strong nucleophilicity and without a steric effect may facilitate further nucleophilic substitution with acetic anhydride to yield diacetyl-substituted compounds **6e–h**. Therefore, the experimental results suggest that the mechanism of the reaction between compounds **3** and acetic anhydride follows Scheme 3.

Substituted 1,3,4-thiadiazoles have attracted considerable attention due to their wide-ranging biological activities, including antimicrobial, antituberculosis, anesthetic,

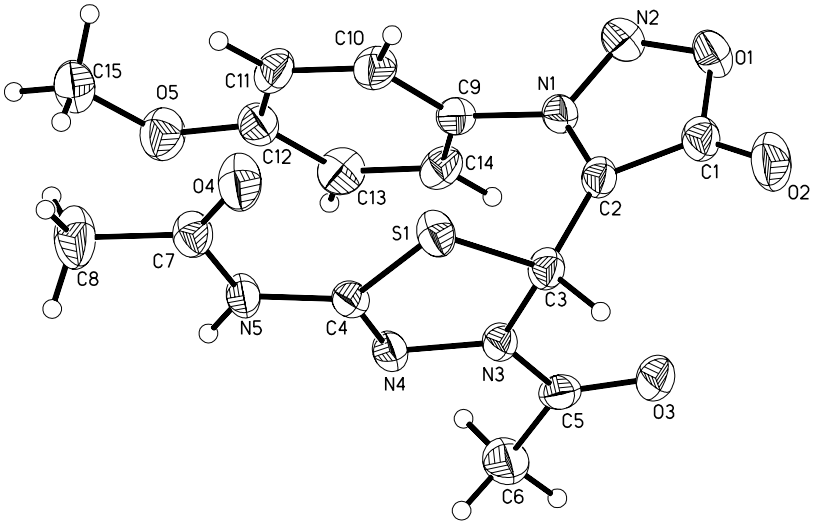
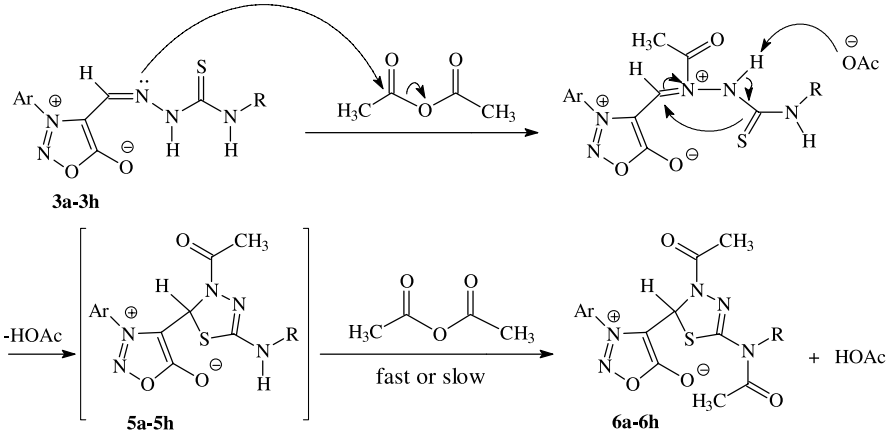
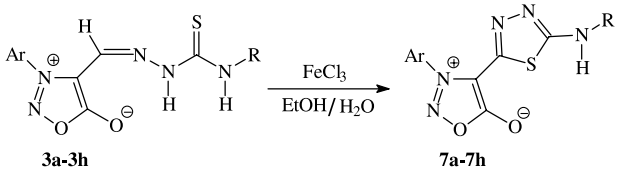


Figure 4. Crystal structure of compound **6g**.

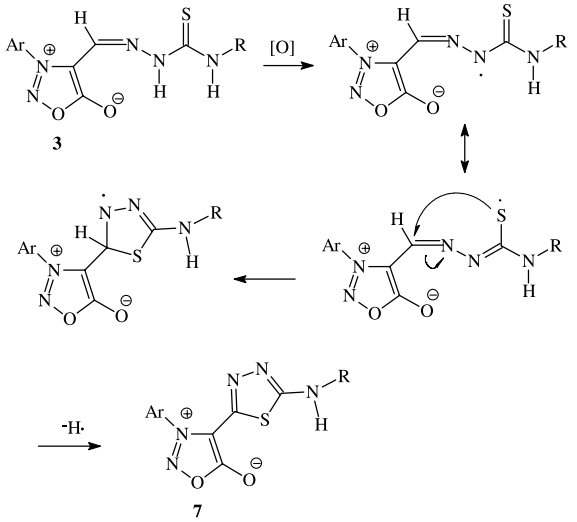


Scheme 3. The mechanism of reaction of compounds **3** with acetic anhydride.

antithrombotic, anticonvulsant, antihypertensive, antiinflammatory and antiulcer activities.[28,29] Based on these facts, the preparation of a new series of compounds with both sydnone and 1,3,4-thiadiazoles moiety is reported herein, with the aim of developing novel and potentially biological active compounds. The thiosemicarbazones **3a–d** were treated with ferric chloride in aqueous ethanol and stirred continuously at 80 °C for 1–2 days to produce the desired products **7a–d** (Scheme 4). However, when the thiosemicarbazones **3e–h** were treated with ferric chloride at 60 °C, the reaction took only 6–8 h to run to completion



Scheme 4. Compounds **3a**, **3e**: Ar = C_6H_5; **3b**, **3f**: Ar = *p*-$CH_3C_6H_4$; **3c**, **3g**: Ar = *p*-$CH_3OC_6H_4$; **3d**, **3h**: Ar = *p*-$C_2H_5OC_6H_4$; **3a–3d**: R = C_6H_5; **3e–3h**: R = H.



Scheme 5. The mechanism of reaction of compounds **3** with ferric chloride.

Table 2. Crystal data of compounds **6g** and **7e**

Compound	**6g**	**7e**
Diffractometer	Bruker Smart Apex CCD	Bruker Smart Apex CCD
Formula	$C_{15}H_{15}N_5O_5S$	$C_{10}H_7N_5O_2S$
Formula weight	377.38	261.27
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	*C c*
a (Å)	11.602(3)	9.833(5)
b (Å)	12.153(3)	17.248(9)
c (Å)	13.434(3)	6.987(4)
α (°)	86.143(4)	90.00
β (°)	70.245(4)	112.157(8)
γ (°)	80.080(4)	90.00
V (Å^3)	1756.1(7)	1097.4(10)
Z	2	4
D_{calcd} (g cm^{-3})	1.461	1.581
F_{000}	804.00	536.00
μ (Mo K_α) (cm^{-1})	2.26	2.97
Crystal size (mm)	0.21×0.29×0.36	0.2×0.26×0.27
Temperature (K)	298	298
Scan type	Phi-omega scan	Phi-omega scan
θ_{max}, (°)	28.33	28.34
Reflections measured	Total: 8218	Total: 2495
No. observations ($I>2.00\sigma(I)$)	6033	2223
No. variables	540	191
Residuals: *R*; R_w	0.0820; 0.1747	0.0444; 0.0912
GoF	1.140	1.081

and produce the corresponding sydnonyl substituted thiadiazoles **7e–h** (Scheme 4). The suggested reaction mechanism is shown in Scheme 5. Figure 5 shows the ORTEP drawing of 2-amino-5-(3-phenylsydnon-4-yl)-[1,3,4]thiadiazole (**7e**). Table 2 lists all of the crystallographic data of compounds **6g** and **7e**.

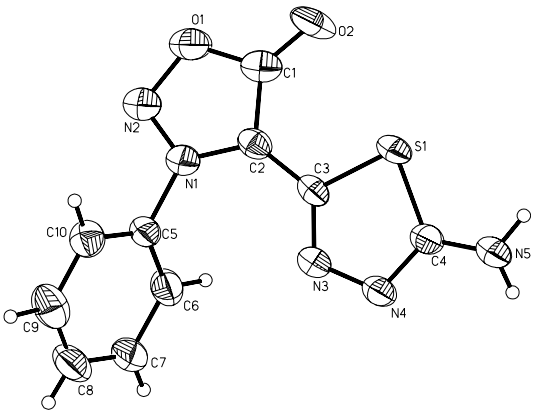


Figure 5. Crystal structure of compound **7e**.

3. Conclusion

In summary, many potentially biological active compounds that contain a thiadiazoline or thiadiazole moiety were synthesized. This work reported an efficient method of obtaining sydnonyl-substituted thiadiazolines and thiadiazoles. Applying this method to the cyclization of thiosemicarbazones **3a–h** with acetic anhydride (**4a**) provides access to the target compounds, such as monoacetyl-substituted thiadiazolines **5a–d** and diacetyl-substituted thiadiazolines **6a–h**, depending on the reaction time, temperature, and the reactivity of starting materials **3a–h**. In the reaction of compounds **3a–d**, both of monoacetyl-substituted thiadiazolines **5a–d** and diacetyl-substituted thiadiazolines **6a–d** were obtained. However, under a similar method, compounds **3e–h** produced only diacetyl-substituted thiadiazolines **6e–h**. All the reactions of **3a–h** with acetic anhydride proceed through the intermediates **5a–h** to give diacetyl-substituted thiadiazolines **6a–h**. The result is explained by the nucleophilicity, resonance and steric effect. Compounds **3a–h** could also undergo self-cyclization by the oxidation of ferric chloride (**4b**) to yield the corresponding thiadiazoles **7a–h**. Both the reaction results of compounds **3a–h** with acetic anhydride and ferric chloride reveal that compounds **3e–h** are more reactive than compounds **3a–d**.

4. Experimental

4.1. General

All melting points were determined on an England Electrothermal Digital Melting Point apparatus and are uncorrected. IR spectra were recorded on a MATTSON/SATELLITE 5000 FT-IR spectrophotometer. Mass spectra were measured on a VG Quattro GC/MS/MS/DS spectrometer. ^{1}H NMR spectra were run on a Bruker AMX-200 NMR spectrometer, using TMS as an internal standard. ^{13}C NMR spectra were carried out with complete ^{1}H decoupling and assignments were made through additional DEPT experiments. Elemental analyses were taken with a Heraeus CHN-O-Rapid Analyzer or Elementar Vario EL-III Analyzer. X-ray spectra were performed on a Bruker AXS SMART APEX CCD diffractometer.

4.2. Starting materials

3-Aryl-4-formylsydnone 4′-phenylthiosemicarbazones **3a–d** and 3-aryl-4-formylsydnone thiosemicarbazones **3e–h** were prepared from the corresponding 3-aryl-4-formylsydnones **1a–d** according to the literature.[19]

4.3. Syntheses of 4-acetyl-2-phenylamino-5-(3-aryl-sydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles (5a–d)

To a solution of 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbazone (**3a**, 1.017 g, 3.00 mmol) in dichloromethane (30 mL) was added 15 mL of acetic anhydride. The mixed solution was heated at 75 °C for 18 h and then allowed to stand at room temperature. The reaction mixture was slowly added to 400 mL of ice-cooled water, and then stirred at room temperature. It was extracted with 600 mL of *n*-hexane–ethyl acetate (2/1). The combined organic layer was vigorously washed with sodium hydrogencarbonate solution (200 mg of sodium hydrogencarbonate in 50 mL of water); dried with anhydrous sodium sulfate, and decolorized with charcoal. The filtrate was concentrated to a small volume to give an orange solid. The solid was collected by filtration and washed with *n*-hexane, yielding 823 mg of orange solid. The crude product was recrystallized from 95% ethanol to afford 4-acetyl-2-phenylamino-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (**5a**) as yellow crystals (711 mg, 62%). The chemical and physical spectral characteristics of these products **5a–d** are given below.

4.3.1. 4-Acetyl-2-phenylamino-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (5a). Yellow crystals from EtOH; yield 62%; mp 196–197 °C; IR (KBr) 3314, 1728, 1649, 1624, 1599, 1258 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.13 (s, 3H), 6.74 (s, 1H), 6.92–6.99 (m, 1H), 7.25–7.43 (m, 4H), 7.64–7.90 (m, 5H), 9.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.27, 58.03, 106.67, 117.70, 121.98, 125.84, 129.10, 130.07, 132.61, 133.29, 140.52, 146.01, 164.85, 167.26; EIMS (30 eV) *m/z* (%): 381 (M^+, 43), 339 (8), 178 (100). Anal. Calcd for $C_{18}H_{15}N_5O_3S$: C, 56.68; H, 3.96; N, 18.36; S, 8.41. Found: C, 56.63; H, 4.01; N, 18.39; S, 8.33. X-ray analytical data is listed in Table 1. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 277498.

4.3.2. 4-Acetyl-2-phenylamino-5-[3-(4-methylphenyl)-sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (5b). Pale yellow powder from EtOH; yield 64%; mp 192–193 °C; IR (KBr) 3298, 1735, 1658, 1636, 1600, 1261 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.12 (s, 3H), 2.28 (s, 3H), 6.73 (s, 1H), 6.92–6.99 (m, 1H), 7.25–7.40 (m, 6H), 7.71 (d, J=8.4 Hz, 2H), 9.57 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.92, 22.26, 57.84, 106.88, 117.64, 121.92, 125.58, 129.07, 130.39, 130.74, 140.48, 142.87, 145.78, 164.90, 167.14; EIMS (30 eV) *m/z* (%): 395 (M^+, 33), 353 (4), 178 (100). Anal. Calcd for $C_{19}H_{17}N_5O_3S$: C, 57.71; H, 4.33; N, 17.71; S, 8.11. Found: C, 57.63; H, 4.38; N, 17.60; S, 7.93.

4.3.3. 4-Acetyl-2-phenylamino-5-[3-(4-methoxyphenyl) sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (5c). Yellow powder from EtOH; yield 60%; mp 128–130 °C; IR (KBr) 3278, 1747, 1653, 1600, 1258 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.13 (s, 3H), 3.71 (s, 3H), 6.74 (s, 1H), 6.92–7.00 (m, 1H), 7.14 (d, J=9.0 Hz, 2H), 7.25–7.41 (m, 4H), 7.79 (d, J=9.0 Hz, 2H), 9.59 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.31, 55.81, 57.93, 106.95, 115.06, 117.65, 121.96, 125.77, 129.10, 140.49, 145.86, 162.08, 164.96, 167.22; FABMS *m/z* (%): 412 (M^++H, 100), 411 (M^+, 51). Anal. Calcd for $C_{19}H_{17}N_5O_4S$: C, 55.47; H, 4.16; N, 17.02; S, 7.79. Found: C, 55.30; H, 4.17; N, 16.89; S, 7.64.

4.3.4. 4-Acetyl-2-phenylamino-5-[3-(4-ethoxyphenyl) sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (5d). Yellow crystals from EtOH; yield 70%; mp 122–123 °C; IR (KBr) 3278, 1726, 1658, 1617, 1599, 1259 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (t, J=7.1 Hz, 3H), 2.11 (s, 3H), 3.91 (q, J=7.1 Hz, 2H), 6.72 (s, 1H), 6.90–6.97 (m, 1H), 7.08 (d, J=8.9 Hz, 2H), 7.23–7.38 (m, 4H), 7.72 (d, J=8.9 Hz, 2H), 9.53 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.58, 22.31, 57.85, 63.91, 107.01, 115.35, 117.59, 121.88, 125.56, 127.34, 129.06, 140.46, 145.75, 161.38, 164.96, 167.14; FABMS *m/z* (%): 426 (M^++H, 100), 425 (M^+, 60). Anal. Calcd for $C_{20}H_{19}N_5O_4S$: C, 56.46; H, 4.50; N, 16.46; S, 7.54. Found: C, 56.24; H, 4.67; N, 16.25; S, 7.44. X-ray analytical data is listed in Table 1. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 277499.

4.4. Syntheses of 4-acetyl-2-(*N*-phenylacetamido)-5-(3-arylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles (6a–d)

To a solution of 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbazone (**3a**, 1.017 g, 3.0 mmol) in dichloromethane (30 mL), 15 mL of acetic anhydride was added. The mixed solution was heated at 75 °C for 45 h until the reaction was completed and then allowed to stand at room temperature. The reaction mixture was slowly added to 300 mL of ice-cooled water, and then stirred to room temperature. The reaction mixture was extracted with 300 mL of *n*-hexane–ethyl acetate (2/1). The combined organic layer was vigorously washed with sodium hydrogencarbonate solution (200 mg of sodium hydrogencarbonate in 50 mL of water), dried with anhydrous sodium sulfate and decolorized with charcoal. The filtrate was concentrated to a small volume to give yellow solid. The resulted solid was collected by filtration and washed with *n*-hexane to afford 583 mg (46%) of 4-acetyl-2-(*N*-phenylacetamido)-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (**6a**) as yellow crystals. The chemical and physical spectral characteristics of these products **6a–d** are given below.

4.4.1. 4-Acetyl-2-(*N*-phenylacetamido)-5-(3-phenyl-sydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (6a). Yellow crystals from EtOAc/*n*-hexane; yield 46%; mp 173–175 °C; IR (KBr) 3050, 2971, 1744, 1685, 1652, 1600, 1401, 1300 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.69 (s, 3H), 1.91 (s, 3H), 6.58 (s, 1H), 7.42–7.57 (m, 5H), 7.67–7.90 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 21.30, 23.43, 58.41, 106.52, 125.80, 128.69, 129.30, 129.70, 130.16, 132.68, 133.23, 139.29, 147.95, 165.05, 168.28, 170.87; EIMS (30 eV) *m/z* (%): 423 (M^+, 43), 381 (39), 220 (62), 178 (100). Anal. Calcd for $C_{20}H_{17}N_5O_4S$: C, 56.73; H, 4.05; N, 16.54; S, 7.57. Found: C, 56.75; H, 4.08; N, 16.48; S, 7.62. X-ray analytical data is listed in Table 1. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 277500.

4.4.2. 4-Acetyl-2-(*N*-phenylacetamido)-5-[3-(4-methylphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (6b). Yellow powder from EtOAc/*n*-hexane; yield 40%; mp 165–166 °C; IR (KBr) 3070, 2960, 1744, 1685, 1664, 1594,

1397, 1299 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.69 (s, 3H), 1.91 (s, 3H), 2.44 (s, 3H), 6.56 (s, 1H), 7.41–7.52 (m, 7H), 7.74 (d, J=8.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 21.08, 21.31, 23.45, 58.41, 106.50, 125.52, 128.70, 129.31, 129.70, 130.55, 130.80, 139.29, 142.91, 147.87, 165.08, 168.25, 170.87; EIMS (30 eV) m/z (%): 437 (M^+, 32), 395 (31), 220 (89), 178 (100). Anal. Calcd for $C_{21}H_{19}N_5O_4S$: C, 57.66; H, 4.38; N, 16.01; S, 7.33. Found: C, 57.76; H, 4.46; N, 15.93; S, 7.38.

4.4.3. 4-Acetyl-2-(*N*-phenylacetamido)-5-[3-(4-methoxyphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (6c). White powder from EtOAc/*n*-hexane; yield 52%; mp 220–222 °C; IR (KBr) 3084, 2973, 1749, 1675, 1667, 1601, 1396, 1367, 1302 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.69 (s, 3H), 1.91 (s, 3H), 3.86 (s, 3H), 6.56 (s, 1H), 7.21 (d, J=9.2 Hz, 2H), 7.40–7.53 (m, 5H), 7.78 (d, J=9.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 21.33, 23.43, 56.04, 58.43, 106.59, 115.19, 125.78, 127.33, 128.68, 129.30, 129.69, 139.29, 147.87, 162.09, 165.08, 168.25, 170.85; EIMS (30 eV) m/z (%): 453 (M^+, 35), 411 (29), 220 (98), 178 (100). Anal. Calcd for $C_{21}H_{19}N_5O_5S$: C, 55.62; H, 4.22; N, 15.44; S, 7.07. Found: C, 55.63; H, 4.31; N, 15.29; S, 7.08.

4.4.4. 4-Acetyl-2-(*N*-phenylacetamido)-5-[3-(4-ethoxyphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (6d). Yellow powder from EtOAc/*n*-hexane; yield 46%; mp 170–171 °C; IR (KBr) 3074, 2991, 1748, 1680, 1664, 1591, 1368, 1311, 1251 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.37 (t, J=7.1 Hz, 3H), 1.70 (s, 3H), 1.91 (s, 3H), 4.14 (q, J=7.1 Hz, 2H), 6.57 (s, 1H), 7.20 (d, J=9.1 Hz, 2H), 7.41–7.54 (m, 5H), 7.77 (d, J=9.1 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 14.65, 21.34, 23.43, 58.47, 64.14, 106.59, 115.55, 125.63, 127.30, 128.68, 129.32, 129.69, 139.31, 147.86, 161.41, 165.11, 168.28, 170.87; EIMS (30 eV) m/z (%): 467 (M^+, 32), 425 (19), 220 (100), 178 (69). Anal. Calcd for $C_{22}H_{21}N_5O_5S$: C, 56.52; H, 4.53; N, 14.98; S, 6.86. Found: C, 56.34; H, 4.58; N, 14.91; S, 6.83.

4.5. Syntheses of 4-acetyl-2-acetamido-5-(3-arylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles (6e–h)

The solution of 3-phenyl-4-formylsydnone 4′-thiosemicarbarzone (**3e**, 526 mg, 2.0 mmol) in acetic anhydride (12 mL) was heated at 60 °C for 7–9 h until the reaction was completed and then allowed to attain room temperature. The reaction mixture was slowly added to 300 mL of ice-cooled water, and the mixture was stirred to room temperature. The water solution was extracted with 200 mL of ethyl acetate–*n*-hexane (1/3). The combined organic layer was vigorously washed with sodium hydrogencarbonate solution (150 mg of sodium hydrogencarbonate in 50 mL of water), dried with anhydrous sodium sulfate and decolorized with charcoal. The filtrate was concentrated to a small volume to give orange solid. The resulted solid was collected by filtration and washed with *n*-hexane to afford 592 mg (85%) of 4-acetyl-2-acetamido-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (**6e**) as orange powder. The chemical and physical spectral characteristics of these products **6e–h** are given below.

4.5.1. 4-Acetyl-2-acetamido-5-(3-phenylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazole (6e). Orange powder from EtOAc/*n*-hexane; yield 85%; mp 206–207 °C; IR (KBr) 3167, 3089, 2975, 1731, 1687, 1662, 1618, 1340, 1243 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 2.05 (s, 3H), 6.50 (s, 1H), 7.65–7.87 (m, 5H), 11.69 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.95, 22.54, 57.12, 106.63, 125.82, 130.15, 132.67, 133.20, 144.95, 164.88, 167.96, 169.76; EIMS (30 eV) m/z (%): 347 (M^+, 25), 305 (26), 186 (19), 144 (100). Anal. Calcd for $C_{14}H_{13}N_5O_4S$: C, 48.41; H, 3.77; N, 20.16; S, 9.23. Found: C, 48.39; H, 3.81; N, 20.05; S, 9.26.

4.5.2. 4-Acetyl-2-acetamido-5-[3-(4-methylphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (6f). Yellow powder from EtOAc/*n*-hexane; yield 88%; mp 210–211 °C; IR (KBr) 3158, 3079, 2962, 1726, 1685, 1664, 1610, 1398, 1238 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (s, 3H), 2.06 (s, 3H), 2.43 (s, 3H), 6.49 (s, 1H), 7.49 (d, J=8.3 Hz, 2H), 7.72 (d, J=8.3 Hz, 2H), 11.70 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.08, 21.96, 22.52, 57.12, 106.60, 125.56, 130.51, 130.74, 142.96, 144.89, 164.91, 167.95, 169.76; EIMS (30 eV) m/z (%): 361 (M^+, 25), 319 (18), 186 (24), 144 (100). Anal. Calcd for $C_{15}H_{15}N_5O_4S$: C, 49.86; H, 4.18; N, 19.38; S, 8.87. Found: C, 50.02; H, 4.24; N, 19.11; S, 8.77.

4.5.3. 4-Acetyl-2-acetamido-5-[3-(4-methoxyphenyl)-sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (6g). Pale yellow crystals from EtOAc/*n*-hexane; yield 92%; mp 173–175 °C; IR (KBr) 3156, 3079, 2968, 1728, 1681, 1663, 1512, 1395, 1243 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (s, 3H), 2.07 (s, 3H), 3.87 (s, 3H), 6.50 (s, 1H), 7.21 (d, J=9.1 Hz, 2H), 7.77 (d, J=9.1 Hz, 2H), 11.71 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.98, 22.52, 56.02, 57.12, 106.73, 115.17, 125.75, 127.33, 144.90, 162.11, 164.93, 167.93, 169.73; EIMS (30 eV) m/z (%): 377 (M^+, 17), 335 (13), 186 (35), 144 (100). Anal. Calcd for $C_{15}H_{15}N_5O_5S$: C, 47.74; H, 4.01; N, 18.56; S, 8.50. Found: C, 47.76; H, 4.06; N, 18.56; S, 8.52. X-ray analytical data is listed in Table 2. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 277501.

4.5.4. 4-Acetyl-2-acetamido-5-[3-(4-ethoxyphenyl)sydnon-4-yl]-4,5-dihydro-[1,3,4]thiadiazole (6h). Yellow powder from EtOAc/*n*-hexane; yield 91%; mp 170–171 °C; IR (KBr) 3166, 3089, 2982, 2939, 1736, 1694, 1660, 1620, 1397, 1250 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.35 (t, J=7.1 Hz, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 4.13 (q, J=7.1 Hz, 2H), 6.49 (s, 1H), 7.18 (d, J=8.9 Hz, 2H), 7.74(d, J=8.9 Hz, 2H), 11.70 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.67, 22.02, 22.56, 57.18, 64.13, 106.72, 115.56, 125.63, 127.35, 144.93, 161.44, 164.96, 167.95, 169.77; EIMS (30 eV) m/z (%): 391 (M^+, 19), 349 (5), 186 (35), 144 (100). Anal. Calcd for $C_{16}H_{17}N_5O_5S$: C, 49.10; H, 4.38; N, 17.89; S, 8.19. Found: C, 49.01; H, 4.45; N, 17.73; S, 8.17.

4.6. Syntheses of 5-(3-arylsydnon-4-yl)-2-phenylamino-[1,3,4]thiadiazoles (7a–d)

To a solution of 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbarzone (**3a**, 339 mg, 1.00 mmol) in 95% ethanol (1 mL) was slowly added an aqueous solution (6 mL) of ferric chloride (649 mg, 4.00 mmol). The mixed solution was heated at 80 °C for 24 h and then cooled. The

precipitating solid was collected by filtration and washed with ice-cold water and cold ethanol. The collected solid was recrystallized from acetone–ethanol to afford 155 mg (46%) of 5-(3-phenylsydnon-4-yl)-2-phenylamino-[1,3,4]thiadiazole (**7a**) as yellow needles. The chemical and physical spectral characteristics of these products **7a–d** are given below.

4.6.1. 5-(3-Phenylsydnon-4-yl)-2-phenylamino-[1,3,4]thiadiazole (7a). Yellow needles from CH_3COCH_3/EtOH; yield 46%; mp 291–292 °C; IR (KBr) 3315, 1731, 1605, 1557, 1497, 1488, 1446 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.00–7.86 (m, 10H); 10.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 103.06, 117.79, 122.41, 126.11, 129.27, 129.73, 132.55, 134.63, 140.35, 142.59, 164.08, 165.74; FABMS *m/z* (%): 338 (M^++H, 100), 337 (M^+, 33), 280 (M^++H–NO–CO, 22), 279 (M^+−NO–CO, 26). Anal. Calcd for $C_{16}H_{11}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76. Found: C, 56.84; H, 3.30; N, 20.57.

4.6.2. 5-[3-(4-Methylphenyl)sydnon-4-yl]-2-phenylamino-[1,3,4]thiadiazole (7b). Yellow powder from CH_3COCH_3/EtOH; yield 48%; mp 280–281 °C; IR (KBr) 3254, 1740, 1602, 1572, 1504, 1453, 1435 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.43 (s, 3H); 6.97 (t, J=7.8 Hz, 1H), 7.30 (t, J=7.8 Hz, 2H), 7.46 (d, J=8.4 Hz, 2H), 7.55 (d, J=7.8 Hz, 2H), 7.70 (d, J=8.4 Hz, 2H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.14, 102.94, 117.77, 122.39, 125.84, 129.26, 130.10, 132.14, 140.35, 142.64, 142.71, 164.05, 165.74; FABMS *m/z* (%): 352 (M^++H, 100), 351 (M^+, 37), 294 (M^++H–NO–CO, 47), 293 (M^+−NO–CO, 70). Anal. Calcd for $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93. Found: C, 58.04; H, 3.82; N, 19.87.

4.6.3. 5-[3-(4-Methyoxyphenyl)sydnon-4-yl]-2-phenylamino-[1,3,4]thiadiazole (7c). Yellow powder from CH_3COCH_3/EtOH; yield 60%; mp 275–276 °C; IR (KBr) 3325, 1731, 1602, 1550, 1493, 1444 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.88 (s, 3H); 6.99 (t, J=7.9 Hz, 1H), 7.20 (d, J=9.0 Hz, 2H), 7.31 (t, J=7.9 Hz, 2H), 7.57 (d, J=7.9 Hz, 2H), 7.77 (d, J=9.0 Hz, 2H), 10.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 56.00, 103.08, 114.77, 117.78, 122.41, 127.11, 127.71, 129.30, 140.38, 142.81, 162.09, 164.00, 165.76; FABMS *m/z* (%): 368 (M^++H, 100), 367 (M^+, 36). Anal. Calcd for $C_{17}H_{13}N_5O_3S$: C, 55.58; H, 3.57; N, 19.06. Found: C, 55.72; H, 3.68; N, 18.81.

4.6.4. 5-[3-(4-Ethoxyphenyl)sydnon-4-yl]-2-phenylamino-[1,3,4]thiadiazole (7d). Yellow powder from CH_3COCH_3/EtOH; yield 40%; mp 280–282 °C; IR (KBr) 3322, 1731, 1605, 1556, 1500, 1490, 1443 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.36 (t, J=6.9 Hz, 3H), 4.13 (q, J=6.9 Hz, 2H), 6.97 (t, J=7.8 Hz, 1H), 7.16 (d, J=9.0 Hz, 2H), 7.30 (t, J=7.8 Hz, 2H), 7.56 (d, J=7.8 Hz, 2H), 7.74 (d, J=9.0 Hz, 2H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.65, 64.02, 103.00, 115.07, 117.75, 122.36, 126.88, 127.65, 129.23, 140.35, 142.76, 161.37, 163.99, 165.67; FABMS *m/z* (%): 382 (M^++H, 100), 381 (M^+, 30), 324 (M^++H–NO–CO, 38), 323 (M^+−NO–CO, 62). Anal. Calcd for $C_{18}H_{15}N_5O_3S$: C, 56.68; H, 3.96; N, 18.36. Found: C, 56.64; H, 4.01; N, 18.41.

4.7. Syntheses of 2-amino-5-(3-arylsydnon-4-yl)-[1,3,4] thiadiazoles (7e–h)

To a solution of 3-phenyl-4-formylsydnone 4′-thiosemicarbarzone (**3e**, 263 mg, 1.00 mmol) in 95% ethanol (1 mL), the solution of ferric chloride (649 mg, 4.00 mmol) in water (6 mL) was added dropwise. The mixed solution was heated at 60 °C for about 7 h until the reaction was completed and then cooled. The precipitating solid was collected by filtration and washed with ice-cold water, cold ethanol. The collected solid was recrystallized from dichloromethane–ethanol to afford 131 mg (50%) of 2-amino-5-(3-phenylsydnon-4-yl)-[1,3,4]thiadiazole (**7e**) as yellow crystals. The chemical and physical spectral characteristics of these products **7e–h** are given below.

4.7.1. 2-Amino-5-(3-phenylsydnon-4-yl)-[1,3,4]thiadiazole (7e). Yellow crystals from CH_2Cl_2/EtOH; yield 50%; mp 257–258 °C; IR (KBr) 3349, 3282, 3168, 1730, 1621, 1478, 1264 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.45 (s, 2H), 7.62–7.82 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 103.28, 126.07, 129.69, 132.44, 134.58, 141.03, 165.61, 168.79; FABMS *m/z* (%): 262 (M^++H, 100), 261 (M^+, 30), 204 (M^++H–NO–CO, 20), 203 (M^+−NO–CO, 28). Anal. Calcd for $C_{10}H_7N_5O_2S$: C, 45.97; H, 2.70; N, 26.81. Found: C, 45.85; H, 2.72; N, 26.61. X-ray analytical data is listed in Table 2. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 277502.

4.7.2. 2-Amino-5-[3-(4-methylphenyl)sydnon-4-yl]-[1,3,4]thiadiazole (7f). Yellow powder from CH_2Cl_2/EtOH; yield 45%; mp 258–259 °C; IR (KBr) 3429, 3275, 3122, 1740, 1625, 1504, 1438, 1259 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.41 (s, 3H), 7.41 (s, 2H), 7.43 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 21.09, 103.14, 125.78, 130.06, 132.08, 141.08, 142.57, 165.56, 168.81; FABMS *m/z* (%): 276 (M^++H, 100), 275 (M^+, 27), 218 (M^++H–NO–CO, 33), 217 (M^+−NO–CO, 47). Anal. Calcd for $C_{11}H_9N_5O_2S$: C, 47.99; H, 3.30; N, 25.44. Found: C, 47.77; H, 3.43; N, 25.22.

4.7.3. 2-Amino-5-[3-(4-methoxyphenyl)sydnon-4-yl]-[1,3,4]thiadiazole (7g). Brown powder from CH_2Cl_2/EtOH; yield 60%; mp 219–220 °C; IR (KBr) 3425, 3273, 3119, 1739, 1625, 1605, 1503, 1438, 1253 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.87 (s, 3H), 7.18 (d, J=8.9 Hz, 2H), 7.44 (s, 2H), 7.73 (d, J=8.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 55.93, 103.26, 114.72, 127.04, 127.62, 141.17, 161.97, 165.54, 168.74; FABMS *m/z* (%): 292 (M^++H, 100), 291 (M^+, 26), 234 (M^++H–NO–CO, 26), 233 (M^+−NO–CO, 42). Anal. Calcd for $C_{11}H_9N_5O_3S$: C, 45.36; H, 3.11; N, 24.04. Found: C, 45.55; H, 3.25; N, 23.85.

4.7.4. 2-Amino-5-[3-(4-ethoxyphenyl)sydnon-4-yl]-[1,3,4]thiadiazole (7h). Brown powder from CH_2Cl_2/EtOH; yield 65%; mp 225–226 °C; IR (KBr) 3411, 3267, 3089, 1743, 1629, 1608, 1592, 1510, 1439, 1256 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.36 (t, J=6.9 Hz, 3H), 4.13 (q, J=6.9 Hz, 2H), 7.15 (d, J=8.8 Hz, 2H), 7.44 (s, 2H), 7.71 (d, J=8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 14.64, 64.02, 103.25, 115.07, 126.86, 127.62, 141.23, 161.29, 165.53, 168.78; FABMS *m/z* (%): 306 (M^++H, 100), 305 (M^+, 21), 248

(M^+ +H–NO–CO, 29), 247 (M^+ −NO–CO, 50). Anal. Calcd for $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.63; N, 22.94. Found: C, 47.18; H, 3.72; N, 22.66.

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References and notes

1. Imashiro, Y.; Masuda, K. Japan Patent 6932411, 1969; *Chem. Abstr.* **1970**, *72*, 111482q.
2. Saito, Y.; Kamitani, T. Japan Patent 7021710, 1970; *Chem. Abstr.* **1970**, *73*, 87926k.
3. Masuda, K.; Okutani, T. Japan Patent 7020903, 1970; *Chem. Abstr.* **1970**, *74*, 87928n.
4. Satyanarayana, K.; Rao, M. N. A. *J. Pharm. Sci.* **1995**, *84*, 263–266.
5. Satyanarayana, K.; Rao, M. N. A. *Eur. J. Med. Chem.* **1995**, *30*, 641–645.
6. Kavali, J. R.; Badami, B. V. *II Farmaco* **2000**, *55*, 406–409.
7. Pan, K.; Scott, M. K.; Lee, D. H. S.; Fitzpatrick, L. J.; Crooke, J. J.; Rivero, R. A.; Rosenthal, D. I.; Vaidya, A. H.; Zhao, B.; Reiz, A. B. *Bioorg. Med. Chem.* **2003**, *11*, 185–192.
8. Jung, K. Y.; Kim, S. K.; Gao, Z. G.; Gross, A. S.; Melman, N.; Jacobson, K. A.; Kim, Y. C. *Bioorg. Med. Chem.* **2004**, *12*, 613–623.
9. Foroumadi, A.; Asadipour, A.; Mirzaei, M.; Karimi, J.; Emami, S. *II Farmaco* **2002**, *57*, 765–769.
10. Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M.; Daneshtalab, M.; Shafiee, A. *II Farmaco* **2002**, *58*, 63–68.
11. Leung-Toung, R.; Wodzinska, J.; Li, W.; Lowrie, J.; Kukreja, R.; Desilets, D.; Karimian, K.; Tam, T. F. *Bioorg. Med. Chem.* **2003**, *11*, 5529–5537.
12. Desai, N. C.; Parekh, B. R.; Thaker, K. A. *J. Indian Chem. Soc.* **1987**, *64*, 491–493.
13. Shih, M. H.; Lu, L. H.; Yeh, M. Y. *J. Chin. Chem. Soc.* **2001**, *48*, 883–892.
14. Shih, M. H.; Her, K. H.; Yeh, M. Y. *J. Chin. Chem. Soc.* **2001**, *48*, 1143–1152.
15. Shih, M. H.; Lee, M. J.; Yeh, M. Y. *J. Chin. Chem. Soc.* **2002**, *49*, 361–368.
16. Shih, M. H. *Tetrahedron* **2002**, *58*, 10437–10445.
17. Shih, M. H.; Yeh, M. Y. *Tetrahedron* **2003**, *59*, 4103–4111.
18. Shih, M. H. *Synthesis* **2004**, *1*, 26–32.
19. Shih, M. H.; Ke, F. Y. *Bioorg. Med. Chem.* **2004**, *12*, 4633–4643.
20. Shih, M. H.; Yeh, M. Y.; Lee, M. J. *Synthesis* **2004**, *17*, 2877–2885.
21. Shukla, H. K.; Desai, N. C.; Astik, R. R.; Thaker, K. A. *J. Indian Chem. Soc.* **1984**, 168–169.
22. Desai, N. C.; Shukla, H. K.; Parekh, B. P.; Thaker, K. A. *J. Indian Chem. Soc.* **1984**, 455–457.
23. Marusawa, H.; Setoi, H.; Kuroda, A.; Sawada, A.; Seki, J.; Motoyama, Y.; Tanaka, H. *Bioorg. Med. Chem.* **1999**, *7*, 2635–2645.
24. Tarasconi, P.; Capacchi, S.; Pelosi, G.; Cornia, M.; Albertini, R.; Bonati, A.; Dall'Aglio, P. P.; Lunghi, P.; Pinelli, S. *Bioorg. Med. Chem.* **2000**, *8*, 157–162.
25. Gruttadauria, M.; Buccheri, F.; Cusmano, G.; Meo, P. L.; Noto, R.; Werber, G. *J. Heterocycl. Chem.* **1993**, *30*, 765–770.
26. EL Ashry, E. S. H.; Nassr, M. A.; EL Kilany, Y.; Mousaad, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3405–3409.
27. Kubota, S.; Ueda, Y.; Fujkane, K.; Toyooka, K.; Shibuya, M. *J. Org. Chem.* **1980**, *45*, 1473–1477.
28. Li, Z.; Wang, X.; Da, Y. *Synth. Commun.* **2001**, *31*, 1829–1936.
29. Supuran, C. T.; Briganti, F.; Tilli, S.; Chegwidden, W. R.; Scozzafava, A. *Bioorg. Med. Chem.* **2001**, *9*, 703–714.

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Horseradish peroxidase (HRP) catalyzed oxidative coupling reactions using aqueous hydrogen peroxide: an environmentally benign procedure for the synthesis of azine pigments

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Abstract—The horseradish peroxidase (HRP) catalyzed oxidative coupling of 2-hydrazono-4-thiazolines with α-naphthol using aqueous hdrogen peroxide. These transformations allow an environmentally benign synthesis of *p*-naphthoquinone-thiazol-2-on-azines under mild conditions.

1. Introduction

The development of transition metal or enzyme catalyzed oxidations using stoichiometric amounts of hydrogen peroxide are of considerable interest in green chemistry since they represent environmentally benign processes.[1] These transformations significantly reduce the formation of waste since hydrogen peroxide is reduced to water and only catalytic amounts of transition metal or enzyme are required. In addition, they are low-cost processes, which allow the use of aqueous solvent systems and non-toxic starting materials. In the course of our efforts directed towards the development of environmentally friendly catalytic procedures, the oxidative dimerization of salicylic esters by air in aqueous solution catalysed by a laccase (multi-copper oxidase) has been recently reported.[2] Some years ago, one of us reported the horseradish peroxidase (HRP) catalysed synthesis of 4-(Δ^4-thiazolin-2-ylidene-hydrazono)-Δ^4-pyrazolin-5-ones using stoichiometric amounts of hydrogen peroxide.[3,4] HRP represents a haem-containing enzyme; its catalytic pathway has been recently studied by crystal structure analyses.[5] Recently, the synthesis of azine pigments by HRP catalyzed oxidative coupling of 3-alkyl-2-hydrazono-4-thiazolines and α-naphthol in the presence of hydrogen peroxide has been studied.[6] Herein, full details of our study are reported.

2. Results and discussion

Our starting point was the development of an efficient method for the synthesis of the starting materials, for example, 2-hydrazono-4-thiazolines. These molecules are not readily available, since the cyclization of α-haloketones with thiosemicarbazides can result in the formation of up to four regioisomeric products depending on the substituents and reaction conditions.[7] Some years ago, one of us has reported the synthesis of 2-hydrazono-4,5-diphenyl-4-thiazolines by acid catalyzed hydrolysis of 2-isopropylidenehydrazono-4-thiazolines.[8] This approach was successfully applied to the synthesis of alkyl substituted thiazolines, such as **4a** and **4b** (Scheme 1, method A): the reaction of α-bromopropiophenone (**1**) with thiosemicarbazones **2a**,**b** regioselectively afforded the protected thiazolines **3a** and **3b** in good yields. Treatment of **3a**,**b** with aqueous hydrochloric acid (18%) resulted in deprotection and formation of the desired 2-hydrazono-4-thiazolines **4a** and **4b** in 44 and 82% yield, respectively. The isolation of **4a**,**b** in form of their hydrochlorides proved mandatory, due to the oxygen sensitivity of the free bases. However, the synthesis of 2-hydrazono-3-alkyl-4-thiazolines **4** by method A is limited by the fact that, under the harsh reaction conditions

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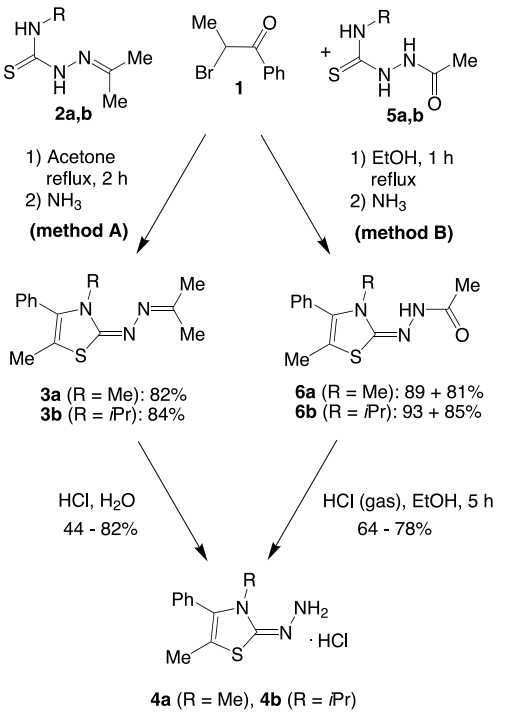


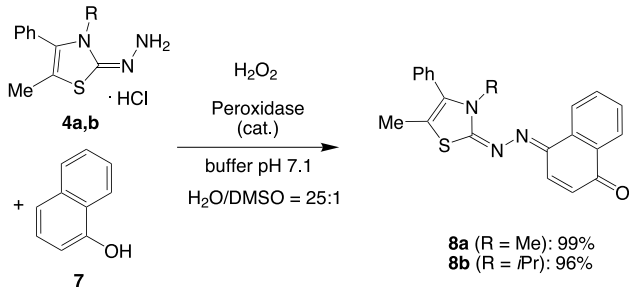
Scheme 1. Synthesis of hydrazones **4a**,**b**.

required, the products readily underwent a rearrangement into the isomeric 3-amino-2-alkylimino-4-thiazolines.[9]

To overcome the limitations associated with method A a new synthesis of 2-hydrazono-4-thiazolines **4** was developed (Scheme 1, method B): the reaction of **1** with 1-acetyl-4-alkyl-thiosemicarbazides **5a**,**b** afforded the 2-(*N*-acetylhydrazono)-3-alkyl-4-phenyl-4-thiazoline hydrobromides **6a**·**HBr** and **6b**·**HBr** in 89 and 93% yield, respectively. The hydrobromides were transformed by treatment with concentrated aqueous ammonia into the free bases **6a** and **6b** in 81 and 85% yield, respectively. The acetyl group was cleaved under mild conditions by using an ethanol solution saturated with hydrogen chloride gas. The desired thiazolines **4a**,**b** were isolated in 64–78% yield.

The classical oxidative coupling of hydrazone **4a** with α-naphthol (**7**)—using stoichiometric amounts of potassium hexacyanoferrate(III)—afforded the *p*-naphthoquinonethiazol-2-onazine **8a** in quantitative yield.[10] The horseradish peroxidase (HRP) catalyzed reaction of **4a** with **7** using aqueous hydrogen peroxide afforded **8a**, after optimization of the conditions, in up to 99% yield (Scheme 2). In the absence of HRP the rate of the reaction was extremely low and almost no conversion was observed. The starting material **4a** had to be used in the form of its hydrochloride, because of the high water solubility of the latter. The reaction of **7** with thiazoline **4b** afforded the azine **8b** in 96% yield. The azines **8a**,**b** can be regarded as meroyanine dyes containing a push–pull heterocyclic system and were obtained as green to nearly black crystals. All reactions were arried out on a 1 mmol scale.

In summary, we have reported the horseradish peroxidase (HRP) catalyzed oxidative coupling of 2-hydrazono-4-thiazolines



Scheme 2. Peroxidase catalyzed synthesis of pigments **8a**,**b** using aqueous H_2O_2.

with α-naphthol using aqueous hydrogen peroxide. These reactions allow an environmentally benign synthesis of *p*-naphthoquinone-thiazol-2-on-azines under mild conditions.

3. Experimental

3.1. General

3.1.1. 3,5-Dimethyl-2-isopropylidenehydrazono-4-phenyl-1,3-thiazoline (3a). An acetone solution (20 mL) of 4-methyl-1-isopropylidene-thiosemicarbazone (3.04 g, 20 mmol) and α-bromopropiophenone (4.26 g, 20 mmol) was refluxed for 2 h. After cooling to ambient temperature and addition of concentrated aqueous ammonia (20 mL) a crystalline precipitate was formed. The product was filtered off and recrystallized from EtOH to give **3a** as slight yellow needles (4.30 g, 82%), mp 112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.98 (s, 3H, 5-Me), 2.05, 2.07 (2×s, 2×3H, N=CMe_2), 3.15 (s, 3H, NMe), 7.25–7.48 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=12.73, 18.07, 24.95, 33.32, 109.18, 128.68, 128.73, 130.13, 130.60, 134.66, 158.02, 166.05. IR (KBr, cm^{-1}): $\tilde{\nu}$ 702 (m), 786 (m), 982 (m), 1067 (m), 1259 (m), 1346 (s), 1413 (s), 1566 (s), 1626 (s), 2911 (m). Anal. Calcd for $C_{14}H_{17}N_3S$ (259.38): C, 64.83; H, 6.61; N, 16.20. Found: C, 65.00; H, 6.78; N, 15.96.

3.1.2. 3-Isopropyl-2-isopropylidenehydrazono-5-methyl-phenyl-1,3-thiazoline (3b). Product **3b** was obtained from 4-isopropyl-1-isopropylidene-thiosemicarbazone (1.73 g, 10 mmol) and α-bromopropiophenone (2.13 g, 10 mmol) in acetone (20 mL) as described for **3a**. Yield: 2.41 g, 84%, yellow lamella, mp 131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.44–1.46 [d, 2×3H, 2×CH(CH_3)$_2$], 1.87 (s, 3H, 5-CH_3), 2.04, 2.06 [2×s, 2×3H, N=C(CH_3)$_2$], 3.84–3.89 (m, 1H, NCH), 7.23–7.44 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=12.70, 18.44, 18.82, 24.64, 50.51, 108.40, 128.51, 130.03, 131.79, 134.81, 157.33, 164.21. IR (KBr, cm^{-1}): $\tilde{\nu}$ 703 (m), 735 (m), 788 (m), 812 (m), 1075 (m), 1109 (m), 1253 (m), 1303 (s), 1334 (s), 1369 (m), 1445 (m), 1558 (s), 1623 (m), 1645 (m), 2917 (m), 2928 (m), 2970 (m). Anal. Calcd for $C_{16}H_{21}N_3S$ (287.43): C, 66.86; H, 7.36; N, 14.62. Found: C, 66.82; H, 7.46; N, 14.58.

3.1.3. 2-(*N*-Acetylhydrazono)-3,5-dimethyl-4-phenyl-1,3-thiazoline (6a). An EtOH solution (50 mL) of 1-acetyl-4-methyl-thiosemicarbazide (1.47 g, 10 mmol) and α-bromopropiophenone (2.16 g, 10 mmol) was refluxed for 1 h. After cooling to ambient temperature and addition of Et_2O a

crystalline precipitate was formed, which was recrystallized from EtOH to give **6a·HBr** as colourless rods (3.05 g, 89%). Anal. Calcd for $C_{13}H_{16}N_3BrOS$ (342.26): C, 45.62; H, 4.71; N, 12.28. Found: C, 45.75; H, 4.86; N, 12.08. Synthesis of the free base **6a**: hydrobromide **6a·HBr** (3.42 g, 10 mmol) was dissolved in EtOH (20 mL) and concentrated aqueous ammonia (20 mL) was added dropwise to give a colourless precipitate. The solid was recrystallized from EtOH to give **6a** as colourless prisms (2.13 g, 81%), mp 189–190 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ=1.85 (s, 3H, 5-Me), 1.94 (s, 3H, Me–CO), 3.02 (s, 3H, NMe), 7.37–7.56 (m, 5H, ArH), 9.87 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ=12.18, 21.08, 32.88, 106.15, 128.76, 128.98, 129.42, 129.91, 134.70, 164.66, 165.50. IR (KBr, cm^{-1}): $\tilde{\nu}$ 705 (m), 789 (m), 1004 (m), 1346 (m), 13.72 (m), 1421 (m), 1444 (m), 1566 (s), 1578 (s), 1629 (s), 1646 (s), 2948 (m), 2971 (m), 3152 (m). Anal. Calcd for $C_{13}H_{15}N_3OS$ (261.34): C, 59.75; H, 5.78; N, 16.08. Found: C, 59.82; H, 5.86; N, 16.08.

3.1.4. 2-(*N*-Acetylhydrazono)-3,5-dimethyl-4-phenyl-1,3-thiazoline (6b). The compound was obtained from 1-acetyl-4-isopropyl-thiosemicarbazide (1.75 g, 10 mmol) and α-bromopropiophenone (2.16 g, 10 mmol) in EtOH (50 mL) as described for **6a**. Yield of **6b·HBr**: 3.45 g, 93%, colourless rods (EtOH), mp 152–155 °C. Yield **6b**: 2.46 g, 85%, colourless prisms (EtOH), mp 208–209 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.40–1.43 [d, 2×3H, $CH(CH_3)_2$], 1.89 (s, 3H, 5-CH_3), 2.15 (s, 3H, CH_3CO), 3.82–3.91 [m, 1H, $CH(CH_3)_2$], 7.14–7.49 (m, 5H, ArH), 9.90 (s, 1H, NH). IR (KBr, cm^{-1}): $\tilde{\nu}$ 734 (m), 787 (m), 1007 (m), 1108 (m), 1215 (m), 1297 (s), 1335 (m), 1443 (m), 1544 (s), 1579 (s), 1655 (s), 1676 (m), 3051 (m), 3228 (m). Anal. Calcd for $C_{15}H_{19}N_3OS$ (289.39): C, 62.25; H, 6.62; N, 14.52. Found: C, 62.32; H, 6.86; N, 14.58.

3.1.5. 3,5-Dimethyl-2-hydrazono-4-phenyl-1,3-thiazoline hydrochloride (4a). *Method A*. Thiazoline **3a** (7.80 g, 30 mmol) was dissolved in an aqueous solution of HCl (200 mL, 18%). A steam distillation of the mixture gave 5–6 l of an aqueous solution. The hot solution was filtered, cooled and subsequently NH_3 was added. A yellow oil was separated, which was washed with H_2O. The oil was dissolved in EtOH/HCl (50 mL) and treated with Et_2O (150 mL) until the solution became cloudy. After a few minutes a colourless precipitate was formed, which was separated by filtration. The product was recrystallized from EtOH/Et_2O to give **4a** as colourless rods (3.40 g, 44%), mp 185–187 °C.

Method B. An EtOH (20 mL, saturated with HCl gas) of thiazoline **6a** (1.71 g, 5 mmol) was refluxed for 5 h. After cooling and addition of Et_2O a colorless precipitate was formed, which was recrystallized from EtOH/Et_2O to give **4a** as colorless rods (0.83 g, 64%), mp 185–187 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.13 (s, 3H, 5-Me), 3.58 (s, 3H, NMe), 3.69–3.79 (br, 2H, NH_2), 7.24–7.56 (m, 5H, ArH), 11.98 (s, 1H, 3-NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ=17.7, 18.46, 34.53, 55.89, 127.87, 128.95, 129.76, 130.29, 136.59. IR (KBr, cm^{-1}): $\tilde{\nu}$ 709 (m), 787 (m), 1124 (m), 1431 (m), 1459 (m), 1588 (s), 1665 (s), 2834 (s), 2984 (s), 3132 (s), 3242 (s), 3325 (m). Anal. Calcd for $C_{11}H_{14}N_3ClS$ (255.77): C, 51.66; H, 5.52; N, 16.24. Found: C, 51.83; H, 5.71; N, 16.24.

3.1.6. 2-Hydrazono-3-isopropyl-5-methyl-4-phenyl-1,3-thiazoline hydrochloride (4b). The compound was prepared from **3b** (2.87 g, 10 mmol, method A) or from **6b** (2.89 g, 10 mmol, method B) as described for the synthesis of **4a**.Yield: method A: 2.32 g (82%); method B: 2.2 g, 78%: **4b·HBr**, mp 196–204 °C, colourless prisms (EtOH, HCl, Et_2O). Anal. Calcd for $C_{13}H_{18}N_3ClS$ (283.82): C, 55.01; H, 6.39; N, 14.81. Found: C, 55.12; H, 6.56; N, 14.88. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.52–1.54 [d, 2× 3H, $CH(CH_3)_2$], 2.02 (s, 3H, 5-CH_3), 4.39–4.44 (m, 1H, CH), 5.37 (br, 2H, NH_2), 7.26–7.57 (m, 5H, ArH), 11.67 (s, 1H, NH^+). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=11.75, 19.21, 53.17, 116.58, 128.58, 129.06, 130.18, 137.50, 169.67. IR (KBr, cm^{-1}): $\tilde{\nu}$ 699 (s), 730 (m), 809 (w), 1125 (w), 1198 (s), 1316 (m), 1326 (m), 1567 (m), 1661 (s), 2817 (m), 2946 (m), 3162 (m), 3255 (m). Anal. Calcd for $C_{23}H_{21}N_3OS$ (387.51): C, 71.29; H, 5.46; N, 10.84. Found: C, 71.45; H, 5.56; N, 10.88.

3.1.7. [1,2-Diaza-2-(3,5-dimethyl-4-phenyl-1,3-thiazolin-2-ylidene)ethylidene]naphthalen-1-one (8a). To an aqueous solution (100 mL) of hydrazone **4a** (255 mg, 1 mmol) was added a solution (volume ratio: H_2O/DMSO 3.5:1 or H_2O/DMF 3.5:1, 90 mL) of α-naphthol (145 mg, 1 mmol). To the mixture was added dropwise an aqueous solution of H_2O_2 (0.15 mL, 30%). Addition of an aqueous solution (sodium phosphate buffer pH 7.1, 10 mL, 0.1 M) of horseradish peroxidase (10 mg, specific activity 533 mmol/s kg protein) resulted in the formation of a precipitate. After addition H_2O, the precipitate was filtered off, washed with H_2O and recrystallized from 2-ethoxyethanol to give **8a** as green prisms (0.72 g, 99%), mp 275 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.61 (s, 3H, Me), 2.12 (s, 3H, Me), 6.60–8.51 (m, 10H, ArH, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=12.80, 34.21, 114.73, 123.01, 125.90, 128.03, 128.10, 128.65, 129.08, 129.28, 129.56, 130.23, 130.42, 131.74, 135.73, 136.22, 143.72, 172.76, 186.15. IR (KBr, cm^{-1}): $\tilde{\nu}$ 769 (m), 825 (m), 1002 (m), 1130 (s), 1241 (m), 1309 (s), 1388 (s), 1410 (s), 1438 (s), 1473 (s), 1536 (s), 1592 (s), 1630 (s), 2061 (s). UV (EtOH, nm): λ_{max} (log ε)= 244 (4.41), 300 (4.27), 530 (4.66). Anal. Calcd for $C_{21}H_{17}N_3OS$ (359.4): C, 70.18; H, 4.77; N, 11.69. Found: C, 69.90; H, 5.16; N, 11.88.

3.1.8. [1,2-Diaza-2-(3-isopropyl-5-dimethyl-4-phenyl-1, 3-thiazolin-2-ylidene)ethylidene]-naphthalen-1-one (8b). Compound **8b** was obtained from **4b** (284 mg, 1 mmol) following the procedure reported for **8a**. Yield: 0.372 g (96%), mp 157–158 °C, red-brown lamella (2-methoxyethanol). IR (KBr, cm^{-1}): $\tilde{\nu}$ 818 (s), 944 (s), 1007 (s), 1041 (m), 1126 (s), 1199 (s), 1233 (s), 1260 (m), 1309 (s), 1364 (s), 1433 (s), 1473 (m), 1536 (m), 1596 (s), 1634 (s), 2973 (w), 2997 (w), 3057 (w). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.57–1.59 [d, 2×3H, $CH(CH_3)_2$], 2.02 (s, 3H, 5-CH_3), 4.09–4.15 (m, 1H, CH), 6.61–8.20 (m, 10H, ArH, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=12.93, 19.98, 52.48, 119.39, 122.92, 125.90, 127.79, 128.37, 128.51, 129.13, 129.56, 130.31, 131.71, 132.71, 132.95, 135.82, 136.61, 145.21, 172.20, 186.12. UV (EtOH, nm): λ_{max} (log ε)=246 (4.36), 298 (3.05), 540 (4.42). Anal. Calcd for $C_{23}H_{21}N_3OS$ (387.51):

C, 71.29; H, 5.46; N, 10.84. Found: C, 71.30; H, 5.36; N, 10.88.

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References and notes

1. For transition metal-catalyzed oxidations using hydrogen peroxide, see: Tse, M. K.; Döbler, C.; Bhor, S.; Klawonn, M.; Mägerlein, W.; Hugl, H.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *116*, 5367. *Angew. Chem., Int. Ed.* **2004**, *43*, 5255 and references cited therein.
2. (a) Ciecholewski, S.; Hammer, E.; Manda, K.; Bose, G.; Nguyen, V. T. H.; Langer, P.; Schauer, F. *Tetrahedron* **2005**, *61*, 4615. for the kinetic enzymatic resolution of butenolides, see: (b) Kirschner, A.; Langer, P.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **2004**, *15*, 2871.
3. Pfeiffer, W.-D.; Ahrens, N.; Bulka, E. Ger. Offen. DE 4113223 A1, 1992.
4. Pfeiffer, W.-D.; Bulka, E.; Ahrens, N. *J. Prakt. Chem.* **1992**, *334*, 365.
5. Berglund, G. I.; Carlsson, G. H.; Smith, A. T.; Szöke, H.; Henriksen, A.; Hajdu, J. *Nature* **2002**, *417*, 463 and references cited therein.
6. Bodtke, A.; Pfeiffer, W.-D.; Ahrens, N.; Langer, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1509.
7. Beyer, H. *Z. Chem.* **1969**, *10*, 361.
8. Pfeiffer, W.-D.; Dilk, E.; Bulka, E. *Z. Chem.* **1977**, *6*, 218.
9. Pfeiffer, W.-D. Houben-Weyl Methods of Organic Chemistry, Thieme: Stuttgart, 1997; Vol. E 9c, 923 pp.
10. (a) Hünig, S.; Fritsch, K. H. *Liebigs Ann. Chem.* **1957**, *609*, 143. (b) Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1958**, *70*, 215.

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Indium triflate catalyzed allylation of ketones with diallyldibutyltin

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Abstract—A series of ketones underwent an allylation reaction using diallyldibutyltin in the presence of a catalytic amount of $In(OTf)_3$. The method was found to be superior to most of the known methods. Thus, a new allyltin reagent $Bu_2Sn(allyl)_2/In(OTf)_3$ for ketones was developed.

1. Introduction

Allylation of carbonyl groups by various allylic metals is a highly efficient tool for the synthesis of homoallylic alcohols with the formation of a new carbon–carbon bond.[1] Among the various allylic metals, allyltin is an important reagent with its suitable activity, low cost and easily available. Diastereoselective and enantioselective allylation with different allyltin derivatives have been studied mostly for aldehydes[2] but rarely for ketones[3,4] since the lower reactivity of carbonyl group in ketones.

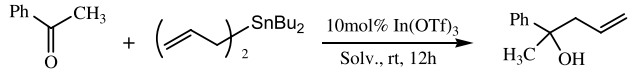
Recently, it was reported that a combination of zinc triflate and a base such as 2,6-lutidine or pyridine could catalyze the allylation of ketones with tetra-allyltin.[5] It was described that allylation of acetophenone with 1 equiv of different allylstannanes such as tetra-allylatin, diallyldibutyltin, and allyltributyltin gave 94, 59, and 19% yield of 1-phenyl-1-methylbut-3-en-1-ol (PMB), respectively, in the presence of 10 mol% $Zn(OTf)_2$ and 10 mol% pyridine. However, zinc triflate alone was ineffective as only a 16% yield of PMB was obtained in the case of acetophenone with tetra-allyltin. While working on the $In(OTf)_3$-catalyzed reactions, we observed that allylation of acetophenone with diallyldibutyltin afforded PMB in 95% yield. The reaction did not require any Lewis base as co-catalyst and it could be extended to the enantioselective version. Herein, we report a new allylation system for various ketones. Thus, it was extended to the other allyltin reagent for allylation of ketones compared to the previous only limited to tetra-allyltin.[6,7]

2. Results and discussion

Firstly, the effect of the solvents on the reaction of acetophenone (1 equiv) and diallyldibutyltin (1 equiv) in the presence of $In(OTf)_3$ (10 mol%) at room temperature was examined. The results in Table 1 showed that dichloromethane was a good choice over the other solvents such as MeCN, ether, THF, toluene, and DMSO.

Then different metal triflates (See Table 2) were examined and the indium triflate gave the best result. Furthermore, we also investigated the effect of the different amount of $In(OTf)_3$ on this reaction. The results showed that 10 mol% catalyst was the best choice for this reaction (Table 3).

Table 1. Effect of different solvents on allylation of acetophenone with diallyldibutyltin



Entry	Solvent	Yield (%)[a]
1	**CH_2Cl_2**	**95**
2	MeCN	37
3	Et_2O	81
4	THF	72
5	Toluene	84
6	DMSO	61

[a] Isolated yields.

Keywords: Allylation; Ketone; Diallyldibutyltin; $In(OTf)_3$.
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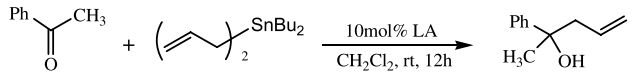
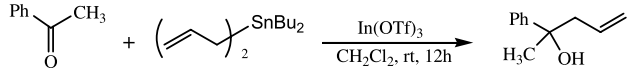
Table 2. Effect of different triflates' Lewis acids on allylation of acetophenone with diallyldibutyltin



Entry	Lewis acid	Yield (%)[a]
1	—	27
2	**$In(OTf)_3$**	**95**
3	$Yb(OTf)_3$	74
4	AgOTf	71
5	$Y(OTf)_3$	89
6	$Cu(OTf)_2$	51
7	$Zn(OTf)_2$	48

[a] Isolated yields.

Table 3. Effect of different $In(OTf)_3$ amount on allylation of acetophenone with diallyldibutyltin



Entry	Solvent	Temperature (°C)	Amount of $In(OTf)_3$ (mol%)	Yield (%)[a]
1	CH_2Cl_2	Room temperature	1	38
2	CH_2Cl_2	Room temperature	5	68
3	CH_2Cl_2	Room temperature	10	95

[a] Isolated yields.

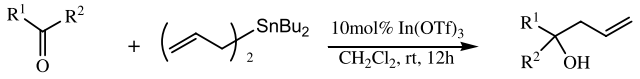
In order to ascertain whether both allyl groups could all be transferred, 1 and 0.5 equiv of diallyldibutyltin were used in two separate experiments by taking an example of the acetophenone. It was observed that on use of 0.5 equiv of the diallyldibutyltin, only 31% yield of the product was obtained even after 24 h at room temperature. Similar experiments were carried out with other ketones such as 4-bromo-acetophenone (entry 4) and cycloheptanone (entry 15). The yields of allylated products dropped from 86 to 35% for entry 4 and from 90 to 40% for entry 15, respectively. Thus, it was concluded that the second allyl group of diallyldibutyltin was uneasily transferred under the current reaction condition.

In a word, the optimized reaction condition was that ketones were treated with an equal mol of diallyldibutyltin in the presence of 10 mol% $In(OTf)_3$ in CH_2Cl_2 at room temperature for 12 h.

The extended investigation on different kinds of ketones with diallyldibutyltin was examined under the optimized conditions. High yields were obtained in most of the cases (Table 4).

Arylmethyl ketones bearing an electron-withdrawing group at the *para*-position of the aromatic ring gave the corresponding allylation products in high yields (entries 2–4). Arylmethyl ketones bearing an electron-donor group such as *p*-Me or *p*-MeO gave the products in moderate yields (entries 9 and 10). Moreover, the former proceeded much faster by TLC monitoring. Even after stirred for 12 h, the arylmethyl ketones bearing an EDG at the *para*-position could not react completely, as the starting material was recovered. The *p*-NH_2 substituted phenylmethyl ketone did

Table 4. Allylation of ketones with diallyldibutyltin catalyzed by $In(OTf)_3$



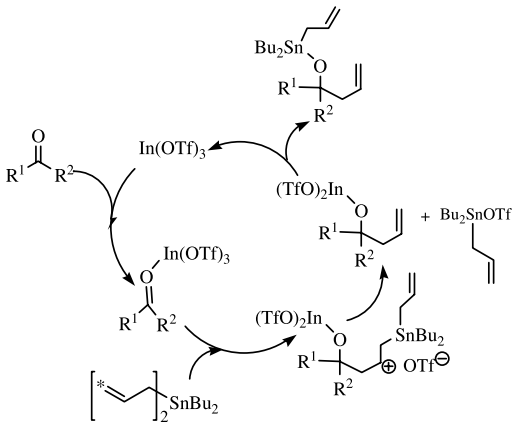
Entry	R^1	R^2	Yield (%)[a]
1	Ph	CH_3	95
2	*p*-FC_6H_4	CH_3	81
3	*p*-ClC_6H_4	CH_3	75
4	*p*-BrC_6H_4	CH_3	86
5	*p*-$NO_2C_6H_4$	CH_3	66
6	*m*-$NO_2C_6H_4$	CH_3	71
7	*m*-BrC_6H_4	CH_3	93
8	*m*-$CF_3C_6H_4$	CH_3	90
9	*p*-MeC_6H_4	CH_3	58
10	*p*-$MeOC_6H_4$	CH_3	50
11	*p*-$NH_2C_6H_5$	CH_3	—
12	Ph	Ph	42
13			78
14			82
15			90
16	$CH_2CH_2CH_3$	CH_3	45
17	$CH_2CH(CH_3)_2$	CH_3	27
18	*p*-$MeOC_6H_4$	H	80

[a] Isolated yields.

not afford the desired homoallylic alcohol but complicated products tracing by ^1H NMR (entry 11), the reason for which was not clear at present. Surprisingly, substituent in the *meta*-position of the aromatic ring underwent allylation in higher yield than the corresponding substituent in the *para*-position of the aromatic ring (entries 4 and 7, 5 and 6). In addition, aliphatic ketones afforded the allylation products in the moderate to good yields (entries 13–17). Furthermore, benzophenone could also react smoothly (entry 12) with a moderate yield. To confirm the reaction system could be applied in aldehyde too, *p*-anisaldehyde, which usually showed a relatively lower reactivity for allylation, was chosen to react with the diallyldibutyltin under the same conditions. And the homoallylic alcohol was obtained in 80% yield (entry 18).

The mechanism of this reaction was preliminarily studied. According to the previous reports, the Lewis acids catalyzed the allylation of carbonyl compounds with allylic metal reagents via an acyclic transition state.[8] Herein, we postulated a possible mechanism of this reaction according to the ^1H NMR tracing (Scheme 1). By using *p*-anisaldehyde as a representative substrate coordinated with 1 equiv $In(OTf)_3$, we found that the peak corresponding to this aldehyde proton in ^1H NMR showed a down-field shift (δ 9.732–9.872 ppm). This suggested some evidence of activation of aldehyde by $In(OTf)_3$.

In addition, we also selected several typical homoallylic alcohols to analyze their properties by ESI mass spectrometric analysis. As a result, we found that the molecular ion peaks of the general homoallylic alcohols were weak and easily decomposed by pulling off water to turn into the *tert*-carbonium ions, which were the highest response peak [(M+1)−18] except for *m*-trifluoromethyl acetophenone.



Scheme 1. Probable acyclic transition-state mechanism.

Since all the products were known compounds, only ^{1}H NMR and selected ^{13}C NMR and Mass spectra were determined for confirming the products. And all spectra were available in the supporting material.

3. Conclusion

In summary, we have found that diallyldibutyltin /$In(OTf)_3$ was a novel efficient system for the allylation of ketones under a mild condition. The reaction did not require any base as an additive and could be applied for various ketones with modest to high yields. Further investigation on diastereo- and enantio-selective allylation is currently in progress in our laboratory.

4. Experiment

4.1. General

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification except petroleum ether, dichloromethane, ether were fractionally distilled. Ketones were used without purification. Analytical thin-layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate. Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian Mercury Plus 400 (^{1}H 400 MHz) ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (*n*) for a given resonance is indicated by *n*H. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). Mass spectrometric analysis was carried out on a ThermoFinnigan LCQ Advantage LC/MS with an electrospray ionization mode (ESI).

4.2. Synthesis

Preparation of dibromodiallyltin ($(CH_2{=}CHCH_2)_2SnBr_2$). To an oven dried 250 ml four-necked flask equipped with a magnetic stirring bar, a reflux condenser and a thermometer was added 150 ml toluene, tin powder (17.8 g, 0.15 mol) and $HgCl_2$ (0.5 g, 0.002 mol). The mixture was refluxed for 30 min, then cooled to room temperature, triethylamine (0.275 ml) was added and the mixture was heated until reflux, and 1-bromopropene (18.2 g, 0.15 mol) was added dropwise within 30 min. The reaction mixture was kept at reflux for 3 h and then cooled to room temperature, filtered, concentrated in vacuo. The residual crude product was distilled under reduced pressure and resulted in 19.5 g of a slightly yellow colored oil: bp 70–72 °C/0.5 mmHg, Yield 72%. The oil was analyzed by ^{1}H NMR.

Preparation of diallyldibutyltin ($(CH_2{=}CHCH_2)_2SnBu_2$). Placed of dry magnesium turnings (5 g, 0.208 mol) and freshly distilled ether (25 ml) in a 250 ml four-necked flask equipped with a magnetic stirring bar, a reflux condenser with a drying tube, a dropping funnel charged with the solution of *n*-butyl chloride (19.3 g, 0.208 mol) and ether (10 ml). After addition of about one third of *n*-butyl chloride solution into the flask, a small iodine crystal was added to the mixture. The reaction started immediately and the color of iodine disappeared. The remaining *n*-butyl chloride solution was added slowly into the reaction mixture with gentle reflux (about 30 min). When all of the *n*-butyl chloride solution was dropped into the flask, the reaction was continued for an additional 30 min on a heated water bath until magnesium turning disappeared.

The resulting Grignard reagent was cooled to room temperature using a cold water bath. A solution of the freshly prepared dibromodiallyltin (27.0 g, 0.075 mol) in 10 ml dried ether was added dropwise. The dropping rate was controlled so that the mixture was refluxed gently. After the addition was finished, the reaction mixture was refluxed for further 30 min and then cooled in an ice-bath. Under constant stirring a solution of 1 N hydrochloride (about 80 ml) was added and the stirring was continued until the solid was dissolved. The organic layer was separated and the aqueous layer was extracted for three times with ether ($3\times$ 25 ml). The combined organic layers were dried with anhydrous sodium sulfate, filtered, concentrated in vacuo. The residual crude product was distilled under reduced pressure and resulted in 15.26 g of a colorless liquid, Yield 63%. The liquid was analyzed by ^{1}H NMR.

4.2.1. Preparation of 1-phenyl-1-methylbut-3-en-1-ol (1). To an oven dried 10 ml tube equipped with a magnetic stirring bar was added acetophenone (60 mg, 0.5 mmol) and diallyldibutyltin (157 mg, 0.5 mmol), then added $In(OTf)_3$

(28 mg, 0.05 mmol) and dichloromethane (2 ml). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with 2 ml saturated aqueous $NaHCO_3$ solution, extracted with ether (3×10 ml), washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colorless oil (95% yield). MS: $m/z=162.39$ (M^+), $m/z=145.49$ [(M+1)−18]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.23 (m, 5H, Ar*H*), 5.66–5.58 (m, 1H, C*H*), 5.13 (t, $J=8$ Hz, 2H, CH=CH_2), 2.71–2.47 (m, 2H, CH_2), 2.09 (br, 1H, O*H*), 1.54 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 30.0, 48.7, 73.9, 119.6, 125.0, 126.9, 128.4, 134.0, 148.0.

4.2.2. 1-*p*-Fluorophenyl-methylbut-3-en-ol (2). Homoallylic alcohol **2** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.30 (m, 2H, Ar*H*), 7.01 (t, $J=8$ Hz, 2H, Ar*H*), 5.63–5.55 (m, 1H, C*H*), 5.14 (d, $J=12$ Hz, 2H, CH=CH_2), 2.63–2.45 (m, 2H, CH_2), 2.07 (br, 1H, O*H*), 1.53 (s, 3H, CH_3).

4.2.3. 1-*p*-Chlorophenyl-1-methylbut-3-en-1-ol (3). Homoallylic alcohol **3** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.25 (m, 4H, Ar*H*), 5.53 (s, 1H, C*H*), 5.24–5.08 (m, 2H, CH=CH_2), 2.57–2.41 (m, 2H, CH_2), 2.02 (br, 1H, O*H*), 1.46 (t, $J=4$ Hz, 3H, CH_3).

4.2.4. 1-*p*-Bromophenyl-1-methylbut-3-en-1-ol (4). Homoallylic alcohol **4** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.29 (m, 4H, Ar*H*), 5.59–5.55 (m, 1H, C*H*), 5.14–5.11 (d, $J=12$ Hz, 2H, CH=CH_2), 2.66–2.44 (m, 2H, CH_2), 2.08 (br, 1H, O*H*), 1.51–1.49 (d, $J=10.8$ Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 30.1, 48.5, 73.7, 120.1, 120.8, 127.0, 131.4, 133.4, 146.9.

4.2.5. 1-*p*-Nitrophenyl-1-methylbut-3-en-1-ol (5). Homoallylic alcohol **5** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18–7.23 (m, 4H, Ar*H*), 5.57–5.55 (m, 1H, C*H*), 5.16–5.14 (t, $J=2.8$ Hz, 2H, CH=CH_2), 2.65–2.51 (m, 2H, CH_2), 2.14 (br, 1H, O*H*), 1.55–1.54 (d, $J=4$ Hz, 3H, CH_3).

4.2.6. 1-*m*-Nitrophenyl-1-methylbut-3-en-1-ol (6). Homoallylic alcohol **6** was obtained using the same procedure as **1**: slight yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32–7.26 (m, 4H, Ar*H*), 5.62–5.56 (m, 1H, C*H*), 5.17–5.13 (t, $J=7.6$ Hz, 2H, CH=CH_2), 2.70–2.51 (m, 2H, CH_2), 2.16 (br, 1H, O*H*), 1.58 (s, 3H, CH_3).

4.2.7. 1-*m*-Bromophenyl-1-methylbut-3-en-1-ol (7). Homoallylic alcohol **7** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.18 (m, 4H, Ar*H*), 5.60–5.56 (m, 1H, C*H*), 5.14–5.12 (d, $J=9.2$ Hz, 2H, CH=CH_2), 2.65–2.44 (m, 2H, CH_2), 2.08 (br, 1H, O*H*), 1.51–1.50 (d, $J=4.8$ Hz, 3H, CH_3).

4.2.8. 1-*m*-Trifluoromethylphenyl-1-methylbut-3-en-1-ol (8). Homoallylic alcohol **8** was obtained using the same procedure as **1**: colorless oil; MS: $m/z=230.35$ (M^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.45 (m, 4H, Ar*H*), 5.63–5.55 (m, 1H, C*H*), 5.17–5.13 (m, 2H, CH=CH_2), 2.70–2.49 (m, 2H, CH_2), 2.17 (s, 1H, O*H*), 1.56 (s, 3H, CH_3).

4.2.9. 1-*p*-Methylphenyl-1-methylbut-3-en-1-ol (9). Homoallylic alcohol **9** was obtained using the same procedure as **1**: colorless oil; MS: $m/z=176.39$ (M^+), $m/z=159.58$ [(M+1)−18]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.15 (m, 4H, Ar*H*), 5.69–5.59 (m, 1H, C*H*), 5.16–5.11 (m, 2H, CH=CH_2), 2.71–2.47 (m, 2H, CH_2), 2.35 (s, 3H, CH_3-Ar), 2.02 (br, 1H, O*H*), 1.54 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 21.2, 30.1, 48.7, 73.8, 119.4, 125.0, 129.1, 134.1, 136.3, 145.0.

4.2.10. 1-*p*-Methoxyphenyl-1-methylbut-3-en-1-ol (10). Homoallylic alcohol **10** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–6.85 (m, 4H, Ar*H*), 5.64–5.58 (m, 1H, C*H*), 5.13–5.09 (t, $J=7.6$ Hz, 2H, CH=CH_2), 3.80 (s, 3H, CH_3O), 2.67–2.44 (m, 2H, CH_2), 1.98 (br, 1H, O*H*), 1.57 (s, 3H, CH_3).

4.2.11. 1,1-Diphenyl-1-but-3-en-1-ol (12). Homoallylic alcohol **12** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.18 (m, 10H, Ar*H*), 5.63–5.60 (m, 1H, C*H*), 5.23–5.12 (m, 2H, CH=CH_2), 3.03 (br, 1H, O*H*), 2.52–2.28 (m, 2H, CH_2).

4.2.12. 1-Cyclopentyl-1-but-3-en-1-ol (13). Homoallylic alcohol **13** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94–5.84 (m, 1H, C*H*), 5.15–5.12 (m, 2H, CH=CH_2), 2.34–2.16 (t, $J=7.6$ Hz, 2H, CH_2), 1.79–1.24 (m, 8H, cyclopentyl).

4.2.13. 1-Cyclohexyl-1-but-3-en-1-ol (14). Homoallylic alcohol **14** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93–5.84 (m, 1H, C*H*), 5.14–5.07 (t, $J=10.4$ Hz, 2H, CH=CH_2), 2.34–2.19 (t, $J=6.8$ Hz, 2H, CH_2), 1.70–1.24 (m, 10H, cyclohexyl).

4.2.14. 1-Cycloheptyl-1-but-3-en-1-ol (15). Homoallylic alcohol **15** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89–5.85 (m, 1H, C*H*), 5.15–5.08 (t, $J=10.8$ Hz, 2H, CH=CH_2), 2.22–2.15 (t, $J=6.8$ Hz, 2H, CH_2), 1.63–1.37 (m, 12H, cycloheptyl); ^{13}C NMR (400 MHz, $CDCl_3$): δ 22.6, 30.0, 41.3, 48.1, 75.1, 118.9, 134.3.

4.2.15. 1-Methyl-1-propyl-1-but-3-en-1-ol (16). Homoallylic alcohol **16** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89–5.83 (m, 1H, C*H*), 5.15–5.09 (t, $J=8.4$ Hz, 2H, CH=CH_2), 2.22–2.20 (d, $J=7.6$ Hz, 2H, CH_2), 1.57–0.91 (m, 10H, CH_3, C_3H_7)

4.2.16. 1-Methyl-1-isobutyl-1-but-3-en-1-ol (17). Homoallylic alcohol **17** was obtained using the same procedure as **1**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88–5.82 (m, 1H, C*H*), 5.14–5.08 (t, $J=9.6$ Hz, 2H, CH=CH_2), 2.23 (m, 2H, CH_2), 1.82–0.95 (m, 12H, CH_3, *i*-C_4H_9).

4.2.17. 1-*p*-Methoxylphenyl -1-but-3-en-1-ol (18). Homoallylic alcohol **18** was obtained using the same procedure as

1: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.28 (m, 2H, Ar*H*), 6.91–6.89 (m, 2H, Ar*H*), 5.88–5.75 (m, 1H, C*H*═CH_2), 5.20–5.13 (m, 2H, CH═CH_2), 4.72–4.68 (t, J=6.6 Hz, 1H, C*H*), 3.82 (s, 3H, CH_3O), 2.54–2.49 (m, 2H, CH_2), 2.18 (s, 1H, O*H*).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.101

References and notes

1. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
2. (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357–386. (b) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555–566. (c) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243–249. (d) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723–4724.
3. Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958–6960.
4. Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 7525–7526.
5. Hamasaki, R.; Chounan, Y.; Horino, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 9883–9887.
6. Kii, S.; Maruoka, K. *Chirality* **2003**, *15*, 68–70.
7. (a) Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998**, *8*, 743–744. (b) Casolari, S.; Addario, D. D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061–1063. (c) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697–3699.
8. Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, *103*, 2763–2794.

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Tetrathiafulvalene-hydroxyamides and -oxazolines: hydrogen bonding, chirality, and a radical cation salt

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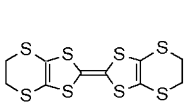
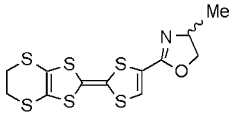
Abstract—Racemic and enantiopure ethylenedithio-tetrathiafulvalene (EDT-TTF) derivatives featuring β-hydroxyamide or oxazoline (OX) groups bearing methyl or isopropyl substituents have been synthesized starting from the corresponding amino alcohols. Crystal structure analysis shows in the case of the racemic methyl-β-hydroxyamide donor the development of a unique hydrogen bond network, characterized by short C═O···H–O and N–H···O–H intermolecular distances. The enantiopure (*S*)-EDT-TTF-methyl-OX crystallizes in the monoclinic non-centrosymmetric space group $P2_1$, whereas the isopropyl counterparts, (*R*)-and (*S*)-EDT-TTF-isopropyl-OX, crystallize in the orthorhombic non-centrosymmetric space group $P2_12_12_1$. All of them adopt a *s-trans* conformation in which TTF and oxazoline units are coplanar. Electrocrystallization experiments with the racemic EDT-TTF-methyl-OX, in the presence of $(n\mathrm{Bu}_4)_2\mathrm{Mo}_6\mathrm{Cl}_{14}$ as supporting electrolyte, afford a radical cation salt, formulated as $[(\pm)\text{-EDT-TTF-methyl-OX}]_2\mathrm{Mo}_6\mathrm{Cl}_{14}$, in which the donors associate in strong dimers, which further stack along the b direction to form quasi-homochiral helix-like ribbons.

1. Introduction

The introduction of chirality within conducting molecular materials based on tetrathiafulvalene (TTF) derivatives, a well known class of organosulfur electron donors extensively studied in the search for molecular conductors and superconductors,[1] currently receives a growing interest, also encouraged by Rikken et al.'s recent report of electrical magnetochiral anisotropy in chiral carbon nanotubes.[2] This feature is in line with the quest for multifunctional molecular materials, a trend of much interest in contemporary materials science, aiming at combining in the solid state at least two physical properties, such as conductivity and optical activity.[3] The question of whether the chirality influences the electrical properties of TTF based radical cation salts had been previously addressed by Dunitz and others, but the lack of suitable enantiopure materials together with their racemic form did not allow deeper investigations.[4] Yet, structural differences between racemic and enantiomeric forms may occur, since enantiopure radical cation salts are expected to suffer less from structural disorder than the racemates, whose crystal structures may accommodate the enantiomers exchanging places. It is well established that structural disorder can strongly influence the electronic conductivity in molecular conductors,[5] therefore the chirality can already play a paramount role at this level. A straightforward strategy to introduce chirality within TTF based materials lies in the utilization of chiral TTF's as precursors for radical cation salts, although the complementary strategy, consisting of the use of chiral counter-ions with achiral donors can be envisioned, as recently described in the BEDT-TTF (bisethylenedithio-tetrathiafulvalene) salt with the chiral antimony (*L*)-tartrate dimer, $[\mathrm{Sb}_2(L\text{-tart})_2]^{2-}$.[6] The advantage of the former strategy, despite more synthetically-demanding efforts than for the second one, is that, once the synthesis of a chiral donor optimized, a large panel of anions, be they chiral or achiral, can be explored.


BEDT-TTF



EDT-TTF-OX

The first examples of enantiopure TTF derivatives were described by Dunitz and Wallis,[7] and since then other chiral TTF's were synthesized, most of them featuring a functionalized BEDT-TTF skeleton.[8] The latter, along with closely related donors, have been recently extensively

Keywords: Tetrathiafulvalenes; Chirality; Oxazolines; Crystalline structures; Electrocrystallization; Radical cation salts.
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surveyed by Wallis et al.[4] Moreover, enantiopure TTF derivatives containing chiral binaphthyl frameworks[9] or oxazoline rings[10] were also synthesized. The latter were tested as ligands in the catalytic allylic substitution reaction, showing though a rather modest catalytic activity.

In a recent communication we briefly described the straightforward synthesis of EDT-TTF (ethylenedithiotetrathiafulvalene) substituted with a chiral 4-methyloxazoline and a diphenylphosphino group.[11] The chirality provided by the oxazoline ring is perfectly controlled and easily introduced in the synthesis by the use of racemic or enantiopure amino alcohols. By synthesizing the EDT-TTF-Me-Oxazolines (EDT-TTF-OX), our purpose was to access a class of chiral donors, which could serve as precursors for chiral molecular materials. Indeed, this strategy proved to be highly promising for future developments, since we succeeded in preparing the first complete series of mixed-valence metallic salts based on chiral tetrathiafulvalenes bearing the (*R*)-, (*S*)-, or racemic (±)-methyl-oxazoline heterocycle and the AsF_6^- monoanion. The single crystal conductivity for the enantiopure salts was one order of magnitude higher than that of the racemic one, very likely because of the structural disorder observed in the latter.[12] In the present paper, we describe the detailed synthesis and characterization of chiral EDT-TTF-β-hydroxyamides and -oxazolines, in methyl and isopropyl series, in their racemic and (*R*) and (*S*) enantiopure forms. In depth analyses of crystal structures of racemic Me-hydroxyamide, enantiopure (*S*)-Me-oxazoline and (*R*) and (*S*)-*i*Pr-oxazolines are presented, along with that of a radical cation salt of racemic EDT-TTF-Me-oxazoline with the $Mo_6Cl_{14}^{2-}$ anion, obtained upon electrocrystallization.

2. Results and discussion

In order to introduce a chirality center on the oxazoline ring, our first choice to use a methyl substituent was motivated by the concern to have a minimum steric bulk, provided by the redox inert oxazoline part of the donor, in the radical cation salts of EDT-TTF-OX. This feature would favor a maximization of π–π overlap and van der Waals intermolecular interactions in the solid state. Secondly, in a parallel series of donors, an isopropyl substituent was used instead of methyl, in order to gain in solubility, but also to insure a steric protection for potential catalytic applications.

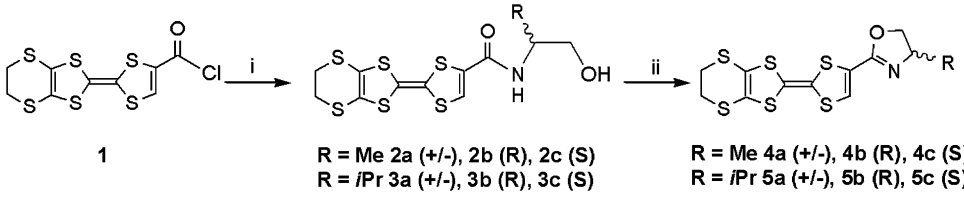
2.1. Synthesis

It is well established that EDT-TTF-COCl (**1**) smoothly reacts with primary amines to afford in good yields secondary amides.[13] Paralleling this strategy, two racemic (±) or enantiopure (*R*) and (*S*) amino alcohols, namely alaninol and valinol, were reacted with **1**, and, after stirring at room temperature for up to 12 h and chromatographic work up, the corresponding EDT-TTF-β-hydroxyamides **2a–c** and **3a–c** were isolated and characterized by spectroscopic methods and elemental analysis (Scheme 1). An X-ray crystal structure analysis was undertaken for compound **2a** (vide infra). Note these are the first examples of TTF's bearing both amide and alcohol functional groups, whereas numerous homofunctional derivatives of either amide,[13,14] thioamide[15] or alcohol[16] type were described so far. Subsequently, cyclization reactions in the presence of methanesulfonyl chloride (MsCl) and triethylamine were performed on β-hydroxyamides to yield the series **4a–c** (methyl) and **5a–c** (isopropyl) of (±), (*R*) and (*S*) EDT-TTF-oxazolines (EDT-TTF-OX). All analytical data and elemental analyses are in good agreement with the proposed structures. Suitable single crystals for X-ray analysis were obtained for the enantiopure donors **4c**, **5b** and **5c**.

2.2. X-ray crystal structures of donors

Suitable single crystals for the β-hydroxyamide **2a** were obtained upon recrystallization in ethyl acetate. The donor crystallizes in the monoclinic system, space group $P2_1/c$, with one independent molecule in the unit cell. As expected for a racemic mixture, both enantiomers, related to each other through the inversion center, are present in the structure. Selected bond lengths are listed in Table 1.

All values are typical for a neutral TTF, which, in this case, is moderately folded along both S···S hinges, that is, 15.33(18)° for S1···S2 and 19.9(3)° for S3···S4, as often encountered within crystalline structures of such neutral donors. The amide group is coplanar with the TTF unit, and disposed in an antiparallel manner with respect to C7=C8 and C9=O1 double bonds, as evidenced in Figure 1. Certainly, the most peculiar feature in the crystalline structure of **2a** is the hydrogen bond network established thanks to amide and alcohol groups. As observed for another β-hydroxyamide,[17] both functionalities participate as hydrogen bond donor and acceptor groups, with the carbonyl oxygen atom O1 acting as acceptor towards the alcoholic proton H2 and the amidic proton H1 as donor towards the alcoholic oxygen atom O2. The consequence of the balance between these requirements and the typical intermolecular S···S van der Waals contacts and stacking tendency of TTF type derivatives, is the organization of the donors in infinite ladders along a, through two types of hydrogen bond motifs (Fig. 1). Indeed, according to M. Etter's nomenclature,[18] one can identify $R_2^2(14)$ and $R_2^2(10)$ rings, characterized by short and rather linear hydrogen bonds of C=O···H–O and N–H···O–H type, respectively.

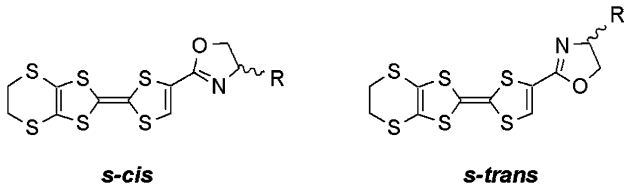


Scheme 1. Reagents and conditions: (i) (±), (*R*) or (*S*)-alaninol for **2a–c** and valinol for **3a–c**, NEt_3, THF, 12 h, rt; (ii) NEt_3, THF, MsCl at 0 °C, then 20 h at 50 °C.

Table 1. Selected bond lengths (Å) and torsion dihedral angles (°) for **2a**, **4c**, **5b**, **5c** and $(\mathbf{4a})_2Mo_6Cl_{14}$

	2a	**4c**	**5b**	**5c**	$(\mathbf{4a})_2Mo_6Cl_{14}$
			Bond lengths (Å)		
C3–C4	1.322(11)	1.336(5)	1.317(9)	1.314(8)	1.338(8)
C5–C6	1.339(8)	1.339(4)	1.335(8)	1.332(7)	1.398(7)
C7–C8	1.337(10)	1.333(5)	1.342(12)	1.322(10)	1.330(8)
C7–C9	1.500(10)	1.449(5)	1.448(14)	1.468(13)	1.454(8)
C17–C18					1.393(8)
C5–S4	1.752(7)	1.756(3)	1.749(7)	1.753(7)	1.723(5)
C5–S3	1.761(7)	1.748(3)	1.760(7)	1.766(6)	1.716(5)
C6–S2	1.761(7)	1.753(3)	1.743(7)	1.731(6)	1.732(5)
C6–S1	1.751(7)	1.763(3)	1.760(7)	1.761(6)	1.712(5)
			Torsion angles (°)		
S1···S2	15.33(18)	5.8(2)	13.5(3)	14.6(3)	0.43(9)
S3···S4	19.9(3)	3.1(2)	21.6(5)	21.0(5)	3.95(9)
S7···S8					2.73(6)
S9···S10					2.56(13)
Oxazoline···TTF (*s-trans*)		7.3(5)	8.7(6)	10.1(7)	3.9(2) (**N1**)
Oxazoline···TTF (*s-trans*)					15.3(4) (**N2A**)
oxazoline···TTF (*s-cis*)					18.6(5) (**N2B**)

Furthermore, the donors stack along b, with the shortest S···S intermolecular distance amounting at 3.58 Å. Clearly, the presence of amide and alcohol groups within the same donor allows original hydrogen bond supramolecular patterns in the TTF series, with respect to homofunctional derivatives, whose crystalline structures have been recently extensively reviewed.[19]



In the case of oxazoline derivatives **4** and **5**, two planar conformations are possible, namely *s-cis* and *s-trans*, if one considers the mutual orientations of the C7═C8 and C9═N double bonds. In the crystalline structure of **4b**, previously published,[11] the conformation was *s-trans*, with TTF and oxazoline units lying in the same plane. Single crystals of **4c** were obtained upon recrystallization in a THF/cyclohexane 1:1 mixture. Like its enantiomeric counterpart **4b**, the oxazoline **4c** crystallized in the monoclinic non-centrosymmetric space group $P2_1$, with one independent molecule in the unit cell. Note the *s-trans* conformation (Fig. 2) of the donor, with bond lengths in the typical range for a neutral TTF and only slight folding about S···S hinges. TTF and oxazoline units are coplanar, with the corresponding dihedral angle amounting at 7.3(5)°, an important feature in view of obtaining radical cation salts based on EDT-TTF-Me-OX **4a–c**.

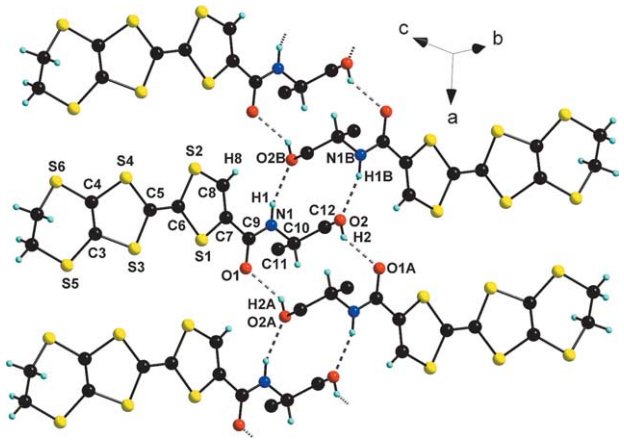


Figure 1. Hydrogen bond network in the crystalline structure of **2a**. Hydrogen atoms at C11 and C12 have been omitted for clarity. Intermolecular distances (Å) and angles (°): O1···O2A ($-x$, $1-y$, $-z$) 2.62, O1···H2A 1.96, O1–H2A–O2A 137.0 for $R_2^2(14)$ ring; N1···O2B ($-1-x$, $1-y$, $-z$) 2.82, H1···O2B 1.99, N1–H1–O2B 160.0 for $R_2^2(10)$ ring.

The donors **4c** stack along the b direction, leading to a herring bone type packing (Fig. 3), which is the mirror image of the **4b** packing.

Furthermore, formation of isopropyl-oxazolines **5a–c** was also confirmed by X-ray diffraction analyses, on single crystals obtained upon slow evaporation of a ethyl acetate solution, for both enantiomers *R* (**5b**) and *S* (**5c**). They are isostructural and crystallized in the non-centrosymmetric orthorhombic space group $P2_12_12_1$, with one independent molecule in the unit cell. As represented in Figure 4, **5b** and **5c** are the images each other in a mirror plane, and, like their methyl analogue **4c**, adopt a quasi-planar *s-trans* conformation, with torsion angles TTF···oxazoline amounting at 8.7(6) and 10.1(7)°, respectively. Geometrical parameters (Table 1) are in the expected range.

Interestingly, the packing of **5b** and **5c** is completely different when compared with **4b**, since in these cases the

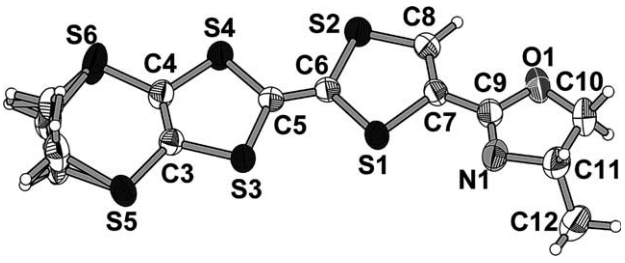


Figure 2. ORTEP view of (*S*)-EDT-TTF-OX **4c** (thermal ellipsoids set at 50% probability).

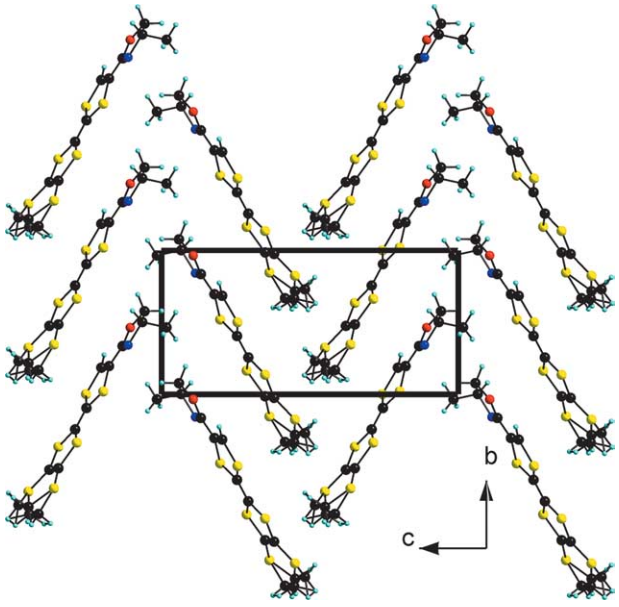


Figure 3. Packing diagram of **4c**.

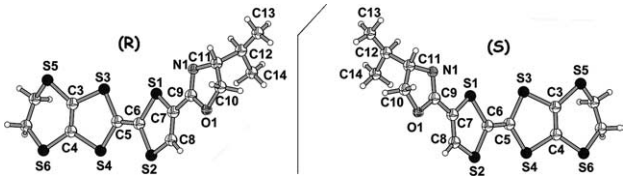


Figure 4. View of the two enantiomers **5b** and **5c**.

donors arrange in pairs, almost perpendicular to each other along b, as observed in Figure 5.

2.3. Redox properties of donors

In order to evaluate the redox properties of the donors synthesized so far we have performed cyclic voltammetry experiments to determine the oxidation potentials and the reversibility of the processes. The corresponding half-wave potentials for all the compounds are listed in Table 2.

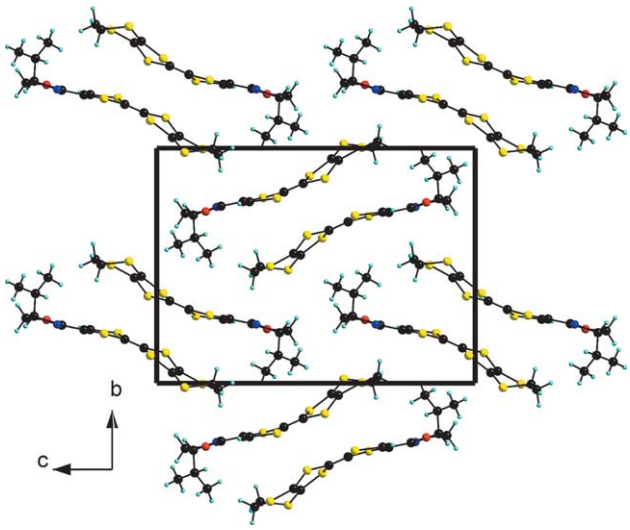


Figure 5. Packing diagram of **5c**.

Both mono-electronic oxidations are fully reversible, with potential values very similar to that of EDT-TTF-amides (0.66 and 0.92 V vs SCE for $E_1^{1/2}$ and $E_2^{1/2}$, respectively).[13] As already mentioned (vide supra),[12] we recently described a first complete series of mixed-valence metallic salts obtained upon electrocrystallization of the donors **4a–c** with the AsF_6^- monoanion. This time the $(TBA)_2Mo_6Cl_{14}$ dianionic salt was used as supporting electrolyte in a series of electrocrystallization experiments with the same **4a–c** donors. Unlike the case of the AsF_6^- monoanion, with the $Mo_6Cl_{14}^{2-}$ dianion only the racemic TTF-OX **4a** afforded suitable single crystals for X-ray analysis, of a salt formulated as $(\mathbf{4a})_2Mo_6Cl_{14}$, whereas crystalline plates of poor quality were obtained for the enantiopure **4b** and **4c**.

Table 2. Oxidation potentials (V vs SCE, nBu$_4$NPF$_6$, 0.1 M in CH_2Cl_2 at 0.1 Vs^{-1}, at 20 °C)

	$E_1^{1/2}$	$E_2^{1/2}$
2a–c	0.60	1.09
3a–c	0.60	1.09
4a–c	0.63	1.11
5a–c	0.63	1.11

2.4. Crystal structure of $(\mathbf{4a})_2Mo_6Cl_{14}$

The salt crystallizes in the monoclinic system, space group $P2_1/c$, with two independent donor molecules in general positions and two half-clusters located on inversion centers in the unit cell. According to the stoichiometry within the salt, both donor molecules are oxidized into radical cations, which is also confirmed by the variation of C=C and C–S central bonds, that is, elongation for C5=C6 and C17=C18 and shortening for C–S when compared to neutral donors (Table 1). As expected for fully oxidized donors the TTF units are practically planar, with folding angles about S···S hinges close to 0°. Interestingly, one donor (OX1) adopts a *s-trans* conformation, being coplanar with the TTF core, whereas the other (OX2) is disordered on two positions, corresponding to both *R* (0.75) and *S* (0.25) enantiomers on the same site, the first as *s-trans* and the second as *s-cis* conformers, with moderate TTF···oxazoline dihedral angles (Fig. 6 and Table 1).

There is no organic–inorganic segregation within the structure, but rather $Mo_6Cl_{14}^{2-}$ dianions wrapped in helix-like ribbons of donors developing along b (Fig. 7). Interestingly, the ribbons are homochiral if we consider only the major enantiomer (sof = 0.75) in the case of OX2. As often observed in the case of fully oxidized TTF-based donors, the radical cations strongly dimerize within the ribbons, in a 'head-to-tail' conformation, to form dicationic $[(\mathbf{4a})_2]^{2+}$ species.

The dimerization occurs between the two independent donor molecules OX1 and OX2 and within this dyad there are intermolecular S···S contacts as short as 3.37–3.45 Å, with a $\beta_{HOMO-HOMO}$ interaction energy overlap, calculated by the extended Hückel method, amounting at 0.86 eV (interaction **I**). Longer intra-ribbon S···S contacts, in the

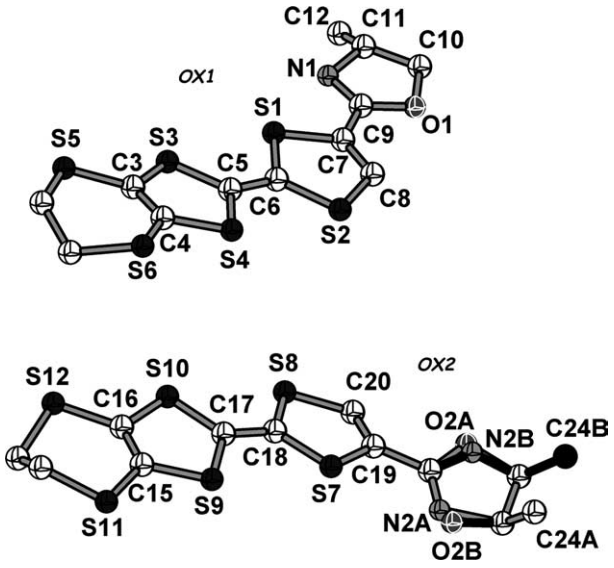


Figure 6. View of the two independent donor radical cations in the structure of $(\mathbf{4a})_2Mo_6Cl_{14}$. The bottom molecule corresponds to the disordered enantiomers on the same site, with the *S* one, in a *s-cis* conformation, having darkened bonds and the methyl carbon atom C24B in black. Hydrogen atoms have been omitted for clarity.

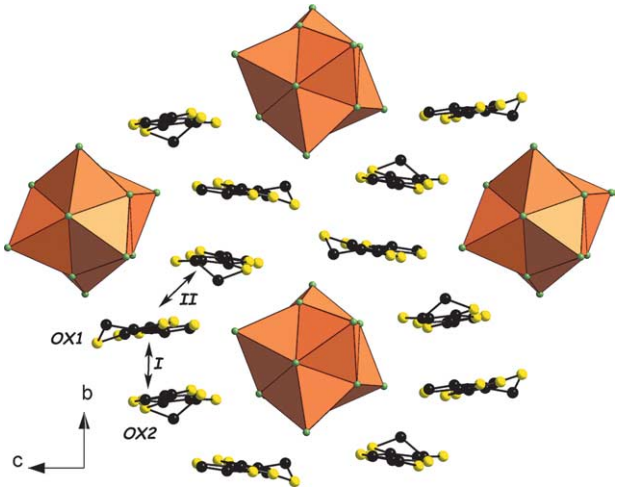


Figure 7. Mixed organic-inorganic slabs in the structure of $(\mathbf{4a})_2Mo_6Cl_{14}$. Hydrogen atoms and oxazoline rings have been omitted for clarity. Calculated $\beta_{HOMO-HOMO}$ interaction energies are as follows: interaction **I** OX1···OX2 ($-x$, $-y$, $1-z$) 0.86 eV, interaction **II** OX1···OX2 (x, $0.5-y$, $0.5+z$) 0.15 eV.

range of 3.6–3.8 Å, are observed between the dyads, with a much weaker interaction of only 0.15 eV (interaction **II**). Inter-ribbons S···S distances are over 4 Å, quite larger than the sum of van der Waals radii of two sulfur atoms.[20] The strong structural and energetic dimerization observed herein would, very likely, lead to an insulating behavior. Yet, the preparation of this radical cation salt demonstrates once again that the new class of donors is suitable for the synthesis of racemic or enantiopure molecular materials.

3. Conclusions

Two series of racemic and enantiopure EDT-TTF-β-hydroxyamides and EDT-TTF-oxazolines were synthesized. X-ray crystal structure of the racemic methyl-β-hydroxyamide, with an emphasis on the hydrogen bond network in which both amide and alcohol groups are involved, is described. The hydrogen bond donor and acceptor requirements are entirely fulfilled by the establishment of C═O···H–O and N–H···O–H intermolecular interactions. Furthermore, X-ray structures of enantiopure *S*-methyl and *R*- and *S*-isopropyl oxazolines, which crystallized in non-centrosymmetric space groups, are analyzed. A radical cation salt involving the racemic EDT-TTF-methyl-oxazoline and the $Mo_6Cl_{14}^{2-}$ anion was synthesized. Its crystalline structure shows association of radical cations in dimers, characterized by a high energy overlap interaction, and formation of quasi-homochiral ribbons out of donor molecules. The use of these electroactive β-hydroxyamides and oxazolines as precursors for chiral molecular materials is currently being investigated.

4. Experimental

4.1. General comments

Dry CH_2Cl_2 was obtained by distillation over P_2O_5 and THF was distilled over sodium and benzophenone. Nuclear magnetic resonance spectra were recorded on a Bruker Avance DRX 500 spectrometer operating at 500.04 MHz for ^1H, 125.75 MHz for ^{13}C. Chemical shifts are expressed in parts per million (ppm) downfield from external TMS. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. MALDI-TOF MS spectra were recorded on Bruker Biflex-IIITM apparatus, equipped with a 337 nm N_2 laser. Elemental analyses were performed by the 'Service d'Analyse du CNRS' at Gif/Yvette, France.

4.2. General procedure for β-hydroxy amides

In anhydrous THF (10 mL) 0.2 mL of the appropriate aminoalcohol (2.46 mmol) was diluted, and then 0.55 mL of dry triethylamine (3.95 mmol) was added. The colorless solution thus obtained was stirred for 10 min under N_2 before dropwise addition of a solution of freshly prepared ethylenedithio-tetrathiafulvalene carbonyl chloride (**1**) (0.700 g, 1.96 mmol) in 30 mL dry THF. The orange resulting solution was stirred for 6–12 h at room temperature. Then the mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude product was chromatographed through silica gel, with THF as eluent, to give the hydroxy-amides as orange-red solids.

4.2.1. 2-(+/−)-*N*-(1-Hydroxy-propyl)-ethylenedithio-tetrathiafulvalene-amide (2a). From (+/−)-alaninol (0.19 g), orange solid (0.57 g, 73% yield), mp 166–167 °C. ^1H NMR ($CDCl_3$): δ 1.24 (d, $^3J=6.8$ Hz, 3H, CH_3), 3.30 (s, 4H, S–CH_2–CH_2–S), 3.59 (dd, $^2J=11.0$ Hz, $^3J=5.4$ Hz, 1H of CH_2O), 3.72 (dd, $^3J=11.0$ Hz, $^2J=3.7$ Hz, 1H of CH_2O), 4.14 (m, 1H, NH–*CH*–CH_2O), 5.76 (d, $^3J=7.0$ Hz, 1H, NH), 7.11 (s, 1H, ═CH). IR (KBr, cm^{-1}): 1571 ($\nu_{C=C}$), 1615 ($\nu_{C=O}$), 3186 (ν_{OH}). *m/z* (MALDI-TOF): 395.08 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2S_6$: C, 36.43; H, 3.31; N, 3.54. Found: C, 36.53; H, 3.35; N, 3.42.

4.2.2. 2-(*R*)-*N*-(1-Hydroxy-propyl)-ethylenedithio-tetrathiafulvalene-amide (2b). From (*R*)-alaninol (0.32 g, air sensitive) and 1.2 g of EDT-TTF-COCl, red solid (0.84 g, 63% yield), mp 148–150 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, ^3J=6.8 Hz, 3H, CH_3), 3.30 (s, 4H, S–CH_2–CH_2–S), 3.60 (dd, ^3J=11.0 Hz, ^2J=5.4 Hz, 1H of CH_2O), 3.72 (dd, ^3J=11.0 Hz, ^2J=3.7 Hz, 1H of CH_2O), 4.13 (m, 1H, NH–*CH*–CH_2O), 5.78 (d, ^3J=7.3 Hz, 1H, NH), 7.11 (s, 1H, =CH). IR (KBr, cm^{-1}): 1571 ($\nu_{C=C}$), 1615 ($\nu_{C=O}$), 3186 (ν_{OH}). *m/z* (MALDI-TOF): 394.96 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2S_6$: C, 36.43; H, 3.31; N, 3.54. Found: C, 36.63; H, 3.37; N, 3.47.

4.2.3. 2-(*S*)-*N*-(1-Hydroxy-propyl)-ethylenedithio-tetrathiafulvalene-amide (2c). From (*S*)-alaninol (0.26 g, air sensitive) and 1.05 g of EDT-TTF-COCl, red solid (0.93 g, 80% yield), mp 148–150 °C. ^{1}H NMR, IR and MS spectra are identical with those of **2b**. Anal. Calcd for $C_{12}H_{13}NO_2S_6$: C, 36.43; H, 3.31; N, 3.54. Found: C, 36.57; H, 3.41; N, 3.42.

4.2.4. 2-(+/−)-*N*-(1-Hydroxy-3-methylbutyl)-ethylenedithio-tetrathiafulvalene-amide (3a). From (+/−)-valinol (0.18 g), orange crystals (0.3 g, 52% yield), mp 176–177 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, ^3J=6.8 Hz, 3H, CH_3), 0.99 (d, ^3J=6.8 Hz, 3H, CH_3), 1.93 (m, 1H, *CH*–$(CH_3)_2$), 3.30 (s, 4H, S–CH_2–CH_2–S), 3.74 (d, ^3J=3.7 Hz, 2H, CH_2O), 3.79 (m, 1H, NH–*CH*–CH_2O), 5.75 (d, ^3J=8.5 Hz, 1H, NH), 7.12 (s, 1H, =CH). IR (KBr, cm^{-1}): 1571 ($\nu_{C=C}$), 1615 ($\nu_{C=O}$), 3186 (ν_{OH}). *m/z* (MALDI-TOF): 423.03 (M^+). Anal. Calcd for $C_{14}H_{17}NO_2S_6$: C, 39.69; H, 4.04; N, 3.31. Found: C, 39.82; H, 4.05; N, 3.24.

4.2.5. 2-(*R*)-*N*-(1-Hydroxy-3-methylbutyl)-ethylenedithio-tetrathiafulvalene-amide (3b). From (*R*)-valinol (0.472 g) and 1.28 g of EDT-TTF-COCl, orange solid (1.34 g, 88% yield), mp 163–164 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, ^3J=6.8 Hz, 3H, CH_3), 0.98 (d, ^3J=6.8 Hz, 3H, CH_3), 1.93 (m, 1H, *CH*–$(CH_3)_2$), 3.30 (s, 4H, S–CH_2–CH_2–S), 3.74 (d, ^3J=4.2 Hz, 2H, CH_2O), 3.80 (m, 1H, NH–*CH*–CH_2O), 5.75 (d, ^3J=8.5 Hz, 1H, NH), 7.12 (s, 1H, =CH). IR (KBr, cm^{-1}): 1571 ($\nu_{C=C}$), 1615 ($\nu_{C=O}$), 3186 (ν_{OH}). *m/z* (MALDI-TOF): 422.91 (M^+). Anal. Calcd for $C_{14}H_{17}NO_2S_6$: C, 39.69; H, 4.04; N, 3.31. Found: C, 39.91; H, 4.12; N, 3.17.

4.2.6. 2-(*S*)-*N*-(1-Hydroxy-3-methylbutyl)-ethylenedithio-tetrathiafulvalene-amide (3c). From (*S*)-valinol (0.556 g) and 1.48 g of EDT-TTF-COCl, orange solid (1.48 g, 84% yield), mp 163–164 °C. ^{1}H NMR, IR and MS spectra are identical with those of **3b**. Anal. Calcd for $C_{14}H_{17}NO_2S_6$: C, 39.69; H, 4.04; N, 3.31. Found: C, 39.89; H, 4.15; N, 3.18.

4.3. General procedure for oxazolines

To a solution of hydroxy-amide **2**–**3** (5.06 mmol) and dry triethylamine (1.5 mL, 10.76 mmol) in 150 mL of dry THF, cooled at 0 °C, was added in one portion methanesulfonyl chloride (0.8 mL, 10.34 mmol). After stirring at 0 °C for 30 min, another portion of triethylamine was added (6.3 mL, 45.2 mmol), then the reaction mixture was heated at 50 °C for approximately 20 h, that is, until the initially formed mesylate disappeared, as monitored by TLC: AcOEt/cyclohexane 2:1. Then the mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude product was chromatographed on silica gel (AcOEt/cyclohexane 2:1) to give a yellow-orange solid. Recrystallization in acetonitrile (or a mixture of THF and cyclohexane) affords orange crystalline solids.

4.3.1. (+/−)-2-(Ethylenedithio-tetrathiafulvalenyl)-4-methyl-oxazoline (4a). From 0.2 g of **2a**, orange-yellow solid (0.16 g, 83% yield), mp 181–186 °C. ^{1}H NMR ($CDCl_3$): δ 1.31 (d, ^3J=6.6 Hz, 3H, CH_3), 3.29 (s, 4H, S–CH_2–CH_2–S), 3.88 (t, ^3J=^2J=7.9 Hz, 1H of CH_2O, H_{syn}/CH_3), 4.31 (qdd, ^3J=9.2 Hz, ^3J=7.9 Hz, ^3J=6.6 Hz, 1H, N–*CH*–CH_2O), 4.45 (dd, ^3J=9.2 Hz, ^2J=7.9 Hz, 1H of CH_2O, H_{anti}/CH_3), 6.97 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ 21.8 (CH_3), 30.8, 30.9 (S–CH_2–CH_2–S), 63.1 (CH–N), 75.5 (CH_2O), 107.9, 114.3, 115.0, 116.5 (2C=C), 125.1 (=CH), 126.6 (=*C*–C=N), 157.3 (C=N). IR (KBr, cm^{-1}): 1571 ($\nu_{C=C}$), 1634 ($\nu_{C=N}$). *m/z* (MALDI-TOF): 376.93 (M^+). Anal. Calcd for $C_{12}H_{11}NOS_6$: C, 38.17; H, 2.94; N, 3.71. Found: C, 38.05; H, 2.97; N, 3.62.

4.3.2. (*R*)-2-(Ethylenedithio-tetrathiafulvalenyl)-4-methyl-oxazoline (4b). From 0.84 g of **2b**, orange crystals (0.74 g, 92% yield), mp 202–203 °C. ^{1}H NMR ($CDCl_3$): δ 1.31 (d, ^3J=6.7 Hz, 3H, CH_3), 3.29 (s, 4H, S–CH_2–CH_2–S), 3.88 (t, ^3J=^2J=7.9 Hz, 1H of CH_2O, H_{syn}/CH_3), 4.31 (qdd, ^3J=9.2 Hz, ^3J=7.9 Hz, ^3J=6.7 Hz, 1H, N–*CH*–CH_2O), 4.45 (dd, ^3J=9.2 Hz, ^2J=7.9 Hz, 1H of CH_2O, H_{anti}/CH_3), 6.97 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ 21.1 (CH_3), 30.1, 30.2 (S–CH_2–CH_2–S), 62.3 (CH–N), 74.8 (CH_2O), 107.1, 113.5, 114.3, 115.8 (2C=C), 124.3 (=CH), 125.9 (=*C*–C=N), 156.6 (C=N). IR (KBr, cm^{-1}): 1571 ($\nu_{C=C}$), 1634 ($\nu_{C=N}$). *m/z* (MALDI-TOF): 376.94 (M^+). Anal. Calcd for $C_{12}H_{11}NOS_6$: C, 38.17; H, 2.94; N, 3.71. Found: C, 38.43; H, 2.93; N, 3.68.

4.3.3. (*S*)-2-(Ethylenedithio-tetrathiafulvalenyl)-4-methyl-oxazoline (4c). From 0.93 g of **2c**, orange crystals (0.65 g, 73% yield), mp 202–203 °C. ^{1}H NMR, ^{13}C NMR, IR and MS spectra are identical with those of **4b**. Anal. Calcd for $C_{12}H_{11}NOS_6$: C, 38.17; H, 2.94; N, 3.71. Found: C, 38.16; H, 2.87; N, 3.75.

4.3.4. (+/−)-2-(Ethylenedithio-tetrathiafulvalenyl)-4-isopropyl-oxazoline (5a). From 0.25 g of **3a**, orange solid (0.21 g, 88% yield), mp 156–157 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (d, ^3J=6.7 Hz, 3H, CH_3), 0.97 (d, ^3J=6.7 Hz, 3H, CH_3), 1.81 (m, 1H, *CH*–$(CH_3)_2$), 3.29 (s, 4H, S–CH_2–CH_2–S), 4.03 (m, 1H, N–*CH*–CH_2O), 4.06 (t, ^3J=^2J=7.3 Hz, 1H of CH_2O, H_{syn}/*i*Pr), 4.45 (dd, ^2J=7.3 Hz, ^3J=1.3 Hz, 1H of CH_2O, H_{anti}/*i*Pr), 6.95 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ 18.6 (CH_3), 19.5 (CH_3), 30.8, 30.9 (S–CH_2–CH_2–S), 33.2 (*CH*–$(CH_3)_2$), 71.5 (CH–N), 73.5 (CH_2O), 107.7, 114.3, 115.0, 116.9 (2C=C), 125.2 (=CH), 126.3 (=*C*–C=N), 157.1 (C=N). IR (KBr, cm^{-1}): 1564 ($\nu_{C=C}$), 1641 ($\nu_{C=N}$). *m/z* (MALDI-TOF): 404.89 (M^+). Anal. Calcd for $C_{14}H_{15}NOS_6$: C, 41.45; H, 3.73; N, 3.45. Found: C, 41.14; H, 3.86; N, 3.36.

4.3.5. (*R*)-2-(Ethylenedithio-tetrathiafulvalenyl)-4-isopropyl-oxazoline (5b). From 1.34 g of **3b**, orange solid

Table 3. Crystal and structure refinement data for **2a**, **4c**, **5b**, **5c** and $(\mathbf{4a})_2Mo_6Cl_{14}$

	2a	**4c**	**5b**	**5c**	$(\mathbf{4a})_2Mo_6Cl_{14}$
Elemental formula	$C_{12}H_{13}NO_2S_6$	$C_{12}H_{11}NOS_6$	$C_{14}H_{15}NOS_6$	$C_{14}H_{15}NOS_6$	$C_{24}H_{22}Cl_{14}Mo_6N_2O_2S_{12}$
Formula weight	395.64	377.58	405.63	405.63	1827.10
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic
Space group	*P*21/*c*	*P*21	*P*212121	*P*212121	*P*21/*c*
a (Å)	6.5992(9)	6.3167(5)	6.4416(5)	6.4450(6)	19.433
b (Å)	16.143(2)	7.7578(7)	14.3025(15)	14.313(2)	13.634
c (Å)	15.824(2)	16.2434(12)	19.3132(16)	19.360(2)	22.395
α (°)	90	90	90	90	90
β (°)	98.466(17)	99.960(9)	90	90	92.96
γ (°)	90	90	90	90	90
Cell volume, *V* (Å^3)	1667.4(4)	783.99(11)	1779.3(3)	1785.9(4)	5925.7
No. of formula units/cell, *Z*	4	2	4	4	4
Absorption coefficient (mm^{-1})	0.821	0.865	0.768	0.765	2.313
Temperature (K)	293(2)	293(2)	293(2)	293(2)	293(2)
Total no. of refl. measured	12937	6116	14353	11220	68687
No. of unique refl.	3056	2911	3455	3455	13514
No. of 'observed' refl. ($I>2\sigma_I$)	1162	2719	1907	1247	8169
R_1, wR_2 ('observed' data)[a]	0.057, 0.111	0.037, 0.101	0.058, 0.122	0.043, 0.071	0.044, 0.097
R_1, wR_2 (all data)[a]	0.179, 0.140	0.040, 0.104	0.121, 0.145	0.150, 0.094	0.102, 0.115

[a] $R(F_o)=\Sigma||F_o|-|F_c||/\Sigma|F_o|$; $R_w(F_o^2)=[\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

(1.22 g, 95% yield), mp 150–151 °C. ^{1}H NMR ($CDCl_3$): δ 0.87 (d, $^3J=6.7$ Hz, 3H, CH_3), 0.97 (d, $^3J=6.7$ Hz, 3H, CH_3), 1.81 (m, 1H, *CH*–$(CH_3)_2$), 3.29 (s, 4H, S–*CH*$_2$–*CH*$_2$–S), 4.01–4.08 (m, 2H, N–*CH*–CH_2O and 1H of CH_2O, H_{syn}/*i*Pr), 4.33 (dd, $^2J=7.4$ Hz, $^3J=1.3$ Hz, 1H of CH_2O, H_{anti}/*i*Pr), 6.95 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ 18.0 (CH_3), 18.9 (CH_3), 30.1, 30.2 (S–CH_2–CH_2–S), 32.5 (*CH*–$(CH_3)_2$), 70.9 (CH–N), 72.8 (CH_2O), 106.9, 113.6, 114.3, 116.2 (2C=C), 124.5 (=CH), 125.6 (=*C*–C=N), 156.4 (C=N). IR (KBr, cm^{-1}): 1564 ($\nu_{C=C}$), 1641 ($\nu_{C=N}$). *m*/*z* (MALDI-TOF): 404.90 (M^+). Anal. Calcd for $C_{14}H_{15}NOS_6$: C, 41.45; H, 3.73; N, 3.45. Found: C, 41.59; H, 3.85; N, 3.41.

4.3.6. (*S*)-2-(Ethylenedithio-tetrathiafulvalenyl)-4-isopropyl-oxazoline (5c). From 1.48 g of **3c**, orange solid (1.35 g, 95% yield), mp 150–151 °C. ^{1}H NMR, ^{13}C NMR, IR and MS spectra are identical with those of **5b**. Anal. Calcd for $C_{14}H_{15}NOS_6$: C, 41.45; H, 3.73; N, 3.45. Found: C, 41.47; H, 3.79; N, 3.36.

4.4. Electrocrystallization

Two-compartment cell was used together with platinum electrodes (2 cm long, 1 mm in diameter) and a current of 1 μA at room temperature (20±2 °C). $[(n\text{-}Bu)_4N]_2Mo_6Cl_{14}$ 0.015 M in CH_2Cl_2 (20 mL) was used as electrolyte with the donor **4a** (5 mg), dissolved in the anodic compartment. Electrolysis was performed during 7 days, after which air stable plate-shaped crystals were harvested on the anode and washed with little CH_2Cl_2.

4.5. X-ray crystallography

Details about data collection and solution refinement are given in Table 3. Data were collected on a Stoe Imaging Plate System (IPDS) for the structures **2a**, **4c**, **5b** and **5c** and on a Bruker-CCD System for the structure $(\mathbf{4a})_2Mo_6Cl_{14}$, both operating with a Mo Kα X-ray tube with a graphite monochromator. The structures were solved (SHELXS-97) by direct methods and refined (SHELXL-97) by full-matrix least-square procedures on F^2.[21] Hydrogen atoms were introduced at calculated positions (riding model), included in structure factor calculations but not refined. All the heavy atoms, but C24A and C24B in the structure $(\mathbf{4a})_2Mo_6Cl_{14}$, have been refined anisotropically. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 262767–262771 (CIF files). Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

4.6. Theoretical calculations

The overlap interaction energies ($\beta_{HOMO-HOMO}$) were of extended-Hückel type.[22] A modified Wolfsberg-Helmholtz formula was used to calculate the non-diagonal $H_{\mu\nu}$ values.[23] Double-ζ orbitals for C, S, N and O were used.

4.7. Cyclic voltammetry

Cyclic voltammetry studies were performed in a three-electrode cell equipped with a platinum millielectrode of 0.126 cm^2 area, an Ag/AgCl reference and a platinum wire counter-electrode. The electrolytic media involved a 0.1 mol L^{-1} solution of $(n\text{-}Bu_4N)PF_6$ in dichloromethane. All experiments have been performed at room temperature at 0.1 V s^{-1}.

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References and notes

1. (a) Williams, J. M.; Ferraro, J. R.; Thorn, R. J.; Carlson, K. D.; Geiser, U.; Wang, H. H.; Kini, A. M.; Whangbo, M.-H. In

Organic superconductors (including fullerenes), synthesis, structure, properties and theory; Grimes, R. N., Ed.; Prentice-Hall: Englewoods: Cliffs, NJ, 1992. (b) Segura, J. L.; Martin, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 1372. (c) Yamada, J.-I. TTF Chemistry: Fundamentals and Applications of Tetrathiafulvalene; Springer: Berlin and Heidelberg, 2004.

2. (a) Krstic, V.; Roth, S.; Burghard, M.; Kern, K.; Rikken, G. L. J. A. *J. Chem. Phys.* **2002**, *117*, 11315. (b) Krstic, V.; Rikken, G. L. J. A. *Chem. Phys. Lett.* **2002**, *364*, 51.
3. (a) Coronado, E.; Day, P. *Chem. Rev.* **2004**, *104*, 5419. (b) Coronado, E.; Galán-Mascarós, J. R. *J. Mater. Chem.* **2005**, *15*, 66.
4. Wallis, J. D.; Griffiths, J.-P. *J. Mater. Chem.* **2005**, *15*, 347.
5. (a) Grüner, G. *Rev. Mod. Phys.* **1988**, *60*, 1129. (b) Jérome, D.; Schulz, H. J. *Adv. Phys.* **1982**, *31*, 299.
6. Coronado, E.; Galán-Mascarós, J. R.; Gómez-Garcia, C. J.; Murcia-Martinez, A.; Canadell, E. *Inorg. Chem.* **2004**, *43*, 8072.
7. (a) Dunitz, J. D.; Karrer, A.; Wallis, J. D. *HeIv. Chim. Acta* **1986**, *69*, 69. (b) Karrer, A.; Wallis, J. D.; Dunitz, J. D.; Hilti, B.; Mayer, C. W.; Bürkle, M.; Pfeiffer, J. *Helv. Chim. Acta* **1987**, *70*, 942.
8. Griffiths, J.-P.; Nie, H.; Brown, R. J.; Day, P.; Wallis, J. D. *Org. Biomol. Chem.* **2005**, *3*, 2155.
9. (a) Gomez, R.; Segura, J. L.; Martin, N. *Org. Lett.* **2000**, *2*, 1585. (b) Gomez, R.; Segura, J. L.; Martin, N. *J. Org. Chem.* **2000**, *65*, 7566.
10. Chesney, A.; Bryce, M. R. *Tetrahedron: Asymmetry* **1996**, *7*, 3247.
11. Réthoré, C.; Fourmigué, M.; Avarvari, N. *Chem. Commun.* **2004**, 1384.
12. Réthoré, C.; Avarvari, N.; Canadell, E.; Auban-Senzier, P.; Fourmigué, M. *J. Am. Chem. Soc.* **2005**, *127*, 5748.
13. (a) Heuzé, K.; Fourmigué, M.; Batail, P. *J. Mater. Chem.* **1999**, *9*, 2373. (b) Devic, T.; Avarvari, N.; Batail, P. *Chem. Eur. J.* **2004**, *10*, 3697.
14. Baudron, S. A.; Avarvari, N.; Canadell, E.; Auban-Senzier, P.; Batail, P. *Chem. Eur. J.* **2004**, *10*, 4498.
15. Moore, A. J.; Bryce, M. R.; Batsanov, A. S.; Heaton, J. N.; Lehmann, C. W.; Howard, J. A. K.; Robertson, N.; Underhill, A. E.; Perepichka, I. F. *J. Mater. Chem.* **1998**, *8*, 1541.
16. (a) Liu, S.-X.; Neels, A.; Stoeckli-Evans, H.; Pilkington, M.; Wallis, J. D.; Decurtins, S. *Polyhedron* **2004**, *23*, 1185. (b) Wang, C.; Bryce, M. R.; Batsanov, A. S.; Stanley, C. F.; Beeby, A.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1671.
17. Taguchi, T.; Kawara, A.; Watanabe, S.; Oki, Y.; Fukushima, H.; Kobayashi, Y.; Okada, M.; Ohta, K.; Iitaka, Y. *Tetrahedron Lett.* **1986**, *27*, 5117.
18. Etter, M. *Acc. Chem. Res.* **1990**, *23*, 120.
19. Fourmigué, M.; Batail, P. *Chem. Rev.* **2004**, *104*, 5379.
20. (a) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441. (b) Spackman, M. A. *J. Chem. Phys.* **1986**, *85*, 6579.
21. Sheldrick, G. M. *Programs for the Refinement of Crystal Structures*; University of Göttingen: Göttingen (Germany), 1996.
22. Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397.
23. Ammeter, J. H.; Bürgi, H.-B.; Thibeault, J.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 3686.

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Bis- and tris-bicyclophosphites of D-glucofuranoside. Unexpected catalysis of P(III/V)-oxidation by triethylamine

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Abstract—The synthesis and characterization of several new bicyclophosphites via reactions of (i) ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite with acid chlorides (phthalic or butylphosphoric), (ii) ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite with 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane and (iii) the tetraol system of ethyl 1-thio-α-D-glucofuranoside and hexaethyltriamidophosphite are reported. Unusual catalytic transformation of P(III)-compounds into the respective P(V)-spieces under extraordinary mild conditions by reaction with sulfur and selenium in the presence of triethylamine was discovered for the first time.

1. Introduction

Carbohydrates are of central importance in many life affecting processes and the main parts in a variety of important biologically relevant molecules, for example, DNA, RNA, lipids, vitamins, cell membranes.[1,2] Along with their beyond controversy role in living organisms, they possess great importance in synthetic organic chemistry. The application of carbohydrates in catalysis is based on the well defined chemistry accompanied by the wide range of derivatization possibilities (in particular, incorporation of donor atoms is able to transfer this compound class into mono- or multidentate ligands).[3–6] Additionally, a favorable property of carbohydrates is the accessibility of their structure as central element in newly developed molecules due to their natural occurrence.

The derivatization of the sugar moiety with phosphorus donors has already a long-lasting history in chemistry. Phosphorus ligands are successfully used in many catalytic processes. Their high affinity towards transition metals, like Rh, Pd, Pt, Cu, Mo, Cr, Ni, etc., results in the formation of highly catalytically active species.[7–11]

Sugars containing two phosphorus(III) atoms are well known as useful ligands in different enantioselective reactions.[12–15] Diphosphorus compounds usually form chelate structures when the P-atoms are located at appropriate distance to each other. The establishment of the latter structure type is a crucial step to obtain high enantioselectivities in certain catalytic processes.[16] Nevertheless, there are several known examples of natural polyol-derivatives in which the P-atoms are not appropriately arranged to act as bidentate ligand-phosphites of mannitol, of dihydromannitol, and of other carbohydrates.[17–19] All these systems are rather rigid which is on the one hand advantageous for their catalytic potential. On the other hand, the rigid backbone of such structures prevents the chelate formation with transition metals. The limitation of such P(III)-compounds is that the phosphorus atom can be hydrolyzed or oxidized (formation of P(V) residues).[14,20,21]

In contrast, bicyclophosphites with carbohydrate backbone can overcome such disadvantageous behavior of their close relatives—they are easy to handle and surprisingly rather stable.[22,23] Hence, they possess some obvious properties outclassing their non-cyclic analogues. Additionally, bicyclophosphites represent a class of ligands with interesting coordination properties. Examples of their coordination with transition metal centers are known, for example, Cu(I), Ag(I), Cr(0), Mo(0), Pt(II), and Rh(I).[24]

Combining the stable bicyclophosphite moiety based on a

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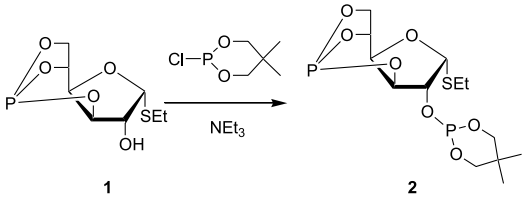
glucose backbone with a flexible linker system can create structures with very promising properties. Until now only a few examples of ligands, which contain two bicyclophosphite moieties based on a nonchiral backbone connected with a rather flexible linker have been reported.[25,26]

Herein, the syntheses of bis- and tris-bicyclophosphites of D-glucofuranoside and investigations on the catalytic transformation of the P(III)-compounds into the respective P(V)-species by triethylamine are presented.

2. Results and discussion

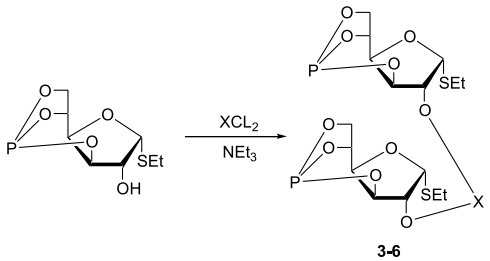
Ethyl 2-*O*-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)-1-thio-α-D-glucofuranoside 3,5,6-phosphite **2** was synthesized through an acylation reaction of ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite **1** with 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (Scheme 1).

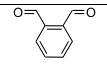
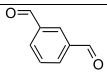
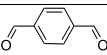


Scheme 1. Derivatization of the 2-hydroxo group of the glucofuranoside **1** yielding ethyl 2-*O*-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)-1-thio-α-D-glucofuranoside 3,5,6-phosphite.

The reaction was carried out at room temperature in dry benzene or in 1,4-dioxane in the presence of 10% excess of triethylamine as an HCl-acceptor. The formation of the diphosphite **2** was monitored by means of ^{31}P NMR—the disappearance of the signal assigned to the acylation agent 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane at 146 ppm and the arising of two new signals at 120 and 118 ppm with equal integral from the cyclophosphite and the bicyclophosphite moieties, respectively, were found to be indicative of the reaction progress. In ^{1}H NMR spectra the decreasing signal of the hydroxy-proton, the shift (from 3.9 to 4.5 ppm) of the **H2** proton of the carbohydrate to low field, and the appearance of the signals from the 5,5-dimethyl-1,3,2-dioxaphosphorinane moiety are feasible to follow the course of reaction. Additionally, the multiplicity of the **H2** proton in ^{1}H NMR (d, $^{3}J_{P2H2}$= 9.8 Hz) and of the carbon atoms **C1** and **C2** in ^{13}C NMR spectra (d, $^{2}J_{C2P}$=12.0 Hz; d, $^{3}J_{C1P}$=2.5 Hz, respectively) were changed.

The acid chlorides of *o*-, *m*-, and *p*-phthalic acid as well as of *n*-butylphosphoric acid were used as acylation reagents to form bis-bicyclophosphite derivatives of ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite **1** under similar conditions applied for the synthesis of **2** (Scheme 2). When phthalic acid isomers were used as linkers, ^{31}P NMR was found to be unsuitable to monitor the reaction progress (the shift of the P-signals was less then 0.1 ppm) and therefore the reaction was followed only by means of TLC. Compounds **3–5** were isolated as P(III) derivatives by column chromatography on silica gel while the hydrolytically unstable phosphite **6** was

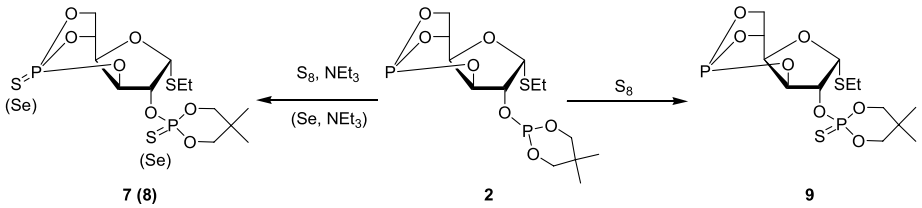


Compound	X
3	
4	
5	
6 [6` P(V)]	POBu

Scheme 2. Synthesis of the bridged bicyclophosphites **3–6**.

isolated as the respective P(V) compound **6′** after addition of sulfur to the reaction mixture.

For compounds **2–6** the stability against oxidation processes was investigated with elemental sulfur and selenium. From literature it is known that the 3,5,6-bicyclophosphite derivatives of glucofuranoside show unusual stability towards oxidation reagents like sulfur, selenium, or nitrogen(II) oxide.[22] Reactions with sulfur were carried out at elevated temperature (90–120 °C) and resulted in relatively low yield probably due to carbonization.[27,28] Oxidation with oxygen can be performed under UV-irradiation or in ozone atmosphere.[29] Taking into account the chemical stability of bicyclophosphites towards oxidizine agents, it was expected that after the addition of sulfur to the reaction mixture of phosphite **2** at room temperature, only the 5,5-dimethyl-1,3,2-dioxaphosphorinane moiety would be involved in the sulfurization reaction. Surprisingly, the ^{31}P NMR spectra after 24 h contained only signals of thiophosphates (73 and 58 ppm, 1:1). The same behavior was observed when adding sulfur to the reaction mixture of the phosphite **6**—after 24 h signals at 74.6 and 74.4 ppm from bicyclothiophosphate and at 70 ppm from butylthiophosphate moieties (integral of NMR signals 1:1:1) were observed. Softening the sulfurization conditions (reaction at room temperature) also led to the formation of the corresponding P(V)-species. This might be explained either by the influence of the different type of phosphorus atoms on each other or by catalysis of a component of the reaction mixture. Since it is not possible to isolate phosphite **6**, the influence of phosphorus atom-types was investigated with the more stable phosphite **2** (Scheme 3). Elemental sulfur was added to a solution of **2** in benzene at room temperature and, after 12 h in the reaction mixture, conversion of 5,5-dimethyl-1,3,2-dioxaphosphorinane into 5,5-dimethyl-2-sulfide-1,3,2-dioxaphosphorinane was observed, whereas the bicyclophosphite part remained unchanged—this was proven by recording ^{31}P NMR signals at 118 and 59 ppm with an integral ratio of 1:1. Increasing the reaction time up to one week and raising the temperature to 45–50 °C does not affect the reaction. This experiment gives rise to the hypothesis that the oxidative addition is facilitated by the



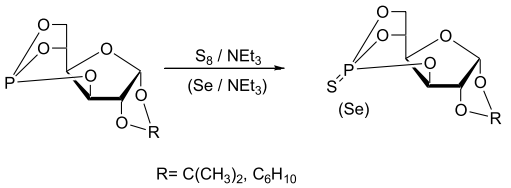
Scheme 3. Reaction of compound **2** with sulfur/NEt_3, selenium/NEt_3, or sulfur.

influence of different phosphorus types on each other in one molecule.

Most likely, the catalyst in this reaction is the amine (NEt_3), which was used as acceptor of HCl. Similar catalytic effects of triethylamine were reported in the reaction of triphenylphosphine with sulfur.[30] In order to prove this hypothesis, triethylamine (1–5%) was added to a reaction mixture of phosphite **2** and sulfur immediately after the addition of sulfur or after ca. 10 h (when the reaction between 5,5-dimethyl-1,3,2-dioxaphosphorinane and sulfur is completed). In both cases, within 12 h after the addition of triethylamine P(III) was completely converted into P(V).

Monitoring the addition of sulfur to phosphite **2** showed that the 5,5-dimethyl-1,3,2-dioxaphosphorinane-group was oxidized faster then the bicyclophosphite group—after a reaction time of 4 h almost complete conversion of the phosphorinane was determined by ^{31}P NMR, while the quantitative oxidation of the bicyclophosphite needed at least 12–16 h.

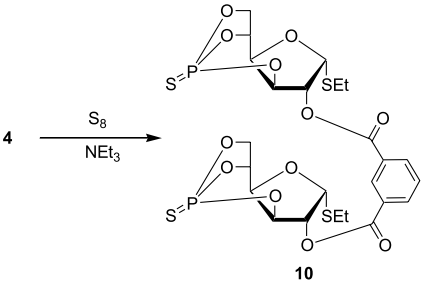
In order to investigate the catalytic potential of triethylamine, its effect on known bicyclophosphites of glucofuranoside (1,2-*O*-isopropylidene-3,5,6-bicyclophosphite-α-D-glucofuranoside; 1,2-*O*-cyclohexylidene-3,5,6-bicyclophosphite-α-D-glucofuranoside) was evaluated (Scheme 4). The mechanism of catalysis is supposed to be similar to that reported by Davis and co-workers.[30] The reactions were allowed to proceed for 24 h at room temperature, the products were isolated by column chromatography on silica gel (80–95% yield) and their melting points and NMR spectra (^1H, ^{13}C, ^{31}P) were equivalent to those described in the literature.[31,32]



Scheme 4. Oxidation of 1,2-*O*-isopropylidene-3,5,6-bicyclophosphite-α-D-glucofuranoside and 1,2-*O*-cyclohexylidene-3,5,6-bicyclophosphite-α-D-glucofuranoside by sulfur or selenium catalyzed by NEt_3.

When changing the oxidation reagent from sulfur to selenium and applying the same soft reaction conditions (catalytic amounts of triethylamine, room temperature) the corresponding selenophosphates were obtained. In the ^{31}P NMR spectra satellite signals with coupling constants of 1016 and 1092 Hz were found.

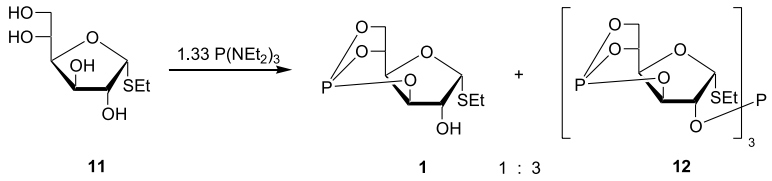
A comparative study on the catalytic properties of different amines in the oxidative sulfurization and the oxidative selenization was then performed with triphenylphosphite.[33] Triphenylphosphite was chosen for this study as a model compound for the synthesis of triarylthiophosphates, which are widely used additives to transmission oil and lubricants.[34–36] Primary diamines were found to be the best catalysts in the discussed processes (e.g., 1,2-diaminoethane, 1,3-diaminopropane) and used for sulfurization of several sterically hindered triarylphosphites (e.g., 4-*tert*-butyl, 4-C12–C15). However, taking into account that triethylamine was already added to most of the reaction mixtures (as HCl-acceptor) no other amines were utilized for the oxidative sulfurization of the synthesized glucose compounds. For example, applying soft reaction conditions (room temperature, triethylamine as catalyst) led to the conversion of the diphosphite **4** and the dithiophosphate **10** was isolated by column chromatography with 75% yield (Scheme 5).



Scheme 5. Sulfurization of the bis-bicyclophosphite **4** catalyzed by NEt_3.

Compounds with multiple phosphorus centers are available via the reaction of hexaethyltriamidophosphite with carbohydrates. Reacting hexaethyltriamidophosphite with ethyl 1-thio-α-D-glucofuranoside **11** at different molar ratios resulted in the formation of mono-, bis-, and/or tris-bicyclophosphite systems. The **C2** hydroxy group of the glucofuranoside structure of, for example, compound **11** can only be phosphorylated with hexaethyltriamidophosphite at 120–130 °C (the latter is also used as solvent).

When using for the reaction a 33% excess of the phosphorylation agent (Scheme 6), in the ^{31}P NMR spectra of the reaction mixture after 2 h there were seen two signals at 149 and 118 ppm with integration 1:4. In addition, there were found two spots from compounds bearing phosphite groups (specific visualization by iodine vapor) on the TLC plate. After separation of the reaction mixture by column chromatography on silica gel, compounds **1** and **12** were obtained and characterized by NMR spectroscopy as well as by elemental analysis. In the ^{31}P NMR spectra of **12** two signals at 149 and 118 ppm with a ratio of the integrals of 1:3 were found. In the ^1H and ^{13}C NMR spectra the coupling



Scheme 6. Phosphorylation of **11** with hexaethyltriamidophosphite at a molar ratio of 3:4.

constants of $^{3}J_{H2P}=10.2$ Hz, $^{3}J_{C1P}=3.5$ Hz/$^{2}J_{C2P}=8.7$ Hz, respectively, confirmed the formation of the tris-bicyclic compound.

As a result of increasing the excess of hexaethyltriamidophosphite in the reaction with ethyl 1-thio-α-D-glucofuranoside (Scheme 7), three singlets in the region of P(III)-compounds with chemical shifts of 151, 149, and 118 ppm and an integration ratio of 1:1:4 were observed in the ^{31}P NMR spectra of the reaction mixture. Unstable P(III) products were transformed into the respective P(V) species by reaction with sulfur and three different compounds were isolated by column chromatography on silica gel. In the ^{31}P NMR spectrum of the fastest eluting species there were found two singlets at 75 and 72 ppm with an integration of 1:2 that allowed for identification of bis-[2-(3,5,6-bicyclophosphothioate-ethyl-1-thio-α-D-glucofuranoside)]diethylamidophosphothioate. The compound isolated from the second chromatographic fraction showed only one ^{31}P-singlet at 72 ppm and thus was characterized as 3,5,6-bicyclophosphothioate-ethyl-1-thio-α-D-glucofuranoside. The ^{31}P NMR spectrum of the compound obtained from the slowest eluting fraction contained two singlets at 71 and 70 ppm with an integration of 3:1. The compound was ascribed to tris[2-(3,5,6-bicyclophosphothioate-ethyl-1-thio-α-D-glucofuranoside)]phosphothioate, which can also be synthesized by direct addition of sulfur to the phosphite **12** in the presence of a catalytic amount of triethylamine. The structures of compounds **14–16** were been proven by ^{1}H and ^{13}C NMR as well as elemental analysis.

3. Conclusions

Carbohydrates synthesized here contain more than one phosphorus atom so that either the phosphorus atoms are attached to only one sugar-moiety, two sugar moieties being bridged by an aromatic spacer, or a suitable phosphorus-group is used as bridging group resulting in compounds containing even three or four P-atoms. All obtained compounds were characterized by NMR-spectroscopy and elemental analysis.

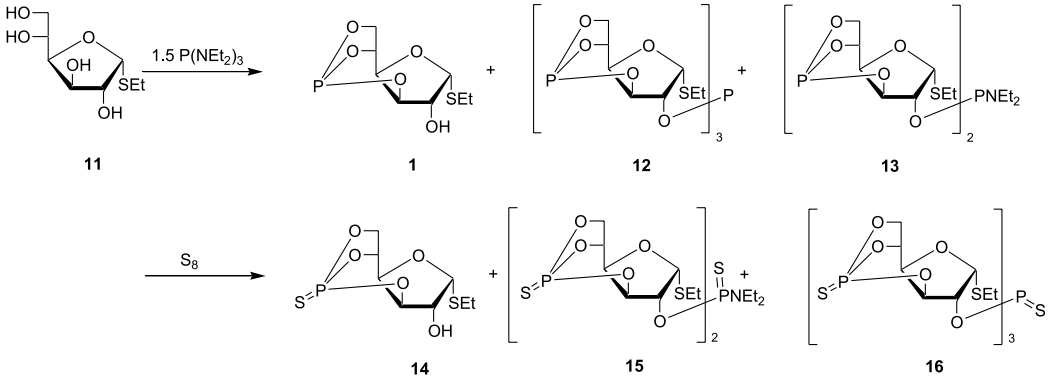
Usually P(III)-atoms in bicyclophosphites are oxidized by elemental sulfur or selenium only under rather harsh conditions—ca. 100 °C. Surprisingly, the addition of catalytic amounts of triethylamine led to the respective thio- or seleno-P(V)-product already at room temperature.

Due to the electron donor-properties of the phosphorus(III)-moieties, the newly synthesized compounds may find application as ligands in transition metal-catalyzed reactions. The catalyzed oxidation of stable phosphorus (III)-groups is also of interest for the synthesis of additives to transmission oils and lubricants.

4. Experimental

4.1. General

All reactions were carried out in dry solvents and under argon atmosphere. Chemicals obtained from different commercial suppliers were used as received. Analytical grade solvents were purified by standard methods.[37] Ethyl 1-thio-α-D-glucofuranoside,[38] ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite,[23] 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane,[39] hexaethyltriamidophosphite[40] and butyl dichlorophosphite[41] were prepared according to literature procedures. The NMR spectra were recorded on the Bruker instruments WM-200 (^{1}H at 200 MHz, with TMS as an internal standard), AC-200 P (^{13}C at 50.3 MHz, with TMS as an internal standard), and W-80 SY (^{31}P at 32.4 MHz, with 85% H_3PO_4 as an external standard). Melting points were determined in open capillaries and are uncorrected. Silica gel plates Siluphol UV-254 and silica gel were used with solvent mixtures 1,4-dioxane–benzene (1/5) (A)



Scheme 7. Phosphorylation of **11** with hexaethyltriamidophosphite at a molar ratio of 2:3 followed by oxidation with sulfur.

or 1,4-dioxane–benzene (1/10) (B) for thin layer and preparative column chromatography, respectively.

4.1.1. Ethyl 2-*O*-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)-1-thio-α-D-glucofuranoside 3,5,6-phosphite (2). A solution of 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (0.168 g, 1 mmol) in 3 mL of benzene was added dropwise to a solution of ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite (0.25 g, 1 mmol) and triethylamine (0.11 g, 1.1 mmol) in 5 mL of benzene and the reaction mixture was stirred for 24 h. The triethylamine hydrochloride was filtered off and the solvent was reduced in vacuum. The crude product was purified by column chromatography. Yield 0.23 g (60%), syrup, R_f 0.74 (A). ^{1}H NMR (C_6D_6) δ: 5.62 (d, 1H, Glc-H1, ^3J=3.8 Hz), 4.50 (dd, 1H, Glc-H2, ^3J=3.8, 9.8 Hz), 4.37 (dd, 1H, Glc-H3, ^3J=3.0, 2.5 Hz), 5.30 (dd, 2H, OCH_2, ^2J=8.9 Hz, ^3J=3.0 Hz), 4.18 (m, 1H, Glc-H5), 3.82 (m, 1H, Glc-H4), 3.26 (dd, 2H, OCH_2, ^2J=8.9 Hz, ^3J=4.3 Hz), 3.18 (m, 1H, Glc-H6), 3.11 (m, 1H, Glc-H6′), 2.49 (m, 2H, SCH_2CH_3), 1.17 (tr, 3H, SCH_2CH_3, ^3J=7.6 Hz), 1.09 (s, 3H, CH_3), 0.36 (s, 3H, CH_3); ^{13}C{1H} NMR (C_6D_6) δ: 89.42 (Glc-C1, ^3J=2.5 Hz), 78.67 (Glc-C2, ^2J=12.0 Hz), 78.33 (OCH_2), 77.38 (Glc-C4, ^3J=4.2 Hz), 73.95 (Glc-C3, ^2J=1.4 Hz), 71.39 (Glc-C5, ^2J=4.2 Hz), 66.27 (Glc-C6, ^2J=5.8 Hz), 32.33 [$C(CH_3)_2$, ^3J=4.7 Hz], 25.72 (SCH_2CH_3), 22.38 (CH_3), 22.10 (CH_3), 15.22 (SCH_2CH_3); ^{31}P{1H} (C_6D_6) δ: 121.4, 118.5. Anal. Calcd for $C_{13}H_{22}O_7P_2S$: C 40.62, H 5.76, P 16.11. Found: C 40.78, H 5.43, P 15.82.

4.1.2. 1,2-Bis[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite)]benzenedicarboxylate (3). A solution of 1,2-benzenedicarbonyl dichloride (0.10 g, 0.5 mmol) in 3 mL of benzene was added dropwise to a solution of **1** (0.25 g, 1 mmol) and triethylamine (0.11 g, 1.1 mmol) in 5 mL of benzene at 0 °C and the reaction mixture was stirred for 24 h at room temperature. The triethylamine hydrochloride was filtered off and the solvent was reduced in vacuum. The crude product was purified by column chromatography. Yield 0.23 g (72%), mp 63–65 °C, R_f 0.75 (A). ^{1}H NMR (C_6D_6) δ: 7.79–7.61 (m, 4H, Ar-H), 5.82 (d, 2H, Glc-H1, ^3J=4.3 Hz), 4.50 (d, 2H, Glc-H2, ^3J=4.3 Hz), 4.80 (m, 2H, Glc-H5), 4.63 (d, 2H, Glc-H3, ^3J=3.8 Hz), 4.28 (dd, 2H, Glc-H6, ^2J=9.0 Hz, ^3J=4.3 Hz), 4.17 (m, 2H, Glc-H4), 3.91 (m, 2H, Glc-H6′), 2.76 (q, 4H, SCH_2CH_3, ^3J=7.3 Hz), 1.33 (tr, 6H, SCH_2CH_3, ^3J=7.3 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 164.68 [C(O)], 130.92 (Ar-C), 129.78 (Ar-C), 128.29, (Ar-C), 86.81 (Glc-C1), 77.08 (Glc-C2), 76.43 (Glc-C4), 71.89 (Glc-C3, ^2J=2.5 Hz), 70.64 (Glc-C5, ^2J=4.3 Hz), 65.69 (Glc-C6, ^2J=5.7 Hz), 25.38 (SCH_2CH_3), 14.60 (SCH_2CH_3); ^{31}P{1H} (C_6D_6) δ: 118.1. Anal. Calcd for $C_{24}H_{28}O_{12}P_2S_2$: C 45.42, H 4.44, P 9.76. Found: C 45.30, H 4.37, P 9.82.

4.1.3. 1,3-Bis[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite)]benzenedicarboxylate (4). Following the same procedure as described for **3**, compound **4** was obtained from 1,3-benzenedicarbonyl dichloride (0.10 g, 0.5 mmol) and **1** (0.25 g, 1 mmol). Yield 0.25 g (78%), mp 90–92 °C, R_f 0.80 (A).^{1}H NMR (C_6D_6) δ: 9.05 (s, 1H, Ar-H), 8.18 (dd, 2H, Ar-H, ^3J=7.7 Hz, ^4J=1.7 Hz), 6.95 (tr, 1H, Ar-H, ^3J=7.7 Hz), 5.72 (d, 2H, Glc-H1, ^3J=4.7 Hz), 5.63 (d, 2H, Glc-H2, ^3J=4.7 Hz), 4.28 (d, 2H, Glc-H3, ^3J=3.8 Hz), 4.20 (m, 2H, Glc-H5), 3.70 (m, 2H, Glc-H4), 3.35 (dd, 2H, Glc-H6, ^2J=9.0 Hz, ^3J=4.3 Hz), 3.14 (m, 2H, Glc-H6′), 2.32 (q, 4H, SCH_2CH_3, ^3J=7.3 Hz), 1.06 (tr, 6H, SCH_2CH_3, ^3J=7.3 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 164.46 [C(O)], 135.10 (Ar-C), 138.88 (Ar-C), 130.70, (Ar-C), 129.74 (Ar-C), 86.87 (Glc-C1), 81.02 (Glc-C2), 78.21 (Glc-C4, ^3J=4.1 Hz), 74.10 (Glc-C3), 72.27 (Glc-C5, ^2J=4.0 Hz), 67.06 (Glc-C6, ^2J=5.6 Hz), 26.54 (SCH_2CH_3), 15.92 (SCH_2CH_3); ^{31}P{1H} (C_6D_6) δ: 118.0. Anal. Calcd for $C_{24}H_{28}O_{12}P_2S_2$: C 45.42, H 4.44, P 9.76. Found: C 45.51, H 4.18, P 9.92.

4.1.4. 1,4-Bis[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite)]benzenedicarboxylate (5). Following the same procedure as described for **3**, compound **5** was obtained from 1,4-benzenedicarbonyl dichloride (0.10 g, 0.5 mmol) and **1** (0.25 g, 1 mmol). Yield 0.22 g (69%), mp 86–88 °C, R_f 0.80 (A). ^{1}H NMR ($CDCl_3$) δ: 5.87 (d, 2H, Glc-H1, ^3J=4.3 Hz), 5.50 (d, 2H, Glc-H2, ^3J=4.3 Hz), 4.20 (m, 2H, Glc-H5), 4.54 (d, 2H, Glc-H3, ^3J=3.8 Hz), 3.25 (dd, 2H, Glc-H6, ^2J=9.3 Hz, ^3J=4.3 Hz), 4.21 (m, 2H, Glc-H4), 3.91 (m, 2H, Glc-H6′), 2.74 (q, 4H, SCH_2CH_3, ^3J=7.7 Hz), 1.30 (tr, 6H, SCH_2CH_3, ^3J=7.3 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 164.31 [C(O)], 134.00 (Ar-C), 130.47 (Ar-C), 88.57 (Glc-C1), 80.60 (Glc-C2), 77.82 (Glc-C4, ^3J=4.4 Hz), 73.7 (Glc-C3, ^2J=2.6 Hz), 71.90 (Glc-C5, ^2J=4.3 Hz), 66.81 (Glc-C6, ^2J=5.8 Hz), 26.32 (SCH_2CH_3), 15.59 (SCH_2CH_3); ^{31}P{1H} ($CDCl_3$) δ: 118.4. Anal. Calcd for $C_{24}H_{28}O_{12}P_2S_2$: C 45.42, H 4.44, P 9.76. Found: C 45.56, H 4.26, P 9.82.

4.1.5. Butyl-bis[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphorothioate)]phosphorothioate (6′). A solution of butyl dichlorophosphite (87 mg, 0.5 mmol) in 3 mL of benzene was added dropwise to a solution of **1** (0.25 g, 1 mmol) and triethylamine (0.11 g, 1.1 mmol) in 5 mL of benzene at 0 °C and the reaction mixture was stirred for 24 h at room temperature. The triethylamine hydrochloride was filtered off, sulfur (48 mg, 1.5 mmol) was added and the reaction mixture was stirred for another 12 h. The solvent was reduced in vacuum and the crude product was purified by column chromatography. Yield 0.27 g (76%), mp 63–65 °C, R_f 0.75 (B). ^{1}H NMR (C_6D_6) δ: 5.46 (dd, 1H, Glc-H1, ^3J=4.3 Hz, ^4J=3.0 Hz), 5.37 (dd, 1H, Glc-H1′, ^3J=4.3 Hz, ^4J=2.1 Hz), 5.31 (dd, 1H, Glc-H2, ^3J=11.0 Hz, ^3J=4.3 Hz), 5.29 (br s, 1H, Glc-H3), 5.23 (dd, 1H, Glc-H2′, ^3J=11.1 Hz, ^3J=4.3 Hz), 4.78 (tr, 1H, Glc-H3′, ^3J=3.8 Hz), 4.16 (m, 2H, $POCH_2(CH_2)_2CH_3$), 3.98 (m, 2H, Glc-H5), 3.82 (m, 1H, Glc-H4), 3.61 (m, 1H, Glc-H4′), 3.29 (m, 2H, Glc-H6), 2.94 (m, 2H, Glc-H6′), 2.36 (m, 2H, SCH_2CH_3), 2.33 (m, 2H, SCH_2CH_3), 1.47 (m, 2H, $POCH_2CH_2CH_2CH_3$), 1.22 (m, 2H, $POCH_2CH_2CH_2CH_3$), 1.09 (tr, 3H, SCH_2CH_3, ^3J=7.3 Hz), 1.03 (tr, 3H, SCH_2CH_3, ^3J=7.3 Hz), 0.79 (tr, 3H, $POCH_2CH_2CH_2CH_3$, ^3J=7.7 Hz); ^{13}C{1H} NMR (C_6D_6) δ: 89.00 (Glc-C1, ^3J=9.0 Hz), 88.52 (Glc-C1′, ^3J=8.3 Hz), 83.10 (Glc-C2, ^2J=9.1 Hz), 82.33 ($POCH_2(CH_2)_2CH_3$, ^2J=8.7 Hz), 76.94 (Glc-C4), 75.70 (Glc-C3, ^2J=5.5 Hz), 75.30 (Glc-C5, ^2J=5.7 Hz), 70.07 (Glc-C6, ^2J=5.5 Hz), 32.04 ($POCH_2CH_2CH_2CH_3$), 26.34 (SCH_2CH_3), 26.16 (SCH_2CH_3), 18.09 ($POCH_2CH_2CH_2CH_3$), 15.53 (SCH_2CH_3), 15.30 (SCH_2CH_3), 13.63 ($POCH_2CH_2CH_2CH_3$); ^{31}P{1H} (C_6D_6) δ: 71.5, 68.4. Anal. Calcd for

$C_{20}H_{33}O_{11}P_3S_5$: C 34.18, H 4.73, P 13.22. Found: C 34.28, H 4.69, P 12.99.

4.1.6. Ethyl 2-*O*-(5,5-dimethyl-2-sulfide-1,3,2-dioxaphosphorinane-2-yl)-1-thio-α-D-glucofuranoside 3,5,6-phosphorothioate (7). Sulfur (0.08 g, 2.5 mmol) was added to a solution of **2** (0.38 g, 1 mmol) and triethylamine (0.01 g, 0.1 mmol) in 5 mL of benzene and the reaction mixture was stirred for 8 h at room temperature. The solvent was removed in vacuum and compound **7** was isolated by column chromatography. Yield 0.29 g (65%), mp 182–184 °C, R_f 0.65 (A). ^{1}H NMR ($CDCl_3$) δ: 5.71 (dd, 1H, Glc-H1, ^3J=3.4 Hz, ^4J=2.6 Hz), 5.01 (dd, 1H, Glc-H2, ^3J=3.4, 10.2 Hz), 5.34 (dd, 1H, Glc-H3, ^3J=3.4, 2.6 Hz), 5.11 (m, 1H, Glc-H5), 4.52 (m, 2H, OCH_2), 4.36 (m, 1H, Glc-H4), 4.31 (m, 1H, Glc-H6), 3.90 (m, 2H, OCH_2), 3.90 (m, 1H, Glc-H6′), 2.82 (m, 2H, SCH_2CH_3), 1.38 (tr, 3H, SCH_2CH_3, ^3J=7.3 Hz), 1.28 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); ^{13}C{1H} NMR ($CDCl_3$) δ: 88.79 (Glc-C1, ^3J=8.3 Hz), 81.85 (Glc-C2, ^2J=10.0 Hz), 81.68 (OCH_2), 78.16 (Glc-C4), 77.98 (Glc-C3, ^2J=8.5 Hz), 75.8 (Glc-C5, ^2J=5.5 Hz), 68.82 (Glc-C6, ^2J=4.0 Hz), 32.18 [$C(CH_3)_2$, ^3J=6.5 Hz], 26.65 (SCH_2CH_3), 21.88 (CH_3), 20.68 (CH_3), 15.60 (SCH_2CH_3); ^{31}P{1H} ($CDCl_3$) δ: 72.6, 58.4. Anal. Calcd for $C_{13}H_{22}O_7P_2S_3$: C 34.81, H 4.94, P 13.81. Found: C 34.97, H 5.02, P 14.11.

4.1.7. Ethyl 2-*O*-(5,5-dimethyl-2-selenide-1,3,2-dioxaphosphorinane-2-yl)-1-thio-α-D-glucofuranoside 3,5,6-phosphoroselenoate (8). Following the same procedure as described for **7**, compound **8** was obtained from **2** (0.38 g, 1 mmol), selenium (0.2 g, 2.5 mmol) and triethylamine (0.01 g, 0.1 mmol). Yield 0.28 g (52%), mp 170–171 °C, R_f 0.36 (A). ^{1}H NMR ($CDCl_3$) δ: 5.41 (dd, 1H, Glc-H1, ^3J=3.4 Hz, ^4J=2.1 Hz), 5.03 (dd, 1H, Glc-H2, ^3J=3.4, 11.1 Hz), 4.10 (m, 2H, OCH_2), 3.98 (dd, 1H, Glc-H3, ^3J=3.4, 2.6 Hz), 3.91 (m, 1H, Glc-H5), 3.89 (m, 2H, OCH_2), 3.73 (m, 1H, Glc-H4), 3.21 (m, 1H, Glc-H6), 2.67 (m, 1H, Glc-H6′), 2.31 (m, 2H, SCH_2CH_3), 1.05 (tr, 3H, SCH_2CH_3, ^3J=7.7 Hz), 0.72 (s, 3H, CH_3), 0.33 (s, 3H, CH_3); ^{13}C{1H} NMR ($CDCl_3$) δ: 88.52 (Glc-C1, ^3J=7.5 Hz), 82.74 (OCH_2), 82.21 (Glc-C2, ^2J=10.0 Hz, ^3J=4.1 Hz), 77.63 (Glc-C3), 78.16 (Glc-C4, ^3J=5.9 Hz), 75.7 (Glc-C5, ^2J=5.9 Hz), 69.25 (Glc-C6, ^2J=6.1 Hz), 32.31 [$C(CH_3)_2$, ^3J=6.8 Hz], 26.40 (SCH_2CH_3), 21.85 (CH_3), 20.64 (CH_3), 15.46 (SCH_2CH_3); ^{31}P{1H} ($CDCl_3$) δ: 75.2 ($J_{P,Se}$=1092.7 Hz), 61.8 ($J_{P,Se}$=1015.9 Hz). Anal. Calcd for $C_{13}H_{22}O_7P_2SSe_2$: C 28.79, H 4.09, P 11.42. Found: C 28.68, H 4.37, P 11.56.

4.1.8. Ethyl 2-*O*-(5,5-dimethyl-2-sulfide-1,3,2-dioxaphosphorinane-2-yl)-1-thio-α-D-glucofuranoside 3,5,6-phosphite (9). Sulfur (48 mg, 1.5 mmol) was added to a solution of **2** (0.38 g, 1 mmol) in 5 mL of benzene. The reaction mixture was stirred for 12 h at 55–60 °C. The solvent was removed in vacuum and the product was isolated by column chromatography. Yield 0.28 g (67%), mp 153–154 °C, R_f 0.75 (A). ^{1}H NMR ($CDCl_3$) δ: 5.71 (dd, 1H, Glc-H1, ^3J=3.4 Hz, ^4J=2.1 Hz), 4.87 (d, 1H, Glc-H2, ^3J=3.4 Hz), 4.83 (dd, 1H, Glc-H3, ^3J=3.4, 2.6 Hz), 4.80 (m, 1H, Glc-H5), 4.50 (m, 2H, OCH_2), 4.28 (m, 1H, Glc-H6), 4.21 (m, 1H, Glc-H4), 3.89 (m, 2H, OCH_2), 3.91 (m, 1H, Glc-H6′), 2.82 (m, 2H, SCH_2CH_3), 1.38 (tr, 3H, SCH_2CH_3, ^3J=7.3 Hz), 1.26 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C{1H} NMR ($CDCl_3$) δ: 88.31 (Glc-C1, ^3J=8.4 Hz), 81.09 (OCH_2), 77.84 (Glc-C2, ^2J=9.6 Hz, ^3J=4.6 Hz), 77.70 (Glc-C3), 73.04 (Glc-C4), 71.57 (Glc-C5, ^2J=4.1 Hz), 66.39 (Glc-C6, ^2J=4.0 Hz), 32.31 [$C(CH_3)_2$, ^3J=7.0 Hz], 26.56 (SCH_2CH_3), 21.82 (CH_3), 20.98 (CH_3), 15.49 (SCH_2CH_3); ^{31}P{1H} ($CDCl_3$) δ: 118.5, 58.8. Anal. Calcd for $C_{13}H_{22}O_7P_2S_2$: C 37.49, H 5.32, P 14.87. Found: C 37.64, H 5.37, P 15.04.

4.1.9. 1,3-Bis[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphorothioate)]benzenedicarboxylate (10). Following the same procedure as described for **7**, compound **10** was obtained from **4** (0.63 g, 1 mmol), sulfur (0.08 g, 2.5 mmol) and triethylamine (0.01 g, 0.1 mmol). Yield 0.52 g (75%), mp 134–135 °C, R_f 0.55 (A). ^{1}H NMR (C_6D_6) δ: 9.00 (s, 1H, Ar-H), 8.10 (dd, 2H, Ar-H, ^3J=7.7 Hz, ^4J=1.7 Hz), 7.01 (tr, 1H, Ar-H, ^3J=7.7 Hz), 5.63 (d, 2H, Glc-H1, ^3J=4.3 Hz), 5.55 (d, 2H, Glc-H2, ^3J=4.3 Hz), 4.43 (d, 2H, Glc-H3, ^3J=3.4 Hz), 4.13 (m, 2H, Glc-H5), 3.57 (m, 2H, Glc-H4), 3.40 (m, 2H, Glc-H6), 3.10 (m, 2H, Glc-H6′), 2.30 (q, 4H, SCH_2CH_3, ^3J=7.3 Hz), 1.02 (tr, 6H, SCH_2CH_3, ^3J=7.3 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 163.60 [C(O)], 134.80 (Ar-C), 131.32 (Ar-C), 129.21 (Ar-C), 88.17 (Glc-C1), 81.91 (Glc-C2, ^3J=8.9 Hz), 79.13 (Glc-C4, ^3J=9.3 Hz), 76.80 (Glc-C3), 75.11 (Glc-C5, ^2J=5.5 Hz), 69.07 (Glc-C6, ^2J=4.0 Hz), 25.94 (SCH_2CH_3), 15.12 (SCH_2CH_3); ^{31}P{1H} (C_6D_6) δ: 71.4. Anal. Calcd for $C_{24}H_{28}O_{12}P_2S_4$: C 41.25, H 4.03, P 8.86. Found: C 41.39, H 4.08, P 8.65.

4.1.10. Tris[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphite)]phosphite (12). A mixture of **11** (0.67 g, 3 mmol) and hexaethyltriamidophosphite (1.00 g, 4 mmol) was kept for 4 h at 120–130 °C at atmospheric pressure and for 1 h at 100–110 °C at 80–60 mbar. The reaction mixture was allowed to cool to room temperature, was dissolved in benzene (2 mL) and the product was isolated by column chromatography on silica gel. Yield 0.11 g (24%), mp 163–165 °C, R_f 0.75 (B). ^{1}H NMR (C_6D_6) δ: 5.64 (d, 3H, Glc-H1, ^3J=3.8 Hz), 4.77 (dd, 3H, Glc-H2, ^2J=10.2 Hz, ^3J=4.3 Hz), 4.71 (d, 3H, Glc-H3, ^3J=3.8 Hz), 4.10 (m, 3H, Glc-H5), 3.88 (m, 3H, Glc-H4), 3.47 (dd, 3H, Glc-H6, ^2J=9.4 Hz, ^3J=3.4 Hz), 3.05 (m, 3H, Glc-H6′), 2.46 (m, 6H, SCH_2CH_3), 1.13 (tr, 9H, SCH_2CH_3, ^3J=7.7 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 91.11 (Glc-C1, ^3J=3.2 Hz), 84.14 (Glc-C2, ^3J=8.7 Hz), 77.54 (Glc-C3), 77.09 (Glc-C4, ^3J=10.5 Hz), 76.10 (Glc-C5, ^2J=5.0 Hz), 69.06 (Glc-C6, ^2J=4.3 Hz), 26.22 (SCH_2CH_3), 16.14 (SCH_2CH_3); ^{31}P{1H} (C_6D_6) δ: 148.3, 118.1. Anal. Calcd for $C_{26}H_{36}O_{15}P_4S_3$: C 36.73, H 4.62, P 15.79. Found: C 36.55, H 4.47, P 15.91.

4.1.11. Ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphothioate (14), bis[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphothioate)]diethylamidophosphothioate (15), tris[2-*O*-(ethyl 1-thio-α-D-glucofuranoside 3,5,6-phosphothioate)]phosphothioate (16). A mixture of ethyl 1-thio-α-D-glucofuranoside **11** (0.45 g, 2 mmol) and hexaethyltriamidophosphite (0.74 g, 3 mmol) was stirred for 2 h at 120–130 °C. The reaction mixture was allowed to cool to room temperature, and sulfur (0.13 g, 4 mmol) in 5 mL of benzene was added. The reaction mixture was stirred for

12 h, the solvent was reduced in vacuum and the products were separated by column chromatography on silica gel.

Compound **14**. Yield: 0.06 g (10%), mp 122–124 °C, R_f 0.30 (A). ^{1}H NMR (C_6D_6) δ: 5.56 (d, 1H, Glc-H1, ^3J=3.4 Hz), 4.12 (d, 1H, Glc-H3, ^3J=3.4 Hz), 3.94 (m, 1H, Glc-H5), 3.78 (d, 1H, Glc-H2, ^3J=3.4 Hz), 3.41 (m, 1H, Glc-H4), 3.18 (m, 1H, Glc-H6), 2.84 (m, 1H, Glc-H6′), 2.13 (q, 2H, SC*H*$_2$CH$_3$, ^3J=7.3 Hz), 0.92 (tr, 3H, SCH$_2$C*H*$_3$, ^3J=7.3 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 91.29 (Glc-C1, ^3J=3.2 Hz), 84.30 (Glc-C2, ^3J=8.7 Hz), 77.61 (Glc-C3), 77.12 (Glc-C4, ^3J=11.3 Hz), 76.24 (Glc-C5, ^2J=5.3 Hz), 69.08 (Glc-C6, ^2J=4.3 Hz), 26.20 (S*C*H$_2$CH$_3$), 16.17 (SCH$_2$*C*H$_3$); ^{31}P{1H} (C_6D_6) δ: 72.5. Anal. Calcd for $C_8H_{13}O_5PS_2$: C 33.79, H 4.60, P 10.89. Found: C 33.41, H 4.67, P 10.52.

Compound **15**. Yield: 0.18 g (25%), mp 114–115 °C, R_f 0.60 (A). ^{1}H NMR (C_6D_6) δ: 5.30 (d, 3H, Glc-H1, ^3J=3.8 Hz), 5.28 (d, 3H, Glc-H3, ^3J=3.0 Hz), 5.12 (dd, 3H, Glc-H2, ^2J=10.6 Hz, ^3J=3.8 Hz), 3.95 (m, 3H, Glc-H5), 3.74 (m, 3H, Glc-H4), 3.23 (m, 6H, Glc-H6, Glc-H6′), 2.27 (m, 6H, SC*H*$_2$CH$_3$), 1.05 (tr, 9H, SCH$_2$C*H*$_3$, ^3J=7.3 Hz); ^{13}C{1H} NMR ($CDCl_3$) δ: 89.28 (Glc-C1, ^3J=9.4 Hz), 84.20 (Glc-C2, ^2J=11.3 Hz, ^3J=3.8 Hz), 82.52 (Glc-C4, ^3J=8.3 Hz), 77.46 (Glc-C3), 76.35 (Glc-C5, ^2J=5.5 Hz), 68.95 (Glc-C6), 27.13 (S*C*H$_2$CH$_3$), 15.86 (SCH$_2$*C*H$_3$); ^{31}P{1H} (C_6D_6) δ: 71.0, 70.0. Anal. Calcd for $C_{20}H_{34}NO_{10}P_3S_5$: C 34.23, H 4.88, P 13.24. Found: C 34.25, H 4.81, P 12.94.

Compound **16**. Yield: 0.10 g (16%), mp 156–158 °C, R_f 0.18 (A). ^{1}H NMR (C_6D_6) δ: 5.56 (dd, 1H, Glc-H1, ^3J=4.7 Hz, ^4J=1.3 Hz), 5.44 (dd, 1H, Glc-H1′, ^3J=3.8 Hz, ^4J=2.1 Hz), 5.41 (d, 1H, Glc-H3, ^3J=3.0 Hz), 5.05–4.95 (m, 2H, Glc-H2, Glc-H2′), 5.01 (d, 1H, Glc-H3′, ^3J=2.1 Hz), 4.14 (m, 1H, Glc-H5), 4.00 (m, 1H, Glc-H5′), 3.78 (m, 1H, Glc-H4), 3.67 (m, 1H, Glc-H4′), 3.40 (m, 1H, Glc-H6), 3.36 (m, 1H, Glc-H6), 3.27 (m, 2H, Glc-H6′), 3.16 [m, 2H, PN(C*H*$_2$CH$_3$)$_2$], 2.36 (m, 2H, SC*H*$_2$CH$_3$), 2.32 (m, 2H, SC*H*$_2$CH$_3$), 1.10 (m, 6H, SCH$_2$C*H*$_3$), 0.98 (m, 3H, SCH$_2$C*H*$_3$, ^3J=7.3 Hz PN(CH$_2$C*H*$_3$)$_2$); ^{31}P{1H} (C_6D_6) δ: 75.0, 72.1. Anal. Calcd for $C_{24}H_{36}O_{15}P_4S_7$: C 31.57, H 3.97, P 13.57. Found: C 31.73, H 4.05, P 13.86.

References and notes

1. Lindhorst, T. K. *Essentials of carbohydrate chemistry and biochemistry*; Wiley-VCH: Kiel, 2003; p 219.
2. Kennedy, J. F. *Book carbohydrate chemistry*; Oxford University Press: New York, 1988; p 678.
3. Consiglio, G. *Catal. Asymmetric Synth.* **1993**, 273–302.
4. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
5. Gyurcsik, B.; Nagy, L. *Coord. Chem. Rev.* **2000**, *203*, 81–149.
6. Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189–3215.
7. Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79–101.
8. Agbossou-Niedercorn, F. *Applied homogeneous catalysis with organometallic compounds*; Wiley-VCH: Weinheim, 2002; pp 1014–1033.
9. Brunner, H. *Curr. Org. Chem.* **2002**, *6*, 441–451.
10. Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259–268.
11. Dieguez, M.; Pamies, O.; Ruiz, A.; Diaz, Y.; Castillon, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165–2192.
12. Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479–483.
13. Cullen, W. R.; Sugi, Y. *Tetrahedron Lett.* **1978**, *19*, 1635–1636.
14. Nazarov, A. A.; Hartinger, C. G.; Arion, V. B.; Giester, G.; Keppler, B. K. *Tetrahedron* **2002**, *58*, 8489–8492.
15. Dieguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957–2963.
16. Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443–1452.
17. Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625–1634.
18. Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179–181.
19. Gilbertson, S. R.; Chang, C.-W.T. *J. Org. Chem.* **1995**, *60*, 6226–6228.
20. Brown, J. M.; Cook, S. J.; Khan, R. *Tetrahedron* **1986**, *42*, 5105–5109.
21. Kadyrov, R.; Heller, D.; Selke, R. *Tetrahedron: Asymmetry* **1998**, *9*, 329–340.
22. Koroteev, M. P.; Nifant'ev, E. E. *Zh. Obshch. Khim.* **1993**, *63*, 481–521.
23. Nazarov, A. A.; Koroteev, M. P.; Vasyanina, L. K.; Bel'skii, V. K.; Kosarev, G. V.; Nifant'ev, E. E. *Zh. Obshch. Khim.* **2000**, *70*, 1510–1514.
24. Nifantyev, E. E.; Koroteev, M. P.; Koroteev, A. M.; Belsky, V. K.; Stash, A. I.; Antipin, M. Y.; Lysenko, K. A.; Cao, L. *J. Organomet. Chem.* **1999**, *587*, 18–27.
25. Magdeeva, R. K.; Kozhemyakin, A. V.; Kostryukova, T. V.; Vasyanina, L. K.; Nifant'ev, E. E. *Zh. Obshch. Khim.* **1999**, *69*, 147–148.
26. Pike, R. D.; Reinecke, B. A.; Dellinger, M. E.; Wiles, A. B.; Harper, J. D.; Cole, J. R.; Dendramis, K. A.; Borne, B. D.; Harris, J. L.; Pennington, W. T. *Organometallics* **2004**, *23*, 1986–1990.
27. Nifant'ev, E. E.; Koroteev, M. P.; Pugashova, N. M.; Bekker, A. R.; Bel'skii, V. K.; Magomedova, N. S.; Il'inets, A. M. *Zh. Obshch. Khim.* **1990**, *60*, 1412–1419.
28. Nifant'ev, E. E.; Koroteev, M. P.; Sychev, V. A.; Bekker, A. R.; Vasyanina, L. K.; Nevskii, N. N. *Carbohydr. Res.* **1992**, *224*, 49–58.
29. Koroteev, M. P.; Sychev, V. A.; Kon'kova, T. V.; Bekker, A. R.; Magomedova, N. S.; Bel'skii, V. K.; Nifant'ev, E. E. *Zh. Obshch. Khim.* **1993**, *63*, 583–592.
30. Bartlett, P. D.; Cox, E. F.; Davis, R. E. *J. Am. Chem. Soc.* **1961**, *83*, 103–109.
31. Koroteev, M. P.; Pugashova, A. R.; Bekker, A. R.; Magomedova, N. S.; Bel'skii, V. K.; Il'inets, A. M.; Nifant'ev, E. E. *Zh. Obshch. Khim.* **1990**, *60*, 2312–2321.
32. Nifant'ev, E. E.; Koroteev, M. P.; Pugashova, N. M.; Borisenko, A. A.; Kochetkov, N. K. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1986**, 1917–1918.
33. Koroteev, M. P.; Nazarov, A. A.; Burmistrov, S. Y.; Kaziev, G. Z.; Nifant'ev, E. E. Ru Patent 2180666 C2, 2002.
34. Kulieva, K. N.; Smolenkova, V. S.; Isaeva, F. Y. *Prisadki k Smazochnym Maslam* **1981**, *7*, 130–135.
35. Igarashi, J. *Petrotech* **1990**, *13*, 546–553.

36. Sagawa, T.; Ueno, T.; Wada, H.; Aoki, T. WO Patent 2002097017, 2002.
37. Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory chemicals*; Butterworth-Heinemann: Oxford, 1997; p 512.
38. Pacsu, E.; Wilson, E. J., Jr. *J. Am. Chem. Soc.* **1939**, *61*, 1450–1454.
39. Patois, C.; Ricard, L.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1577–1581.
40. Montanari, V.; DesMarteau, D. D. *J. Org. Chem.* **1992**, *57*, 5018–5019.
41. Broeders, N. L. H. L.; Koole, L. H.; Buck, H. M. *J. Am. Chem. Soc.* **1990**, *112*, 7475–7482.

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Experimental and DFT study of the aza-Diels–Alder reaction between cyclopentadiene and protonated benzylimine derivated from glyoxylates

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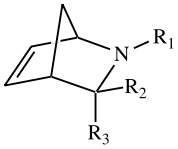
Abstract—The Diels–Alder reaction of protonated *N*-benzyl imine of methyl glyoxylate with cyclopentadiene in different solvents gave mixtures of *exo*/*endo* adducts. The *exo*/*endo* selectivity of the reaction was elucidated by NMR experiments. Theoretical calculations by means of density functional theory (DFT) at the B3LYP/6-31G(d) level have also been performed to elucidate the molecular mechanism of this reaction. The DFT results suggest a highly asynchronous concerted mechanism, which in turn can explain the preferred *exo* stereoselectivity of the reaction. Inclusion of solvent effects enhances the *exo* selectivity, and this effect increases with the polarity of the solvent, in good agreement with the experimental findings.

1. Introduction

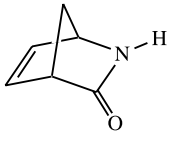
The development of synthetic methodologies based on aza-Diels–Alder reactions of imine derivatives and dienes to obtain six-membered heterocycles has attracted much interest in recent years.[1] In particular, a wide variety of imine derivatives has been successfully used as key intermediates in stereoselective synthesis of ligands and synthetic precursors.[2] These cycloadditions are highly accelerated by the addition of Lewis acids, which promote the formation of an iminium cation complex that rapidly undergoes cycloaddition with dienes even at very low temperatures.[2a]

Among the various azadienophiles known to react well with cyclopentadiene,[1a] we have chosen iminium ions derived from glyoxylates because they are easily prepared and undergo cycloaddition to dienes under mild conditions.[2a,d]

Functionalized 2-azabicyclo[2.2.1]hept-5-enes (**1a**) are useful as synthetic intermediates in the preparation of diverse biologically active compounds,[3] including several carbocyclic nucleosides.[3a,e,f] For example, lactam **1b** (or in some cases its enantiomer) has been used in the preparation of herbicides,[3b] cyclic analogues of GABA,[3d] the antibiotic amidomycin,[3c] and several anti-viral agents, including the anti-HIV agent (−)-carbovir,[3a] an anti-viral agent similar to Zidovudine (AZT).[3e,f]



1a



1b

In the recent past, Diels–Alder (DA) reactions have been the subject of several theoretical studies, but the mechanism of cycloaddition of the dienophile to the 1,3-diene system has remained unexplored for almost two decades.[4–6] It has been shown that the electronic nature of the substituents at the diene/dienophile pair may strongly influence the reaction pathways and determine either a concerted mechanism

Keywords: DFT Study; B3LYP/6-31G(d); Aza-Diels–Alder; NMR spectroscopy.
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(synchronous or asynchronous) or a stepwise one with the formation of an intermediate.[4,7–13] In addition, experimentalists have always employed catalysts to change the kinetics of this class of reactions. In particular, a wide range of homogeneous and heterogeneous Lewis acids have been used to improve the rate and *exo*/*endo* selectivities of these reactions.[14,15]

The purpose of the theoretical contribution of this work is to rationalize the present DA reaction. In order to obtain reliable results, high-level density functional theory (DFT) calculations, which include electron correlation effects, were carried out. The solvent effects have also been taken into account in this study, in order to get a more realistic model of the reaction. In particular, a mean electrostatic field of the bulk was included in the hamiltonian since it might influence the energetics of such polarized DA reaction.

2. Results and discussion

2.1. Experimental section

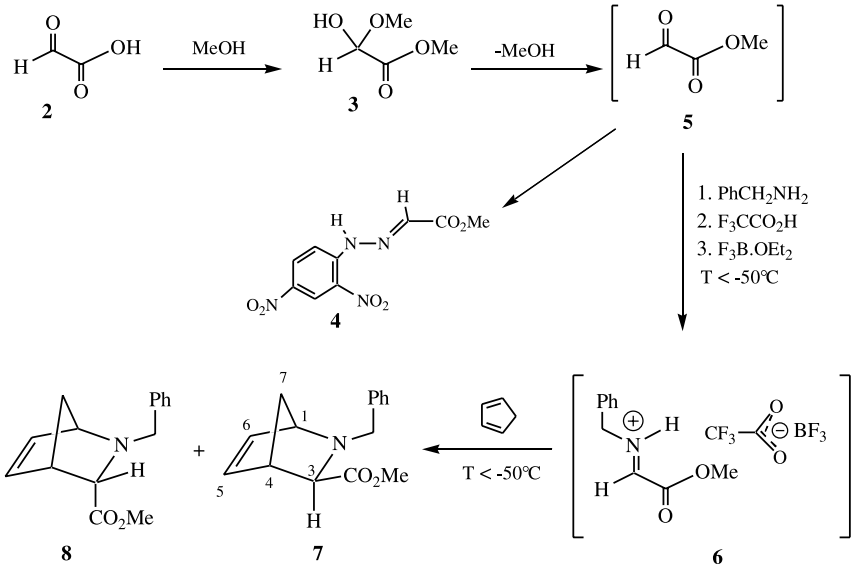
Treatment of hemiacetal (**3**)[16] with equimolar amounts of benzylamine, trifluoroacetic acid and boron trifluoride etherate, in dry aprotic organic solvents, generated the corresponding iminiun ion (**6**), which was reacted in situ with excess cyclopentadiene at low temperature under an argon atmosphere (Scheme 1). Following work-up of the resulting cycloadducts (**7**/**8**), obtained as a racemic mixture of the (±)-*exo*/(±)-*endo* isomers, the major racemic *exo* adduct [(±)-**7**] was easily separated by chromatography and the minor racemic *endo* adduct [(±)-**8**] was obtained after a second chromatographic purification. ^{1}H NMR studies allowed to determine the *exo*/*endo* ratio of the reaction mixture by comparing the most cleanly observed characteristic signals [(±)-**7**]: 3.88 δ (s, 1-H); 2.32 δ (s, 3*endo*-H); 3.09 δ (s, 4-H); 6.24 δ (dd, 5-H); 1.96 δ (d, 7*syn*-H); (±)-**8**: 3.72 δ (s, 1-H); 3.39 δ (s, 2H, 3*exo*-H and 4-H); 6.15 δ (dd, 5-H); 1.84 δ (d, 7*syn*-H)]. The *exo*- and *endo*-configurations of the adducts were confirmed by NOE difference spectroscopy (see Section 4).

The use of anhydrous dichloromethane as solvent at −78 °C led to the best reaction yield of adducts (94%) and an *exo*/*endo* stereoselectivity of 85/15. The use of anhydrous DMF at −50 °C led to a lower yield of adducts (50%) but an *exo*/*endo* ratio of 96/4 although the reaction was carried out at higher temperature than the former one with dichloromethane. Finally, anhydrous THF led to the lowest reaction yield of adducts (24%) and an *exo*/*endo* stereoselectivity of 83/17 similar to that obtained in dichloromethane. (Table 1).

2.2. Theoretical section

The cycloaddition between the reactants cyclopentadiene (CP) and the protonated benzylimine of methyl glyoxylate (IMIGLX) can take place along two different reaction pathways depending on the type of approach (*exo* and *endo*) of CP to IMIGLX (see Scheme 1).

Starting from the fully-optimized reactant's geometries, a thorough exploration of the potential energy surface (PES) of the reaction allowed us to identify two molecular complexes (MCs) in its early stage, located on a very shallow minima region, which give access to the different reactive channels. These MCs correspond to van der Waals complexes that are characterized by a large distance between the reactants (2.9–3.6 Å) and were found to be lower in energy by ca. 12–13 kcal/mol in relation to the isolated reactants (CP and IMIGLX). Notice also that, for both the *exo* and *endo* approaches, the MCs can adopt two different geometrical orientations (enantiomers) depending on the relative positions of the CP and IMIGLX reactants. However, these enantiomeric species have the same electronic energy and vibrational behavior. In fact, our DFT calculations in vacuum confirmed that the reactions involving those MC enantiomers are undistinguishable in terms of energetic barriers and products formed. Therefore, only the results for one of the enantiomers are considered here. Figure 1 shows the most relevant geometrical



Scheme 1.

Table 1. Aza-Diels–Alder reaction of iminium salt (**6**) with cyclopentadiene: influence of reaction conditions (Scheme 1).

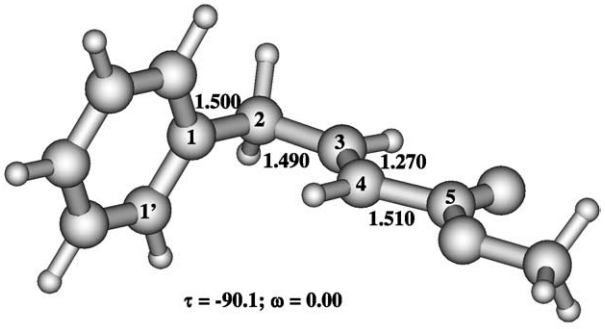
Solvent	Temperature (°C)	Time (h)	Yield (%)[a] [*exo*/*endo*]	*exo*:*endo* [**7**:**8**][a,b]
CH_2Cl_2	−78	6	80/14	85:15
DMF	−50	8	48/2	96:4
THF	−78	8	20/4	83:17

[a] The yields of adducts (±)*exo*/(±)*endo* were determined by separation and isolation of the diastereoisomers and by integration of the signals on the crude ^{1}H NMR.
[b] The *exo*/*endo* configurations of **7** and **8**, respectively, were confirmed by 1D NOE NMR data (see Section 4).

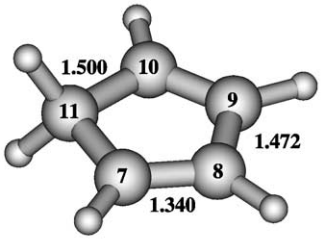
parameters of the reactants, including the labeling of the atoms, while Figure 2 depicts those of the full-optimized MCs found along the two reactive channels.

By further analysis of the PES, we were able to characterize two transition states (TS-*endo* and TS-*exo*) and two cycloadducts (PROD-*endo* and PROD-*exo*) related to the two approach reactive channels. Notice that any attempt to find on the PES intermediates preceding the formation of the products was unsuccessful. Moreover, the computed IRCs starting from the TSs demonstrated that such points connect nicely the MCs with the cycloadduct products. As an example, the IRC for the *endo* approach channel is depicted in Figure 3. Therefore, our results revealed that these cycloadditions follow a concerted mechanism.

The relative energies of the stationary points along the different reaction pathways are listed in Table 2, together with the relative enthalpies at $T=183$, 195 K, while Figure 4 displays the optimized geometries of the TSs. In the gas-phase, formation of the cycloadducts PROD-*endo* and

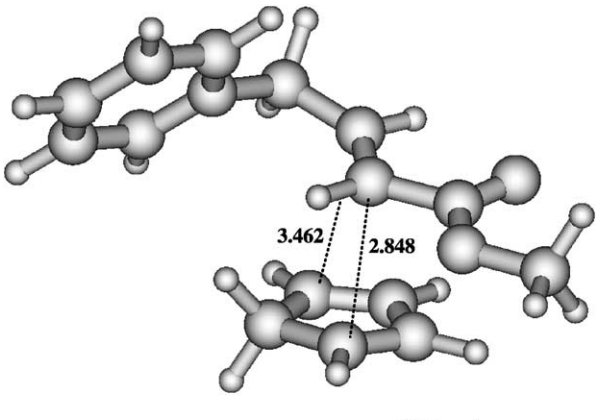


IMIGLX

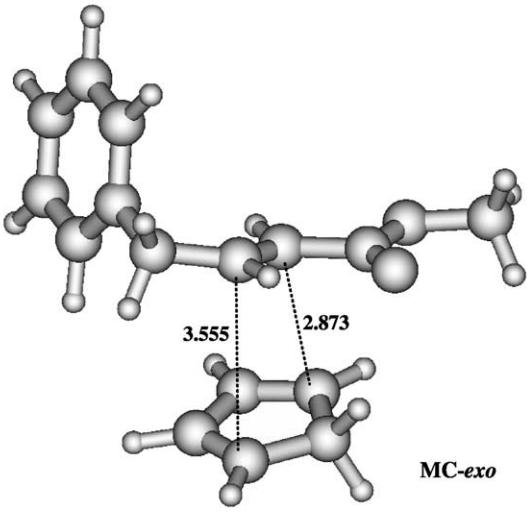


CP

Figure 1. Predicted structures for the reactants protonated benzylimine of methyl glyoxylate (IMIGLX) and cyclopentadiene (CP) optimized at the B3LYP/6-31G(d) level. Bond lengths are given in angstroms and the dihedral angles, $\tau = \angle C_{1'}–C_1–C_2–N_3$ and $\omega = \angle C_1–C_2–N_3–C_4$, in degrees.



MC-*endo*



MC-*exo*

Figure 2. Predicted structures for the molecular complexes for the *endo* (MC-*endo*) and *exo* (MC-*exo*) approach channels optimized at the B3LYP/6-31G(d) level. Bond lengths are given in angstroms.

PROD-*exo* are exothermic processes; for instance, at 195K, $\Delta H_{endo} = -25.7$ kcal/mol and $\Delta H_{exo} = -28.0$ kcal/mol. Looking at the values of the relative energies of TS-*endo* and TS-*exo* with respect to the corresponding molecular complexes (MC-*endo* and MC-*exo*), one can also realize that this cycloaddition is *exo*-stereoselective in the gas-phase. Furthermore, the lengths of the C_4–C_7 forming bonds, 1.985 Å at TS-*endo* and 2.030 Å at TS-*exo*, are

Table 2. Total energies, relative energies and enthalpies[a] (in parentheses) for the stationary points corresponding to the cycloaddition reactions of cyclopentadiene (CP) with the protonated benzylimine of methyl glyoxylate (IMIGLX) in vacuum

	Energies		Enthalpies (kcal/mol)	
	(au)	(kcal/mol)	183 K	195 K
CP	−194.10106			
IMIGLX	−593.24198			
MC-*endo*	−787.35602	(0.00)	(0.00)	(0.00)
TS-*endo*	−787.34919	(5.13)	(4.58)	(4.54)
PROD-*endo*	−787.38380	(−12.91)	(−13.93)	(−14.02)
MC-*exo*	−787.35767	(0.00)	(0.00)	(0.00)
TS-*exo*	−787.35255	(3.95)	(3.41)	(3.37)
PROD-*exo*	−787.38746	(−14.22)	(−15.22)	(−15.30)

[a] Energies and enthalpies are relative to the MC-*endo* and MC-*exo* molecular complexes and include the zero-point vibrational corrections. Enthalpies include additionally the thermal translational, rotational and vibrational contributions computed at $T=183$ or 195 K.

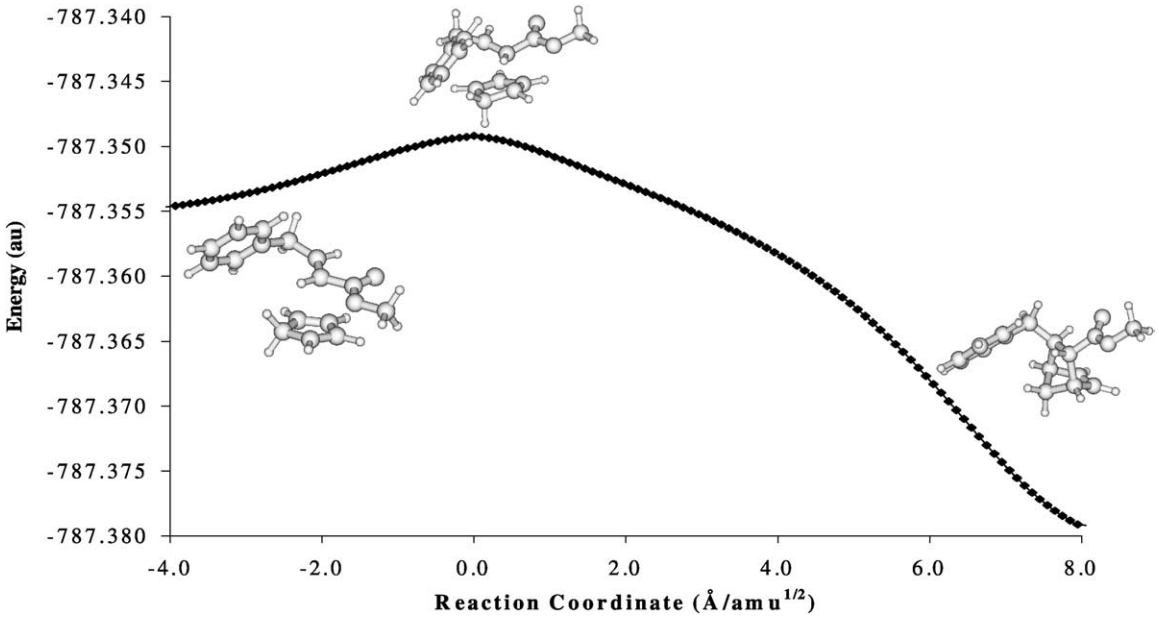


Figure 3. B3LYP/6-31G(d) IRC plots for the *endo* approach channel of the DA reaction.

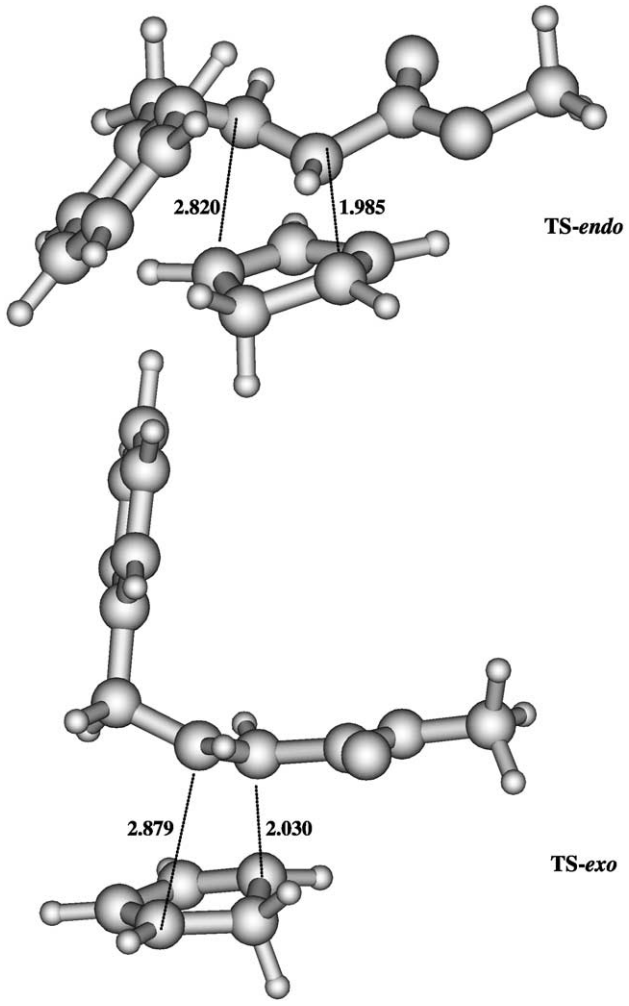


Figure 4. Predicted structures for the transition states for the *endo* (TS-*endo*) and *exo* (TS-*exo*) approach channels optimized at the B3LYP/6-31G(d) level. Bond lengths are given in angstroms.

shorter than the lengths of the N_3–C_{10} forming bonds, 2.820 Å at TS-*endo* and 2.879 Å at TS-*exo*. These data point up to concerted but highly asynchronous bond formation processes where the C_4–C_7 bond is being formed in a larger extent than the N_3–C_{10} one. On the other hand, the computed imaginary wave numbers for the TS-*endo* is 245 cm^{-1}, while that for the TS-*exo* is 224 cm^{-1}, and this follows the degree of asynchronicity of the respective channels (*endo* < *exo*).

The polar nature of the two processes can be assessed by a charge transfer analysis at the corresponding TSs. The atomic charges have been partitioned between the donor CP and the acceptor IMIGLX. The negative charge transferred from CP to IMIGLX along the concerted processes is 0.51e at TS-*endo* and 0.53e at TS-*exo*. The large amount of charge transfer denotes the high polar nature of both processes. It correlates with the asynchronicity of the channels (*endo* < *exo*) and with the lowering of the energy barrier on going from the *endo* approach mode to the *exo* one. Alternatively, the cycloaddition reaction can be analyzed in terms of the global electronic index—the electrophilicity power ω—that might be defined within the DFT. This static index may roughly explain the global reactivity pattern observed in Diels–Alder reactions and is easily estimated using the frontier molecular orbitals of the reactants.[17a] The reactant IMIGLX has a much higher electrophilicity power (ω = 14 eV) than the reactant CP (ω = 0.83 eV), the former being classified as a strong electrophile and the latter as the nucleophile. On the other hand, the difference between the electrophilicities of IMIGLX and CP ($\Delta\omega$ = 13 eV) confirms the polar character of the present cycloaddition, which in turn is much higher than that, for instance, of the archetypal butadiene/ethylene one ($\Delta\omega$ = 0.32 eV), that is classified as a non-polar pericyclic process.[17]

Concerning the solvent effects, Table 3 presents the relative energies for the reactions in the solvents tetrahydrofuran, dichloromethane and dimethylformamide. These energies

Table 3. Total energies and relative energies[a] (in parentheses) for the cycloaddition reactions of cyclopentadiene (CP) with the protonated benzylimine of methyl glyoxylate (IMIGLX) in solution

Solvent	Tetrahydrofuran ($\varepsilon=7.58$)		Dichloromethane ($\varepsilon=8.93$)		Dimethylformamide ($\varepsilon=38.3$)	
	(au)	(kcal/mol)	(au)	(kcal/mol)	(au)	(kcal/mol)
CP	−194.10211		−194.10215		−194.10493	
IMIGLX	−593.30462		−593.30625		−593.33380	
MC-*endo*	−787.41106	(0.00)	−787.41244	(0.00)	−787.43710	(0.00)
TS-*endo*	−787.40437	(5.04)	−787.40576	(5.03)	−787.43069	(4.87)
PROD-*endo*	−787.43960	(−13.39)	−787.44105	(−13.43)	−787.46518	(−13.09)
MC-*exo*	−787.41245	(0.00)	−787.41383	(0.00)	−787.43662	(0.00)
TS-*exo*	−787.40865	(3.11)	−787.41007	(3.09)	−787.43492	(1.80)
PROD-*exo*	−787.44356	(−15.05)	−787.44501	(−15.09)	−787.46874	(−15.68)

[a] Energies are relative to the MC-*endo* and MC-*exo* molecular complexes and include the zero-point vibrational corrections computed in the gas-phase.

were obtained by performing single-point energy calculations on top of the gas-phase stationary points, and modeling the solvent as a polarizable continuum. As can be seen, the inclusion of the solvent stabilizes more the TSs than the MCs because large charge transfers occur along these cycloadditions. Therefore, the more polar the solvents are, the lower the reaction barriers (see Tables 2 and 3). Since this outcome is more pronounced for the *exo* channel, the solvent effects increase the *exo* selectivity of the process when compared to the one found in the gas-phase. Actually, the activation energy of the *endo* approach is lowered only by ca. 0.1–0.3 kcal/mol, whereas that of the *exo* approach is by ca. 0.8–2 kcal/mol. Besides, the polarity of the solvent enhances the *exo*-selectivity of this reaction. Most likely this stems from the greater dipole moment of the *exo* species (MC-*exo*: 1.5 D; TS-*exo*: 5.2 D) over those of the *endo* counterparts (MC-*endo*: 0.7 D; TS-*endo*: 3.4 D), as stressed by Cativiela et al.[18] Moreover, the theoretical results follow the experimentally observed trends (THF: *exo*/*endo* ratio = 83/17; CH_2Cl_2: *exo*/*endo* ratio = 85/15; DMF: *exo*/*endo* ratio = 96/4). Finally, as the solvent effects stabilize more the reactants CP + IMIGLX than the products, the exothermicity of both reactions in solution is expected to decrease.

3. Conclusion

The formation of methyl glyoxylate (**5**), in situ, from hemiacetal (**3**) was confirmed through the isolation of the corresponding 2,4-dinitrophenylhydrazone (**4**) in acidic conditions. The cycloaddition reaction between cyclopentadiene and the iminium cation (**6**), generated by treatment of benzylamine with methyl glyoxylate (**5**) in the presence of TFA and $BF_3 \cdot Et_2O$, afforded racemic *exo*-adduct (majority) and racemic *endo*-adduct. The *exo*/*endo* ratio increased with the polarity of the solvent.

Theoretical calculations at B3LYP/6-31G(d) level enabled us to characterize two reaction paths that lead to the *exo* and *endo* final products. The analysis of the reaction kinetics suggests a concerted mechanism with a prior formation of a stable molecular complex, similar to previous theoretical studies on reactions of the same type.[6,17] The *exo*/*endo* ratio of epimers **7/8** was predicted to increase with the solvent polarity in good agreement with the experimental findings. Even though a qualitative interpretation of the experimental results has been achieved with the model adopted for studying the reaction, there is still room for improvement in the quantitative prediction of its stereoselectivity. For instance, one obvious step forward would be a completely relaxation of the molecular structures inside the solvent continuum, but previous studies on DA cycloadditions of strong polar nature have shown that the inclusion of solvent effects does not significantly modify the gas-phase geometries.[17] Further, tuning the value of the dielectric constant for the experimental temperature and, specially, including a few explicit individual solvent molecules in the reactants' first solvation shell, to take into account local molecular solvent-solute interactions, might as well introduce interesting effects on the predictions. Finally, though the present study tried to mimic the effect of the catalyst by considering the charged reactant IMIGLX, an explicit inclusion of the catalyst may well alter both bond-formation processes in a different manner and, therefore, allow a more refined selectivity prediction.

4. Experimental

4.1. General

Silica gel was purchased from Merck. The efficient drying of DMF is achieved by standing with powdered $CaSO_4$, followed by distillation under reduced pressure. The DMF distillate is stored over Type 3Å molecular sieve. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Flash column chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical thin-layer chromatography (TLC) on pre-coated silica gel plates (Merck 60 GF_{254}) using iodine vapour and/or UV light for visualization. Melting points were determined on a Reichert Kofler Thermopan or in capillary tubes on a Büchi 510 apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1640-FT spectrophotometer and the main bands are given in cm^{-1}. ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded on a Bruker WM AMX spectrometer using TMS as internal standard (chemical shifts (δ) in ppm, J in Hz). The 1D difference NOE experiments were all performed on a Varian Inova 750 MHz spectrometer using 6 K data files. In these experiments a 90° pulse width was used with an irradiation time corresponding to $5 \times T1$. Elemental analyses were obtained on a Perkin-Elmer 240B microanalyser by the Microanalysis Service of the University of Santiago de Compostela. Mass spectra were performed on a Hewlett-Packard HP5988A mass spectrometer by electron impact (EI). Optical rotations at the sodium D-line were determined using a Perkin-Elmer 241 thermostated polarimeter.

4.1.1. Methyl glyoxylate hemiacetal, 3.[5] A solution of glyoxylic acid monohydrate (**2**) (23.0 g; 250 mmol) in dry methanol (125 mL) was refluxed overnight. The solution was cooled to room temperature and neutralized with solid $KHCO_3$. The neutral solution was evaporated in vacuo and the oily residue was dissolved in CH_2Cl_2 and dried with Na_2SO_4. Evaporation of the solvent afforded the methyl glyoxylate hemiacetal in 82% yield. $[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$). IR (NaCl): 3383 (O–H), 2959, 1748 (CO), 1449, 1360, 1231, 1086, 799 cm^{-1}. ^1H NMR ($CDCl_3$): 3.54 (s, 3H, 2-OCH_3), 3.84 (s, 4H, 1-OCH_3), 4.90 (s, 1H, 2-H), 5.40 (s, D_2O exch., 1H, OH). ^{13}C NMR ($CDCl_3$): 53.35 (2-OCH_3), 55.82 (1-OCH_3), 93.61 (C-2), 170.13 (C-1). MS (EI, *m*/*z*): 120 (M^+). Anal. Calcd for $C_4H_8O_4$ C 40.00, H 6.71, found C 39.88, H 6.84.

The crude oily product was used in the following reactions without further purification.

4.1.2. Methyl glyoxylate 2,4-dinitrophenylhydrazone, 4. To a solution of 2,4-dinitrophenylhydrazine (0.10 g; 0.50 mmol) in absolute methanol (5 mL) and concn H_2SO_4. (0.4 mL) that had been warmed and filtered, was added a solution of **3** (48 mg; 0.40 mmol) in 5 mL of absolute methanol. The solid formed was filtered, washed several times with cold absolute methanol, and recrystallized from methanol affording methyl glyoxylate 2,4-dinitrophenylhydrazone. Yield 106 mg (99%). Mp 199–201 °C (MeOH). $[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$). IR (KBr): 3288 (N–H), 3088, 1731 (CO), 1619 (CN), 1576, 1498 (arom. C=C), 1429, 1316, 1236, 1204, 1138, 1105, 925, 850, 744, 709, 630, 535 cm^{-1}. ^1H NMR (DMSO-d_6): 3.78 (s, 3H, CH_3), 7.89 (d, 1H, J=9.5 Hz, arom., 6-H), 8.06 (s, 1H, 2-H), 8.44 (dd, 1H, J=9.5, 2.65 Hz, arom., 5-H), 8.80 (d, 1H, J=2.65 Hz, arom., 3-H), 11.90 (s, 1H, D_2O exch., –NH–). ^{13}C NMR (DMSO-d_6): 52.48 (OCH_3), 117.68, 122.82, 130.33, 131.78, 137.75, 139.30, 144.04, 163.41 (C-1). MS (EI, *m*/*z*): 268 (M^+). Anal. Calcd for $C_9H_8N_4O_6$ C 40.31, H 3.01, N 20.89, found C 40.15, H 3.22, N 20.79.

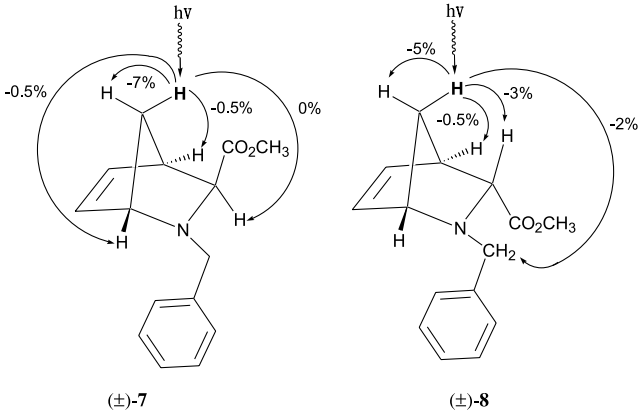
4.2. Methyl [2-benzyl-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylate, (±)-(*exo*)-7 and methyl [2-benzyl-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylate, (±)-(*endo*)-8

A solution of benzylamine (16.4 mL; 16.0 g; 150 mmol) in dry CH_2Cl_2 (100 mL) was added under argon to a stirred suspension of **3** (18.01 g; 150 mmol) and 3 Å molecular sieve pearls (100 g) in dry CH_2Cl_2 (400 mL) at 0 °C. When the addition was complete the reaction mixture was cooled to −78 °C and treated successively with trifluoroacetic acid (11.5 mL; 17.1 g; 150 mmol), boron trifluoride etherate (18.8 mL; 21.3 g; 150 mmol) and freshly distilled cyclopentadiene (25 mL; ca. 300 mmol). After 6 h a mixture of saturated aqueous $NaHCO_3$ solution (300 mL) and then solid $NaHCO_3$ (35 g) were added, the mixture was allowed to reach room temperature and filtered. The organic layer was separated from the filtrate and washed with water and CH_2Cl_2 on a celite pad, after which the organic layer of the resulting mixture was separated and put aside, and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The pooled organic layers were washed with saturated $NaHCO_3$ solution (150 mL) and brine (150 mL), and were dried with Na_2SO_4. Removal of the solvent in a rotary evaporator left an oily residue (ca. 45 g) that upon chromatography on silica gel (900 g) with 6:1 hexane/EtOAc as eluent afforded (±)-**7** (29.19 g; 80%) in the early fractions as a colorless oil and compound (±)-**8** in the later fractions (not homogenous by TLC). Compound **8** was further purified by column chromatography on silica gel (170 g) with 4:1 hexane/EtOAc as eluent, affording (±)-**8** as a yellow oil (5.11 g; 14%). The procedure with THF and DMF as solvents at low temperature is similar (Table 1).

4.2.1. Compound (±)-7. $[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$). IR (NaCl): 3060, 2993, 2950, 1743, 1603, 1562, 1434, 1235, 1167, 909, 845, 736 cm^{-1}. ^1H NMR ($CDCl_3$): 1.395 (d, 1H, J=8.3 Hz, 7_{anti}-H), 1.96 (d, 1H, J=8.3 Hz, 7_{syn}-H), 2.32 (s, 1H, 3_{endo}-H), 3.09 (s, 1H, 4-H), 3.43 and 3.58 (AB system, 2H, J=12.63 Hz, NCH_2Ph), 3.59 (s, 3H, CO_2CH_3), 3.88 (s, 1H, 1-H), 6.24 (dd, 1H, J=5.5, 1.6 Hz, 5-H), 6.47 (dd, 1H, J=5.5, 2.7 Hz, 6-H), 7.19–7.38 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): 46.85 (C-7), 48.72 (C-4), 52.10 (CO_2CH_3), 59.16 (NCH_2Ph), 64.47 (C-1), 65.04 (C-3), 127.28 (C-4′), 128.41 (C-2′+C-6′), 129.35 (C-3′+C-5′), 133.88 (C-5), 136.80 (C-6), 139.23 (C-1′), 174.78 (*C*OO). MS (EI, *m*/*z*): 243 (M^+). Anal. Calcd for $C_{15}H_{17}NO_2$ C 74.05, H 7.04, N 5.76, found C 73.91, H 7.17, N 5.79.

4.2.2. Compound (±)-8. $[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$). IR (NaCl): 3062, 2992, 1747, 1603, 1435, 1198, 909, 857, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 1.57 (d, 1H, J=8.5 Hz, 7_{anti}-H), 1.83 (d, 1H, J=8.5 Hz, 7_{syn}-H), 3.57 (s, 3H, CO_2CH_3), 3.83 and 3.89 (AB system, 2H, J=12.9 Hz, NCH_2Ph), 6.15 (dd, 1H, J=5.5, 2.4 Hz, 5-H), 6.49 (dd, 1H, J=5.5, 2.9 Hz, 6-H), 7.20–7.44 (m, 5H, C_6H_5). MS (EI, *m*/*z*): 243 (M^+). Anal. Calcd for $C_{15}H_{17}NO_2$ C 74.05, H 7.04, N 5.76, found C 74.19, H 7.10, N 5.84.

The stereochemistry of adducts **7** and **8** was determined through 1 D NOE NMR experiments at room temperature. The NOE effects were observed between 7-H_{syn} and 3-H and protons in a close vicinity, as shown in the following figure.



(±)-**7** (±)-**8**

4.3. Computational methods

In this work, DFT calculations have been carried out using the B3LYP[19,20] exchange-correlation functionals, together with the standard 6-31G(d) basis set. The PES for the cycloaddition reaction was scanned systematically for all possible intermediates and transition state structures.

Stationary points found on the PES were optimized without any geometrical constraint by the Berny analytical gradient optimization algorithm.[21] Harmonic frequencies were computed at the full-optimized geometries, allowing the assignment of stationary points as minima or transition states and the determination of zero-point vibrational energies and thermal vibrational contributions ($T=183$ and 195 K). To verify that each saddle point connects two putative minima, intrinsic reaction coordinate (IRC) calculations were performed in forward and backward directions, that is, by following the eigenvector associated to the unique negative eigenvalue of the Hessian matrix, using the González and Schlegel integration method.[22] The electronic structures of stationary points were analyzed by the natural bond orbital method,[23] and global electronically indexes,[17] defined in the context of the DFT, were also computed for the reactants. In addition, solvent effects have been considered by performing, on top of the optimized geometries, single-point energy calculations using the self-consistent reaction field method based on the polarizable continuum model of Tomasi and co-workers.[24] The dielectric constants used in the latter calculations, $\varepsilon=7.58$, 8.93 and 38.3, correspond to the solvents employed in the experiments, namely tetrahydrofuran, dichloromethane and dimethylformamide, respectively. Finally, thermodynamic properties were evaluated at the experimental temperatures $T=183$ and 195 K. All calculations were carried out with Gaussian 98 package of programs.[25]

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References and notes

1. (a) Boger, D. L.; Weinred, S. M.; Wasserman, H. H. In *Hetero Diels–Alder methodology in organic synthesis*; Wasserman, H. H., Ed.; Organic Chemistry; Academic: New York, 1987; Vol. 47; Chapter 2. (b) Weinreb, S. M. In Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 5, pp 401–449.
2. (a) Stella, L.; Abraham, H.; Feneau-Dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2063. (b) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045. (c) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337. (d) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263. (e) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707. (f) Bailey, P. D.; Londesbroungh, D. J.; Hancox, T. C.; Hefferman, J. D.; Holmes, A. B. *J. Chem. Soc. Chem. Commun.* **1994**, 2543. (g) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633.
3. (a) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611 and references cited therein. (b) Bush, B. D.; Fitchett, G. V.; Gates, D. A.; Langley, D. *Phytochemistry* **1993**, *32*, 737. (c) Nakamura, S. *Chem. Pharm. Bull.* **1961**, *9*, 641. (d) Allan, R. D.; Johnston, G. A. R. *Med. Res. Rev.* **1983**, *3*, 91–118 and references cited therein. (e) Coats, J. A. V.; Ingall, H. J.; Pearson, B. A.; Penn, C. R.; Storer, R.; Williamson, C.; Cameron, J. M. *Antiviral Res.* **1991**, *15*, 161. (f) Miller, W. H.; Daluge, S. M.; Garvey, E. P.; Hopkins, S.; Reardon, J. E.; Boyd, F. L.; Miller, R. L. *J. Biol. Chem.* **1992**, *267*, 21220.
4. Domingo, L. R.; Arnó, M.; Contreras, R.; Pérez, P. *J. Phys. Chem. A* **2002**, *106*, 952.
5. Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.
6. Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *25*, 81.
7. Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129.
8. Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172.
9. Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.
10. Jorgensen, W. L.; Dongchul, L.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 2936.
11. Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* **1996**, *118*, 12562.
12. Domingo, L. R.; Picher, M. T.; Andrés, J.; Safont, V. S. *J. Org. Chem.* **1997**, *62*, 1775.
13. Sustmann, R.; Tappanchai, S.; Bandmann, H. *J. Am. Chem. Soc.* **1996**, *118*, 12555.
14. Alves, C. N.; da Silva, A. B. F.; Marti, S.; Moliner, V.; Oliva, M.; Andrés, J.; Domingo, L. R. *Tetrahedron* **2002**, *58*, 2695.
15. Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415.
16. Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.
17. (a) Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417. (b) Domingo, L. R.; Arnó, M.; Andrés, J. *J. Org. Chem.* **1999**, *64*, 5867. (c) Domingo, L. R.; Andrés, J.; Alves, C. N. *Eur. J. Org. Chem.* **2002**, *15*, 2557. (d) Domingo, L. R. *J. Org. Chem* **2001**, *66*, 3211.
18. Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, *25*, 209.
19. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
20. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1992**, *45*, 13244.
21. González, C.; Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214.
22. (a) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523. (b) González, C.; Schlegel, H. B. *J. Chem. Phys.* **1991**, *95*, 5853.
23. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
24. (a) Cances, M. T.; Mennunci, V.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (b) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327. (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.
25. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakreswki, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuk, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowki, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.3; Gaussian Inc: Pittsburgh, PA, 1998.

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Mild and efficient cyclization reaction of 2-ethynylaniline derivatives to indoles in aqueous medium

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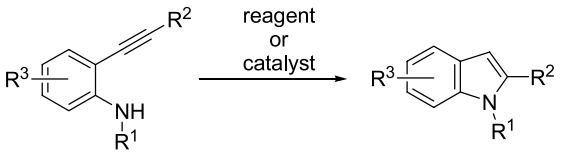
Abstract—Results of the optimized cyclization reaction of 2-ethynylaniline derivatives to indoles catalyzed by copper(II) salts are described. The reactions can be carried out in a mixture of H_2O and MeOH in the presence of 1-ethylpiperidine at room temperature. These conditions can be applied to a bulky substrate, which is difficult to be cyclized efficiently by existing reaction conditions. Furthermore, this reaction condition was applied to a catalyst recycling reaction system.

1. Introduction

Heterocyclic compounds, particularly indoles, occur widely in nature as partial structures of alkaloids and have unique biological activities.[1] Among the many methods for indole ring synthesis, the ring closing reactions of 2-ethynylaniline derivatives are some of the most efficient because methods for synthesizing a variety of functionalized starting materials have already been established (Scheme 1).[2] Thus far, many kinds of reagents and reaction conditions have been reported for indole syntheses from 2-ethynylaniline derivatives, including basic conditions,[2c,3] early transition metal-catalyzed reactions,[4] gold(III),[5] copper(I),[2b,6,10a] copper(II) salt-catalyzed reactions,[7] and ammonium fluoride-mediated reactions.[8] The most frequently used reagents or catalysts for these ring-closing reactions are the palladium complexes,[2d,3a,5b,9,10,11] and many applications together with polymer-supported reactions[12] have also been established.



Scheme 1. Cyclization reaction of 2-ethynylaniline derivatives to indole derivatives.

Recent interest in indole synthesis from 2-ethynylaniline derivatives has focused on versatile applicability, convenient reagents and conditions, and tandem or sequential reactions. For such purposes, iodine-promoted cyclization to yield 3-iodoindoles[13], sequential cyclization-C3 functionalization reactions catalyzed by palladium complexes[5b,11] or gold(III) salt,[14] and carbazoles synthesis[15] were established. We have previously developed both copper(II) salt-catalyzed synthesis of indoles from 2-ethynylaniline derivatives[7a,c] and palladium-complex-catalyzed sequential coupling-cyclization reactions between methyl propiolate and 2-iodoaniline derivatives, with the latter's application to duocarmycin SA synthesis.[10d]

Copper(II) salt-catalyzed reactions can be applied to a variety of 2-ethynylaniline derivatives, including ones with the following features: (1) electron-donating or electron-withdrawing groups on the aromatic ring, (2) an alkyl, aryl, hydroxymethyl, or even methoxycarbonyl group on the acetylene terminal, and (3) sulfonamide, non-substituted aniline derivatives and carbamates (depending on the structure of the substrate). However, problems with efficiency (low solubility of the catalysts in organic media) and high temperature requirements ($>70\,^{\circ}C$) must be solved for copper(II) salt-catalyzed reactions to be useful. Herein, we describe solutions to these problems and improved procedures for copper(II) salt-catalyzed cyclization reactions of 2-ethynylaniline derivatives.

Keywords: Indole; Copper(II) salt; 2-Ethynylaniline; Cyclization reaction.
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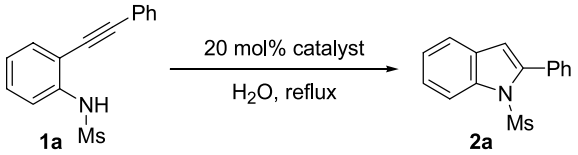
2. Results and discussion

2.1. Improvement of the reaction conditions

Copper(II) salt-catalyzed indole formation reactions appear as suspensions due to low solubility of the salts in organic solvents such as 1,2-dichloroethane. We have previously described how the ionic character of the copper–oxygen bond in copper(II) sulfonate is required for effective catalyst of the cyclization, which makes suspension in an organic solvent unavoidable.[7a] However, the bulky counter-anion in copper(II) carbonate (e.g., stearic acid) does not improve solubility or catalytic activity.[16] Therefore, we changed the solvent to H_2O. The results are summarized in Table 1. It was known that sulfonamides possess the highest reactivity among 2-ethynylaniline derivatives, so the mesylamide **1a** was selected as the substrate for establishing the new reaction conditions. Most of the copper(II) salts tested dissolved into H_2O except for $Cu(OBz)_2$, but the reaction medium was again a suspension because of the low solubility of **1a** in H_2O. The copper(II) salts that catalyze the reactions in organic solvent [$Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(OBz)_2$, and $Cu(OCHO)_2\cdot xH_2O$] did not provide satisfactory results (Table 1, entries 1–4). Surprisingly, only $Cu(OCOCF_3)_2\cdot xH_2O$ catalyzed the reaction, even though it forms a suspension in the reaction mixture (Table 1, entry 5). Why only this copper(II) salt works is not yet clear. However, it is apparent that CF_3COOH is not a catalyst for this reaction (Table 1, entry 6). We selected $Cu(OCOCF_3)_2\cdot xH_2O$ as the catalyst for further improvement of the reaction conditions.

Table 1. Copper(II) salt-catalyzed cyclization reactions of **1a** in H_2O



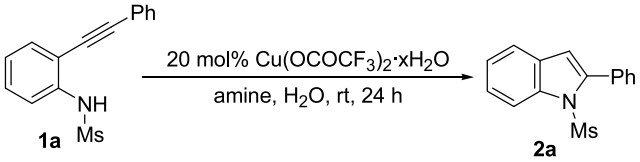
Entry	Catalyst	Time (h)	Yield of **2a** (%)
1	$Cu(OAc)_2$	23	Trace
2	$Cu(OTf)_2$	24	7 (76)[a]
3	$Cu(OBz)_2$	24	18 (66)[a]
4	$Cu(OCHO)_2\cdot xH_2O$	24	22 (75)[a]
5	$Cu(OCOCF_3)_2\cdot xH_2O$	24	96
6	CF_3COOH	23	No reaction

[a] The numbers in parentheses are the yields of recovered **1a**.

High temperature is essential for the cyclization reactions of 2-ehtynylaniline derivatives catalyzed by copper(II) salts and the substrates can be recovered perfectly at room temperature. However, we have previously reported that the rate of copper(II) salt-catalyzed cyclization reactions is accelerated in the presence of 1-ethylpiperidine and realized the reaction at room temperature (room temperature for 72 h with 2.0 equiv of 1-ethylpiperidine, 76% yield).[7a] We now apply the $Cu(OCOCF_3)_2\cdot xH_2O$-catalyzed cyclization reaction of **1a** with various amines in H_2O. The results are summarized in Table 2.

The rate acceleration effect of the amine in H_2O was less than in 1,2-dichloroethane. The addition of a tertiary aliphatic amine slightly accelerated the reaction, but the yield of **2a** was less than the amount of added catalyst and more than 80% of **1a** was recovered (Table 2, entries 1–3). Addition of a tertiary aromatic amine or pyridine did not accelerate the reaction (Table 2, entries 4 and 5). The addition of secondary amines (piperidine or *N*,*N*-diisopropylamine) or primary amines (butylamine, aniline, or ethylenediamine) also did not promote the reaction, and the starting material **1a** was completely recovered (data not shown). Since the reactions in H_2O appear as a suspension, we speculated that the reason for the reactivity difference between H_2O and 1,2-dichloroethane might be the low solubility of **1a** in H_2O. Therefore, we attempted the reaction in a mixed solvent system, with and without 1-ethylpiperidine (Table 3).

Table 2. $Cu(OCOCF_3)_2\cdot xH_2O$-catalyzed cyclization reaction of **1a** in the presence of various amines



Entry	Amine (2.0 equiv)	Yield of **2a** (%)
1	1-Ethylpiperidine	14 (85)[a]
2	Triethylamine	10 (88)[a]
3	*N*,*N*-diisopropylethylamine	17 (83)[a]
4	*N*,*N*-dimethylaniline	No reaction
5	Pyridine	No reaction

[a] The numbers in parentheses are the yields of recovered **1a**.

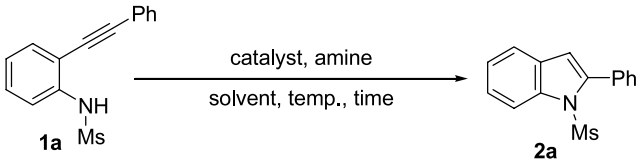
We wanted to dissolve both the catalyst and the substrate, so we chose an alcohol as the second solvent. Surprisingly, we discovered that the efficiency of the reaction is closely related to the carbon number of employed alcohol: as the carbon number of the alcohol solvent increased, the yield decreased (Table 3, entries 1–3). It is apparent from the above results that the reactivity is controlled by the balance of the solubility of the catalyst and the substrate. However, even with the second alcohol solvent, the reaction did not proceed at room temperature (Table 3, entry 4). The effect of 1-ethylpiperidine was remarkable, and the amount of catalyst could be reduced from 20 to 5 mol% (Table 3, entries 6 and 7). Note that less expensive $Cu(OAc)_2$, which did not show catalytic activities in H_2O alone (Table 1, entry 1), can be used as the catalyst under optimized reaction conditions (Table 3, entry 8). While the reaction could be promoted with 1-ethylpiperidine in the absence of a copper(II) salt, the low yield can be disregarded (Table 3, entry 5).

2.2. Application to various kinds of substrates

Having established the cyclization reaction in aqueous solvent at room temperature, we applied it to other substrates. To avoid too long reaction time, we used same reaction condition shown in Table 3 entry 6 [20 mol% of $Cu(OCOCF_3)_2\cdot H_2O$] and the results are summarized in Table 4.

For the substituents at the alkyne terminal, this condition

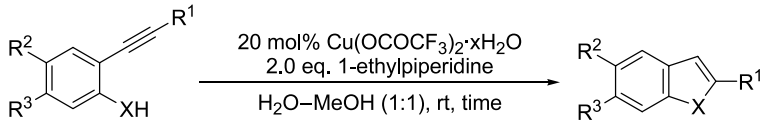
Table 3. Copper(II) salt-catalyzed cyclization reaction of **1a** in a mixed solvent system



Entry	Catalyst (mol%)	Amine (2.0 equiv)	Solvent	Temperature	Time (h)	Yield (%)
1	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–^{t}BuOH (1/1)	~90 °C	24	10 (86)[a]
2	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–EtOH (1/1)	~90 °C	24	85 (7)[a]
3	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–MeOH (1/1)	~90 °C	21	93
4	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–MeOH (1/1)	Room temperature	23	No reaction
5	—	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	24	14 (85)[a]
6	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	24	92
7	$Cu(OCOCF_3)_2 \cdot xH_2O$ (5)	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	24	95
8	$Cu(OAc)_2$ (10)	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	17	96

[a] The numbers in parentheses are the yields of recovered **1a**.

Table 4. Applications of the copper(II) salt-catalyzed cyclization reaction in aqueous solvent



1b-h, 3-5 **2b-h, 6**

Entry	Substrate					Time (h)	Yield of **2** and **6** (%)
	Number	X	R^1	R^2	R^3		
1	**1b**	NMs	Bu	H	H	13	**2b**:98
2	**1c**	NMs	TMS	H	H	14	**2i**:91 (R^2=H)
3	**1d**	NMs	^{t}Bu	H	H	10	**2d**:90
4	**1e**	NMs	Ph	NO_2	H	14	**2e**:85
5	**1f**	NMs	Ph	Br	H	72	**2f**:99
6	**1g**	NMs	Ph	Me	H	27	**2g**:99
7	**1h**	NMs	Ph	H	OMe	21	**2h**:99
8	**3**	NH	Ph	H	H	24	No reaction
9	**4**	NBoc	Ph	H	H	24	No reaction
10	**5**	O	Ph	H	H	11	**6**:87 (7)[a]

[a] The number in parentheses is the yield of recovered **5**.

can be applied not only to the alkyl group (Table 4, entry 1) and hydrogen (Table 4, entry 2; TMS group eliminated before cyclization reaction), but also in the presence of a bulky ^{t}Bu group (Table 4, entry 3). To our knowledge, only one report[5b] had been published for a high yield of an indole from 2-ethynylaniline derivatives with a quaternary center at the C-3′ position.[7a] Substituents on the aromatic ring generally did not affect the efficiency of the reaction (Table 4, entries 4–7). Disappointingly, this reaction has the limitation about the substituents on the nitrogen atom: the

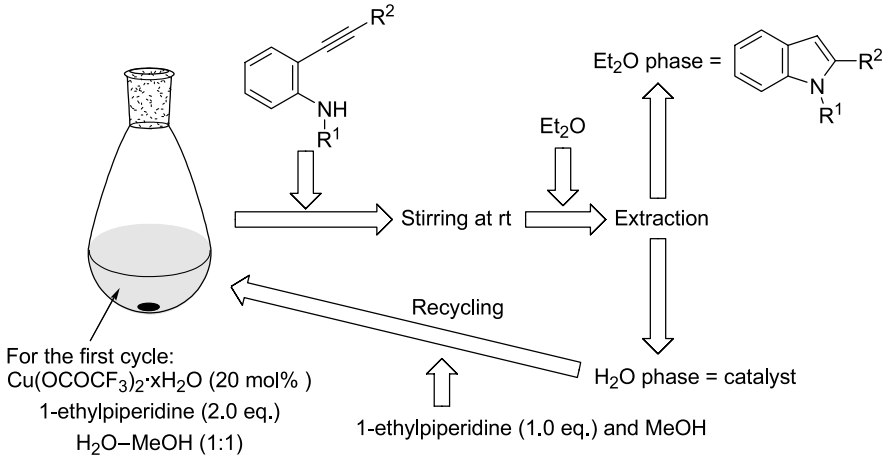
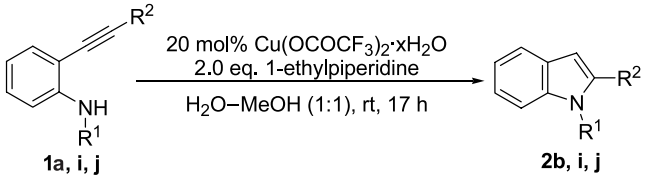


Figure 1. The general form of the catalyst recycling reaction.

Table 5. The catalyst recycling reaction for 2-ethynylaniline derivatives



1a, i, j **2b, i, j**

Entry	Substrate			Yield of **2** (%)		
	Number	R^1	R^2	First cycle	Second cycle	Third cycle
1	**1a**	Ms	Ph	99	94	97
2	**1i**	Ms	H	73	84	89
3	**1j**	Ts	CH_2OH	96	99	98

sulfonamides could be cyclized, but not the aniline derivative or the carbamate (Table 4, entries 8 and 9). However, this reaction condition could be applied to the synthesis of the benzofuran derivative **6** (Table 4, entry 10).

2.3. Catalyst recycling reaction

This reaction, in which the copper(II) salts dissolve into H_2O while the indole products dissolve into the organic solvent, allows constructions of a catalyst recycling reaction, depicted in Figure 1.

The reaction was started by adding the 2-ethynylaniline derivatives to a solution of $Cu(OCOCF_3)_2 \cdot xH_2O$ (20 mol%) and 1-ethylpiperidine (2.0 equiv) in H_2O–MeOH (1/1). After being stirred at room temperature, the mixture was extracted with Et_2O. The desired indole derivatives were extracted in essentially pure form from the Et_2O phase, and the catalyst-containing H_2O phase could be recycled after adding more 1-ethylpiperidine (1.0 equiv) and MeOH. The results of three cycles for three 2-ethynylaniline derivatives are listed in Table 5. The catalytic activity of $Cu(OCOCF_3)_2 \cdot xH_2O$ did not change over the three cycles.

3. Conclusion

We improved the cyclization reaction of 2-ethynylaniline derivatives to indoles. While the original conditions require heating, the optimized reaction can be carried out at room temperature in a mixture of H_2O and MeOH in the presence of 1-ethylpiperidine. Further, the reaction does not require an argon atmosphere and can be done as open-flask reaction. This reaction condition was applied to a catalyst recycling reaction system. Although the substrates for this reaction condition are limited to sulfonamides, the reaction conditions will be useful for versatile synthesis of indole derivatives, especially in large-scale reactions.

4. Experimental

4.1. General

All melting points were determined with a Yazawa Micro Melting Point BY-2 and are uncorrected. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a JEOL JMN AL-400 spectrometer. Chemical shifts (δ) are given from TMS (0 ppm) as the internal standard for ^{1}H NMR and $^{13}CDCl_3$ (77.0 ppm) as the internal standard for ^{13}C NMR. Standard and high-resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. IR spectra were recorded on a Shimadzu FTIR-8400.

4.2. General procedure for the selected entries for Tables 1, 3, and 4.

Copper(II) salt was added to a suspension of 2-ethynylaniline derivatives **1a**–**h** or 2-(2-phenylethynyl)phenol **5** in H_2O or in mixed solution of H_2O and alcohol, then the mixture was stirred under reflux or at room temperature for the reaction time listed in Tables 1, 3, and 4. The reaction mixture was extracted with AcOEt (three times). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure.

4.2.1. 1-Methylsulfonyl-2-phenylindole (2a) (Table 3, entry 7). A suspension of **1a** (89.6 mg, 0.33 mmol), $Cu(OCOCF_3)_2 \cdot xH_2O$ (4.9 mg, 0.017 mmol) and 1-ethylpiperidine (0.090 mL, 0.65 mmol) in mixed solution of H_2O (5 mL) and MeOH (5 mL) was stirred for 24 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2a**[7a,8] (85.0 mg, 95%) as a colorless solid; mp 115–117 °C (colorless needles from AcOEt–hexane, lit.[7a] mp 115–117 °C, lit.[8] mp 115–116 °C); IR (film, cm^{-1}) 1367, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (3H, s), 6.70 (1H, s), 7.34 (1H, td, J=7.4, 1.5 Hz), 7.37 (1H, td, J=7.4, 1.5 Hz), 7.40–7.46 (3H, m), 7.52–7.61 (3H, m), 8.12 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.5, 113.0, 115.7, 120.9, 124.5, 125.0, 127.6, 128.8, 130.0, 130.2, 131.9, 137.9, 141.8; MS m/z 271 (M^+, 51), 190 (100), 165 (52); HRMS calcd for $C_{15}H_{13}NO_2S$ 271.0667, found 271.0673.

4.2.2. 1-Methylsulfonyl-2-butylindole (2b) (Table 4, entry 1). A suspension of **1b** (102.5 mg, 0.41 mmol), $Cu(OCOCF_3)_2 \cdot xH_2O$ (21.2 mg, 0.073 mmol), and 1-ethylpiperidine (0.113 mL, 0.82 mmol) in mixed solution of H_2O (5.5 mL) and MeOH (5.5 mL) was stirred for 13 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2b**[7a,8] (100.8 mg, 98%) as a colorless solid; mp 80–81 °C (colorless needles from AcOEt–hexane, lit.[7a] mp 80–81 °C, lit.[8] mp 81–82 °C); IR (film, cm^{-1}) 1366, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ

0.97 (3H, t, J=7.5 Hz), 1.46 (2H, sex, J=7.5 Hz), 1.75 (2H, sex, J=7.5 Hz), 2.95 (2H, t, J=7.5 Hz), 3.00 (3H, s), 6.45 (1H, s), 7.21–7.29 (2H, m), 7.48 (1H, dd, J=7.7, 2.7 Hz), 7.99 (1H, dd, J=7.9, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 28.6, 31.0, 40.3, 108.3, 114.0, 120.1, 123.5, 123.8, 129.7, 136.7, 142.3; MS m/z 251 (M^+, 37), 209 (40), 130 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.1012.

4.2.3. 1-Methylsulfonylindole (2i) (Table 4, entry 2). A suspension of **1c** (33.5 mg, 0.13 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (8.0 mg, 0.028 mmol), and 1-ethylpiperidine (0.034 mL, 0.25 mmol) in mixed solution of H_2O (1.5 mL) and MeOH (1.5 mL) was stirred for 14 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2i**[7a,8] (22.2 mg, 91%) as a colorless oil; IR (neat, cm^{-1}) 1361, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (3H, s), 6.69 (1H, d, J=3.7 Hz), 7.28 (1H, d, J=7.7 Hz), 7.35 (1H, t, J=7.7 Hz), 7.42 (1H, d, J=3.7 Hz), 7.61 (1H, d, J=7.7 Hz), 7.90 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6, 108.7, 112.8, 121.5, 123.4, 124.7, 125.9, 130.5, 134.7; MS m/z 195 (M^+, 55), 116 (100); HRMS calcd for $C_9H_9NO_2S$ 195.0354, found 195.0359.

4.2.4. 1-Methylsulfonyl-2-(1,1-dimethylethyl)indole (2d) (Table 4, entry 3). A suspension of **1d** (52.0 mg, 0.21 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (12.1 mg, 0.042 mmol), and 1-ethylpiperidine (0.057 mL, 0.41 mmol) in mixed solution of H_2O (2.5 mL) and MeOH (2.5 mL) was stirred for 10 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2d**[5b,7a] (46.9 mg, 90%) as a colorless oil; IR (neat, cm^{-1}) 1371, 1176; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.93 (3H, s), 6.61 (1H, s), 7.24 (1H, td, J=7.4, 1.9 Hz), 7.28 (1H, td, J=7.4, 1.9 Hz), 7.48 (1H, dd, J=7.4, 1.9 Hz), 8.07 (1H, br d, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 34.8, 39.5, 110.1, 115.3, 120.5, 123.8, 124.5, 129.4, 138.5, 151.8; MS m/z 251 (M^+, 42), 236 (51), 172 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0966.

4.2.5. 1-Methylsulfonyl-5-nitro-2-phenylindole (2e) (Table 4, entry 4). A suspension of **1e** (56.7 mg, 0.18 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (9.1 mg, 0.031 mmol), and 1-ethylpiperidine (0.049 mL, 0.35 mmol) in mixed solution of H_2O (2.5 mL) and MeOH (2.5 mL) was stirred for 14 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2e** (48.4 mg, 85%) as a pale yellow solid; mp 187–188 °C (pale yellow needles from acetone–hexane); IR (film, cm^{-1}) 1518, 1344, 1165; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (3H, s), 6.81 (1H, s), 7.44–7.50 (3H, m), 7.53–7.58 (2H, m), 7.25 (2H, d, J=1.5 Hz), 8.51 (1H, t, J=1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.4, 112.2, 115.7, 116.9, 119.9, 127.9, 129.62, 129.63, 130.3, 130.6, 140.4, 144.3, 144.7; MS m/z 316 (M^+, 91), 237 (100); HRMS calcd for $C_{15}H_{12}N_2O_4S$ 316.0518, found 316.0500.

4.2.6. 5-Bromo-1-methylsulfonyl-2-phenylindole (2f) (Table 4, entry 5). A suspension of **1f** (104.0 mg, 0.30 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (17.0 mg, 0.059 mmol), and 1-ethylpiperidine (0.082 mL, 0.59 mmol) in mixed solution of H_2O (4 mL) and MeOH (4 mL) was stirred for 72 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2f**[7a] (103.4 mg, 99%) as a colorless solid; mp 186–187 °C (colorless needles from AcOEt–hexane, lit[7a] mp 186–187 °C); IR (film, cm^{-1}) 1361, 1177; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (3H, s), 6.62 (1H, s), 7.40–7.47 (4H, m), 7.51–7.56 (2H, m), 7.71 (1H, d, J=1.7 Hz), 7.98 (1H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 111.8, 117.1, 117.8, 123.5, 127.67, 127.73, 129.1, 130.1, 131.2, 131.8, 136.5, 143.0; MS m/z 351 (M^++2, 66), 349 (M^+, 65), 272 (99), 270 (100); HRMS calcd for $C_{15}H_{12}BrNO_2S$ 348.8772, found 348.9763.

4.2.7. 1-Methylsulfonyl-5-methyl-2-phenylindole (2g) (Table 4, entry 6). A suspension of **1g** (69.0 mg, 0.24 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (12.5 mg, 0.043 mmol), and 1-ethylpiperidine (0.067 mL, 0.49 mmol) in mixed solution of H_2O (3 mL) and MeOH (3 mL) was stirred for 27 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/3)] to afford **2g**[7a] (68.4 mg, 99%) as a colorless solid; mp 137–138 °C (colorless needles from AcOEt–hexane, lit.[7a] mp 137–138 °C); IR (film, cm^{-1}) 1366, 1173; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (3H, s), 2.70 (3H, s), 6.65 (1H, s), 7.19 (1H, d, J=8.5 Hz), 7.37–7.45 (4H, m), 7.53–7.57 (2H, m), 7.98 (1H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 39.0, 113.0, 115.5, 120.9, 126.4, 127.6, 128.7, 130.0, 130.5, 132.0, 134.2, 136.2, 142.1; MS m/z 285 (M^+, 48), 206 (100). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.35; H, 5.43; N, 4.52.

4.2.8. 1-Methylsulfonyl-6-methoxy-2-phenylindole (2h) (Table 4, entry 7). A suspension of **1h** (71.7 mg, 0.24 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (13.8 mg, 0.048 mmol), and 1-ethylpiperidine (0.066 mL, 0.48 mmol) in mixed solution of H_2O (3 mL) and MeOH (3 mL) was stirred for 21 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2h**[7a] (70.7 mg, 99%) as a colorless solid; mp 134–135 °C (colorless prisms from AcOEt–hexane, lit.[7a] mp 134–135 °C); IR (film, cm^{-1}) 1612, 1367, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (3H, s), 3.88 (3H, s), 6.62 (1H, s), 6.96 (1H, dd, J=8.5, 2.2 Hz), 7.36–7.40 (3H, m), 7.44 (1H, d, J=8.5 Hz), 7.50–7.55 (2H, m), 7.67 (1H, d, J=2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0, 55.7, 110.1, 113.0, 113.5, 121.3, 123.9, 127.5, 128.4, 129.8, 132.0, 139.1, 140.6, 158.0; MS m/z 301 (M^+, 41), 222 (100). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.73; H, 4.95; N, 4.60.

4.2.9. 2-Phenylbenzofuran (6) (Table 4, entry 10). A suspension of **5** (94.7 mg, 0.49 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (24.9 mg, 0.086 mmol), and 1-ethylpiperidine (0.135 mL, 0.98 mmol) in mixed solution of H_2O (5 mL) and MeOH (5 mL) was stirred for 11 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/20)] to afford **6**[17] (82.4 mg, 87%) as a colorless solid. From the later fraction, **5** (7.0 mg, 7%) was recovered; **6**; mp 117–118 °C (colorless scales from hexane, lit.[17] mp 118–120 °C); IR (film, cm^{-1}) 1215, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, d, J=0.7 Hz), 7.22 (1H, td, J=7.5, 1.3 Hz), 7.28 (1H, td, J=7.5, 1.3 Hz), 7.35 (1H, t, J=7.5 Hz), 7.45 (2H, d, J=7.5 Hz), 7.52 (1H, d, J=7.5 Hz),

7.58 (1H, d, J=7.5 Hz), 7.86 (2H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.3, 111.1, 120.8, 122.9, 124.2, 124.9, 128.5, 128.7, 129.1, 130.4, 154.8, 155.8; MS *m/z* 194 (M^+, 100); HRMS calcd for $C_{14}H_{10}O$ 194.0732, found 194.0727.

4.3. General procedure for Table 5

1-Ethylpiperidine (2.0 equiv), 2-ethynylaniline derivatives and $Cu(OCOCF_3)\cdot xH_2O$ in mixed solution of H_2O and MeOH was stirred for 17 h at room temperature. Et_2O (7 mL) was added to the reaction mixture and stirred for 10 min, and then Et_2O phase were separated. This operation was repeated again. The combined Et_2O phase was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel chromatography [AcOEt–hexane (1/5) for **2b**, (1/3) for **2i**, and (1/2) for **2j**]. For the second and third cycles, a solution of 1-ethylpiperidine (1.0 equiv) and 2-ethynylaniline derivatives in MeOH was added to a catalyst solution in H_2O, and then the mixture was stirred for 17 h at room temperature and worked up and purified as above.

4.3.1. 1-Methylsulfonyl-2-phenylindole (2a) (Table 5, entry 1).

Substrate and reagents	First cycle	Second cycle	Third cycle
1a	98.7 mg, 0.36 mmol	96.5 mg, 0.36 mmol	94.4 mg, 0.35 mmol
$Cu(OCOCF_3)_2\cdot xH_2O$	21.7 mg, 0.075 mmol	—	—
1-Ethylpiperidine	0.099 mL, 0.72 mmol	0.049 mL, 0.35 mmol	0.049 mL, 0.35 mmol
H_2O	5 mL	—	—
MeOH	5 mL	3 mL	3 mL
Yield	97.6 mg, 99%	90.6 mg, 94%	91.4 mg, 97%

4.3.2. 1-Methylsulfonylindole (2i) (Table 5, entry 2).

Substrate and reagents	First cycle	Second cycle	Third cycle
1i	71.9 mg, 0.37 mmol	73.8 mg, 0.38 mmol	70.4 mg, 0.36 mmol
$Cu(OCOCF_3)_2\cdot xH_2O$	21.2 mg, 0.073 mmol	—	—
1-Ethylpiperidine	0.102 mL, 0.74 mmol	0.051 mL, 0.37 mmol	0.050 mL, 0.36 mmol
H_2O	5 mL	—	—
MeOH	5 mL	3 mL	3 mL
Yield	52.5 mg, 73%	61.8 mg, 84%	62.8 mg, 89%

4.3.3. 1-*p*-Tolylsulfonyl-2-hydroxymethylindole (2j) (Table 5, entry 3).

Substrate and reagents	First cycle	Second cycle	Third cycle
1j	111.1 mg, 0.37 mmol	113.3 mg, 0.38 mmol	116.7 mg, 0.39 mmol
$Cu(OCOCF_3)_2\cdot xH_2O$	21.4 mg, 0.074 mmol	—	—
1-Ethylpiperidine	0.107 mL, 0.78 mmol	0.053 mL, 0.38 mmol	0.053 mL, 0.38 mmol
H_2O	5 mL	—	—
MeOH	5 mL	3 mL	3 mL
Yield	106.8 mg, 96%	112.7 mg, 99%	114.9 mg, 98%

Mp 91–92 °C (colorless scales from AcOEt–hexane, lit.[7a] mp 91–92 °C); IR (film, cm^{-1}) 3566, 3425, 1367, 1173; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 3.11 (1H, t, J=7.4 Hz), 4.90 (2H, d, J=7.4 Hz), 6.64 (1H, s), 7.20 (2H, d, J=8.6 Hz), 7.22 (1H, t, J=7.7 Hz), 7.29 (1H, t, J=7.7 Hz), 7.48 (1H, d, J=7.7 Hz), 7.71 (2H, d, J=8.6 Hz), 8.04 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 58.6, 111.2, 114.3, 121.1, 123.7, 124.9, 126.3, 129.0, 129.9, 135.5, 136.9, 140.0, 145.0; MS *m/z* 301 (M^+, 68), 129 (100). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.82; H, 5.02; N, 4.46.

References and notes

1. (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73–103 and reference cited for the previous review. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
2. (a) Amemiya, R.; Fujii, A.; Yamaguchi, M. *Tetrahedron Lett.* **2004**, *45*, 4333–4335. (b) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; García-Martín, M. A.; González, J. M. *J. Org. Chem.* **1996**, *61*, 5804–5812. (c) Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741–2746. (d) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866. For a review about related cyclization reactions, see: (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (f) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198.
3. (a) Sun, L.-P.; Huang, X.-H.; Dai, W.-M. *Tetrahedron* **2004**, *60*, 10983–10992. (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571–1587. (c) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699–7702. (d) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275–5278. (e) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490. (f) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 647–649. (g) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507–6511. (h) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823–1828. (i) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1845–1847. (j) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 31–32.
4. (a) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592–11593. (b) McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103–3106. (c) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687–7690.
5. (a) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610–618. (b) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799–1802.
6. (a) Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35–38. (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846. (c) Reboredo, F. J.; Treus, M.; Estévez, J. C.; Castedo, L.; Estévez, R. J. *Synlett* **2003**, 1603–1606. (d) Soloducho, J. *Tetrahedron Lett.* **1999**, *40*, 2429–2430. (e) Kumar, V.; Dority, J. A.; Bacon, E. R.; Singh, B.; Lesher, G. Y. *J. Org. Chem.* **1992**, *57*, 6995–6998.

(f) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255–1261. (g) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078. (h) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. For related CuX catalyzed reactions, see: (i) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139–5142.

7. (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136. (b) Dai, W.-M.; Guo, D.-S.; Sun, L.-P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2919–2922. (c) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280. (d) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841–7844. For related CuX_2 catalyzed reactions, see: (e) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251 and references therein. (f) Ma, S.; Xie, H. *Tetrahedron* **2005**, *61*, 251–258 and references therein. (g) Huang, X.; Zhou, H.; Chen, W. *J. Org. Chem.* **2004**, *69*, 839–842.
8. (a) Suzuki, N.; Yasaki, S.; Yasuhara, A.; Sakamoto, T. *Chem. Pharm. Bull.* **2003**, *51*, 1170–1173. (b) Yasuhara, A.; Suzuki, N.; Yoshino, T.; Takeda, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 6579–6582. (c) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534.
9. For a review, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (c) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115–2134. (d) Cacchi, S.; Marinelli, F. In Negishi, E., Ed.; Handbook of organopalladium chemistry for organic synthesis; Wiley: New York, 2002; Vol. 2, pp 2227–2244. (e) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111–124.
10. (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439–442. (b) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 8258–8265. (c) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129–4132. (d) Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* **2004**, *6*, 2953–2956. (e) Pal, M.; Subramanian, V.; Batchu, V. R.; Dager, I. *Synlett* **2004**, 1965–1969. (f) van Esseveldt, B. C. J.; van Delft, F. L.; Smits, J. M. M.; de Gelder, R.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2004**, *346*, 823–834. (g) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693–697. (h) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Heterocycles* **2004**, *64*, 475–482. (i) van Esseveldt, B. C. J.; van Delft, F. L.; de Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717–1720. (j) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412–420. (k) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551–1553. (l) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662. (m) Yu, M. S.; de Leon, L. L.; McGuire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347–9350. (n) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355–5358. (o) Park, S. S.; Choi, J.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627–630. (p) Blurton, P.; Brickwood, A.; Dhanak, D. *Heterocycles* **1997**, *45*, 2395–2403. (q) Botta, M.; Summa, V.; Corelli, F.; Pietro, G. D.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263–1266. (r) Chen, C.-y.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J.; Cottrell, I. F.; Houghton, P. G. *Tetrahedron Lett.* **1994**, *35*, 6981–6984. (s) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289–296. (t) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471–6474. (u) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 2823–2826. (v) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. (w) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581–2584. (x) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305–1308. For a related Pd-catalyzed cyclization reaction, see: (y) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257–4260.
11. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Org. Chem.* **2005**, *70*, 6213–6217. (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synthesis* **2004**, 1889–1894. (c) Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis* **2003**, 728–734. (d) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671–2681. (e) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355–1358. (f) Yasuhara, A.; Takeda, Y.; Suzuki, N.; Sakamoto, T. *Chem. Pharm. Bull.* **2002**, *50*, 235–238. (g) Arcadi, A.; Cacchi, S.; Cassetta, A.; Fabrizi, G.; Parisi, L. M. *Synlett* **2001**, 1605–1607. (h) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 394–396. (i) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620–622. (j) Yasuhara, A.; Kaneko, M.; Sakamoto, T. *Heterocycles* **1998**, *48*, 1793–1799. (k) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001–1011. (l) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363–1366. (m) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812. (n) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437–452. (o) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915–3918. (p) Kondo, Y.; Sakamoto, T.; Yamanaka, H. *Heterocycles* **1989**, *29*, 1013–1016. For related cyclization reactions, see: (q) Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764–4771 and references therein.
12. (a) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011–6019 and references therein. For a recent review, see: (b) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885–939.
13. (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037–1040. (b) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539–541. (c) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409. For a recent utilization of 3-iodoindoles, see: (d) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654–1657.
14. Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265–2273.
15. (a) Serra, S.; Fuganti, C. *Synlett* **2005**, 809–812. (b) Lee, C.-Y.; Lin, C.-F.; Lee, J.-L.; Chiu, C.-C.; Lu, W.-D.; Wu, M.-J. *J. Org. Chem.* **2004**, *69*, 2106–2110.
16. The indole **2a** was afforded from the reaction of **1a** in the presence of 10 mol% of Cu(II) stearate in refluxing 1,2-dichloroethane for 72 h in 84% yield (Hiroya, K.; Itoh, S.; Sakamoto, T. unpublished results).
17. Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028.

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Conformational preferences of the aldol adducts of oxadiazinones. ^{1}H NMR spectroscopy and computational studies of N_4-methyl and N_4-isopropyloxadiazinones

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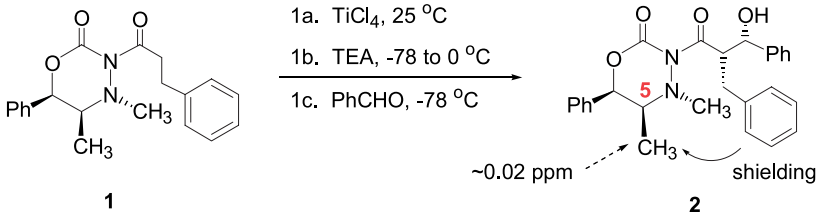
Abstract—The conformational properties of the aldol adducts of some N_4-isopropyl-oxadiazinones have been investigated by ^{1}H NMR spectroscopy and computational studies. An earlier study of the *syn*-aldol adducts of N_4-methyl-oxadiazinone **2** led to the conclusion that the solution and solid state conformation of these compounds involve *syn*-parallel arrangement of the C_2- and N_3-carbonyls of the oxadiazinones. However, the synthesis and asymmetric aldol reactions of an N_3-hydrocinnamoyl-N_4-isopropyl-oxadiazinone **4** has yielded aldol adducts **5a–e** in which the orientation of the C_2- and N_3-carbonyls are most likely in the *anti*-parallel arrangement. These aldol adducts have been studied by ^{1}H NMR spectroscopy and the shielding aspect observed clearly suggests the presence of the *anti*-parallel arrangement. The installment of a N_4-d_6-isopropyl group further confirmed this assertion. Computational studies support the conclusion that solution state conformation of the N_4-methyl and N_4-isopropyl-oxadiazinones involves *anti*-parallel carbonyls in contrast to the solid state evidence of the X-ray crystallographic data of oxadiazinone **2**.

1. Introduction

We recently reported on the conformational analysis of the aldol addition adducts of a (1*R*,2*S*)-ephedrine based N_3-hydrocinnamoyloxadiazinone.[1] It was determined that the C_5-methyl group of oxadiazinone **2** became strongly shielded and shifted from the average value of 0.85 ppm to a value of 0.02 ppm (Scheme 1). It was concluded from a solution state NOESY study that the C_5-methyl group was being shielded by the proximal aromatic ring of the N_3-side chain. In contrast, solid state X-ray crystallographic studies suggested that the terminal aromatic ring was responsible for the shielding.

It was concluded that the conformation of **2** that gave rise to the shielding of the C_5-methyl group resembled the solid state X-ray crystal structure involving a nearly *syn*-parallel arrangement of the carbonyls, but had a different orientation of the proximal aromatic ring of the N_3-substituent. This conformation was believed to be dominant in solution and in the solid state based on an earlier study of oxadiazinones that included ^{13}C NMR spectroscopic data, X-ray crystallographic data, and computational data.[2,3] Herein, we report on the synthesis of the new oxadiazinones derivatives, ^{1}H NMR studies, and computational studies that strongly suggest that the dominant conformation in solution is the *anti*-parallel carbonyl arrangement, not the *syn*-parallel



Scheme 1.

Keywords: Oxadiazinone; Aldol addition reaction; Conformational analysis; Computational study.
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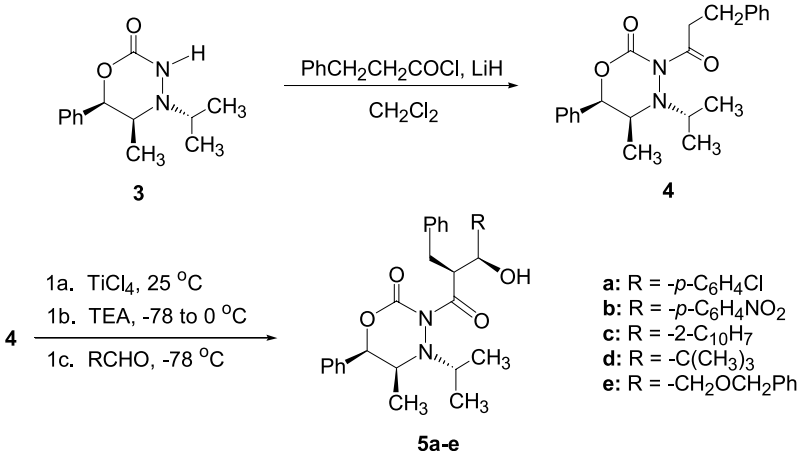
arrangement. Furthermore, a computational reinvestigation of the previously studied oxadiazinone **2** suggests that the lowest energy gas phase conformer has an *anti*-parallel carbonyl arrangement and that the dominant conformation in solution state is also likely to be the *anti*-parallel carbonyl arrangement.

2. Results and discussion

The new oxadiazinone derivatives were synthesized using an N_4-isopropyloxadiazinone (**3**) derived from (1*R*,2*S*)-norephedrine. This oxadiazinone was prepared as described previously[4] and was subsequently acylated with hydrocinnamoyl chloride to afford the desired N_3-hydrocinnamoyl-N_4-isopropyloxadiazinone (**4**) in 64% yield after chromatography (Scheme 2). The acylated oxadiazinone was dissolved in tetrahydrofuran and treated with titantium tetrachloride at 25 °C. The temperature of the reaction mixture was cooled to −78 °C and triethylamine was added. After 45 min, a selected aldehyde was then added to the reaction mixture to yield aldol adducts **5a**–**e**.

Interestingly, all of the adducts exhibited a signal in their respective 400 MHz ^{1}H NMR spectra that had an average chemical shift of −0.15 ppm (Fig. 1). The same shielding effect was observed in the ephedrine based N_4-methyl-oxadiazinone **2**, which was believed to have the *syn*-parallel arrangement of the C_2- and N_3-carbonyl groups.[1] This was intriguing as our previous results concerning the N_4-isopropyloxadiazinones suggested that the dominant conformation involved an *anti*-parallel arrangement of the carbonyls.[4] This putative difference prompted a more detailed investigation of the conformational aspects of the N_4-methyl-oxadiazinones as compared to the aldol adducts of the N_4-isopropyl-oxadiazinones. From the previous study it was already established that the signal that was being shielded in the ephedrine based N_4-methyloxadiazinones aldol adducts was the C_5-methyl group.[1] Likewise, the identity of the signal that was shielded in the N_4-isopropyl-oxadiazinone aldol adducts **5a**–**e** was also determined to be the C_5-methyl group based on an analysis of the observed coupling constants (Fig. 1).

There was some concern that the shielded signal could be attributed to one of the methyl groups of the isopropyl group although this was unlikely based on the aforementioned coupling constants. The identity of the signal was unambiguously determined by the synthesis of an N_4-d_6-isopropyloxadiazinone aldol adduct. Thus, (1*R*,2*S*)-norephedrine (**6**) was reductively alkylated with acetone-d_6 and sodium borohydride in 72% yield (Scheme 3). The amine was *N*-nitrosated in 88% yield by treatment with sodium nitrite and hydrochloric acid.[5] The *N*-nitrosamine **8** was reduced to the 1,1′-disubstituted hydrazine **9** by lithium aluminum hydride and subsequently cyclized in 24% yield from **8** by reaction with diethylcarbonate and lithium hydride to afford oxadiazinone **10**. This material was acylated with hydrocinnamoyl chloride and lithium hydride in 92% yield. The resultant N_3-hydrocinnamoyl-oxadiazinone was reacted with titanium tetrachloride in THF (0.3 M), deprotonated with triethylamine at −78 °C over



Scheme 2. Asymmetric aldol reactions with the N_4-isopropyloxadiazinone.

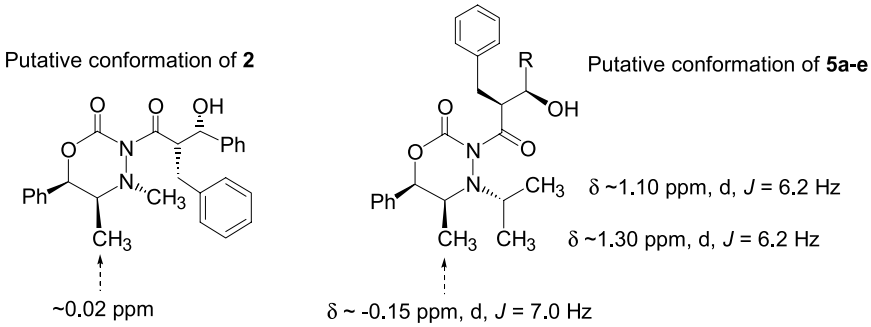
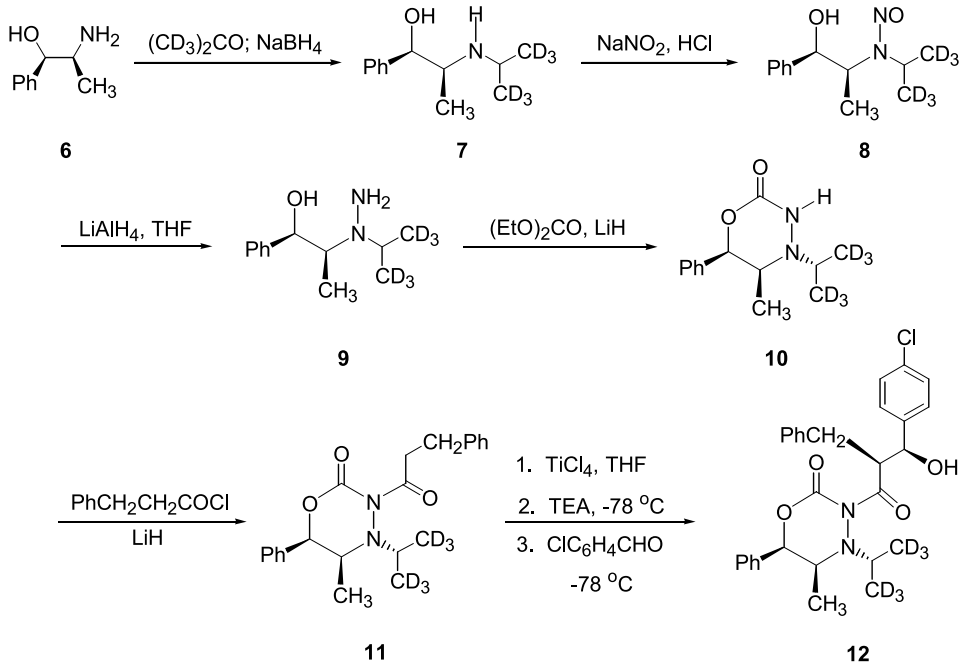


Figure 1.



Scheme 3.

a period of 45 min, and subsequently treated with 4-chlorobenzaldehyde. This process afforded the target aldol adduct **12** in 97% yield and greater than 95:5 diastereoselectivity based on the analysis of the related 400 MHz ^{1}H NMR spectrum.

The ^{1}H NMR spectrum of deuterated aldol adduct **12** exhibited a single doublet at −0.15 ppm. This provided clear evidence that the C_5-methyl group was being strongly shielded by an aromatic ring of the N_3-substituent. The aromatic ring of the N_3-side chain responsible for the shielding effect was determined by comparing the 400 MHz ^{1}H NMR spectra of aldol adducts **5a–c** against aldol adducts **5d–e** (Fig. 2). All of the adducts, **5a–e**, exhibited a strongly shielded signal near −0.15 ppm. The oxadiazinone adducts **5a–c** possess two aromatic rings on the N_3-side chain whereas adducts **5d–e** possess only a single aromatic ring. It was concluded that the aromatic ring from the original

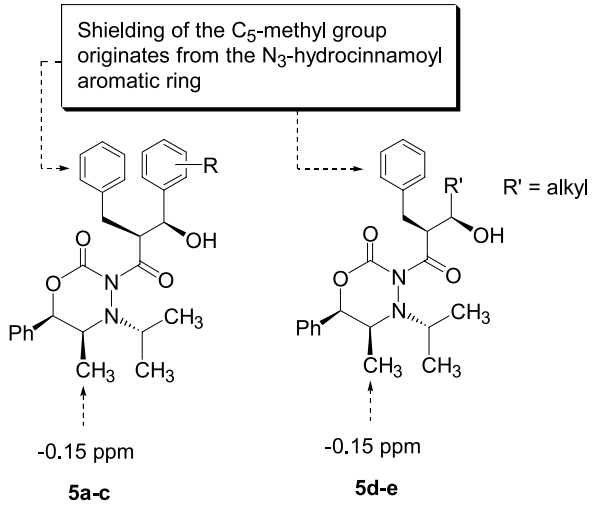


Figure 2. Origin of shielding effect.

N_3-hydrocinnamoyl side chain was responsible for the shielding. This observation was in agreement with the earlier study[1] that the proximal aromatic ring was responsible for the shielding of the C_5-methyl group.

A NOESY experiment was conducted with deuterated adduct **12** to support this argument (Fig. 3). This spectroscopic data conclusively demonstrated that the shielding involved the aforementioned C_5-methyl group and the N_3-side chain. Specifically, when the signal at −0.15 ppm was irradiated there was an enhancement of the aromatic signals centered at 7.03 and 7.11 ppm. There was no observed enhancement of the aromatic proton signals attributed to the *p*-chlorophenyl group.

A second irradiation experiment was conducted wherein irradiation of the protons of the *p*-chlorophenyl substituent did not cause an enhancement of the C_5-methyl group. The combined results of the 400 MHz ^{1}H NMR spectra of **5a–e**, the synthesis and analysis of the N_4-d_6-isopropyloxadiazinone adduct, and the NOESY evidence established the relationship between the C_5-methyl group and the aromatic ring. The ephedrine based oxadiazinone adduct **2** from the earlier study was observed to have the same characteristics of shielding of the C_5-methyl group but the conformation was believed to be have the *syn*-parallel arrangement of the carbonyls. In contrast the oxadiazinone adducts **5a–e** are believed to the have the *anti*-parallel arrangement of the carbonyls (Fig. 4). Computational studies were employed to resolve the conformational differences between the two sets of oxadiazinone substrates.

A conformation search employing the AM1 semiempirical molecular orbital method was carried out in the gas phase out to locate low energy conformations of the N_4-isopropyloxadiazinone **5**. The conformation search was performed using the Spartan02 software package for Linux.[6] In order to

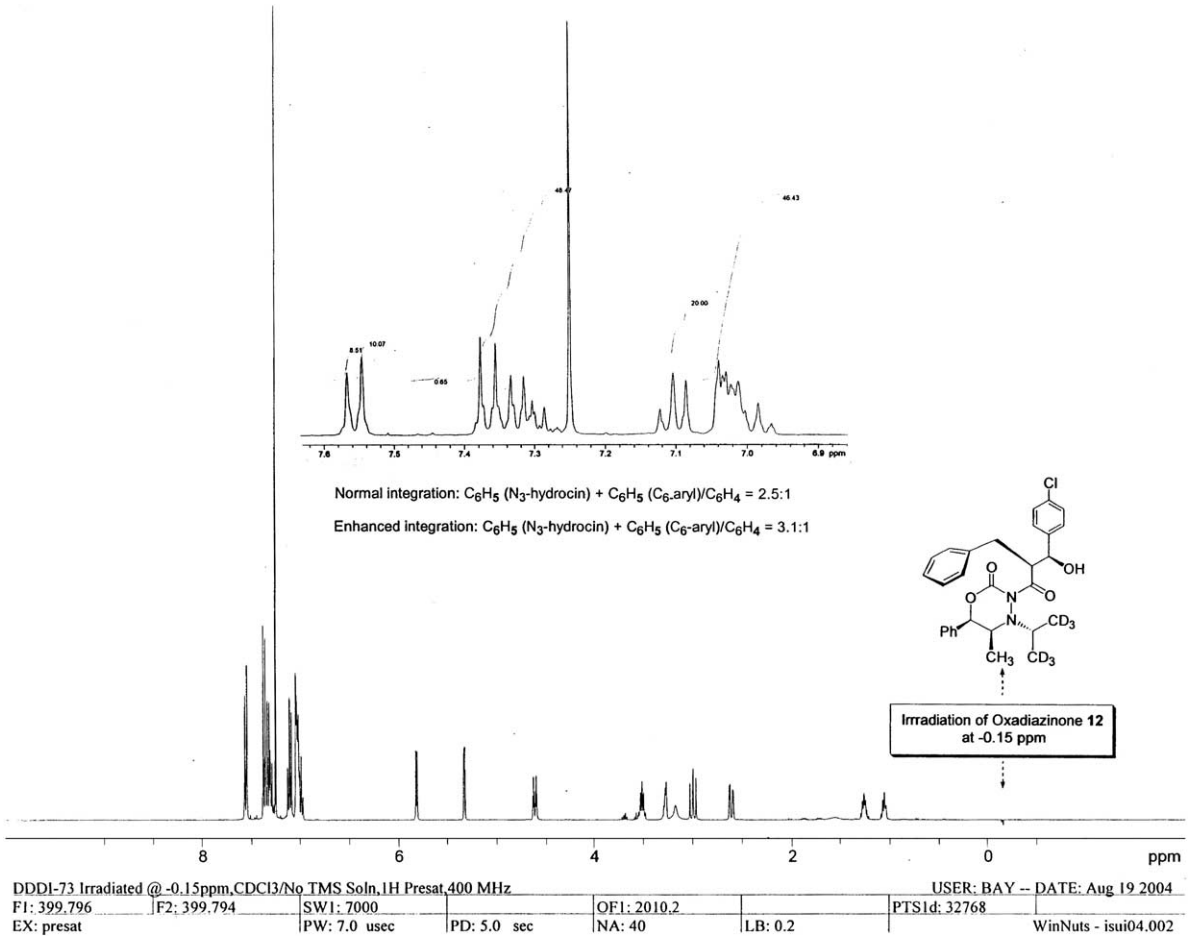


Figure 3. 400 MHz ^{1}H NMR NOESY spectrum of **12** with irradiation at −0.15 ppm. The signals located at 1.05 and 1.25 ppm are attributed to the residual coupling from the $(CD_3)_2CH$– substituent.

include both *syn*- and *anti*-parallel arrangements of the carbonyl groups, one conformation search was carried out in which the starting structure had an approximately *syn*-parallel carbonyl arrangement and a second conformation search was carried out in which the starting structure had an approximately *anti*-parallel carbonyl arrangement. Systematic conformation searches were performed in which the key rotatable dihedral angles responsible for positioning of the aromatic ring of the N_3-hydrocinnamoyl unit and the aromatic ring at the terminus of the N_3-substituent chain (Fig. 5) were varied to obtain initial structures, which were then subjected to geometry optimization. A vibrational frequency calculation was performed for each unique structure found in the conformation searches in order to verify that it corresponded to a minimum on the potential energy surface. The ^{1}H NMR chemical shifts of the protons of the methyl group attached to the C_5 position of oxadiazinone **5** were determined for each conformation from single-point energy density functional calculations at the B3LYP/DZP level of theory using the gauge invariant atomic orbital (GIAO) method. The PQS 3.1 software package[7] was employed for all the density functional calculations.

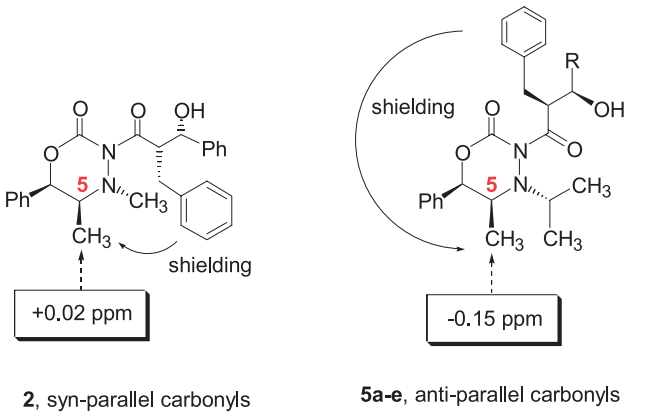


Figure 4. Comparison of oxadiazinone adducts.

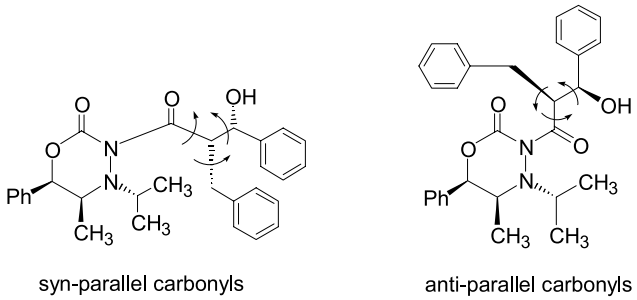


Figure 5. Rotatable dihedral angles included in conformation searches.

Table 1. Computational results for low-energy conformers of oxadiazinone **5**

Conformation	Relative ΔH, kJ/mol (kcal/mol)	Dihedral angle (°)[a]	Average C_5 methyl ^{1}H chemical shift (ppm)	Distance to benzene centroid (Å)[b]
1	0.00 (0.00)	−125.4	0.141	3.90
2	4.70 (1.12)	34.5	0.978	
3	7.42 (1.77)	−115.7	0.856	
4	8.72 (2.09)	−145.7	0.024	3.94
5	12.74 (3.04)	−163.1	0.514	4.65
15	19.05 (4.55)	28.9	0.040	3.79

[a] The dihedral angle listed is the O–C–C–O dihedral angle between the two carbonyl groups.
[b] The distance reported is the average distance from the protons of the methyl attached to C_5 to the centroid of the benzene ring in close contact.

From the conformer searches, five conformers were located within 13 kJ/mol (3.1 kcal/mol) of the lowest energy conformer and a total of 16 conformers were located within 20 kJ/mol (4.8 kcal/mol) of the lowest energy conformer. Calculated results for the five lowest energy conformers plus one other are listed in Table 1.

The lowest energy conformer (Fig. 6) and four of the first five lowest energy conformers of oxadiazinone **5** have approximately *anti*-parallel arrangements of the carbonyl groups. Of these, two (conformers 1 and 4) exhibit unusually low ^{1}H chemical shifts (0.0–0.1 ppm) for the protons of the methyl group at the C_5 position and a third (conformer 5) exhibits a partial decrease in the chemical shift (0.5 ppm) compared to a typical chemical shift of around 1 ppm for methyl protons. In previous work,[1] the unusual chemical shift of the methyl protons was attributed to close contact with one of the substituent benzene rings of the N_3-substituent. In conformers 1 and 4, the aromatic ring of the N_3-hydrocinnamoyl unit is in close proximity (at a average distance of 3.9 Å) to the protons of the C_5-methyl group and this interaction is responsible for the unusually low chemical shift that was observed. In conformer 5, the aromatic ring of the N_3-hydrocinnamoyl unit is interacting with the protons of the C_5-methyl group but at a larger distance of 4.7 Å so the chemical shift of the methyl protons is only reduced to about 0.5 ppm.

To further explore the question of whether oxadiazinone **5** prefers the *syn*-parallel or *anti*-parallel arrangement of carbonyl groups, results are included in Table 1 for conformer 15, which is the lowest energy conformer with a *syn*-parallel carbonyl arrangement that also exhibits an unusual C_5-methyl ^{1}H chemical shift. This *syn*-parallel conformer is 19 kJ/mol above the lowest energy *anti*-parallel conformer. In addition, it is the terminal aromatic ring of the N_3-substituent rather than the aromatic ring of the N_3-hydrocinnamoyl unit that is in close contact (3.8 Å) with the C_5-methyl protons in conformer 15 and thus, is the interaction responsible for the unusual chemical shift. The NOE study established this relationship as described earlier.

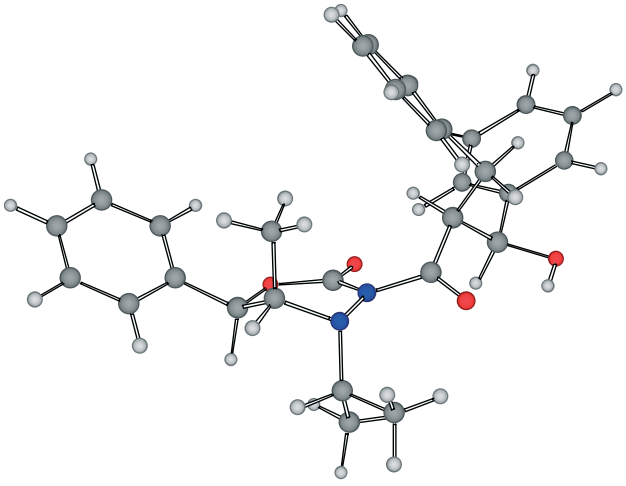


Figure 6. Lowest energy conformer of oxadiazinone **5**.

The general trend observed in the conformer search is that the lower energy conformers tend to have the *anti*-parallel arrangement of carbonyl groups while conformers with the *syn*-parallel carbonyl arrangement tend to occur at higher energy. The interaction responsible for the unusual chemical shift of the C_5-methyl protons in conformers with an approximately *anti*-parallel carbonyl arrangement is in close contact with the aromatic ring of the N_3-hydrocinnamoyl unit (Fig. 7). On the other hand, the interaction responsible for the unusual chemical shift of the C_5-methyl protons in conformers with an approximately *syn*-parallel carbonyl arrangement is in close contact with the terminal aromatic ring of the N_3-substituent (Fig. 7).

Previous work on the ephedrine based N_4-methyl-oxadiazinone **2** involved X-ray crystallography, solution phase NMR (including NOE studies), and gas phase computational studies.[1] The X-ray crystallography results indicated that the carbonyls adopt a *syn*-parallel orientation in the solid state. Solution phase NOE results and computational studies were carried out and interpreted based on the assumption that the system also would adopt a *syn*-parallel orientation in solution and gas phases. These observations lead to a discrepancy as to which conformation was responsible for the unusual chemical shift of the C_5-methyl protons. Based on the results obtained in this work for

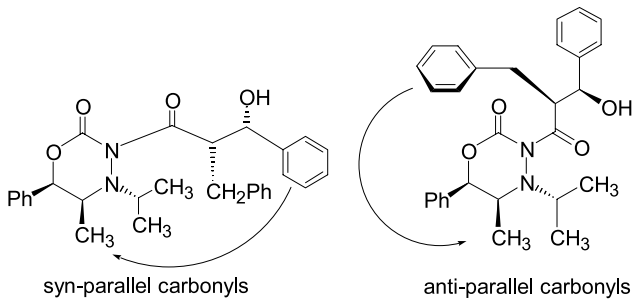


Figure 7. Origin of unusual chemical shift of C_5-methyl protons in oxadiazinone **5** with *syn*- and *anti*-parallel carbonyl arrangements.

oxadiazinone **5**, further computational studies have been performed on oxadiazinone **2**.

Conformation searches starting from both the *syn*- and *anti*-parallel arrangements of the carbonyl groups were performed using the AM1 semiempirical method as implemented in the Spartan02 software package for Linux.[6] The same dihedral angles shown in Figure 5 were allowed to vary in the conformation searches of oxadiazinone 2. NMR chemical shifts again were determined from single-point energy calculations at the B3LYP/DZP level of theory using GIAO method implemented in the PQS 3.1 software package.[7]

For oxadiazinone **2**, five conformers were located within 13 kJ/mol (3.1 kcal/mol) of the lowest energy conformer and a total of 28 conformers were located within 20 kJ/mol (4.8 kcal/mol) of the lowest energy conformer. Calculated results for the seven lowest energy conformers are listed in Table 2.

The two lowest energy conformers of oxadiazinone **2** are very similar to those found for N_4-isopropyl-oxadiazinone **5**. The lowest energy conformer (Fig. 8) and five of the first six conformers of oxadiazinone **2** have approximately *anti*-parallel carbonyl arrangements. The lowest energy conformer exhibits an unusually low ^{1}H chemical shift (0.065 ppm) for the protons of the C_5-methyl group and two other conformers (3 and 5) exhibit a partial decrease in the chemical shift (0.3–0.4 ppm). In agreement with results found for oxadiazinone **5**, the unusual chemical shift of the C_5-methyl protons of conformer 1 arises because the aromatic ring of the N_3-hydrocinnamoyl unit is in close contact (at a average distance of 4.3 Å) with the protons of the C_5-methyl group. In conformers 3 and 5, the aromatic ring of the N_3-hydrocinnamoyl unit interacts with the protons of the C_5-methyl group at a larger distance (4.7–4.8 Å), leading to a partial reduction in the chemical shift of the C_5-methyl protons. The lowest energy conformer with a *syn*-parallel carbonyl arrangement to exhibit an unusual C_5-methyl ^{1}H chemical shift is conformer 7, 13.2 kJ/mol above the lowest energy conformer.

In accord with the findings for oxadiazinone **5**, the terminal aromatic ring of the N_3-substituent is in close contact with the C_5-methyl protons in conformers with *syn*-parallel carbonyl arrangements (such as conformer 7) and is the interaction responsible for the unusual chemical shift of the C_5-methyl protons (Fig. 8).

In the conformer search for oxadiazinone **2**, conformer 4 has an orientation in which close contact between the aromatic ring of the N_3-hydrocinnamoyl unit is observed and the C_5-methyl group is in the *anti*-parallel carbonyl arrangement. In comparing conformers 1 and 4, the dihedral angle between the carbonyls is very similar (−124 vs −143°) as

Table 2. Computational results for low-energy conformers of oxadiazinone **2**

Conformation	Relative Δ*H*, kJ/mol (kcal/mol)	Dihedral angle (°)[a]	Average C_5 methyl ^{1}H chemical shift (ppm)	Distance to benzene centroid (Å)[b]
1	0.00 (0.00)	−123.6	0.065	4.29
2	6.57 (1.57)	32.0	0.950	
3	8.73 (2.09)	−145.6	0.288	4.65
4	10.12 (2.42)	−142.9	0.959	4.34
5	12.82 (3.07)	−173.2	0.420	4.79
6	12.95 (3.10)	−136.0	0.976	
7	13.24 (3.17)	31.8	−0.370	3.66

[a] The dihedral angle listed is the O–C–C–O dihedral angle between the two carbonyl groups.
[b] The distance reported is the average distance from the protons of the C_5-methyl group to the centroid of the benzene ring in close contact.

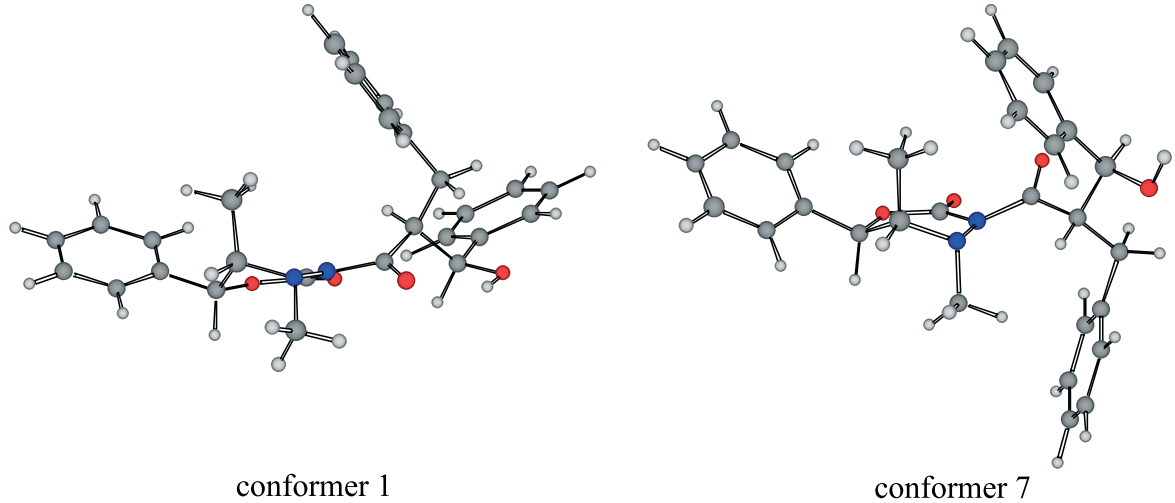


Figure 8. Conformers of oxadiazinone **2**. Conformer 1 shows the *anti*-parallel carbonyl arrangement and close contact between the aromatic ring of the N_3-hydrocinnamoyl unit and the C_5-methyl group. Conformer 7 shows the *syn*-parallel carbonyl arrangement and close contact between the terminal aromatic ring of the N_3-substituent and the C_5-methyl group.

is the average distance between the C_5-methyl protons and the centroid of the benzene ring of the N_3-hydrocinnamoyl unit (4.3 Å). It would be expected, therefore, that the C_5-methyl protons of conformer 4 would exhibit a chemical shift of close to 0 ppm, however, the chemical shift is calculated to be normal (0.96 ppm). Further investigation of the lack of unusual chemical shift suggests that not only must the aromatic ring be in close proximity to the C_5-methyl group but that the C_5-methyl must be positioned between the aromatic ring of the N_3-hydrocinnamoyl unit and the aromatic ring at the C_6 position. This is illustrated in Figure 9 where a comparison between conformer 1 (unusual C_5-methyl shift) and conformer 4 (normal C_5-methyl shift) is shown. A normal chemical shift for the C_5-methyl group protons also is observed in one other conformer of oxadiazinone 2 (conformer 8, relative $\Delta H = 13.6$ kJ/mol). This conformer also has the aromatic ring of the N_3-hydrocinnamoyl unit in close contact with the C_5-methyl group but exhibits a normal C_5-methyl chemical shift for the same reasons illustrated in Figure 9.

3. Summary

The conformational properties of the aldol adducts of N_4-isopropyl-oxadiazinones **5a–e** have been investigated by ^{1}H NMR spectroscopy, NOE studies, and computational studies. An earlier study of the *syn*-aldol adducts of N_4-methyl-oxadiazinone **2** suggested that these compounds have *syn*-parallel arrangement of the C_2- and N_3-carbonyls of the oxadiazinones in the solution state and solid state. The results of the current body of work have revealed that the earlier analysis was not complete. The syntheses and asymmetric aldol reactions of an N_3-hydrocinnamoyl-N_4-isopropyl-oxadiazinone **4** has yielded aldol adducts **5a–e** in which the orientation of the C_2- and N_3-carbonyls are most likely in the *anti*-parallel arrangement. These aldol adducts were studied by ^{1}H NMR spectroscopy and the shielding aspect observed in the N_4-isopropyl-oxadiazinone clearly suggests the presence of the *anti*-parallel arrangement. The installment of a N_4-d_6-isopropyl group further confirmed this assertion.

The computational studies of the N_4-isopropyl-oxadiazinones **5** and N_4-methyl-oxadiazinone **2** in the gas phase yield a set of consistent results. First, most of the lowest energy conformers of oxadiazinones **5** and **2** have the *anti*-parallel carbonyl arrangement, which supports the conclusion that it is the most stable orientation of both oxadiazinones **5** and **2**. Conformers of oxadiazinones **5** and **2** that exhibit the *syn*-parallel carbonyl arrangement tend to have higher energies than those with *anti*-parallel carbonyl groups.

Some of the low energy conformers of the oxadiazinones exhibit unusually low ^{1}H chemical shifts of the C_5-methyl

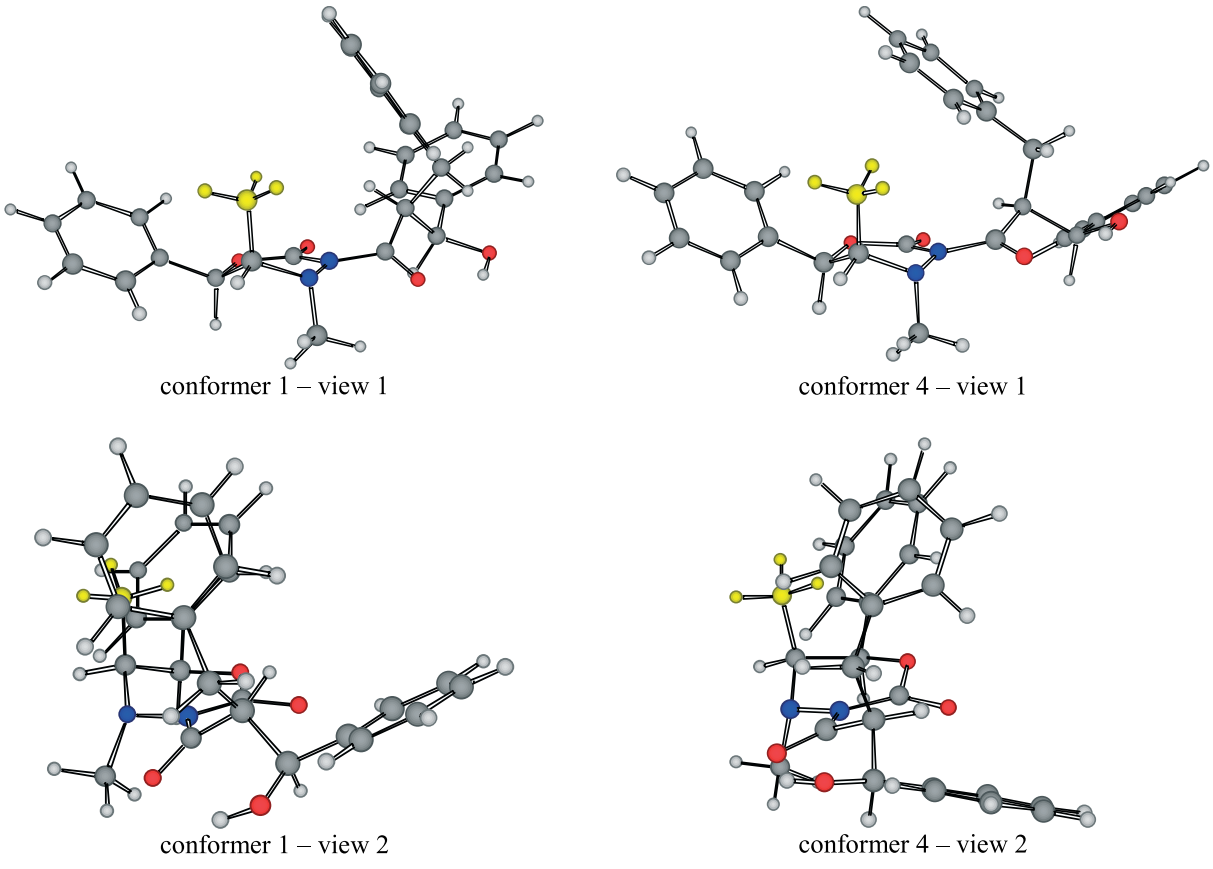


Figure 9. Two views of conformers 1 and 4 of oxadiazinone **2**. The C_5-methyl group is highlighted in yellow. View 1 shows the *anti*-parallel carbonyl arrangement and close contact between the aromatic ring of the N_3-hydrocinnamoyl unit and the C_5-methyl group. View 2 shows the aromatic ring at the C_6 position overlaying the aromatic ring of the N_3-hydrocinnamoyl unit. The C_5-methyl group is positioned between the rings in conformer 1 but is outside the rings in conformer 4.

protons. The low chemical shifts of about 0 ppm arise due to close contact between the aromatic ring of the N_3-hydrocinnamoyl unit and the C_5-methyl protons. Furthermore, from the studies of oxadiazinone **2**, in order for the interaction to lead to a low chemical shift, the C_5-methyl group must be positioned between the aromatic ring attached to the C_6 position and the aromatic ring of the N_3-hydrocinnamoyl unit.

Finally, the synthetic studies, ^{1}H NMR spectroscopic studies (including the NOE studies) and computational studies all suggest together that the dominant conformation is that of the *anti*-parallel carbonyls. Interestingly, the X-ray crystallographic data of **2** and related compounds point to a solid state structure wherein the carbonyls are in a *syn*-parallel arrangement. It would seem that there is a conformational change in the structure of oxadiazinones as there is a change in state. This change may be due to steric interactions, lone pair-lone pair repulsions, or hydrogen bonding phenomena.

4. Experimental

4.1. General remarks

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a potassium/sodium alloy with benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Varian spectrometer in $CDCl_3$ operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). The NOESY spectra was collected by Spectral Data Services, Inc. Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and were uncorrected.

4.1.1. (5*S*,6*R*)-4-Isopropyl-5-methyl-6-phenyl-3-(3-phenylpropanoyl)-2*H*-1,3,4-oxadiazinan-2-one (4). In a flame-dried, nitrogen purged 500 mL round-bottom flask fitted with a condenser was placed N_4-isopropyloxadiazinone **3** (6.0 g, 25.61 mmol) and dissolved in dichloroethane (26 mL). To this stirred mixture was added hydrocinnamoyl chloride (5.71 mL, 38.42 mmol). This mixture was heated to reflux and LiH (0.22 g, 28.17 mmol) was added in portions. After 18 h, the reaction was quenched with saturated NH_4Cl solution (150 mL) and extracted with EtOAc (3×100 mL). The combined extracts were washed with a saturated brine solution (150 mL) and dried ($MgSO_4$). The solvents were removed by evaporation and the crude products were purified via column chromatography (EtOAc/hexanes 1:3). The purified product was isolated as a brown oil and gave a yield of 64%; R_f=0.37 (EtOAc/hexanes 30:70). ^{1}H NMR ($CDCl_3$): 0.67 (d, J=6.6 Hz, 3H), 1.09 (d, J=6.2 Hz, 3H) 1.34 (d, J=6.2 Hz, 3H), 2.69 (apparent triplet, J=7.3, 8.4 Hz, 2H), 2.92–3.08 (m, 1H), 3.17–3.25 (m, 1H), 3.80–3.41 (m, 2H), 5.93 (d, J=5.1 Hz, 1H), 7.12–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$): 12.8, 20.2, 20.6, 30.8, 38.8, 51.2, 53.7, 78.7, 124.7, 126.0, 128.0, 128.2, 128.5, 128.5, 135.8, 140.6, 148.7, 173.9. IR (neat): 2980, 1728, 1242, 754 cm^{-1}. HRMS calcd for $C_{22}H_{26}N_2O_3$: 366.1943. Found: 366.1936.

4.2. General procedures for aldol adducts 5a–e

In a 100 mL round-bottom flask was placed oxadiazinone **4** (1.0 g, 2.73 mmol) and dissolved in THF (8.9 mL). To this mixture was added $TiCl_4$ (0.65 mL, 5.92 mmol). This mixture was allowed to stir for 25 min at room temperature and then cooled to −78 °C for a period of 5 min. Triethylamine (0.43 mL, 3.11 mmol) was added and the solution was allowed to warm to room temperature over a period of 45 min. After this time, the solution was again cooled to −78 °C. After stirring for an additional 5 min, the appropriate aldehyde (3.85 mmol) was added and the solution was allowed to come to room temperature and react for 18 h. The reaction was quenched with a saturated NH_4Cl solution (50 mL) and extracted with EtOAc (2× 50 mL). The combined extracts were washed with a saturated brine solution (50 mL) and dried ($MgSO_4$). The solvents were removed by evaporation and the crude products were purified via column chromatography (EtOAc/hexanes 1:1).

4.2.1. (5*S*,6*R*)-[(2*S*,3*S*)-3-(2-Benzyl-3-(4-chlorophenyl)-3-hydroxypropanoyl)]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (5a). The crude product was purified by silica gel column chromatography with EtOAc:hexanes 2:3 to yield 0.519 g of **5a** (73%) as a yellow oil: $[\alpha]_D^{25}$ −18.3 (c 0.329, $CHCl_3$); R_f=0.28 (EtOAc/hexanes, 2:3). ^{1}H NMR ($CDCl_3$): −0.16 (C_5-methyl, d, J=7.0 Hz, 3H), 1.10 (d, J=6.2 Hz, 3H), 1.30 (d, J=6.2 Hz, 3H), 2.61 (dd, J=10.3, 3.3 Hz, 1H), 3.00 (dd, J=13.6, 12.1 Hz, 1H), 3.20 (s, 1H), 3.31 (septet, J=6.2 Hz, 1H), 3.53 (C_5-methine, septet, J=7.0 Hz, 1H), 4.61 (dt, J=5.9, 3.3 Hz, 1H), 5.34 (br s, 1H), 5.82 (d, J=5.5 Hz, 1H), 6.98–7.40 (m, 12H), 7.57 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 12.0, 20.3, 20.6, 31.8, 50.8, 53.8, 54.1, 72.8, 79.6, 124.8, 126.3, 127.7, 128.2, 128.3, 128.4, 128.5, 129.3, 133.2, 135.4, 138.8, 139.4, 149.7, 175.3. IR (CCl_4): 3442, 2980, 1733, 1239, 734 cm^{-1}. HRMS calcd for $C_{29}H_{31}ClN_2O_4$: 506.1972. Found: 506.1962. HPLC: 10 μ silica, 4.6 mm× 25 cm, EtOAc/hexanes 35:65, R_T=9.67 min, crude ratio= 15:1.

4.2.2. (5*S*,6*R*)-[(2*S*,3*S*)-3-(2-Benzyl-3-hydroxy-3-(4-nitrophenyl)propanoyl)]-4-isopropyl-5-methyl-6-phenyl-1,3,4-2*H*-oxadiazinan-2-one (5b). The crude product was purified by silica gel column chromatography with EtOAc/hexanes 1:1 to yield 1.100 g of **5b** (84%) as a brown oil: $[\alpha]_D^{25}$ −10.2 (c 0.311, $CHCl_3$); R_f=0.38 (EtOAc/hexanes 50:50). ^{1}H NMR ($CDCl_3$): −0.14 (C_5-methyl, d, J=7.0 Hz, 3H), 1.15 (d, J=6.2 Hz, 3H), 1.33 (d, J=6.2 Hz, 3H), 2.52 (dd, J=13.4, 3.3 Hz, 1H), 3.03 (dd, J=13.4, 12.0 Hz, 1H), 3.35 (septet, J=6.2 Hz, 1H), 3.43 (s, 1H), 3.56 (C_5-methine, septet, J=7.0 Hz, 1H), 4.64 (dt, J=12.0, 3.3 Hz, 1H), 5.47 (br s, 1H), 5.85 (d, J=5.1 Hz, 1H), 7.00–7.38 (m, 10H), 7.82 (d, J=8.8 Hz, 2H), 8.27 (d, J=8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 12.1, 20.3, 20.6, 31.7, 50.9, 53.8, 53.9, 72.6, 79.7, 123.5, 124.8, 126.5, 127.2, 128.3, 128.4, 128.6, 129.2, 135.2, 138.3, 147.4, 148.3, 149.9, 175.1. IR (neat): 3437, 2981, 1728, 1604, 1521, 1346, 1240,

699 cm^{-1}. HRMS calcd for $C_{29}H_{31}N_3O_6$: 517.2213. Found: 517.2207. HPLC: 10 μ silica, 4.6 mm×25 cm, EtOAc/hexanes 35:65, R_T=13.08 min, crude ratio=55:1.

4.2.3. (5*S*,6*R*)-[(2*S*,3*S*)-3-(2-Benzyl-3-hydroxy-3-naphthalen-2-yl-propanoyl)]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one (5c). The crude product was purified by silica gel column chromatography with EtOAc/hexanes 1:1 to yield 0.613 g of **5c** (40%) as a brown solid: mp =136–138 °C; R_f=0.38 (EtOAc/hexanes 1:1). ^{1}H NMR ($CDCl_3$): −0.13 (C_5-methyl, d, J=7.0 Hz, 3H), 1.09 (d, J=6.2 Hz, 3H), 1.29 (d, J=6.2 Hz, 3H), 2.68 (dd, J=13.4, 3.2 Hz, 1H), 2.97 (dd, J=13.4, 12.0 Hz, 1H), 3.21–3.24 (m, 1H), 3.49–3.59 (C_5-methine, dq, J=7.0, 5.5 Hz, 1H), 4.77–4.80 (dt, J=12.0, 3.2 Hz, 1H), 5.55 (m, 1H), 5.83 (d, J=5.1 Hz, 1H), 6.96–7.40 (m, 10H), 7.47–7.52 (m, 2H), 7.58–7.68 (m, 1H), 7.78 (dd, J=8.8, 1.8 Hz, 1H), 7.86–8.09 (m, 2H), 8.36 (s, 1H). The alcoholic proton was not observed. ^{13}C NMR ($CDCl_3$): 12.1, 20.3, 20.6, 31.9, 50.9, 53.8, 54.1, 73.4, 79.6, 124.3, 124.9, 125.1, 125.8, 126.0, 126.2, 127.6, 128.1, 128.2, 128.3, 128.5, 129.3, 132.9, 133.2, 135.5, 138.4, 139.0, 149.6, 175.7. IR (CCl_4): 3496, 2983, 1741, 1697, 1220, 736 cm^{-1}. HRMS calcd for $C_{33}H_{34}N_2O_4$: 522.2519. Found: 522.2514. HPLC: 10 μ silica, 4.6 mm×25 cm, EtOAc/hexanes 35:65, R_T= 10.25 min, crude ratio>20:1.

4.2.4. (5*S*,6*R*)-[(2*S*,3*S*)-3-(2-Benzyl-3-hydroxy-4,4-dimethylpentanoyl)]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (5d). The crude product was purified by silica gel column chromatography with EtOAc/hexanes 2:3 to yield 0.622 g of **5d** (91%) as a brown oil: $[\alpha]_D^{25}$ −9.80 (*c* 0.320, $CHCl_3$); R_f=0.37 (EtOAc/hexanes 2:3). ^{1}H NMR ($CDCl_3$): −0.22 (C_5-methyl, d, J= 7.0 Hz, 3H), 1.10 (d, J=6.2 Hz, 3H), 1.17 (s, 9H), 1.29 (d, J=6.2 Hz, 3H), 2.93 (s, 1H), 3.07 (dd, J=13.9, 11.7 Hz, 1H), 3.14 (dd, J=13.9, 4.8 Hz, 1H), 3.30 (septet, J=6.2 Hz, 1H), 3.50 (C_5 methine, dq, J=7.0, 5.5 Hz, 1H), 3.67 (s, 1H), 4.93 (dd, J=11.7, 4.8 Hz, 1H), 5.77 (d, J=5.5 Hz, 1H), 7.00–7.06 (m, 5H), 7.16–7.36 (m, 5H). Diastereomeric excess (400 MHz ^{1}H NMR): crude ratio=19:1. ^{13}C NMR ($CDCl_3$): 11.9, 20.3, 20.7, 27.5, 32.7, 36.2, 48.5, 50.7, 53.8, 78.2, 79.5, 124.8, 126.4, 128.1, 128.4, 128.5, 129.5, 135.6, 139.3, 149.0, 177.8. IR (neat): 3525, 2977, 1733, 1232, 730 cm^{-1}. HRMS calcd for $C_{27}H_{36}N_2O_4$ (M^++1): 453.2675. Found: 453.2751.

4.2.5. (5*S*,6*R*)-[(2*S*,3*S*)-3-(2-Benzyl-4-benzyloxy-3-hydroxybutanoyl)]-4-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazinan-2-one (5e). The crude product was purified by silica gel column chromatography with EtOAc/hexanes 1:1 to yield 0.689 g of **5e** (51%) as a brown oil: $[\alpha]_D^{25}$ −17.2 (*c* 0.312, $CHCl_3$); R_f=0.35 (EtOAc/hexanes 1:1). ^{1}H NMR ($CDCl_3$): −0.09 (C_5-methyl, d, J=7.0 Hz, 3H), 1.09 (d, J= 6.2 Hz, 3H), 1.29 (d, J=6.2 Hz, 3H), 2.96 (dd, J=13.6, 4.4 Hz, 1H), 3.08 (dd, J=13.6, 11.0 Hz, 1H), 3.27 (septet, J=6.2 Hz, 1H), 3.54 (C_5 methine, dq, J=7.0, 5.1 Hz, 1H), 3.66 (dd, J=9.9, 7.7 Hz, 1H), 3.72 (dd, J=9.9, 4.0 Hz, 1H), 4.33–4.37 (m, 1H), 4.50 (dt, J=11.0, 4.4 Hz, 1H), 4.57 (d, J=12.2 Hz, 1H), 4.65 (d, J=12.2 Hz, 1H), 5.80 (d, J= 5.1 Hz, 1H), 7.04–7.39 (m, 15H). The alcoholic proton was not observed. ^{13}C NMR ($CDCl_3$): 12.0, 20.3, 20.7, 33.6, 50.1, 50.8, 53.8, 71.4, 71.9, 73.3, 79.4, 124.8, 126.3, 127.7, 127.8, 128.1, 128.3, 128.4, 128.5, 129.4, 135.5, 137.9, 139.1, 149.7, 174.6. IR (neat): 3458, 2982, 1728, 1240, 733 cm^{-1}. HRMS calcd for $C_{31}H_{36}N_2O_5$: 516.2624. Found: 516.2637. HPLC: 10 μ silica, 4.6 mm×25 cm, EtOAc/hexanes 35:65, R_T=11.50 min, crude ratio=99:1.

4.2.6. 2-d_6-Isopropylamino-1-phenylpropan-1-ol (7). In a 2 L round-bottom flask was placed (1*R*,2*S*)-norephedrine (25.0 g, 165 mmol) and dissolved in Ethanol (400 mL). Acetone-d_6 (21.0 mL, 258 mmol) and $MgSO_4$ (8.5 g) were added to the solution and the reaction mixture was allowed to stir overnight. After stirring overnight, the reaction flask was placed into an ice bath and $NaBH_4$ (15.65 g, 412.5 mmol) was added over the course of 15 min. The reaction was diluted with 6 M NaOH (100 mL) and stirred for 15 min. After this time, the EtOH was evaporated and the product extracted with EtOAc, $NaHCO_3$, and brine, then dried with $MgSO_4$. EtOAc was removed by rotary evaporation and the purified product was isolated via crystallization (hexanes/EtOAc 2:1), affording 20.49 g of a white solid in 63% yield. ^{1}H NMR ($CDCl_3$): δ 0.80 (d, J= 6.6 Hz, 3H), 2.94 (br s,1H), 3.04 (dq, J=6.6, 4.0 Hz, 1H), 4.69 (d, J=4.0 Hz, 1H), 7.24–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): (15.2, 22.7, 22.9, 23.0 (–CD_3), 45.3, 45.4, 45.4, 55.1, 73.4, 126.1, 126.9, 128.0, 141.4. IR ($CHCl_3$): 3500, 703 cm^{-1}. HRMS (FAB): Anal. Calcd for $C_{12}H_{13}D_6NO$: 200.1921. Found: 200.1920.

4.2.7. 2-d_6-Isopropylamino-*N*-nitroso-1-phenylpropan-1-ol (8). In a 1 L round-bottom flask was placed deuterated amino alcohol **7** (20.5 g, 103 mmol). To this solution was added 45 mL of HCl (2.74 M, 123 mmol) and THF (50 mL) was then added, followed by $NaNO_2$ (8.15 g, 118 mmol). The solution was stirred overnight. The THF was removed by rotary evaporation and the reaction mixture was extracted with EtOAc and brine then dried with $MgSO_4$. The EtOAc was removed by rotary evaporation and the product was isolated via crystallization (hexanes/EtOAc 2:1) to afford 13.75 g of a yellow solid in 59% yield. ^{1}H NMR ($CDCl_3$): δ 1.55 (d, J=6.6 Hz, 3H), 3.19 (br s, 1H), 4.06 (dq, J=6.6, 5.5 Hz, 1H), 4.38 (s, 1H), 5.15 (d, J= 5.5 Hz, 1H), 7.26–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, mixture of diastereomers): 10.3, 17.4, 21.9 (–CD_3), 44.6, 54.4, 59.2, 60.2, 74.2, 76.8, 126.1, 126.7, 128.1, 128.2, 128.58, 128.63, 141.6, 142.0. IR: 3345, 1219, 757, 702 cm^{-1}. HRMS (FAB): Anal. Calcd for $C_{12}H_{12}D_6N_2O_2$: 229.1823. Found: 229.1827.

4.2.8. 3,4,5,6-Tetrahydro-4-d_6-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one (10). In a flame-dried, nitrogen-purged, 3 L round-bottom flask fitted with a Claisen adapter fitted with a condenser and an addition funnel was placed lithium aluminum hydride (4.50 g, 121 mmol) and THF (1 L). This stirred mixture was brought to reflux and *N*-nitrosamine **8**, (13.8 g, 60.3 mmol) dissolved in THF (250 mL), was added to the flask dropwise via the addition funnel. After the last drop, the reaction stirred and allowed to reflux for 2 h, and at the end of this time cooled with an ice bath. NaOH (3 M, 200 mL) was added dropwise to quench the reaction. The reaction mixture was extracted with EtOAc, Rochelle's salt, and brine, then dried with $MgSO_4$. The EtOAc was evaporated

to afford hydrazine **9**, which immediately underwent cyclization without characterization.

To a nitrogen-purged 1 L round-bottom flask fitted with a condenser was placed the hydrazine and dissolved in hexanes (120 mL) and stirred. To this solution was added diethyl carbonate (5.4 mL, 45 mmol) and heated to a gentle reflux. At this time, LiH (0.210 g, 25.2 mmol) was added and the solution stirred overnight. The reaction was cooled to room temperature and quenched with saturated NH_4Cl and the THF evaporated. The contents of the flask were extracted with EtOAc and brine then dried with $MgSO_4$. The solvent was evaporated, yielding a white solid. The purified product (3.44 g) was isolated via crystallization (hexanes/EtOAc 2:1) in 24% yield. ^{1}H NMR ($CDCl_3$): δ 0.92 (d, $J=7.0$ Hz, 3H), 3.21 (br s, 1H), 3.50 (dq, $J=7.0$, 3.3 Hz, 1H), 5.69 (br s,1H), 6.73 (br s, 1H), 7.26–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.2 (CH_3), 19.9 ($2\times CD_3$), 52.2, 55.4, 55.5, 55.5, 75.8, 125.3, 127.9, 128.6, 137.0, 152.1. IR (nujol): 3230, 1693, 1049, 745, 702 cm^{-1}. HRMS (ESI): Anal. Calcd for $C_{13}H_{12}D_6N_2O_2$: 241.1823. Found: 241.1819.

4.2.9. 3-Hydrocinnamoyl-4-d_6-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one (11). In a flame-dried, nitrogen-purged 1 L round-bottom flask fitted with a condenser was placed **10** (3.44 g, 14.3 mmol) and CH_2Cl_2 (15 mL). To this stirred solution was added hydrocinnamoyl chloride (3.0 mL, 18 mmol) and the solution was refluxed. While refluxing, LiH (0.16 g, 22 mmol) was added and the solution stirred overnight. The contents of the flask were extracted with CH_2Cl_2 and washed with NH_4Cl and brine, then dried with $MgSO_4$. The solvent was evaporated yielding an oil, which upon standing turned into a solid. The solid was purified via column chromatography (hexanes/EtOAc 65:35) affording 4.91 g an off-white solid in 92% yield. ^{1}H NMR ($CDCl_3$): δ 0.67 (d, $J=7.0$ Hz, 3H), 2.95–3.07 (m, 1H), 3.16–3.35 (m, 2H), 3.71–3.77 (m, 1H), 5.93 (d, $J=5.1$ Hz, 1H), 7.14–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$): (12.9 (CH_3), 20.3 ($2\times CD_3$), 31.0, 39.0, 51.5, 53.6, 78.9, 124.8, 126.1, 128.1 128.4, 128.6, 128.7, 136.1, 140.8, 148.9, 173.9. IR ($CHCl_3$): 1715, 1049, 703, 754 cm^1. HRMS (ESI): Anal. Calcd for $C_{22}H_{20}D_6N_2O_3$: 373.2398. Found: 373.2402.

4.2.10. 3-[2-Benzyl-3-(4-chlorophenyl)-3-hydroxypropionyl]-4-d_6-isopropyl-5-methyl-6-phenyl-2*H*-1,3,4-oxadiazin-2-one (12). To a flame-dried, nitrogen-purged, 100 mL round-bottom flask was added **11** (1.0 g, 2.7 mmol) and THF (10 mL). $TiCl_4$ (0.56 mL, 5.7 mmol) was added to this stirred solution and allowed to sit at room temperature for 25 min. After this time, the solution was cooled to −78 °C and after 5 min triethylamine (0.43 mL, 3.1 mmol) was introduced to the flask via syringe. Over the course of 45 min the solution was allowed to warm up while the enolate formed. After the 45 min had elapsed, the solution was chilled to −78 °C again and after 5 min, 4-chlorobenzaldehyde (0.57 g, 4.1 mmol) was added to the flask. The bath was removed and the reaction stirred overnight. The reaction mixture was extracted with $CHCl_3$ and washed with NH_4Cl and brine, then dried with $MgSO_4$. The solvent was removed by rotary evaporation and the crude product was purified via column chromatography (hexanes/EtOAc 70:30). A light-yellow oil (1.34 g) was isolated as the purified product in 97% yield. Diastereomeric excess ^{1}H NMR ($CDCl_3$): crude ratio $\geq$19:1 ($CDCl_3$): δ −0.15 (d, $J=7.0$ Hz, 3H), 2.61 (dd, $J=13.4$, 10.2 Hz, 1H), 3.00 (dd, $J=13.4$, 12.1 Hz, 1H), 3.19 (s, 1H), 3.29 (s, 1H), 4.61 (dt, $J=12.1$, 3.5 Hz, 1H), 5.34 (br s, 1H), 5.83 (d, $J=5.1$ Hz, 1H), 7.00–7.05 (m, 5H), 7.10–7.14 (m, 2H), 7.30–7.39 (m, 5H), 7.57 (d, $J=8.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 12.1 (CH_3), 19.9 ($2\times CD_3$), 31.9, 50.9, 53.5, 54.1, 72.9, 79.7, 124.8, 126.4, 127.7, 128.2, 128.3, 128.4, 128.6, 129.3, 133.3, 135.5, 138.9, 139.5, 149.8, 175.4. IR ($CHCl_3$): 3438, 1729, 1239, 736, 700 cm^{-1}. HRMS (FAB): Anal. Calcd for $C_{29}H_{25}D_6N_2O_4Cl$: 512.2349. Found: 512.2351.

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References and notes

1. Burgeson, J. R.; Renner, M.; Hardt, I.; Ferrence, G. M.; Standard, J. M.; Hitchcock, S. R. *J. Org. Chem.* **2004**, *69*, 727–734.
2. Casper, D. M.; Blackburn, J. R.; Maroules, C. D.; Brady, T.; Esken, J. M.; Ferrence, G. M.; Standard, J. M.; Hitchcock, S. R. *J. Org. Chem.* **2002**, *67*, 8871–8876.
3. Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrence, G. M.; Szczepura, L. F.; Standard, J. M. *Tetrahedron* **2001**, *57*, 9789–9798.
4. Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M.; Esken, J. M. *J. Org. Chem.* **2004**, *69*, 714–718.
5. Caution. It should be noted that many *N*-nitrosamines are potentially carcinogenic and should be handled with great care. For more information on *N*-nitrosamines, please see: Lawley, P. D. In *Chemical Carcinogens*; Searle, C. D., Ed.; ACS monograph 182; American Chemical Society: Washington, DC, 1984.
6. *Spartan 02*; Wavefunction, Inc.: 18401 Von Karman Avenue, Suite 370, Irvine, CA, USA, 2002.
7. *PQS version 3.1*; Parallel Quantum Solutions: 2013 Green Acres, Suite A, Fayetteville, AR, USA, 2003.

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Photophysical and electrochemical properties of π-extended molecular 2,1,3-benzothiadiazoles

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Abstract—The reaction of 4,7-dibromo-2,1,3-benzothiadiazole with arylboronic acids (phenyl, 1-naphthyl, 4-methoxyphenyl, 4-chlorophenyl and 4-trifluoromethylphenyl) in the presence of catalytic amounts of a NCP-pincer palladacycle affords photoluminescent π-extended 4,7-diaryl-2,1,3-benzothiadiazoles **4a–e** in high yields. These 4,7-diaryl-2,1,3-benzothiadiazoles exhibit high fluorescent quantum yields, high electron affinities and adequate band gap values for testing as OLEDs. The 4,7-bis-naphthyl-2,1,3-benzothiadiazole **4b** presents two different lifetimes (bi-exponential decay) due to the presence of two atropisomers. The Sonogashira coupling reaction of 4,7-diethynyl-2,1,3-benzothiadiazole **6** with the corresponding halo-aryl compounds (iodobenzene, 1-bromonaphthalene, 4-iodoanisole, 4-bromo-*N*,*N*-dimethylaniline and 2-bromopyridine) afforded the photoluminescent π-extended 4,7-bis-alkynylaryl-2,1,3-benzothiadiazoles **7a–e**, also in high yields. These 4,7-diethynyl-2,1,3-benzothiadiazoles also present high fluorescent quantum yields, high electron affinities and adequate band gap values for testing as OLEDs. The 4,7-disubstituted-2,1,3-benzothiadiazoles **4a–e** and **7a–e** exhibit different electrochemical behavior. The presence of two ethynyl spacers in 2,1,3-benzothiadiazoles **7a–e** shifts the reduction potentials to less cathodic values and also results in two well-defined and distinct reduction processes.

1. Introduction

Fluorescent compounds have found widespread use in scientific and technological areas, especially as organic light-emitting diodes (OLEDs).[1] Due to their potential as constituents of OLEDs, much attention has been focused on π-conjugated molecules, their luminescent properties and their electronic and optoelectronic functions.[2] Only a few types of molecular building blocks have been exploited in the organic electronic area,[3a] such as quinoxalines,[3b] benzimidazoles[3c] and certain polymers.[3d] Among these building blocks, benzothiadiazoles are one of the most important classes due to their relatively high reduction potential and electron affinity, necessary for utilization in light-emitting diode (LED) technology. Indeed, the HOMO/LUMO levels of π-extended conjugated molecules are defined by their electron affinity (EA) and ionization potential (IP), which are correlated with electrochemical reduction and oxidation potentials. 2,1,3-Benzothiadiazole derivatives have several desirable characteristics: (a) benzothiadiazole-containing compounds can afford well-ordered crystal structures; and (b) benzothiadiazole derivatives normally are efficient fluorophores.[4] Highly fluorescent π-conjugated molecules are also of interest in other applications such as electroluminescent (EL) devices.[5] Surprisingly, the synthesis of benzothiadiazole derivatives and investigations of their photoluminescent properties are relatively limited. In fact, most of these studies have been centered on the preparation of 4,7-diphenyl-2,1,3-benzothiadiazole, 4,7-bis(4-methoxy-phenyl)-2,1,3-benzothiadiazole and 4,7-bis[(2-pyridyl)-ethynyl]-2,1,3-benzothiadiazole derivatives, which were obtained in moderate yields.[6] Moreover, only a few photophysical and electrochemical properties have been reported so far. In view of the very promising photoluminescent properties of these π-conjugated molecules, it is of a great interest to have a simple synthetic methodology for their preparation.

We report here that palladium promoted C–C coupling reactions of the Suzuki and Sonogashira type are effective methods for the construction of a new class of more highly luminescent π-extended 4,7-disubstituted-2,1,3-benzothiadiazoles. We also present the electrochemical and photoluminescent properties of ten such compounds, which indicate that they are indeed potential candidates for OLED devices.

Keywords: Sonogashira coupling; Spectrometry; OLED; Photoluminecent; Benzothiadiazoles.
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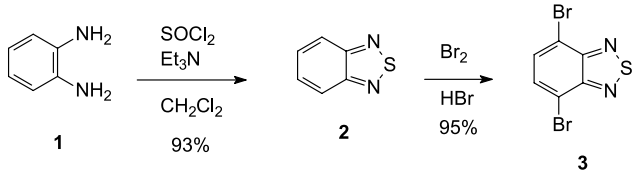
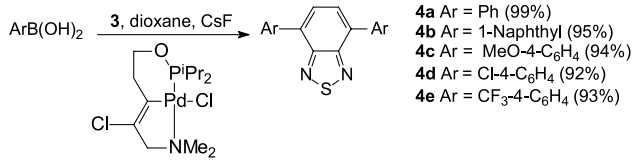
2. Results and discussion

Commercially available *o*-phenylenediamine, **1**, was treated with freshly distilled thionyl chloride in the presence of triethylamine in CH_2Cl_2 as solvent, affording 2,1,3-benzothiadiazole, **2**, in 93% yield after steam distillation.[7] Upon reaction with molecular bromine (added drop-wise very slowly) in hydrobromic acid, compound **2** gives exclusively the 4,7-disubstituted regioisomer **3** in 95% yield (Scheme 1).[8]



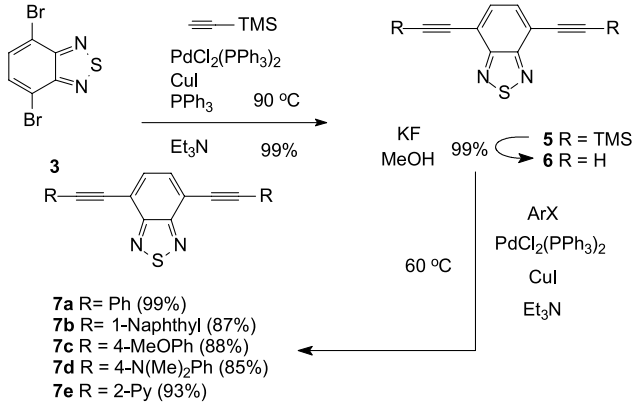
Scheme 1. Synthesis of benzothiadiazole **3**.

The Suzuki coupling reaction of compound **3** with phenyl or 1-naphthyl boronic acid, catalyzed by the NCP pincer palladacycle,[9] produced the desired bis-coupled π-extended 4,7-diarylsubstituted 2,1,3-benzothiadiazoles **4a–e** in excellent yields after column chromatographic purification (Scheme 2). Although compounds **4a** and **4c** have previously been prepared by using the classical Suzuki Pd coupling catalyst,[10] the yields were only 48%. With our methodology, these compounds are obtained in much higher yields (94–99% yield).



Scheme 2. Synthesis of π-extend benzothiadiazoles **4a–e**.

The Sonogashira cross-coupling reaction of **3** with trimethylsilylacetylene in the presence of $PdCl_2(PPh_3)_2$, CuI, and PPh_3 in NEt_3 at 90 °C produced the bis-coupling product **5**.[11] The de-protection of **5** with KF afforded **6** in quantitative yield after column chromatographic purification. A second Sonogashira cross-coupling reaction was conducted in the presence of $PdCl_2(PPh_3)_2$ and CuI, in NEt_3 at 60 °C with iodobenzene, 1-bromonaphthalene, 4-bromoanisole, 4-bromo-*N*,*N*-dimethylaniline or 2-bromopyridine, affording the desired products **7a–e**, respectively, in excellent yields after column purification (Scheme 3).[12] Although **7e** is a known compound,[6] the reported synthesis via a single Sonogashira coupling step had only a 47% yield and the electrochemical properties of the compound were not reported. Our methodology improves the yield to 93% in the final Sonogashira coupling, with a global yield of 87% for the synthesis.



Scheme 3. Synthesis of π-extend benzothiadiazoles **7a–e**.

All new compounds were fully characterized by FTIR, ^1H NMR and ^{13}C NMR, and high-resolution mass spectrometry (HRMS) and the data are in full accord with the proposed structures. Differential scanning calorimetry (DSC) was used to determine the thermal properties of compounds **4a–e** and **7a–e** (melting or decomposition temperatures). Table 1 summarizes the results of UV–vis (recorded in acetonitrile solution), fluorescence and electrochemical analyses (by cyclic voltammetry)[13] of the synthesized photoluminescent compounds **4a–e** and **7a–e** and some other known compounds (Scheme 4).

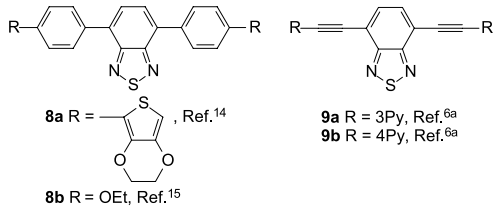
For all compounds, for which both the optical (E_{gap}^{op}) and electrochemical (E_{gap}^{el}) band gaps could be calculated,[17] there is excellent agreement between the two values. Moreover, the values are in the appropriate range (between 1.5 and 5.5 eV) for application in OLED devices.[18] For example, copolymers with the benzothiadiazole unit has a band gap values in the range of 2.03–8.61 eV[2c] and zinc complex with the 2,1,3-benzothiadiazole moiety has a band gap of 1.88 eV.[19] Many other examples with values in this range can be found in the literature.[20] The electron affinity (EA) and ionization potential (IP) have been determined using a known method ($EA = E_{red}^{onset} + 4.4$ eV and $IP = E_{oxi}^{onset} + 4.4$ eV).[3a] Molecules **4a–c** and **7a–e** also have high values of EA (2.72–3.72 eV). This is fundamental in order to allow electron injection from stable metal cathodes.[21] Comparison of **4a** and **7a** and of **4b** and **7b** indicates that the insertion of a triple bond does not significantly affect the band gap energies in molecules without electron donor or electron withdrawing groups, although the EA and IP diminish by about 0.5 eV upon extending the conjugation. A similar behavior is observed when a MeO group is inserted into molecules **4c** and **7c**. The insertion of a $N(Me)_2$ group in molecule **7d** indicates that the presence of an electron donating group does not significantly affect the electrochemical behavior of the compounds. With an electron withdrawing group, as in molecule **7e** (2-pyridyl, in this case), the reduction process begins at less cathodic values (−0.68 V) compared to molecules **7c** and **7d** (OMe and $N(Me)_2$ groups), which begin at −0.95 and −1.37 V, respectively. This fact indicates that electron withdrawing groups facilitate the reduction process. The presence of the triple bonds (compare compounds **4** and **7**) affects the electrochemical charge transfer processes by shifting the electrochemical window to more cathodic values.

Compounds **4a**, **4b**, **4c**, and **7a** exhibit oxidation and reduction peaks (Fig. 1), which suggests the possibility of both hole and electron transport, leading to a single-layer electroluminescent device.[22] This fact is very important since it would not be necessary to employ different

Table 1. UV–vis, fluorescence and some electrochemical data for compounds **4a–e**, **7a–e**, **8a–b**, and **9a–b**[a]

Compound	E_{red}^{onset} (V)[b]	EA[c] (eV)	E_{oxi}^{onset} (V)[d]	IP[e] (eV)	E_{gap}^{el} (eV)[f]	Log ε	λ_{abs}^{max} (nm)	λ_{em}^{max} (nm)	Stoke's shift (nm)	Φ_f[g]	τ_f (Singlet) (ns)[h]	τ_T (Triplet) (μs)[i]	E_{gap}^{op} (eV)[j]
4a	−1.05	3.35	1.65	6.05	2.70	4.04	402, (380)[k], (379)[l]	487, (490)[k], (490)[l]	85	0.80, (0.80)[k], (0.74)[l]	12.2	—	2.73
4b	−1.18	3.22	1.44	5.84	2.62	4.08	360	517	157	0.17	4.96 and 2.38[m]	14.4	2.68
4c	−1.23	3.17	1.32	5.72	2.55	3.52	362	547	185	0.51	12.70	—	2.54
4d[k]	—	—	—	—	—	5.30	368	479	111	0.50	10.40	4.18	2.75
4e[k]	—	—	—	—	—	3.86	355	453	98	0.22	6.31	6.04	2.74
7a	−1.57	2.83	1.02	5.42	2.59	4.99	403	497	94	0.37	5.53	21.6	2.57
7b	−1.68	2.72	1.23	5.63	2.91	3.56	363	434	71	0.36	8.37	6.05	2.99
7c[n]	−0.95	3.45	1.47	5.87	2.42	4.40	393	542	149	0.29	6.42	20.01	2.37
7d	−1.37	3.03	1.61	6.01	2.98	4.11	407	438	31	0.15	8.18	23.02	2.93
7e	−0.68	3.72	1.93	6.33	2.61	4.40 (4.48)[o]	394 (393)[o]	469 (473)[o]	75	0.86 (0.87)[p]	4.52	29.50	2.60
8a[l]	na	na	na	na	na	na	481	630	149	0.75	na	na	na
8b[p]	na	na	na	na	na	4.07	410	546	136	0.75	na	na	na
9a[o]	na	na	na	na	na	4.45	396	479	83	0.80	na	na	na
9b[o]	na	na	na	na	na	4.43	388	464	76	0.87	na	na	na

[a] Electrochemical experiments in MeCN–CH_2Cl_2 (3/7 v/v) and potentials against ferrocene (Ref. 3a). Platinum was used as working electrode and as a counter electrode. All potentials were recorded versus Ag/AgCl (saturated) as a reference electrode.
[b] Onset cathode potential.
[c] Electron affinity.
[d] Onset anode potential.
[e] Ionization potential.
[f] Energy of the band gap (electrochemical).
[g] Quantum yield of fluorescence (quinine sulfate (Riedel) in 1 M H_2SO_4, Φ_f=0.55, as standard).
[h] Singlet lifetime, by single photon counting.
[i] Triplet lifetime, by nanosecond laser flash photolysis.
[j] Energy of the band gap (optical).
[k] The molecule did not form a film to be analyzed by thin film CV (only in solution).
[l] Ref. 14.
[m] Biexponential decay (two lifetimes).
[n] The monomer properties have not been described (Ref. 16). na, not available.
[o] Ref. 6a.
[p] Ref. 15.



Scheme 4. Other known benzothiadiazole systems.

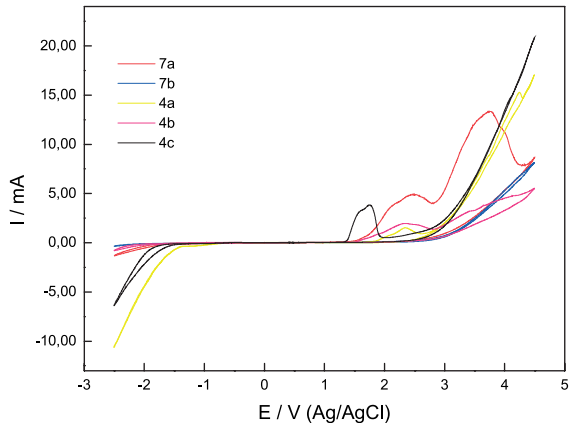


Figure 1. CV (thin film coated onto a Pt wire electrode) of compounds **4a–c** and **7a–b** recorded at scan rate = 40 mV/s in MeCN–CH_2Cl_2 (3/7 v/v).

molecules in the electron-transporting and hole-transporting layers of organic light emitting devices. Compound **7b** did not show current peaks associated with oxidation/reduction processes. In contrast, molecules **7c–d** (voltammograms not shown) do not show well-defined oxidation peaks. Compounds **4a–b** and **7a** exhibit two oxidation peaks involving multiple deelectronation processes. All molecules, however, show well-defined reduction peaks and, in some cases, two well-defined peaks (**4a** and **7b**). Due to the impossibility of forming films of molecules **4d** and **4e**, they could not be analyzed as a thin film coated onto a Pt wire electrode, only in solution.

Compounds **7a–e** exhibit different electrochemical behavior from that of compounds **4a–e**, by comparing both series dissolved in solution. The former exhibit two well-defined sets of reduction peaks (from −1.0 to −1.3 V and from −1.7 to −1.9 V). This suggests the occurrence of two different processes when the species are reduced. Most

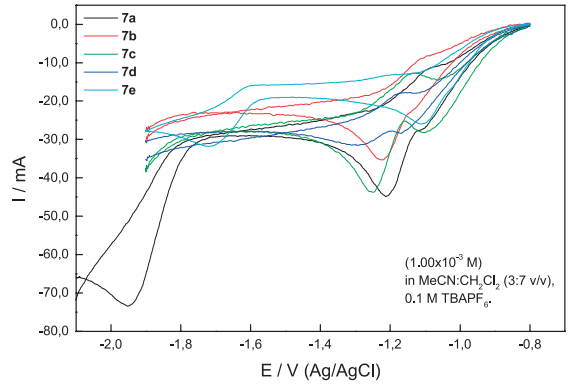


Figure 2. CV of compounds **7a–e** (1.00 mmol L^{-1}) dissolved in MeCN–CH_2Cl_2 (3/7 v/v) recorded at scan rate = 200 mV/s.

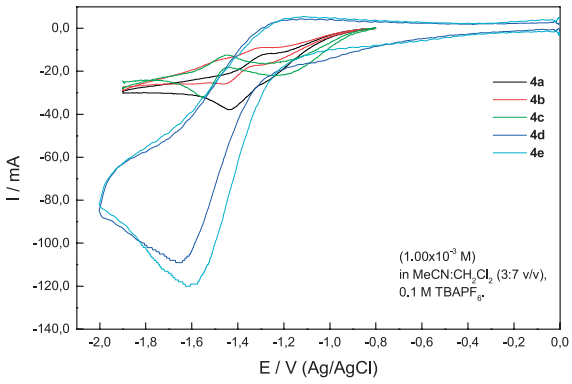


Figure 3. CV of compounds **4a–e** (1.00 mmol L^{-1}) dissolved in MeCN–CH_2Cl_2 (3/7 v/v) recorded at scan rate = 200 mV/s.

probably the first charge transfer process involves a quasi-reversible reduction of the benzothiadiazole ring (observed in both series), while the second is associated with reduction of the triple bond (Figs. 2 and 3). Apparently, the second charge transfer is an irreversible electrochemical process. As noted, both series exhibit the first process. This is indicated by the fact that the current versus potential curves have the same shape for all compounds (**4a–e** and **7a–e**, Table 2—see all individual CV curves in the Supporting information). Since compounds **4a–e** have no triple bond, the well-defined reduction process can only be attributed to reduction of the benzothiadiazole ring. A plausible mechanism for this process has been presented by Hirao et al.[23] An exception occurs in benzothiadiazole **4e**, which shows one defined irreversible reduction peaks, but in the same potential range.

Compounds **7a** and **7e** show two well-defined and very distinct reduction processes. The first one is similar to compounds **4a–e**, indicating that the benzothiadiazole ring is reduced in preference to the triple bond in those systems. The second process is the reduction of the triple bond, a process that cannot occur in molecules **4a–e**. Comparison of the reduction behavior of compounds **7a** and **7e** indicates that the second reduction process for **7a** occurs at much more cathodic values than that of **7e**. The origin of this difference is still not clear.

All compounds have rather good fluorescence quantum yields, especially **4a** ($\Phi_f = 0.80$) and **7e** ($\Phi_f = 0.86$), and show large Stoke's shifts (31–185 nm). The fluorescence quantum yield of benzothiadiazole **3** (without π-extended conjugation), which has not been reported before, is very low ($\Phi_f = 0.006$). The lowest energy absorption bands (in acetonitrile) are assigned to π–π* transitions by virtue of their large molar extinction coefficients (log ε values in the range of 3.52–5.30). The absorption (λ_{abs}^{max}) and emission (λ_{em}^{max}) maxima lie between 355–407 nm and 434–547 nm, respectively (Figs. 4 and 5). Molecules **4c** and **7c** (with a MeO group) have large Stoke's shifts, 185 and 149 nm, respectively. This indicates a very efficient intramolecular charge transfer (ICT) in the excited state between the terminal methoxy group and the benzothiadiazole nucleus.

Compound **4b** not only exhibits a large Stoke's shift (157 nm), but it is also the only compound whose

Table 2. Reduction and oxidation data of compounds **4a–e**, **7a–e**, **8a–b**, and **9a–b**

Compound	E^{o}_{red} (V) First process	E^{o}_{red} (V) Second process	E^{o}_{oxi} (V) First process	E^{o}_{oxi} (V) Second process	Reference
4a	−1.43 (−1.36)[a]	—[b]	1.48 (1.82)[a]	4.25 (−)[a]	This work and 14
4b	−1.45	—[b]	1.91	4.77	This work
4c	−1.55	—[b]	1.74	—	This work
4d	−1.66	—[b]	—[c]	—[c]	This work
4e	−1.62	—[b]	—[c]	—[c]	This work
7a	−1.21	−1.98	2.50	3.77	This work
7b	−1.13	—[b]	—[d]	—[d]	This work
7c	−1.10	—[b]	—[d]	—[d]	This work
7d	−1.16	—[b]	—[d]	—[d]	This work
7e	−1.11 (−1.18)[e]	−1.72 (−)[e]	3.54 (−)[e]	4.12 (−)[e]	This work and 6a
8a	−1.40	na	0.92	na	14
8b	na	na	na	na	15
9a	−1.08	na	na	na	6a
9b	−1.00	na	na	na	6a

[a] Ref. 14.
[b] The molecule has just one process.
[c] The molecule did not form a film to be analyzed by thin film CV (only in solution).
[d] The molecule did not show an oxidation peak, only E_{onset}.
[e] Ref. 6a. na, not available.

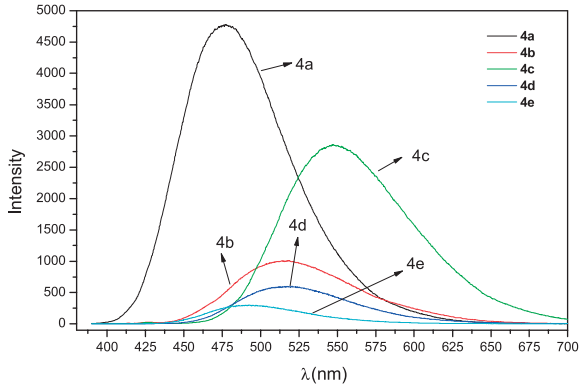


Figure 4. Fluorescence spectra of compounds **4a–e** in acetonitrile.

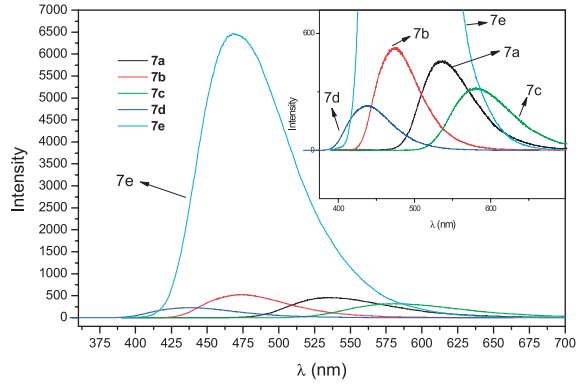


Figure 5. Fluorescence spectra of compounds **7a–e** in acetonitrile.

fluorescence decay exhibits two lifetimes (4.96 and 2.38 ns). Likewise, the ^{1}H and ^{13}C-{1*H*} NMR spectra of **4b** in DMSO-d_6 at room temperature (see Supporting information, also for fluorescence decay) show two sets of signals, indicating the presence of two isomers. The fact that these two sets of signals coalesce at 90–100 °C points to the existence at room temperature of two atropisomers in which the α-naphthyl groups are in *syn* or *anti* geometries (Fig. 6).

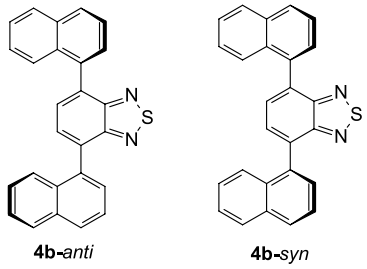


Figure 6. Compound **4b** atropisomers.

Although the presence of the triple bonds in compounds **7a–e** extends the π-conjugation compared to **4a–e**, this has only a secondary effect on the photophysical properties of the compounds, indicating that this structural change is not fundamental for the fluorescence process itself.

All compounds exhibit strong fluorescence and, with the exception of **4b**, a single fluorescence lifetime. Radiative decay rate constants ($=\Phi_f/\tau_f$) are in the range of 5×10^{7} s^{-1}, consistent with the observed range of log ε values for absorption, and are insensitive to the presence of the triple bond spacers. With the exception of molecules **4a** and **4c**, the remaining molecules show strong triplet–triplet absorption by laser flash photolysis (355 nm excitation, Nd-YAG laser) in the absence of oxygen, with triplet lifetimes in the range of 4–30 μs, indicating efficient intersystem crossing in these eight compounds. The strong triplet–triplet absorption and lack of noticeable laser-induced decomposition indicate high chemical stability also in the excited state. The only limitation would be the necessity of the absence oxygen, since the triplet states of all of the compounds are efficiently quenched by molecular oxygen (presumably via energy transfer to form singlet oxygen). The motives for the failure to observe triplet–triplet absorption with **4a** and **4c** are unclear and would require more detailed photophysical studies for clarification.

All of the compounds also present fluorescence in the solid state (Table 3).

Table 3. Excitation and emission maxima and Stoke's shifts for 2,1,3-benzothiadiazoles **4a–e** and **7a–e** in the solid state

Compound	λ_{abs}^{max} (nm)	λ_{em}^{max} (nm)	Stoke's shift (nm)
4a	426	493	67
4b	427	495	68
4c	418	526	108
4d	495	544	49
4e	430	501	71
7a	424	543	119
7b	422	500	78
7c	522	590	68
7d	442	514	72
7e	452	543	91

The absorption maxima are red-shifted in all cases and, with the exception of compounds **4b** and **4c**, so are the fluorescence emission maxima. The resultant Stoke's shifts in the solid state are smaller for compounds **4a–e** and **7c**, but larger for compounds **7a**,**b**,**d**,**e**.

3. Conclusion

In summary, the Suzuki and Sonogashira couplings of 4,7-dibromo-2,1,3-benzothiazole with arylboronic acids and alkynes represent simple and effective methods for π-extension to obtain 4,7-disubstituted-2,1,3-benzothiadiazoles. The 4,7-diaryl-2,1,3-benzothiadiazoles **4a–e** possess moderate to high fluorescence quantum yields (0.17–0.80) and high electron affinities (3.17–3.35 eV). The fluorescence of 4,7-binaphthyl-2,1,3-benzothiadiazole, **4b**, exhibits bi-exponential decay, attributed to the presence of two atropisomers. The band gap values of 4,7-biaryl-2,1,3-benzothiadiazoles **4a–e** are in the adequate range (2.54–2.75 eV) for testing as OLEDs. The presence of ethynyl spacers in the 2,1,3-benzothiadiazoles **7a–e** does not have a negative impact on the photo-electronic properties of those compounds and their fluorescent quantum yields are likewise high (0.15–0.86). These alkynyl benzothiazoles do, however, possess different electrochemical behavior due to the presence of the reducible triple bond. The electron affinities of 4,7-bis-ethynylaryl-2,1,3-benzothiadiazoles **7a–e** are also high (2.72–3.72 eV) and their band gap values in the appropriate range for testing as OLEDs (2.37–2.99 eV).

4. Experimental

4.1. General

All catalytic reactions were carried out under an argon or nitrogen atmosphere in oven-dried resealable Schlenk tubes. All substrates were purchased from Acros and used without further purification. The PCN palladacycle catalyst precursor was prepared according to the reported method.[9] All new compounds were fully characterized after purification. NMR spectra were recorded on a Varian Inova 300 MHz or Varian Gemini 200 MHz spectrometers. Infrared spectra were registered on a Bomem B-102 spectrometer. Melting points were measured on a 12000 PL-DSC apparatus at a heating rate of 5 °C/min or in a Electrothermal IA9000 Melting Point apparatus. The purity of compounds **4a–e** and **7a–e** was checked by CG analysis on a HP-5890A chromatograph fitted with a DB17 capillary column (25 m) with temperature programming from 100 °C up to 250 °C at a heating rate of 15 °C/min. The pressure at the column head was 10 psi. Cyclic voltammograms (CV) were recorded on an Autolab PGSTAT 30 Potentiostat. A thin layer of molecules **4** and **7** was coated from its solution in CH_2Cl_2, using similar procedure employed for diphenylanthrazolines.[3a] UV–vis absorption spectra were taken on a Cary 50 Varian spectrophotometer or a Shimadzu Model UV-1601PC. For fluorescence quantum yields (quinine sulfate (Riedel) in 1 M H_2SO_4, $\Phi_f=0.55$, as standard), a Shimadzu UV-1601PC spectrophotometer and a Hitachi Model F-4500 spectrofluorometer were employed. Fluorescence decays were collected by the time-correlated single photon counting technique with an Edinburgh Analytical Instruments FL900 lifetime Spectrometer (H_2 lamp excitation source). Lifetimes were determined from the decays by using the FL900 convolution and fitting routines for mono- and bi-exponential decay. Nanosecond laser flash photolysis experiments were performed at 20 °C on air-equilibrated solutions (MeCN) and on solutions deoxygenated by exhaustive purging with solvent-vapor-saturated argon in cuvettes capped with a rubber septum. The Edinburgh Analytical Instruments LP900 laser flash photolysis system is equipped with a 450W Xe high pressure monitoring lamp and excitation was carried out with the third harmonic (355 nm) of a Surelite II-10 Nd-YAG laser. Solutions (MeCN) were stirred between each laser shot and 10 laser shots averaged to obtain the transient absorption decays. Solutions were monitored for laser-induced decomposition by conventional UV–vis absorption spectroscopy (Hewlett-Packard 8452A diode array spectrometer) and replaced by fresh solution at the first signs of decomposition. The standard exponential decay routines of the LP900 system software were used to analyze the decays of the transient and obtain the lifetimes of the excited species.

4.1.1. General procedure for the synthesis of benzothiadiazole 2. To a 1000 mL flask were added commercial *o*-phenylenediamine **1** (10.00 g, 92.47 mmol), 300 mL of CH_2Cl_2 and triethylamine (37.44 g, 369.98 mmol). The solution was stirred until total dissolution of the diamine **1**. Thionyl chloride was added dropwise very slowly and the mixture refluxed for 4 h. The solvent was removed in a rotatory evaporator and 700 mL of water added. Concentrated HCl was added to a final pH of 2. The desired compound was purified by direct steam distillation following addition of water to the mixture. The steam distilled mixture was extracted three times with 200 mL of CH_2Cl_2, dried over $MgSO_4$ and filtered. The solvent was removed, affording pure compound **2** in 93% yield (11.71 g, 85.99 mmol).

^{1}H NMR ($CDCl_3$): δ ppm 7.99 (dd, 2H, $J=3.3$, 4.6 Hz); 7.57 (dd, 2H, $J=3.1$, 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ ppm 154.6; 129.1; 122.4. FTIR (KBr, cm^{-1}): 1659, 1433, 1264, 1104, 747. Mp 43.6–44.4. Lit.[7a,b] 44 °C.

4.1.2. General procedure for the synthesis of 4,7-dibromobenzothiadiazole 3. To a 500 mL two-necked round bottom flask were added benzothiadiazole **2** (10.00 g,

73.44 mmol) and 150 mL of HBr (47%). A solution containing Br_2 (35.21 g, 220.32 mmol) in 100 mL of HBr was added dropwise very slowly (slow addition is essential!). If necessary, an additional 100 mL of HBr can be added to the solution. After total addition of the Br_2, the solution was refluxed for 6 h. Precipitation of an orange solid was noted. The mixture was allowed to cool to room temperature and sufficient saturated solution of $NaHSO_3$ added to consume completely any excess Br_2. The mixture was filtered under vacuum and washed exhaustively with water. The solid was then washed once with cold Et_2O and dried under vacuum for ca. 20 h, affording the desired dibrominated product **3** in 95% yield (20.51 g, 69.77 mmol).

^{1}H NMR ($CDCl_3$/DMSO-d_6—two drops): δ ppm 7.73 (s, 2H). ^{13}C NMR ($CDCl_3$/DMSO-d_6—two drops): δ ppm 152.6; 132.1; 113.6. Mp 187–188 °C. Lit.[8] 188–189 °C.

4.2. General procedure for the Suzuki coupling reactions

An oven-dried resealable Schlenk tube was evacuated and back-filled with Ar and charged with CsF (568 mg, 3.74 mmol), arylboronic acid (3.74 mmol) and the NCP pincer palladacycle (1 mol%).[9] Compound **3** (500 mg, 1.70 mmol) was added in 1,4-dioxane (5 mL). The reaction mixture was stirred at 130 °C for 18 h. The solution was then allowed to cool to room temperature and the solvent evaporated under reduced pressure. The crude material was chromatographed directly on silica gel with Et_2O.

4.2.1. Benzothiadiazole 4a. ^{1}H NMR ($CDCl_3$): δ ppm 8.23 (d, 2H, J=6.4 Hz), 7.97–7.24 (m, 10H). ^{13}C NMR ($CDCl_3$): δ ppm 137.3, 136.5, 133.9, 133.2, 113.8, 113.0. FTIR (KBr, cm^{-1}): 1586, 1463, 1424, 1333. Mp 84 °C HRMS calcd for $C_{18}H_{12}N_2S$ 288.07212, found 288.07212.

4.2.2. Benzothiadiazole 4b. ^{1}H NMR ($CDCl_3$): δ ppm 8.02–7.25 (m, 16H). ^{1}H NMR (DMSO-d_6, 20 °C): δ ppm 8.42–8.33 (m, 2H), 8.22–8.02 (m, 2H), 7.94–7.81 (m, 4H), 7.77–7.58 (m, 3H), 7.52–7.41 (m, 5H). ^{1}H NMR (DMSO-d_6, 100 °C): δ ppm 8.21–8.10 (m, 2H), 7.98–7.86 (m, 2H), 7.63–7.42 (m, 5H), 7.40–7.28 (m, 4H). ^{13}C NMR (DMSO-d_6): δ ppm 153.8, 152.7, 135.5, 134.5, 133.2, 132.9, 132.3, 131.9, 130.9, 130.6, 129.1, 128.7, 128.3, 128.2, 128.1, 127.9, 127.7, 127.4, 126.4, 126.0, 125.9, 125.7, 125.5, 125.4, 125.3, 124.9. FTIR (KBr, cm^{-1}): 3037, 1589, 1506, 1483, 1396, 1325, 1265. Mp 184 °C. HRMS calcd for $C_{26}H_{16}N_2S$ 388.10342, found 388.10445.

4.2.3. Benzothiadiazole 4c. ^{1}H NMR ($CDCl_3$): δ ppm 3.89 (s, 6H), 7.08 (d, 4H, J=8.4 Hz), 7.70 (s, 2H), 7.32 (d, 4H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$): δ ppm 159.6, 154.1, 132.2, 130.3, 129.9, 127.4, 114.0, 55.4. FTIR (KBr, cm^{-1}): 3029, 2954, 1604, 1519, 1284. Mp 207 °C. HRMS calcd for $C_{20}H_{16}N_2O_2S$ 348.09325, found 348.09323.

4.2.4. Benzothiadiazole 4d. ^{1}H NMR (DMSO-d_6): δ ppm 8.20–7.70 (m, 6H) 7.69–47 (m, 4H). ^{13}C NMR (DMSO-d_6): δ ppm 153.1, 152.3, 133.5, 132.6, 130.9, 128.7, 112.8. FTIR (KBr, cm^{-1}): 3045, 1529, 1469, 1094. Mp 170 °C. HRMS calcd for $C_{18}H_{10}Cl_2N_2S$ 355.994176, found 355.99416.

4.2.5. Benzothiadiazole 4e. ^{1}H NMR ($CDCl_3$): δ ppm 8.14–7.58 (m, 10H). ^{13}C NMR ($CDCl_3$): δ ppm 153.8, 153.7, 152.9, 152.8, 129.5, 129.4, 128.7, 128.4, 125.6, 125.59, 113.8. FTIR (KBr, cm^{-1}): 2924, 1669, 1334, 1169. Mp 103 °C. HRMS calcd for $C_{20}H_{10}F_6N_2S$ 424.046890, found 424.04688.

4.3. General procedure for the Sonogashira coupling reactions

A mixture of **3** (1.593 g, 5.42 mmol), trimethylsilylacetylene (1.410 g, 14.35 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg), cuprous iodide (20 mg), and triphenylphosphine (70 mg) was suspended in triethylamine (20 mL), and the resulting suspension was stirred and heated at 90 °C for 4 h. The solvent was evaporated and the crude product chromatographed directly with diethyl ether, affording a yellow solid. The isolated product **5** (air unstable) was dissolved in methanol (25 mL), treated with potassium fluoride (1.260 g, 21.68 mmol) and stirred at room temperature overnight. The solvent was evaporated and the crude product chromatographed directly with ether, affording a yellow solid. Compound **6** (very unstable) was immediately submitted to a second Sonogashira reaction. A mixture of **6** (0.998 g, 5.42 mmol), the corresponding halogenated compound (11.38 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg), and cuprous iodide (20 mg) was suspended in triethylamine (20 mL), and the resulting suspension was stirred and heated at 60 °C for 18 h. The solvent was then evaporated and the crude product chromatographed directly with ether–*n*-hexane (20/80), affording the desired products **7a–e**.

4.3.1. Benzothiadiazole 5. Compound **5** is unstable and becomes a dark brown solid in a few minutes. ^{1}H NMR ($CDCl_3$): δ ppm 7.37 (s, 2H), 0.10 (s, 18H). ^{13}C NMR ($CDCl_3$): δ ppm 154.15, 133.08, 117.21, 103.58, 99.96, 0.11. FTIR (KBr, cm^{-1}): 2152, 1536, 1248, 842.

4.3.2. Benzothiadiazole 6. Compound **6** is unstable and becomes a dark brown solid in a few minutes. ^{1}H NMR ($CDCl_3$): δ ppm 7.76 (s, 2H), 3.69 (s,2H). ^{13}C NMR ($CDCl_3$): δ ppm 154.23, 133.14, 116.65, 85.33, 78.87. FTIR (KBr, cm^{-1}): 3052, 2988, 2294, 1545, 1426.

4.3.3. Benzothiadiazole 7a. ^{1}H NMR ($CDCl_3$): δ ppm 8.69 (d, 2H, J=4.6 Hz), 7.89 (s, 2H), 7.79–7.68 (m, 4H), 7.35–7.27 (m, 2H). ^{13}C NMR ($CDCl_3$): δ ppm 154.26, 132.37, 131.92, 129.02, 128.37, 122.39, 117.08, 97.41, 85.23. FTIR (KBr, cm^{-1}): 3037, 1537, 840, 750, 688. Mp 159 °C. HRMS calcd for $C_{22}H_{12}N_2S$ 336.07212, found 336.07217.

4.3.4. Benzothiadiazole 7b. ^{1}H NMR ($CDCl_3$): δ ppm 8.21 (d, 2H, J=8.2 Hz), 7.80–7.23 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 154.14, 134.47, 133.08, 131.84, 129.78, 128.19, 127.81, 127.21, 126.96, 126.58, 126.07, 122.71, 116.56, 78.85. FTIR (KBr, cm^{-1}): 2935, 2860,1585, 1265, 844, 742, 615. Mp 116 °C. HRMS calcd for $C_{30}H_{16}N_2S$ 436.10342, found 436.10340.

4.3.5. Benzothiadiazole 7c. ^{1}H NMR ($CDCl_3$): δ ppm 7.74 (s, 2H), 7.61 (d, 4H, J=8.8 Hz), 6.92 (d, 4H, J=8.8 Hz), 3.85 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 160.14, 154.30, 133.51, 132.08, 117.02, 114.53, 114.04, 97.60, 84.31, 55.33. FTIR

(KBr, cm^{-1}): 3044, 1599, 1509, 1289. Mp 201 °C. HRMS calcd for $C_{24}H_{16}N_2O_2S$ 396.093250, found 396.09407.

4.3.6. Benzothiadiazole 7d. ^1H NMR ($CDCl_3$): δ ppm 7.76 (d, 2H, $J=1.0$ Hz), 7.29 (d, 4H, $J=9.0$ Hz), 6.58 (d, 4H, $J=8.8$ Hz) 2.92 (s, 3H) 2.91 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 154.31, 149.45, 133.22, 131.63, 116.71, 114.04, 108.44, 85.33, 78.89. FTIR (KBr, cm^{-1}): 3089, 2924, 1574, 1489, 1444, 1239. Mp 178 °C. HRMS calcd for $C_{26}H_{22}N_4S$ 422.156519, found 422.15663.

4.3.7. Benzothiadiazole 7e. ^1H NMR ($CDCl_3$): δ ppm 8.69 (d, 2H, $J=4.6$ Hz) 7.89 (s, 2H), 7.79–7.68 (m, 4H), 7.35–7.27 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 154.27, 150.29, 142.70, 136.19, 133.06, 127.96, 123.41, 116.97, 96.39, 84.45. FTIR (KBr, cm^{-1}): 3049, 2924, 1574, 1489, 1444, 1239. Mp 233 °C. Lit.[6a]=232–234. Anal. Calcd For $C_{20}H_{10}N_4S$ C, 70.99; H, 2.98; N, 16.56; S, 9.48. Found: C, 70.51; H, 2.94; N, 16.55.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.093. The complete set of the UV–vis, ^1H and ^{13}C NMR and Fluorescence spectra, and cyclic voltammograms and HRMS of the new compounds are available.

References and notes

1. (a) Lee, M. T.; Yen, C. K.; Yang, W. P.; Chen, H. H.; Liao, C. H.; Tsai, C. H.; Chen, C. H. *Org. Lett.* **2004**, *6*, 1241–1244. (b) Odom, S. A.; Parkin, S. R.; Anthony, J. E. *Org. Lett.* **2003**, *5*, 4245–4248. (c) Shen, W. J.; Dodda, R.; Wu, C. C.; Wu, F. I.; Liu, T. H.; Chen, H. H.; Chen, C. H.; Shu, C. F. *Chem. Mater.* **2004**, *16*, 930–934.
2. (a) Akhtaruzzaman, M.; Tomura, M.; Nishida, J.; Yamashita, Y. *J. Org. Chem.* **2004**, *69*, 2953–2958. (b) Sun, S.-S.; Lees, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 8956–8967. (c) Hou, Q.; Zhou, Q.; Zhang, Y.; Yang, W.; Yang, R.; Cao, Y. *Macromolecules* **2004**, *37*, 6299–6305.
3. (a) Tonzola, C. J.; Alam, M. M.; Kaminsky, W.; Jenekhe, S. A. *J. Am. Chem. Soc.* **2003**, *125*, 13548–13558. (b) Cui, Y.; Zhang, X.; Jenekhe, S. A. *Macromolecules* **1999**, *32*, 3824–3826. (c) Gao, Z. Q.; Lee, C. S.; Bello, I.; Lee, S. T.; Wu, S. K.; Yan, Z. L.; Zhang, X. H. *Synth. Met.* **1999**, *105*, 141–144. (d) Kim, D. Y.; Lee, S. K.; Kim, J. L.; Kim, J. K.; Lee, H.; Cho, H. N.; Hong, S. I.; Kim, C. Y. *Synth. Met.* **2001**, *121*, 1707–1708.
4. (a) Justin, K. R.; Lin, J. T.; Velusamy, M.; Tao, Y-T. ; Chuen, C-H. *Adv. Funct. Mater.* **2004**, *14*, 83–90. (b) Zhang, X.; Gorohmaru, H.; Kadowaki, M.; Kobayashi, T.; Ishi-I, T.; Thiemann, T.; Mataka, S. *J. Mater. Chem.* **2004**, *14*, 1901–1904.
5. Kraft, A.; Grimsdale, C. A.; Homes, B. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 402–428.
6. (a) Akhtaruzzaman, M.; Tomura, M.; Zaman, M. B.; Nishida, J.; Yamashita, Y. *J. Org. Chem.* **2002**, *67*, 7813–7818. (b) Akhtaruzzaman, M.; Tomura, M.; Nishida, J.; Yamashita, Y. *Synth. Met.* **2003**, *137*, 873–874.
7. (a) Khaletskii, A. M.; Pesin, V. G.; Chi-Chun, C. *Doklady Akad. Nauk. S.S.S.R.* **1956**, *106*, 88–91. *Chem. Abstr.* **1956**, *50*, 13885c. (b) Hinsberg, O. *Chem. Ber.* **1889**, *22*, 2895–2902. (c) Weinstock, L. M.; Davis, P.; Handclelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823–2829. (d) Carmack, M.; Street, R. W.; Komim, A. P. *J. Org. Chem.* **1975**, *40*, 2749–2752.
8. Pilgran, K.; Zupan, M.; Skiles, R. *J. Heterocycl. Chem.* **1970**, *7*, 629–633.
9. (a) Rosa, G. R.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Synthesis* **2003**, 2894–2897. (b) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.
10. Fang, Q.; Tanimoto, A.; Yamamoto, T. *Synth. Met.* **2005**, *73*, 150.
11. Consorti, C. S.; Ebeling, G.; Rodembusch, F.; Stefani, V.; Livotto, P. R.; Rominger, F.; Quina, F. H.; Yihwa, C.; Dupont, J. *Inorg. Chem.* **2004**, *43*, 530–536.
12. Chen, X.; Wang, K.; Li, H.; Wen, J. *Liq. Cryst.* **2002**, *29*, 989–993.
13. Platinum was used as working electrode and as a counter electrode. All potentials were recorded versus Ag/AgCl (saturated) as a reference electrode.
14. Blanchard, P.; Raimundo, J.-M.; Roncali, J. *Synth. Met.* **2001**, *119*, 527–528.
15. Zhang, X.; Gorohmaru, H.; Kadowaki, M.; Kobayashi, T.; Ishi-i, T.; Thiemann, T.; Mataka, S. *J. Mater. Chem.* **2004**, *14*, 1901–1904.
16. Köhler, A.; Wilson, J. S.; Friend, R. H.; Al-Suti, M. K.; Khan, M. S.; Gerhard, A.; Bässler, H. *J. Chem. Phys.* **2002**, *116*, 9457–9463.
17. (a) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1996**, *8*, 579–589. (b) Yang, C. J.; Jenekhe, S. A. *Macromolecules* **1995**, *28*, 1180–1196. (c) Alam, M. M.; Jenekhe, S. A. *J. Phys. Chem. B* **2002**, *106*, 11172–11177. (d) Jegou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 7926–7928.
18. Ortiz, R. P.; Delgado, M. C. R.; Casado, J.; Hernández, V.; Kim, O.-K.; Woo, H. Y.; Navarrete, J. T. L. *J. Am. Chem. Soc.* **2004**, *126*, 13363–13376.
19. Susumo, K.; Duncan, T. V.; Thierien, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 5186–5195.
20. (a) Yang, R.; Tian, R.; Yan, J.; Zhang, Y.; Yang, J.; Hou, Q.; Yang, W.; Zhang, C.; Cao, Y. *Macromolecules* **2005**, *38*, 244–253. (b) Velusamy, M.; Thomas, K. R. J.; Lin, J. T.; Hsu, Y-C. ; Ho, K-C. *Org Lett.* **2005**, *7*, 1899–1902. (c) Shi, C.; Wu, Y.; Zeng, W.; Xie, Y.; Yang, K.; Cao, Y. *Macromol. Chem. Phys.* **2005**, *206*, 1114–1125.
21. Raimundo, J. M.; Blanchard, P.; Brisset, H.; Akoudad, S.; Roncali, J. *Chem. Commun.* **2000**, 939–940.
22. Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011–2014.
23. Sakurai, H.; Ritonga, M. T. S.; Shibatani, H.; Hirao, T. *J. Org. Chem.* **2005**, *70*, 2754–2762.

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Rh(I)-catalyzed allenic Pauson–Khand reaction: first construction of the bicyclo[6.3.0]undecadienone ring system

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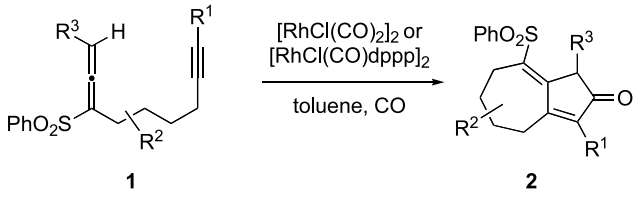
Abstract—The Rh(I)-catalyzed Pauson–Khand reaction of allenynes afforded the bicyclo[6.3.0]undecadienones as well as their benzo and furo derivatives. In addition, a novel $[RhCl(CO)_2]_2$-catalyzed [2,3]-sigmatropic rearrangement of the sulfinic ester species of propargyl alcohols was developed.

1. Introduction

The $Co_2(CO)_6$-mediated Pauson–Khand reaction (PKR)[1] of enynes is well recognized as one of the most convenient and straightforward methods for the construction of the bicyclo[3.3.0]octenone as well as bicyclo[4.3.0]nonenone ring systems. However, this attractive ring-closing reaction could not be generally used for the preparation of the C_1-carbon homologated bicyclic framework, namely a bicyclo[5.3.0]decenone skeleton.[2,3] Recent efforts from this laboratory[4] have led to the development of an effective method for the construction of bicyclo[5.3.0] ring system based on the Rh(I)-catalyzed PKR of allenynes.[5] Thus, a solution of 3-(phenylsulfonyl)octa-1,2-dien-7-yne derivatives **1** was heated in the presence of a catalytic amount of $[RhCl(CO)_2]_2$ or $Rh[Cl(CO)dppp]_2$ in toluene under CO pressure to produce the corresponding 2-phenylsulfonylbicyclo[5.3.0]deca-1,7-dien-9-ones **2** in high to reasonable yields (Scheme 1).[6] Our endeavors were then directed towards confirming the limitations of this newly developed Rh(I)-catalyzed ring-closing reactions. In particular, we were interested in the preparation of the bicyclo[6.3.0]-undecadienone skeleton,[7] because to our best knowledge no reports on the synthesis of the bicyclo[6.3.0] ring system by PKR is so far available. We now describe the first example of PKR for the preparation of bicyclo[6.3.0]undeca-1,8-dien-10-ones, and their benzo and furo congeners.



1 2

Scheme 1.

2. Results and discussion

The simple linear allenyne **7** was chosen as a first starting material for Rh(I)-catalyzed PKR and prepared as follows (Scheme 2). Treatment of 7-iodo-1-(trimethylsilyl)hept-1-yne (**3**)[8] with the acetylide, derived from 3-(*tert*-butyldiphenylsiloxy)prop-1-yne, afforded the coupled product **4** in 51% yield, the desilylation of which was subsequently carried out by exposure to tetrabutylammonium fluoride (TBAF) to provide the propargyl alcohol derivative **5** in 93% yield. The Sonogashira reaction of **5** with iodobenzene furnished the phenylacetylene derivative **6** in 79% yield, and this compound was transformed into the desired allenyne **7** in a 68% overall yield by successive exposure to benzenesulfenyl chloride (PhSCl) and *m*-chloroperbenzoic acid (*m*CPBA).[4] With the required allenyne **7** in hand, this compound was used for the ring-closing reaction in the presence of a catalytic amount (5 mol%) of $[RhCl(CO)dppp]_2$ in refluxing toluene for 7 h under an atmosphere of CO, that had been established for the preparation of bicyclo[4.3.0]nona-1,6-dien-8-ones and bicyclo[5.3.0]deca-1,7-dien-9-ones.[4] However, no eight-membered bicyclic compounds could be detected in the reaction mixture. Changing the catalyst from $[RhCl(CO)dppp]_2$ to $[RhCl(CO)_2]_2$ (5 mol%) in refluxing

Keywords: Pauson–Khand reaction; Allenyne; Bicyclo[6.3.0]undecadienone; [2,3]-Sigmatropic rearrangement; $[RhCl(CO)_2]_2$; $[RhCl(CO)dppp]_2$.
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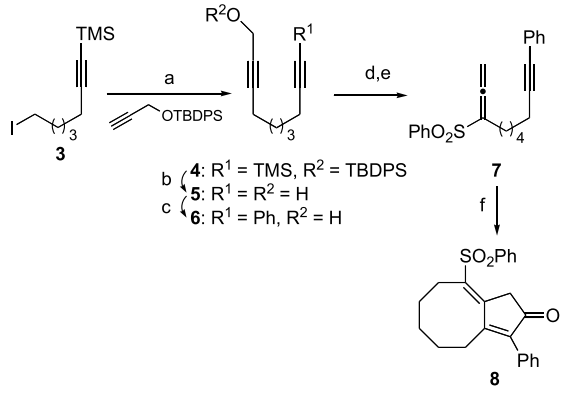
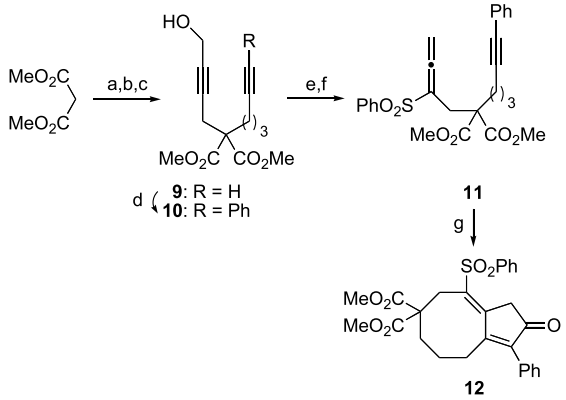


Scheme 2. Reagents and conditions: (a) ^{n}BuLi, THF–DMPU, −78 °C to rt, (51%); (b) TBAF, THF, rt, (93%); (c) PhI, $Pd(PPh_3)_2Cl_2$, CuI, $^{i}Pr_2NH$, THF, rt, (79%); (d) PhSCl, Et_3N, THF, −78 °C; (e) *m*CPBA, CH_2Cl_2, 0 °C, (68%); (f) 20 mol% of $[RhCl(CO)_2]_2$, 1 atm of CO, refluxing xylene, (23%).

toluene for 96 h led to the isolation of the desired bicyclo[6.3.0]undeca-1,8-dien-10-one **8** in a low yield (11%). When the ring-closing reaction was carried out in the presence of 10 mol% of $[RhCl(CO)_2]_2$ in refluxing xylene, compound **8** was obtained in 18% yield. Although the increasing load of the catalyst (20 mol%) with a higher reaction temperature (in refluxing xylene for 0.5 h) brought about further improvement of the chemical yield (23%), a satisfactory chemical yield of **8** has not yet been attained. The other catalysts were examined, but the chemical yields were much less than 23%. For instance, the allenyne **7** was exposed to 10 mol% of $(PPh_3)_3RhCl$ in refluxing xylene to furnish **8** in 14% yield.

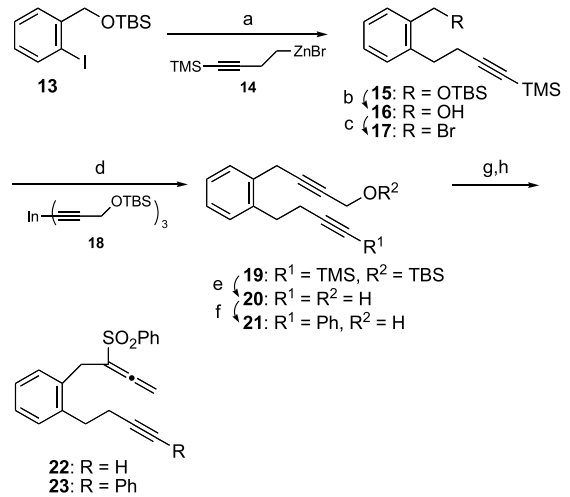
We next investigated the Rh(I)-catalyzed PKR of the allenyne **11** possessing a *gem*-bis(methoxycarbonyl) functionality on the carbon appendage hoping for the Thorpe-Ingold-type effect[9] in the ring-closing step. Thus, the dimethyl malonate was successively alkylated with 5-iodopent-1-yne[10] and 4-iodo-1-(*tert*-butyldiphenylsiloxy)but-2-yne[4b] to afford the dialkylated product, which was subsequently desilylated with TBAF to produce **9** in a 44% overall yield. Conversion of **9** into the allenyne **11** via **10** (71 and 77%, respectively) was realized according to the procedure described for the preparation of **7** from **5**. Upon exposure to 10 mol% of $[RhCl(CO)_2]_2$ in refluxing xylene for 2.5 h, the allenyne **11** underwent the ring-closing reaction to furnish the bicyclo[6.3.0] derivative **12** in 43% yield. When a similar reaction was performed in the presence of $[RhCl(CO)dppp]_2$ instead of $[RhCl(CO)_2]_2$, the desired compound **12** was also obtained, but the yield was much lower (29%) compared to $[RhCl(CO)_2]_2$ (Scheme 3). As a result, the introduction of a *gem*-bis(methoxycarbonyl) group on the carbon appendage of the allenynes made significant improvement in the chemical yield of the cyclized products (23–43%).



Scheme 3. Reagents and conditions: (a) 5-iodopent-1-yne, NaH, THF, 0 °C to rt; (b) 4-iodo-1-(TBDPSO)but-2-yne, NaH, THF, 0 °C to rt; (c) TBAF, THF, rt, (44%); (d) PhI, $Pd(PPh_3)_2Cl_2$, CuI, $^{i}Pr_2NH$, THF, rt, (77%); (e) PhSCl, Et_3N, THF, −78 °C; (f) *m*CPBA, CH_2Cl_2, 0 °C, (71%); (g) 10 mol% of $[RhCl(CO)_2]_2$, 1 atm of CO, refluxing xylene, (43%).

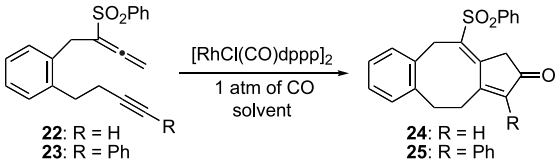
Our endeavors then turned to application of this Rh(I)-catalyzed PKR to the 1,2-disubstituted-aromatic substrates bearing a butyne as well as a buta-1,2-diene residue in which the template effect of the aromatic ring would be expected to facilitate the ring-closing step like the *gem*-bis(methoxycarbonyl) moiety of **11**. According to the literature procedure,[11] 4-bromo-1-(trimethylsilyl)but-1-yne[12] was transformed into the corresponding zinc reagent **14** in situ, which was then coupled with the iodobenzene derivative **13**[13] under the Negishi coupling conditions[14] to provide **15**. A *tert*-butyldimethylsilyl (TBS) group on the primary hydroxyl moiety of **15** was removed by acid treatment to furnish **16** in a 62% overall yield. The second coupling reaction between the benzyl bromide derivative **17**, derived from **16** using a conventional procedure in 99%, and the indium species **18**, prepared in situ from the reaction of 3-(*tert*-butyldimethylsiloxy)prop-1-yne with ^{n}BuLi and $InCl_3$,[15] under the palladium coupling conditions gave **19**, which was subsequently desilylated by TBAF to produce **20** in a 65% overall yield. Compound **20** was converted into the phenylacetylene derivative **21** under the Sonogashira conditions (73%) and two compounds, **20** and **21**, were then transformed into the corresponding allenynes **22** (50%) and **23** (43%) by the standard method (Scheme 4).

A solution of **22** and 10 mol% of $[RhCl(CO)_2]_2$ in xylene was refluxed for 0.5 h (disappearance of the starting material was



Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$, DMA, 80 °C; (b) TsOH, THF, rt, (62%); (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, (99%); (d) $Pd(dppf)Cl_2$, THF, reflux; (e) TBAF, THF, 0 °C, (65%); (f) PhI, $Pd(PPh_3)_2Cl_2$, CuI, $^{i}Pr_2NH$, THF, rt, (73%); (g) PhSCl, Et_3N, THF, −78 °C; (h) *m*CPBA, CH_2Cl_2, 0 °C, **22** (50%), **23** (43%).

Table 1. Rh(I)-catalyzed ring-closing reaction of compounds **22** and **23**



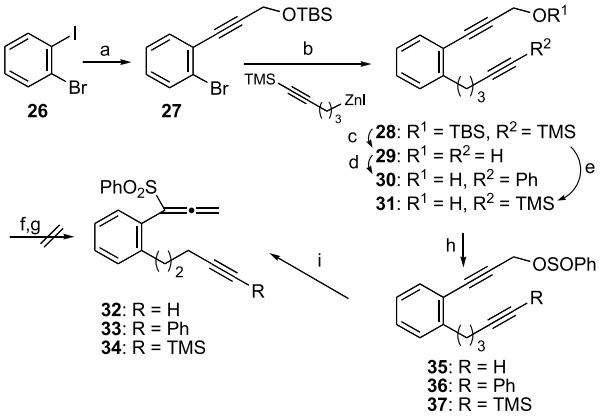
Entry	Substrate	R	Rh (mol%)	Solvent	Temperature	Time (h)	Product	Yield (%)
1	**22**	H	10[a]	Xylene	Reflux	0.5	**24**	63
2	**22**	H	10	Toluene	80 °C	1	**24**	87
3	**22**	H	5[b]	Toluene	80 °C	4	**24**	90
4	**23**	Ph	10[c]	Xylene	Reflux	2	**25**	83
5	**23**	Ph	5	Xylene	Reflux	2	**25**	76

[a] Compound **24** was isolated in 35% yield when $[RhCl(CO)_2]_2$ was used.
[b] When 2.5 mol% of $[RhCl(CO)dppp]_2$ was employed in toluene at 80 °C for 24 h, **24** was obtained in 66% yield along with the recovery of compound **22** in 4% yield.
[c] No reaction took place in toluene at 80 °C for 24 h.

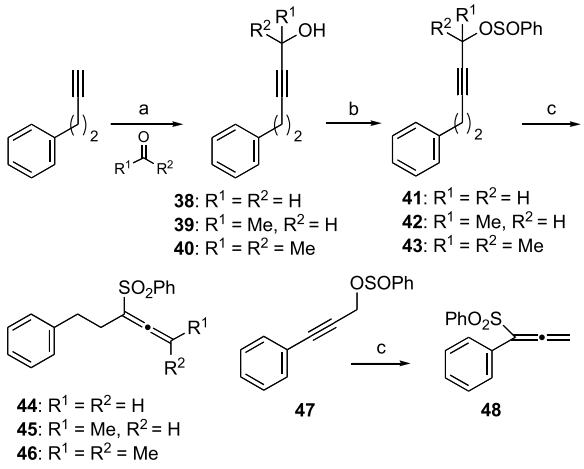
monitored by TLC) to produce the cyclized product **24** in 35% yield. Upon exposure to $[RhCl(CO)dppp]_2$ instead of $[RhCl(CO)_2]_2$ under the same conditions, **22** produced **24** in a significantly improved yield (63%) (Table 1, entry 1). The best result (90%) was obtained when **22** was treated with 5 mol% of $[RhCl(CO)dppp]_2$ in toluene at 80 °C for 4 h (entry 3). A similar result was observed when 10 mol% of $[RhCl(CO)dppp]_2$ was used (entry 2). Interestingly, the optimized conditions for the preparation of **24** (5 or 10 mol% of $[RhCl(CO)dppp]_2$ in toluene at 80 °C) was found to be no longer effective for the phenyl congener **23** resulting in no reaction. The desired phenyl derivative **25** was constructed in 83 and 76% yields when **23** was heated in refluxing xylene (entries 4 and 5). Thus, we have succeeded in the synthesis of the benzene ring-fused bicyclo[6.3.0]undecadienone frameworks in high yields by taking advantage of the template effect of the aromatic ring.

Investigation of the Rh(I)-catalyzed PKR of the regioisomers **32–34** regarding the benzene ring of allenynes **22** and **23** was the next objective of this program. Three propargyl alcohol derivatives **29–31** were prepared by conventional means as depicted in Scheme 5. Unexpectedly, the direct transformation of the propargyl alcohols **29–31** into the allenyl sulfones **32–34** by the standard two-step procedure was troublesome. In fact, compound **29** was successively exposed to PhSCl and *m*CPBA, however, the desired allenyl sulfone **32** could not be isolated in more than trace quantities. Thus, an alternative method for the preparation of the allenyl sulfones **32–34** was necessary. One of the possible solutions for this issue would involve the consecutive formation of benzene sulfinic ester derivatives from the propargyl alcohol derivatives and their thermal [2,3]-sigmatropic rearrangement.[16] Treatment of the propargyl alcohols **29–31** with benenesulfinyl chloride[17] in THF in the presence of $^{i}Pr_2NEt$ at −78 °C provided the corresponding sulfinic ester derivatives **35–37** without any difficulties. The thermal [2,3]-sigmatropic rearrangement of compounds **35** was attempted under several conditions, but the desired **32** was obtained only in trace quantities. The major product isolated from the reaction mixture was the hydrolyzed product **29** (15–33%).

Hiroi and co-workers[18] reported the efficient Pd-catalyzed [2,3]-sigmatropic rearrangement of the sulfinic esters of propargyl alcohols resulting in the formation of the corresponding allenyl sulfones. Thus, we became interested in determining if the Rh(I) catalyst would be able to catalyze the [2,3]-sigmatropic rearrangement of sulfinic esters **35–37**. To this end, the simpler sulfinic ester **41**, derived from the propargyl alcohol **38**, was treated with 5 mol% of $[RhCl(CO)_2]_2$ in toluene at 80 °C for 0.5 h under an atmosphere of N_2 to give the rearranged product **44** in 57% yield (Scheme 6). It should be noted that **44** was obtained in 28% yield when heated at 80 °C in toluene in the absence of $[RhCl(CO)_2]_2$ for 36 h. This result was different from the case of **35**, having a more sterically congested framework (1,2-disubstituted benzene ring), where no rearranged product could be isolated (Scheme 5). $[RhCl(CO)_2]_2$ was found to accelerate the transformation of **41** into **44** more effectively even at room temperature. As a matter of fact, **44** was formed in 82% yield upon exposure of **41** to 5 mol% of $[RhCl(CO)_2]_2$ in toluene at room temperature for 0.5 h. Neither $[RhCl(CO)dppp]_2$ nor $RhCl(PPh_3)_3$ was active for this transformation at room temperature leading to the complete recovery of the starting material. $[RhCl(COD)]_2$ and $[IrCl(COD)]_2$ furnished the desired product **44** at room temperature in the respective



Scheme 5. Reagents and conditions: (a) 3-(*tert*-butyldimethylsiloxy)prop-1-yne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, rt, (85%); (b) $Pd(PPh_3)_4$, DMA, 80 °C; (c) TBAF, THF, 0 °C, (74%); (d) PhI, $Pd(PPh_3)_2Cl_2$, CuI, $^{i}Pr_2NH$, THF, rt, (73%); (e) 10% aqueous HCl, THF, rt, (78% from **27**); (f) PhSCl, Et_3N, THF, −78 °C; (g) *m*CPBA, CH_2Cl_2, 0 °C; (h) PhSOCl, $^{i}Pr_2NEt$, THF, −78 °C, **35** (94%), **36** (93%), **37** (86%); (i) 5 mol% of $[RhCl(CO_2)]_2$, toluene, rt, **32** (26%), **33** (56%), **34** (75%) and recovery of **37** (16%).

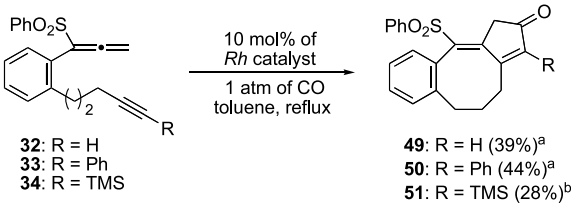


Scheme 6. Reagents and conditions: (a) ^{n}BuLi, THF, −78 °C, **38** (97%), **39** (94%), **40** (79%); (b) PhSOCl, $^{i}Pr_2NEt$, THF, −78 °C, **41** (75%), **42** (90%), **43** (65%); (c) 5 mol% of $[RhCl(CO_2)]_2$, toluene, rt, **44** (82%), **45** (86%), **46** (78%), **48** (63%).

yields of 58 and 74%, although a prolonged reaction time was necessary for complete consumption of the starting material (24 h in both cases). Toluene has so far provided the best result (82%) compared to other solvents like CH_2Cl_2, acetonitrile, DMF, and 1,4-dioxane (11–64%). The secondary and tertiary propargyl alcohols **42** and **43**, derived from the corresponding alcohols **39** and **40**,[19] respectively, were then submitted to the best conditions (5 mol% of $[RhCl(CO)_2]_2$ in toluene at room temperature for 0.25–1 h) to afford the corresponding allenyl sulfones **45** and **46** in the respective yields of 86 and 78%. The phenylacetylene derivative **47**, which was prepared by the reaction of 2-phenylprop-2-yn-1-ol with benzenesulfinyl chloride[17] and has a structure similar to **35**, was chosen as the next substrate. Compound **47** was treated with 5 mol% of $[RhCl(CO)_2]_2$ in toluene at room temperature for 2 h to provide the rearranged product **48** in a slightly lower yield (63%) compared to those of **44**–**46**. Thus, it became evident that $[RhCl(CO)_2]_2$ was effective for our purpose under mild conditions.

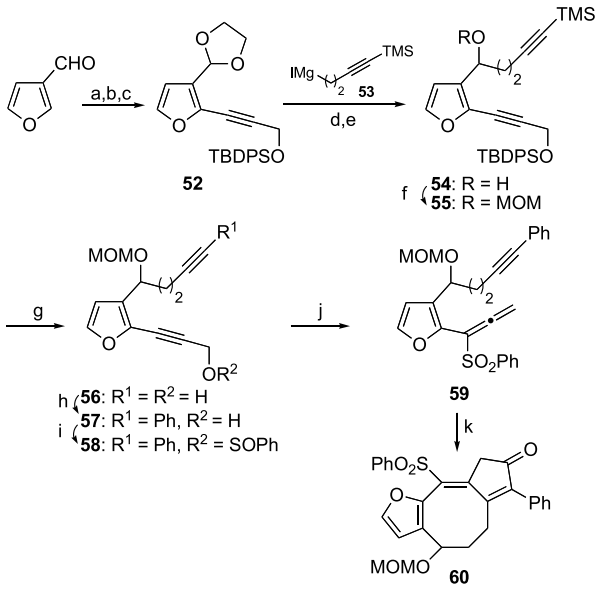
With these results available, we examined the Rh(I)-catalyzed synthesis of the allenyl sulfones **32**–**34** from **35**–**37** (Scheme 5). It took a prolonged reaction time (70 h) for consumption of the starting material, but gave the desired product **32** in 26% yield when the sulfinic ester **35** was exposed to the best conditions (5 mol% of $[RhCl(CO)_2]_2$ in toluene at room temperature). Heating the reaction mixture in toluene at 80 °C did not produce any improvement in the chemical yield (27%). The similar reaction was carried out under an atmosphere CO instead of N_2, hoping for spontaneous PKR, to afford the allenyl sulfone **32** in 30% yield as the sole isolatable product. The bicyclo[6.3.0] derivative (PKR product) could not be observed in the reaction mixture. In contrast to the case of **35** into **32**, the transformation of the TMS and phenyl congeners **36** and **37** into the corresponding allenyl sulones **33** and **34** smoothly proceeded at room temperature in the respective yields of 56 and 75%.

According to the procedure described for the conversion of **22** into **24** (Table 1, entry 3), the prepared allenyl sulfone **32** was exposed to a catalytic amount of $[RhCl(CO)dppp]_2$ in refluxing toluene under an atmosphere of CO to give the ring-closed product **49** in 39% yield. The phenyl congener **33** provided the bicyclo[6.3.0] derivative **50** in a higher yield (44%) under typical ring-closing conditions. For the TMS derivative **34**, $[RhCl(CO)_2]_2$ was found to be superior to $[RhCl(CO)dppp]_2$ furnishing **51** in 28% yield ($[RhCl(CO)dppp]_2$ gave **51** in 5% yield). Although the ring-closed products **49**–**51** could be constructed by the Rh(I)-catalyzed PKR irrespective of the substituent at the triple bond terminus, the yields of which were much less than those of their regioisomers **24** and **25** (see Table 1, Scheme 7).



Scheme 7. Reagents and conditions: (a) $[RhCl(CO)dppp]_2$ was used. (b) $[RhCl(CO_2)]_2$, was used.

By taking application of this method to total synthesis of natural products into account, we next investigated the Rh(I)-catalyzed PKR of the furan derivative **59** as a preliminary examination, because a 1,2-disubstituted furan moiety would not only serve as the template in the ring-closing step, but also provide some opportunities for further chemical elaboration leading to more complex functionalities. Thus, the substrate **59** for the ring-closing reaction was prepared as depicted in Scheme 8.



Scheme 8. Reagents and conditions: (a) LiTMEDA, ^{n}BuLi, then I_2, THF, −78 °C; (b) ethylene glycol, TsOH, benzene, reflux; (c) 3-(*tert*-butyldiphenylsiloxy)prop-1-yne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, rt, (52%); (d) 10% aqueous HCl, THF, rt; (e) **53**, Et_2O, 0 °C to rt, (85%); (f) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C to rt, (95%); (g) TBAF, THF, rt, (90%); (h) PhI, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, rt, (91%); (i) PhSOCl, $^{i}Pr_2NEt$, THF, −78 °C, (98%); (j) 5 mol% of $[RhCl(CO_2)]_2$, toluene, rt, (55%); (k) 10 mol% of $[RhCl(CO)dppp]_2$, CO, toluene, reflux, (39%).

3-Furaldehyde was iodinated by the literature procedure[20] to afford 2-iodo-3-furaldehyde, the acetalization of which with ethylene glycol was followed by the Sonogashira coupling reaction with 3-(*tert*-butyldiphenylsiloxy)prop-1-yne providing **52** in a 52% overall yield. The carbon-homologation of **52** was performed by consecutive acid hydrolysis and the Grignard reaction with **53** to produce **54** in 85% yield, and the resulting secondary hydroxyl group of **54** was subsequently protected with a methoxymethyl (MOM) group to furnish **55** in 95% yield. Conversion of **55** into the target molecule **59** (55% from **58**) was easily achieved by the aforementioned procedures via compounds **56** (90%), **57** (91%), and **58** (98%). The Rh(I)-catalyzed PKR of compound **59** carried out in refluxing toluene in the presence of 10 mol% of $[RhCl(CO)dppp]_2$ under an atmosphere of CO for 2 h to furnish the desired bicyclo[6.3.0] skeleton **60** in 39% yield. Several different conditions were examined, but found to be inferior to the above result. It is noteworthy that compound **60** was directly prepared in 16% yield from the sulfinic ester derivative **58** by refluxing in toluene in the presence of 10 mol% of $[RhCl(CO)_2]_2$ under an atmosphere of CO. Compound **60** has a furan ring as well as a protected hydroxyl group, both of which would provide the foothold for further chemical modification of the functionalities.

3. Conclusions

In summary, we have shown that the Rh(I)-catalyzed PKR of allenynes can be applicable for constructing medium-sized bicyclo[6.3.0] frameworks. In fact, the bicylo[6.3.0] undecadienones as well as their benzo and furo derivatives could be formed in reasonable yields. In addition, the $[RhCl(CO)_2]_2$-catalyzed [2,3]-sigmatropic rearrangement of the sulfinic ester species of propargyl alcohols was developed. This procedure proceeds at room temperature to afford the allenyl sulfone derivatives in high yield. Thus, it would become a useful method when the thermal [2,3]-sigmatropic rearrangement of the sulfinic ester species of propargyl alcohols is troublesome.

4. Experimental

Melting points are uncorrected. Infrared spectra were measured in $CHCl_3$. ^1H NMR spectra were taken in chloroform-*d* ($CDCl_3$). $CHCl_3$ (7.26 ppm) for silyl compounds and tetramethylsilane (0.00 ppm) for compounds without a silyl group was used as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ with $CDCl_3$ (77.0 ppm) as an internal standard. All reactions were carried out under N_2 atmosphere unless otherwise stated. Silica gel (Silica gel 60, 40–50 μm) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

4.1. General procedure for preparation of allenyl sulfones with PhSCl and *m*CPBA

To a solution of propargyl alcohol in THF (0.1 M) were added successively Et_3N (3.0 equiv) and PhSCl (1.5 equiv) at −78 °C. The reaction mixture was stirred until complete disappearance of the starting material monitored by TLC. The reaction mixture was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt to afford the crude sulfoxide. To a solution of the crude sulfoxide in CH_2Cl_2 (0.1 M) was added a solution of *m*CPBA (1.5 equiv) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred until complete disappearance of the starting material monitored by TLC. The reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt to afford allenyl sulfones. Chemical yields were summarized in Schemes.

4.1.1. 10-Phenyl-3-(phenylsulfonyl)deca-1,2-dien-9-yne (7). A colorless oil: IR 2253, 1971, 1940, 1308, 1150 cm^{-1}; ^1H NMR δ 7.93–7.86 (m, 2H), 7.66–7.47 (m, 3H), 7.40–7.23 (m, 5H), 5.34 (t, 2H, J=3.6 Hz), 2.35 (t, 2H, J=6.6 Hz), 2.31–2.21 (m, 2H), 1.62–1.35 (m, 6H); ^{13}C NMR δ 207.7, 140.1, 133.4, 131.4, 129.0, 128.1, 128.0, 127.5, 123.9, 113.2, 89.9, 84.4, 80.8, 28.2, 27.9, 26.8, 26.5, 19.2; MS *m*/*z* 350 (M^+, 0.5); HRMS calcd for $C_{22}H_{22}O_2S$ 350.1340, found 350.1336.

4.1.2. 5,5-Bis(methoxycarbonyl)-10-phenyl-3-(phenylsulfonyl)deca-1,2-dien-9-yne (11). A colorless oil: IR 1967, 1936, 1732, 1308, 1153 cm^{-1}; ^1H NMR δ 7.93–7.84 (m, 2H), 7.66–7.47 (m, 3H), 7.31–7.23 (m, 5H), 5.32 (t, 2H, J=3.3 Hz), 3.65 (s, 6H), 2.93 (t, 2H, J=3.3 Hz), 2.32 (t, 2H, J=6.9 Hz), 2.12–2.01 (m, 2H), 1.43–1.20 (m, 2H); ^{13}C NMR δ 208.1, 170.4, 139.7, 133.6, 131.5, 129.1, 128.2, 127.6, 123.8, 108.9, 89.1, 85.5, 81.1, 56.6, 52.6, 31.1, 28.5, 23.4, 19.4; MS *m*/*z* 466 (M^+, 1.9); HRMS calcd for $C_{26}H_{26}O_6S$ 466.1450, found 466.1445.

4.1.3. 1-(But-3-ynyl)-2-[2-(phenylsulfonyl)buta-2,3-dienyl]benzene (22). A colorless oil: IR 3308, 2118, 1967, 1935, 1308, 1151 cm^{-1}; ^1H NMR δ 7.92–7.82 (m, 2H), 7.66–7.57 (m, 1H), 7.56–7.47 (m, 2H), 7.19–6.99 (m, 4H), 5.17 (t, 2H, J=3.6 Hz), 3.62 (t, 2H, J=3.6 Hz), 2.62 (t, 2H, J=7.6 Hz), 2.28 (td, 2H, J=7.6, 2.6 Hz), 1.94 (t, 1H, J=2.6 Hz); ^{13}C NMR δ 208.3, 139.9, 138.5, 133.8, 133.5, 130.4, 129.2, 129.0, 127.9, 127.3, 126.5, 113.2, 84.7, 83.3, 69.1, 31.0, 30.8, 19.6; MS *m*/*z* 322 (M^+, 0.5). Anal. Calcd for $C_{20}H_{18}O_2S$: C, 74.50; H, 5.63. Found: C, 74.30; H, 5.65.

4.1.4. 1-(4-Phenylbut-3-ynyl)-2-[2-(phenylsulfonyl)buta-2,3-dienyl]benzene (23). A colorless oil: IR 1967, 1935, 1308, 1151 cm^{-1}; ^1H NMR δ 7.92–7.84 (m, 2H), 7.62–7.44 (m, 3H), 7.38–7.00 (m, 9H), 5.18 (t, 2H, J=4.0 Hz), 3.67 (t, 2H, J=4.0 Hz), 2.69 (t, 2H, J=7.3 Hz), 2.50 (t, 2H, J=7.3 Hz); ^{13}C NMR δ 208.4, 140.1, 138.9, 133.9, 133.5, 131.4, 130.5, 129.6, 129.1, 128.2, 128.1, 127.7, 127.3, 126.6, 123.7, 113.4, 89.1, 84.7, 81.5, 31.4, 30.9, 20.8; MS *m*/*z* 399 (M^+, 0.3). Anal. Calcd for $C_{26}H_{22}O_2S$: C, 78.36; H, 5.56. Found: C, 78.02; H, 5.60.

4.2. General procedure for preparation of propargyl sulphinates

To a solution of propargyl alcohol in THF (0.1 M) were added successively $^{i}Pr_2NEt$ (3.0 equiv) and PhSOCl (1.5 equiv) at −78 °C. After stirring for 1.5 h, the reaction mixture was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt to afford propargyl sulfinate. Chemical yields were summarized in Schemes.

4.2.1. 5-Phenylpent-2-yn-1-yl benzenesulfinate (41). A colorless oil: ^{1}H NMR δ 7.74–7.71 (m, 2H), 7.56–7.53 (m, 3H), 7.31–7.17 (m, 5H), 4.62 (dt, 1H, J=15, 2.2 Hz), 4.33 (dt, 1H, J=15, 2.2 Hz), 2.79 (t, 2H, J=7.6 Hz), 2.48 (tt, 2H, J=7.6, 2.2 Hz); ^{13}C NMR δ 144.4, 140.3, 132.3, 129.0, 128.4, 128.3, 126.3, 125.3, 88.5, 74.6, 52.9, 34.6, 20.9; MS m/z 284 (M^+, 3.6); HRMS calcd for $C_{17}H_{16}O_2S$ 284.0871, found 284.0870.

4.2.2. 6-Phenylhex-3-yn-2-yl benzenesulfinate (42). As a mixture of diastereomers. Compound **42** was a colorless oil: IR 2245 cm^{-1}; ^{1}H NMR for one isomer δ 7.72–7.69 (m, 2H), 7.55–7.49 (m, 3H), 7.32–7.20 (m, 5H), 5.04 (qt, 1H, J=6.6, 2.0 Hz), 2.86 (t, 2H, J=7.6 Hz), 2.56 (td, 2H, J=7.6, 2.0 Hz), 1.49 (d, 3H, J=6.6 Hz); ^{13}C NMR for one isomer δ 145.6, 140.3, 132.1, 128.9, 128.5, 128.4, 126.4, 125.1, 87.5, 79.4, 65.4, 34.7, 23.3, 20.9; ^{1}H NMR data for the other isomer δ 7.74–7.71 (m, 2H), 7.54–7.47 (m, 3H), 7.31–7.15 (m, 5H), 5.00 (qt, 1H, J=6.6, 2.0 Hz), 2.71 (t, 2H, J=7.6 Hz), 2.37 (td, 2H, J=7.6, 2.0 Hz), 1.55 (d, 3H, J=6.6 Hz); ^{13}C NMR data for the other isomer δ 144.8, 140.4, 132.0, 128.8, 128.4, 128.3, 126.3, 125.4, 86.9, 79.2, 63.3, 34.6, 24.1, 20.8; MS m/z 298 (M^+, 2.7); HRMS calcd for $C_{18}H_{18}O_2S$ 298.1027, found 298.1025.

4.2.3. 2-Methyl-6-phenylhex-3-yn-2-yl benzenesulfinate (43). A colorless oil: IR 2241 cm^{-1}; ^{1}H NMR δ 7.70–7.65 (m, 2H), 7.52–7.48 (m, 3H), 7.35–7.17 (m, 5H), 2.88 (t, 2H, J=7.4 Hz), 2.60 (t, 2H, J=7.4 Hz), 1.74 (s, 3H), 1.62 (s, 3H); ^{13}C NMR δ 146.6, 140.3, 131.5, 128.8, 128.5, 128.3, 126.3, 125.0, 88.0, 82.0, 76.4, 34.7, 31.2, 31.0, 20.9; MS m/z 312 (M^+, 11.3); HRMS calcd for $C_{19}H_{20}O_2S$ 312.1184, found 312.1190.

4.2.4. 3-Phenylprop-2-ynyl benzenesulfinate (47). A colorless oil: IR 2228 cm^{-1}; ^{1}H NMR δ 7.83–7.76 (m, 2H), 7.62–7.53 (m, 3H), 7.42–7.26 (m, 5H), 4.84, 4.58 (AB-q, 2H, J=5.6 Hz); ^{13}C NMR δ 144.2, 144.1, 132.4, 131.8, 129.1, 128.8, 128.2, 125.3, 87.9, 82.8, 52.5; MS m/z 256 (M^+, 1.2); HRMS calcd for $C_{15}H_{12}O_2S$ 256.0558, found 256.0565.

4.2.5. 1-(Pent-4-ynyl)-2-[3-(phenylsulfinyloxy)prop-1-ynyl]benzene (35). A pale yellow oil: IR 3308, 2224, 2116 cm^{-1}; ^{1}H NMR δ 7.81–7.77 (m, 2H), 7.59–7.53 (m, 3H), 7.38–7.11 (m, 4H), 4.89, 4.61 (AB-q, 2H, J=16 Hz), 2.85 (t, 2H, J=7.6 Hz), 2.20 (td, 2H, J=6.9, 2.6 Hz), 1.97 (t, 1H, J=2.6 Hz), 1.83 (quin, 2H, J=6.9 Hz); ^{13}C NMR δ 144.0, 132.7, 132.4, 129.1, 129.0, 128.9, 125.9, 125.4, 125.3, 121.4, 86.6, 86.3, 84.2, 68.7, 52.9, 33.3, 29.3, 18.0; MS m/z 322 (M^+, 0.4); HRMS calcd for $C_{20}H_{18}O_2S$ 322.1027, found 322.1023.

4.2.6. 1-(5-Phenylpent-4-ynyl)-2-[3-(phenylsulfinyloxy)prop-1-ynyl]benzene (36). A colorless oil: IR 2224 cm^{-1}; ^{1}H NMR δ 7.78–7.75 (m, 2H), 7.55–7.51 (m, 3H), 7.41–7.36 (m, 3H), 7.31–7.22 (m, 5H), 7.19–7.12 (m, 1H), 4.85, 4.58 (AB-q, 2H, J=16 Hz), 2.90 (t, 2H, J=7.6 Hz), 2.41 (t, 2H, J=7.3 Hz), 1.92 (quin, 2H, J=7.3 Hz); ^{13}C NMR δ 144.3, 144.0, 132.7, 132.4, 131.5, 129.1, 129.0, 128.2, 127.6, 125.9, 125.3, 123.9, 121.4, 89.8, 86.7, 86.3, 81.1, 53.0, 33.5, 29.4, 19.0; FABMS m/z 399 (M^++1, 3.3); FABHRMS calcd for $C_{26}H_{23}O_2S$ 399.1419, found 399.1428.

4.2.7. 1-[3-(Phenylsulfinyloxy)prop-1-ynyl]-2-[5-(trimethylsilyl)pent-4-ynyl]benzene (37). A pale yellow oil: IR 2224, 2172 cm^{-1}; ^{1}H NMR δ 7.81–7.77 (m, 2H), 7.59–7.53 (m, 3H), 7.38–7.35 (m, 1H), 7.29–7.11 (m, 3H), 4.89, 4.62 (AB-q, 2H, J=16 Hz), 2.82 (t, 2H, J=7.3 Hz), 2.23 (t, 2H, J=7.3 Hz), 1.83 (quin, 2H, J=7.3 Hz), 0.15 (s, 9H); ^{13}C NMR δ 144.3, 144.0, 132.7, 132.4, 129.1, 129.0, 125.9, 125.3, 121.3, 107.0, 86.7, 86.3, 84.9, 52.9, 33.4, 29.3, 19.4, 0.1; FABMS m/z 395 (M^++1, 2.2); FABHRMS calcd for $C_{23}H_{27}O_2SiS$ 395.1501, found 395.1509.

4.2.8. 3-[1-(Methoxymethoxy)-5-phenylpent-4-ynyl]-2-[3-(phenylsulfinyloxy)prop-1-ynyl]furan (58). As a mixture of diastereomers. Compound **58** was a colorless oil: IR 2230 cm^{-1}; ^{1}H NMR δ 7.75–7.71 (m, 2H), 7.55–7.49 (m, 3H), 7.41–7.35 (m, 2H), 7.33 (d, 1H, J=2.0 Hz), 7.28–7.23 (m, 3H), 6.42 (d, 1H, J=2.0 Hz), 4.92–4.86 (m, 1H), 4.80–4.74 (m, 1H), 4.59–4.45 (m, 3H), 3.37 (m, 3H), 2.59–2.43 (m, 2H), 2.18–2.09 (m, 1H), 1.96–1.87 (m, 1H); ^{13}C NMR δ 144.3, 144.1, 144.1, 133.8, 133.7, 132.4, 131.7, 131.7, 131.4, 129.0, 128.2, 127.6, 125.3, 125.2, 123.7, 109.7, 94.2, 90.4, 88.9, 88.9, 81.2, 76.7, 68.6, 55.6, 52.3, 52.3, 35.0, 35.0, 15.8, 15.8; FABMS m/z 449 (M^++1, 13.7); FABHRMS calcd for $C_{26}H_{25}O_5S$ 449.1422, found 449.1415.

4.3. General procedure for Rh(I)-catalyzed synthesis of allenyl sulfones from propargyl sulfinates

To a solution of sulfinates (0.1 mmol) in toluene (1 mL) was added 5 mol% of $[RhCl(CO)_2]_2$. Then the reaction mixture was stirred at room temperature for several hours. The solvent was evaporated off, and the residue was chromatographed to afford allenyl sulfones. Chemical yields were summarized in Schemes.

4.3.1. 5-Phenyl-3-(phenylsulfonyl)penta-1,2-diene (44). A colorless oil: IR 1969, 1940, 1317, 1150 cm^{-1}; ^{1}H NMR δ 7.89–7.86 (m, 2H), 7.63–7.50 (m, 3H), 7.26–7.06 (m, 5H), 5.31 (t, 2H, J=3.3 Hz), 2.74 (t, 2H, J=7.2 Hz), 2.58–2.50 (m, 2H); ^{13}C NMR δ 208.0, 140.2, 140.1, 133.4, 129.1, 128.4, 128.3, 128.1, 126.2, 112.4, 84.5, 33.6, 28.4; MS m/z 284 (M^+, 8.3); FABHRMS calcd for $C_{17}H_{17}O_2S$ 285.0949, found 285.0952 (M^++1).

4.3.2. 6-Phenyl-4-(phenylsulfonyl)hexa-2,3-diene (45). A colorless oil: IR 1963, 1315, 1148 cm^{-1}; ^{1}H NMR δ 7.87–7.84 (m, 2H), 7.61–7.51 (m, 3H), 7.26–7.05 (m, 5H), 5.66

(qt, 1H, J=7.4, 2.8 Hz), 2.76–2.71 (m, 2H), 2.58 (qd, 2H, J=8.1, 2.8 Hz), 1.60 (d, 3H, J=7.4 Hz); ^{13}C NMR δ 204.8, 140.3, 140.1, 133.2, 129.0, 128.4, 128.3, 128.0, 126.1, 111.9, 96.4, 33.5, 28.3, 13.2; MS *m/z* 298 (M^+, 5.3); FABHRMS calcd for $C_{18}H_{19}O_2S$ 299.1106, found 299.1104 ($M^+ + 1$).

4.3.3. 2-Methyl-6-phenyl-4-(phenylsulfonyl)hexa-2,3-diene (46). A colorless oil: IR 1963, 1313, 1148 cm^{-1}; ^{1}H NMR δ 7.86–7.82 (m, 2H), 7.62–7.47 (m, 3H), 7.26–7.06 (m, 5H), 2.75 (t, 2H, J=6.9 Hz), 2.61 (t, 2H, J=6.9 Hz), 1.58 (s, 6H); ^{13}C NMR δ 202.2, 140.6, 140.3, 133.0, 128.9, 128.3, 128.2, 127.9, 126.0, 110.2, 107.3, 33.6, 28.1, 19.5; MS *m/z* 312 (M^+, 10.8); FABHRMS calcd for $C_{19}H_{21}O_2S$ 313.1262, found 313.1264 ($M^+ + 1$).

4.3.4. 1-Phenyl-1-(phenylsulfonyl)propa-1,2-diene (48). A colorless oil: IR 1963, 1927, 1321, 1153 cm^{-1}; ^{1}H NMR δ 7.82–7.79 (m, 2H), 7.56–7.26 (m, 8H), 5.55 (s, 2H); ^{13}C NMR δ 209.1, 140.3, 140.2, 133.4, 128.9, 128.8, 128.6, 128.5, 128.2, 115.2, 83.9; MS *m/z* 256 (M^+, 7.2); FABHRMS calcd for $C_{15}H_{13}O_2S$ 257.0637, found 257.0657 ($M^+ + 1$).

4.3.5. 1-(Pent-4-ynyl)-2-[1-(phenylsulfonyl)propa-1,2-dienyl]benzene (32). A pale yellow oil: IR 3308, 1967, 1931, 1321, 1153 cm^{-1}; ^{1}H NMR δ 7.71–7.12 (m, 9H), 5.47 (s, 2H), 2.45 (t, 2H, J=7.9 Hz), 2.10 (td, 2H, J=6.9, 2.6 Hz), 1.98 (t, 1H, J=2.6 Hz), 1.57 (quin, 2H, J=6.9 Hz); ^{13}C NMR δ 208.2, 141.7, 139.6, 133.5, 131.1, 129.6, 129.4, 128.8, 128.7, 127.5, 125.9, 112.5, 84.0, 82.9, 68.8, 31.8, 29.5, 18.3; MS *m/z* 322 (M^+, 0.4); HRMS calcd for $C_{20}H_{18}O_2S$ 322.1028, found 322.1024.

4.3.6. 1-(5-Phenylpent-4-ynyl)-2-[1-(phenylsulfonyl)propa-1,2-dienyl]benzene (33). A colorless oil: IR 2232, 1967, 1931, 1321, 1153 cm^{-1}; ^{1}H NMR δ 7.68–7.66 (m, 2H), 7.58–7.54 (m, 1H), 7.44–7.34 (m, 4H), 7.32–7.28 (m, 4H), 7.26–7.15 (m, 3H), 5.46 (s, 2H), 2.51 (t, 2H, J=7.9 Hz), 2.33 (t, 2H, J=6.9 Hz), 1.64 (quin, 2H, J=6.9 Hz); ^{13}C NMR δ 208.1, 141.9, 139.4, 133.5, 131.5, 131.1, 129.6, 129.4, 128.8, 128.6, 128.3, 127.7, 127.5, 125.9, 123.7, 112.4, 89.6, 82.9, 81.2, 32.0, 29.8, 19.2; MS *m/z* 398 (M^+, 24.9); HRMS calcd for $C_{26}H_{22}O_2S$ 398.1341, found 398.1342.

4.3.7. 1-[1-(Phenylsulfonyl)propa-1,2-dienyl]-2-[5-(trimethylsilyl)pent-4-ynyl]benzene (34). A pale yellow oil: IR 2170, 1967, 1931, 1321, 1153 cm^{-1}; ^{1}H NMR δ 7.70–7.56 (m, 3H), 7.47–7.41 (m, 2H), 7.30–7.14 (m, 4H), 5.50 (s, 2H), 2.44 (t, 2H, J=7.9 Hz), 2.14 (t, 2H, J=6.9 Hz), 1.55 (quin, 2H, J=6.9 Hz), 0.18 (s, 9H); ^{13}C NMR δ 208.2, 141.9, 139.6, 133.5, 131.0, 129.6, 129.4, 128.8, 128.6, 127.5, 125.9, 112.4, 106.9, 85.1, 82.9, 32.0, 29.7, 19.7, 0.2; MS *m/z* 394 (M^+, 1.6). Anal. Calcd for $C_{23}H_{26}OSSi$: C, 70.01; H, 6.64. Found: C, 69.99; H, 6.96.

4.3.8. 3-[1-(Methoxymethoxy)-5-phenylpent-4-ynyl]-2-[1-(phenylsulfonyl)propa-1,2-dienyl]furan (59). A colorless oil: IR 1965, 1917, 1325, 1153 cm^{-1}; ^{1}H NMR δ 7.86 (d, 2H, J=7.3 Hz), 7.58 (t, 1H, J=7.3 Hz), 7.50–7.43 (m, 3H), 7.42–7.38 (m, 2H), 7.34–7.28 (m, 3H), 6.40 (d, 1H, J=1.7 Hz), 5.56 (s, 2H), 4.69 (dd, 1H, J=9.3, 4.4 Hz), 4.34, 4.28 (AB-q, 2H, J=6.9 Hz), 3.33 (s, 3H), 2.54–2.33 (m, 2H), 1.99–1.87 (m, 1H), 1.60–1.50 (m, 1H); ^{13}C NMR δ 209.4, 144.3, 140.2, 138.0, 133.6, 131.4, 128.9, 128.3, 128.2, 127.7, 127.3, 123.7, 109.9, 106.5, 93.6, 89.1, 84.4, 81.2, 67.2, 55.5, 34.9, 15.8; MS *m/z* 448 (M^+, 22.1); FABHRMS calcd for $C_{26}H_{25}O_5S$ 449.1422, found 449.1435 ($M^+ + 1$).

4.4. General procedure for Rh(I)-catalyzed PKR

To a solution of allenylalkyne (0.1 mmol) in solvent (1 mL) was added Rh(I) catalyst (5, 10 or 20 mol%). Then the reaction mixture was warmed to the temperature shown in text under CO atmosphere until complete disappearance of the starting material monitored by TLC. The solvent was evaporated off, and the residue was chromatographed to afford cyclized products. Chemical yields were summarized in Schemes.

4.4.1. 9-Phenyl-2-(phenylsulfonyl)bicyclo[6.3.0]undeca-1,8-dien-10-one (8). Colorless needles: mp 184.5–187 °C ($CHCl_3$–hexane); IR 1707, 1306, 1150 cm^{-1}; ^{1}H NMR δ 7.93–7.89 (m, 2H), 7.64 (t, 1H, J=7.3 Hz), 7.57 (t, 2H, J=7.3 Hz), 7.46–7.35 (m, 3H), 7.25–7.19 (m, 2H), 3.79 (s, 2H), 3.07 (t, 2H, J=6.8 Hz), 2.93 (t, 2H, J=7.1 Hz), 1.78 (quin, 2H, J=7.1 Hz), 1.66–1.49 (m, 4H); ^{13}C NMR δ 201.6, 164.9, 148.6, 147.0, 140.7, 134.7, 133.5, 130.6, 129.3, 129.1, 128.8, 128.4, 127.6, 40.9, 28.3, 27.6, 27.4, 26.1, 21.5; MS *m/z* 378 (M^+, 64.5); HRMS calcd for $C_{23}H_{22}O_3S$ 378.1289, found 378.1288.

4.4.2. 4,4-Bis(methoxycarbonyl)-9-phenyl-2-(phenylsulfonyl)bicyclo[6.3.0]undeca-1,8-dien-10-one (12). Colorless powders: mp 254–256 °C ($CHCl_3$–hexane); IR 1730, 1709, 1308, 1150 cm^{-1}; ^{1}H NMR δ 7.94–7.86 (m, 2H), 7.69–7.52 (m, 3H), 7.46–7.34 (m, 3H), 7.22–7.14 (m, 2H), 3.94–3.71 (m, 8H), 3.61 (d, 1H, J=17 Hz), 3.34 (d, 1H, J=22 Hz), 3.00–2.70 (m, 2H), 2.36–2.12 (m, 2H), 1.85–1.60 (m, 2H); ^{13}C NMR δ 200.6, 171.3, 170.8, 163.2, 149.7, 149.2, 141.1, 133.6, 133.4, 130.2, 129.5, 129.1, 128.5, 127.6, 56.7, 53.1, 40.8, 32.2, 27.5, 26.8, 24.0; MS *m/z* 494 (M^+, 16.3); FABHRMS calcd for $C_{27}H_{27}O_7S$ 495.1477, found 495.1488 ($M^+ + 1$).

4.4.3. 11-(Phenylsulfonyl)-1,4,5,10-tetrahydro-2*H*-benzo[*g*]cyclopentacycloocten-2-one (24). Colorless powders: mp 155–157 °C (hexane–AcOEt); IR 1701, 1308, 1150 cm^{-1}; ^{1}H NMR δ 7.81–7.75 (m, 2H), 7.66–7.57 (m, 1H), 7.55–7.45 (m, 2H), 7.17–6.98 (m, 4H), 6.33 (s, 1H), 4.23 (br s, 2H), 3.45–3.14 (m, 6H); ^{13}C NMR δ 202.2, 171.7, 146.4, 140.6, 138.8, 137.9, 136.2, 135.6, 133.6, 131.5, 131.3, 129.3, 127.7, 127.2, 126.6, 41.9, 34.0, 32.6, 29.7; MS *m/z* 350 (M^+, 43.3); HRMS calcd for $C_{21}H_{18}O_3S$ 350.0977, found 350.0975.

4.4.4. 3-Phenyl-11-(phenylsulfonyl)-1,4,5,10-tetrahydro-2*H*-benzo[*g*]cyclopentacycloocten-2-one (25). Pale yellow powders: mp 227–229 °C ($CHCl_3$–hexane); IR 1709, 1308, 1148 cm^{-1}; ^{1}H NMR δ 7.87–7.79 (m, 2H), 7.67–7.37 (m, 6H), 7.33–7.24 (m, 2H), 7.15–7.01 (m, 3H), 6.96–6.89 (m, 1H), 4.25 (br s, 2H), 3.59 (br s, 2H), 3.24 (s, 4H); ^{13}C NMR δ 200.8, 164.7, 148.8, 146.8, 140.7, 136.9, 136.6, 136.6, 133.5, 130.9, 130.8, 130.3, 129.3, 129.3, 129.2, 128.5,

127.8, 127.3, 127.0, 41.8, 34.8, 33.0, 28.3; MS *m/z* 426 (M^+, 29.6); FABHRMS calcd for $C_{27}H_{23}O_3S$ 427.1368, found 427.1368 ($M^+ + 1$).

4.4.5. 11-(Phenylsulfonyl)-1,4,5,6-tetrahydro-2*H*-benzo[*f*]cyclopentacycloocten-2-one (49). Colorless powders: mp 126–129 °C ($CHCl_3$–hexane); IR 1701, 1321, 1150 cm^{-1}; ^1H NMR δ 7.79–7.72 (m, 1H), 7.48–7.45 (m, 3H), 7.33–7.25 (m, 4H), 6.96–6.95 (m, 1H), 6.27 (s, 1H), 3.85, 3.80 (AB-q, 2H, $J=22$ Hz), 2.46–2.38 (m, 2H), 2.26 (td, 1H, $J=13$, 5.9 Hz), 1.85–1.70 (m, 2H), 1.66–1.57 (m, 1H); ^{13}C NMR δ 202.7, 171.9, 146.3, 139.9, 139.7, 138.2, 138.1, 135.3, 133.2, 131.2, 131.0, 130.3, 128.6, 127.8, 125.9, 41.6, 31.2, 30.2, 27.2; MS *m/z* 350 (M^+, 100); HRMS calcd for $C_{21}H_{18}O_3S$ 350.0977, found 350.0979.

4.4.6. 3-Phenyl-11-(phenylsulfonyl)-1,4,5,6-tetrahydro-2*H*-benzo[*f*]cyclopentacycloocten-2-one (50). Pale yellow plates: mp 219–221.5 °C ($CHCl_3$–hexane); IR 1707, 1321, 1150 cm^{-1}; ^1H NMR δ 7.76–7.74 (m, 1H), 7.52–7.20 (m, 12H), 6.97–6.95 (m, 1H), 4.01, 3.92 (AB-q, 2H, $J=22$ Hz), 2.63–2.58 (m, 1H), 2.49–2.41 (m, 1H), 2.37 (td, 1H, $J=13$, 4.9 Hz), 1.80–1.75 (m, 2H), 1.60–1.56 (m, 1H); ^{13}C NMR δ 201.2, 164.9, 147.7, 146.1, 140.2, 140.0, 135.0, 133.1, 131.4, 131.2, 130.5, 130.3, 129.1, 128.8, 128.6, 128.4, 127.8, 127.6, 125.9, 40.8, 31.3, 30.4, 24.2; MS *m/z* 426 (M^+, 60.1); FABHRMS calcd for $C_{27}H_{23}O_3S$ 427.1368, found 427.1357 ($M^+ + 1$).

4.4.7. 11-(Phenylsulfonyl)-3-(trimethylsilyl)-1,4,5,6-tetrahydro-2*H*-benzo[*f*]cyclopentacycloocten-2-one (51). Pale yellow needles: mp 153.5–156 °C (hexane–THF); IR 1695, 1317, 1148 cm^{-1}; ^1H NMR δ 7.75–7.68 (m, 1H), 7.50–7.42 (m, 3H), 7.35–7.20 (m, 4H), 6.98–6.90 (m, 1H), 3.81, 3.70 (AB-q, 2H, $J=22$ Hz), 2.61 (dt, 1H, $J=13$, 2.8 Hz), 2.45–2.34 (m, 1H), 2.27 (td, 1H, $J=13$, 5.9 Hz), 1.82 (td, 1H, $J=13$, 4.6 Hz), 1.75–1.50 (m, 2H), 0.23 (s, 9H); ^{13}C NMR δ 207.2, 177.4, 150.6, 147.7, 140.2, 140.1, 134.0, 133.5, 131.2, 131.1, 130.2, 128.6, 127.8, 127.6, 125.8, 42.0, 31.6, 30.3, 26.4, −0.3; MS *m/z* 422 (M^+, 1.9). Anal. Calcd for $C_{24}H_{26}O_3SSi$: C, 68.21; H, 6.20. Found: C, 68.25; H, 6.49.

4.4.8. 4-(Methoxymethoxy)-7-phenyl-10-(phenylsulfonyl)-4,5,6,9-tetrahydro-8*H*-cyclopentacycloocta[5,6-*b*]furan-8-one (60). Pale yellow powders: mp 219–221 °C ($CHCl_3$–hexane); IR 1710, 1310, 1151 cm^{-1}; ^1H NMR δ 7.89 (d, 2H, $J=7.6$ Hz), 7.56–7.38 (m, 7H), 7.30–7.20 (m, 2H), 6.39 (d, 1H, $J=1.7$ Hz), 4.59 (dd, 1H, $J=12$, 6.1 Hz), 4.51, 4.39 (AB-q, 2H, $J=6.8$ Hz), 3.97, 3.85 (AB-q, 2H, $J=23$ Hz), 3.33 (s, 3H), 2.76 (d, 1H, $J=13$ Hz), 2.22–2.10 (m, 1H), 1.91 (td, 1H, $J=13$, 5.1 Hz), 1.86–1.76 (m, 1H); ^{13}C NMR δ 200.7, 163.2, 149.6, 141.7, 141.0, 133.4, 130.4, 129.4, 129.1, 129.0, 128.9, 128.6, 127.5, 127.0, 108.6, 94.9, 69.3, 55.8, 40.5, 37.2, 25.0; MS *m/z* 476 (M^+, 37.9); FABHRMS calcd for $C_{27}H_{25}O_6S$ 477.1372, found 477.1371 ($M^+ + 1$).

4.5. Preparation of propargyl alcohol derivatives

4.5.1. 10-(*tert*-Butyldiphenylsiloxy)-1-(trimethylsilyl) deca-1,8-diyne (4). To a solution of 3-(*tert*-butyldiphenylsiloxy)prop-1-yne (2.96 g, 10.0 mmol) in THF–DMPU (5/1, 90 mL) was added ^{n}BuLi (1.38 M in hexane solution, 8.40 mL, 11.6 mmol) at −78 °C. After stirring for 30 min, a solution of **3** (2.28 g, 7.73 mmol) in THF–DMPU (5/1, 10 mL) was gradually added to the reaction mixture, which was stirred at room temperature for 14 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (10/1) to afford **4** (2.33 g, 51%) as a colorless oil: IR 2170 cm^{-1}; ^1H NMR δ 7.78–7.69 (m, 4H), 7.46–7.34 (m, 6H), 4.32 (t, 2H, $J=2.0$ Hz), 2.27–2.10 (m, 4H), 1.60–1.37 (m, 6H), 1.07 (s, 9H), 0.16 (s, 9H); ^{13}C NMR δ 135.6, 133.4, 129.7, 127.6, 107.4, 85.5, 84.4, 78.6, 53.0, 28.2, 28.0, 27.9, 26.7, 19.8, 19.2, 18.7, 0.2; FABMS *m/z* 461 ($M^+ + 1$, 3.3). Anal. Calcd for $C_{29}H_{40}OSi$: C, 75.59; H, 8.75. Found: C, 75.67; H, 8.75.

4.5.2. Deca-2,9-diyn-1-ol (5). To a solution of **4** (2.33 g, 5.06 mmol) in THF (50 mL) was added TBAF (1.0 M in THF solution, 12 mL, 12 mmol) at room temperature. After stirring for 30 min, THF was evaporated off, and the residue was chromatographed with hexane–AcOEt (5/1) to afford **5** (0.710 g, 93%) as a colorless oil: IR 3609, 3441, 2226 cm^{-1}; ^1H NMR δ 4.23 (t, 2H, $J=2.3$ Hz), 2.28–2.13 (m, 4H), 1.94 (t, 1H, $J=2.6$ Hz), 1.72 (br s, 1H), 1.59–1.42 (m, 6H); ^{13}C NMR δ 86.3, 84.4, 78.5, 68.3, 51.4, 28.0, 27.9, 27.9, 18.6, 18.3; MS *m/z* 150 (M^+, 3.6); HRMS calcd for $C_{10}H_{14}O$ 150.1044, found 150.1053.

4.5.3. 10-Phenyldeca-2,9-diyn-1-ol (6). To a solution of **5** (580 mg, 3.83 mmol) in THF (38 mL) were added $Pd(PPh_3)_2Cl_2$ (26.9 mg, 3.83×10^{-2} mmol) and CuI (14.6 mg, 7.66×10^{-2} mmol) at room temperature. Iodobenzene (0.85 mL, 7.7 mmol) and $^i Pr_2NH$ (5.02 mL, 38.3 mmol) were then added dropwise to the reaction mixture. After being stirred for 24 h, the reaction mixture was filtered by suction. The filtrate was concentrated, and the residue was chromatographed with hexane–AcOEt (5/1) to afford **6** (688 mg, 79%) as a colorless oil: IR 3609, 3445, 2253, 2226 cm^{-1}; ^1H NMR δ 7.42–7.36 (m, 2H), 7.30–7.24 (m, 3H), 4.23 (s, 2H), 2.41 (t, 2H, $J=6.8$ Hz), 2.28–2.20 (m, 2H), 1.70 (br s, 1H), 1.66–1.52 (m, 6H); ^{13}C NMR δ 131.5, 128.1, 127.5, 124.0, 90.0, 86.2, 80.8, 78.5, 51.3, 28.2, 28.1, 28.0, 19.2, 18.6; MS *m/z* 226 (M^+, 4.3); HRMS calcd for $C_{16}H_{18}O$ 226.1358, found 226.1354.

4.5.4. 5,5-Bis(methoxycarbonyl)deca-2,9-diyn-1-ol (9). To a solution of dimethyl malonate (1.14 mL, 10.0 mmol) in THF (70 mL) was added NaH (60% in mineral oil, 520 mg, 13.0 mmol) at 0 °C. After stirring for 30 min, a solution of 5-iodopent-1-yne (3.19 g, 12.0 mmol) in THF (30 mL) was gradually added to the reaction mixture, which was stirred at room temperature for 36 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (4/1) to afford the crude alkyne. To a solution of the crude alkyne in THF (70 mL) was added NaH (60% in mineral oil, 416 mg, 10.4 mmol) at 0 °C. After stirring for 10 min, a solution of 4-iodo-1-(*tert*-butyldiphenylsiloxy)but-2-yne (3.16 g, 7.27 mmol) in THF (17 mL) was gradually added to the reaction mixture, which was

stirred at room temperature for 1.5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (6/1) to afford the crude diyne. To a solution of the crude diyne in THF (44 mL) was added TBAF (1.0 M in THF solution, 4.9 mL, 4.9 mmol) at room temperature. After stirring for 1.5 h, THF was evaporated off, and the residue was chromatographed with hexane–AcOEt (3/1) to afford **9** (1.17 g, 44%) as a colorless oil: IR 3607, 3508, 3308, 2118, 1726 cm^{-1}; ^1H NMR δ 4.19 (br s, 2H), 3.73 (s, 6H), 2.84 (t, 2H, $J=2.0$ Hz), 2.21 (td, 2H, $J=6.9$, 2.6 Hz), 2.17–2.07 (m, 2H), 1.96 (t, 1H, $J=2.6$ Hz), 1.93 (br s, 1H), 1.50–1.33 (m, 2H); ^{13}C NMR δ 170.5, 83.3, 81.7, 79.6, 68.7, 56.5, 52.6, 50.5, 31.2, 23.1, 23.0, 18.3; MS *m/z* 266 (M^+, 0.7); HRMS calcd for $C_{14}H_{18}O_5$ 266.1155, found 266.1161.

4.5.5. 5,5-Bis(methoxycarbonyl)-10-phenyldeca-2,9-diyn-1-ol (10). According to the procedure for preparation of **6** from **5**, **10** (530 mg, 77%) was obtained from **9** (532 mg, 2.00 mmol) as a colorless oil: IR 3607, 3471, 1732 cm^{-1}; ^1H NMR δ 7.43–7.33 (m, 2H), 7.31–7.24 (m, 3H), 4.20–4.10 (m, 2H), 3.74 (s, 6H), 2.88 (t, 2H, $J=2.3$ Hz), 2.44 (t, 2H, $J=7.3$ Hz), 2.26–2.16 (m, 2H), 1.95–1.81 (m, 1H), 1.60–1.42 (m, 2H); ^{13}C NMR δ 170.7, 131.5, 128.2, 127.6, 123.8, 89.2, 81.7, 81.2, 80.3, 56.9, 52.7, 51.0, 31.5, 23.6, 23.3, 19.5; MS *m/z* 342 (M^+, 2.4); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1465.

4.5.6. 2-(Hydroxymethyl)-1-[4-(trimethylsilyl)but-3-ynyl]benzene (16). To a suspension of zinc powder (1.31 g, 20.0 mmol) in DMA (8.0 mL) was added I_2 (254 mg, 1.00 mmol) at room temperature. The reaction mixture was stirred until the red color of I_2 disappeared. Then a solution of 4-bromo-1-(trimethylsilyl)but-1-yne (2.05 g, 10.0 mmol) in DMA (2.0 mL) was added and the reaction mixture was warmed to 80 °C. After stirring for 3 h, a solution of **13** (1.76 g, 5.05 mmol) in DMA (1.0 mL) and $Pd(PPh_3)_4$ (289 mg, 0.250 mmol) were added to the reaction mixture, which was stirred at 80 °C for 1 h. The reaction mixture was filtered through a Celite pad, and the filtrate was diluted with 10% aqueous HCl and extracted with Et_2O. The extract was washed with water and brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (20/1) to afford the crude **15**. To a solution of the crude **15** in THF (50 mL) was added TsOH–H_2O (476 mg, 2.50 mmol) at room temperature. After being stirred for 13 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (4/1) to afford **16** (727 mg, 62%) as a colorless oil: IR 3609, 3503, 2170 cm^{-1}; ^1H NMR δ 7.40–7.20 (m, 4H), 4.74 (s, 2H), 2.94 (t, 2H, $J=7.6$ Hz), 2.55 (t, 2H, $J=7.6$ Hz), 1.71 (s, 1H), 0.14 (s, 9H); ^{13}C NMR δ 138.8, 138.5, 129.7, 128.6, 128.0, 126.7, 106.7, 85.6, 63.1, 31.1, 21.9, 0.0; MS *m/z* 232 (M^+, 4.5). Anal. Calcd for $C_{14}H_{20}OSi$: C, 72.36; H, 8.67. Found: C, 72.11; H, 8.95.

4.5.7. 2-(Bromomethyl)-1-[4-(trimethylsilyl)but-3-ynyl]benzene (17). To a solution **16** (349 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) were added PPh_3 (637 mg, 3.00 mmol) and CBr_4 (746 mg, 2.25 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. CH_2Cl_2 was evaporated off, and the residue was chromatographed with hexane–AcOEt (30/1) to afford **17** (438 mg, 99%) as a colorless oil: IR 2172 cm^{-1}; ^1H NMR δ 7.38–7.15 (m, 4H), 4.59 (s, 2H), 2.98 (t, 2H, $J=7.6$ Hz), 2.59 (t, 2H, $J=7.6$ Hz), 0.15 (s, 9H); ^{13}C NMR δ 139.4, 135.7, 130.5, 130.1, 129.0, 127.0, 106.1, 85.7, 31.6, 31.1, 21.4, 0.0; MS *m/z* 294 (M^+, 1.2), 296 (M^+, 1.2). Anal. Calcd for $C_{14}H_{19}BrSi$: C, 56.94; H, 6.49. Found: C, 56.77; H, 6.56.

4.5.8. 2-(But-3-ynyl)-1-(4-hydroxybut-2-ynyl)benzene (20). Lithium acetylide, prepared from 1-(*tert*-butyldimethylsiloxy)prop-2-yne (766 mg, 4.50 mmol) and ^{n}BuLi (1.42 M in hexane, 3.24 mL, 4.60 mmol), in THF (1.3 mL) was added to a suspension of $InCl_3$ (354 mg, 1.60 mmol) in THF (10 mL) at −78 °C. After being stirred for 30 min, the resulting solution was then added to a solution of **17** (809 mg, 2.74 mmol) and $Pd(dppf)Cl_2$ (CH_2Cl_2 complex, 22.4 mg, 2.70×10^{-2} mmol) in THF (12 mL). The reaction mixture was refluxed for 18.5 h, quenched by addition of MeOH and 10% aqueous HCl, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (50/1) to afford the crude diyne **19**. To a solution of the crude **19** in THF (23 mL) was added TBAF (1.0 M in THF solution, 7.0 mL, 7.0 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. THF was evaporated off, and the residue was chromatographed with hexane–AcOEt (4/1) to afford **20** (354 mg, 65%) as a colorless oil: IR 3606, 3439, 3306, 2118 cm^{-1}; ^1H NMR δ 7.42–7.36 (m, 1H), 7.22–7.16 (m, 3H), 4.25 (t, 2H, $J=2.4$ Hz), 3.61 (t, 2H, $J=2.4$ Hz), 2.89 (t, 2H, $J=7.8$ Hz), 2.48 (td, 2H, $J=7.8$, 2.4 Hz), 2.10 (br s, 1H), 1.99 (t, 1H, $J=2.4$ Hz); ^{13}C NMR δ 138.1, 134.4, 129.2, 129.0, 127.1, 126.8, 83.7, 83.6, 80.6, 69.1, 51.2, 31.3, 22.8, 19.6; MS *m/z* 198 (M^+, 2.4); HRMS calcd for $C_{14}H_{14}O$ 198.1044, found 198.1042.

4.5.9. 1-(4-Hydroxybut-2-ynyl)-2-(4-phenylbut-3-ynyl)benzene (21). According to the procedure for preparation of **6** from **5**, **21** (301 mg, 73%) was obtained from **20** (297 mg, 1.50 mmol) as a colorless oil: IR 3607, 3383, 2226 cm^{-1}; ^1H NMR δ 7.44–7.34 (m, 3H), 7.30–7.18 (m, 6H), 4.26 (t, 2H, $J=2.0$ Hz), 3.66 (t, 2H, $J=2.0$ Hz), 2.97 (t, 2H, $J=7.8$ Hz), 2.70 (t, 2H, $J=7.8$ Hz), 1.83 (br s, 1H); ^{13}C NMR δ 138.3, 134.5, 131.5, 129.4, 129.0, 128.2, 127.7, 127.2, 126.8, 123.6, 89.3, 83.8, 81.4, 80.6, 51.3, 31.7, 22.9, 20.8; MS *m/z* 274 (M^+, 2.1); HRMS calcd for $C_{20}H_{18}O$ 274.1357, found 274.1349.

4.5.10. 1-Bromo-2-[3-(*tert*-butyldimethylsiloxy)prop-1-ynyl]benzene (27). According to the procedure for preparation of **6** from **5**, **27** (552 mg, 85%) was obtained from **26** (0.25 mL, 2.00 mmol) as a colorless oil: ^1H NMR δ 7.57 (dd, 1H, $J=7.9$, 1.3 Hz), 7.46 (dd, 1H, $J=7.9$, 1.7 Hz), 7.25 (td, 1H, $J=7.6$, 1.3 Hz), 7.15 (td, 1H, $J=7.6$, 1.7 Hz), 4.59 (s, 2H), 0.94 (s, 9H), 0.18 (s, 6H); ^{13}C NMR δ 133.6, 132.4, 129.4, 126.9, 125.4, 125.1, 92.5, 83.2, 52.3, 25.8, 18.3, −5.0; MS *m/z* 323 (M^+, 2.5), 325 (M^+, 2.6). Anal. Calcd for $C_{15}H_{21}OBrSi$: C, 55.38; H, 6.51. Found: C, 55.06; H, 6.45.

4.5.11. 1-(3-Hydroxyprop-1-ynyl)-2-(pent-4-ynyl)benzene (29). According to the procedure for preparation of **15** from **13**, the crude **28** was obtained from **27** (975 mg, 3.00 mmol). To a solution of the crude **28** in THF (20 mL) was added TBAF (1.0 M in THF solution, 5.0 mL, 5.0 mmol) at 0 °C. After stirring for 10 min, THF was evaporated off, and the residue was chromatographed with hexane–AcOEt (4/1) to afford **29** (438 mg, 74%) as a colorless oil: IR 3607, 3431, 3306, 2233, 2116 cm^{-1}; ^1H NMR δ 7.43–7.40 (m, 1H), 7.29–7.13 (m, 3H), 4.53 (d, 2H, J=6.0 Hz), 2.90 (t, 2H, J=7.6 Hz), 2.24 (td, 2H, J=6.9, 2.6 Hz), 2.01 (t, 1H, J=2.6 Hz), 1.87 (quin, 2H, J=7.0 Hz), 1.71 (t, 1H, J=6.0 Hz); ^{13}C NMR δ 143.7, 132.4, 129.0, 128.6, 126.0, 122.0, 90.8, 84.5, 84.3, 68.6, 51.8, 33.3, 29.2, 18.1; MS m/z 198 (M^+, 2.5); FABHRMS calcd for $C_{14}H_{14}ONa$ 221.0943, found 221.0954 (M^++23).

4.5.12. 1-(3-Hydroxyprop-1-ynyl)-2-(5-phenylpent-4-ynyl)benzene (30). According to the procedure for preparation of **6** from **5**, **30** (120 mg, 73%) was obtained from **29** (118 mg, 0.600 mmol) as a colorless oil: IR 3607, 3425, 2232 cm^{-1}; ^1H NMR δ 7.44–7.39 (m, 3H), 7.31–7.13 (m, 6H), 4.46 (d, 2H, J=6.3 Hz), 2.96 (t, 2H, J=7.9 Hz), 2.46 (t, 2H, J=6.9 Hz), 1.96 (quin, 2H, J=6.9 Hz), 1.63 (t, 1H, J=6.3 Hz); ^{13}C NMR δ 143.8, 132.5, 131.5, 129.0, 128.6, 128.3, 127.7, 125.9, 123.9, 122.0, 90.8, 90.0, 84.3, 81.1, 51.7, 33.5, 29.4, 19.1; MS m/z 274 (M^+, 4.7); FABHRMS calcd for $C_{20}H_{18}ONa$ 297.1256, found 297.1246 (M^++23).

4.5.13. 1-(3-Hydroxyprop-1-ynyl)-2-[5-(trimethylsilyl)pent-4-ynyl]benzene (31). According to the procedure for preparation of **15** from **13**, the crude **28** was obtained from **27** (846 mg, 2.60 mmol). To a solution of the crude **28** in THF (20 mL) was added 10% aqueous HCl (5.0 mL) at room temperature. After being stirred for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (3/1) to afford **31** (557 mg, 78%) as a colorless oil: IR 3607, 3454, 2233, 2170 cm^{-1}; ^1H NMR δ 7.42–7.39 (m, 1H), 7.28–7.11 (m, 3H), 4.52 (s, 2H), 2.87 (t, 2H, J=7.6 Hz), 2.27 (t, 2H, J=7.3 Hz), 1.95 (s, 1H), 1.87 (quin, 2H, J=7.3 Hz), 0.17 (s, 9H); ^{13}C NMR δ 143.7, 132.4, 129.0, 128.6, 125.9, 122.0, 107.3, 90.8, 85.0, 84.3, 51.6, 33.5, 29.2, 19.5, 0.2; MS m/z 270 (M^+, 0.2). Anal. Calcd for $C_{17}H_{22}OSi$: C, 75.50; H, 8.20. Found: C, 75.23; H, 8.58.

4.5.14. 5-Phenylpent-2-yn-1-ol (38). To a solution of 4-phenylbut-1-yne (1.36 g, 10.5 mmol) in THF (100 mL) was added ^{n}BuLi (1.47 M in hexane solution, 10.7 mL, 15.8 mmol) at −78 °C. After stirring for 1 h, $(HCHO)_n$ (1.58 g, 52.5 mmol) was added to the reaction mixture, which was stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (2/1) to afford **38** (1.64 g, 97%) as a colorless oil: IR 3609, 3427, 2222 cm^{-1}; ^1H NMR δ 7.33–7.20 (m, 5H), 4.23 (dt, 2H, J=5.9, 2.1 Hz), 2.83 (t, 2H, J=7.6 Hz), 2.51 (tt, 2H, J=7.6, 2.1 Hz), 1.53 (t, 1H, J=5.9 Hz); ^{13}C NMR δ 140.5, 128.3, 128.2, 126.3, 87.9, 85.6, 51.2, 34.9, 20.8; MS m/z 160 (M^+, 3.7); FABHRMS calcd for $C_{11}H_{12}ONa$ 183.0786, found 183.0794 (M^++23).

4.5.15. 6-Phenylhex-3-yn-2-ol (39). To a solution of 4-phenylbut-1-yne (421 mg, 3.23 mmol) in THF (32 mL) was added ^{n}BuLi (1.47 M in hexane solution, 3.30 mL, 4.85 mmol) at −78 °C. After stirring for 1 h, CH_3CHO (0.91 mL, 16 mmol) was added to the reaction mixture, which was stirred for 1 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (5/1) to afford **39** (529 mg, 94%) as a colorless oil: IR 3603, 3420, 2241 cm^{-1}; ^1H NMR δ 7.33–7.20 (m, 5H), 4.64–4.55 (m, 1H), 2.82 (t, 2H, J=7.6 Hz), 2.49 (td, 2H, J=7.6, 1.8 Hz), 1.70 (d, 1H, J=5.1 Hz), 1.41 (d, 3H, J=6.4 Hz); ^{13}C NMR δ 140.6, 128.4, 128.3, 126.3, 83.9, 83.1, 58.5, 35.0, 24.6, 20.8; MS m/z 174 (M^+, 2.8); FABHRMS calcd for $C_{12}H_{14}ONa$ 197.0942, found 197.0951 (M^++23).

4.5.16. 2-Methyl-6-phenylhex-3-yn-2-ol (40).[19] According to the procedure for preparation of **39**, **40** (495 mg, 79%) was obtained from 4-phenylbut-1-yne (435 mg, 3.34 mmol) and CH_3COCH_3 (1.20 mL, 16.7 mmol) as a colorless oil: IR 3599, 3431, 2235 cm^{-1}; ^1H NMR δ 7.33–7.20 (m, 5H), 2.81 (t, 2H, J=7.6 Hz), 2.47 (t, 2H, J=7.6 Hz), 1.84 (s, 1H), 1.47 (s, 6H).

4.5.17. 2-[3-(*tert*-Butyldiphenylsiloxy)prop-1-ynyl]-3-(2,5-dioxolanyl)furan (52). To a solution of *N*,*N*,*N*′-trimethylethylenediamine (3.40 mL, 26.0 mmol) in THF (40 mL) was added ^{n}BuLi (1.46 M in hexane solution, 16.8 mL, 24.0 mmol) at −78 °C. After stirring for 10 min, 3-furaldehyde (1.73 mL, 20.0 mmol) was gradually added, and the reaction mixture was stirred for 20 min. Then ^{n}BuLi (35.0 mL, 50.0 mmol) was added dropwise to the reaction mixture, which was stirred for 2 h. A solution of I_2 (25.4 g, 100 mmol) in THF (10 mL) was added to the reaction mixture. After being stirred for 1 h, the reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (5/1) to afford the crude iodide. To a solution of the crude iodide in benzene (31 mL) were added ethylene glycol (2.09 mL, 37.5 mmol) and TsOH–H_2O (476 mg, 2.50 mmol), and the reaction mixture was refluxed for 1.5 h under azeotropic removal of water. The reaction mixture was quenched by addition of Et_3N and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (5/1) to afford the crude acetal. According to the procedure for preparation of **6** from **5**, **52** (4.49 g, 52%) was obtained from the crude acetal as a pale yellow oil: ^1H NMR δ 7.76–7.68 (m, 4H), 7.48–7.35 (m, 6H), 7.32 (d, 1H, J=2.0 Hz), 6.47 (d, 1H, J=2.0 Hz), 5.79 (s, 1H), 4.56 (s, 2H), 4.18–3.91 (m, 4H), 1.07 (s, 9H); ^{13}C NMR δ 143.4, 135.7, 135.5, 132.8, 129.8, 127.7, 109.1, 97.8, 94.9, 73.6, 65.1, 53.0, 26.6, 19.1; MS m/z 432 (M^+, 2.2). Anal. Calcd for $C_{26}H_{28}O_4Si$: C, 72.19; H, 6.52. Found: C, 71.95; H, 6.58.

4.5.18. 2-[3-(*tert*-Butyldiphenylsiloxy)prop-1-ynyl]-3-[1-hydroxy-5-(trimethylsilyl)pent-4-ynyl]furan (54). To a solution of **52** (433 mg, 1.00 mmol) in THF (10 mL) was added 10% aqueous HCl (3.0 mL) at room temperature. After being stirred for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (10/1) to afford the crude aldehyde. To a solution of **53** (1.0 M in Et_2O solution, 9.9 mL, 9.9 mmol) was added crude aldehyde in Et_2O (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of 10% aqueous HCl and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (8/1) to afford **54** (868 mg, 85%) as a pale yellow oil: IR 3599, 3524, 2172 cm^{-1}; ^1H NMR δ 7.75–7.71 (m, 4H), 7.48–7.37 (m, 6H), 7.31 (d, 1H, $J=2.0$ Hz), 6.44 (d, 1H, $J=2.0$ Hz), 4.78 (dd, 1H, $J=7.8$, 5.1 Hz), 4.57 (s, 2H), 2.32 (td, 2H, $J=7.3$, 1.0 Hz), 2.05 (br s, 1H), 2.04–1.94 (m, 1H), 1.92–1.83 (m, 1H), 1.08 (s, 9H), 0.14 (s, 9H); ^{13}C NMR δ 143.6, 135.6, 133.2, 132.9, 132.9, 129.8, 127.7, 109.3, 106.5, 95.2, 85.3, 74.1, 65.9, 53.1, 36.1, 26.7, 19.2, 16.4, 0.1; MS *m/z* 514 (M^+, 0.8). Anal. Calcd for $C_{31}H_{38}O_3Si_2$: C, 72.33; H, 7.44. Found: C, 71.97; H, 7.46.

4.5.19. 2-[3-(*tert*-Butyldiphenylsiloxy)prop-1-ynyl]-3-[1-(methoxymethoxy)-5-(trimethylsilyl)pent-4-ynyl]furan (55). To a solution of **54** (419 mg, 0.814 mmol) in CH_2Cl_2 (8.1 mL) were added $^iPr_2NEt$ (0.28 mL, 1.6 mmol) and MOMCl (0.12 mL, 1.63 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 9 h. The reaction mixture was quenched by addition of water, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (8/1) to afford **55** (432 mg, 95%) as a pale yellow oil: IR 2172 cm^{-1}; ^1H NMR δ 7.79–7.74 (m, 4H), 7.49–7.41 (m, 6H), 7.33 (d, 1H, $J=2.0$ Hz), 6.41 (d, 1H, $J=2.0$ Hz), 4.78 (dd, 1H, $J=8.1$, 5.4 Hz), 4.62–4.56 (m, 3H), 4.53 (d, 1H, $J=6.6$ Hz), 3.38 (s, 3H), 2.36 (td, 2H, $J=7.8$, 2.0 Hz), 2.13–2.04 (m, 1H), 1.95–1.86 (m, 1H), 1.12 (s, 9H), 0.17 (s, 9H); ^{13}C NMR δ 143.6, 135.6, 134.5, 132.9, 132.9, 130.2, 129.8, 127.7, 109.7, 106.4, 94.9, 94.3, 84.9, 73.9, 68.9, 55.6, 53.1, 35.2, 26.7, 19.2, 16.4, 0.1; MS *m/z* 558 (M^+, 0.4). Anal. Calcd for $C_{33}H_{42}O_4Si_2$: C, 70.92; H, 7.58. Found: C, 70.55; H, 7.72.

4.5.20. 2-(3-Hydroxyprop-1-ynyl)-3-[1-(methoxymethoxy)pent-4-ynyl]furan (56). According to the procedure for preparation of **5** from **4**, **56** (28.5 mg, 90%) was obtained from **55** (71.4 mg, 0.128 mmol) as a colorless oil: IR 3603, 3420, 3308, 2118 cm^{-1}; ^1H NMR δ 7.33 (d, 1H, $J=2.0$ Hz), 6.40 (d, 1H, $J=2.0$ Hz), 4.83 (dd, 1H, $J=8.3$, 5.9 Hz), 4.64–4.46 (m, 4H), 3.39 (s, 3H), 2.61 (br s, 1H), 2.37–2.25 (m, 2H), 2.17–2.01 (m, 1H), 1.99 (t, 1H, $J=$ 2.6 Hz), 1.95–1.79 (m, 1H); ^{13}C NMR δ 143.9, 134.7, 130.4, 109.5, 95.1, 93.9, 83.5, 74.7, 68.8, 68.2, 55.7, 51.4, 34.6, 15.0; MS *m/z* 248 (M^+, 1.2); FABHRMS calcd for $C_{14}H_{17}O_4$ 249.1126, found 249.1112 ($M^+ + 1$).

4.5.21. 2-(3-Hydroxyprop-1-ynyl)-3-[1-(methoxymethoxy)-5-phenylpent-4-ynyl]furan (57). According to the procedure for preparation of **6** from **5**, **57** (369 mg, 91%) was obtained from **56** (310 mg, 1.25 mmol) as a pale yellow oil: IR 3601, 3422, 2230 cm^{-1}; ^1H NMR δ 7.43–7.39 (m, 2H), 7.33 (d, 1H, $J=2.0$ Hz), 7.31–7.24 (m, 3H), 6.42 (d, 1H, $J=2.0$ Hz), 4.95 (dd, 1H, $J=8.3$, 5.6 Hz), 4.63, 4.53 (AB-q, 2H, $J=6.8$ Hz), 4.37 (s, 2H), 3.41 (s, 3H), 2.65–2.42 (m, 3H), 2.22–2.12 (m, 1H), 1.99–1.89 (m, 1H); ^{13}C NMR δ 143.9, 134.8, 131.4, 130.3, 128.2, 127.7, 123.8, 109.5, 95.1, 93.8, 89.0, 81.3, 74.5, 68.2, 55.6, 51.2, 34.7, 16.0; MS *m/z* 324 (M^+, 0.5). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.85; H, 6.52.

Acknowledgements

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References and notes

1. For leading reviews, see: (a) Pauson, P. L. In *Aspects of a Modern Interdisciplinary Field*; de Meijere, A., tom Dieck, H., Eds.; Organometallics in Organic Synthesis; Springer: Berlin, 1988. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. (c) Schore, N. E. *Org. React.* **1991**, *40*, 1–90. (d) Schore, N. E. In Trost, B. M., Ed.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 5, pp 1037–1064. (e) Schore, N. E. In Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Comprehensive Organometallic Chemistry II; Elsevier: New York, 1995; Vol. 12, pp 703–739. (f) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523–596. (g) Jeong, N. In Beller, H., Bolm, C., Eds.; Transition Metals in Organic Synthesis; Wiley-VCH: Weinheim, 1998; Vol. 1, pp 560–577. (h) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911–914. (i) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297–341. (j) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283. (k) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795–9833.
2. For attempts at constructing the bicyclo[5.3.0]decenone skeleton via the intramolecular PKR of enynes, see: (a) Wender, P. A.; McDonald, F. E. *Tetrahedron Lett.* **1990**, *31*, 3691–3694. (b) Mukai, C.; Sonobe, H.; Kim, J. S.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6654–6659.
3. For construction of seven and larger-membered rings via PKR of enynes with an aromatic ring as a template, see: (a) Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Commun.* **2001**, 2602–2603. (b) Krafft, M. E.; Fu, Z.; Boñaga, L. V. R. *Tetrahedron Lett.* **2001**, *42*, 1427–1431. (c) Lovely, C. J.; Seshadri, H.; Wayland, B. R.; Cordes, A. W. *Org. Lett.* **2001**, *3*, 2607–2610. (d) Barluenga, J.; Sanz, R.; Fañanás, F. J. *Chem. Eur. J.* **1997**, *3*, 1324–1336.
4. (a) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755–1758. (b) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376–1385. (c) Mukai, C.; Inagaki, F.; Yoshida, T.; Yoshitani, K.; Hara, Y.; Kitagaki, S., *J. Org. Chem.*, **2005**, *70*, 7159–7171.

5. Brummond and co-workers reported the $[RhCl(CO)_2]_2$-catalyzed PKR of allenynes, which involves three successful examples of the formation of the bicyclo[5.3.0]decadienone skeleton: Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002**, *4*, 1931–1934.
6. For other examples of the formation of the bicyclo[5.3.0] decane skeleton via the transition metal-catalyzed PKR of allenynes, see: (a) Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 911–919. (b) Ahmar, M.; Locatelli, C.; Colombier, D.; Cazes, B. *Tetrahedron Lett.* **1997**, *38*, 5281–5284.
7. For construction of the cyclooctanoid systems, see: Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930.
8. van der Louw, J.; van der Baan, J. L.; Komen, C. M. D.; Knol, A.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 6105–6122.
9. For a recent review, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
10. (a) Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1950**, 3650–3656. (b) Büchi, G.; Wüest, H. *J. Org. Chem.* **1979**, *44*, 546–549.
11. Huo, S. *Org. Lett.* **2003**, *5*, 423–425.
12. Hammound, A.; Descoins, C. *Bull. Soc. Chim. Fr.* **1978**, 299–303. Part 2.
13. Lautens, M.; Paquin, J.-F.; Piquel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127–8134.
14. Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3823–3824.
15. Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160.
16. (a) Stirling, C. J. M. *Chem. Commun.* **1967**, 131. (b) Saalfrank, R. W.; Welch, A.; Haubner, M.; Bauer, U. *Liebigs Ann.* **1996**, 171–181.
17. (a) Kurzer, F.; *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, pp 937–939. (b) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977–5985.
18. (a) Hiroi, K.; Kato, F.; Nakasato, H. *Chem. Lett.* **1998**, 553–554. (b) Hiroi, K.; Kato, F. *Tetrahedron* **2001**, *57*, 1543–1550.
19. Pasto, D. J.; Miles, M. F. *J. Org. Chem.* **1976**, *41*, 425–432.
20. Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104–109.

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Aerobic oxidation of 1,3,5-triisopropylbenzene using *N*-hydroxyphthalimide (NHPI) as key catalyst

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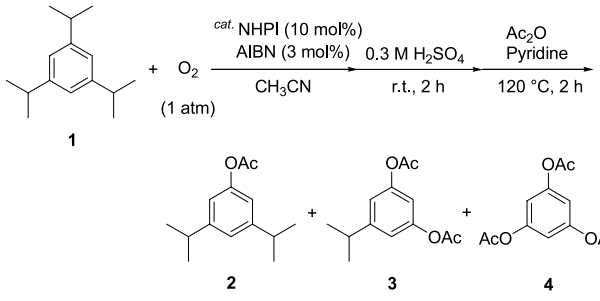
Abstract—The first systematic study on the aerobic oxidation of 1,3,5-triisopropylbenzene was examined by the use of *N*-hydroxyphthalimide (NHPI) as a key catalyst. It was found that 1,3,5-triisopropylbenzene was efficiently oxidized with O_2 in the presence of a catalytic amount of NHPI and azobisisobutyronitrile (AIBN) at 75 °C. Upon treatment of the resulting products with sulfuric acid followed by acetic anhydride led to 5-acetoxy-1,3-diisopropylbenzene and 3,5-diacetoxy-1-isopropylbenzene as major products and a small amount of 1,3,5-triacetoxybenzene. When *t*-butylperoxypivalate (BPP) was employed as a radical initiator, the oxidation could be achieved in good yield even at 50 °C. This oxidation provides a facile method for preparing phenol derivatives bearing an isopropyl moiety, which can be used as pharmaceutical starting materials.

1. Introduction

Aerobic oxidation of alkylbenzenes is a very important industrial process for the production of primary chemicals and monomer materials. For instance, the aerobic oxidation of *p*-xylene to terephthalic acid is practiced in large scale in the chemical industry worldwide.[1] Another important aerobic oxidation is the conversion of isopropylbenzene to cumene hydroperoxide which on subsequent treatment with sulfuric acid affords phenol and acetone.[2] The aerobic oxidation of *m*- and *p*-diisopropylbenzenes leading to resorcinol and hydroquinone is also an important autoxidation process.[3] In recent years, we have developed a new catalytic method for the aerobic oxidation of alkylbenzenes using *N*-hydroxyphthalimide (NHPI) as a key catalyst,[4] and applied to the aerobic oxidation of *m*- and *p*-diisopropylbenzenes to develop an alternative route to resorcinol and hydroquinone.[5]

However, there has been little study so far of the aerobic oxidation of 1,3,5-triisopropylbenzene (**1**) except for several patent works.[6] Therefore, the aerobic oxidation of **1** to obtain the corresponding phenol derivatives is thought to be interesting. In this paper, we would like to report the first systematic study on the aerobic oxidation of **1** using NHPI as a key catalyst in the presence or absence of a radical initiator (Eq. 1).



(1)

2. Results and discussion

The oxidation of **1** under atmospheric dioxygen in the presence of NHPI and AIBN under various conditions is shown in Table 1.

Compound **1** (3 mmol) was reacted with atmospheric dioxygen (1 atm) under the influence of NHPI (0.3 mmol) and AIBN (0.09 mmol) in acetonitrile (5 mL) at 75 °C for 2 h, followed by treatment with 0.3 M sulfuric acid in acetonitrile (1 mL) at room temperature. The reaction solution was evaporated and then treated with acetic anhydride (10 mmol) containing pyridine (50 mg) under reflux for 2 h to convert the resulting hydroxyl benzenes into

Keywords: Aerobic oxidation; 1,3,5-Triisopropylbenzene; Hydroperoxide; *N*-hydroxyphthalimide.
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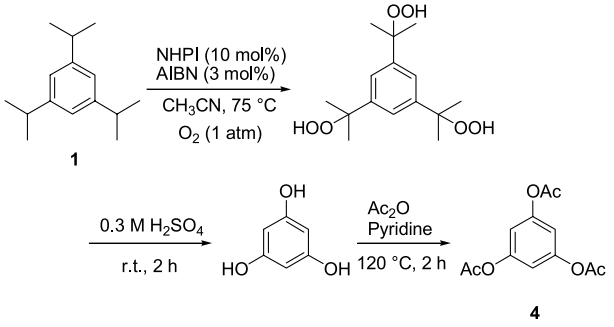
Table 1. Aerobic oxidation of 1,3,5-triisopropylbenzene (**1**) by NHPI under various conditions[a]

Entry	Temperature/°C	Time/h	Conversion/%	Yield/%[b]		
				2	**3**	**4**
1	75	2	78	52 (67)	15 (19)	1 (1.3)
2[c]	75	5	85	45 (53)	30 (35)	1 (1.1)
3	75	7	96	30 (31)	52 (55)	2 (2.1)
4[d]	75	5	63	51 (81)	11 (17)	nd
5	65	3	71	51 (73)	17 (24)	nd
6	65	5	84	47 (56)	29 (35)	2 (2.4)
7[e]	75	2	30	25 (83)	3 (10)	nd
8[f]	75	2	nr			

[a] Compound **1** (3 mmol) was reacted in the presence of NHPI (10 mol%) and AIBN (3 mol%) under O_2 (1 atm) in CH_3CN (5 mL). See text.
[b] Numbers in parenthesis show selectivity based on **1** reacted.
[c] CH_3CN (10 mL).
[d] O_2/N_2 (0.5 atm/0.5 atm).
[e] Without AIBN.
[f] Without NHPI.

acetoxybenzene derivatives whose quantities are determined by GC measurement. As an example, the reaction step of this transformation of **1** to 1,3,5-triacetoxybenzene derivative is shown in Scheme 1. Thus, the amount of phenol derivatives obtained by the oxidation of **1** was estimated as the amount of acetoxybenzene derivatives.



Scheme 1. Sequential transformation of **1** to **4**.

The oxidation of **1** followed by above treatment led to 3,5-diisopropyl-1-acetoxybenzene (**2**) (52%), 3-isopropyl-1,5-diacetoxybenzene (**3**) (15%), and 1,3,5-triacetoxybenzene (**4**) (1%) along with small amounts of decomposed oxidation products like 1-isopropenyl-3,5-diisopropylbenzene (**5**) and 1-acetoxy-3,5- diisopropylbenzene (**6**) at 78% conversion (entry 1).The reaction in acetonitrile (10 mL) for 5 h gave **2** and **3** in 45 and 30% yields, respectively, along with **4** (1%) at 85% conversion (entry 2). Elongation of the reaction time for 7 h under these conditions resulted in the preferential formation of diacetate **3** (52%) over monoacetate **2** (30%) (entry 3). When oxygen concentration was halved under these conditions, **2** was formed in 51% at higher selectivity (81%) (entry 4). The reaction took place smoothly even at 65 °C, affording **2** (51%) and **3** (17%) for 3 h and **2** (47%) and **3** (29%) for 5 h (entries 5 and 6). The reaction in the absence of AIBN led to **2** and **3** in lower yields, and no reaction took place at all in the absence of NHPI (entries 7 and 8).

To inspect suitable solvents to convert **1** into **2**, **3**, and **4**, the effect of several solvents was studied under O_2 (1 atm) at 75 °C for 2 and 5 h (Table 2).

The solvent effect was clearly observed in shorter-time reactions. For example, the oxidation of **1** for 2 h gave rise to **2** (52%) and **3** (15%) at higher conversion (78%) in CH_3CN, but the oxidation in AcOEt afforded **2** (36%) and **3** (6%) at low conversion (42%), although the selectivity of **2** was high (86%) (entries 1 and 2). In the oxidation for 5 h, however, the conversion of **1** was attained up to over 90% in both solvents. On the contrary, the conversions of the oxidations in PhCN and $PhCF_3$ for 2 h were low compared with that in CH_3CN, but the total selectivities of **2** and **3** of the reaction in both solvents were very high (entries 3 and 4). Acetic acid, which is a good solvent in the NHPI-catalyzed oxidation of toluene to benzoic acid,[7] was not suited for the present oxidation, since a part of the resulting hydroperoxides was subject to decomposition by acetic acid to form phenols, which serve as radical inhibitors. In fact,

Table 2. Aerobic oxidation of 1,3,5-triisopropylbenzene (**1**) by NHPI under several solvents[a]

Entry	Solvent	Time/h	Conversion/%	Yield/%[b]		
				2	**3**	**4**
1	CH_3CN	2	78	52 (67)	15 (19)	1 (1.2)
		5	96	29 (30)	51 (53)	2 (2.1)
2	AcOEt	2	42	36 (86)	6 (14)	nd
		5	92	31 (34)	44 (48)	1 (1.1)
3	PhCN	2	66	42 (64)	22 (33)	nd
		5	76	46 (61)	28 (37)	nd
4	$PhCF_3$	2	55	36 (65)	16 (29)	1 (1.8)
		5	81	33 (41)	36 (44)	1 (1.2)
5	AcOH	2	25	24 (96)	1 (4.0)	nd
		5	30	25 (83)	3 (10)	nd

[a] Compound **1** (3 mmol) was reacted in the presence of NHPI (10 mol%) and AIBN (3 mol%) under O_2 (1 atm) in solvent (5 mL) for 2 or 5 h at 75 °C.
[b] Numbers in parenthesis show selectivity based on **1** reacted.

the conversion in the oxidation of **1** for 2 h was almost the same as that for 5 h (entry 5). This fact indicates that the oxidation in acetic acid is inhibited at an early stage of the reaction owing to the formation phenols. On the basis of these results, acetonitrile is thought to be a good solvent for the oxidation of **1** from viewpoints of the reaction rate and selectivity among the solvents examined.

In order to obtain further insight into the reaction course, the time-dependence of the oxidation of **1** by the NHPI/AIBN system under O_2 (1 atm) in acetonitrile at 75 °C was followed by GC at an appropriate time interval (Figure 1).

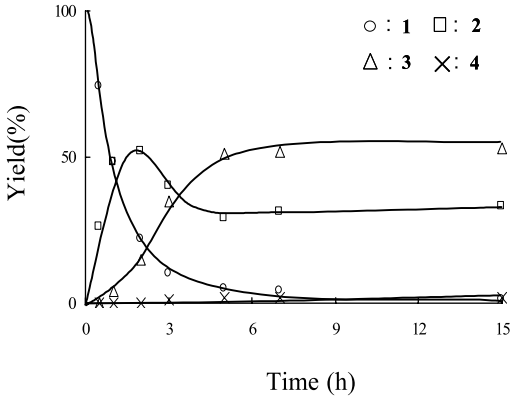


Figure 1. Time-dependence curves for the oxidation of **1** (3 mmol) under O_2 (1 atm) by NHPI (10 mol%) and AIBN (3 mol%) in CH_3CN (5 mL) at 75 °C.

Compound **1** was almost linearly oxidized in 2 h under these conditions to give **2**, and **3** with higher selectivity, and the yield of **2** attained maximum (50%) after 2 h. A slightly rapid increase of **3** was observed with the elapse of 1.5 h, but the yield of **3** was not increased beyond 50% and the reaction was stopped at around 6 h. From the consideration of the time-dependence curves of **1**, **2**, and **3**, the reactivity of **2** is thought to be slightly decreased by introduction of OOH group to **1** than that of the stating **1**. However, the difficulty of the formation of **4** is believed to be other reasons rather than decrease of the reactivity of **3** by two OOH groups as discussed later.

In order to clarify the reason why the oxidation is stopped at around 6 h, the recovery of NHPI catalyst after the oxidation was examined. Most of the NHPI was found to be recovered without decomposition after 6 h. This fact indicates that the termination of the reaction is not due to the decomposition of NHPI in the course of the oxidation. Consequently, it is reasonable to assume the formation of phenol derivatives, which inhibit the radical chain transfer. It is well known that hydroperoxides undergo the rapid self-decomposition when their concentration increases over the boundary concentration. In fact, we confirmed the formation of 5-isopropyl resorcinol (2%) in the oxidation of **1** with O_2 (1 atm) in the presence of NHPI (10 mol%) and AIBN (3 mol%) in acetonitrile at 75 °C for 6 h. These phenol derivatives generated during the reaction is increased with time and inhibited the further oxidation of **1** to **3** and **4**. As a result, the yield of 1,3,5-triacetoxybenzene **4** was not increased with time.

To achieve the reaction at lower temperature, the reaction was carried out under several conditions (Table 3).

The oxidation of **1** was examined using *t*-butylperoxypivarate (BPP), which decomposes at lower temperature ($t_{1/2}=10$ h at 55 °C in benzene) than AIBN ($t_{1/2}=10$ h at 65 °C in toluene), in CH_3CN at 50 °C for 6 h.[8] It was found that **1** is selectively converted into **2** (48%) and **3** (27%) at 81% conversion (entry 1). In the oxidation at lower temperature, **4** was not formed at all. By the oxidation using AIBN at 50 °C, the conversion was only 38%, but **2** was selectively produced (entry 2). In a previous paper, we showed that Co(II) reacts with dioxygen to generate a Co(III)-dioxygen complex, which can initiate the NHPI-catalyzed oxidation.[7] Thus, the oxidation of **1** by NHPI combined with $Co(OAc)_2$ in place of radical initiators like AIBN and BPP was examined at 50 °C for 1 h. The oxidation was also induced by the NHPI/$Co(OAc)_2$ to give **2** in high selectivity (91%) in moderate conversion (44%) (entry 3), but the formation of **3**, and **4** was very low. When the reaction time was prolonged to 6 h, the conversion was increased to 95% to lead to **3** (52%) in preference to **2** (34%). High total selectivity of **2**, and **3** indicates that the resulting hydroperoxides are relatively stable and do not undergo rapid decomposition by Co ions under these conditions. In contrast, since Cu ions promote the redox decomposition of hydroperoxides, the oxidation of **1** using the NHPI/$Cu(OAc)_2$ system resulted in a complex mixture compared with that of the NHPI/$Co(OAc)_2$ system probably because of side reactions caused by decomposition of the resulting hydroperoxides by Cu ions (entry 6).

Figure 2 shows the time-dependence curves for the oxidation of **1** by NHPI combined with BPP or AIBN at 50 °C. The reaction by the NHPI/AIBN system proceeded more slowly than that by the NHPI/BPP system owing to the difficulty of the decomposition of AIBN at 50 °C. After

Table 3. Aerobic oxidation of 1,3,5-triisopropylbenzene (**1**) by NHPI at 50 °C in the presence of various initiators[a]

Entry	Initiator (mol%)	Time/h	Conversion/%	Yield/%[b]		
				2	**3**	**4**
1	BPP (3)	6	81	48 (59)	27 (33)	nd
2	AIBN (3)	6	38	37 (97)	1 (2.6)	nd
3	$Co(OAc)_2$ (0.1)	1	44	40 (91)	1 (2.6)	1 (1.2)
4	$Co(OAc)_2$ (0.1)	6	95	34 (36)	52 (55)	2 (2.1)
5	$Cu(OAc)_2$ (0.1)	1	55	41 (81)	7 (13)	nd
6	$Cu(OAc)_2$ (0.1)	6	Complex mixture			

[a] Compound **1** (3 mmol) was reacted in the presence of NHPI (10 mol%) and radical initiator under O_2 (1 atm) in CH_3CN (5 mL) at 50 °C for 1 or 6 h.
[b] Numbers in parenthesis show selectivity based on **1** reacted.

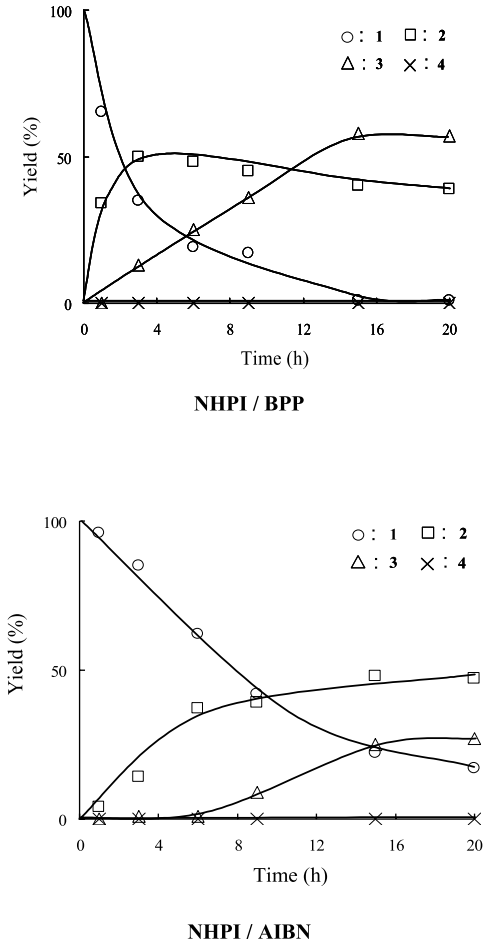
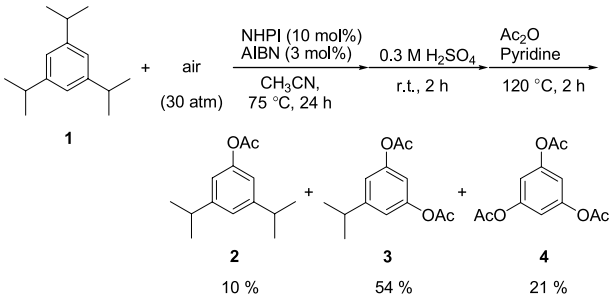


Figure 2. Time-dependence curves for aerobic oxidation of **1** (3 mmol) under O_2 (1 atm) by NHPI (10 mol%)/AIBN (3 mol%) or NHPI (10 mol%)/BPP (3 mol%) in CH_3CN (5 mL) at 50 °C.

15 h, the yields of **2**, **3**, and **4** in the oxidation of **1** by the NHPI/BPP system attained 40, 58, and 1% yields, respectively, while in the oxidation by the NHPI/AIBN system the starting **1** was remained even after 15 h. These observations suggest that the NHPI/BPP system is more efficient than the NHPI/AIBN one in the oxidation of **1** to **2**, and **3** at 50 °C.

Since it was difficult to obtain 1,3,5-triacetoxybenzene **4** by the oxidation of **1** under O_2 (1 atm), the oxidation of **1** under pressurized air (30 atm) was carried out by use of the NHPI/AIBN system at 75 °C for 24 h (Eq. 2).



(2)

The reaction afforded **4** in 21% yield along with **3** (54%) and **2** (10%), although **4** was difficult to obtain selectively. The fact that the yield of **4** by the oxidation of **1** with air was increased compared with that with pure oxygen is believed to be due to the slower formation of phenol derivatives, which serve as radical inhibitor, with air than that with O_2.

In conclusion, we have first examined the aerobic oxidation of **1** to obtain polyphenols by the use of combined catalytic system of NHPI with a radical initiator like AIBN or BPP. The NHPI/AIBN system was found to be a good system for the oxidation of **1** to **2**, and **3**, and the NHPI/BPP system showed high performance for the oxidation of **1** at lower temperature. The oxidation of **1** by NHPI in the presence of AIBN under pressurized air (30 atm) followed by above treatment led to 1,3,5-triacetoxybenzene **4** in fair yield (21%).

3. Experimental

3.1. General procedure

^1H NMR and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr press disk. A GLC analysis was performed with a flame ionization detector using a 0.2 mm×25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

3.2. General procedure for the oxidation of 1,3,5-triisopropylbezene (1) to acetoxylbenzene derivatives, 2, 3, and 4

An acetonitrile (5 mL) solution of 1,3,5-triisopropylbenzene (**1**) (3 mmol), AIBN (3 mol%), and NHPI (10 mol%) was placed in a two-necked flask equipped with a balloon filled with O_2, and the solution was stirred at 75 °C for 2–7 h. The reactant was treated with 0.3 M H_2SO_4 in CH_3CN (1 mL) at 25 °C for 2 h. In this reaction, the resulting hydroperoxides are conformed to be converted into phenol derivatives and acetone by GC–MS measurement. After removal of solvent under reduced pressure, the mixture was treated with acetic anhydride (10 mmol) containing pyridine (50 mg) under reflux for 1 h to covert into acetoxybenzene derivatives whose quantities are determined by GC measurement. The resulting products were purified by column chromatography on silica gel using *n*-hexane to give 5-acetoxy-1,3-diisopropylbenzene (**2**), 3,5-diacetoxy-1-isopropylbenzene (**3**), 1,3,5-triacetoxybenzene (**4**). These products were characterized by ^1H and ^{13}C NMR, IR, and HRMS, respectively.

3.2.1. 5-Acetoxy-1,3-diisopropylbenzene (2). ^1H NMR δ 6.94 ppm (s, 1H), 6.75 ppm (d, J=1.4 Hz, 2H), 2.91–2.83 ppm (m, 2H), 2.28 ppm (s, 3H), 1.23 ppm (d, J=6.9 Hz, 12H); ^{13}C NMR 169.4, 150.6, 150.1, 122.3, 116.7, 34.1, 24.0, 21.2; IR(NaCl) 2961, 2871, 1768, 1458, 1207, 872, 704 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{20}O_2$ $[M-H]^+$: 220.1436; found: 220.1463.

3.2.2. 3,5-Diacetoxy-1-isopropylbenzene (3). ^{1}H NMR δ, 6.78 ppm (q, $J=2.4$ Hz, 2H), 6.74 ppm (s, 1H) 2.91–2.88 ppm (m, 1H), 2.28 ppm (s, 3H), 1.23 ppm (d, $J=6.9$ Hz, 6H); ^{13}C NMR 169.1, 151.3, 150.8, 117.0, 112.7, 33.9, 23.6, 21.1; IR(NaCl) 2956, 2871, 1771, 1455, 1198, 891, 707 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{16}O_4$ $[M-H]^+$: 236.1051; found: 236.1049.

3.2.3. 1,3,5-Triacetoxybenzene (4). ^{1}H NMR δ 6.83 ppm (s, 3H), 2.27 ppm (2, 9H); ^{13}C NMR 168.4, 151.0, 21.2; IR(NaCl) 3091, 1772, 1457, 1189, 918, 670 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{12}O_6$ $[M-H]^+$: 252.0658; found: 252.0634.

Acknowledgements

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References and notes

1. (a) Park, C.; Sheehan, J. R. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Wiley: New York, Vol. 18W, 1996. (b) Partenheimer, W. *Catal. Today* **1995**, *23*, 69. (c) Parshall, G. W.; Ittel, S. D. *Heterogeneous Catalysis*, 2nd ed.; Wiley: New York, 1992.
2. (a) Hock, H.; Lang, S. *Ber. Dtsch. Chem. Ges.* **1944**, *B77*, 257. (b) Jordan, W.; Van Barneveld, H.; Gerlich, O.; Boymann, M. K.; Ullrich, J.; Ullmann's Encyclopedia of Industrial Organic Chemicals; Wiley-VCH: Weinheim, 1985; Vol. A9; pp 299–312.
3. (a) Wessermel, K.; Arpe, H.-J. Industrial Organic Chemistry.; Wiley-VCH: Weinheim, 2003; pp 364–366.(b) Ching Y. W. Eur. Patent 322245, 1989.
4. Fukuda, O.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2001**, *343*, 809.
5. (a) Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **2005**, *61*, 5219. (b) Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2001**, *346*, 199. (c) Arends, I. W. C. E.; Sasiidharan, M.; Kuhnle, A.; Duda, M.; Jost, C.; Sheldon, R. A. *Tetrahedron* **2002**, *58*, 9055.
6. (a) Ogino, T. JP 03044344, 1991. (b) Mizuno, K. JP 61152635, 1986.(c) Reichle, W. T.; Konrad, F. M.; Brooks, J. R. *Benzene and its Industrial Derivatives*; Benn: London, 1975.
7. Yoshino, Y.; Hayashi, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.
8. It has been reported that the self-accelerating decomposition temperatures of AIBN and BPP were 50.0 and 27.0 °C, respectively; Bosch, C. M.; Velo, E.; Recasens, F. *Chem. Eng. Sci.* **2001**, *56*, 1451.

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Neighboring effect of the lactam functionality in select reactions of 6-azaspiro[4.5]decane-1,7-dione

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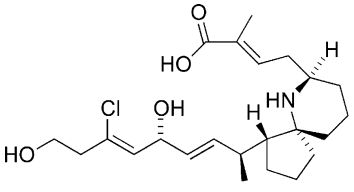
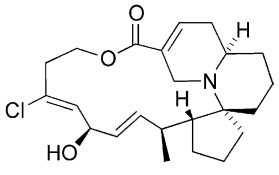
Abstract—The susceptibility of 6-azaspiro[4.5]decane-1,7-dione (**4**) to nucleophilic attack was evaluated. Although steric effects preclude the 1,2-addition of many reagents, more reactive lithium and Grignard species react. Attack from the direction *syn* to the lactam functionality predominates. The acid-catalyzed rearrangement of select products delivered allylic alcohols carrying their double bond at varying distances from the spirocyclic carbon. These designed systems undergo hydrogenation predominantly from that π-surface *syn* to the amide component, the more so when a hydroxyl is proximate to these hetero atoms. The same phenomenon operates when *N*-benzoylated intermediates are hydrolyzed with potassium carbonate in methanol.

1. Introduction

The structural features peculiar to spirocyclic compounds have fascinated organic chemists for several decades. In carbocyclic systems, great strides have been made since the chemical and chiroptical properties of Fecht's acid[1] and spiro[3.3]hepta-1,5-diene[2] were elucidated in the 1970s. Particularly striking in the intervening years have been the many developments involving the adaptation of new reagents and tactics to bring about spirocyclization events.[3] The elaboration of oxygen- and sulfur-containing analogs has recently been extended to include spirocyclic nucleosides.[4] Nature has contributed to the heightened interest in nitrogen derivatives[5] by serving as the source of bioactive alkaloids such as perhydrohistrionicotoxin,[6] pinnaic acid,[7] and halichlorine.[8]

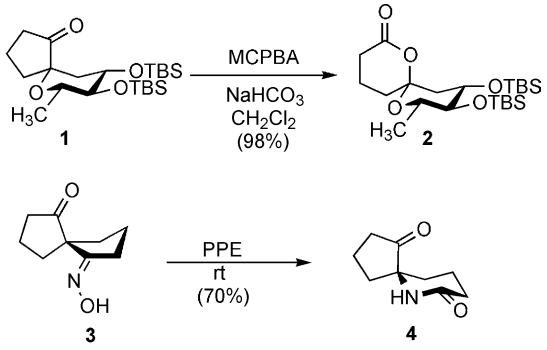


pinnaic acid



halichlorine

Despite the advances made in this area, surprisingly little use has been made of stereospecific ring expansion reactions to generate functionalized targets. The Baeyer-Villiger oxidation of **1** to give **2**[9] and the Beckmann rearrangement of **3** to form **4**[10] are illustrative examples. As a consequence, there has been minimal exploration of spiroacetals and keto lactams having these general structural characteristics (Scheme 1). In this report, we detail a selection of reactions to which **4** has been subjected. Functional group compatibility and chemoselectivity are, of course, two ever-present issues. Where relevant and possible, the level of stereocontrol and the preferred direction of reagent approach are established unequivocally. As will be made clear, the amide moiety exerts profound consequences on the stereochemical course of reactions occurring at the neighboring five-membered ring. An example is also provided of reciprocal effects



Scheme 1.

Keywords: Spirocycles; Lactams; Carbonyl additions; Rupe rearrangement; Heteroatomic effects.
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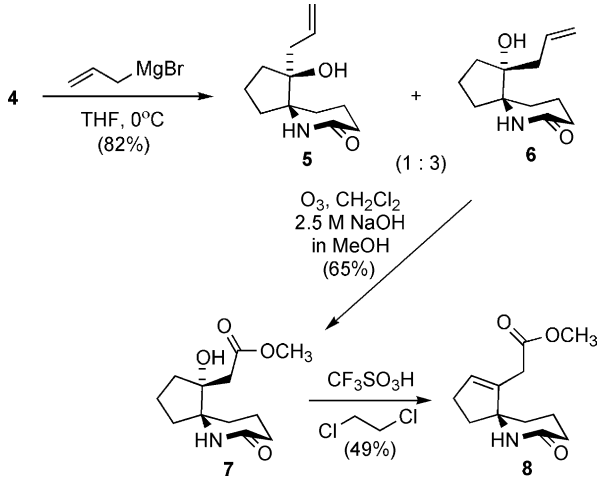
2. Results and discussion

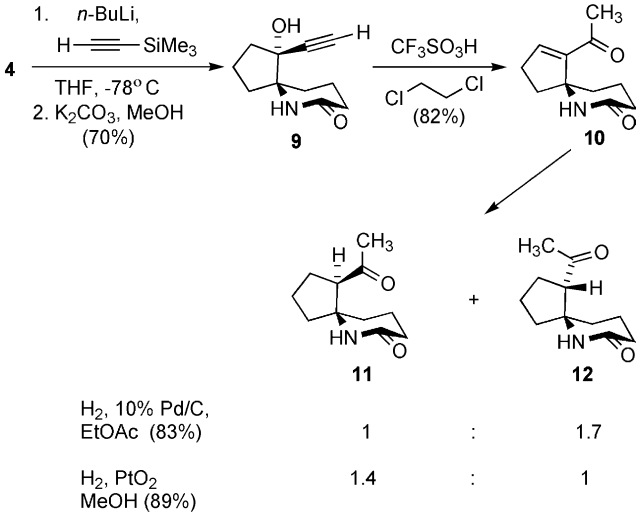
The determination of S_N2 solvolysis rates, which showed neopentyl systems to react at a level 10^{-5} that exhibited by the corresponding ethyl derivative,[11] provided a proper forum for appreciating the strong deceleration effect of alkyl substitution proximal to a reaction center.[12] In a similar manner, the tetrahedral mechanism for substitution at a carbonyl carbon is equally slowed or blocked completely when steric crowding is elevated.[13] The pronounced deceleration associated with both processes is adequate to render such substrates synthetically useless in most cases. These consequences can be expected to complicate the chemistry of **4**, although in more subtle ways. With regard to the diastereotopic faces of the ketone carbonyl group in this spirocycle, one is *syn* to a polymethylene chain while the other is flanked by the nitrogen atom that is part of the lactam functionality. Depending on the basicity of the reagent to which **4** is being subjected, deprotonation may operate at N, chelation may become an operational factor, and other forms of complexation could play a role in making matters more mechanistically complex. The extent to which the title compound is sensitive to one or more of these phenomena is certain to impact upon its reactivity and to offer intriguing opportunities for control of stereoselectivity during nucleophilic capture when operational.

In line with the points of emphasis made above, **4** proved to be totally unreactive to such well-known transformations as the Horner-Wadsworth-Emmons,[14] Wittig,[15] Reformatsky,[16] and Peterson reactions.[17] When we uncovered the comparative inertness of **4** toward lithium ynolates such as $H_3C–\equiv–O^-Li^+$,[18] it was quite apparent that recourse needed to be made to more reactive organometallic reagents. To this end, **4** was admixed at 0 °C with 3 equiv of allylmagnesium bromide in THF. In this instance, the diastereomeric carbinols **5** and **6** were formed in a 1:3 ratio and a combined yield of 82% (Scheme 2). The ease of chromatographic separation of **5** from **6** facilitated the stereochemical assignments which were made by analogy to **9** (see below) and concluded that the preferred trajectory of attack was from that direction *syn* to the amide linkage. Attempts to gain further confirmation by NOE methods proved inclusive. However, this product partitioning is of no consequence if dehydration is ultimately contemplated. For example, ozonolysis of **6** in the presence of methanolic sodium hydroxide[19] results in smooth conversion to hydroxy ester **7**. Alternate involvement of the **5/6** mixture gave rise to a diastereomeric mixture with comparable efficiency. Subsequent treatment of **7** with triflic acid in 1,2-dichloroethane[20] provided β,γ-unsaturated ester **8** with a minimum of Wagner-Meerwein rearrangement products.



Scheme 2.

Next to be considered was the possibility of introducing an acetylide side chain for the purpose of implementing a subsequent Rupe rearrangement.[21] Admixture of **4** with an excess of lithiated trimethylsilylacetylene resulted in a rapid reaction at −78 °C and gave rise to a single carbinol, the stereochemistry of which was assumed to be as shown in Scheme 3 as a result of the reduced size of the sp-hybridized nucleophile. Following application of the conventional protodesilylation protocol,[22] the action of potassium carbonate in methanol on this adduct furnished **9**, the three-dimensional features of which were unequivocally established by X-ray crystallographic analysis. The isomerization of **9** under the standard conditions of sulfuric acid–acetic acid at the reflux temperature[23] gave **10**, although only in an average yield of 25%. An extended search for an improved way to accomplish this transformation was rewarded with the discovery that modest quantities of triflic acid (ca. 5 equiv) in 1,2-dichloroethane at rt promotes rapid and efficient conversion to the α,β-unsaturated keto lactam **10** (82%).

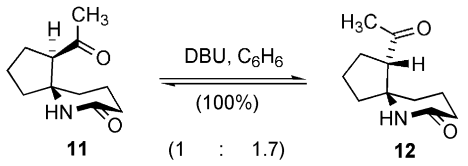


Scheme 3.

Interestingly, the stereochemical outcome of the hydrogenation of **10** at 1 atm proved to be catalyst dependent. When recourse was made to 10% palladium on charcoal in ethyl acetate, **11** and **12** were produced in a 1:1.7 ratio (Scheme 3). When the alternative use of platinum oxide in methanol or ethyl acetate was screened, diastereomer **11** now predominated. Accordingly, either dihydro product can be generated as the major constituent simply by switching the catalyst system.

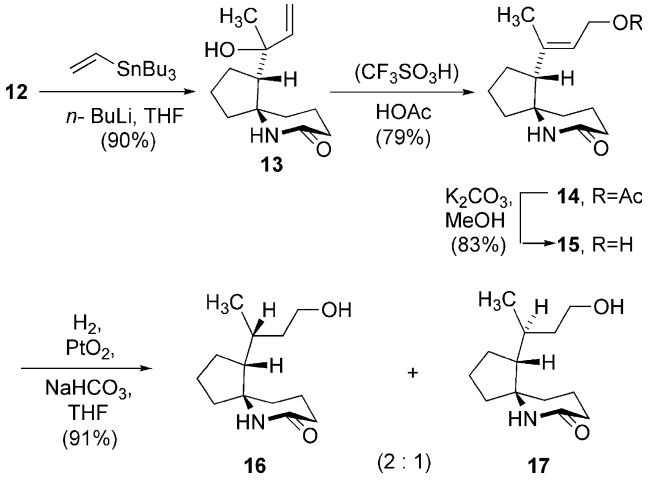
Our ability to separate **11** from **12** by chromatographic means allowed for proper assessment of their equilibrium

distribution as well as unequivocal definition of their three-dimensional structure. Independent admixing of pure samples of **11** and **12** with DBU in benzene at rt resulted in quantitative conversion to a 1:1.7 mixture favoring **12** in both instances as determined by ^{1}H NMR prior to chromatography. These findings reveal the greater thermodynamic advantage associated with that arrangement where the acetyl group is oriented anti to the amide functionality (Scheme 4).

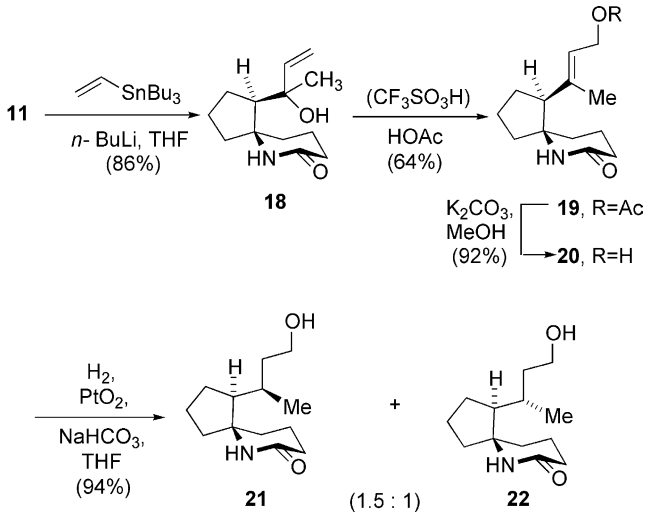


Scheme 4.

With **11** and **12** available, the stage was set to scrutinize the level of stereoselective hydrogenation that operates at an olefinic site more distal from the spirocyclic carbon. This phase of the investigation began by exploring the feasibility of adding vinyllithium individually to this pair of methyl ketones. In the event, **12** gave rise to the single 1,2-adduct **13** (Scheme 5), whereas **11** was transformed into a 3:1 mixture of diastereomeric carbinols **18** (Scheme 6). This distinction was not an issue of consequence since our focus was to effect allylic rearrangement to **14** and **19**, respectively. Best results were achieved with triflic acid as the promoter in acetic acid solution. In both series, the geometry about the newly introduced double bond follows rigorously from unambiguous NMR spectral features that reveal a *syn* relationship of the CH_3 and CH_2OAc groups. Following the conversion of **14** and **19** to **15** and **20**, respectively, these alcohols were subjected to an array of hydrogenation catalysts under H_2 at different pressures. In all cases, hydrogenolytic removal of the hydroxyl group prevailed heavily or operated exclusively. These data conform to the steric crowding about the double bond and its trisubstituted nature. Usefully, this unwanted reaction could be effectively skirted simply by performing the reduction in THF over a mixture of $NaHCO_3$ and PtO_2.[24] Under these conditions, **15** led to a 2:1 mixture of the



Scheme 5.



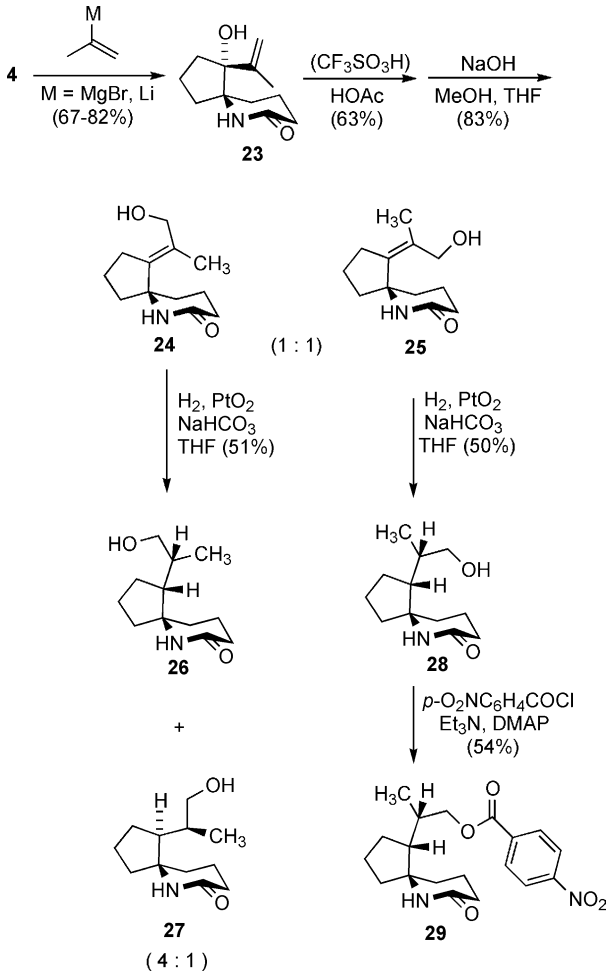
Scheme 6.

chromatographically separable carbinols **16** and **17**. Proper structural definition of these diastereomers was achieved by X-ray crystallographic analysis of the latter. This distinction revealed the more favored saturation of the double bond in **15** to occur from that π-surface *syn* to the heteroatomic component of the lactam in the conformation shown.

While the hydrogenation of **20** proved to be equally optimal at 94%, we were unable to bring about the separation of **21** from **22**. ^{1}H NMR analysis indicated the production distribution to be 1.5:1, but more specific stereochemical characterization was not posssible.

It is well to recognize at this point that addition of the 2-propenyl Grignard or lithium reagent to **4** holds the prospect of ultimately introducing a double bond that is both tetrasubstituted and positioned immediately adjacent to the spirocyclic carbon. Another distinction that sets **24** and **25** apart is the rigidly fixed nature of their geometry. As indicated in Scheme 7, the efficiency associated with use of the lithium reagent (82%) is more elevated than that of the bromomagnesium counterpart (67%). Both coupling reactions gave **23** as a single diastereomer that was directly rearranged and hydrolyzed as before. The R_f values of **24** and **25** on silica gel are widely disparate, thereby facilitating their clean separation. The connectivity between **24** and its dihydro derivatives **26** and **27** rests entirely on the directionality of hydrogen attachment. In this example, a 4:1 mixture of **26** and **27** was generated. The stereochemistry assigned to major product **26** followed convincingly from the results of an X-ray crystallographic determination. This finding established that the saturation of **24** occurs preferably from that direction *syn* to the lactam nitrogen. In the companion example involving **25**, a lone dihydro product was obtained and formulated as **28** by analogy. Further verification via the preparation of **29** was not realized because of the poor crystalline quality of the *p*-nitrobenzoate.

Beyond this, it was of interest to functionalize the amide group with a view of assessing possible divergences in favored reaction pathways operational in at least one set of geometric isomers. To this end, **23** was transformed into a 3:2 mixture of allylic formates **30** (89%), direct

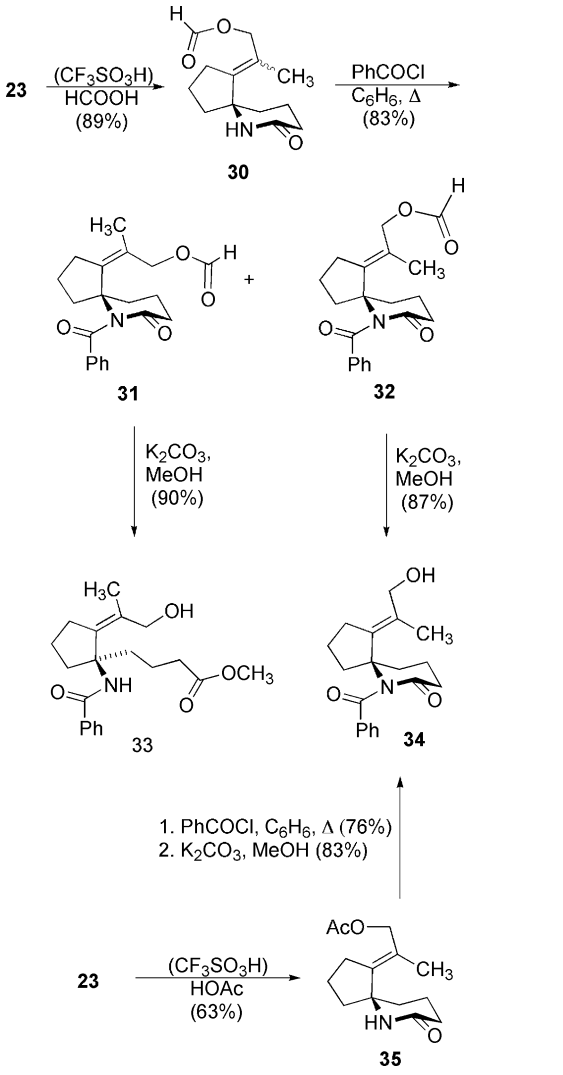


Scheme 7.

benzoylation of which at nitrogen was achieved by stirring with benzoyl chloride in benzene at the reflux temperature[25] (Scheme 8). In practice, this transformation made possible the independent isolation of **31** and **32**. These isomers were unequivocally identified by three-step chemical conversion of the previously characterized **23** to **34**. Once this issue had been clarified, it was recognized that brief (15 min) hydrolysis of **31** and **32** with K_2CO_3 in methanol had quite different consequences. Where **32** is concerned, removal of the formate residue was kinetically dominant. Deacylation was also experienced by **31**, but cleavage of the lactam ring to furnish **33** was clearly competitive if not faster. These observations clearly implicate the operation of neighboring group participation involving the allylic hydroxyl. When the latter is in close proximity to the amide linkage, its methanolysis is significantly accelerated.

3. Conclusions

6-Azaspiro[4.5]decane-1,7-dione (**4**) has proven to be a versatile device for clarifying the stereoselectivities of select chemical transformations involving functionalized, nitrogen-containing spirocycles. Various ways have been taken to further develop the basic functionality resident in **4** and to identify the chemical consequences of such structural modifications. The hindered nature of the ketone carbonyl in



Scheme 8.

4 requires recourse to reactive Grignard and lithium reagents to achieve 1,2-addition. These reactions proceed with a reasonable preference for attack *syn* to the amido group. These transformations can be followed by acid-catalyzed rearrangement to generate intermediates carrying a double bond at various distances from the spirocyclic carbon. Despite the diversity in architecture of the resulting unsaturated alcohols, their catalytic hydrogenation proceeds most often with an appreciable bias for *syn*-selective saturation. This stereoselectivity reaches a maximum when a hydroxyl group is situated in close proximity to the lactam functionality. Finally, the differing hydrolysis pathways adopted by **31** and **32** indicate that this type of molecular structure has an intrinsic capability to rely on neighboring group participation involving hetero atoms resident on the opposite rings.

4. Experimental

4.1. General

4.1.1. Allylmagnesium bromide addition to 4. A solution of **4** (0.60 g, 3.6 mmol) in dry THF (50 mL) was cooled to

0 °C and treated dropwise with 21.5 mL of 0.5 M allylmagnesium bromide (10.7 mmol) in the same solvent. The reaction mixture was allowed to warm to rt and quenched after 10 min with saturated NH_4Cl solution. The separated aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 10% methanol in 1:1 ethyl acetate/hexanes gave 188 mg (25%) of **5** and 428 mg (57%) of **6**, both as colorless oils.

Compound **5**. IR (neat, cm^{-1}) 3390 (br), 1650, 1449; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.85 (m, 1H), 5.17 (s, 1H), 5.12 (d, $J=8.5$ Hz, 1H), 2.31–2.11 (m, 4H), 2.07 (s, 1H), 1.99–1.41 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 133.6, 119.3, 83.1, 68.0, 39.5, 38.4, 35.8, 31.5, 27.1, 18.5, 18.2; ES HRMS calcd for $C_{12}H_{19}NO_2Na^+$ *m/z* 232.1308, obsd 232.1316.

Compound **6**. IR (neat, cm^{-1}) 3381 (br), 1634, 1466; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H), 5.83 (m, 1H), 5.09 (s, 1H), 5.03 (d, $J=8.5$ Hz, 1H), 3.52 (s, 1H), 2.31–2.00 (m, 4H), 1.90–1.59 (m, 7H), 1.53–1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 133.5, 118.6, 81.3, 65.9, 39.5, 35.6, 35.2, 31.1, 27.0, 17.8, 17.5; ES HRMS calcd for $C_{12}H_{19}NO_2Na^+$ *m/z* 232.1308, obsd 232.1310.

4.1.2. Ozonolysis of 6. An 88 mg (0.42 mmol) sample of **6** was dissolved in CH_2Cl_2 (5 mL), cooled to −78 °C, and treated with 0.84 mL of 2.5 M sodium hydroxide in methanol. Ozone was introduced at this temperature until a blue color developed. The reaction mixture was diluted with ether and water, and warmed to rt. The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (elution with 10% methanol in 1:1 ethyl acetate/hexanes) afforded 65 mg (65%) of **7** as a colorless oil; IR (neat, cm^{-1}) 3381 (br), 1734, 1646; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (br s, 1H), 5.60 (s, 1H), 3.68 (s, 3H), 2.56 (d, $J=15.5$ Hz, 1H), 2.42 (d, $J=15.5$ Hz, 1H), 1.98–1.36 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 171.9, 80.2, 66.1, 52.0, 37.9, 35.0, 34.8, 31.2, 27.0, 17.8, 17.5; ES HRMS calcd for $C_{12}H_{19}NO_4Na^+$ *m/z* 264.1206, obsd 264.1214.

4.1.3. Dehydration of 7. A solution of **7** (22 mg, 0.09 mmol) in CH_2Cl_2 was treated with trifluoromethanesulfonic acid (0.161 mL, 1.83 mmol) at rt under N_2. After 15 min, ice water was added and the product was extracted in CH_2Cl_2 (3×). The combined organic layers were dried and evaporated to leave 10 mg (49%) of oily **8**; IR (neat, cm^{-1}) 1737, 1658, 1642; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.78 (s, 1H), 3.69 (s, 3H), 3.04 (q, $J=15.0$ Hz, 2H), 2.51–2.10 (m, 4H), 2.04–1.73 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 172.0, 139.2, 131.8, 69.3, 52.3, 39.3, 32.2, 31.3, 30.3, 28.7, 18.6; ES HRMS calcd for $C_{12}H_{17}NO_3Na^+$ *m/z* 246.1101, obsd 246.1109.

4.1.4. Acetylenic carbinol 9. A cold (−78 °C) solution of trimethylsilylacetylene (5.75 mL, 40.7 mmol) in dry THF (100 mL) was treated with *n*-butyllithium (26.3 mL of 1.55 M in hexane, 40.7 mmol) and allowed to warm to rt. After return to −78 °C, a solution of **4** (1.7 g, 10.2 mmol) in 50 mL of THF was introduced dropwise. The reaction mixture was allowed to warm slowly to rt, stirred for 2 h, quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and freed of solvent to leave the protected propargyl alcohol that was immediately taken up in methanol (20 mL), treated with 3 equiv of potassium carbonate and stirred for 30 min. Water was added and the product was extracted into CH_2Cl_2 (3×). The combined organic phases were dried and evaporated to leave a residue that was purified by chromatography on silica gel. Elution with 8% methanol in 1:1 ethyl acetate/hexanes gave **9** (1.39 g, 70%) as a white solid, mp 165 °C; IR (neat, cm^{-1}) 3243 (br), 1642, 1402; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (br s, 1H), 3.49 (s, 1H), 2.64 (s, 1H), 2.41–2.10 (m, 4H), 2.00–1.52 (series of m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 84.6, 78.1, 75.7, 67.1, 37.0, 35.8, 31.2, 25.7, 17.6, 17.2; ES HRMS calcd for $C_{11}H_{15}NO_2Na^+$ *m/z* 216.0995, obsd 216.0995.

4.1.5. Rupe rearrangement of 9. A solution of **9** (0.60 g, 3.1 mmol) in dichloroethane (60 mL) was blanketed with N_2 and treated dropwise with trifluoromethanesulfonic acid (1.37 mL, 15.5 mmol). The reaction mixture developed a red/purple hue with slow formation of a brown oil, and was poured onto ice water after 4 h. The product was extracted into CH_2Cl_2 (4×), dried, and evaporated. Chromatography of the residue on silica gel (elution with 8% methanol in 1:1 ethyl acetate/hexanes) furnished 498 mg (82%) of **10** as a white solid, mp 188–189 °C (from 1:1 ethyl acetate/hexanes); IR (neat, cm^{-1}) 3192 (br), 1651, 1404; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (t, $J=1.3$ Hz, 1H), 5.77 (br s, 1H), 2.64–2.35 (m, 4H), 2.42 (s, 3H), 2.22–2.14 (m, 2H), 2.00–1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 172.4, 146.7, 146.6, 67.4, 40.3, 31.2, 30.5, 29.1, 28.0, 18.7; ES HRMS calcd for $C_{11}H_{15}NO_2Na^+$ *m/z* 216.0995, obsd 216.1003.

4.1.6. Hydrogenation of 10. *A. Over 10% palladium on charcoal*. To a solution of **10** (180 mg, 0.93 mmol) in ethyl acetate (30 mL) was added 18 mg of 10% Pd/C. Hydrogen was bubbled into the mixture, which was stirred under a balloon of H_2 for 30 min prior to filtration through a pad of Celite and evaporation of solvent. Chromatography of the residue on silica gel (elution with 5% isopropyl alcohol in CH_2Cl_2) afforded 55 mg of **11** and 95 mg of **12** (83% total) as colorless oils that solidified on standing.

Compound **11**. IR (neat, cm^{-1}) 3207 (br), 1704, 1659; ^1H NMR (500 MHz, $CDCl_3$) δ 6.23 (br s, 1H), 2.93 (t, $J=6.3$ Hz, 1H), 2.35 (t, $J=6.2$ Hz, 2H), 2.20 (s, 3H), 2.01–1.87 (m, 8H), 1.74–1.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 171.4, 64.8, 59.5, 40.2, 34.0, 31.4, 31.2, 27.4, 21.4, 18.0; ES HRMS calcd for $C_{11}H_{17}NO_2Na^+$ *m/z* 218.1151, obsd 218.1144.

Compound **12**. Mp 138–139 °C; IR (neat, cm^{-1}) 3391 (br), 1703, 1655; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (br s, 1H), 2.96 (t, $J=8.9$ Hz, 1H), 2.37 (t, $J=4.9$ Hz, 1H), 2.32–2.22 (m, 1H), 2.18 (s, 3H), 2.10–2.02 (m, 1H), 2.01–1.93 (m, 1H), 1.91–1.83 (m, 1H), 1.81–1.68 (m, 5H), 1.67–1.62 (m, 1H), 1.57–1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 172.8, 65.3, 61.4, 40.5, 32.0, 31.3, 27.7, 24.7, 20.1,

17.9; ES HRMS calcd for $C_{11}H_{17}NO_2Na^+$ *m/z* 218.1151, obsd 218.1159.

B. Over platinum oxide. A solution of **10** (290 mg, 1.5 mmol) in methanol (50 mL) was admixed with platinum oxide (20 mg) and stirred under H_2 at 1 atm for 1.5 h prior to filtration through Celite, solvent evaporation, and chromatography as above. There was isolated 110 mg of **12** and 150 mg of **11**.

4.1.7. Base-promoted equilibration of 11 with 12. Either keto lactam **11** or its diastereomer **12** (300 mg, 1.54 mmol) was dissolved in benzene (30 mL), blanketed with N_2, and treated with DBU (1.15 mL, 7.68 mmol). Stirring was maintained for 3 days prior to removal of the solvent under reduced pressure. The residue was subjected to chromatography (elution with 5% isopropyl alcohol in CH_2Cl_2) to afford in both cases 189 mg of **12** and 111 mg of **11**.

Vinylation of **12**. A cold (−78 °C) solution of tributylvinyltin (0.45 mL, 1.54 mmol) in dry THF (6 mL) was treated with *n*-butyllithium (1.0 mL of 1.55 M in hexane), allowed to warm to rt, returned to −78 °C, and admixed dropwise with ketone **12** (100 mg, 0.50 mmol) dissolved in THF (4 mL). The reaction mixture was stirred for 1 h, warmed to rt, and quenched with saturated NH_4Cl solution. The product was extracted into CH_2Cl_2 (3×), and the combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 8% methanol in 1:1 ethyl acetate/hexanes afforded colorless oily **13** as a single diastereomer; IR (neat, cm^{-1}) 3375 (br), 1643, 1408; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (br s, 1H), 5.94 (dd, J=10.7, 17.2 Hz, 1H), 5.16 (dd, J=1.2, 17.2 Hz, 1H), 4.98 (dd, J=1.2, 10.8 Hz, 1H), 2.39–2.23 (m, 3H), 2.00–1.45 (m, 11H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 145.6, 111.0, 74.2, 64.4, 56.7, 40.4, 29.8, 28.7, 26.1, 24.0, 19.0, 17.8; ES HRMS calcd for $C_{13}H_{21}NO_2Na^+$ *m/z* 246.1464, obsd 246.1474.

4.1.8. Allylic acetate 14. A solution of **13** (147 mg, 0.63 mmol) in acetic acid (12 mL) was treated with triflic acid (61 μL, 0.69 mmol), stirred for 30 min, and quenched with cold water. The product was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried and evaporated. The residue was chromatographed on silica gel (elution with 8% methanol in 1:1 ethyl acetate/hexanes) to give **14** (125 mg, 73%) as a colorless oil; IR (neat, cm^{-1}) 1738, 1658, 1405; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (br s, 1H), 5.38 (t, J=5.7 Hz, 1H), 4.61 (d, J=6.4 Hz, 1H); 2.42–2.15 (m, 3H), 2.03 (s, 3H), 1.87–1.60 (m, 12H), 1.51–1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 171.0, 139.2, 121.5, 64.8, 61.2, 57.7, 40.3, 31.3, 27.8, 26.7, 21.0, 20.1, 17.54, 17.51; ES HRMS calcd for $C_{15}H_{23}NO_3Na^+$ *m/z* 288.1570, obsd 288.1575.

4.1.9. Chemoselective hydrolysis of 14. Acetate **14** (125 mg, 0.47 mmol) was dissolved in 5:1 THF/methanol (6 mL), treated with 3 N sodium hydroxide solution (3 equiv), and stirred for 15 min. After dilution with water and CH_2Cl_2, the separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried and evaporated. Purification of the residue by chromatography on silica (elution with 8% methanol in 1:1 ethyl acetate/hexanes) afforded **15** as a colorless oil; IR (neat, cm^{-1}) 3280 (br), 1649, 1407; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 5.45 (t, J=5.3 Hz, 1H), 4.18 (dd, J=3.6, 6.5 Hz, 2H), 2.44–2.33 (m, 1H), 2.27 (t, J=4.3 Hz, 1H), 2.20–2.11 (m, 1H), 1.89–1.51 (series of m, 12H), 1.49–1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 136.2, 126.9, 64.7, 59.2, 57.4, 40.0, 31.2, 27.6, 26.0, 20.0, 17.5, 17.3; ES HRMS calcd for $C_{13}H_{21}NO_2Na^+$ *m/z* 246.1464, obsd 246.1469.

4.1.10. Hydrogenation of 15. A 44 mg (0.20 mmol) sample of **15** in THF (5 mL) was admixed with sodium bicarbonate (45 mg) and platinum oxide (4.5 mg). Hydrogen was bubbled though the mixture for 5 min and stirring was maintained for 1 h under a balloon filled with H_2. The reaction mixture was filtered through Celite and concentrated. Subsequent chromatography on silica gel (elution with 10% hexanes in acetone) furnished 28 mg of **16** and 14 mg of **17** (91% total).

Compound **16**. White solid, mp 148 °C; IR (neat, cm^{-1}) 3278 (br), 1649, 1408; ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 1H), 3.75–3.70 (m, 1H), 3.67–3.62 (m, 1H), 2.49–2.16 (m, 3H), 2.10–1.89 (m, 2H), 1.88–1.49 (series of m, 10H), 1.40–1.31 (m, 2H), 0.97 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 64.2, 60.3, 54.4, 40.2, 38.3, 31.4, 30.8, 27.7, 24.9, 19.2, 18.0, 17.5; ES HRMS calcd for $C_{13}H_{23}NO_2Na^+$ *m/z* 248.1621, obsd 248.1625.

Compound **17**. White solid, mp 165–166 °C; IR (neat, cm^{-1}) 3399 (br), 1654, 1414; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 3.76–3.64 (m, 1H), 3.62–3.55 (m, 1H), 2.38–2.27 (m, 2H), 1.98–1.47 (m, 12H), 1.41–1.30 (m, 2H), 0.89 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 64.8, 59.9, 53.0, 40.0, 37.8, 31.2, 29.8, 27.4, 26.2, 19.8, 18.7, 18.3; ES HRMS calcd for $C_{13}H_{23}NO_2Na^+$ *m/z* 248.1621, obsd 248.1630.

4.1.11. Allylic acetate 19. Reaction of **11** (174 mg, 0.89 mmol) in dry THF (5 mL) with vinyllithium prepared in the manner described above from tri-*n*-butylvinylstannane (1.04 mL, 3.56 mmol) was followed by an analogous workup protocol. Chromatography afforded an inseparable 3:1 mixture of diastereomers **18** as a colorless oil (171 mg, 86%). This mixture was dissolved in acetic acid (10 mL), treated with triflic acid (67.3 μL, 0.76 mmol) and processed in the prescribed manner to deliver 130 mg (64%) of **19** as a colorless oil; IR (neat, cm^{-1}) 3203, 1738, 1658; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 1H), 5.41 (t, J=6.8 Hz, 1H), 4.58 (d, J=6.8 Hz, 2H), 2.36–2.13 (m, 3H), 2.03 (s, 3H), 1.90–1.56 (series of m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.0, 140.3, 122.5, 64.8, 61.0, 57.2, 41.0, 33.7, 31.0, 28.3, 21.1, 21.0, 18.1, 16.9; ES HRMS calcd for $C_{15}H_{23}NO_3Na^+$ *m/z* 288.1570, obsd 288.1575.

4.1.12. Allylic alcohol 20. A solution of **19** (125 mg, 0.47 mmol) in methanol (10 mL) and water (1 mL) was treated with K_2CO_3 (232 mg, 1.68 mmol), stirred for 2 h, and worked up in the manner described above. There was isolated 100 mg (92%) of **20** as a colorless oil; IR (neat, cm^{-1}) 3263 (br), 1650, 1406; ^1H NMR (300 MHz, $CDCl_3$)

δ 7.48 (s, 1H), 5.51 (t, J=6.0 Hz, 1H), 4.21 (dd, J=8.3, 12.2 Hz, 1H), 4.00 (dd, J=5.8, 12.2 Hz, 1H), 3.49 (br s, 1H), 2.39–2.31 (m, 1H), 2.28–2.24 (m, 2H), 1.90–1.71 (m, 8H), 1.68 (s, 3H), 1.67–1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 139.3, 126.4, 64.9, 58.7, 55.3, 39.2, 33.8, 30.9, 28.7, 20.8, 18.4, 17.8; ES HRMS calcd for $C_{13}H_{21}NO_2Na^+$ *m/z* 246.1464, obsd 246.1469.

4.1.13. Hydrogenation of 20. A solution of **20** (100 mg, 0.45 mmol) in THF (10 mL) was treated sequentially with $NaHCO_3$ (100 mg) and platinum oxide (10 mg). The mixture was stirred under a balloon of H_2 for 2 h, filtered through Celite, and freed of solvent. The residue was chromatographed on silica gel (elution with 10% hexanes in acetone) to give 95 mg (94%) of a 1.5:1 mixture of inseparable diastereomers consisting of **21** and **22**.

For the composite: IR (neat, cm^{-1}) 3275 (br), 1649, 1407; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 and 6.64 (s, 1H), 3.70–3.55 (m, 2H), 3.02 (s, 1H), 2.41–2.21 (m, 2H), 1.90–1.20 (m, 14H), 0.93 and 0.88 (d, J=6.7, 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.7, 64.4, 64.2, 60.6, 60.3, 54.2, 53.4, 42.7, 42.2, 39.5, 37.1, 35.6, 35.4, 31.4, 31.3, 29.7, 29.3, 28.1, 27.8, 22.0, 21.9, 20.1, 18.4, 18.3, 17.6; ES HRMS calcd for $C_{13}H_{23}NO_2Na^+$ *m/z* 248.1621, obsd 248.1618.

4.1.14. Stereoselective formation of 23. *A. With 2-propenylmagnesium bromide*. A cold (0 °C) solution of **4** (0.125 g, 0.75 mmol) in dry THF was treated with 2-propenylmagnesium bromide (3.7 mL, 0.60 M in ether, 2.22 mmol), stirred for 30 min, and quenched with saturated NH_4Cl solution. The product was extracted into CH_2Cl_2 (3×), dried, concentrated, and chromatographed on silica gel. Elution with 10% methanol in 1:1 ethyl acetate/hexanes) gave **23** as a white solid (105 mg, 67%), mp 144 °C; IR (neat, cm^{-1}) 3365 (br), 1645, 1451; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.09 (d, J=1.4 Hz, 1H), 5.04 (d, J=1.4 Hz, 1H), 2.35–2.10 (m, 3H), 2.09–1.92 (m, 2H), 1.85 (s, 3H), 1.84–1.61 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 146.7, 114.6, 85.0, 68.2, 39.3, 36.6, 31.2, 26.8, 21.7, 18.6, 18.3; ES HRMS calcd for $C_{12}H_{19}NO_2Na^+$ *m/z* 232.1308, obsd 232.1317.

B. With 2-propenyllithium. A solution of 2-bromopropene (232 mg, 1.91 mmol) in dry THF (10 mL) was blanketed with N_2, treated with *tert*-butyllithium (2.55 mL of 1.5 M in hexanes, 3.83 mmol) at −78 °C, warmed to 0 °C, stirred for 30 min, and returned to −78 °C prior to the introduction of **4** (80 mg, 0.48 mmol) dissolved in dry THF (5 mL). The reaction mixture was stirred for 2 h, warmed to rt, and quenched with saturated NH_4Cl solution. The product was extracted into CH_2Cl_2 (3×), and the combined organic layers were dried and evaporated to leave a residue that was chromatographed on silica gel (elution with 8% methanol in 1:1 ethyl acetate/hexanes). There was isolated 82 mg (82%) of **23** identical to the material generated in part A.

4.1.15. Allylic alcohols 24 and 25. A solution of **23** (330 mg, 1.58 mmol) in acetic acid (10 mL) was treated very slowly with triflic acid (0.28 mL, 3.16 mmol). The reaction mixture gradually darkened while being stirred during 2 days. Following dilution with cold water and CH_2Cl_2, the separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (elution with hexanes/acetone 1:1) provided the rearranged allylic acetates in a 1:1 ratio (250 mg total, 63%). Both are colorless oils.

For the less polar isomer subsequently identified as **35**: IR (neat, cm^{-1}) 1731, 1657, 1230; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (br s, 1H), 4.68 (s, 2H), 2.41–2.28 (m, 4H), 2.08–2.03 (m, 4H), 1.88–1.69 (m, 6H), 1.63 (s, 3H), 1.52–1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 171.0, 145.1, 125.5, 64.5, 63.0, 41.9, 31.7, 31.1, 30.9, 21.2, 20.9, 18.5, 18.4; ES HRMS calcd for $C_{14}H_{21}NO_3Na^+$ *m/z* 274.1414, obsd 274.1420.

For the more polar isomer: IR (neat, cm^{-1}) 1736, 1651, 1230; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (br s, 1H), 4.50 (s, 2H), 2.49–2.20 (m, 4H), 2.07 (s, 3H), 2.01–1.61 (m, 10H), 1.53–1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 171.1, 156.2, 127.8, 68.6, 64.6, 42.0, 30.5, 30.2, 21.6, 20.9, 20.2, 18.6, 15.2.

The acetate mixture (166 mg, 0.66 mmol) was dissolved in THF (5 mL) and methanol (1 mL), treated with 3 M sodium hydroxide (0.88 mL), and stirred for 45 min. Water was introduced and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried and freed of solvent. The residue was chromatographed on silica gel (elution with 6% isopropyl alcohol in CH_2Cl_2) to furnish **24** and **25** in a 1:1 ratio (83% total).

Compound **24**. Colorless oil; IR (neat, cm^{-1}) 3360 (br), 1643, 1406; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (br s, 1H), 4.49 (d, J=11.4 Hz, 1H), 3.76 (d, J=11.4 Hz, 1H), 2.52–2.16 (m, 4H), 2.10–2.00 (m, 2H), 1.87–1.60 (m, 8H), 1.59–1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.9, 130.4, 64.3, 60.8, 41.6, 32.6, 31.2, 30.7, 21.2, 18.7, 18.3; ES HRMS calcd for $C_{12}H_{19}NO_2Na^+$ *m/z* 232.1308, obsd 232.1311.

Compound **25**. White solid, mp 182–183 °C; IR (neat, cm^{-1}) 3270 (br), 1649, 1406; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (br s, 1H), 4.10 (d, J=11.6 Hz, 1H), 3.97 (d, J=11.6 Hz, 1H), 2.51–2.25 (m, 3H), 2.21–1.98 (m, 4H), 1.97–1.50 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 141.5, 130.4, 65.7, 64.2, 41.8, 31.1, 30.4, 30.0, 21.8, 18.5, 15.3; ES HRMS calcd for $C_{12}H_{19}NO_2Na^+$ *m/z* 232.1308, obsd 232.1319.

4.1.16. Hydrogenation of 24. A mixture of **24** (50 mg, 0.24 mmol), sodium bicarbonate (50 mg), platinum oxide (5 mg), and THF (5 mL) was stirred overnight over 55 psi of H_2, filtered through Celite, and concentrated. Chromatography of the residue on silica gel (elution with 5% isopropyl alcohol in CH_2Cl_2) afforded 20 mg of **26** and 5 mg of **27**.

Compound **26**. White crystals, mp 164 °C (from ethyl acetate); IR (neat, cm^{-1}) 3387, 1656, 1415; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J=10.1 Hz, 1H), 3.68 (dd, J=3.9, 10.7 Hz, 1H), 3.44 (dd, J=4.1, 10.7 Hz, 1H), 2.97 (br s, 1H), 2.43–2.18 (m, 2H), 1.95–1.48 (m, 11H),

1.41–1.30 (m, 1H) 0.97 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 65.2, 64.0, 49.1, 39.3, 35.2, 31.4, 26.8, 24.9, 19.1, 17.4, 16.8. ES HRMS calcd for $C_{12}H_{21}NO_2Na^+$ m/z 234.1464, obsd 234.1466.

Compound **27**. White solid, mp 149–150 °C; IR (neat, cm^{-1}) 3274 (br), 2959, 1652; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (br s, 1H), 3.64 (dd, J=3.4, 10.5 Hz, 1H), 3.45 (dd, J=6.1, 10.5 Hz, 1H), 2.45–2.36 (m, 1H), 2.25 (dq, J=6.6, 18.0 Hz, 1H), 2.02–1.73 (m, 5H), 1.70–1.51 (m, 7H), 1.41–1.32 (m, 1H), 1.05 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 67.4, 64.2, 51.3, 40.1, 36.7, 31.5, 27.6, 25.1, 19.3, 17.6, 16.0; ES HRMS calcd for $C_{12}H_{21}NO_2Na^+$ m/z 234.1464, obsd 234.1467.

4.1.17. Hydrogenation of 25. A 45 mg (0.21 mmol) sample of **25** was hydrogenated at 55 psi of H_2 in the presence of sodium bicarbonate (45 mg) and platinum oxide (4 mg) as described above. The analogous workup delivered 26 mg (50%) of **28** as a white solid, mp 153 °C; IR (neat, cm^{-1}) 3384 (br), 1652; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (br s, 1H), 3.65 (dd, J=3.5, 10.6 Hz, 1H), 3.48 (dd, J=3.5, 6.3 Hz, 1H), 2.38 (dd, J=3.5, 12.2 Hz, 1H), 2.24–2.20 (m, 1H), 2.02–1.79 (m, 5H), 1.67–1.50 (m, 7H), 1.37–1.25 (m, 1H), 1.07 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 67.3, 64.1, 51.1, 40.0, 36.7, 31.5, 27.6, 25.0, 19.3, 17.5, 16.0; ES HRMS calcd for $C_{12}H_{21}NO_2Na^+$ m/z 234.1464, obsd 234.1449.

p-Nitrobenzoate **29** proved to be a white solid exhibiting a mp of 194 °C; IR (neat, cm^{-1}) 1724, 1657, 1529, 1277; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J=7.0 Hz, 2H), 8.20 (d, J=7.0 Hz, 2H), 6.60 (s, 1H), 4.37 (dd, J=3.6, 10.8 Hz, 1H), 4.15 (dd, J=6.6, 10.8 Hz, 1H), 2.49–2.35 (m, 1H), 2.28–2.16 (m, 1H), 2.03–1.75 (m, 5H), 1.72–1.50 (m, 6H), 1.50–1.39 (m, 1H), 1.13 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 164.7, 150.5, 135.6, 130.7, 123.6, 70.3, 64.1, 51.2, 39.8, 34.2, 31.5, 27.6, 24.9, 19.2, 17.6, 16.5; ES HRMS calcd for $C_{19}H_{24}N_2O_5Na^+$ m/z 383.1577, obsd 383.1665.

4.1.18. Formylation of 23. Alcohol **23** (236 mg, 1.13 mmol) was dissolved in formic acid (15 mL), cooled to 10 °C, and treated slowly with triflic acid (0.2 mL, 2.25 mmol). The mixture was stirred overnight at rt, diluted with cold water, and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 5% isopropyl alcohol in CH_2Cl_2) to leave 238 mg (89%) of **30** as a 3:2 mixture of isomers.

This material was taken up into dry benzene (25 mL), treated with benzoyl chloride (0.58 mL, 5.0 mmol), heated at reflux for 10 h, and evaporated. Chromatography of the residue on silica gel (elution with 25% ethyl acetate in hexanes) afforded **31** (84 mg) and **32** (150 mg) (83% combined).

Compound **31**. White solid, mp 152 °C; IR (neat, cm^{-1}) 1718, 1685, 1249; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.56 (d, J=8.0 Hz, 2H), 7.48–7.40 (m, 1H), 7.39–7.32 (m, 2H), 5.28 (d, J=11.7 Hz, 1H), 4.39 (d, J=11.7 Hz, 1H), 2.82–2.40 (m, 5H), 2.08–1.91 (m, 6H), 1.63 (s, 3H), 1.60–1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 173.7, 161.2, 146.3, 136.0, 131.8, 128.3, 128.1, 121.3, 71.1, 63.2, 37.9, 34.9, 34.1, 31.0, 22.5, 19.4, 18.2; ES HRMS calcd for $C_{20}H_{23}NO_4Na^+$ m/z 364.1519, obsd 364.1509.

Compound **32**. Colorless oil; IR (neat, cm^{-1}) 1737, 1641, 1454; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (t, J=0.9 Hz, 1H), 7.56 (d, J=8.5 Hz, 2H), 7.47–7.41 (m, 1H), 7.39–7.30 (m, 2H), 4.71 (d, J=11.9 Hz, 1H), 4.41 (d, J=11.9 Hz, 1H), 2.73–2.52 (m, 4H), 2.52–2.43 (m, 1H), 2.21–2.11 (m, 1H), 2.05–1.87 (m, 5H), 1.82 (s, 3H), 1.61–1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 173.6, 161.0, 145.6, 136.0, 131.5, 128.2, 128.1, 121.5, 71.0, 66.8, 37.6, 34.9, 32.3, 30.8, 22.6, 19.1, 16.4; ES HRMS calcd for $C_{20}H_{23}NO_4Na^+$ m/z 364.1519, obsd 364.1500.

4.1.19. Hydrolysis of 32. A solution of **32** (106 mg, 0.31 mmol) in methanol (6 mL) was treated with potassium carbonate (54 mg, 0.59 mmol), stirred for 15 min, diluted with water, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with ethyl acetate–hexanes (1/1) afforded **34** (85 mg, 87%) as a white solid, mp 148–149 °C; IR (neat, cm^{-1}) 3360, 1684, 1252; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J=6.6 Hz, 2H), 7.54–7.30 (m, 3H), 3.95 (q, J=11.8 Hz, 2H), 2.79–2.38 (m, 5H), 2.29–2.15 (m, 1H), 2.01–1.90 (m, 6H), 1.86 (s, 3H), 1.55–1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 173.9, 141.8, 136.0, 131.5, 128.2, 128.1, 126.9, 71.2, 65.7, 37.6, 34.9, 32.3, 30.4, 22.7, 19.2, 16.2; ES HRMS calcd for $C_{19}H_{23}NO_3Na^+$ m/z 336.1570, obsd 336.1576.

4.1.20. Hydrolysis of 31. The formate **31** (130 mg, 0.38 mmol) in methanol (15 mL) was treated with potassium carbonate (53 mg, 0.38 mmol) and stirred for 2 h prior to the addition of NH_4Cl and extraction with CH_2Cl_2 (3×). The combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 50% ethyl acetate in hexane gave **33** as a colorless oil (125 mg, 90%); IR (neat, cm^{-1}) 3362 (br), 1738, 1644; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=6.9 Hz, 2H), 7.50–7.32 (m, 3H), 7.07 (s, 1H), 4.30 (d, J=11.3 Hz, 1H), 4.14 (d, J=11.3 Hz, 1H), 3.67 (s, 3H), 2.69–1.89 (series of m, 9H), 1.80 (s, 3H), 1.72–1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 166.5, 143.1, 135.2, 131.2, 128.5, 128.4, 126.9, 65.4, 62.6, 51.8, 38.0, 37.9, 33.4, 32.3, 22.6, 20.0, 19.2; ES HRMS calcd for $C_{20}H_{27}NO_4Na^+$ m/z 368.1832, obsd 368.1841.

4.1.21. Conversion of 35 to 34. A solution of **35** (44 mg, 0.175 mmol), generated from **23** as illustrated in Scheme 7, in dry benzene (5 mL) was blanketed with N_2, treated with benzoyl chloride (81 μL, 0.70 mmol), and refluxed for 10 h. After solvent removal and chromatographic purification (silica gel, 50% ethyl acetate in hexane), there was isolated 45 mg (76%) of the benzoyl protected amide as a colorless oil; IR (neat, cm^{-1}) 1734, 1684, 1247; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J=8.1 Hz, 2H), 7.49–740 (m, 1H), 7.39–7.30 (m, 2H), 4.61 (d, J=12.1 Hz, 1H), 4.31 (d, J=12.1 Hz, 1H), 2.73–2.38 (m, 6H), 2.24–2.15 (m, 1H), 2.06–1.81 (m, 7H), 1.79 (s, 3H), 1.55–1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 173.5, 171.0, 144.4, 136.0, 131.4, 128.1, 128.0, 122.1, 71.0, 67.1, 37.5, 34.8, 32.2, 30.7, 22.5, 20.8,

19.0, 16.2; ES HRMS calcd for $C_{21}H_{25}NO_4Na^+$ *m/z* 378.1676, obsd 378.1681.

The above material (12.3 mg, 0.035 mmol) was dissolved in methanol (3 mL), treated with potassium carbonate (5 mg, 0.035 mmol), and stirred for 2 h. Following the addition of saturated NH_4Cl solution, the product was extracted into CH_2Cl_2 (3×) and worked up as before to deliver 9.1 mg (83%) of **34**, which proved to be identical spectroscopically with the material isolated earlier.

4.2. X-ray crystallographic data available

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 274536, CCDC 274537, and CCDC 274538. 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].

References and notes

1. (a) Wynberg, H.; Houbiers, J. P. M. *J. Org. Chem.* **1971**, *36*, 834. (b) Hulshof, L. A.; Wynberg, H.; van Dijk, B.; de Boer, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 2733.
2. (a) Hulshof, L. A.; Wynberg, H. *J. Am. Chem. Soc.* **1974**, *96*, 2191. (b) Hulshof, L. A.; McKervey, M. A.; Wynberg, H. *J. Am. Chem. Soc.* **1974**, *96*, 3906.
3. For exemplary carbon spirocycle reports, consult: (a) Pearson, A. J.; Wang, X.; Dorange, I. B. *Org. Lett.* **2004**, *6*, 2535. (b) Beaulieu, P.; Ogilvie, W. W. *Tetrahedron Lett.* **2003**, *44*, 8883. (c) Ohno, H.; Okamura, M.; Maeda, S.-I.; Iwasaki, H.; Wakayama, R.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 7722. (d) Wang, X.; Chakrapani, H.; Stengone, C. N.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 1755. (e) Minor, K. P.; Overman, L. E. *Tetrahedron* **1987**, *53*, 8927.
4. Paquette, L. A. *Aust. J. Chem.* **2004**, *57*, 7.
5. (a) Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441. (b) Hayakawa, I.; Arimoto, H.; Uemura, D. *Chem. Commun.* **2004**, 1222. (c) Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079. (d) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249. (e) Hurley, P. B.; Dake, G. R. *Synlett* **2003**, 2131. (f) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453. (g) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450. (h) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871. (i) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413. (j) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *2*, 1847. (k) Wright, D. L.; Shulte, J. P., II,; Page, M. A. *Org. Lett.* **2000**, *2*, 1847. (l) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529. (m) Clive, D. L.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. (n) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921. (o) Lee, S.; Zhao, Z. *Org. Lett.* **1999**, *1*, 681. (p) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583. (q) Kean, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739.
6. For reviews see: (a) Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370. (b) Grössinger, E. In *The alkaloids*; Brossi, A., Ed.; Academic: New York, 1983; pp 139–251. (c) Inubushi, Y.; Ibuka, T. *Heterocycles* **1982**, *17*, 507. For more recent total syntheses, consult: (d) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598. (e) Diedrichs, N.; Krelaus, R.; Gedrath, I.; Westermann, D. *Can. J. Chem.* **2002**, *80*, 686. (f) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494. (g) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (h) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875. (i) Luzzio, F. A.; Fitch, R. W. *J. Org. Chem.* **1999**, *64*, 5485. (j) Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427. (k) Comins, D. L.; Zhang, Y.; Zheng, X. *Chem. Commun.* **1998**, 2509. (l) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907. (m) Kim, D.; Hong, S. W.; Park, C. W. *Chem. Commun.* **1997**, 2263. (n) Compain, P.; Gore, J.; Vatele, J. M. *Tetrahedron Lett.* **1995**, *36*, 4063. (o) Maezaki, N.; Fukuyama, H.; Yagi, S.; Tanaka, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1835. (p) Zhu, J.; Royer, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 2485. (q) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852. For synthetic approaches, see: (r) Malassene, R.; Vanquelef, E.; Toupet, L.; Hurvois, J. P.; Moinet, C. *Org. Biol. Chem.* **2003**, *1*, 547. (s) Comins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681. (t) Parsons, P. J.; Angell, R.; Naylor, A.; Tyrell, E. *J. Chem. Soc., Chem. Commun.* **1993**, 366. (u) Thompson, C. M. *Heterocycles* **1992**, *34*, 379. (v) Venit, J. J.; DiPierro, M.; Magnus, P. *J. Org. Chem.* **1989**, *54*, 4298.
7. (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861.
8. Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.
9. Paquette, L. A.; Kinney, M. J.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713.
10. Hilmey, D. G.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 2067.
11. Streitwieser, A., Jr. *Solvolytic displacement reactions*; McGraw-Hill: New York, 1962; p 13.
12. Lowry, T. H.; Richardson, K. S. *Mechanism and theory in organic chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 376–381.
13. Wright, G. F. In *Steric effects in organic chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 8.
14. Involving $MeO_2CCH_2P(O)(OMe)_2$ and $MeO_2CCH(CH_3)P(O)(OMe)_2$: (a) Wadsworth, W. S., Jr., *Org. React.* **1977**, *25*, 73. (b) Borszeky, K.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3745.
15. With $Ph_3P{=}CH_2$ and $Ph_3P{=}CHOMe$: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Edmonds, M.; Abell, A. In *Modern carbonyl olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 1–17.
16. By means of $BrCH_2COOMe$ with Zn, and with *n*-Bu_3P/Zn: (a) Fürstner, A. *Synthesis* **1989**, 571. (b) Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* **1988**, *47*, 6119.
17. With $TMSCH_2COOEt$ and LDA: (a) Ager, D. J. *Org. React.* **1990**, *38*, 1. (b) Kano, N.; Kawashima, T. In *Modern carbonyl olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 18–103.

18. (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411.
19. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3657.
20. Attempts to effect this dehydration in other ways, for example, with thionyl chloride in pyridine, methanesulfonyl chloride and triethylamine, or the Burgess reagent, were to no avail.
21. Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.
22. Bakthavachalam, V.; D'Alarcao, M.; Leonard, N. J. *J. Org. Chem.* **1984**, *49*, 289.
23. Ford, J. H.; Thompson, C. D.; Marvel, C. S. *J. Am. Chem. Soc.* **1935**, *57*, 2619.
24. Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263.
25. Koutsourea, A. I.; Aresenou, E. S.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 659.

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A bis(η^5-cyclopentadienyl)cobalt complex of a bis-dithiolene: a chemical analogue of the metal centres of the DMSO reductase family of molybdenum and tungsten enzymes, in particular ferredoxin aldehyde oxidoreductase

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Abstract—The synthesis is described of a bis-ene-1,2-dithiolate pro-ligand, designed to model the stereochemical situation in the cofactor of the tungsten enzyme ferredoxin aldehyde oxidoreductase from *Pyrococcus furiosus*. Each masked ene-1,2-dithiolate unit is mounted on a pyrano[2,3-*b*]tetrahydroquinoxaline tricycle, comparable to the pyrano[2,3-*g*]tetrahydropteridines found in all molybdoenzymes and tungsten analogues. Hydrolytic release of the bis-ligand was confirmed by its entrapment as a double (η^5-C_5H_5)Co complex.

1. Introduction

The nature of the cofactors of molybdenum and tungsten enzymes that catalyse oxygen atom transfer has been determined by a series of degradative and spectroscopic investigations, notably by Rajagopalan et al.,[1] followed by several X-ray crystallographic structural studies.[2–6] These investigations identified molybdopterin (**1**, R=H or a nucleotide), present as the doubly *S*,*S*′-dideprotonated ene-dithiolate (dithiolene[7]), as the ubiquitous ligand for the metal in these enzymes. Based on the nature of the metal centre in the oxidized form of the enzymes, molybdenum enzymes can be placed into one of three groups, known as the xanthine oxidase, sulfite oxidase and DMSO reductase, families.[8] In some of the enzymes the molybdenum is co-ordinated by just one ene-dithiolate unit, but intriguingly in others—the DMSO-reductase family—by two MPT units; tungsten enzymes[5,6,9] also belong to this family. In the tungsten enzyme ferredoxin aldehyde oxidoreductase from *Pyrococcus furiosus*, the two MPTs (R=H), which ligand tungsten are oriented via linkage, through a phosphate oxygen in each case, to a magnesium cation, meaning that there is a nine-atom chain joining the two tricyclic ligands (Fig. 1).[5]

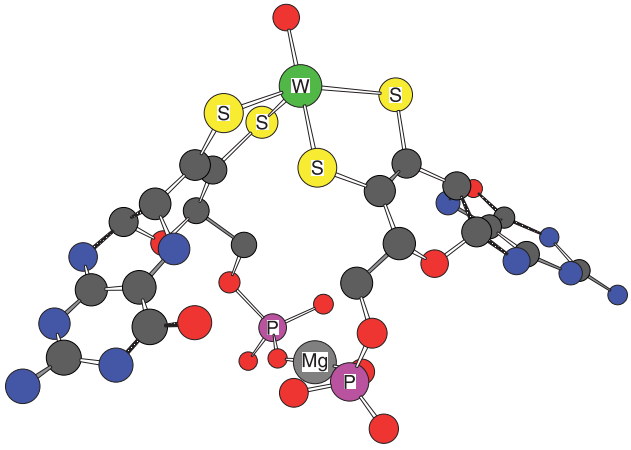

Figure 1. Chem3D drawing of tungsten centre in ferredoxin aldehyde oxidoreductase from X-ray co-ordinates,[5] showing the linking of the two MPT units via phosphate oxygens to a magnesium cation.

It has long been our supposition that the MPT unit in these enzymes is not simply a spectator ligand, but is intimately and actively involved in the mechanism of action of the enzymes, and we have discussed how this could operate, involving electronic interaction between the metal centre and the pterin, initiated by cleavage of the C–O bond in the N–C–O unit.[10] In order to gain experimental evidence for this view through in vitro electrochemical studies on chemical analogues, we have developed[11] flexible routes

Keywords: Aldehyde; Tungsten; Ligand; DMSO reductase family; Pyrano[2,3-*b*]quinoxaline; Enedithiolate.
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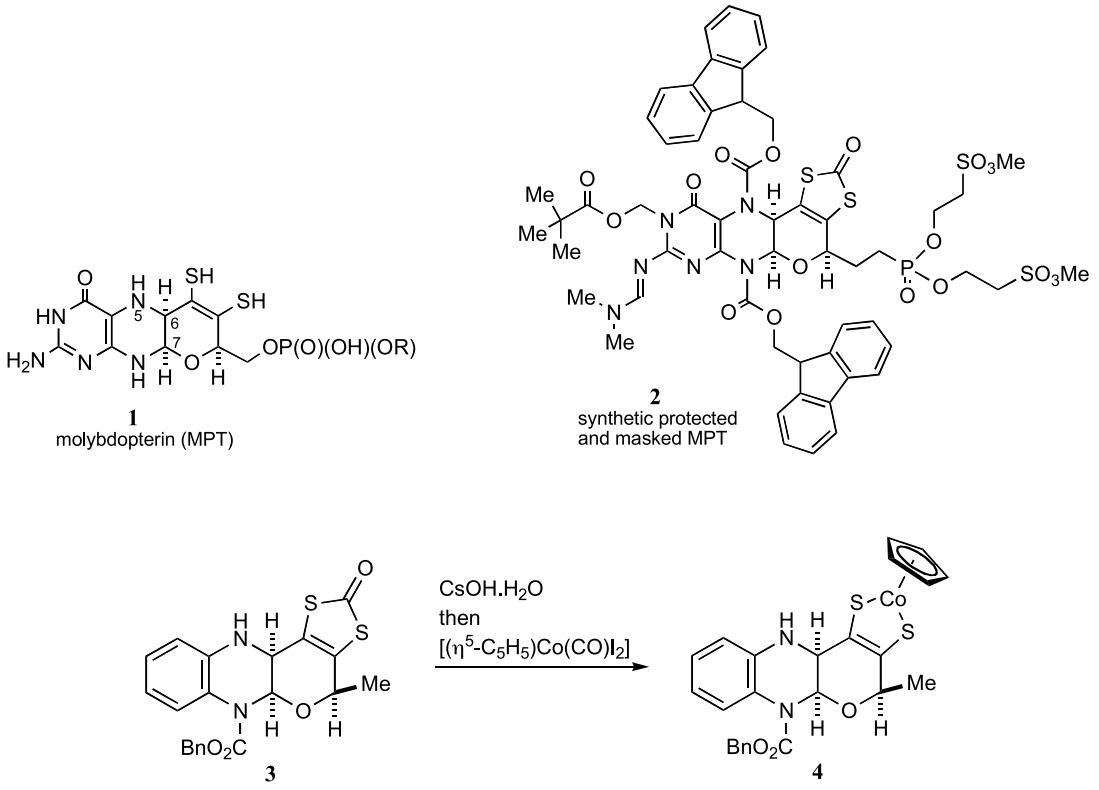
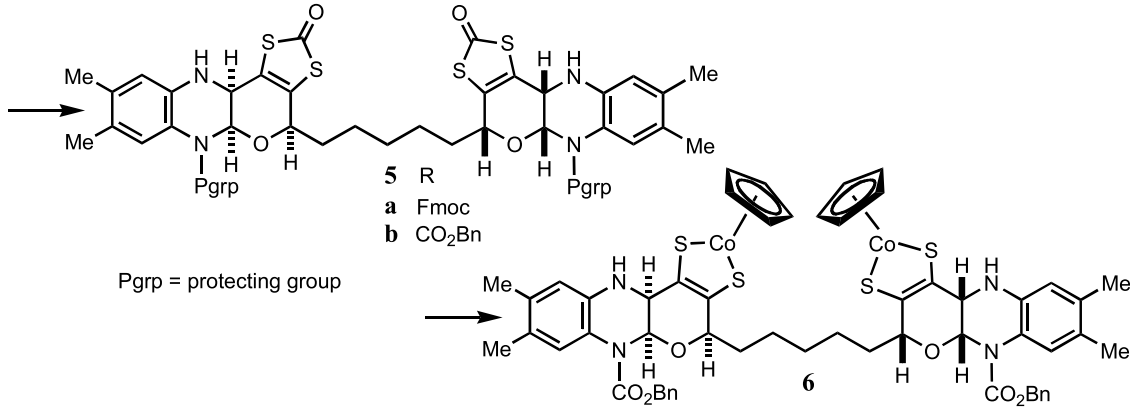
for the synthesis of tricyclic pyrano[2,3-*b*]tetrahydroquinoxaline- and pyrano[2,3-*g*]tetrahydropteridine-1,3-dithiol-2-one pro-ligands, which are amenable to modification and variation, as might be required. We have described the conversion of pro-ligands, such as **3**, into neutral, easily purified, stable, diamagnetic (η^5-cyclopentadienyl)cobalt complexes such as **4**[11f] via hydrolysis of the 1,3-dithiol-2-one unit and then trapping the released ene-dithiolate group on a (η^5-C_5H_5)Co centre. The redox properties of [(η^5-C_5H_5)Co(dithiolene)] complexes can be investigated electrochemically and these studies have provided valuable information concerning the electronic communication between the metal centre and the ligand.[11n] The formation of such neutral cobalt complexes is also seen as a necessary prelude to the synthesis of more labile, paramagnetic Mo and W bis-enedithiolate salts (Scheme 1).

Our programme of organic synthetic chemistry culminated in a synthesis of **2**, MPT itself, in protected and masked form.[11l] The development of the chemistry of metal complexes of chemical relatives of MPT presents several challenges; these include the binding of two ligands to a metal centre, as occurs in the DMSO family of enzymes. As a step towards the realisation of this latter goal, and with specific reference to the structural relationship between the two MPT ligands bound to tungsten in *P. furiosus* aldehyde ferredeoxin oxidoreductase, we describe herein, the synthesis of the bis-pro-ligand **5** and the release of the two dithiolene moieties and their entrapment to form the double (η^5-C_5H_5)Co complex **6** (Scheme 2).

Using the published[5] co-ordinates for the atoms around the tungsten centre in ferredoxin aldehyde oxidoreductase, we



Scheme 1.



Scheme 2.

determined that a molecule with two pyrano-quinoxaline-enedithiolate ligands, linked by a pentamethylene chain, would be able to achieve an almost identical orientation (Fig. 2, hydrogens omitted for clarity), as that observed for the two pyrano-pteridine-enedithiolate ligands in the enzyme (Fig. 1, hydrogens omitted for clarity).

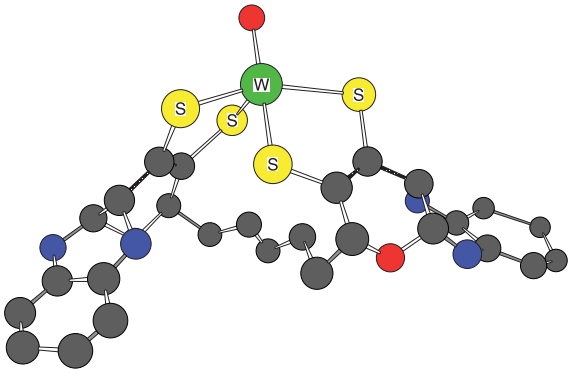


Figure 2. Chem3D drawing of proposed tungsten complex to be formed from a synthetic ligand.

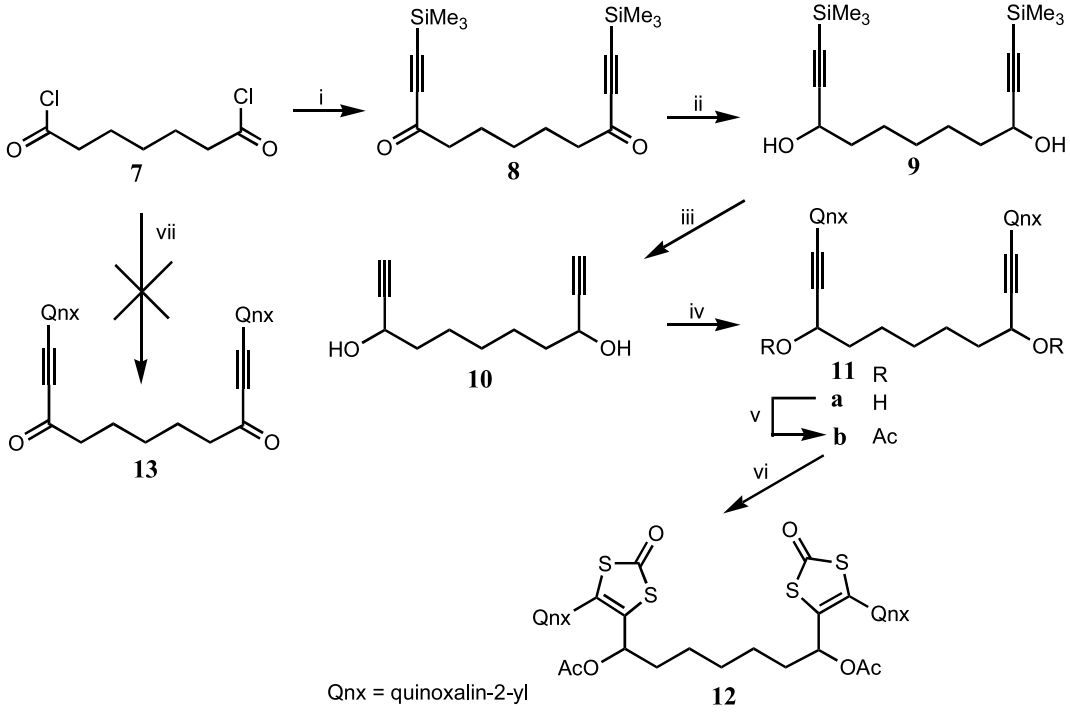
2. Synthesis

In our previous work, we utilised alkynes to synthesise 1,3-dithiole-2-thiones by reaction[11k] with 4,5-dihydro-4-phenyl-1,3-dithiole-2-thione, and to prepare 1,3-dithiol-2-ones by a radical-based reaction[11m] with diisopropyl xanthogen disulfide. 1,3-Dithiole-2-thiones can be trivially and efficiently transformed into the latter, which are the actual pro-ligands, by reaction with mercuric acetate and water. With this background, we began by synthesising diol-diyne **10** and coupling it with 2 mol equiv of 2-chloroquinoxaline to produce **11a**. The starting diol-diyne **10** was made available by the reaction of pimeloyl chloride **7** with bis(trimethylsilyl)acetylene giving a diketone **8**, which was reduced with sodium borohydride, presumably producing a mixture of *meso* and (±) forms of diol **9**, from which the trimethylsilyl groups were removed giving **10**.

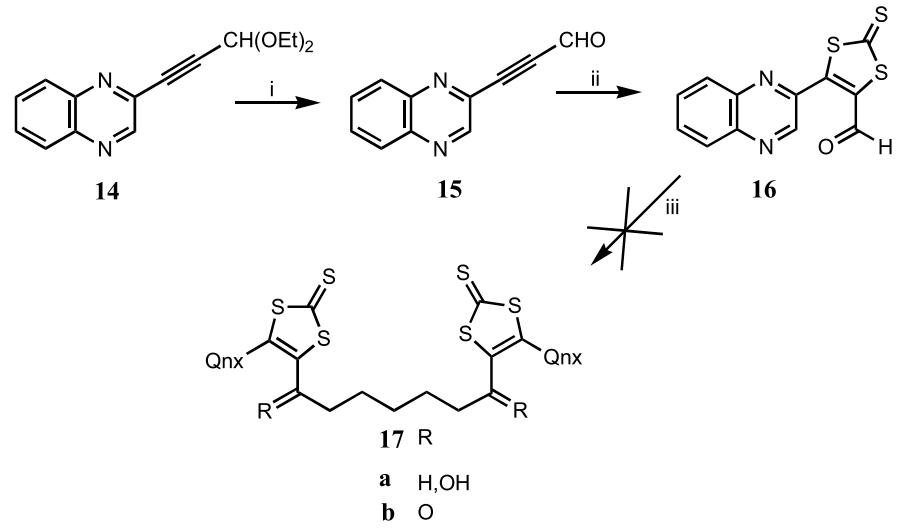
The radical-based process to generate the 1,3-dithiol-2-thione units failed with **11a** and so this was acetylated giving **11b** and from this the desired product **12** was obtained, pure after careful chromatography, albeit in low yield, by reaction with diisopropyl xanthogen disulfide using 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) as initiator (Scheme 3). Unfortunately this strategy had to be abandoned since conditions for the hydrolysis of the acetates in **12** could not be identified, complex mixtures being obtained, presumably reflecting competing attack on the carbonyl of the five-membered heterocycle(s).

In the ^{1}H NMR spectra of all the compounds with chiral centres in this sequence, that is, **9**–**11b**, except the final product **12**, all exhibit duplicate protons, accidentally magnetically equivalent. However, in the ^{1}H NMR spectrum of **12**, two one-hydrogen singlets at low field correspond to the two quinoxaline α-protons in different environments, perhaps signify the presence of a 1:1 mixture of (±)- and *meso*-forms.

A brief examination was made of the possibility of arriving at a diketone **13**, which could then have been reduced to diol-diyne **11a**. The *C*-lithiated derivative of 2-ethynyl-quinoxaline[12] was treated with the double Weinreb amide,



Scheme 3. Reagents: (i) $Me_3SiC{\equiv}CSiMe_3$, $AlCl_3$, CS_2, 0 °C→rt (ca. 100%); (ii) $CeCl_3{\cdot}7H_2O$, MeOH, rt then $NaBH_4$, 0 °C (59%); (iii) aqueous NaOH, $BnMe_3NCl$, MeCN, 0 °C (90%); (iv) 2-chloroquinoxaline, $Pd(OAc)_2$, Ph_3P, CuI, Et_3N, MeCN, reflux (28%); (v) Ac_2O, pyridine, 60 °C (ca. 100%); (vi) $(i\text{-PrOCSS})_2$, ACCN, PhMe, reflux (62%); (vii) Me(MeO)NH, pyridine, rt→$MeO(Me)NCO(CH_2)_5CON(Me)OMe$ (ca. 100%) then treatment of this with Qnx≡H, LDA, THF, −78 °C.



Scheme 4. Reagents: (i) aqueous HCO_2H, CH_2Cl_2, rt (72%); (ii) 4,5-dihydro-4-phenyl-1,3-dithiole-2-thione, 40→80 °C (44%); (iii) $BrMg(CH_2)_5MgBr$.

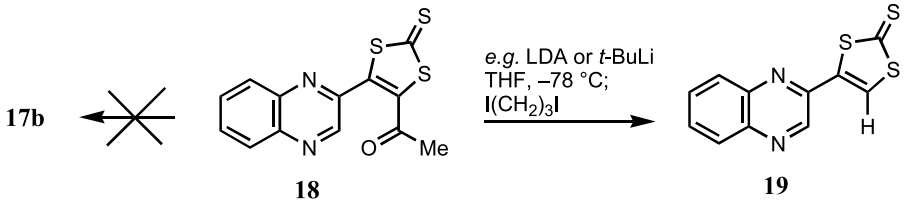
made easily[13] from pimeloyl chloride, but this did not give diketone **13**.

Pursuing an alternative disconnection, reaction of the aldehyde **15**, obtained from acetal **14**,[14] with 4,5-dihydro-4-phenyl-1,3-dithiole-2-thione gave **16** in a moderate yield. Attempted conversion of this into a diol **17a** by reaction with pentamethylenebis(magnesium bromide) failed under several conditions of time and temperature, complex product mixtures always being formed (Scheme 4).

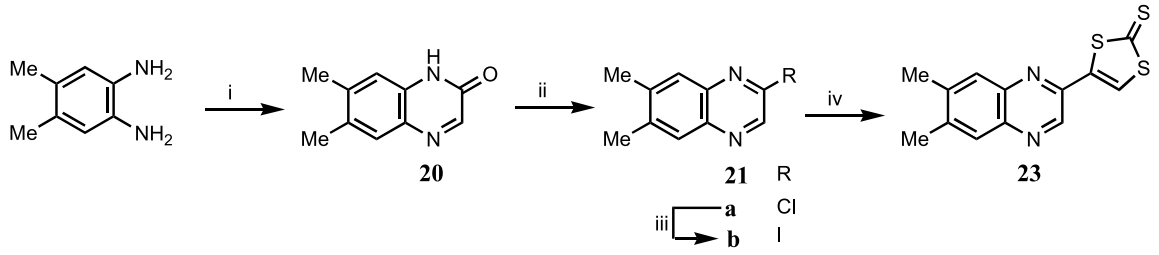
Yet a third alternative disconnection led us to the ketone **18**[11] in which it seemed possible that 2 equiv of an enolate, formed by deprotonation at the methyl group, might react with 1,3-diiodopropane to give diketone **17b**. It was disappointing to find that, using a range of bases, the only transformation we were able to achieve, in yields of 40–70%, was deacetylation of **18**, that is, formation of **19** (Scheme 5). We assume that this must involve nucleophilic addition to the carbonyl group and then C–C cleavage leaving, formally, an anion on the five-membered heterocycle. This clearly speaks to the stabilisation of an anion at that position, and this suggested a fourth strategy, namely that lithiation of **19** could be followed by reaction with either the double Weinreb amide derived from pimeloyl chloride, or with heptane-1,7-dial.

A major practical difficulty emerged in our attempts to lithiate **19**[11b,d,15] (prepared in this work by a much improved cross-coupling[11g] of 2-iodoquinoxaline[16] and 4-tri-*n*-butylstannyl-1,3-dithiole-2-thione) in the form of its very low solubility in the ethereal solvents normally used for such processes. Since alkyl groups on the benzene ring of the target pyrano-quinoxaline-ene-1,2-dithiolates would be expected to influence the planned electrochemical experiments only marginally, the dimethyl-analogue **23** was synthesized and indeed proved to be much more soluble, and amenable to lithiation in THF in the usual way.

Reaction of 4,5-dimethyl-1,2-phenylenediamine with ethyl glyoxylate gave 6,7-dimethylquinoxalin-2-one **20**, which



Scheme 5.

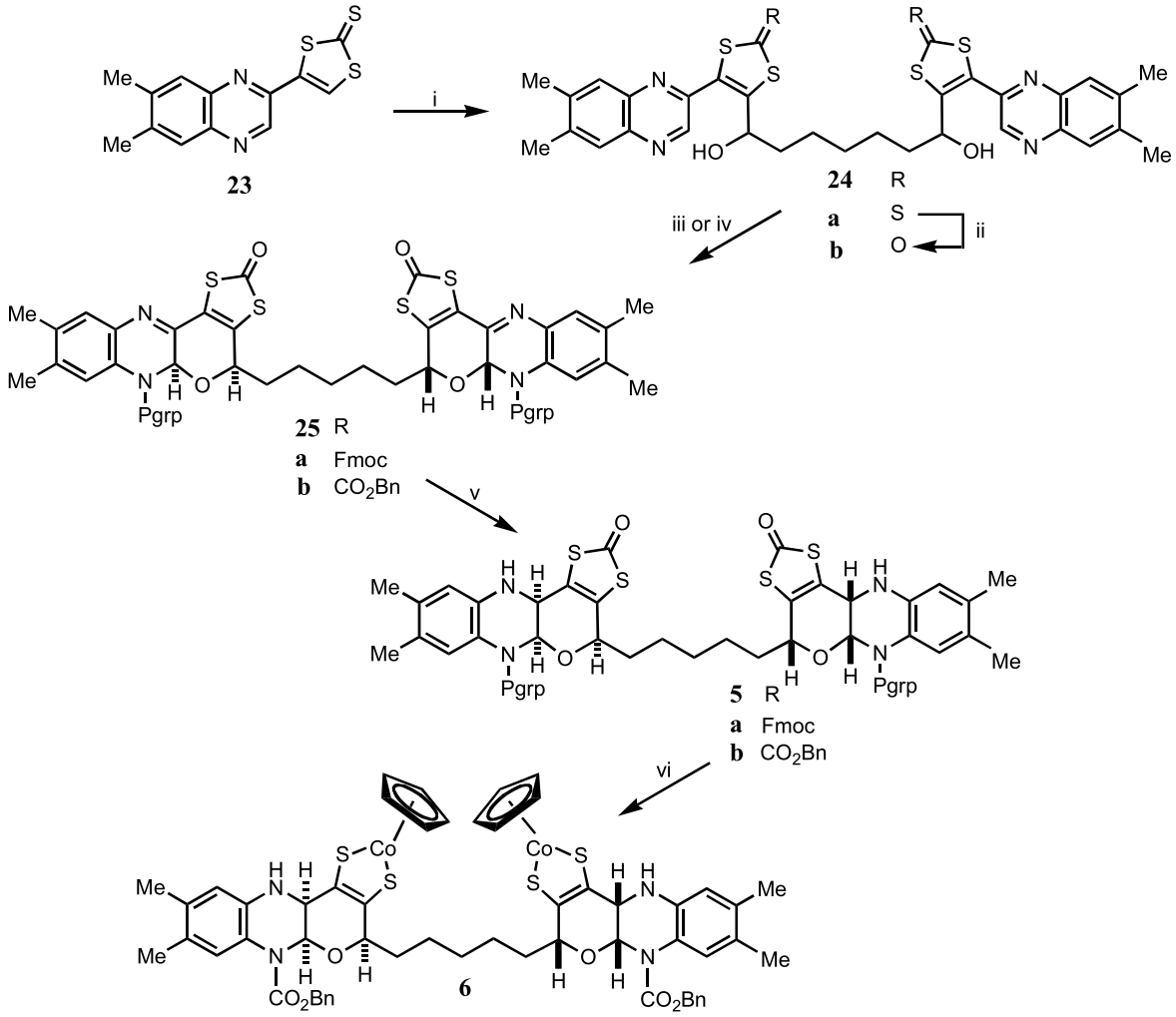


Scheme 6. Reagents: (i) EtO_2CCHO, PhMe, EtOH, reflux (68%); (ii) $POCl_3$, reflux (96%); (iii) HI, NaI, H_2O, Me_2CO, 65 °C (62%); (iv) 4-(tri-*n*-butylstannyl)-1,3-dithiole-2-thione **22**, CuMeSal, THF, reflux (73%).

was converted via the 2-chloride **21a** into 2-iodo-6,7-dimethylquinoxaline **21b**. Coupling the iodide with 4-(tri-*n*-butylstannyl)-1,3-dithiole-2-thione **22** using copper(I) 3-methylsalicylate[17] (CuMeSal) produced the quinoxalinyl-dithiole **23** in 73% yield (Scheme 6).

Heptane-1,7-dial was prepared by oxidation of heptane-1,7-diol with the Dess-Martin periodinane and, on reaction with lithiated **23**, gave the diol **24a** in 68% yield, conversion to the 1,3-dithiol-2-one **24b** being efficient and unexceptional. Closure of the pyran ring followed our earlier developed protocol involving reaction with a chloroformate and intramolecular trapping of the resulting non-isolated quinoxalinium salt by the alcohol giving **25a** and **25b** using FmocCl and $ClCO_2Bn$, respectively. Reduction of the remaining imine using $Na(CN)BH_3$ in the presence of acetic acid produced **5a** and **5b**. Our earlier experiences[11f,j-l] with these pyran-forming ring closures showed that the cis stereoisomer is always the predominant product, and that the subsequent imine reduction is totally stereoselective, giving rise to pyrano-quinoxalines in which, at the three chiral centres, the hydrogens are all on the same side. The cis orientation in the ring closure forming **25a** was confirmed by the observation of an NOE effect between the two relevant hydrogens. At this stage, although we are sure that the final products **5a** and **5b** are homogeneous with regard to the relative stereochemistry around each individual pyran ring (all cis), we cannot be sure whether these bis-pro-ligands have the (desired) relative stereochemistry shown in **5**, that is, that they are derived from the (±)-form of diols **24**, or the undesired stereochemistry, which would result from the *meso*-forms of diols **24**, or indeed a mixture of these. Certainly, the products **25** and **5** gave clean NMR spectra and were homogeneous on chromatographic examination. We take note that six one-hydrogen singlet ^1H NMR signals were observed for the quinoxaline ring protons in both **24a** and **24b**, and this would be consistent with a 1:1 mixture of (±)- and *meso*-forms. The ^1H NMR spectra of the compounds, which followed the diols **24a** and **24b** in the sequence were too complex for a comparable analysis (Scheme 7).

Complications arose on attempted transformation of pro-ligand **5a** into a tetrathiolate by basic hydrolysis, probably involving removal or partial removal of the Fmoc group(s). However, hydrolysis of **5b** with CsOH and addition to the resulting solution of $(\eta^5\text{-}C_5H_5)Co(CO)I_2]$ led to the target double cobalt complex **6**.



Scheme 7. Reagents: (i) *n*-BuLi, −78 °C, $OHC(CH_2)_5CHO$, THF (68%); (ii) $Hg(OAc)_2$, AcOH, Me_2CO, rt (70%); (iii) FmocCl, $NaHCO_3$, H_2O, dioxane, 40 °C (42%); (iv) $ClCO_2Bn$, CH_2Cl_2, rt (22%); (v) $Na(CN)BH_3$, MeOH, CH_2Cl_2, rt **5a**, (70%); **5b**, (95%); (vi) $CsOH\cdot H_2O$, MeOH, CH_2Cl_2, rt then $Co(cp)(CO)I_2$ (36%).

Summarising, we have shown that our earlier methods[11f,j-l] for the synthesis of pyrano-quinoxaline-enedithiolate ligands can be used to prepare bis-pro-ligands, **5**, from which bis(ene-dithiolates) can be liberated and trapped. This pro-ligand has the potential to generate complexes of molybdenum and tungsten bound to two pyrano-quinoxaline-ene-1,2-dithiolate ligands, that is, analogous to the catalytic centres of the DMSO reductase family of enzymes.

3. Experimental

3.1. General

3.1.1. 1,11-Bis(trimethylsilyl)undeca-1,10-diyne-3,9-dione 8. To a suspension of $AlCl_3$ (4.50 g, 34 mmol) in CS_2 (8.5 ml) at 0 °C were added dropwise pimeloyl chloride (2.80 ml, 17 mmol) and then bis(trimethylsilyl)acetylene (7.06 ml, 34 mmol). The mixture was stirred at 0 °C for a further 30 min then allowed to warm to rt. An aqueous solution of HCl (5%, 12 ml) was added slowly, the layers separated, the aqueous layer re-extracted with Et_2O (3× 30 ml) and the combined organic extracts washed with aqueous $NaHCO_3$ (5%), H_2O, then dried ($MgSO_4$), filtered and evaporated. Purification by chromatography over silica eluting with EtOAc/hexane 1:9) gave the dione **8** as a mustard-coloured oil, in essentially quantitative yield; υ_{max} (film)/cm^{-1} 2960, 2902, 2864, 2150, 1678, 1407, 1253, 1104, 1058, 847, 762, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (4H, t, J=7.3 Hz, 2×CH_2CO), 1.69 (4H, quintet, J=7.5 Hz, 2×CH_2CH_2CO), 1.42–1.32 (2H, m), 0.26 (18H, s, 2×Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.2, 98.0, 45.2, 28.4, 23.8, −0.5; *m/z* (CI) 338 (M+NH_4^+, 38%), 321 (MH^+, 38), 303 (100); found, HRMS, M^+ 320.1617. $C_{17}H_{28}O_2Si_2$ requires *M* 320.1622.

3.1.2. 1,11-Bis(trimethylsilyl)undeca-1,10-diyne-3,9-diol 9. To the dione **8** (3.41 g, 11 mmol) dissolved in MeOH (100 ml) was added $CeCl_3\cdot 7H_2O$ (12.00 g, 32 mmol) and the mixture stirred at rt for 15 min. The solution was cooled to 0 °C then $NaBH_4$ (3.00 g, 80 mml) added portionwise. After completion of the reduction (TLC) aqueous satd NH_4Cl was added then the solution brought to pH 1.0 by the addition of cold aqueous HCl (0.5 M). Product was extracted into EtOAc, the combined extracts dried ($MgSO_4$), filtered and evaporated and the residue purified by chromatography over silica (EtOAc/hexane 1:4) to give the diol **9** (2.05 g, 59%) as a pale yellow oil; υ_{max} (film)/cm^{-1} 3351, 2942, 2861, 2172, 1409, 1332, 1250, 1108, 1019, 843, 760, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (2H, t, J=6.5 Hz, 2×CHOH), 1.77–1.70 (5H, m), 1.55–1.42 (5H, m), 0.20 (18H, s, 2×Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.1, 89.7, 63.1, 37.8, 29.1, 25.3, 0.15; *m/z* (CI) 342 (M+NH_4^+, 12%), 325 (MH^+, 10), 90 (90), 73 (100); found, HRMS, M^+ 324.1929. $C_{17}H_{32}O_2Si_2$ requires *M* 324.1935.

3.1.3. Undeca-1,10-diyne-3,9-diol 10. A solution of NaOH (12 M, 5.23 ml) was added dropwise to a solution of diol **9** (2.00 g, 6 mmol) and $BnMe_3NCl$ (65 mg, 0.3 mmol) in MeCN (10 ml), stirred at 0 °C over 10 min. The reaction mixture was diluted with Et_2O, washed with H_2O then brine, dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue over silica, eluting with EtOAc/hexane 1:4, gave diol **10** (1.00 g, 90%) as a colourless oil; υ_{max} (film)/cm^{-1} 3386, 3292, 2938, 2861, 2114, 1725, 1583, 1461, 1374, 1251, 1093, 1047, 1021; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (2H, t, J=6.6 Hz, 2×CHOH), 2.50 (2H, s, 2×C≡CH), 1.95 (2H, br s, 2×OH), 1.79–1.71 (4H, m), 1.56–1.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 73.2, 62.4, 37.7, 29.0, 25.1; *m/z* (CI) 198 (M+NH_4^+, 100%).

3.1.4. 1,11-Bis(quinoxalin-2-yl)undeca-1,10-diyne-3,9-diol 11a and 3,9-bis(acetoxy)-1,11-bis(quinoxalin-2-yl)undeca-1,10-diyne 11b. To a degassed solution of 2-chloroquinoxaline (1.86 g, 11 mmol), diol **10** (0.85 g, 5 mmol), Et_3N (11 ml) in MeCN (30 ml) was added $Pd(OAc)_2$ (0.29 g, 1.25 mmol), Ph_3P (0.37 g, 1.42 mmol) and CuI (0.30 g, 1.62 mmol) and the mixture heated at reflux for 4 h when TLC showed that all the diol had been consumed. The mixture was evaporated to dryness and partial purification achieved by chromatography over silica, eluting with EtOAc/hexane 3:7, yielding the diol **11a** as a dark brown thick oil (0.68 g), which was characterized by acetylation.

A solution of the diol **11a** (0.68 g, 1.6 mmol) in Ac_2O–pyridine (1/1, 4.0 ml) was heated at 60 °C overnight. The cooled reaction mixture was evaporated and the residue purified by chromatography over silica, using EtOAc/hexane 1:4, to give the diacetate **11b** in essentially quantitative yield, as a mustard-coloured oil; υ_{max} (film)/cm^{-1} 2935, 2861, 2236, 1742, 1541, 1486, 1369, 1229, 1130, 1021, 966, 920, 765; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (2H, s, 2×Qnx-3-*H*), 8.10–8.05 (4H, Ar*H*), 7.81–7.75 (4H, Ar*H*), 5.71 (2H, t, J=6.6 Hz, 2×CHOAc), 2.16 (6H, s, 2×CH_3CO), 2.00–1.95 (4H, m), 1.65–1.45 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 147.4, 142.2, 141.4, 138.9, 131.0, 130.9, 129.5, 91.2, 83.0, 64.1, 34.6, 28.9, 25.2, 21.2; *m/z* (CI) 521 ((MH^+, 50%), 401 (20); found, HRMS, M^+ 520.2094. $C_{31}H_{28}N_4O_4$ requires *M* 520.2105.

3.1.5. 1,7-Bis(acetoxy)-1,7-bis(4-(quinoxalin-2-yl)-1,3-dithiol-2-on-5-yl)heptane 12. The diacetate **11b** (0.12 g, 0.23 mmol) was dissolved in PhMe (2 ml) and the solution degassed for 15 min. Diisopropyl xanthogen disulfide[18] (88 mg, 0.33 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) (88 mg, 0.36 mmol) were added and the reaction mixture heated at reflux for 2 h. Further portions of the xanthogen (×3, 88 mg) and ACCN (×3, 88 mg) were added at two-hourly intervals. After a total of 10 h relux, the cooled mixture was evaporated to dryness and the residue purified by chromatography over silica using EtOAc/hexane 1:4, to give the bis-1,3-dithiole **12** (0.10 g, 62%) as a mustard-coloured oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (1H, s, Qnx-3-*H*), 8.97 (1H, s, Qnx-3-*H*), 8.16–8.03 (4H, Ar*H*), 7.86–7.74 (4H, Ar*H*), 6.50–6.42 (2H, m, C*H*OAc), 2.09 (6H, s, 2×CH_3CO), 2.07–1.20 (10H, m).

3.1.6. 3-(Quinoxalin-2-yl)propynal 15. To a solution of 2-(3,3-diethoxypropyn-1-yl)quinoxaline[12] **14** (450 mg, 1.76 mmol) in CH_2Cl_2 (10 ml), was added formic acid (32 ml) and the mixture was stirred at rt for 5 h. After hydrolysis with water (30 ml) and seven extractions with CH_2Cl_2, the combined organic extracts were washed with a solution of $NaHCO_3$ (0.3 N), dried ($MgSO_4$) and

evaporated. The aldehyde **15** was obtained as a yellow solid (231 mg, 72%) sufficiently pure for further reaction. The product was kept under nitrogen at −30 °C to prevent degradation; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (1H, s, CHO), 9.00 (1H, s, Qnx-3-H), 8.15–8.10 (2H, m), 7.87–7.84 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 147.1, 142.3, 141.8, 136.4, 132.1, 131.3, 129.6, 129.4, 89.2, 88.1; *m/z* (CI) 183 (MH^+, 100%); found, HRMS, MH^+ 183.0549. $C_{11}H_7N_2O$ requires $M+H$ 183.0553.

3.1.7. 4-(Quinoxalin-2-yl)-1,3-dithiole-2-thion-5-ylcarboxaldehyde 16. A solution of aldehyde **15** (218 mg, 1.20 mmol) and 4,5-dihydro-4-phenyl-1,3-dithiole-2-thione (1,27 g, 5 equiv) in CH_2Cl_2 (5 ml) was concentrated on a rotary evaporator to produce a homogenous solid. The flask was fitted with a condenser and then heated to 40 °C under nitrogen for one night and then to 80 °C for 4 h. Flash chromatography of the cooled reaction mixture (silica, 0–1% MeOH in CH_2Cl_2) provided the quinoxalinyl-1,3-dithiole-aldehyde **16** (153 mg, 44%) as a yellow solid. The product was kept under nitrogen at −30 °C to prevent degradation; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (1H, s), 8.99 (1H, s), 8.20–8.18 (1H, m), 8.15–8.13 (1H, m), 7.93–7.90 (2H, m); *m/z* (CI) 291 (MH^+, 45%), 187 (100%).

3.1.8. 4-Tri-*n*-butylstannyl-1,3-dithiole-2-thione 22. To a solution of 1,3-dithiole-2-thione (300 mg, 2.23 mmol) in dry THF (4 ml) under nitrogen cooled at −78 °C, LDA (1.8 M in hexane/THF/ethylbenzene, 1.5 ml, 1.2 equiv) was added dropwise with efficient stirring. After 1 h at −78 °C, tri-*n*-butylstannyl chloride (730 µl, 1.2 equiv) was added with stirring and the resultant solution allowed to warm to rt over 2 h. The reaction was quenched by the addition of satd aqueous NH_4Cl (10 ml), the layers separated and the aqueous phase extracted with hexane (3×20 m). The combined organic extracts were washed with brine (15 m), dried and the solvent evaporated under vacuum leaving a brown oil, which was purified by flash chromatography (silica, EtOAc/petroleum ether 5:95) to give the stannane **22** as a brown oil (690 mg, 73%). The product was kept under nitrogen at −30 °C to minimise degradation; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, d, $^3J_{(Sn-H)}=13$ Hz), 1.68–1.49 (6H, m), 1.38–1.26 (8H, m), 1.17–1.11 (4H, m), 0.93–0.87 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.9, 147.8, 133.3, 133.2, 28.7 ($^3J_{(Sn-C)}=11$ Hz), 27.1 ($^2J_{(Sn-C)}=50$, 24 Hz), 17.5, 13.6, 11.4 ($^1J_{(Sn-C)}=176$, 168 Hz); *m/z* (CI) 425 ($M^{Sn120}H^+$, 100%).

3.1.9. 4-(Quinoxalin-2-yl)-1,3-dithiole-2-thione 19. A mixture 2-iodoquinoxaline[14] (312 mg, 1.25 mmol), 4-tri-*n*-butylstannyl-1,3-dithiole-2-thione (1.06 g, 2 equiv) and copper(I) 3-methylsalicylate (539 mg, 2 equiv) under nitrogen in dry THF (6 ml) was heated at reflux for 4 h then cooled to rt. In order to break up the copper complexes, a solution of KCN in aqueous NH_4OH (35% v/v) (4 g/50 ml) was added and the resultant solution was stirred at rt for 30 min. CH_2Cl_2 (50 ml) was added and the yellow precipitate of the quinoxalinyl-1,3-dithiole **19**, which formed was washed twice with CH_2Cl_2 and dried under vacuum (236 mg, 72%). A further quantity (50 mg) was obtained by extraction of the aqueous phase with CH_2Cl_2 but required purification by chromatography (silica, EtOAc/petroleum ether 1:9 with 2% of Et_3N), mp 250–252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.56 (1H, s), 8.84 (1H, s), 8.14–8.09 (1H, m), 8.07–8.02 (1H, m), 7.92–7.86 (2H, m); ^{13}C (75 MHz, DMSO-d_6) δ 213.4, 144.0, 143.8, 142.3, 140.9, 140.5, 132.7, 131.4, 130.9, 129.0, 128.7; *m/z* (CI) 263 (MH^+, 100%); found, HRMS, M^+ 261.9696. $C_{11}H_6N_2S_3$ requires *M* 261.9688.

3.1.10. 6,7-Dimethylquinoxalin-2-one 20. To a solution of 4,5-dimethyl-*o*-phenylenediamine (5 g, 36.7 mol) in absolute ethanol (70 ml), ethyl glyoxylate (50% in toluene) (11.2 ml, 1.5 equiv) was added dropwise with stirring. An orange precipitate was formed and the mixture became hot. After refluxing for 2 h, the solution was cooled to rt and stirred for 1 h after which the solid product was filtered off, rinsed with absolute ethanol and dried in vacuo. The quinoxalinone **20** (5.01 g, 79%) was obtained pure as white powder, mp 310–312 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.30 (1H, s), 8.06 (1H, s), 7.55 (1H, s), 7.06 (1H, s), 2.30 (3H, s), 2.28 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.9, 150.2, 140.3, 131.9, 130.5, 129.7, 128.5, 115.6, 19.7, 18.8; *m/z* (CI) 175 (MH^+, 100%); found, HRMS, MH^+ 175.0866. $C_{10}H_{11}N_2O$ requires $M+H$ 175.0866.

3.1.11. 2-Chloro-6,7-dimethylquinoxaline 21a. 6,7-Dimethylquinoxalin-2-one **20** (2.0 g, 11.5 mmol) was heated under reflux in $POCl_3$ (9 ml, 8 equiv) for 2 h with protection from moisture. After cooling to rt, the mixture was evaporated to dryness under vacuum. Some ice and water (5 ml) were added to the black oil and the mixture obtained was then poured into a large beaker and was neutralized slowly with solid $NaHCO_3$. The aqueous layer was filtered through Celite and then extracted with EtOAc (3×10 ml). After drying ($MgSO_4$), the solution was evaporated in vacuo to leave the 2-chloroquinoxaline **21a** (2.06 g, 94%) as a beige solid, essentially pure, mp 98–99 °C; υ_{max} (film)/cm^{-1} 2978, 2945, 1118, 1091, 960, 753, 420; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, s), 7.83 (1H, s), 7.74 (1H, s), 2.78 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 143.7, 142.0, 140.9, 140.8, 139.8, 128.2, 127.5, 20.4, 20.3; *m/z* (CI) 193/195 (MH^+, 100/53%); found, HRMS, MH^+ 193.0529. $C_{10}H_{10}ClN_2$ requires $M+H$ 193.0527.

3.1.12. 2-Iodo-6,7-dimethylquinoxaline 21b. A mixture of Me_2CO and H_2O (22 ml and 1 ml) was saturated at the boiling point with NaI (~9 g). To the resulting hot solution, 2-chloro-6,7-dimethylquinoxaline **21a** (1.0 g, 5 mmol) was added with stirring. Then a solution of HI (57%, 0.5 ml) in water (2 ml) was added and the mixture stirred at 65 °C for 2 h. The precipitate was filtered off and washed with acetone. The filtrate was dried over anhydrous K_2CO_3/$MgSO_4$ then evaporated, the resultant residue was triturated in Et_2O and the organic layer was filtered. The filtrate was washed with a solution of $Na_2S_2O_5$ (0.2 g in 35 ml of H_2O) and dried ($MgSO_4$). Recrystallisation from pentane (~100 ml) provided the iodide **21b** as a pale yellow solid (0.91 g, 62%), mp 128–130 °C; υ_{max} (film)/cm^{-1} 2988, 2935, 1517, 1067, 938, 424; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, s), 7.79 (1H, s), 7.76 (1H, s), 2.47 (3H, s), 2.46 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 144.1, 141.9, 141.5, 140.2, 128.7, 128.1, 117.0, 20.73, 20.72; *m/z* (CI) 285/286 (MH^+, 100/12%), 159/160 (82/7); found, HRMS, MH^+ 284.9892. $C_{10}H_{10}IN_2$ requires $M+H$ 284.9883.

3.1.13. 4-(6,7-Dimethylquinoxalin-2-yl)-1,3-dithiole-2-thione 23. A mixture 2-iodo-6,7-dimethylquinoxaline **21b** (1.1 g, 3.87 mmol), 4-tri-*n*-butylstannyl-1,3-dithiole-2-thione **22** (3.29 g, 2 equiv) and copper(I) 3-methylsalicylate (1.66 g, 2 equiv) under nitrogen in dry THF (22 m) was heated at reflux for 4 h. After cooling to rt, in order to break the copper complexes, a solution of KCN in aqueous NH_4OH (35% v/v) (20 g/250 ml) was added together with CH_2Cl_2 (250 ml) and the resultant solution was stirred at rt for 30 min. Then, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography (silica, EtOAc/petroleum ether 1:9–6:4 using 2% of Et_3N) provided the quinoxalinyl-dithiole **23** (815 mg, 73%) as a yellow solid, mp 229–231 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (1H, s, Qnx-3-H), 7.86 (1H, s, ArH), 7.83 (1H, s, ArH), 7.78 (1H, s, 1,3-dithiole-thione-5-H), 2.53 (3H, s, $ArCH_3$), 2.52 (3H, s, $ArCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 145.2, 142.9, 142.4, 142.1, 141.8, 140.6, 139.6, 128.3, 128.2, 126.3, 20.5, 20.4; *m/z* (CI) 291 (MH^+, 100%); found, HRMS, M^+ 290.0003. $C_{13}H_{10}N_2S_3$ requires *M* 290.0001.

3.1.14. Heptane-1,7-dial. To a suspension of the Dess-Martin periodinane (4 g, 2.35 equiv) in freshly distilled CH_2Cl_2 (80 ml) under nitrogen was added a solution a 1,7-heptandiol (529 mg, 4 mmol) in freshly distilled CH_2Cl_2 (10 ml) within 10 min. The reaction mixture was stirred at rt for 40 min then Et_2O (200 ml) was added. The reaction mixture was washed with NaOH (1 M, 2×50 ml) then with satd aqueous NH_4Cl (50 ml). The organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography (silica, EtOAc/pentane 3:7) provided the dial (320 mg, 62%) as a colourless oil. The dialdehyde was kept under nitrogen at −30 °C to minimise degradation; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.76 (2H, s, 2×CHO), 2.49–2.40 (4H, m), 1.69–1.57 (4H, m), 1.40–1.34 (2H, m); *m/z* (CI) 146 (MNH_4^+, 100%).

3.1.15. 1,7-Bis(4-(6,7-dimethylquinoxalin-2-yl)-1,3-dithiole-2-thion-5-yl)heptane-1,7-diol 24a. To a solution of 4-(6,7-dimethylquinoxalin-2-yl)-1,3-dithiole-2-thione **23** (275 mg, 0.948 mmol, 2.5 equiv) in dry THF (60 ml) cooled at −78 °C under nitrogen, *n*-BuLi (1.57 M in hexane, 640 µl, 2.6 equiv) was added dropwise with efficient stirring. After 45 min at −78 °C, heptane-1,7-dial (50 mg, 0.385 mmol, 1.0 equiv) was added and the resultant solution was stirred at −78 °C for 1 h and allowed to warm at rt over 1 h. The reaction was quenched by addition of satd aqueous NH_4Cl (30 ml), the layers separated and the aqueous phase extracted with EtOAc (3×50 ml). The combined organic phases were washed with brine (15 ml), dried and the solvent evaporated under vacuum giving a brown solid, which was purified by flash chromatography (alumina, neutral, EtOAc/hexane: 1:9) to give the bis(1,3-dithiol-2-one **24a** as a yellow solid (185 mg, 68%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (1H, s, Qnx-3-*H*), 8.64 (1H, s, Qnx-3-*H*), 7.84 (1H, s, Ar*H*), 7.82 (1H, s, Ar*H*), 7.74 (1H, s, Ar*H*), 7.72 (1H, s, Ar*H*), 5.00 (2H, br s, 2×OH), 4.99–4.92 (2H, m), 2.51 (6H, s), 2.50 (6H, s), 1.90–1.75 (4H, m), 1.65–1.51 (2H, m),1.46–1.30 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0 (2CS), 153.2 (C), 152.9 (C), 142.9 (C), 142.9 (2C), 142.9 (C), 142.7 (C), 142.7 (C), 142.7 (C), 142.7 (C), 140.7 (C), 140.7 (C), 139.9 (2CH), 135.4 (C), 135.4 (C), 128.3 (CH), 128.3 (CH), 127.8 (2CH), 68.4 (2CH), 36.5 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 20.5 ($4CH_3$); *m/z* (ES−) 708 (M^-, 70%), 744 ($MH+Cl^-$, 100%).

3.1.16. 1,7-Bis(4-(6,7-dimethylquinoxalin-2-yl)-1,3-dithiol-2-on-5-yl)heptane-1,7-diol 24b. To the diol **24a** (166 mg, 0.234 mmol) dissolved/suspended in Me_2CO (8 ml) and acetic acid (1.9 ml) was added $Hg(OAc)_2$ (300 mg, 4 equiv) and the solution was stirred for 2 days at rt and then filtered through Celite and the filter cake washed with a portion of EtOAc (8 ml). Satd aqueous $NaHCO_3$ was added to the filtrate, followed by solid $NaHCO_3$ until a neutral pH was attained. The organic layer was separated and the aqueous layer was re-extracted with EtOAc (2×10 ml), the combined organic extracts were washed with brine (10 ml), dried and evaporated to leave the bis(1,3-dithiol-2-one) **24b** as an orange solid (110 mg, 70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (1H, s), 8.75 (1H, s), 7.85 (1H, s), 7.84 (1H, s), 7.76 (1H, s), 7.75 (1H, s), 4.91–4.87 (2H, m), 2.51 (6H, s), 2.49 (6H, s), 1.86–1.82 (2H, m), 1.77–1.73 (2H, m),1.57–1.51 (2H, m, OH), 1.42–1.30 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3 (2CO), 144.0 (2C), 143.1 (2CH), 143.1 (2C), 142.5 (2C), 142.2 (2C), 140.2 (2C), 139.8 (2C), 128.0 (2CH), 127.8 (2CH), 125.4 (2C), 68.4 (2CH), 36.8 ($2CH_2$), 28.8 (CH_2), 25.9 ($2CH_2$), 20.4 ($2CH_3$), 20.4 ($2CH_3$); *m/z* (ES−) 675 (M^-, 70%), 711 ($M+Cl^-$, 100%).

3.1.17. 1,5-Bis(6(5a*H*)-(9*H*-fluoren-9-ylmethyloxycarbonyl)-8,9-dimethyl-2-oxo-4*H*-1,3-dithiolo[4,5]pyrano[2,3-*b*]quinoxalin-4-yl)pentane 25a. A stirred solution of diol **24b** (130 mg, 0.192 mmol), 9*H*-fluoren-9-ylmethyl chloroformate (5.7 g, 115 equiv), solid $NaHCO_3$ (1.85 g, 102 equiv) and 1,4-dioxane–H_2O (10 ml, 19/1) was heated at 40 °C for 24 h. The reaction mixture was filtered with suction and the filtrate evaporated under vacuum. A small amount of hexane was added and the precipitate was purified by extraction using a Soxhlet apparatus with hexane for 2 days. The bis-pyrano-quinoxaline-imine **25a** was obtained as a yellow solid (90 mg, 42%). A NOE was observed between NC*H*O and CH_2CHO confirming the cis orientation; ν_{max} (film)/cm^{-1} 2924, 1733, 1685, 1257, 742, 482; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.73 (3H, m), 7.70 (3H, m), 7.59–7.57 (2H, m), 7.53 (2H, d, J=7.5 Hz), 7.40–7.33 (4H, m), 7.32–7.29 (2H, m), 7.26–7.23 (2H, m), 7.15 (2H, s), 5.12–5.09 (2H, dd, J=5, 11 Hz, $CHCH_2OCON$), 5.07 (2H, br s, NC*H*O), 4.78–4.75 (2H, dd, J=5, 11 Hz, $CHCH_2OCON$), 4.26 (2H, m, $CHCH_2OCON$), 3.98–3.91 (2H, m, H-4), 2.21–2.20 (6H, m), 2.18 (6H, br s), 1.48–1.29 (4H, m), 1.07 (6H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6 (2CO), 154.1 (2C), 149.2 (2C), 143.7 (2C), 142.9 (CH), 141.4 (2C), 141.3 (2C), 140.1 (2C), 138.0 (2C), 132.8 (2C), 131.1 (2C), 129.6 (2CH), 128.0 (2CH), 127.8 (2CH), 127.5 (2CH), 127.4 (2CH), 125.6 (2C), 124.5 (2CH), 124.4 (2CH), 121.4 (2CH), 120.0 (2CH), 119.9 (2CH), 77.1 (2CH), 76.2 (CH), 76.2 (CH), 67.1 (CH_2), 66.99 (CH_2), 47.4 (CH), 47.3 (CH), 35.5 ($2CH_2$), 28.8 (CH_2), 23.2 ($2CH_2$), 20.1 ($2CH_3$), 18.8 ($2CH_3$); *m/z* (ES−) 1155 ($M+Cl^-$, 100%); *m/z* (ES+) 1121 (MH^+, 75%), 1143 ($M+Na^+$, 100%).

3.1.18. 1,5-Bis(6(5a*H*)-(9*H*-fluoren-9-ylmethyloxycarbonyl)-11,11a-dihydro-8,9-dimethyl-2-oxo-4*H*-1,3-dithiolo[4,5]pyrano[2,3-*b*]quinoxalin-4-yl)pentane 5a. To a stirred solution of the bis-pyrano-quinoxaline-imine **25a** (90 mg, 0.08 mmol) in CH_2Cl_2 (2 ml) and MeOH (2 ml) at 0 °C was added acetic acid (two drops) and after 5 min, $NaB(CN)H_3$ (36 mg, 7 equiv) then the resulting mixture was stirred for 24 h at rt. The mixture was diluted with CH_2Cl_2 (5 ml), satd aqueous $NaHCO_3$ was added followed by solid $NaHCO_3$ until a neutral pH was attained. Separation of the aqueous layer and re-extraction with CH_2Cl_2 (2×5 ml) gave combined organic extracts, which were washed with brine (10 ml), dried and evaporated to leave the pyrano-tetrahydroquinoxaline **5a** as a yellow oil (63 mg, 70%) essentially pure. This compound proved to be very sensitive to silica and alumina; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.66 (4H, d, J=7.5 Hz), 7.57 (2H, d, J=7.2 Hz), 7.53 (2H, d, J=7.5 Hz), 7.48 (2H, br s), 7.41–7.32 (6H, m), 7.29–7.25 (4H, m), 6.39 (2H, br s, NH), 5.07 (2H, br s, NC*H*O), 4.99–4.94 (2H, dd, J=5, 11 Hz, CHCH_2OCON), 4.69–4.64 (2H, dd, J=5, 11 Hz, CHCH_2OCON), 4.26–4.24 (2H, m, C*H*CH$_2$OCON), 4.13–4.05 (2H, m, H-4), 3.47 (2H, br s, H-11a), 2.11 (6H, br s), 2.09 (6H, br s), 1.49–1.38 (4H, m), 1.16–0.95 (6H, m); *m*/*z* (ES+) 1125 (MH^+, 100%), 1147 ($M+Na^+$, 34%).

3.1.19. 1,5-Bis(6(5a*H*)-(phenylmethyloxycarbonyl)-8,9-dimethyl-2-oxo-4*H*-1,3-dithiolo[4,5]pyrano[2,3-*b*]-quinoxalin-4-yl)pentane 25b. To diol **24b** (44 mg, 0.063 mmol) in CH_2Cl_2 (1 ml) was added benzyl chloroformate (4 ml, excess) and the mixture was stirred for 24 h at rt. The reaction mixture was diluted with hexane (100 ml) and the resulting mixture was passed through a short column of alumina, eluting with hexane to remove the excess chloroformate. Elution of the column with 5–40% EtOAc in hexane then 0–20% MeOH in CH_2Cl_2 provided the bis-pyrano-quinoxaline-imine **25b** as an orange oil (13 mg, 22%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, s, ArH), 7.96 (1H, s, ArH), 7.38–7.20 (10H, m), 7.12 (1H, s, ArH), 7.09 (1H, s, ArH), 6.00 (1H, s, NC*H*O), 5.96 (1H, s, NC*H*O), 5.35 (2H, d, J=12 Hz, PhCH_2OCON), 5.28–5.24 (1H, d, J=12 Hz, PhCH_2OCON), 5.27–5.23 (1H, d, J=12 Hz, PhCH_2OCON), 4.87–4.83 (2H, q, J=3.3, 3.9 Hz, H-4), 2.25 (3H, s), 2.23 (3H, s), 2.21 (6H, br s), 1.71–1.52 (4H, m), 1.34–1.19 (6H, m); *m*/*z* (ES+) 967 ($M+Na^+$, 100%); found, HRMS, $M+Na^+$ 967.1940. $C_{49}H_{44}O_8N_4NaS_4$ requires *M* 967.1934.

3.1.20. 1,5-Bis(6(5a*H*)-(phenylmethyloxycarbonyl)-11,11a-dihydro-8,9-dimethyl-2-oxo-4*H*-1,3-dithiolo[4,5]-pyrano[2,3-*b*]quinoxalin-4-yl)pentane 5b. To a stirred solution of the bis-pyrano-quinoxaline-imine **25b** (13 mg, 0.014 mmol) in CH_2Cl_2 (2 ml) and MeOH (2 ml) at 0 °C was added acetic acid (two drops) and after 5 min, $NaB(CN)H_3$ (30 mg, 7 equiv) then the resulting mixture was stirred for 24 h at rt. The mixture was diluted with CH_2Cl_2 (5 ml), satd aqueous $NaHCO_3$ was added followed by solid $NaHCO_3$ until a neutral pH was attained. Separation of the aqueous layer and re-extraction with CH_2Cl_2 (2×5 ml) gave combined organic extracts, which were washed with brine (10 ml), dried and evaporated to leave the pyrano-tetrahydroquinoxaline **5b** as a yellow oil (12 mg, 95%) essentially pure. ^{1}H (300 MHz, $CDCl_3$) δ 7.55 (2H, br s, ArH), 7.39–7.34 (7H, m, ArH), 7.31–7.26 (2H, m, ArH), 7.20–7.18 (2H, m, ArH), 7.12–1.09 (1H, m, ArH), 6.43 (2H, br s, 2×NH), 5.92 (2H, br s, 2×NC*H*O), 5.35–5.20 (4H, br s, PhCH_2OCON), 4.66 (2H, br s, 2×C*H*CH$_2$), 3.58 (2H, br s, 2×HNC*H*), 2.12–2.11 (12H, br s), 1.57 (4H, br s), 1.22 (6H, br s); *m*/*z* (ES+) 971 ($M+Na^+$, 84%); *m*/*z* (ES−) 983 ($M+Cl^-$, 100%); found, HRMS, $M+Na^+$ 971.2253. $C_{49}H_{48}O_8N_4NaS_4$ requires *M* 971.2247.

3.1.21. The double cobalt complex 6. To a solution of pyrano-tetrahydroquinoxaline **5b** (12 mg, 0.013 mmol) in CH_2Cl_2–MeOH (v/v, 2 ml) was added a solution of $CsOH\cdot H_2O$ (9 mg, 4.2 equiv) in MeOH (0.5 ml) and the mixture was stirred for 20 min. Carbonyl(cyclopentadienyl)diiodocobalt[19] (21 mg, 4 equiv) was then added and the mixture was stirred for a further 15 min. The reaction was quenched with water (5 ml) and extracted with CH_2Cl_2 (3×5 ml). After dried ($MgSO_4$) and evaporated, the crude was purified by flash chromatography (silica, 0–5% MeOH in CH_2Cl_2) to provide the double cobalt complex **6** (5.3 mg, 36%) as a night-blue solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, br s), 7.45–7.26 (12H, m), 7.12 (1H, s), 6.28 (1H, s, NC*H*O), 6.25 (1H, s, NC*H*O), 5.69–5.66 (2H, m, 2×NH), 5.34 (5H, s, cp), 5.33 (5H, s, cp), 5.29–5.23 (2H, m, PhCH_2OCON), 5.16–5.13 (1H, d, J=13 Hz, PhCH_2OCON), 5.14–5.12 (1H, d, J=13 Hz, PhCH_2OCON), 4.65–4.54 (2H, m, H-4), 4.45–4.37 (2H, m, H-11a), 2.08 (6H, br s), 2.04 (3H, s), 2.03 (3H, s), 1.66–1.51 (4H, m), 1.28–1.02 (6H, m); *m*/*z* (ES+) 1163 ($M+Na^+$, 100%); *m*/*z* (ES−) 1140 (M^-, 74%).

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References and notes

1. For recent work from this group and leading references see: Nichols, J. D.; Rajagopalan, K. V. *J. Biol. Chem.* **2005**, *280*, 7817–7822. George, G. N.; Garrett, R. M.; Prince, R. C.; Rajagopalan, K. V. *Inorg. Chem.* **2004**, *43*, 8456–8460. Enemark, J. H.; Astashkin, A. V.; Raitsimring, A. M.; Feng, C.; Wilson, H. L.; Rajagopalan, K. V. *J. Inorg. Biochem.* **2003**, *96*, 53.
2. Romão, M. J.; Archer, M.; Moura, I.; Moura, J. J. G.; LeGall, J.; Engh, E.; Schneider, M.; Hof, P.; Huber, R. *Science* **1995**, *270*, 1170–1176. Dobbek, H.; Huber, R. *Met. Ions Biol. Syst.* **2002**, *39*, 227–263.
3. Schindelin, H.; Kisker, C.; Hilton, J.; Rajagopalan, K. V.; Rees, D. C. *Science* **1996**, *272*, 1615–1621. Schneider, F.; Löwe, J.; Huber, R.; Schindelin, H.; Kisker, C.; Knäblein, J. *J. Mol. Biol.* **1996**, *263*, 53–69. Kisker, C.; Schindelin, H.; Rees, D. C. *Annu. Rev. Biochem.* **1997**, *66*, 223–267.
4. Bertero, M. G.; Rothery, R. A.; Palak, M.; Hou, C.; Lim, D.; Blasco, F.; Weiner, J. H.; Strynadka, N. C. J. *Nat. Struct. Biol.* **2003**, *10*, 681–687.
5. Chan, M. K.; Mukund, S.; Kletzin, A.; Adams, M. W. W.; Rees, D. C. *Science* **1995**, *267*, 1463–1469.

6. Stewart, L. J.; Bailey, S.; Bennett, B.; Charnock, J. M.; Garner, C. D.; McAlpine, A. S. *J. Mol. Biol.* **2000**, *299*, 593–600.
7. McMaster, J.; Tunney, J. M.; Garner, C. D. *Prog. Inorg. Chem.* **2003**, *52*, 539–583.
8. Hille, R. *Chem. Rev.* **1996**, *96*, 2757–2816.
9. Ellis, P. J.; Conrads, T.; Hille, R.; Kuhn, P. *Structure* **2001**, *9*, 125–132.
10. Armstrong, E. M.; Austerberry, M. S.; Birks, J. H.; Garner, C. D.; Helliwell, M.; Joule, J. A.; Russell, J. R. *J. Inorg. Biochem.* **1991**, *43*, 588. Armstrong, E. M.; Austerberry, M. S.; Birks, J. H.; Beddoes, R. L.; Helliwell, M.; Joule, J. A.; Garner, C. D. *Heterocycles* **1993**, *35*, 563–568. Greatbanks, S. P.; Hillier, I. H.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1529–1534. McNamara, J. P.; Joule, J. A.; Hillier, I. H.; Garner, C. D. *Chem. Commun.* **2005**, 177–179.
11. (a) Rowe, D. J.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1907–1910. (b) Larsen, L.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2311–2316. (c) Larsen, L.; Rowe, D. J.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2317–2327. (d) Dinsmore, A.; Birks, J. H.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 801–807. (e) Davies, E. S.; Beddoes, R. L.; Collison, D.; Dinsmore, A.; Docrat, A.; Joule, J. A.; Wilson, C. R.; Garner, C. D. *J. Chem. Soc., Dalton Trans.* **1997**, 3985–3996. (f) Bradshaw, B.; Dinsmore, A.; Garner, C. D.; Joule, J. A. *Chem. Commun.* **1998**, 417–418. (g) Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54*, 3291–3302. (h) Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54*, 9559–9568. (i) Davies, E. S.; Aston, G. M.; Beddoes, R. L.; Collison, D.; Dinsmore, A.; Docrat, A.; Joule, J. A.; Wilson, C. R.; Garner, C. D. *J. Chem. Soc., Dalton Trans.* **1998**, 3647–3656. (j) Bradshaw, B.; Collison, D.; Garner, C. D.; Joule, J. A. *Chem. Commun.* **2001**, 123–124. (k) Bradshaw, B.; Dinsmore, A.; Collison, D.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3232–3238. (l) Bradshaw, B.; Dinsmore, A.; Collison, D.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3239–3244. (m) Bradshaw, B.; Collison, D.; Garner, C. D.; Joule, J. A. *Org. Biol. Chem.* **2003**, *1*, 129–133. (n) Bhachu, T. S.; Garner, C. D.; Joule, J. A., to be published.
12. Armengol, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 154–158.
13. Jones, G. B.; Wright, J. M.; Plourde, G.; Purohit, H. A. D.; Wyatt, J. K.; Hynd, G.; Fouad, F. *J. Am. Chem. Soc.* **2000**, *122*, 9872–9873.
14. Armengol, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 978–984.
15. Larsen, L.; Rowe, D. J.; Garner, C. D.; Joule, J. A. *Tetrahedron Lett.* **1988**, *29*, 1453–1456.
16. Lont, P. J.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 850. Sugimoto, O.; Mori, M.; Moriya, K.; Tanji, K.-i. *Helv. Chim. Acta* **2001**, *84*, 1112–1118.
17. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91–93.
18. Schroll, A. L.; Barany, G. *J. Org. Chem.* **1986**, *51*, 1866–1881.
19. Heck, R. F. *Inorg. Chem.* **1965**, *4*, 855. Moran, M. *Z. Naturforsch. B: Anorg. Chem. Org. Chem.* **1981**, *36*, 431–433. Bolinger, C. M.; Weatherill, T. D.; Rauchfuss, T. B.; Rheingold, A. L.; Day, C. S.; Wilson, S. R. *Inorg. Chem.* **1986**, *25*, 634–643.

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Poly(benzyl ether) dendrimers with strongly fluorescent distyrylbenzene cores as the fluorophores for peroxyoxalate chemiluminescence: insulating effect of dendritic structures on fluorescent sites

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Abstract—Poly(benzyl ether) dendrimers containing strongly fluorescent distyrylbenzene cores were synthesized, and their fluorescence and electrochemical properties as well as the action as fluorophores in the chemiluminescence reactions were investigated. While all the dendrimers exhibited almost the same properties except for their intensities, a characteristic feature due to the dendritic structure was observed in the electrochemical behaviors. In the peroxyoxalate chemiluminescence reactions using these dendrimers as fluorophores, a bimolecular interaction between the high-energy intermediates and fluorophores was established, and a decrease in the chemiluminescence intensity with an increasing generation was observed, which was connected with the insulating effect of the dendritic structures on the core.

1. Introduction

Much attention has been paid to the architecture of multiform dendrimers,[1] that is, molecules with peculiar structures extending in certain directions from the core, and each branch radiates like a tree. Of the numerous number of dendrimers, the photoresponsive ones are of current interest for chemists because of their unique photochemical properties. For example, the photon-harvesting ability[2,3] and the insulating effect on some of the physical and chemical properties of the cores[4] are typical of their special functions due to their peculiar hyperbranched structures. While the photophysical properties of several dendrimers with fluorescent cores have been investigated and well characterized,[2c,3,5] only a few studies have described the chemiluminescent dendrimers[6] and there is little study using the fluorescent dendrimers during the chemiluminescence reactions.[7] Since an interaction between the high-energy intermediates, usually the cyclic peroxides, and the fluorophores is the crucial process in the peroxyoxalate chemiluminescence,[8] the use of fluorescent dendrimers is quite fascinating, because dendrimers would provide unusual reaction environments when they act as the activators in such reactions. In this paper, we describe the synthesis, fluorescence and electrochemical properties, and the use of Fréchet-type poly(benzyl ether) dendrimers having strongly fluorescent distyrylbenzene cores in peroxyoxalate chemiluminescence.[9]

2. Results and discussion

2.1. Synthesis of the distyrylbenzene core G0 and the dendrimers G1–G3

The synthetic procedure for the substituted distyrylbenzene **G0** and the dendrimers **G1–G3** is shown in Scheme 1. The fluorescent core, (*E*,*E*)-2,5-bis(2-ethylhexyloxy)-1,4-bis(4′-hydroxystyryl)benzene (**1**), was prepared by the Horner–Wadsworth–Emmons reaction[10,11] of 2,5-bis(2-ethylhexyloxy)-1,4-bis(ethylphosphonomethyl)benzene and 4-hydroxybenzaldehyde in the presence of *tert*-BuOK. The side chains, the 2-ethylhexyloxy groups attached at the 2 and 5 positions of the central benzene rings, were introduced for enhancing the solubility in organic solvents as well as the electron-donating ability of the fluorescent moiety.[11] The reaction of **1** and benzyl chloride in the

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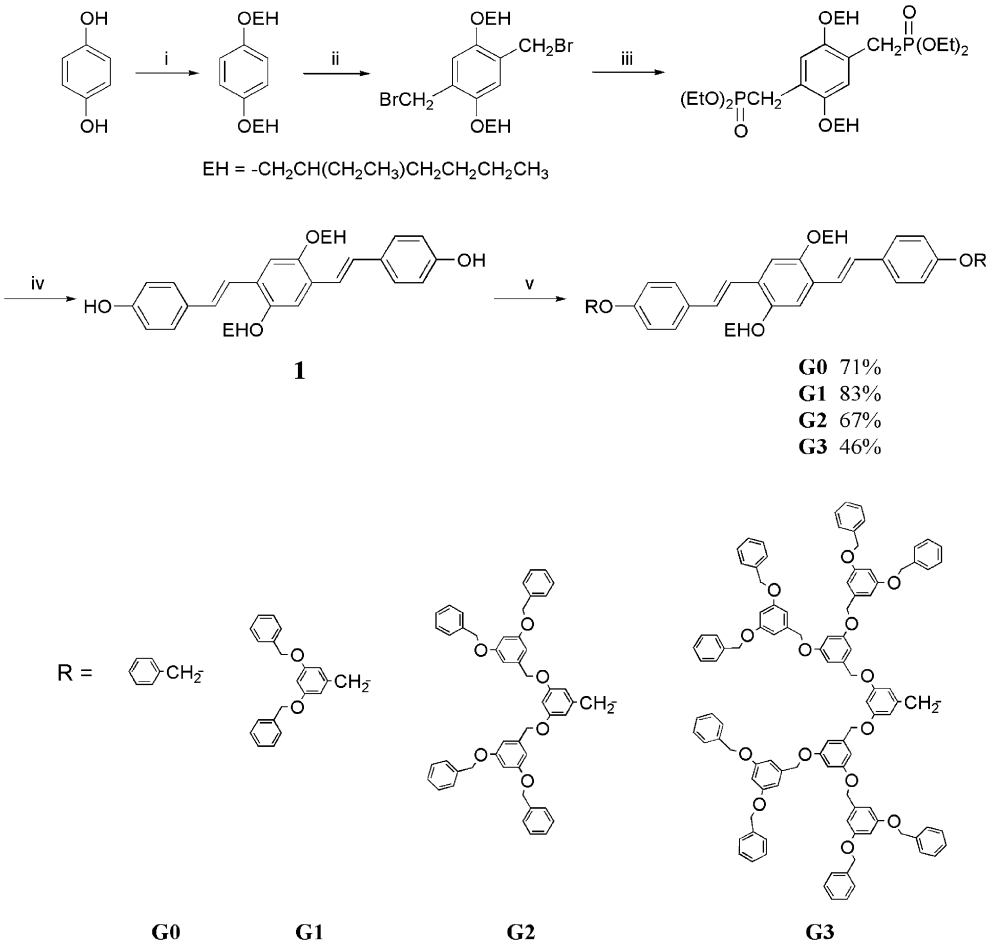


Scheme 1. Reagents and conditions: (i) EHBr, K_2CO_3, DMF, 95%; (ii) $(CH_2O)_n$, NaBr, H_2SO_4, CH_3COOH, 0 °C, 65%; (iii) $P(OEt)_3$, 100 °C, 99%; (iv) 4-hydroxybenzaldehyde, *tert*-BuOK, DMF, rt, 53%; (v) RBr, K_2CO_3, 18-crown-6, THF, reflux.

presence of K_2CO_3 and 18-crown-6 gave **G0**, and a similar procedure employing **1** and the corresponding dendritic benzyl bromides produced the dendrimers **G1**, **G2**, and **G3** with the first, second, and third generation of poly(benzyl ether) branches, respectively, at the peripheral rings, whose structures were confirmed by ^1H and ^{13}C NMR spectra as well as MALDI-TOF MS. Each fluorescent dendrimers showed a single peak in a HPLC by monitoring at 385 nm absorbed by the core.

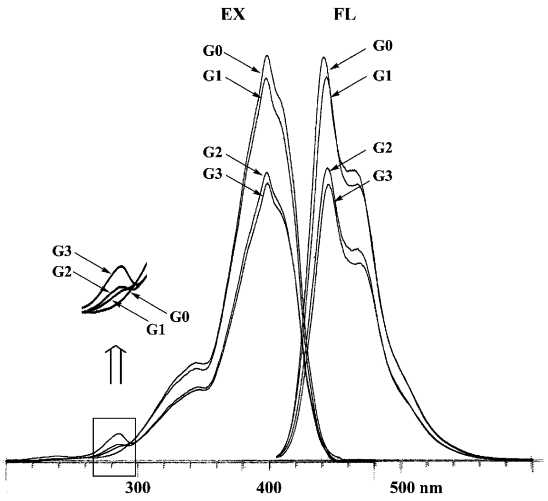


Figure 1. The excitation (EX) and fluorescence (FL) spectra of **G0–G3** in THF (1.0×10^{-6} M).

2.2. Fluorescence property

The fluorescence spectra of **G0–G3** are shown in Figure 1 and the selected spectral data are collected in Table 1. The excitation wavelengths were selected, at which the absorbance was 0.05 in the absorption spectra in THF. Upon excitation of the distyrylbenzene core at 386.5, 389, 396, and 387 nm for **G0**, **G1**, **G2**, and **G3**, respectively, all compounds showed a blue fluorescence at 442–444 nm with large fluorescence quantum yields (Φ_F), whereas the fluorescence intensity tends to decrease along with an increase in the generation. As a fluorescence intensity of each dendrimer was proportional to the concentration within

Table 1. Fluorescence properties for **G0–G3**

	EM λ_{max}	Φ_{Fl}[a]	τ (ns)[b]
G0	442	0.97	1.57
G1	442	0.93	1.57
G2	443	0.92	1.63
G3	444	0.89	1.59

Measured in THF (1.0×10^{-6} M).
[a] The measured Φ_{Fl}s are compared to 9,10-diphenylanthracene (Φ_{Fl}= 0.95).
[b] The lifetime measurements are carried out at a 392.57 nm irradiation.

a range of the measurements, a decrease in the intensity depending on the generation is not due to self-quenching or association, but to the properties of the dendrimers themselves. Although the reason is unclear at present, a variation in the fluorescence quantum yields with generation has been observed in another case of the Fréchet-type dendrimers with the fluorescent pyrrolopyrrole cores.[12] In the fluorescence excitation spectra, the small peaks in the shorter wavelength region at 285 nm increase with a generation increase (Fig. 1). This is due to the singlet energy transfer from the dendron moieties to the core,[2,3] and the efficiency of the energy transfer was estimated to be 0.16 for **G3** by comparing the fluorescence quantum yields with excitation at 285 and 387 nm.

The measurements of the fluorescence decays in THF under a nitrogen atmosphere revealed that all of them could be fitted to a mono-exponential model and all compounds **G0**–**G3** had almost the same fluorescence lifetimes ($\tau = 1.57$–1.63 ns) being much shorter than that for the poly(benzyl ether) dendrimers having the tristyrylbenzene cores,[3c] but comparable with those for the distyrylbenzene structurally close to **G0**[13] and the dendrimers with a stilbene core.[3a]

2.3. Electrochemical behavior

To investigate the electrochemical properties of these dendritically functionalized distyrylbenzenes, cyclic voltammetry (CV) measurements were carried out and the results are illustrated in Figure 2. All compounds **G0**–**G3** exhibited three-stage oxidation waves in dichloromethane. The first step, which might be due to oxidation of the distyrylbenzene core,[11] is almost reversible while the others are irreversible. Although the first half-wave potentials ($E_{1/2}$) for oxidation of the core are almost constant (0.88 V vs SCE) within the error range, the peak separation (ΔE_p) showed a slight increase with the increasing generation (ΔE_p: **G0**, 70; **G1**, 80; **G2**; 110, **G3**; 130 mV). It might be connected with retardation of the electron transfer due to encapsulation of the core by the dendritic moieties toward the electrode.[14] On the other hand, somewhat different electrochemical behaviors were observed in acetonitrile. While **G0** showed reversible redox waves, others showed a much decrease in reversibility. In the case of **G3**, no distinct peak was observable because of its low solubility. Consequently, these electrochemical behaviors indicate that the electron transfer from the

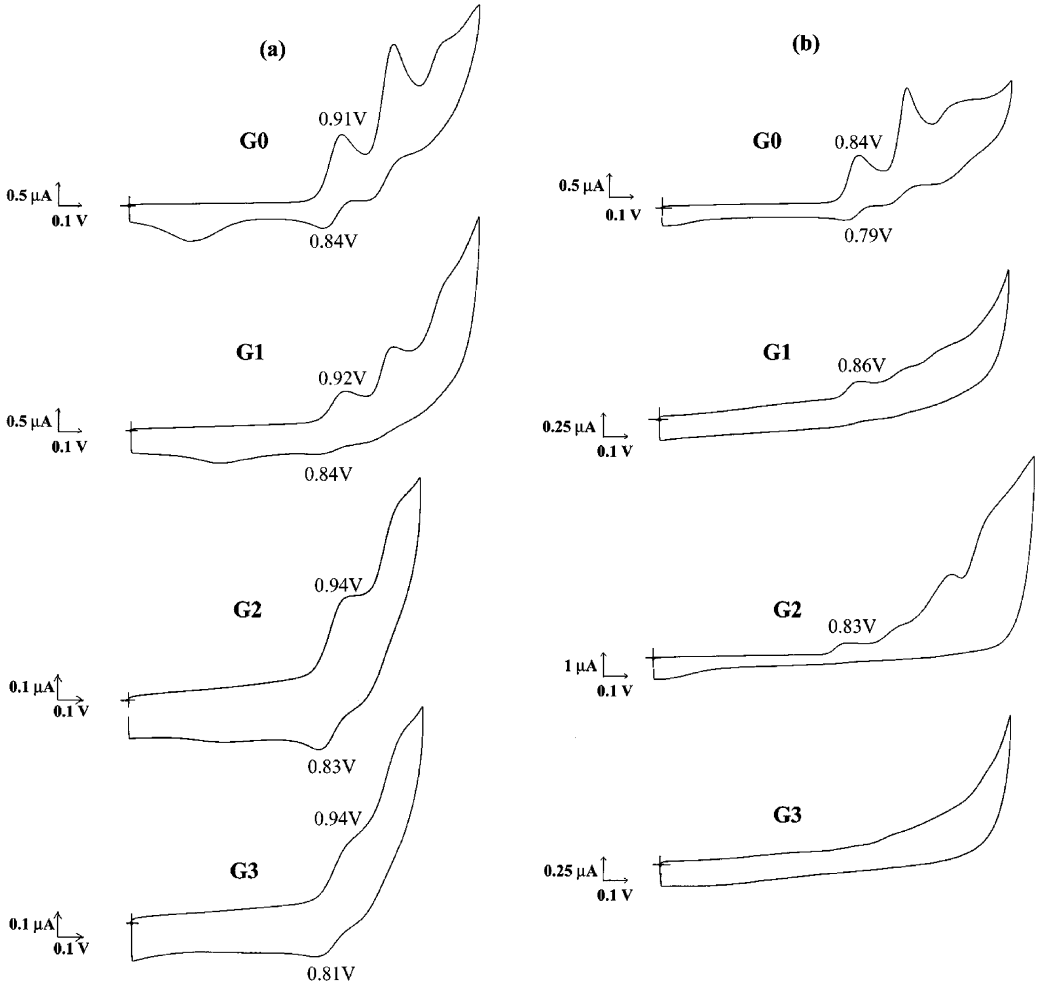


Figure 2. Cyclic voltammetry of **G0**–**G3**, (a) measured in CH_2Cl_2, (b) measured in CH_3CN.

distyrylbenzene core is affected by the insulating effect of the dendritic structures.[15]

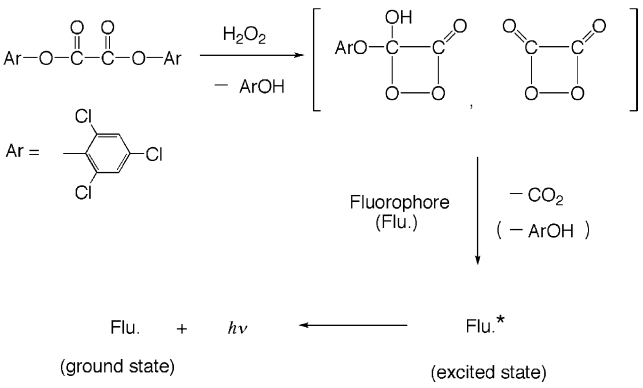
2.4. Use as the fluorophores during peroxyoxalate chemiluminescence

Among the many kinds of chemiluminescence reactions, the peroxyoxalate chemiluminescence reaction is the most convenient and efficient one,[16] where a molecular interaction between the fluorophores and the high-energy intermediates, usually the dioxetanones generated from the reactive oxalates and hydrogen peroxide, produces excited fluorophores that emit light corresponding to their fluorescence (Scheme 2).[8,17] Since the environments around the fluorophores would crucially influence the light forming efficiency,[18] a difference in the chemiluminescence behavior is expected to be presented between the prepared dendrimers having a common fluorescent core but different environments around the cores.

Employing bis(2,4,6-tricholorophenyl) oxalate (TCPO) as a typical luminophore and **G0–G3** as the fluorophores, the chemiluminescence reactions were carried out in the presence of hydrogen peroxide and potassium carbonate in aqueous THF to display a bright blue light emission. The good agreement of all the emission spectra (λ_{max} 443 nm) with the fluorescence spectra of the fluorophores indicates that the light emission was ascribed to the fluorescence from the excited distyrylbenzene cores. To explore the structural effect of the dendritic fluorophores, the chemiluminescence quantum yields of these chemiluminescence reactions were measured by varying the fluorophore concentration using the photon-counting method. According to the established kinetics of the peroxyoxalate chemiluminescence,[9b,17] the double reciprocal plot of Φ_S versus each fluorophore concentration should give a straight line if the high-energy intermediates and the fluorophores interact in a bimolecular reaction fashion. This relationship is expressed by the following equation:

$$\frac{1}{\Phi_s} = \frac{\Phi_{Fl}}{\Phi_{CL}} = \frac{1}{\Phi_r \Phi_S^{\infty}}\left(1 + \frac{k'}{k_{ss}}\frac{1}{[Flu]}\right)$$

where Φ_s is the singlet excitation state quantum yield of the chemiluminescence, Φ_{CL} is the total chemiluminescence quantum yield, Φ_r is the chemical reaction yield and can be regarded as unity because all TCPO was completely consumed during the reactions, Φ_s^{∞} is the singlet excitation state quantum yield at the infinitive fluorophore concentration, Φ_{Fl} is the fluorescence quantum yield of the fluorophores, k' is the rate of the unimolecular decomposition of the high-energy intermediates, k_{ss} is the rate of generation of the singlet excited state, and [Flu] is the concentration of the fluorophores. As shown in Figure 3A, the reciprocal of Φ_S estimated as Φ_{Fl}/Φ_{CL} is a linearly increasing function of the reciprocal of the concentration of **G0–G3**, demonstrating that this chemiluminescence reactions involve the bimolecular interaction process. Of key interest is a decrease in the Φ_{CL} when the dendritic fluorophores with the higher generation were employed at the higher concentration (Fig. 3B), namely, the Φ_Ss for **G0–G3** were almost same at the lower concentration of the dendrimers, while the difference in the Φ_S increased along



Scheme 2. Plausible reaction pathway of peroxyoxalate chemiluminescence.

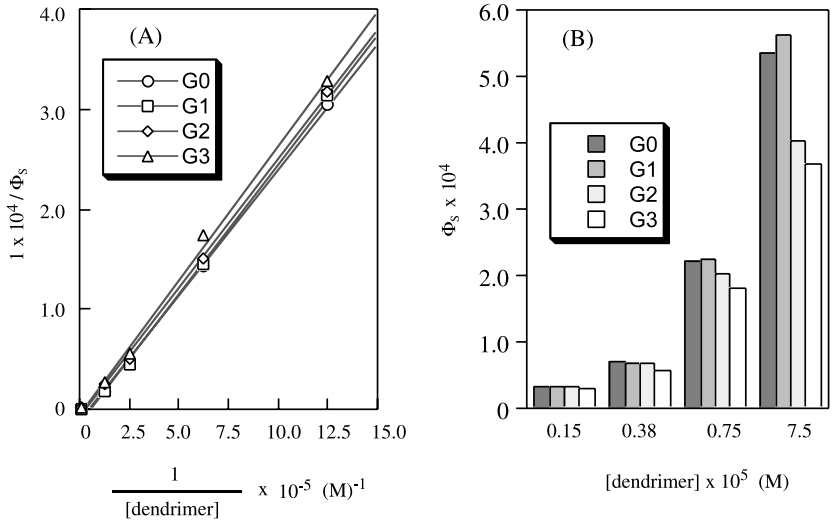


Figure 3. TCPO chemiluminescence in the presence of **G0–G3**. Double reciprocal plot of Φ_S versus [dendrimer] (A) and Φ_S at each [dendrimer] (B). The concentration of the reactants are as follows; [TCPO]=7.5×10^{-5} M, [K_2CO_3]=7.5×10^{-5} M, [H_2O_2]=7.5×10^{-3} M, [dendrimer]$\times10^6$=0.75, 1.5, 3.75, 7.5, 75 M. The slopes for the reciprocal plots are 0.31 M (R^2=0.998) for **G0**; 0.32 M (R^2=0.997) for **G1**; 0.32 M (R^2=0.998) for **G2**; 0.34 M (R^2=0.997) for **G3**.

with an increase in the dendrimer concentration. This indicates that the insulating effect of the dendritic structures with larger branches on the core allows the emission efficiency to decrease. Provided that this chemiluminescence reaction involves a CIEEL (chemically initiated electron exchange luminescence) or a CT (charge transfer) process,[17b,k,19] the rate of electron transfer or the CT interaction is significantly influenced by the electron-donating ability of the core as previously documented in the chemiluminescence using various distyrylbenzenes.[20] The observed variation of Φ_S depending on the structure of the dendrimers reflects the sensitive situation of the cores arising from the dendritic encapsulation because an excitation of the fluorophore needs two electronic process, an electron transfer from the fluorophore to the dioxetane intermediate and a back electron transfer from the radical anion generated by decomposition of the dioxetane to the fluorophore radical cation if the CIEEL mechanism is applied. Therefore, the observed decrease in Φ_S can be related with a decrease in the reversibility of an electron transfer observed in the CV measurements in the polar solvent.[14c] On the other hand, there is also another possible explanation by the site isolation, that is, the large dendritic moieties act as obstacles interrupting the approach of the high-energy intermediate to the fluorescent core, resulting in a decrease in Φ_S. However, differentiation of these effects, electronic or steric, is difficult at present, because the steric hindrance by the large branches retards an electronic interaction as observed in the CV study. Since the peroxyoxalate chemiluminescence is very sensitive to the electronic nature of the fluorophores, there should be much larger difference in Φ_S than observed if the decrease in Φ_S is ascribed to inhibition of an electron transfer. Furthermore, the steric shielding might be insufficient to prevent the interaction between the high-energy intermediate and the core in the case of these dendrimers, considering the ineffective penetration of small quenchers even in the fourth generation poly(aryl ether) dendrimer with the porphyrin core.[21] Identification of the crucial effect on the chemiluminescence efficiency might need architecturally well-designed dendritic fluorophores that provide much more definitive insulating effect. Nevertheless, observation of the structural effect of the fluorescent dendrimers on the chemiluminescence efficiency in this study is novel and provides a foothold of the molecular architecture for the fluorophores useful to control the environment where a light formation proceeds by a molecular interaction.

3. Conclusion

The poly(benzyl ether)dendrimers having strongly fluorescent distyrylbenzene cores were synthesized and their spectral and electrochemical properties were investigated. The dendron moieties hardly affected the spectral properties except for the slight difference in the fluorescence intensities, while retardation of the electron transfer due to encapsulation of the core by the dendritic moieties was detected in the CV measurements. The peroxyoxalate chemiluminescence of TCPO in the presence of **G0–G3** emitted light based on the fluorescent cores, and the decrease in the chemiluminescence efficiency was observed when the dendrimers were employed at the higher generation, which can be explained by the insulating effect of the dendritic structures on the core.

4. Experimental

Solvents and commercially available compounds were purchased from standard suppliers and purified by standard methods. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ as the solvent, and chemical shifts (δ) were given in ppm relative to tetramethylsilane (TMS) as the internal standard. Matrix-assisted laser desporption inonization time-of-flight mass spectral (MALDI-TOF-MS) measurements were taken on using dithranol (1,8,9-anthracentriol) as a matrix. Cyclic voltammetry was performed at room temperature with a three-compartment cell in dry dichloromethane or acetonitrile solution containing the substrate (ca. 10^{-4} M) and a supporting electrolyte (0.1 M tetrabutylammonium perchlorate). Pt disk, Pt wire, and saturated calomel electrode (SCE) were used as the working, counter, and reference electrodes, respectively. The scan rate was 100 mV s^{-1}. Fluorescence lifetimes were measured in THF solution by means of a time-wavelength two-dimensional single photon-counting method coupled with a femtosecond Ti:sapphire regenerative amplifier system. The second harmonics of 392.5 nm of the laser system at the repetition rate of 3 kHz was used as an excitation source. Chemiluminescence quantum yields were measured by a photon-counting method using a Hamamatsu Photonics R456 photomultiplier connected with a photon-counting unit (C3866) and a photon-counting board M8784. The calibration was made by a standard method with the luminol chemiluminescence in the presence of potassium *tert*-butoxide in aerobic DMSO (vide infra).

4.1. Preparation of G0–G3

4.1.1. 2,5-Bis(2′-ethylhexyloxy)-1,4-bis(*p*-hydroxystyryl) benzene (1). To a suspension of *tert*-BuOK (4.59 g, 40.94 mmol) in DMF (15 mL) was added a solution (10 mL) of 2,5-bis(2′-ethylhexyloxy)-1,4-bis(diethylphosphonomethyl)benzene (3.12 g, 4.91 mmol) in DMF (10 mL) and stirred for 30 min. at room temperature. To the slurry was added dropwise a solution of *p*-hydroxybenzaldehyde (1.00 g, 8.19 mmol) in DMF (10 mL). After being stirred for 6 h at room temperature, the solvent was removed by distillation under a reduced pressure. The residue was acidified with 1 M HCl and extracted with ethyl acetate. The organic phase was washed with 1 M HCl twice and brine and then dried over anhydrous Na_2SO_4. After removal of the solvent, the product was recrystallized from ethyl acetate/hexane to give **1** (2.47 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, t, J=7.3 Hz), 0.98 (6H, t, J=7.3 Hz), 1.32–1.62 (16H, m), 3.94 (4H, d, J=5.6 Hz), 6.83 (4H, d, J=8.8 Hz), 7.06 (2H, d, J=16.4 Hz), 7.09 (2H, s), 7.34 (2H, d, J=16.4 Hz), 7.41 (4H, d, J=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.71, 14.49, 23.50, 24.63, 29.66, 31.34, 40.19, 72.24, 110.59, 115.98, 121.98, 127.14, 128.21, 128.35, 131.55, 151.44, 155.41. HRMS (EI) calcd for $C_{38}H_{50}O_4$ $[M]^+$: 570.3709, found 570.3693.

4.1.2. Compound G0. To a suspension of K_2CO_3 (0.194 g, 1.140 mmol) and 18-crown-6 (0.019 g, 0.07 mmol) in THF

(10 mL) was added benzyl chloride (0.089 g, 0.70 mmol) and a solution of **1** (0.20 g, 0.35 mmol) in THF (30 mL). After refluxing for 2 days, the solvent was removed under a reduced pressure. The residue was partitioned between benzene and saturated NH_4Cl solution. The organic phase was washed with satdurated Na_2CO_3 solution and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under a reduced pressure. The crude product was recrystallized from methanol to give **G0** (0.24 g, 92%) as a yellow needle crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, t, J=7.2 Hz), 0.98 (6H, t, J=7.2 Hz), 1.32–1.63 (16H, m), 1.78–1.84 (2H, m), 3.94 (4H, d, J=5.6 Hz), 5.10 (4H, s), 6.97 (4H, d, J=8.6 Hz), 7.08 (2H, d, J=16.4 Hz), 7.09 (s, 2H), 7.33–7.47 (16H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.34, 14.13, 23.13, 24.26, 29.29, 30.97, 39.82, 70.11, 71.84, 110.18, 115.11, 121.66, 126.78, 127.49, 127.65, 128.00, 128.61, 131.22, 137.01, 151.07, 158.36. MALDI-TOF-MS calcd for $C_{52}H_{62}O_4$ $[M]^+$: 750.46, found 750.05. Anal. Calcd for $C_{52}H_{62}O_4$: C, 83.16; H, 8.32. Found: C, 83.47; H, 8.52.

4.1.3. Compound G1. This compound was prepared from 3,5-bis(benzyloxy)benzyl bromide (0.108 g, 0.28 mmol), **1** (0.080 g, 0.14 mmol), K_2CO_3 (0.078 g, 5.6 mmol) and 18-crown-6 (7.4 mg, 0.028 mmol) in a manner similar to that describe above. Recrystallization from benzene/methanol gave **G1** (0.14 g, 83%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, t, J=6.9 Hz), 0.99 (6H, t, J=7.4 Hz), 1.33–1.63 (16H, m), 1.79–1.84 (2H, m), 3.94 (4H, d, J=5.3 Hz), 5.03 (4H, s), 5.05 (8H, s), 6.58 (2H, t, J=2.0 Hz), 6.69 (4H, d, J=2.0 Hz), 6.94 (4H, d, J=8.6 Hz), 7.08 (2H, d, J=16.4 Hz), 7.09 (2H, s), 7.30–7.46 (26H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.34, 14.13, 23.12, 24.27, 29.29, 30.96, 39.82, 69.99, 70.17, 71.82, 101.61, 106.35, 110.17, 115.12, 121.67, 126.77, 127.57, 127.65, 128.02, 128.61, 128.75, 131.26, 136.81, 139.49, 160.22. MALDI-TOF-MS calcd for $C_{80}H_{86}O_8$ $[M]^+$: 1174.63, found 1174.33.

4.1.4. Compound G2. This compound was prepared from 3,5-bis[3′,5′-bis(benzyloxy)benzyloxy]benzyl bromide (0.130 g, 0.16 mmol), **1** (0.045 g, 0.08 mmol), K_2CO_3 (0.043 g, 0.32 mmol) and 18-crown-6 (4.2 mg, 0.016 mmol) in a manner similar to that describe above. Purification by silica gel column chromatography (eluent; benzene) gave **G2** (0.11 g, 67%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.92 (6H, m), 0.96–0.99 (6H, m), 1.34–1.62 (16H, m), 1.77–1.83 (2H, m), 3.93 (4H, d, J=5.5 Hz), 4.98 (8H, s), 5.02 (4H, s), 5.03 (16H, s), 6.54–6.55 (2H, m), 6.57–6.58 (4H, m), 6.68 (12H, d, J=2.1 Hz), 6.95 (4H, d, J=8.8 Hz), 7.07 (2H, d, J=16.4 Hz), 7.08 (2H, s), 7.27–7.45 (46H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.33, 14.13, 23.12, 24.26, 29.28, 30.95, 39.81, 70.05, 70.16, 71.82, 101.60, 101.66, 106.43, 108.25, 110.19, 115.11, 121.68, 126.76, 127.56, 127.65, 128.01, 128.60, 131.27, 136.81, 139.24, 139.48, 151.07, 158.26, 160.12, 160.21. MALDI-TOF-MS calcd for $C_{136}H_{134}O_{16}$ $[M]^+$: 2022.97, found 2023.03.

4.1.5. Compound G3. This compound was prepared from 3,5-bis{3′,5′-Bis[3″,5″-bis(benzyloxy)benzyl-loxy]benzyl-oxy}benzyl bromide (57.7 mg, 0.035 mmol), 1 (9.0 mg, 0.016 mmol), K_2CO_3 (8.8 mg, 0.063 mmol) and 18-crown-6 (1.6 mg, 0.06 mmol) in a manner similar to that describe above. Reaction time was 5 days. Purification by silica gel column chromatography (eluent; ethyl acetate/hexane 1:1) gave **G3** (26.8 mg, 45%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.91 (6H, m), 0.94–0.98 (6H, m), 1.26–1.42 (16H, m), 1.76–1.82 (2H, m), 3.91 (4H, d, J=5.4 Hz), 4.96 (24H, s), 4.98 (4H, s), 5.00 (32H, s), 6.53–6.57 (14H, m), 6.66–6.67 (24H, m), 6.68–6.69 (4H, m), 6.93 (4H, d, J=8.8 Hz), 7.06 (2H, d, J=16.0 Hz), 7.07 (2H, s), 7.29–7.44 (86H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.34, 14.14, 23.11, 24.25, 29.27, 30.94, 39.79, 70.03, 70.13, 71.81, 101.66, 106.41, 106.49, 110.19, 115.08, 121.67, 127.55, 127.65, 127.99, 128.58, 131.26, 136.80, 139.24, 151.07, 158.27, 160.10, 160.19. MALDI-TOF-MS calcd for $C_{248}H_{230}O_{32}$ $[M+H]^+$: 3720.64, found 3721.67.

4.2. Measurement of the CL quantum yields

The measurements were carried out according to the procedure reported previously using the luminol standard in DMSO for calibration of the photomultiplier tube.[22] For a typical run of **G0**-activated TCPO-CL, a solution (1.5 mL) containing TCPO (1.0×10^{-4} M) and **G0** (1.0×10^{-6} M) in distilled THF was place in a 1×1 cm quarts cell in front of the photomultiplier in exactly the same geometry. Photon-counting was initiated simultaneously with the injection of a solution (0.5 mL) containing H_2O_2 (3.0×10^{-4} M) and K_2CO_3 (3.0×10^{-2} M) into the cuvette, and the data collection was continued for 500 s. The similar measurements were carried out using the **G0** solution of different concentration, 2.0×10^{-6}, 5.0×10^{-6}, 1.0×10^{-5}, and 1.0×10^{-4} M in THF. The same procedure was applied to the measurements of the CL quantum yields for other dendrimers **G1**–**G3**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.108

References and notes

1. For reviews: (a) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 885–905. (b) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819–3867.

2. (a) Jang, D.-L.; Aida, T. *Nature* **1997**, *388*, 454–456. (b) Jang, D.-L.; Aida, T. *J. Am. Chem. Soc.* **1998**, *120*, 10895–10901. (c) Sato, T.; Jang, D.-L.; Aida, T. *J. Am. Chem. Soc.* **1999**, *121*, 10658–10659.
3. (a) Mizutani, T.; Ikegami, M.; Nagahata, R.; Arai, T. *Chem. Lett.* **2001**, 1014–1015. (b) Uda, M.; Mizutani, T.; Hayakawa, J.; Momotake, A.; Ikegami, M.; Nagahata, R.; Arai, T. *Photochem. Photobiol.* **2002**, *76*, 13–22. (c) Uda, M.; Momotake, A.; Arai, T. *Org. Biomol. Chem.* **2003**, *1*, 1635–1637.
4. Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74–91.
5. (a) Ranasinghe, M. I.; Hager, M. W.; Gorman, C. B.; Goodson, T., III *J. Phys. Chem. B* **2004**, *108*, 8543–8549. (b) Tomoyose, Y.; Jiang, D. L.; Jin, R. H.; Aida, T.; Yamashita, T.; Horie, K.; Yashima, E.; Okamoto, Y. *Macromolecules* **1996**, *29*, 5236–5238.
6. (a) Nakazono, M.; Ma, L.; Zaitsu, K. *Tetrahedron Lett.* **2002**, *43*, 8185. (b) Adamczyk, M.; Fishpaugh, J.; Mattingly, P. G.; Shreder, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3595.
7. Lehman, M.; Schartel, B.; Hennecke, M.; Meier, H. *Tetrahedron* **1999**, *8*, 3595.
8. Adan, w. Four-membered Ring Peroxides. 1,2-Dioxetanes and α-Peroxylactones. In *The Chemistry of Peroxides*; Patti, S., Ed.; Wiley: New York, 1983; pp 829–920.
9. (a) Chandross, E. A. *Tetrahedron Lett.* **1963**, *12*, 761–765. (b) Rauhut, M. M. *Acc. Chem. Res.* **1969**, *2*, 80–87.
10. Nakatsuji, S.; Matsuda, K.; Uesugi, Y.; Nakashima, K.; Akiyama, S.; Katzer, G.; Fabian, W. *J. Chem. Soc., Perkin Trans. 2* **1991**, 861–867.
11. Pfeifer, S.; Hörhold, H. H. *Macromol. Chem. Phys.* **1999**, *200*, 1870–1878.
12. Verheijen, W.; Hofkens, J.; Metten, B.; Vercammen, J.; Shukla, R.; Smet, M.; Dehaen, W.; Engelborghs, Y.; Schryver, F. D. *Macromol. Chem. Phys.* **2005**, *206*, 25–32.
13. Schweikart, K.-H.; Hanack, M.; Lüer, L.; Oelkrug, D. *Eur. J. Org. Chem.* **2001**, 293–302.
14. (a) Cardona, C. M.; Kaifer, A. E. *J. Am. Chem. Soc.* **1998**, *120*, 4023–4024. (b) Smith, D. K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1563–1565. (c) Gorman, C. B.; Smith, J. C.; Hager, M. W.; Parkhurst, B. L.; Sierzputowska-Gracz, H.; Haney, C. *J. Am. Chem. Soc.* **1999**, *121*, 9958–9966.
15. (a) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1994**, 925–926. (b) Boulas, P. L.; Cómez-Kaifer, M.; Echegoyen, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 216–247. (c) Vögtle, F.; Plevoets, M.; Nieger, M.; Azzellini, G. C.; Credi, A.; Cola, L. D.; Marchis, V. D.; Venturi, M.; Balzani, V. *J. Am. Chem. Soc.* **1999**, *121*, 6290–6298. (d) Armaroli, N.; Barigelletti, F.; Ceroni, P.; Eckert, J.-F.; Nicoud, J. F.; Nierengarten, J.-F. *Chem. Commun.* **2000**, 599–600.
16. Catherall, C. L. R.; Palmer, T. F.; Cundall, R. B. *J. Biolumin. Chemilumin.* **1989**, *3*, 147–154.
17. (a) McCapra, F.; Peering, K.; Hart, R. J.; Hann, R. A. *Tetrahedron Lett.* **1981**, *22*, 5087–5090. (b) Catherall, C. L. R.; Palmer, T. F.; Cundall, R. B. *J. Chem. Soc., Faraday Trans. 2* **1984**, *80*, 823–836. (c) Catherall, C. L. R.; Palmer, R. B.; Cundall, R. B. *J. Chem. Soc., Faraday Trans. 2* **1984**, *80*, 837–849. (d) Alvarez, F. J.; Parekh, N. J.; Matuszewski, B.; Givens, R. S.; Higuchi, T.; Schowen, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 6435–6437. (e) Milofski, R. E.; Birks, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 9715–9723. (f) Prados, P.; Santa, T.; Homma, H.; Imai, K. *Anal. Sci.* **1995**, *11*, 575–580. (g) Stevani, C. V.; de Arruda Campos, I. P.; Baader, W. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1645–1648. (h) Hohman, J. R.; Givens, R. S.; Carlson, R. G.; Orosz, G. *Tetrahedron Lett.* **1996**, *37*, 8273–8276. (i) Stevani, C. V.; Baader, W. J. *J. Phys. Org. Chem.* **1997**, *10*, 593–599. (j) Hadd, A. G.; Seebar, A.; Birks, J. W. *J. Org. Chem.* **2000**, *65*, 2675–2683. (k) Stevani, C. V.; Silva, S. M.; Baader, W. J. *Eur. J. Org. Chem.* **2000**, *24*, 4037–4046. (l) Zhang, Y.; Zheng, X.-R.; You, X.-Z. *J. Chem. Phys.* **2000**, *113*, 7731–7734. (m) Lee, J. H.; Rock, J. C.; Park, S. B.; Schlautmann, M. A.; Carraway, E. R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 802–809. (n) Lee, J. H.; Rock, J. C.; Schlautmann, M. A.; Carraway, E. R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1653–1657. (o) Silva, S. M.; Casallanovo, F.; Oyamaguchi, K. H.; Ciscato, L. F. L. M.; Stevani, C. V.; Baader, W. J. *Luminescence* **2002**, *17*, 313–320. (p) Silva, S. M.; Wagner, K.; Weiss, D.; Beckert, R.; Stevani, C. V.; Baader, W. J. *Luminescence* **2002**, *17*, 362–369. (q) Koike, R.; Motoyoshiya, J.; Takaguchi, Y.; Aoyama, H. *Chem. Commun.* **2003**, 794–795. (r) Lee, J. H.; Je, J.; Schlautman, M. A.; Carraway, E. R. *Chem. Commun.* **2003**, 270–271. (s) Bos, R.; Barnett, N. W.; Dyson, G. A.; Lim, K. F.; Russell, R. A.; Waltson, S. P. *Anal. Chim. Acta* **2004**, *502*, 141–147.
18. (a) Yuan, D.-Q.; Kishikawa, N.; Yang, C.; Koga, K.; Kuroda, N.; Fujita, K. *Chem. Commun.* **2003**, 416–417. (b) For the other chemiluminescence systems: (i) Teranishi, K.; Nishiguchi, T. *Anal. Biochem.* **2004**, *325*, 185–195. (ii) Matsumoto, M.; Hamaoka, K.; Takashima, Y.; Yokokawa, M.; Yamada, K.; Watanabe, N.; Ijuin, H. K. *Chem. Commun.* **2005**, 808–810.
19. Schuster, G. B. *Acc. Chem. Res.* **1979**, *12*, 366–373.
20. Motoyoshiya, J.; Sakai, N.; Imai, Y.; Yamaguchi, Y.; Koike, R.; Takaguchi, Y.; Aoyama, H. *J. Org. Chem.* **2002**, *67*, 7314–7318.
21. (a) Jin, R. H.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1260–1262. (b) Pollak, K. W.; Leon, J. W.; Fréchet, J. M. J.; Maskus, M.; Abruna, H. *Chem. Mater.* **1998**, *10*, 30–38.
22. Lee, J.; Wesley, A. S.; Ferguson, J. F., III; Seliger, H. H. In *Bioluminescence in progress*; Johnson, F. H., Haneda, Y., Eds.; Princeton: Princeton, 1966; p 35.

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Rearrangement of allylic azide and phenylthio groups of 3′-azido- or 3′-phenylthio-4′, 5′-didehydro-5′-deoxyarabinofuranosyluridines

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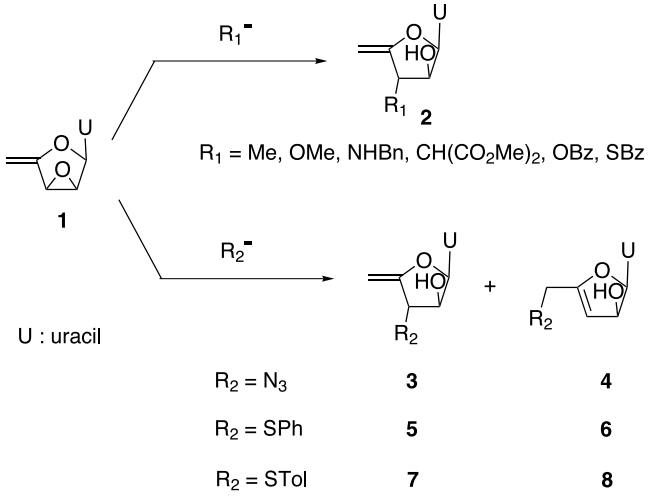
Abstract—The reversible intramolecular [3,3]-sigmatropic rearrangement between 1-(3-azido-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl) uracil (**3**) and 1-(5-azido-3,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)uracil (**4**) and irreversible radical rearrangement of 1-(3,5-dideoxy-3-phenylthio-β-D-*threo*-pent-4-enofuranosyl)uracil (**5**) and 1-[3,5-dideoxy-3-(4-tolyl)thio-β-D-*threo*-pent-4-enofuranosyl]uracil (**7**) into 1-(3,5-dideoxy-5-phenylthio-β-L-*glycero*-pent-4-enofuranosyl)uracil (**6**) and 1-[3,5-dideoxy-5-(4-tolyl)thio-β-L-*glycero*-pent-3-enofuranosyl]uracil (**8**) were attained at room temperature.

1. Introduction

Some modified nucleosides have become useful agents for the treatment of cancer and antiviral diseases due to their good antitumor and antiviral activity.[1] Especially, sugar-modified nucleosides have attracted much attention because of the discovery of potent anti-HIV agents such as Zidovudine (AZT),[2] Zalcitabine (ddC),[3] Stavudine (d4T),[4] Lamivudine (3TC)[5] and so on. Recently, we have reported the regioselective modification of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (**1**) using nucleophiles (Scheme 1).[6] In this case, the 3′-adduct (**2**) was obtained as the sole product by using MeONa, Me_3Al, $BnNH_2$, $CH_2(CO_2Me)_2$, BzOH or BzSH as a nucleophile. On the other hand, when NaN_3, PhSH or TolSH was used as a nucleophile, the corresponding 5′-adduct (**4**, **6**, or **8**) was also obtained together with the major 3′-adduct (**3**, **5**, or **7**), respectively. Interestingly, we were pleased to observe the reversible rearrangement between N_3 compounds (**3** and **4**) and irreversible rearrangement of 3′-phenylthio adducts (**5** and **7**) to 5′-adducts (**6** and **8**). We report here details of the rearrangements including the reaction mechanisms.



Scheme 1. Reaction of **1** with nucleophiles.

2. Results and discussion

At first, we investigated the stability of the 3′-azide adduct (**3**) in DMSO-d_6 at room temperature and the reaction was followed by ^{1}H NMR spectrum. Consequently, time-dependent and significant decrease of **3** and formation of the corresponding 5′-azide adduct (**4**) were observed (Scheme 2). The azide rearrangement of **3** into **4** was not observed in the solid state. The time-course of the azide rearrangements are illustrated in Figure 1. The

Keywords: Nucleosides; Sigmatropic rearrangement; Radical chain mechanism; Azido group; Phenylthio group.
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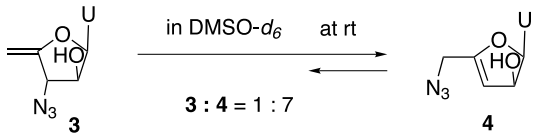


Scheme 2. Allyl azide rearrangement between **3** and **4**.

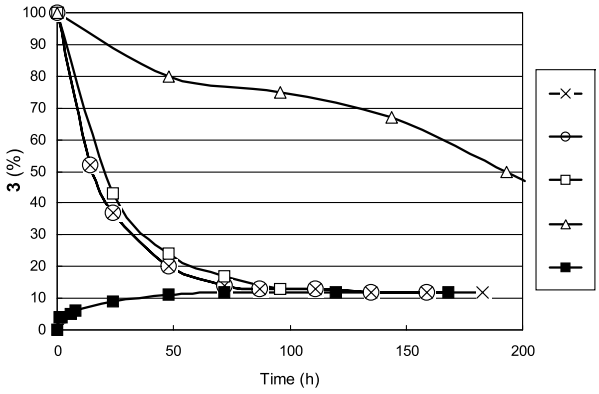
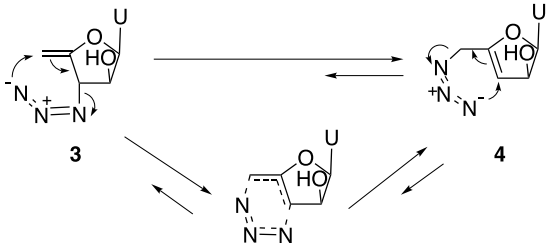


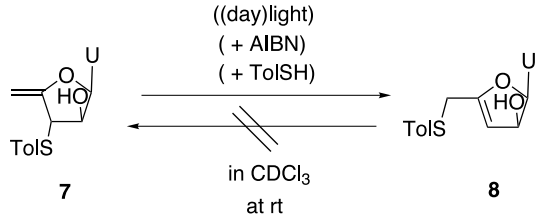
Figure 1. Rearrangement between **3** and **4** at rt. -X-: **3**→**4** in DMSO-d_6, -○-: **3**→**4** in the presence of 1 equiv of NaN_3 in DMSO-d_6, -□-: **3**→**4** in DMSO-d_6 under dark conditions, -△-: **3**→**4** in CD_3OD, -■-: **4**→**3** in DMSO-d_6.

rearrangement of **3** in DMSO-d_6 came to equilibrium after 3 days (Fig. 1 -X-, 72 h) and the ratio of **3** and **4** was roughly 1:7. On the other hand, the reverse conversion from **4** into **3** was also observed in the DMSO-d_6 solution of **4** at room temperature and came to the same equilibrium ratio after 3 days (-■-). The rearrangement was never affected by the addition of another 1 equiv of NaN_3 (-○-) and under light shielding conditions (-□-). The conversion of **3** to **4** also proceeded in CD_3OD, while the conversion rate was apparently reduced (-△-). The equilibrium leaned to the formation of the corresponding primary azide (**4**) as well as other reported examples of allylic azide isomerization.[7] Therefore, it can be proposed that the allylic azide rearrangement is a reversible rearrangement via intramolecular [3,3]-sigmatropic rearrangement accompanying a change in the polarity of the N_3 group (Scheme 3).[7]



Scheme 3. Plausible rearrangement mechanism.

Next, we investigated the rearrangement reaction of phenylthio derivatives (**5** and **7**). The rearrangement of the 3′-(4-tolyl)thio adduct (**7**) into 5′-adduct (**8**) was found by the two-dimensional development of TLC analysis although it was never detected under ordinary TLC development. It was considered that the rearrangement was accelerated by the acidity of silica gel and/or UV radiation to visualize TLC spots. So, we investigated the rearrangement reaction between **7** and **8** in $CDCl_3$ at room temperature using the ^1H NMR spectrum (Scheme 4, Fig. 2). The rearrangement of **7** into **8** was observed under ordinary daylight conditions (Fig. 2, -○-). The ratio of **7** and **8** reached roughly 6:1 for 24 h, and the complete conversion was achieved after 2 days with some accompanying decomposition of the rearrangement product (**8**). The addition of 4-thiocresol induced remarkable acceleration of the rearrangement; complete conversion was observed within 20 h (-△-). It was noteworthy that the decomposition of **8** was totally suppressed by addition of 4-thiocresol, and no by-products were observed even after 4 days by ^1H NMR. The rearrangement was strongly accelerated under light irradiation conditions (60 W electric light bulb) (-●-) and complete conversion was observed within 1 day while the rearrangement was strongly depressed under the light-shielding conditions using aluminum foil and the reaction was not completed even after 2 weeks (-■-). Under the light irradiation conditions, the rearrangement was further accelerated by the addition of AIBN, and the quantitative rearrangement of **7** into **8** was observed within only 4 h (-▲-). The 3′-(4-tolyl)thio adduct (**7**) was entirely stable in the solid state (-□-). On the other hand, the reverse conversion of **8** into **7** was never observed under both light irradiation and dark conditions in $CDCl_3$ (Scheme 4).



Scheme 4. Rearrangement from **7** into **8**.

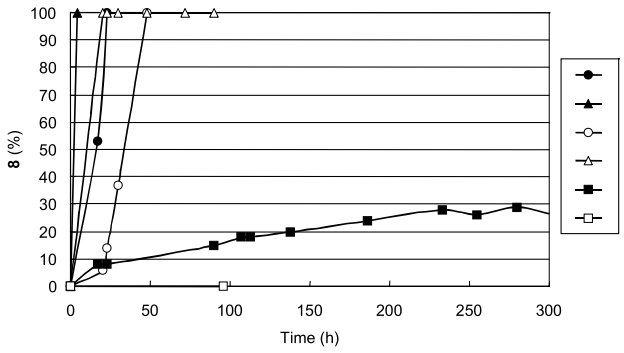
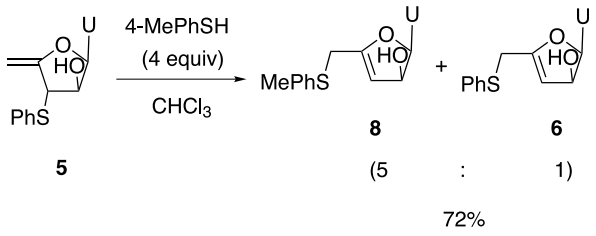


Figure 2. Rearrangement from **7** to **8** at rt in $CDCl_3$. -●-: light irradiation conditions, -▲-: light irradiation conditions in the presence of 1 equiv of AIBN, -○-: daylight conditions, -△-: daylight conditions in the presence of 4 equiv of 4-thiocresol, -■-: dark conditions, -□-: solid state.

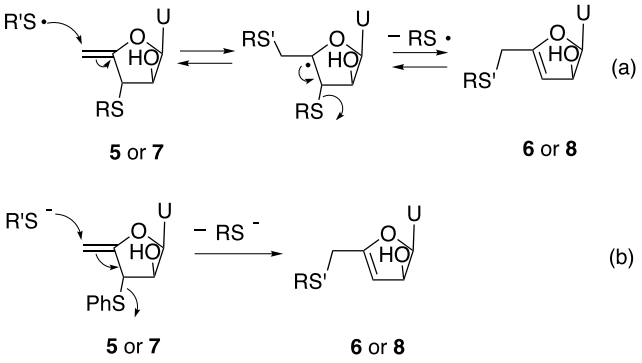
Next, we attempted the reaction of 3′-phenylthio adduct (**5**) in the presence of 4 equiv of 4-thiocresol in $CHCl_3$ at room temperature. Consequently, a mixture of 5′-(4-tolyl)thio (**8**) and 5′-phenylthio (**6**) products was afforded in 5:1 ratio (Scheme 5). Therefore, the conversion of 3′-phenylthio derivatives (**5**) into 5′-phenylthio derivatives (**6** and **8**) was considered as an intermolecular rearrangement reaction occurring by the attack of the thiophenol species derived



Scheme 5. Rearrangement of **5** with 4-thiocresol.

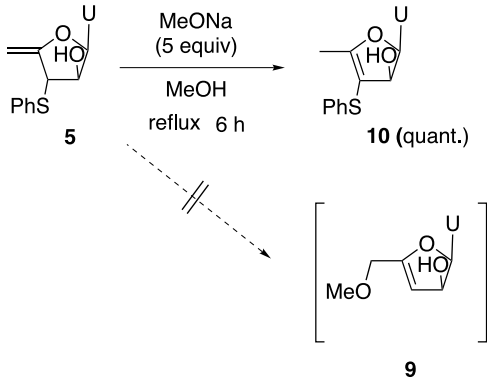
from added 4-thiocresol and thiophenol eliminated from the starting material (**5**).

The results obtained here strongly suggested that the rearrangement of **5** or **7** was initiated by the radical attack of the phenyl or tolyl thiyl radical (Scheme 6a)[8] although the feasibility of an ionic reaction mechanism via S_N2' reaction (Scheme 6b) also still exists.



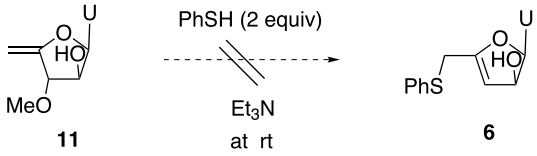
Scheme 6. Plausible rearrangement mechanisms.

Warren et al.[9] reported the rearrangement of allyl sulfide and they indicated that thermal and photochemical rearrangements proceeded by a radical chain mechanism.[8b,10] However, only one example of the rearrangement under basic conditions was reported while the authors never mentioned the reaction mechanism.[11] So, we investigated further reactions to eliminate the possibility of S_N2' reaction sequence. When the reaction of **5** was performed using MeONa as a nucleophile, the anticipated 5′-methoxy adduct (**9**) was not obtained and only an isomerized 3′,4′-unsaturated product (**10**) was quantitatively acquired by the nucleophilic attack of MeO^- on the 3′-H (Scheme 7).



Scheme 7. Reaction of **5** with MeONa.

Furthermore, the reaction of the 3′-*O*-methyl-4′,5′-unsaturated compound (**11**)[6] with 2 equiv of thiophenol in the presence of Et_3N as a base gave only recovery (Scheme 8).



Scheme 8. Reaction of **11** with thiophenol.

From these results, it is apparent that the rearrangement proceeded by the associative radical chain mechanism (Scheme 5a).[8]

3. Conclusion

We have found the reversible rearrangement between azide derivatives (**3** and **4**) and the irreversible rearrangement of 3′-phenylthio derivatives (**5** and **7**) into 5′-phenylthio derivatives (**6** and **8**). According to the detailed experimental results, it has become apparent that the allylic azide rearrangement proceeded via intramolecular [3,3]-sigmatropic rearrangement. On the other hand, the rearrangement of 3′-phenylthio derivatives progressed by an intermolecular radical chain reaction.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a JEOL EX 400 spectrometer or a JEOL GX 270 spectrometer (^{1}H: 400 or 270 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or tetramethylsilane as an internal standard. Low and high-resolution mass spectra were taken on a JEOL JMS-SX 102 or JMS-D300 machine. Melting points were determined on a Yanagimoto micro-melting-point apparatus and were uncorrected. All reagents were commercially available and used without further purification. Compounds known in the literature were characterized by comparison of their ^{1}H NMR data with the previously reported data.

4.1.1. Rearrangement reaction of 1-(3-azido-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (3)[6] or 1-(5-azido-3,5-dideoxy-β-L-*glycero*-pent-3-enofuranosyl)-uracil (4)[6] A solution of **3** (5 mg, 0.02 mmol) in the absence or presence of NaN_3 (1.3 mg, 0.02 mmol) or **4** (5 mg, 0.02 mmol) in DMSO-d_6 (0.7 mL) was allowed to stand at room temperature under daylight conditions. Under the CD_3OD conditions, CD_3OD was used instead of DMSO-d_6 as a solvent. Under dark conditions, the reaction was carried out by wrapping in aluminum foil. The reactions were monitored periodically by measuring ^{1}H NMR spectrum. The ratio of **3** and **4** was estimated by the integration ratios of the ^{1}H NMR spectra of the mixture.

4.1.2. Synthesis of 1-[3,5-dideoxy-3-(4-tolyl)thio-β-D-*threo*-pent-4-enofuranosyl]uracil (7) and 1-[3,5-

dideoxy-5-(4-tolyl)thio-β-L-*glycero*-pent-3-enofuranosyl]-uracil (8). To a stirred solution of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (**1**)[6] (104 mg, 0.50 mmol) in Et_3N (10 mL) was added 4-thiocresol (81 mg, 0.65 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with AcOEt. The organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography (hexane/AcOEt=2:3) to give **7** (94 mg, 54%) as the first fraction and **8** (9 mg, 5%) as the second fraction.

Compound **7**. MASS *m/z* (relative intensity): 332 (M^+, 53%), 314 (M^+-H_2O, 14%), 209 (M^+−S(4-tolyl), 37%), 137 (100%). ^1H NMR ($CDCl_3$) δ: 10.66 (1H, br s, N^3–H), 7.44 (2H, d, J=8.1 Hz, *m*-Ph), 7.44 (1H, d, J=7.5 Hz, 6-H), 7.10 (2H, d, J=8.1 Hz, *o*-Ph), 6.38 (1H, d, J=2.9 Hz, 1′-H), 5.49 (1H, d, J=7.5 Hz, 5-H), 5.01 (1H, d, J=2.9 Hz, 2′-H), 4.76 (1H, br s, 2′-OH), 4.61 (1H, s, 5′-Ha), 4.20 (1H, s, 5′-Hb), 4.15 (1H, br s, 3-H), 2.29 (3H, s, CH_3). Anal. Calcd for $C_{16}H_{16}N_2O_4S_1$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.76; H, 4.90; N, 8.42.

Compound **8**. MASS *m/z* (relative intensity): 332 (M^+, 26%), 314 (M^+-H_2O, 1%), 209 (M^+−S(4-tolyl), 15%), 137 (100%). ^1H NMR ($CDCl_3$) δ: 10.77 (1H, br s, N^3–H), 7.31 (2H, d, J=7.8 Hz, *m*-Ph), 7.29 (1H, d, J=7.8 Hz, 6-H), 7.12 (2H, d, J=7.8 Hz, *o*-Ph), 6.45 (1H, d, J=6.3 Hz, 1′-H), 5.53 (1H, d, J=7.8 Hz, 5-H), 5.12 (2H, br s, 2′-H and 3′-H), 4.60 (1H, d, br s, 2′-OH), 3.60 (2H, br s, 5′-H×2), 2.32 (3H, s, CH_3). HRMS *m/z* Calcd for $C_{16}H_{16}N_2O_4S_1$: 332.0831. Found: 332.0837.

4.1.3. Rearrangement reaction of 1-[3,5-dideoxy-3-(4-tolyl)thio-β-D-*threo*-pent-4-enofuranosyl]uracil (7) and 1-[3,5-dideoxy-5-(4-tolyl)thio-β-L-*glycero*-pent-3-enofuranosyl]uracil (8). A solution of **7** (5 mg, 0.015 mmol) or **8** (5 mg, 0.015 mmol) in $CDCl_3$ (0.7 mL) was allowed to stand at room temperature. Under light irradiation conditions, the light was irradiated using an electric light bulb (60 V) at the distance of 15 cm. As an additive, AIBN (2.5 mg, 0.015 mmol) or 4-thiocresol (7.5 mg, 0.060 mmol) was employed under each conditions. Under dark conditions, the reaction was carried out by wrapping in aluminum foil. The reactions were monitored periodically by measuring the ^1H NMR spectrum. The ratio of **7** and **8** was estimated by the integration ratios of the ^1H NMR spectra of the mixture.

4.1.4. Reaction of 1-(3,5-dideoxy-3-phenylthio-β-D-*threo*-pent-4-enofuranosyl)uracil (5)[6] with 4-thiocresol To a stirred solution of **5** (4 mg, 0.013 mmol) in dry $CHCl_3$ (1.5 mL) was added 4-thiocresol (6.5 mg, 0.052 mmol) under argon atmosphere. The reaction mixture was stirred for 3 days at room temperature and the mixture was evaporated in vacuo. The residue was subjected to silica gel column chromatography (toluene/AcOEt=10:1) to afford **8** and **6** as a mixture (3 mg, 72%, **8**:**6**=5:1). Yields were estimated by the integration ratios of the ^1H NMR spectra of the mixture.

4.1.5. Reaction of 1-(3,5-dideoxy-3-phenylthio-β-D-*threo*-pent-4-enofuranosyl)uracil (5) with MeONa. To a stirred solution of **5** (20 mg, 0.06 mmol) in dry MeOH (2 mL) was added 28% MeOH solution of sodium methoxide (0.06 mL, 0.30 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed for 6 h and the mixture was neutralized with AcOH. The solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography (benzene/AcOEt=3:1) to afford 1-(3,5-dideoxy-3-phenylthio-β-L-*glycero*-pent-3-enofuranosyl)-uracil (**10**) (20 mg, 100%).

Mp: 196–198 °C. MASS *m/z* (relative intensity): 318 (M^+, 51%), 300 (M^+-H_2O, 51%), 206 (S^+-1, 100%). ^1H NMR ($CDCl_3$) δ: 10.46 (1H, br s, N^3–H), 7.14–7.54 (6H, m, 6-H and 3′-SPh), 6.50 (1H, d, J=6.4 Hz, 1′-H), 5.57 (1H, d, J=7.8 Hz, 5-H), 5.00–5.03 (1H, m, 2′-H), 4.58 (1H, br s, 2′-OH), 2.11 (3H, s, 5′–CH_3). Anal. Calcd for $C_{15}H_{14}N_2O_4S_1$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.45; H, 4.52; N, 8.74.

References and notes

1. Townsend, L. R. *Chemistry of Nucleosides and Nucleotides*; Plenum: New York, 1988. Matsuda, A. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 907. Perigaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903. Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440. Camarasa, M.-J.; Perez-Perez, M.-J.; San-Felix, A.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 2721. Perez-Perez, M.-J.; San-Felix, A.; Balzarini, J.; De Clercq, E.; Camarasa, M.-J. *J. Med. Chem.* **1992**, *35*, 2988. De Clercq, E. *Med. Chem. Res.* **2004**, *13*, 439.
2. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
3. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
4. Mansuri, M. M.; Starett, J. E., Jr.; Ghazzouli, I.; Hitchcock, M. J. M.; Sterzycki, R. Z.; Brankovan, V.; Lin, T.-S.; August, E. M.; Prusoff, W. H.; Sommadossi, J.-P.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 461.
5. Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217.
6. Hirota, K.; Takasu, H.; Tsuji, Y.; Sajiki, H. *Chem. Commun.* **1999**, 1827. Takasu, H.; Tsuji, Y.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 8499.
7. Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956. VanderWerf, C. A.; Heasley, V. L. *J. Org. Chem.* **1966**, *31*, 3534. Askin, D.; Angst, C.; Danishefsky, S. J. *J. Org. Chem.* **1985**, *50*, 5005. Arimoto, M.; Yamaguchi, H.; Fujita, E.; Ochiai, M.; Nagao, Y. *Tetrahedron Lett.* **1987**, *28*, 6289. Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292. Kanai, T.; Kanagawa, Y.; Ishii, Y. *J. Org. Chem.* **1990**, *55*, 3274. Safi, M.; Fahrang, R.; Sinou, D. *Tetrahedron Lett.* **1990**, *31*, 527. Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849. Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063. Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383. Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.*

1995, *36*, 8737. Padwa, A.; Sá, M. M. *Tetrahedron Lett.* **1997**, *38*, 5087. Banert, K.; Hagedorn, M.; Liedtke, C.; Melzer, A.; Schöffler, C. *Eur. J. Org. Chem.* **2000**, 257. Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Piccinelli, F.; Tolomelli, A. *Org. Lett.* **2005**, *7*, 533.

8. It was reported that the aryl thiyl radical was generated in the presence of oxygen (air), see: (a) Stacey, F. W.; Harris, J. F. *Org. React.* **1963**, *13*, 164. (b) Bernard, A. M.; Piras, P. P. *J. Chem. Soc., Chem. Commun.* **1994**, 257.
9. Brownbridge, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2125.
10. Brownbridge, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1131. Brownbridge, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2272. Nederlof, P. J. R.; Moolenaar, M. J.; De Waard, E. R.; Huisman, H. O. *Tetrahedron* **1978**, *34*, 2205. Blatcher, P.; Warren, S. *Tetrahedron Lett.* **1979**, *20*, 1247. Fleming, I.; Paterson, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 256. Durman, J.; Hunt, P. G.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 2113. Brownbridge, P.; Hunt, P. G.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 3391. Mandai, T.; Mori, K.; Hasegawa, K.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1984**, *25*, 5225. Mandai, T.; Moriyama, T.; Nakayama, Y.; Sugino, K.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1984**, *25*, 5913. Mandai, T.; Arase, H.; Otera, J.; Kawada, M. *Tetrahedron Lett.* **1985**, *26*, 2677. Blatcher, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1055. Brownbridge, P.; Durman, J.; Hunt, P. G.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1947. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411. Hagen, J. P. *J. Org. Chem.* **1993**, *58*, 506. Breternitz, H.-J.; Schaumann, E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1927.
11. Brocchini, S. J.; Lawton, R. G. *Tetrahedron Lett.* **1997**, *38*, 6319.

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Pelseneeriol-1 and -2: new furanosesquiterpene alcohols from porostome nudibranch *Doriopsilla pelseneeri*

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Abstract—The paper reports the first chemical study of the porostome nudibranch *Doriopsilla pelseneeri* collected off the Portuguese coast (Atlantic Ocean). Two new furanosesquiterpene alcohols, pelseneeriol-1 (**1**) and pelseneeriol-2 (**2**), have been isolated together with known compounds, 15-acetoxy-*ent*-pallescensin-A (**5**), and dendocarbin-A (**6**), from the mantle of the nudibranch, whereas euryfuran (**3**) and drimane ester mixture **4** were identified in the extract of the internal glands. The structures of **1** and **2** have been determined by extensive spectroscopic studies as well as by comparison with literature model compounds. In order to assess the relative stereochemistry of **1** and **2**, full NMR assignment of related sponge metabolite microcionin-2 (**8**) and of co-occurring sesquiterpenes **9**–**11**, that have been re-isolated from the Mediterranean sponge *Fasciospongia cavernosa*, has been also conducted. In particular, the relative stereochemistry of tricyclic sesquiterpene microcionin-1 (**9**) has now been rigorously assigned by detailed analysis of NOE difference experiments.

1. Introduction

Nudibranchs are a group of shell-less opisthobranch molluscs, in which secondary metabolites play an important ecological role as defensive chemical weapons.[1–3] Most of these allomones are accumulated from dietary sources but some of them are biosynthesised de novo or obtained by bio-transformation of dietary metabolites.[4] The family Dendrodoridae is divided into the two genera *Dendrodoris* and *Doriopsilla* and comprises soft-bodied molluscs mostly devoid of mechanical protection, without radula. They suctorially feed exclusively on sponges and are chemically characterised by the presence of drimane sesquiterpenes.[1,2]

Few chemical studies have been published on the genus *Doriopsilla*,[5–7] including the recent reports on *Doriopsilla areolata* that showed the co-occurrence in this mollusc of two groups of sesquiterpenoids exhibiting drimane and *ent*-pallescensin A-like skeleton with opposite A/B ring junction.[6,7]

Further studies demonstrated that *D. areolata* is able to biosynthesise de novo both series of compounds.[8,9] Surprisingly, metabolites of both series were previously reported to co-occur in a sponge of genus *Dysidea*,[10] which was suggested to be potentially included in its diet.[8]

In this paper, we report the first chemical study on the related species *Doriopsilla pelseneeri* d'Oliveira 1895, that has resulted in the isolation of two new furanosesquiterpenes, pelseneeriol-1 (**1**) and pelseneeriol-2 (**2**), along with the known compounds **3**–**6**.

2. Results and discussion

D. pelseneeri is an endemic porostome nudibranch occurring in Iberian coastal waters (Atlantic and Mediterranean).[11] The mollusc (34 specimens) was collected in Arflor, Setúbal, off the Portuguese coast at a depth of 8–10 m, during May 2003, and immediately frozen at −20 °C. The mucus secreted by five individuals was also sampled and frozen. The biological material was subsequently transferred to ICB in Italy for chemical analysis. Frozen specimens were carefully dissected in mantle and inner organs, which were separately extracted by acetone exhaustively under ultrasound vibration. The mucous secretion was directly extracted by diethyl ether. The

Keywords: Molluscs; Marine metabolites; Terpenes and terpenoids.
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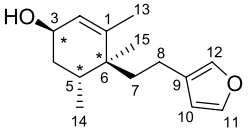
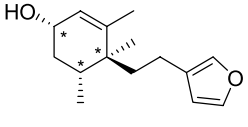
ethereal soluble portions of acetone extracts of both mantle and internal glands were analysed along with mucus extract by TLC chromatography displaying different secondary metabolite patterns. In particular, the extract of the internal

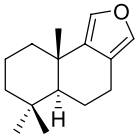


*relative stereochemistry

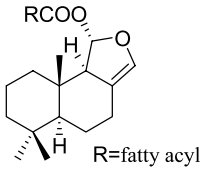
1 pelseneeriol-1



2 pelseneeriol-2

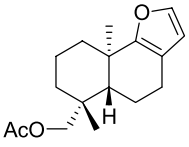


3 euryfuran

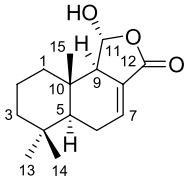


R=fatty acyl

4 drimane esters



5 15-acetoxy-*ent*-pallescensin-A



6 dendocarbin-A

part (539 mg) was characterized by the presence of a main Ehrlich positive spot at R_f 0.5 (light petroleum ether/diethyl ether, 95:5) along with usual lipids and sterols and a minor non-polar compound at R_f 0.5 (light petroleum ether), whereas the mantle and mucus extracts were found to contain a series of metabolites at R_f 0.5 (light petroleum ether/diethyl ether, 9:1) and at R_f 0.40–0.25 (light petroleum ether/diethyl ether, 1:1).

An aliquot (61 mg) of the internal gland extract was purified on a silica-gel column (light petroleum ether/diethyl ether gradient) to give, in order of increasing polarity, euryfuran (**3**, 2.0 mg) and drimane esters mixture (**4**, 9.1 mg).

The mantle extract (196 mg) was chromatographed on a Sephadex LH-20 column using MeOH/$CHCl_3$ 1:1 as eluent. The fraction containing Ehrlich positive spot at R_f 0.5 (light petroleum ether/diethyl ether, 9:1) (8.7 mg) was further purified by a silica-gel column (light petroleum ether/diethyl ether gradient) to give 15-acetoxy-*ent*-pallescensin-A (**5**, 1.0 mg). Fractions containing spots at R_f 0.40–0.25 (light petroleum ether/diethyl ether, 1:1) were submitted to *n*-phase HPLC (*n*-hexane/EtOAc, 85:15) to obtain two unprecedented compounds, **1** (0.8 mg) and **2** (0.7 mg), and the known dendocarbin-A (**6**, 0.5 mg), in order of increasing retention time.

The mucus extract (5.9 mg) was purified by Sephadex LH-20 chromatography in the same manner as mantle extract, to obtain compound **5** (1.0 mg), and a mixture (0.9 mg) which was analysed by HPLC resulting to be constituted by compounds **1**, **2** and **6**.

The known compounds, drimane ester mixture **4** and its work-up derivative euryfuran (**3**), isolated from the internal glands, 15-acetoxy-*ent*-pallescensin-A (**5**) and dendocarbin-A (**6**), isolated from both mantle and mucus, were identified by comparison of spectral data with those reported in the literature. Drimane ester mixture **4** has been reported to occur in several dendrodorid nudibranch species,[1,2] whereas 15-acetoxy-*ent*-pallescensin-A (**5**) has been previously isolated only from the mantle of different collections of *D. areolata*[5–7] and dendocarbin-A (**6**) has been recently found in *Dendrodoris carbunculosa*.[12]

The structure of compound **6** was previously reported[12] except for the relative stereochemistry at C-11, due to the difficulty of detecting both H-11 and C-11 signals in NMR spectra either in CD_3OD or in C_6D_6. We were able to perform NOE difference experiments in $CDCl_3$ on dendocarbin-A (**6**) that led to the assignment of the relative configuration at C-11 as reported. In fact, in addition to expected NOE interactions between H-5 (δ 1.36) and H-9 (δ 2.48), a diagnostic NOE effect was observed between H-11 (δ 5.64) and H_3-15 (δ 0.85). However, the assigned stereochemistry matches that established for the acetyl derivative of dendocarbin-A.[12]

The structures of the novel sesquiterpene alcohols **1** and **2**, that we named pelseneeriol-1 and pelseneeriol-2, respectively, were determined as follows. HRESIMS analysis indicated that compounds **1** and **2** were isomers with the same molecular formula $C_{15}H_{22}O_2$. Comparison of their ^{1}H NMR spectra (Table 1) clearly suggested a close relationship between the two molecules, both exhibiting a terminal β-substituted furan moiety [δ 7.34 (H-11), 7.21 (H-12) and 6.26 (H-10) in **1**; δ 7.34 (H-11), 7.20 (H-12) and 6.25 (H-10) in **2**], a trisubstituted double bond [δ 5.64 (H-2) in **1**; δ 5.49 (H-2) in **2**], and a secondary hydroxyl function [δ 4.08 (H-3) in **1**; δ 4.23 (H-3) in **2**]. The presence of three methyl signals [a singlet (H_3-15) at δ 0.85 in **1**, 0.92 in **2**; a doublet (H_3-14) at δ 0.92 in **1**, 0.91 in **2**; a broad singlet (H_3-13) at δ 1.70 in **1**, 1.68 in **2**] in the ^{1}H NMR spectra of both molecules was consistent with sesquiterpene structures, that were further supported by ^{13}C NMR data (Table 1). Analysis of 2D NMR (^{1}H–^{1}H COSY, HSQC and HMBC) spectra of **1** and **2** suggested for both compounds a rearranged $\Delta^{1,6}$ monocyclofarnesol skeleton, exhibiting an hydroxyl group at C-3. In fact, diagnostic ^{1}H–^{1}H COSY correlations were observed between the carbinolic proton H-3 (δ 4.08 in **1**; δ 4.23 in **2**) and either the olefinic proton H-2 (δ 5.64 in **1**; δ 5.49 in **2**) or the methylene H_2-4 (δ 1.62–1.64 in **1**; δ 1.39–1.82 in **2**), which was further coupled to the methine H-5 (δ 2.09 in **1**; δ 1.85 in **2**). This structural hypothesis was further supported by comparison of ^{1}H NMR values of **1** and **2** with those of literature sesterterpenes containing the same cyclic

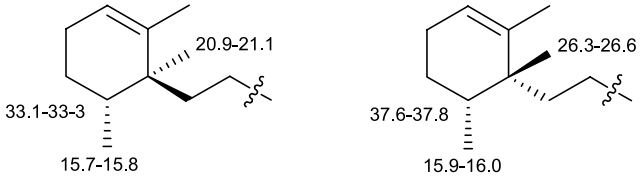
Table 1. NMR data[a] of pelseneeriol-1 (**1**), pelseneeriol-2 (**2**), fulvanin-1 (**7**) and microcionin-2 (**8**)

	1				**2**				**7**	**8**
Position	δ ^{13}C[b]	δ ^{1}H[c]	m, J (Hz)	HMBC[d]	δ ^{13}C[b]	δ ^{1}H[c]	m, J (Hz)	HMBC[d]	δ ^{13}C[e]	δ ^{13}C[e]
1	145.4	—	—	H_3-13, H_3-15	142.9	—	—	H_3-13, H_3-15	139.0	139.1
2	126.0	5.64	br d, 5	H_3-13	129.2	5.49	br s	H_3-13	124.7	123.0
3	64.4	4.08	br s	—	67.9	4.23	m ($w_{1/2}$=20)	—	25.5	24.0
4	35.9	1.62	m	H_3-14	37.3	1.39	ddd (H_{ax}), 12,12,10	H_3-14	27.0	27.5
		1.64	m			1.82	m (H_{eq})			
5	27.6	2.09	m	H_3-14, H_3-15	31.6	1.85	m	H_3-14, H_3-15	33.3	37.7
6	41.0	—	—	H_3-13, H_3-14, H_3-15	41.0	—	—	H_3-13, H_3-14, H_3-15	40.5	39.6
7	36.2	1.68	m	H_3-15	36.0	1.63	m	H_3-15	34.4	36.3
8	19.6	2.04	m	—	19.5	2.02	ddd, 6,12,15	—	35.8	20.9
		2.41	ddd, 6, 9, 14			2.34	ddd, 4,11,15			
9	125.4	—	—	—	125.4	—	—	H-11, H-12	161.6	126.1
10	110.9	6.26	br s	—	110.9	6.25	br s	—	114.7	110.9
11	142.8	7.34	br s	—	142.8	7.34	br s	H-10, H-12	167.3	142.6
12	138.4	7.21	br s	—	138.4	7.20	br s	H-10, H-11	19.1	138.4
13	19.1	1.70	br s	—	18.9	1.68	br s	—	19.1	19.7
14	15.6	0.92	d, 7	—	15.9	0.91	d, 7	—	15.8	16.0
15	19.5	0.85	s	—	20.6	0.92	s	—	21.0	26.3

[a] Bruker DPX 500 and AVANCE 400 MHz spectrometers, $CDCl_3$, chemical shifts (ppm) referred to $CHCl_3$ (δ 7.26) and to $CDCl_3$ (δ 77.0).
[b] By DEPT, HSQC and HMBC (J=10 Hz) experiments.
[c] By ^{1}H–^{1}H COSY and HSQC experiments.
[d] Significant HMBC correlations (J=10 Hz).
[e] Assignments from Refs. 14 and 15.

moiety.[13] All proton and carbon assignments of pelseneeriols are reported in Table 1.

Comparison of proton spectra and in particular of the carbinolic signal multiplicity indicated that the structures of the two compounds could differ only in the relative stereochemistry of the hydroxyl group, which was suggested to be axially oriented in pelseneeriol-1 (**1**) (H-3$_{eq}$ resonates at δ 4.08 as a broad singlet), and equatorial in pelseneeriol-2 (**2**) [H-3$_{ax}$ resonates at δ 4.23 as a multiplet ($w_{1/2}$=20 Hz)]. Analysis of carbon values of the cyclohexene ring of both compounds further supported this suggestion. In fact, the different shift values at C-3, C-4, and C-5 due to axial or equatorial hydroxyl substituent were in agreement with the expected calculated effects.[14] In addition, for pelseneeriol-2 (**2**), a diagnostic positive NOE effect was observed between H-3 (δ 4.23) and H-5 (δ 1.85 m), thus inferring that both H-5 and H-3 were axially oriented.



a **b**

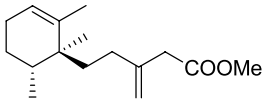
The relative stereochemistry of the methyl groups at C-5 and C-6 was suggested to be *cis* in both sesquiterpenes by comparison of the ^{13}C chemical shift of Me-14 (δ 15.6 in **1** and δ 15.9 in **2**) and Me-15 (δ 19.5 in **1** and δ 20.6 in **2**) with carbon values of natural terpenes containing *cis* (**a**) or *trans* (**b**) substructure. The ^{13}C chemical shift of Me-14 has similar value (15.7–16.0 ppm) in *cis*[15,16] and *trans*[17–19] isomers whereas the carbon value of Me-15 is smaller in *cis* (20.9–21.1 ppm) than in *trans* (26.3–26.6 ppm) isomer due to the greater γ-type interactions between the two methyl groups in *cis* compounds.

In particular, two model sponge sesquiterpenes exhibiting **a** or **b** substructure, (+)-5*R*,6*S*-fulvanin-1 (**7**)[15,16,20] and (−)-5*R*,6*R*-microcionin-2 (**8**),[18,21,22] the stereochemistry of which have been secured by stereospecific synthesis,[18,20] were considered (see Table 1). The close similarity of carbon data of pelseneeriols with those of fulvanin-1 clearly indicated the same relative *cis*-stereochemistry of the methyl groups at C-5 and C-6. However, unfortunately, the absolute stereochemistry of compounds **1** and **2** was not determined due to the instability of both molecules that slowly degraded in chloroform solution.

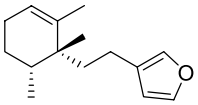
Metabolites related to pelseneeriols, the above cited microcionin-2 (**8**), along with microcionin-1 (**9**), microcionin-3 (**10**) and microcionin-4 (**11**), were found in the Mediterranean sponge *Fasciospongia cavernosa* (incorrectly reported in the first paper as *Microciona toxystila*),[21] which could potentially be a prey of the nudibranch. In fact, even though microcionin-2 (**8**) and microcionin-4 (**11**) exhibit the methyl groups at C-5 and C-6 *trans*-oriented, the co-occurring microcionin-3 (**10**) could be a possible precursor of both series of compounds: microcionins in *F. cavernosa* and pelseneeriols in *D. pelseneeri*.

In the course of this study, microcionins 1–4 have been re-isolated from a new collection of the sponge *F. cavernosa* and fully characterised by extensive NMR analysis. Proton and carbon assignments of compounds **8–11** are reported in the Section 4. The relative stereochemistry of microcionin-4 (**11**), which is closely related to microcionin-2 (**8**), was suggested by biogenetic considerations whereas the relative stereochemistry of microcionin-1 (**9**), which surprisingly exhibits H$_3$-14 and H$_3$-15 *cis*-oriented, was established by detailed analysis of 1D and 2D NMR experiments and in particular of NOE difference spectra. In fact, a diagnostic

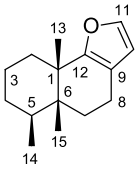
NOE effect observed between H_3-15 (δ 0.85) and H_3-13 (δ 1.08) inferred the 1,6-*cis*-junction of the carbon skeleton of **9**. Furthermore, irradiation of H_3-15 (δ 0.85) induced significant enhancements on H_2-2_{ax} (δ 1.51) and H_2-4_{ax} (δ 1.22), implying the axial orientation of H_3-15 and, consequently, the equatorial orientation of H_3-13. Finally, analysis of the coupling constants of H-5 (δ 1.68), that were calculated as $J_{H5ax-H4ax}=12$ Hz, $J_{H5ax-H4eq}=4$ Hz by decoupling of geminal methyl H_3-14 (δ 0.83), indicated that H_3-14 was equatorial, *cis*-oriented with respect to H_3-15. Accordingly, irradiation of H-5 only resulted in a weak enhancement of the multiplet at δ 2.34 (H_2-8).



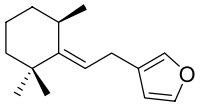
7 (+)-5*R*,6*S*-fulvanin-1



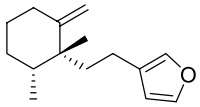
8 (-)-5*R*,6*R*-microcionin-2



9 microcionin-1*



10 microcionin-3*



11 microcionin-4*

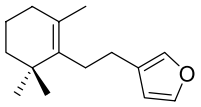
*relative stereochemistry

It is interesting to observe that, among microcionins, the methyls at C-5 and C-6 are *cis*-oriented only in microcionin-1 (**9**). This relative stereochemistry is analogous to that observed in pelseneeriols.

3. Conclusions

Analogously with other *Doriopsilla* species,[5–7] *D. pelseneeri* has been found to contain sesquiterpenes structurally related to typical metabolites of sponges of genus *Dysidea* that could be included in the diet of the nudibranch. So, a dietary origin could be reasonably suggested for compounds **1–6**, even though no direct observation supports this hypothesis. However, recent biosynthetic studies on sesquiterpene metabolites have been rigorously conducted on Atlantic porostome nudibranch *D. areolata*.[8,9] Very interestingly, this mollusc was proved to be able to produce de novo molecules of both *ent*-pallescensin-like and drimane skeleton (e.g., **5** and **6**) which could also characterise an organism included in its diet. In fact, compounds with both carbon skeletons were found to co-occur in an Australian *Dysidea* sponge.[10]

The de novo biosynthesis could also be suggested for all the sesquiterpenes present in *D. pelseneeri*. Preliminary biosynthetic studies on this nudibranch have shown significant incorporation of labelled piruvate into drimane ester mixture (**4**) (Fontana, personal communication). Therefore, *D. pelseneeri* seems to be able to produce its drimane sesquiterpene metabolites as other porostome nudibranchs, whereas the biosynthesis of pelseneeriols and *ent*-pallescensin derived compounds is strongly suspected but remains to be rigorously proved. Butler and Capon suggested that a common hypothetical intermediate **12** could lead to sesquiterpenes of both series, *ent*-pallescensin and drimane, in Australian sponge *Dysidea* sp.[10] Analogously, the isomer of **12**, microcionin-3 (**10**) could be considered an hypothetical intermediate for the three different sesquiterpenes skeletons found in *D. pelseneeri.*



12

4. Experimental

4.1. General experimental procedures

Silica-gel chromatography was performed using pre-coated Merck F_{254} plates and Merck Kieselgel 60 powder. HPLC purification was carried out on a Waters liquid chromatograph equipped with a Waters R401 RI detector. Optical rotations were measured on a Jasco DIP 370 digital polarimeter.

NMR experiments were recorded at ICB NMR Service. 1D and 2D NMR spectra were acquired in $CDCl_3$ (δ values are reported referred to C*H*Cl_3 at 7.26 ppm) on a Bruker Avance-400 operating at 400 MHz, using an inverse probe fitted with a gradient along the *Z*-axis, and on a Bruker DRX-600 operating at 600 MHz, using an inverse TCI CryoProbe fitted with a gradient along the *Z*-axis. ^{13}C NMR were recorded on a Bruker DPX-300 operating at 300 MHz (δ values are reported to C*D*Cl_3, 77.0 ppm) using a dual probe.

EIMS were determined at 70 eV on a HP-GC 5890 series II mass spectometer. High resolution ESIMS were performed on a Micromass Q-TOF Micro™ coupled with a HPLC Waters Alliance 2695. The instrument was calibrated by using a PEG mixture from 200 to 1000 MW (resolution specification 5000 FWHM, deviation <5 ppm RMS in the presence of a known lock mass).

4.2. Biological material

Thirty-four specimens of *D. pelseneeri* (average size 2.5 cm) were collected off Arflor (38°30′24″N; 08°55′09″W), Setúbal, along the Western coast of Portugal, in May 2003, at a depth of 8–10 m. The mollusc was immediately frozen, transferred to ICB, and stored at -20 °C till the extraction. The taxonomic identification of *D. pelseneeri* has been made by one of us (G. Calado). A voucher specimen (preserved in absolute ethanol) is deposited at 'Instituto Português de Malacologia', Portugal, reference number IPM.MO.100.

A sample of *F. cavernosa* was collected at Torre Annunziata, Naples, in January 2005, at a depth of 1 m. A voucher specimen is at ICB (FCav-1).

4.3. Isolation procedure

Frozen *D. pelseneeri* (34 individuals, dry weight 10 g) were dissected into mantle and inner organs. Each part was separately extracted with acetone (3×150 mL, 2 min in ultrasonic bath). Each acetone extract was evaporated under vacuum and the resulting aqueous phases were extracted with Et_2O (3×30 mL). After evaporation of the solvent the organic layers gave crude extracts: 196 mg from the mantle and 539 mg from the inner organs. The mucus was directly extracted by diethyl ether (3×10 mL) to obtain 5.9 mg of a crude extract. A sample of *F. cavernosa* was immersed in acetone (50 mL) and extracted by using ultrasonic vibrations for 2 min. The treatment was repeated three times. The acetone extracts were combined and concentrated, then the aqueous residual was partitioned with diethyl ether (3×30 mL). After removing the solvent, the organic phase gave 957 mg of a crude residue.

An aliquot (61 mg) of the extract of internal glands of the nudibranch was chromatographed on a silica-gel column packed with light petroleum ether and eluted with light petroleum ether with increasing amounts of diethyl ether. Fractions eluted with light petroleum ether and light petroleum ether/diethyl ether, 95:5, were concentrated to give compound **3** (2.0 mg) and drimane ester mixture **4** (9.1 mg), respectively. The mantle extract (196 mg) was chromatographed on a Sephadex LH-20 column using MeOH/$CHCl_3$ 1:1 as eluent. The fraction (8.7 mg) containing the Ehrlich positive spot less polar than sterols was submitted to a pipette-pasteur silica-gel column to obtain compound **5** (1.0 mg). The fraction (6.2 mg) containing spots at R_f 0.40–0.25 was further purified by HPLC [column Phenomenex-Kromasil (5 μm, 100 Å, 250×4.60 mm); *n*-hexane/EtOAc 85:15 (flow 1 mL/min)] to yield **1** (0.8 mg), **2** (0.7 mg) and **6** (0.5 mg), in order of increasing retention time.

The mucus ether extract (5.9 mg) was chromatographed by Sephadex LH-20 column eluted with MeOH/$CHCl_3$ 1:1, to obtain compound **5** (1.0 mg) and a mixture (0.9 mg) which was analysed by HPLC [column Phenomenex-Kromasil (5 μm, 100 Å, 250×4.60 mm); *n*-hexane/EtOAc 85:15 (flow 1 mL/min)] Compounds **1**, **2** and **6** were present in the same ratio as the mantle extract.

An aliquot (300 mg) of the extract of *F. cavernosa* was submitted to a silica-gel column (light petroleum ether/diethyl ether gradient). All fractions containing microcionins were eluted by light petroleum ether. The fraction (10 mg) containing less polar metabolite was submitted to a pipette-pasteur $AgNO_3$–SiO_2 column (light petroleum ether/benzene, 95:5) to obtain pure compound **9** (1.5 mg). The other fractions (130 mg) were combined and purified on a $AgNO_3$–SiO_2 column (light petroleum ether/benzene gradient) to give compounds **8** (22.1 mg), **10** (22.7 mg), and **11** (5.5 mg).

Compounds **3**, **4** and **5** were identified by comparing their spectral data with those of standard samples.

4.3.1. Compound 1. Colourless oil; $[\alpha]_D$ +9.4 (*c* 0.04, $CHCl_3$); ^1H and ^{13}C NMR (Table 1); HRESIMS (positive) *m/z* 257.1521 $[M+Na]^+$ (calcd for $C_{15}H_{22}O_2Na$ 257.1517).

4.3.2. Compound 2. Colourless oil; $[\alpha]_D$ −89.9 (*c* 0.03, $CHCl_3$); ^1H and ^{13}C NMR (Table 1); HRESIMS (positive) *m/z* 257.1507 $[M+Na]^+$ (calcd for $C_{15}H_{22}O_2Na$ 257.1517).

4.3.3. Compound 6. Colourless oil; $[\alpha]_D$ −27.3 (*c* 0.1, $CHCl_3$), $[\alpha]_D$ lit.[12] −10 (*c* 0.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, dd, J=3.3, 6.9 Hz, H-7), 5.64 (1H, br d, J=5.6 Hz, H-11), 3.61 (br s, OH), 2.48 (1H, m, H-9), 2.41 (1H, m, H_2-6a), 2.07 (1H, m, H_2-6b), 1.81 (1H, m, H_2-1a), 1.52 (2H, m, H_2-2), 1.51 (1H, m, H_2-3a), 1.36 (1H, dd, J=5.3, 11.6 Hz, H-5), 1.31 (1H, m, H_2-1b), 1.26 (1H, m, H_2-3b), 0.94 (3H, s, H_3-14), 0.92 (3H, s, H_3-13), 0.85 (3H, s, H_3-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (C-12), 136.6 (C-7), 127.9 (C-8), 98.3 (C-11), 59.1 (C-9), 49.3 (C-5), 42.1 (C-3), 39.2 (C-1), 33.8 (C-10), 33.1 (C-13), 32.9 (C-4), 24.9 (C-6), 21.3 (C-14), 18.2 (C-2), 14.6 (C-15); ^{13}C NMR (75 MHz, CD_3OD) δ 170.3 (C-12), 137.7 (C-7), 129.9 (C-8), 60.5 (C-9), 50.6 (C-5), 43.3 (C-3), 40.5 (C-1), 35.4 (C-10), 33.6 (C-13), 33.6 (C-4), 25.8 (C-6), 21.8 (C-14), 19.3 (C-2), 14.8 (C-15); HRESIMS (positive) *m/z* 259.1660 $[M+Na]^+$ (calcd for $C_{15}H_{24}O_2Na$ 259.1674).

4.3.4. Compound 8. Colourless oil; $[\alpha]_D$ −26.4 (*c* 1.4, $CHCl_3$), $[\alpha]_D$ lit.[21] −58.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, br s, H-11), 7.21 (1H, br s, H-12), 6.27 (1H, br s, H-10), 5.43 (1H, m, H-2), 2.42 (1H, ddd, J=5.5, 13.5, 13.5 Hz, H_2-8a), 2.32 (1H, ddd, J=3.9, 13.5, 13.5 Hz, H_2-8b), 1.98 (2H, m, H_2-3), 1.68 (1H, m, H_2-7a), 1.66 (3H, br s, H_3-13), 1.63 (2H, m, H_2-4a and H-5), 1.53 (1H, m, H_2-7b), 1.47 (1H, m, H_2-4b), 1.08 (3H, s, H_3-15), 0.99d (3H, d, J=6.8 Hz, H_3-14); ^{13}C NMR (Table 1); EIMS *m/z* (%) 218 (M^+, 10), 203 (8), 123 (100), 109 (41), 95 (53), 81 (71).

4.3.5. Compound 9. Colourless oil; $[\alpha]_D$ +47.6 (*c* 0.06, $CHCl_3$), $[\alpha]_D$ lit.[21] +7; ^1H NMR (600 MHz, $CDCl_3$); δ 7.25 (1H, d, J=1.7 Hz, H-11), 6.14 (1H, d, J=1.7 Hz, H-10), 2.34 (2H, m, H_2-8), 2.12 (1H, br d, J=14 Hz, H_2-2eq), 1.71 (1H, m, H_2-7a), 1.68 (1H, m, H-5), 1.58 (1H, m, H_2-7b), 1.51 (1H, m, H_2-2ax), 1.50 (1H, m, H_2-3ax), 1.28 (1H, m, H_2-4eq), 1.22 (1H, ddd, J=13.2, 12.9, 3.2 Hz, H_2-4ax), 1.08 (3H, s, H_3-13), 1.00 (1H, dt, J=13.1, 3.9 Hz, H_2-3eq), 0.85 (3H, s, H_3-15), 0.83 (3H, d, J=6.9 Hz, H_3-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 (C-12), 140.2 (C-11), 115.1 (C-9), 110.1 (C-10), 40.2 (C-1), 39.1 (C-6), 32.3 (C-2), 31.9 (C-5), 30.7 (C-4), 29.3 (C-7), 25.9 (C-13), 23.7 (C-3), 18.6 (C-8), 16.8 (C-14), 14.7 (C-15); EIMS *m/z* (%) 218 (M^+, 32), 203 (100), 147 (20), 133 (28), 109 (20), 91 (18).

4.3.6. Compound 10. Colourless oil; $[\alpha]_D$ +24.4 (*c* 1.70, $CHCl_3$), $[\alpha]_D$ lit.[21] +36.5; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (1H, br s, H-11), 7.20 (1H, br s, H-12), 6.27 (1H, br s, H-10), 5.39 (1H, t, J=7.1 Hz, H-7), 3.21 (1H, dd, J=7.2, 16.4 Hz, H_2-8a), 3.11 (1H, dd, J=7.0, 16.4 Hz, H_2-8b), 2.96 (1H, m, H-1), 1.77 (1H, m, H_2-3a), 1.59 (1H, m, H_2-2a), 1.52 m (1H, m, H_2-2b), 1.45 (1H, m, H_2-4a), 1.43 (1H, m, H_2-3b), 1.29 (1H, m, H_2-4b), 1.15 (3H, d, J=7.6 Hz, H_3-13), 1.11 (3H, s, H_3-14 or H_3-15), 1.08 (3H, s, H_3-15 or H_3-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4 (C-6), 142.7 (C-11), 138.8 (C-12), 124.9 (C-9), 119.0 (C-7), 111.1

(C-10), 41.4 (C-4), 36.2 (C-5), 32.8 (C-2), 31.6 (C-15 or C-14), 30.5 (C-14 or C-15), 29.7 (C-1), 22.9 (C-8), 21.5 (C-13), 17.7 (C-3); EIMS *m/z* (%) 218 (M^+, 60), 175 (10), 147 (42), 109 (75), 95 (53), 81 (100).

4.3.7. Compound 11. Colourless oil; $[\alpha]_D$ +131.2 (*c* 0.05, $CHCl_3$), $[\alpha]_D$ lit.[21] +98.3; ^1H NMR (400 MHz, $CDCl_3$); δ 7.34 (1H, br s, H-11), 7.20 (1H, br s, H-12), 6.26 (1H, br s, H-10), 4.78 (1H, br s, H_2-13a), 4.66 (1H, br s, H_2-13b), 2.19 (2H, m, H_2-8a, H_2-2a), 2.08 (2H, m, H_2-8b, H_2-2b), 1.82 (1H, m, H_2-3a), 1.76 (1H, m, H_2-3b), 1.46 (2H, m, H_2-4), 1.41 (1H, m, H-5), 1.40 (2H, m, H_2-7), 0.89 (3H, d, J= 6.3 Hz, H_3-14), 1.12 (3H, s, H_2-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5 (C-1), 142.6 (C-11), 138.5 (C-12), 125.9 (C-9), 111.1 (C-10), 107.7 (C-13), 43.1 (C-4), 42.0 (C-6), 33.5 (C-2), 31.6 (C-5), 30.6 (C-7), 27.9 (C-3), 22.6 (C-15), 19.2 (C-8), 16.1 (C-14); EIMS *m/z* (%) 218 (M^+, 18), 124 (35), 109 (100), 95 (45), 81 (76).

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References and notes

1. Karuso, P. In *Bioorganic marine chemistry*; Scheuer, P. J., Ed.; Springer: Berlin, 1987; pp 31–60.
2. Cimino, G.; Fontana, A.; Gavagnin, M. *Curr. Org. Chem.* **1999**, *3*, 327–372.
3. Cimino, G.; Ciavatta, M. L.; Fontana, A.; Gavagnin, M. In *Bioactive natural products: isolation, structure elucidation and biology properties*; Tringali, C., Ed.; Taylor and Francis: London, 2001; pp 577–637.
4. Cimino, G.; Fontana, A.; Cutignano, A.; Gavagnin, M. *Phytochem. Rev.* **2004**, *3*, 285–307.
5. Okuda, R. K.; Scheuer, P. J.; Hochlowski, J. E.; Walker, R. P.; Faulkner, D. J. *J. Org. Chem.* **1983**, *48*, 1866–1869.
6. Spinella, A.; Alvarez, L. A.; Avila, C.; Cimino, G. *Tetrahedron Lett.* **1994**, *35*, 8665–8668.
7. Gavagnin, M.; Mollo, E.; Calado, G.; Fahey, S.; Ghiselin, M.; Ortea, J.; Cimino, G. *Chemoecology* **2001**, *11*, 131–136.
8. Gavagnin, M.; Mollo, E.; Castelluccio, F.; Ghiselin, M. T.; Calado, G.; Cimino, G. *Tetrahedron* **2001**, *57*, 8913–8916.
9. Fontana, A.; Tramice, A.; Cutignano, A.; d'Ippolito, G.; Gavagnin, M.; Cimino, G. *J. Org. Chem.* **2003**, *68*, 2405–2409.
10. Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1993**, *46*, 1255–1267.
11. Valdés, A.; Ortea, J. *Veliger* **1997**, *40*, 240–254.
12. Sakio, Y.; Hirano, Y. J.; Hayashi, M.; Komiyama, K.; Ishibashi, M. *J. Nat. Prod.* **2001**, *64*, 726–731.
13. Conte, M. R.; Fattorusso, E.; Lanzotti, V.; Magno, S.; Mayol, L. *Tetrahedron* **1994**, *50*, 13469–13476.
14. Bretmaier, E.; Voelter, W. *Carbon-13 NMR spectroscopy*; VCH: New York, 1987; p 212.
15. Killday, K. B.; Longley, R.; McCarthy, P. J.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **1993**, *56*, 500–507.
16. Casapullo, A.; Minale, L.; Zollo, F. *J. Nat. Prod.* **1993**, *56*, 527–533.
17. Carotenuto, A.; Conte, M. R.; Fattorusso, E.; Lanzotti, V.; Magno, S. *Tetrahedron* **1995**, *51*, 10751–10758.
18. Potvin, S.; Canonne, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2821–2824.
19. Carroll, J.; Jonsson, E. N.; Reiner, E.; Hartman, M. S.; Holman, T. R.; Crews, P. *J. Org. Chem.* **2001**, *66*, 6847–6851.
20. Dagneau, P.; Canonne, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2817–2820.
21. Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, *43*, 3723–3726.
22. Full assignment of carbon values of microcionin-2 (**8**), not reported in Refs. 18 and 21, has been made in this work.

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Caldaphnidines A–F, six new *Daphniphyllum* alkaloids from *Daphniphyllum calycinum*

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Abstract—Six new *Daphniphyllum* alkaloids, namely caldaphnidines A–F (**1–6**), together with eight known ones, deoxycalyciphylline B, deoxyisocalyciphylline B, bukittiggine, calycicine A, methyl homosecodaphniphyllate, daphnilactone B, and daphnezomines L–M, were isolated from the leaves and the seeds of *Daphniphyllum calycinum*. The structure of **1** was determined by a single-crystal X-ray diffraction study, and the structures of **2–6** were established by spectral methods, especially two-dimensional NMR techniques (^{1}H–^{1}H COSY, HMQC, HMBC, and NOESY).

1. Introduction

Plants of the genus *Daphniphyllum* are known to metabolize structurally diversified *Daphniphyllum* alkaloids with highly complex polycyclic skeleton.[1,2] *Daphniphyllum* alkaloids are biosynthesized from six molecules of mevalonic acid via a squalene-like intermediate.[3] *Daphniphyllum* alkaloids have been challenging subjects of natural products, biogenetic and synthetic programs. Heathcock and his co-workers reported a series of synthetic work on *Daphniphyllum* alkaloids, in which, one exceptionally efficient route of biomimetic total syntheses is notable.[4]

Daphniphyllum calycinum Benth (Daphniphyllaceae) is a native evergreen shrub in southern China. Its leaves and seeds are used in traditional Chinese medicine to treat several symptoms, including pyretic, inflammation, and influenza.[5,6b] The previous studies on this species resulted in the isolation of several *Daphniphyllum* alkaloids,[2a,c,6] and some of them showed cytotoxic activity.[2a,c] A few flavonoid glycosides with antioxidative activity were also isolated from this plant.[7] Recently, a number of novel *Daphniphyllum* alkaloids have been isolated from the genus *Daphniphyllum* in our laboratory.[8] In the continuation of our search for the structurally unique *Daphniphyllum* alkaloids, caldaphnidines A (**1**) and B (**2**), deoxycalyciphylline B, deoxyisocalyciphylline B, calycicine A, and bukittiggine were isolated from the leaves of *D. calycinum*. And caldaphnidines C–F (**3–6**), deoxycalyciphylline B, deoxyisocalyciphylline B, methyl homosecodaphniphyllate, daphnilactone B and daphnezomines L–M were isolated from the seeds of *D. calycinum*. Among them, caldaphnidines A–F (**1–6**) are new *Daphniphyllum* alkaloids (Fig. 1). The structure of caldaphnidine A (**1**) was determined by a single-crystal X-ray diffraction study, and the structures of caldaphnidines B–F (**2–6**) were established by spectral methods, especially, two-dimensional NMR techniques (^{1}H–^{1}H COSY, HMQC, HMBC, and NOESY).

2. Results and discussion

Caldaphnidine A (**1**) was obtained as an optically active ($[\alpha]_D^{20}$ +72.0) and colorless quadrate crystal (in CH_3OH). The molecular formula was established as $C_{23}H_{29}NO_3$ by HREIMS at *m/z* 367.2130 $[M]^+$ (calcd 367.2147), indicating the existence of 10 degrees of unsaturation. The strong IR absorption band at 1740 cm^{-1} implied the presence of a ketone carbonyl, which was consistent with the carbon signal at δ 219.0 (in CD_3OD) in the ^{13}C NMR spectrum. The UV absorption band at 297 nm (ε 9591) and IR absorptions at 1699, 1658, 1627 cm^{-1} were typical features of an ester carbonyl conjugated with two double bonds,[9] just as the case in the known alkaloid calycicine A, and was confirmed by a good match of ^{13}C NMR data of the conjugated system in both alkaloids **1** and calycicine A.[6b] Two methyls at δ 1.18 (3H, d, J=7.5 Hz) and 1.04 (3H, s), and one methoxyl group at δ 3.69 (3H, s) were observed in

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the ^{1}H NMR spectrum (Table 1) of **1**. Twenty-three carbon signals corresponding to 23 carbon atoms in the molecular formula were all resolved in the ^{13}C NMR spectrum, comprising eight quaternary carbons, four tertiary carbons, eight secondary carbons and three methyls (one oxygenated). Besides the four degrees of unsaturation occupied by the two carbonyls and two double bonds, the remaining six degrees of unsaturation were ascribed to the occurrence of one hexacyclic ring system in **1** (Fig. 1).

The structure and relative stereochemistry of **1**, as showed in the Figure 2, were finally determined by a single-crystal X-ray diffraction[10] study, it was in good agreement with the structure established by two-dimensional NMR experiments.

Caldaphnidine B (**2**) was obtained as an optically active ($[\alpha]_D^{20}$ −39.0) colorless oil. The molecular formula was established as $C_{23}H_{35}NO_2$ by HREIMS at *m/z* 357.2660 $[M]^+$ (calcd 357.2668), implying the existence of seven degrees of unsaturation. The spectral data of **2** showed a high similarity to those of paxdaphnidine A reported by our research group.[8b] The extensive analysis of two-dimensional NMR spectra (^{1}H–^{1}H COSY, HMQC, HMBC) revealed that **2** had the same planar structure with that of paxdaphnidine A.

The relative stereochemistry of **2** was deduced from the NOESY experiment (Fig. 3). In the NOESY spectrum, correlations between the proton pairs of H_3-21/H-6, H-6/H-11b, H-11b/H-15 and H-15/H-14 indicated that H-6, H-14, H-15, and H_3-21 were in the same side and defined as β-orientation. The structure of caldaphnidine B was therefore elucidated as **2**, which is the diastereoisomer of paxdaphnidine A isolated from *Daphniphyllum paxium*.[8b] Comparing the structure of **2** with that of paxdaphnidine A, the sub-structural fragments involving C-14 and C-15 at the slightly twisted five-membered D- and E-rings in both compounds were actually like a pair of enantiomer (Fig. 4). This explained why the chemical shifts of C-13 to C-17 in both alkaloids were very similar, and the obvious changes of chemical shifts for the carbons at C-ring in both compounds were likely caused by the orientation of the ester group at C-14. In the case of alkaloid **2**, it showed shielding effects to all the carbons in the C-ring except for the C-10. A rationalized biogenetic origin of **2** and paxdaphnidine A, shown in the Scheme 1, may support the structural elucidation.

Caldaphnidine C (**3**) was obtained as an amorphous powder. The molecular formula was established as $C_{22}H_{33}NO_2$ by HREIMS at *m/z* 343.2515 $[M]^+$ (calcd 343.2511), implying the existence of seven degrees of unsaturation. A strong IR absorption band at 1714 cm^{-1} was attributable to the presence of a carbonyl, and was confirmed by the signal at δ 177.8 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum (Table 2) of **3** displayed signals for two methyls at δ 1.23 (3H, s), 1.09 (3H, d, J=6.8 Hz). One trisubstituted double

Table 1. ^{1}H and ^{13}C NMR data of caldaphnidines A–B (**1–2**)

No.	1		2	
	δ_C[a]	δ_H, multi, J (Hz)[a]	δ_C[a]	δ_H, multi, J (Hz)[b]
1	69.8	3.09 (1H, d, 6.2)	56.7	2.55 (1H, d, 3.6)
2	38.7	2.82 (1H, m)	42.4	1.44 (1H, m)
3	40.5	2.54 (2H, m)	29.2	*a*: 1.83 (1H, m) *b*: 1.62 (1H, m)
4	219.0	—	40.8	*a*: 1.63 (1H, m) *b*: 1.54 (1H, m)
5	51.5	—	37.1	—
6	45.0	1.84 (1H, t, 5.6)	44.0	1.60 (1H, m)
7	55.8	*a*: 3.05 (1H, d, 13.0) *b*: 2.86 (1H, m)	48.0	*a*: 2.77 (1H, d, 14.9) *b*: 3.44 (1H, dd, 14.9, 7.0)
8	45.0	—	51.7	—
9	155.1	—	148.4	—
10	152.7	—	136.0	—
11	28.1	*a*: 2.15 (1H, m) *b*: 2.98 (1H, m)	28.5	*a*: 1.48 (1H, m) *b*: 1.85 (1H, m)
12	30.1	*a*: 1.67 (1H, m) *b*: 2.08 (1H, m)	31.1	*a*: 1.47 (1H, m) *b*: 2.21 (1H, m)
13	45.6	*a*: 2.92 (1H, d, 12.0) *b*: 2.97 (1H, d, 12.0)	38.8	*a*: 2.05 (1H, dd, 14.6, 9.2) *b*: 2.51 (1H, dd, 14.6, 3.5)
14	117.7	—	44.1	2.89 (1H, dt, 3.5, 9.6)
15	171.6	—	55.4	3.42 (1H, m)
16	44.9	2.90 (2H, m)	27.1	*a*: 2.34 (1H, m) *b*: 2.18 (1H, m)
17	26.9	*a*: 2.62 (1H, m) *b*: 2.75 (1H, m)	44.1	*a*: 2.42 (1H, dd, 14.9, 9.0) *b*: 2.68 (1H, m)
18	38.1	2.52 (1H, m)	32.2	1.68 (1H, m)
19	64.7	*a*: 3.21 (1H, br t, 9.8) *b*: 2.49 (1H, dd, 9.8, 3.8)	21.8	0.95 (3H, d, 6.6)
20	19.4	1.18 (1H, d, 7.5)	21.9	0.92 (3H, d, 6.4)
21	18.2	1.04 (3H, s)	27.1	1.06 (3H, s)
22	168.9	—	177.2	—
OMe	52.0	3.69 (3H, s)	51.8	3.61 (3H, s)

[a] Measured in CD_3OD, ^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz.
[b] Measured at 600 MHz in CD_3OD.

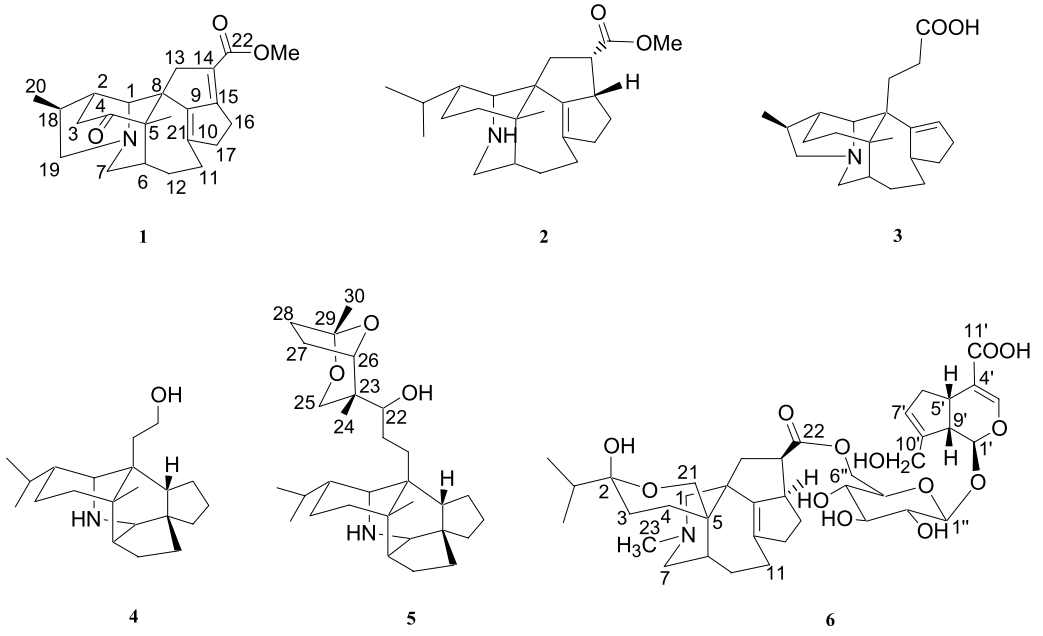


Figure 1. Structures of caldaphnidines A–F.

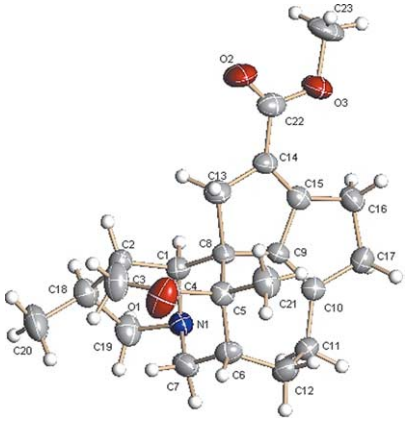


Figure 2. Single-crystal X-ray structure of caldaphnidine A (**1**).

bond was deducted by the proton signal at δ 5.85 (br s) in the ^{1}H NMR and the carbon signals at δ 152.0 and 131.8 in the ^{13}C NMR (Table 2). Consistent with the molecular formula of **3**, 22 carbon signals comprising four quaternary carbons, six tertiary carbons, 10 secondary carbons and two methyls were observed in the ^{13}C NMR spectrum. Two degrees of

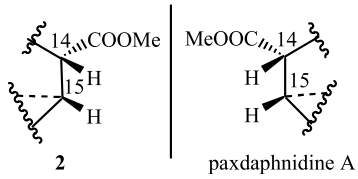


Figure 4. The stereochemistry of C-14–C-15 fragments of **2** and paxdaphnidine A.

unsaturation were occupied by a double bond and a carboxylate group. The remaining five degrees of unsaturation were only assumable to the occurrence of one pentacyclic ring system in **3**.

Analysis of ^{1}H–^{1}H COSY spectrum (combined with HMBC) permitted to establish three structural fragments **a** (C-1 to C-4 and C-18 to C-20), **b** (C-6 to C-7, C-10 to C-12, and C-15 to C-17) and **c** (C-13 and C-14) drawn with bold bond (Fig. 5). The assemblage of three structural fragments **a**–**c**, quaternary carbons and nitrogen atom were mainly made by an excellent performance of HMBC experiment (Fig. 5). The planar structure of **3** was thus established.

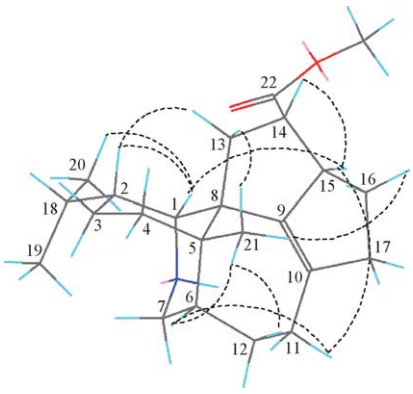


Figure 3. Key NOESY correlations (- - -) and relative stereochemistry of **2**.

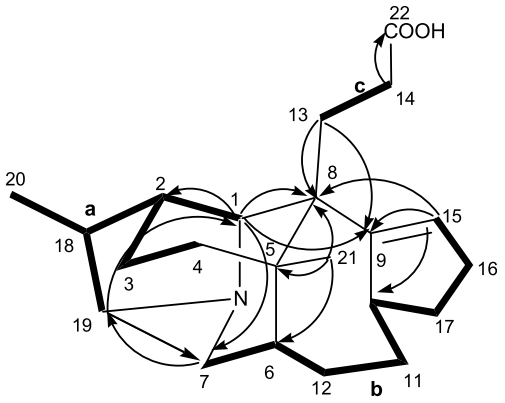
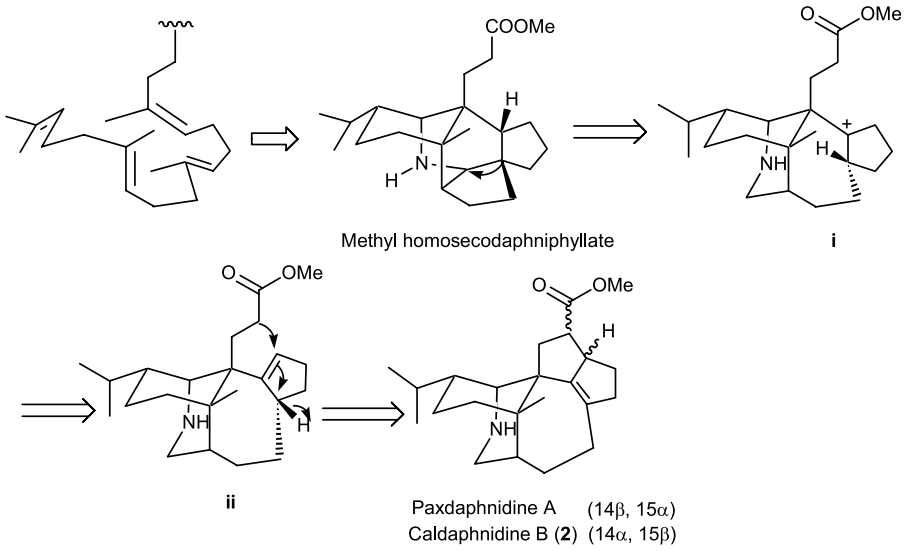


Figure 5. — ^{1}H–^{1}H COSY of **3**, ⤳ selected HMBC of **3** (H→C).



Scheme 1. Biogenetic pathway for caldaphnidine B (**2**) and paxdaphnidine A.

The relative stereochemistry of **3** was deduced from the NOESY experiment as depicted on a three-dimensional structure model (Fig. 6) generated from the computer modeling, in which, MM2 force field calculations was used for energy minimization (CS Chem 3D Pro Version 7.0). In the NOESY spectrum, the correlation pairs of H-6/H_3-21 and H-10/H_3-21 implied that H-6, H-10, and H_3-21 were in the same side and designated as β-orientation; the correlation pairs of H-1/H-2, H-2/H-18 and H-18/H-19a implied that the H-1, H-2, and H-19a were in the α-configuration. As a consequence, the H-19b correlated with H_3-20 was distinguished in β-orientation. The structure of caldaphnidine C was therefore elucidated as **3**.

Table 2. ^{1}H and ^{13}C NMR data of caldaphnidines C–D (**3**–**4**)

No.	**3**		**4**		
	δ_C[a]	δ_H, multi, *J* (Hz)[b]	δ_C[a]	δ_C[c]	δ_H, multi, *J* (Hz)[b]
1	74.0	3.88 (1H, d, 3.9)	50.0	48.4	2.98 (1H, br s)
2	38.3	2.46 (1H, m)	44.6	42.9	1.06 (1H, dd, 17.1, 8.3)
3	21.6	1.70 (2H, m)	21.9	20.7	1.54 (2H, m)
4	40.4	*a*: 2.10 (1H, m)	40.4	38.9	*a*: 1.65 (1H, m)
		b: 1.54 (1H, m)			*b*: 1.18 (1H, m)
5	37.9	—	38.1	36.6	—
6	44.3	2.16 (1H, m)	49.1	47.6	1.92 (1H, t, 5.0)
7	59.0	*a*: 3.58 (1H, dd, 14.8, 11.3)	61.1	59.7	2.55 (1H, d, 4.3)
		b: 3.45 (1H, d, 14.8)			
8	42.6	—	38.0	36.6	—
9	152.0	—	55.2	53.3	1.73 (1H, m)
10	48.3	3.04 (1H, t, 9.2)	51.5	50.2	—
11	34.3	*a*: 1.76 (1H, m)	41.4	39.7	*a*: 1.68 (1H, m)
		b: 1.51 (1H, m)			*b*: 1.52 (1H, m)
12	32.2	*a*: 1.48 (1H, m)	24.1	22.9	*a*: 1.46 (1H, m)
		b: 2.00 (1H, m)			b: 1.67 (1H, m)
13	32.7	*a*: 2.15 (1H, m)	37.3	36.2	1.54 (2H, m)
		b: 1.84 (1H, m)			
14	31.7	*a*: 2.34 (1H, m)	60.5	60.1	*a*: 3.68 (1H, m)
		b: 2.28 (1H, m)			*b*: 3.53 (1H, m)
15	131.8	5.85 (1H, br s)	31.2	29.8	*a*: 1.78 (1H, m)
					b: 1.60 (1H, m)
16	30.8	*a*: 2.44 (1H, m)	27.7	26.6	*a*: 1.79 (1H, m)
		b: 2.23 (1H, m)			b; 1.48 (1H, m)
17	33.9	*a*: 1.64 (1H, m)	37.5	36.4	1.84 (2H, m)
		b: 2.14 (1H, m)			
18	37.5	2.67 (1H, m)	29.9	28.7	1.50 (1H, m)
19	65.8	*a*: 3.96 (1H, t, 11.3)	21.7	21.0	0.92 (3H, d, 6.4)
		b: 2.84 (1H, dd, 11.3, 8.8)			
20	13.7	1.09 (3H, d, 6.8)	21.6	21.0	0.90 (3H, d, 6.4)
21	26.7	1.23 (3H, s)	22.1	21.4	0.80 (3H, s)
22	177.8	—			

[a] Measured at 100 MHz in CD_3OD.
[b] Measured at 600 MHz in CD_3OD.
[c] Measured at 100 MHz in $CDCl_3$.

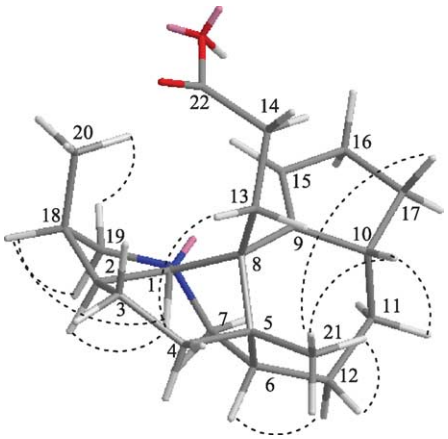


Figure 6. Key NOESY correlations (- - -) and relative stereochemistry of **3**.

Caldaphnidine D (**4**) was obtained as an optically active ($[\alpha]_D^{20}$ −73.0) colorless oil. The molecular formula was established as $C_{21}H_{35}NO$ by HREIMS at *m/z* 317.2727 $[M]^+$ (calcd 317.2719), indicating the existence of five degrees of unsaturation. The IR spectrum of **4** showed a strong absorption band at 3332 cm^{-1} for a hydroxyl or NH group. The ^1H NMR spectrum (in CD_3OD, Table 2) of **4** displayed the presence of three methyls at δ 0.80 (3H, s), 0.90 (3H, d, J=6.4 Hz) and 0.92 (3H, d, J=6.4 Hz), and one hydroxymethyl group at δ 3.68 and 3.53 (each 1H, m). The ^{13}C NMR spectrum (measured in both CD_3OD and $CDCl_3$, Table 2) revealed the presence of 21 carbons: three quaternary carbons, six tertiary carbons, nine secondary carbons and three methyls. Among them, two methines (CH-1: δ_C 50.0, δ_H 2.98; CH-7: δ_C 61.1, δ_H 2.55; in CD_3OD) were ascribed to those attached to the nitrogen. As there was no carbonyl group or double bond in **4**, the five degrees of unsaturation could only assigned to the presence of a pentacyclic system.

The spectral data of **4** were similar to those of methyl homosecodaphniphyllate,[11] except for the absence of methyl carboxylate at C-14 and the presence of a hydroxyl. This was confirmed by the interpretation of 2D NMR (^1H–^1H COSY, HMQC, and HMBC). The relative stereochemistry of **4** was deduced from NOESY spectrum, in which, the correlations of H_3-21/H-9, H-9/H-6 showed that the H_3-21, H-9 and H-6 were in the same side, and defined in β-orientation. Thus, the structure and relative stereochemistry of caldaphnidine D (**4**) were elucidated.

Caldaphnidine E (**5**) was obtained as colorless oil. The HREIMS at *m/z* 471.3710 revealed the molecular formula of $C_{30}H_{49}NO_3$, indicating the existence of seven degrees of unsaturation. The ^1H and ^{13}C NMR data (Table 3) suggested that **5** had the same fused-pentacyclic backbone as that of **4** (N, C-1 to C-21), which was confirmed by the interpretation of 2D NMR. The partial structure of C-23 to C-30 fragment was established by comparing the spectral data with that of daphnezomine C,[2h] and was confirmed by the analysis of 2D NMR. The linkages of the backbone and the fragment (C-23 to C-30) to C-22 were resolved by HMBC correlations of H_2-14/C-22, H_3-24/C-22, and H_3-24/C-23. Herein, the planar structure of **5** was established. The NOESY correlations (Fig. 7) of H-26/H_3-24, H-26/H-25a, H-26/H-27a, and H-26/H-28a showed that the H_3-24, H-25a, H-26, H-27a and H-28a were at the same side and defined in α-orientation. As a consequence, the NOESY correlations of H-25b/H_3-30, H-22/H-27b, and H-22/28b indicated that the H-25b, H-27b, H-28b, and H_3-30 were β-oriented. The

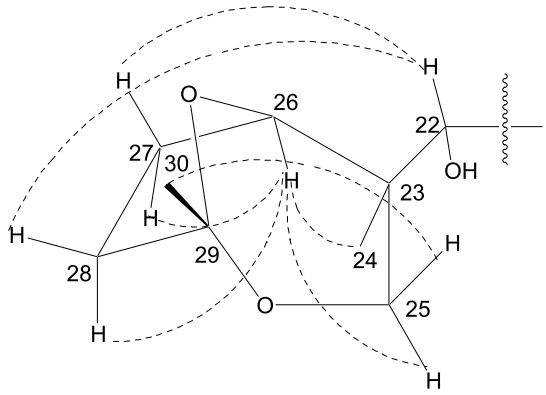


Figure 7. NOESY correlations (- - -) and relative stereochemistry of the side chain of caldaphnidine E (**5**).

Table 3. ^1H and ^{13}C NMR data of caldaphnidine E (**5**)

No.	5		
	δ_C[a]	δ_C[b]	δ_H, multi, J (Hz)[c]
1	49.7	47.6	3.09 (1H, br s)
2	43.7	42.2	1.13 (1H, m)
3	21.7	20.7	1.51 (2H, m)
4	40.4	39.1	*a*: 1.68 (1H, m)
			b: 1.16 (1H, m)
5	38.2	36.8	—
6	49.1	47.4	1.90 (1H, m)
7	61.1	59.8	2.52 (1H, d, 4.5)
8	37.8	36.3	—
9	56.3	54.3	1.71 (1H, m)
10	51.7	50.5	—
11	41.7	40.0	*a*: 1.69 (1H, m)
			b: 1.52 (1H, m)
12	24.1	22.9	*a*: 1.54 (2H, m)
13	26.7	25.2	*b*: 1.68 (2H, m)
14	31.1	29.6	*a*: 1.26 (1H, m)
			b: 1.04 (1H, m)
15	31.6	30.1	*a*: 1.76 (1H, m)
			b: 1.62 (1H, m)
16	27.8	26.7	*a*: 1.80 (1H, m)
			b: 1.44 (1H, m)
17	37.2	36.1	*a*: 1.82 (1H, m)
			b: 1.51 (1H, m)
18	30.0	28.7	1.49 (1H, m)
19	21.8	21.0	0.89 (3H, d, 6.8)
20	21.8	21.0	0.90 (3H, d, 6.8)
21	21.5	21.0	0.69 (3H, s)
22	76.7	75.0	3.41 (1H, d, 9.8)
23	41.3	40.0	—
24	16.4	15.5	1.03 (3H, s)
25	67.2	66.9	*a*: 3.33 (1H, d, 11.3)
			b: 3.27 (1H, d, 11.3)
26	83.8	81.7	4.10 (1H, d, 6.3)
27	24.7	24.8	*a*: 1.95 (1H, m)
			b: 2.13 (1H, m)
28	35.3	33.8	*a*: 1.98 (1H, m)
			b: 1.88 (1H, m)
29	106.6	104.8	—
30	24.7	24.8	1.40 (3H, s)

[a] Measured at 100 MHz in CD_3OD.
[b] Measured at 100 MHz in $CDCl_3$.
[c] Measured at 600 MHz in CD_3OD.

structure and relative stereochemistry of caldaphnidine E (**5**) were thus elucidated.

Caldaphnidine F (**6**) was afforded as a white amorphous powder. The HRESIMS at *m/z* 746.3792 $[M+H]^+$ suggested a molecular formula of $C_{39}H_{55}NO_{13}$ with 13 degrees of unsaturation. A comparison of the spectral data of **6** with that of daphnezomine P[2m] showed a high similarity. The only difference was the absence of the methoxyl at C-11′ and the presence of a carboxylic acid (δ 170.1) in **6**, suggesting **6** was the free acid of daphnezomine P at C-11′. The structure assigned for compound **6** was finally confirmed by 2D NMR spectra (^1H–^1H COSY, HMQC, HMBC, and NOESY).

Eight known alkaloids were identified as deoxycalyciphylline B, deoxyisocalyciphylline B[8a], bukittiggine[4g,12], calycicine A,[6b] daphnilactone-B,[2k] methyl homosecodaphniphyllate,[11] and daphnezomines L–M[13] by comparing the spectral data with those reported in the literature and authentic samples.

3. Experimental

3.1. General experimental procedures

Melting points were recorded on Fisher-Johns melting point apparatus and uncorrected. Optical rotations were determined on a Perkin-Elmer 341 polarimeter (λ 589 nm). UV spectra were determined on a Varian Cary Bio spectrometer. IR spectra were recorded on a Perkin-Elmer 577 spectrometer with KBr disc. NMR spectra were measured on a Bruker AM-400 and Bruker AM-600 spectrometer with TMS as internal standard. Standard pulse sequences were employed to obtain ^1H–^1H COSY, HMBC, HMQC, and NOESY. EIMS (70 eV) was carried out on a Finnigan MAT 95 mass spectrometer instrument. In X-ray crystallography, cell constants were determined by a least-squares fit to the setting parameters of 25 independent reflections measure on a Rigaku AFC7R four circle diffractometer employing graphite monochromated Mo Kα radiation (λ=0.71073 Å) and operating in the ϕ-ω scan mode. Data reduction and empirical absorption corrections (ψ-scans) were performed with the SHELXS-97 package. All solvents used were of analytical grade (Shanghai Chemical Plant). Silica gel (230–400 mesh), amino silica gel (NH-DM 1020, 20–45 μm, Fuji Silysia Chemical Ltd) and C_{18} reverse-phased silica gel (150–200 mesh, Merck) were used for column chromatography. Pre-coated silica gel GF_{254} plates (Qingdao Haiyang Chemical Plant) were used for TLC.

3.2. Plant material

The leaves and seeds of *D. calycinum* were collected from Guangdong and Guangxi Provinces of P.R. China, respectively, and authenticated by Prof. Su-Hua Shi of the Institute of Botany, School of Life Science, Zhongshan University of P.R. China. The voucher specimens have been deposited in the Institute of Materia Medica, SIBS, Chinese Academy of Sciences, and with accession Nos. DS-2003-2Y (for leaves), and DS-2003-2Z (for seeds).

3.3. Extraction and isolation

The isolation of alkaloids **1**–**2** *and known alkaloids from the leaves of D. calycinum*: The powder of leaves of *D. calycinum* (2.8 Kg) was percolated with 95% ethanol to give a crude extract. The crude extract was dissolved in 1 L water to form a suspension, which was then acidified with 0.5 N H_2SO_4 to pH≈5. The acidic suspension was immediately partitioned with ethyl acetate (6×300 mL) to remove the non-alkaloid components. The acidic aqueous phase was adjusted with 2 N Na_2CO_3 to pH≈10 and partitioned with chloroform (6×300 mL) to give the crude alkaloids (640 mg). The crude alkaloids were subjected to silica gel column chromatography eluted with $CHCl_3$–MeOH (40/1–10/1) for two major fractions 1 and 2. Fraction 1 (300 mg) was separated by column chromatography packed with amino silica gel and eluted with cyclohexane–EtOAc (10/1) to yield alkaloids **2** (55 mg, 0.0019%), deoxycalyciphylline B (110 mg, 0.0039%), deoxyisocalyciphylline B (28 mg, 0.001%) and bukittiggine (9 mg, 0.00032%), consecutively. Fraction 2 (80 mg) was also separated by column chromatography packed with amino silica gel and eluted with cyclohexane–EtOAc (6/1) to afford **1** (6.0 mg, 0.00021%) and calycicine A (51 mg, 0.0018%), successively.

The isolation of alkaloids **3**–**6** *and known alkaloids from the seeds of D. calycinum*: The crude alkaloids were obtained mostly by using above isolating procedure. The only difference was that the crude alkaloids, after adjusted with 2 N Na_2CO_3 to pH≈10, were partitioned with $CHCl_3$ (6×300 mL) and *n*-BuOH (3×500 mL) to give two parts. The $CHCl_3$-soluble crude alkaloids were subjected to a silica gel column eluted with $CHCl_3$–MeOH (100/1–10/1, by vol) to give two major fractions C_1 (2.3 g) and C_2 (530 mg). Fraction C_1 was separated by column chromatography packed with amino silica gel and eluted with cyclohexane–EtOAc (10/1, by vol) to yield methyl homosecodaphniphyllate (1.3 g, 0.026%), deoxycalyciphylline B (110 mg, 0.0022%) and deoxyisocalyciphylline B (70 mg, 0.0014%) in turn. Fraction C_2 was also separated by amino silica gel column chromatography eluted with cyclohexane–EtOAc (6/1, by vol) to afford **4** (15.0 mg, 0.0003%), **5** (11.0 mg, 0.0002%), calycicine A (210 mg, 0.0042%) and daphnilactone B (45 mg, 0.0009%). The *n*-BuOH-soluble crude alkaloids were subjected to a column of C_{18} reversed-phase silica gel and eluted with CH_3CN–H_2O (0/10–1/1, by vol) to obtain two fractions B_1 (1.1 g) and B_2 (2.8 g). Fraction B_1 was separated by a silica gel column chromatography eluted with $CHCl_3$–MeOH–HCOOH (6/1/0.05–3/1/0.05, by vol) to afford two major fractions B_{1a} and B_{1b}, which were purified by column chromatography of Sephadex LH-20 eluted with ethanol to give **3** (110 mg, 0.0022%) and **6** (28 mg, 0.00056%), respectively. Fraction B_2 was subjected to a silica gel column eluted with $CHCl_3$–MeOH–HCOOH (10/1/0.05–6/1/0.05, by vol) to collect two major fractions B_{2a} and B_{2b}, each of them was then purified by Sephadex LH-20 column chromatography eluted with methanol to give daphnezomine L (2.2 g, 0.044%) and daphnezomine M (15 mg, 0.0003%), respectively.

3.3.1. Caldaphnidine A (1). Colorless quadrate crystal (CH_3OH); mp 193–194 °C; $[\alpha]_D^{20}$ +72.0 (*c* 0.7, CH_3OH);

UV (MeOH) λ_{max} 223 (ε 3441), 297 (ε 9591); IR (KBr) ν_{max} 2919, 2850, 1740, 1699, 1658, 1627, 1437, 1350, 1713, 1269, 1242, 1111 cm^{-1}; ^1H and ^{13}C NMR see Table 1; EIMS *m/z* (%): 367 $[M]^+$ (100), 352 $[M-Me]^+$ (10), 336 $[M-OCH_3]^+$ (11), 324 (12), 308 $[M-COOCH_3]^+$ (47), 110 (17), 97 (13), 83 (11), 71 (12), 57 (18); HREIMS *m/z*: 367.2130 (calcd for $C_{23}H_{29}NO_3$, 367.2147).

3.3.2. Caldaphnidine B (2). Colorless oil; $[\alpha]_D^{20}$ −39.0 (*c* 0.6, CH_3OH); IR (KBr) ν_{max} 3340, 2918, 1740, 1567, 1458, 1379, 1163, 1091, 968, 821 cm^{-1}; ^1H and ^{13}C NMR see Table 1; EIMS *m/z*: (%): 357 $[M]^+$ (43), 342 (9) 314 (17), 298 (11), 274 (13), 97 (26), 85 (59), 71 (80), 57 (100); HREIMS *m/z*: 357.2660 (calcd for $C_{23}H_{35}NO_2$, 357.2668).

3.3.3. Caldaphnidine C (3). Amorphous powder; $[\alpha]_D^{20}$ −36.3 (*c* 1.0, CH_3OH); IR (KBr) ν_{max} cm^{-1} 3430, 2943, 1714, 1560, 1392, 1173, 752; ^1H and ^{13}C NMR see Table 2; EIMS 70 eV *m/z* (%) 343 ($[M]^+$, 56), 328 (14), 284 (42), 270 (100), 256 (22), 96 (32); HREIMS *m/z* 343.2515 ($C_{22}H_{33}NO_2$, calcd 343.2511).

3.3.4. Caldaphnidine D (4). Colorless oil; $[\alpha]_D^{20}$ −73.0 (*c* 1.5, $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 3332, 2939, 1448, 1383, 1037, 756; ^1H and ^{13}C NMR see Table 2; EIMS 70 eV *m/z* (%) 317 ($[M]^+$, 46), 286 (100), 274 (11), 230 (19), 216 (50), 164 (16), 69 (9), 57 (10); HREIMS *m/z* 317.2727 ($C_{21}H_{35}NO$, calcd 317.2719).

3.3.5. Caldaphnidine E (5). Colorless oil; $[\alpha]_D^{20}$ −97.0 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 3431, 2935, 1462, 1385, 1171, 1034. ^1H and ^{13}C NMR see Table 3; EIMS 70 eV *m/z* (%) 471 ($[M]^+$, 70), 375 (28), 286 (91), 216 (42), 97 (69), 71 (72), 57 (100); HREIMS *m/z* 471.3710 ($C_{30}H_{49}NO_3$, calcd 471.3712).

3.3.6. Caldaphnidine F (6). Amorphous powder; $[\alpha]_D^{20}$ +21.0 (*c* 1.0, H_2O); IR (KBr) ν_{max} cm^{-1} 3413, 2933, 1726, 1601, 1544, 1460, 1396, 1173, 1080, 1043, 797; ^1H and ^{13}C NMR see Table 4; Positive ESIMS *m/z* 746 $[M+1]^+$, Negative ESIMS *m/z* 744 $[M-1]^-$; HRESIMS *m/z* 746.3792 $[M+1]^+$ ($C_{39}H_{56}NO_{13}$, calcd 746.3752).

Table 4. ^1H and ^{13}C NMR data of caldaphnidine F (**6**)

No.	6	
	δ_C[a]	δ_H, multi, *J* (Hz)[b]
1	62.1	*a*: 2.25 (1H, d, 11.6) *b*: 2.12 (1H, d, 11.6)
2	97.8	—
3	26.0	1.72 (2H, m)
4	23.2	*a*: 2.04 (1H, m) *b*: 1.92 (1H, m)
5	37.3	—
6	33.3	2.46 (1H, m)
7	56.4	*a*: 2.67 (1H, d, 11.7) *b*: 2.54 (1H, dd, 11.7, 3.4)
8	47.0	—
9	147.6	—
10	132.9	—
11	27.9	*a*: 2.65 (1H, m) *b*: 2.42 (1H, m)
12	27.9	*a*: 2.02 (1H, m) *b*: 1.70 (1H, m)
13	39.9	*a*: 1.52 (1H, dd, 15.2, 9.8) *b*: 2.91 (1H, m)
14	42.8	2.94 (1H, m)
15	55.4	3.48 (1H, m)
16	28.7	*a*: 1.94 (1H, m) *b*: 1.56 (1H, m)
17	43.0	*a*: 2.44 (1H, m) *b*: 2.26 (1H, m)
18	39.8	2.08 (1H, m)
19	17.9	1.10 (3H, d, 6.8)
20	17.4	1.20 (3H, d, 6.8)
21	63.1	*a*: 4.93 (1H, d, 12.7) *b*: 4.18 (1H, dd, 12.7, 1.5)
22	175.2	—
23	46.8	2.14 (3H, s)
1′	97.6	5.65 (1H, d, 6.9)
3′	151.7	7.92 (1H, s)
4′	113.5	—
5′	36.2	3.50 (1H, dd, 15.7, 7.9)
6′	39.6	*a*: 3.17 (1H, m) *b*: 2.42 (1H, m)
7′	127.2	6.02 (1H, br s)
8′	145.6	—
9′	47.1	3.15 (1H, m)
10′	61.1	*a*: 4.75 (1H, d, 14.7) *b*: 4.62 (1H, d, 14.7)
11′	170.1	—
1″	100.8	5.36 (1H, d, 7.8)
2″	74.9	4.05 (1H, m)
3″	78.2	4.22 (1H, t, 8.5)
4″	71.5	3.97 (1H, m)
5″	75.7	4.06 (1H, m)
6″	64.4	*a*: 5.00 (1H, d, 11.7) *b*: 4.44 (1H, dd, 11.7, 6.4)

[a] Measured at 100 MHz in C_5D_5N.
[b] Measured at 600 MHz in C_5D_5N.

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References and notes

1. For reviews of *Daphniphyllum* alkaloids, see: Kobayashi, J.; Morita, H. In Cordell, G. A., Ed.; The alkaloids; Academic: New York, 2003; Vol. 60, p 165; and references cited therein.
2. (a) Kobayashi, J.; Morita, H. *Org. Lett.* **2003**, *5*, 2895–2898. (b) Kobayashi, J.; Takatsu, H.; Shen, Y.; Morita, H. *Org. Lett.* **2003**, *5*, 1733–1736. (c) Jossang, A.; Bitar, H. E.; Pham, V. C.; Sévenet, T. *J. Org. Chem.* **2003**, *68*, 300–304. (d) Kobayashi, J.; Ueno, S.; Morita, H. *J. Org. Chem.* **2002**, *67*, 6546–6549. (e) Kobayashi, J.; Inaba, Y.; Shiro, M.; Yoshida, N.; Morita, H. *J. Am. Chem. Soc.* **2001**, *123*, 11402–11408. (f) Morita, H.; Yoshida, N.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 3558–3562. (g) Morita, H.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 2641–2646. (h) Morita, H.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 12549–12556. (i) Toda, M.; Niwa, H.; Irikawa, H.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1974**, *30*, 2683–2688. (j) Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477–1484. (k) Niwa,

H.; Toda, M.; Hirata, Y.; Yamaura, S. *Tetrahedron Lett.* **1972**, *13*, 2697–2700. (l) Nakano, T.; Saeki, Y. *Tetrahedron Lett.* **1967**, *8*, 4791–4797. (m) Morita, H.; Takatsu, H.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 3575–3579. (n) Takatsu, H.; Morita, H.; Shen, Y. C.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279–6284.

3. (a) Niwa, H.; Hirata, Y.; Suzuki, K. T.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 2129–2132. (b) Suzuki, K. T.; Okuda, S.; Niwa, H.; Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 799–802.
4. (a) Wallace, G. A.; Heathcock, C. H. *J. Org. Chem.* **2001**, *66*, 450–454. (b) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323–14327. (c) Heathcock, C. H.; Joe, D. *J. Org. Chem.* **1995**, *60*, 1131–1142. (d) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120–1130. (e) Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585–2594. (f) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665–681. (g) Heathcock, C. H.; Stanford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575–2585. (h) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665–681.
5. Zhen, M.; Min, T. L. In *Chinese flora (Zhongguo zhiwu zhi)*, *Vol. 45*; Science: Beijing, 1980; pp 1–11.
6. (a) Arthur, H. R.; Chan, R. P. K.; Loo, S. N. *Phytochemistry* **1965**, *4*, 627–629. (b) Hao, X. J.; Zhou, J.; Node, M.; Fuji, K. *Yunnan Zhiwu Yanjiu* **1993**, *15*, 205–207. (c) Ye, H. Y.; Nie, J. L.; Chen, C. X.; Hao, X. J. *Yunnan Zhiwu Yanjiu* **1996**, *18*, 471–472. (d) Bitar, H. E.; Nguyen, V. H.; Gramain, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2004**, *45*, 515–518. (e) Bitar, H. E.; Nguyen, V. H.; Gramain, A.; Sévenet, T.; Bodo, B. *J. Nat. Prod.* **2004**, *67*, 1094–1099.
7. Gamez, E. J. C.; Luyengi, L.; Lee, S. K.; Zhu, L. F.; Zhou, B. N.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1998**, *61*, 706–708.
8. (a) Yang, S. P.; Yue, J. M. *J. Org. Chem.* **2003**, *68*, 7961–7966. (b) Zhan, Z. J.; Yang, S. P.; Yue, J. M. *J. Org. Chem.* **2004**, *69*, 1726–1729. (c) Yang, S. P.; Yue, J. M. *Org. Lett.* **2004**, *6*, 1401–1404.
9. (a) Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1974**, *15*, 2849–2852. (b) Yamamura, S.; Lamberton, J. A.; Niwa, M.; Endo, K.; Hirata, Y. *Chem. Lett.* **1980**, 393–396.
10. Crystal data: $C_{23}H_{29}NO_3$, $M=367.47$, tetragonal system, space group $P4(3)2(1)2$, $a=9.2616(7)$, $b=9.2616(7)$, $c=44.915(5)$ Å, $V=3852.7(6)$ Å^3, $Z=8$, $d=1.267$ g/cm^3. A crystal of dimensions $0.500\times0.375\times0.340$ mm^3 was used for measurements on a Rigaku AFC7R four circle diffractometer. Crystallagraphic data for the structure of **1** has been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 236744). Copies of these data can be obtained, free of charge, on application to the CCDC via www.ccdc.com.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
11. (a) Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477–1484. (b) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544–2553.
12. Arbain, D.; Byrne, L. T.; Cannon, J. R.; Patrick, V. A.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 185–190.
13. Morita, H.; Kobayashi, J. *Tetrahedron* **2002**, *58*, 6637–6641.