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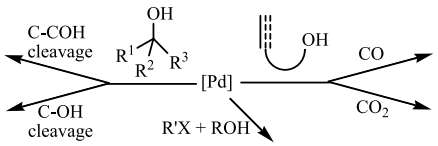
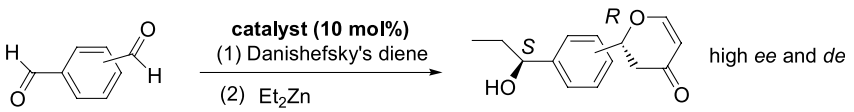
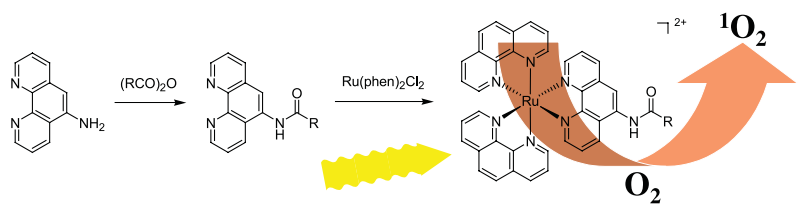
Contents

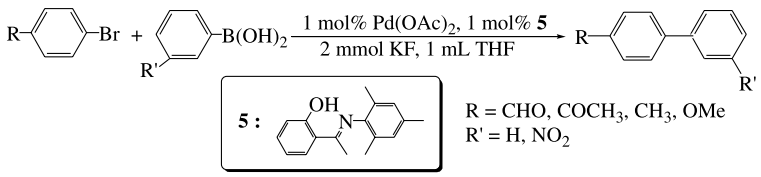
REPORT



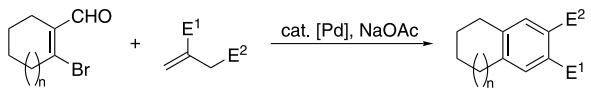
ARTICLES

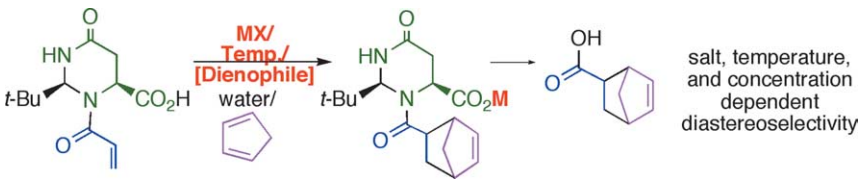


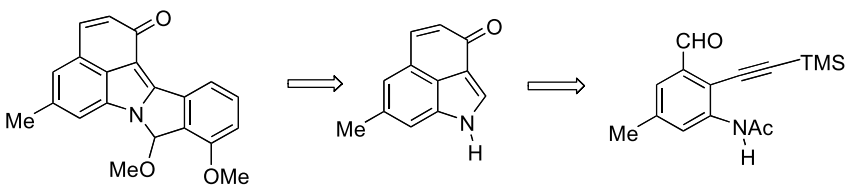


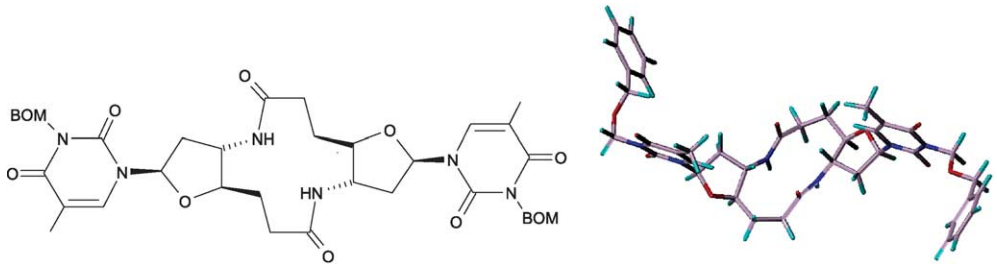


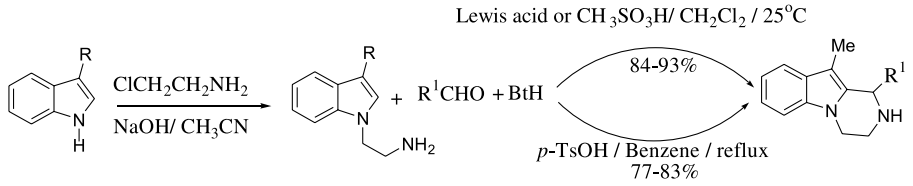
Excellent catalytic reactivity of a *N,O*-bidentate ligand, 2-[1-(2,4,6-trimethyl-phenylimino)-ethyl]-phenol, **5**, in palladium-catalyzed Suzuki cross-coupling reaction was demonstrated.



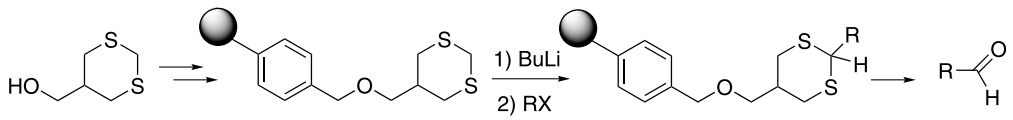


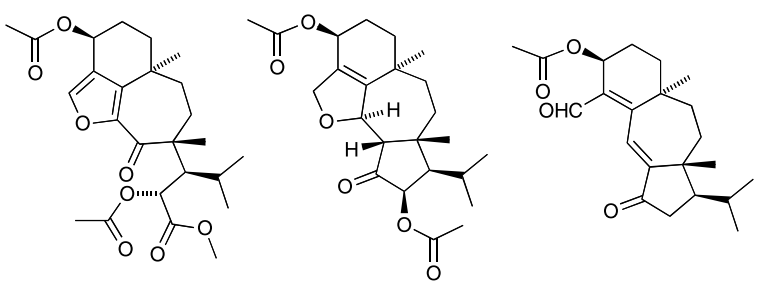


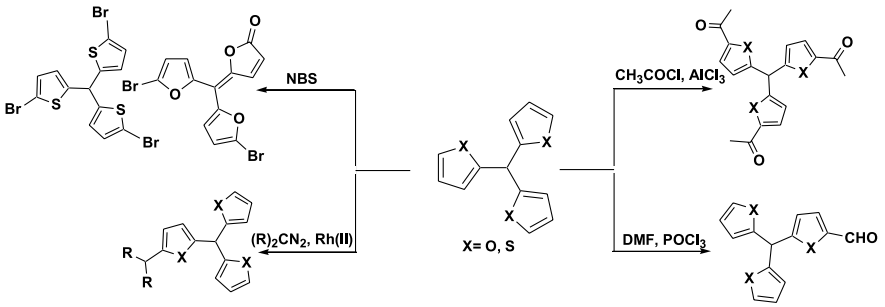


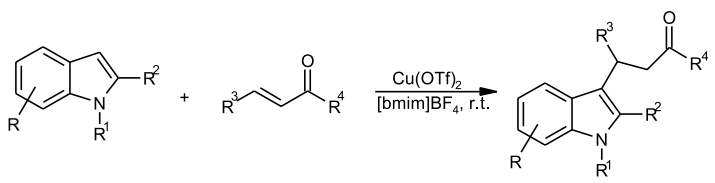


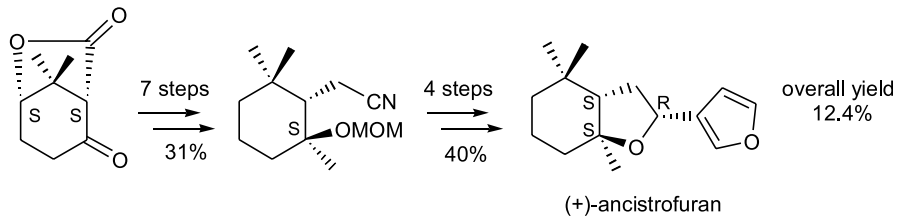
The first general and practical method for the synthesis of 1-substituted-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles is presented.

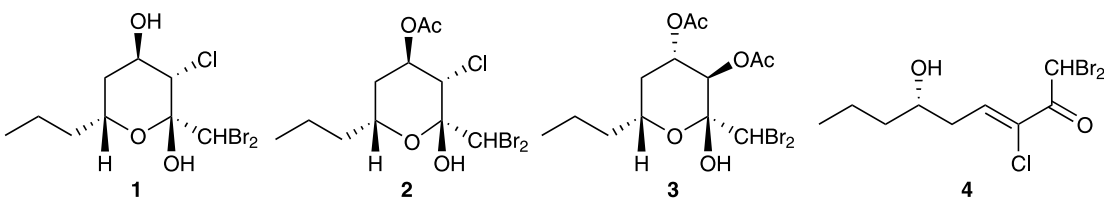


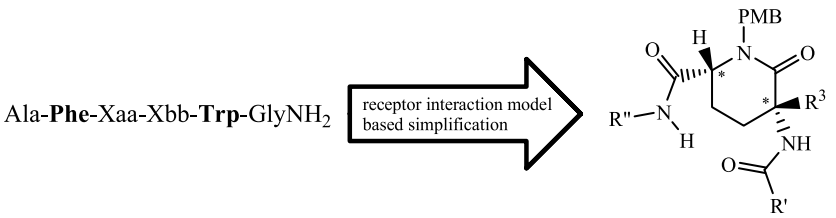


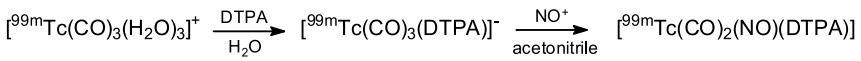




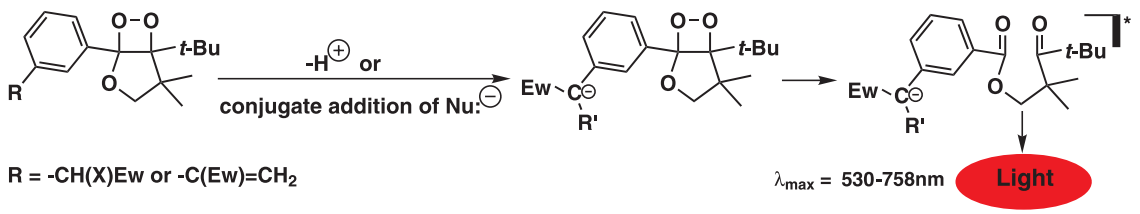


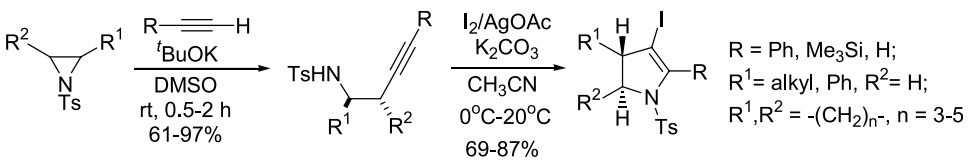


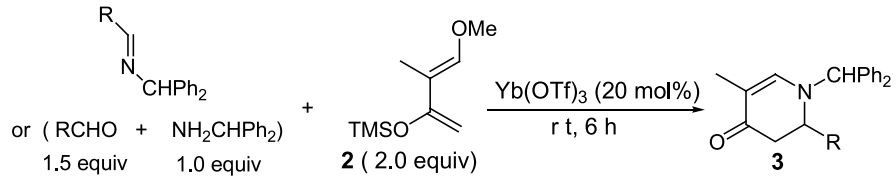


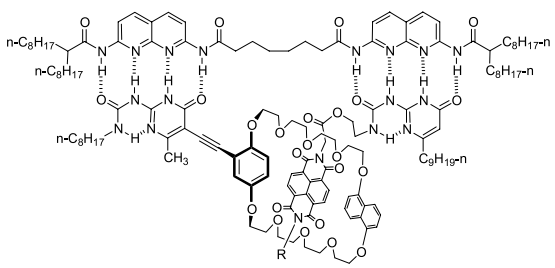


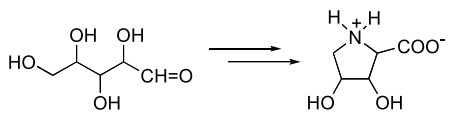
The conversion of a Tc-tricarbonyl complex to a Tc-dicarbonyl-nitrosyl complex using NO^+ reagents offers a synthetic tool for preparing a novel class of ^{99m}Tc labeled compounds. The principle was demonstrated with DTPA as chelating ligand. The biodistribution of the novel ^{99m}Tc(CO)$_2$(NO)–DTPA was compared with that of ^{99m}Tc(CO)$_3$–DTPA and 'classic' ^{99m}Tc–DTPA.

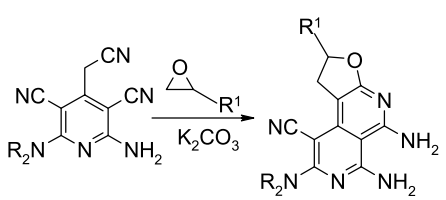


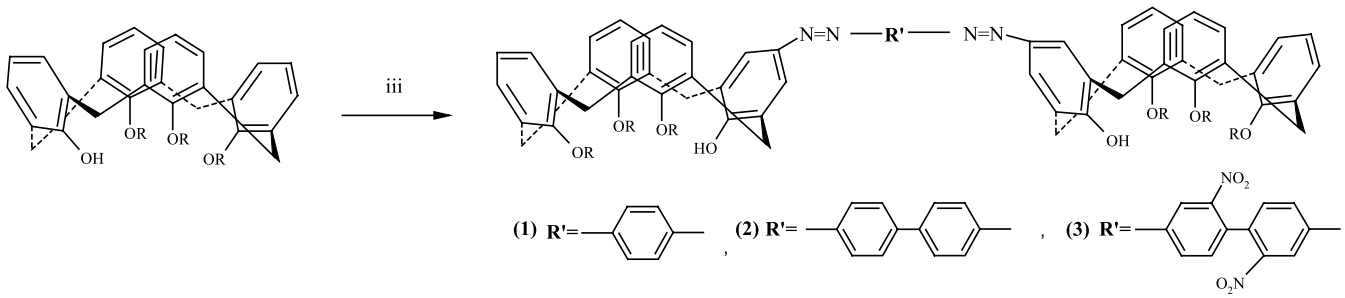


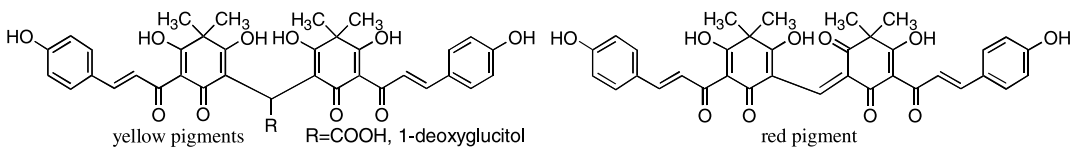


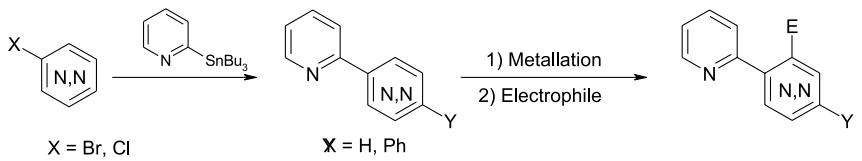












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Palladium-catalysed reactions of alcohols. Part D: Rearrangements, carbonylations, carboxylations and miscellaneous reactions☆

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Dedicated to Professor Françoise Hénin on the occasion of her retirement, with regards and best wishes.

Contents

☆ See Refs. 1–3.

Keywords: Palladium; Catalysis; Alcohols; Rearrangement; Cleavages; Carbonylations; Carboxylations.
Abbreviations: BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; cat., catalytic; conv., conversion; dba, dibenzylidene acetone; de, diastereoisomeric excess; ee, enantiomeric excess; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; (−)-diop, (4*R*,5*R*)-(−)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; dppb, 1,4-bis(diphenylphosphino)butane; dppe, 1,4-bis(diphenylphosphino)ethane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; equiv, equivalent; L, ligand; MS, molecular sieves; rt, room temperature; TON, turnover number.
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1. Introduction

The literature contains an impressive number of palladium-catalysed reactions using alcohols as substrates or reagents, and we are attempting to cover this topic with a series of reviews. The oxidation reactions have been the subject of Part A;[1] Part B has summarised the formation of C–C and C–N bonds from unsaturated alcohols;[2] and the formation of ether linkages has been reviewed in Part C.[3] The present review, which completes the series, is devoted to the rearrangements, cleavages, carbonylations, carboxylations of alcohols and, finally, to particular reactions, which have been less studied. As noted previously, the reports concerning phenols and those where the hydroxy moiety is recovered unmodified at the end of the process are beyond the scope of these reviews.

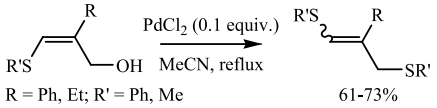
2. Isomerisation

2.1. *Z*/*E* isomerisation

The Pd-catalysed addition/elimination reaction of methanol with the double bond of *Z*-vinyl ethers[4,5] and *Z*-stilbene[6] induces the formation of the corresponding *E*-isomers.

The isomerisation of *Z*-2-buten-1-ol to the *E*-isomer, using the $Pd(acac)_2/PPh_3$ catalytic system at 80 °C,[7] is explainable by the cleavage of the C–OH bond affording the corresponding cationic η^3-allylpalladium complex, followed by the well known $\pi \rightarrow \sigma \rightarrow \pi$ isomerisation[8] and the nucleophilic re-addition of the hydroxide anion (Scheme 1).

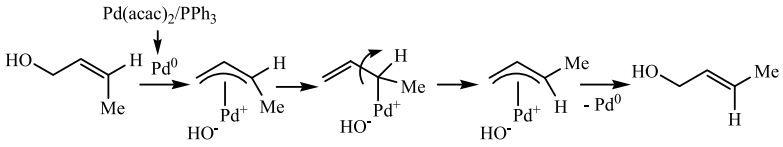
An attempt to isomerise the double bond of primary allylic alcohols β-substituted by a thiol with catalytic amounts of palladium chloride led, in fact, to rearranged products (Eq. 1). It was proposed that this reaction is mediated by hydrogen chloride, liberated from some oxidation of the hydroxy group with $PdCl_2$,[9] because such products are also obtained under acid catalysis.[9,10]



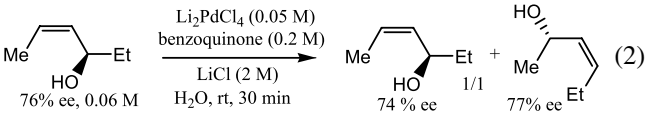
R = Ph, Et; R' = Ph, Me 61-73% (1)

2.2. 1,3-Allylic rearrangement of allylic alcohols

The Wacker oxidation of allylic alcohols can be accompanied by some 1,3-allylic rearrangement of the substrate.[11,12] The proposal that the oxidation of 2-buten-1-ol to 1-buten-3-one, with an oxygenated aqueous solution of $PdCl_2$ and $CuCl_2$, is due to the dehydration of butan-1-ol-3-one formed through a Wacker-type reaction[13] has been rejected by Henry et al.[14] who have studied the mechanism of the Pd-catalysed oxidation of allylic alcohols under various aqueous conditions.[14,15] Using deuteriated propenol/$H_2^{18}O$,[16] and then (*R*)-(*Z*)-4-hexen-3-ol (Eq. 2),[17] Henry's team has demonstrated that, in the presence of a high [Cl^-], the Pd^{II}-catalysed rearrangement involves the hydroxypalladation of the double bond, followed by the Pd–OH elimination.

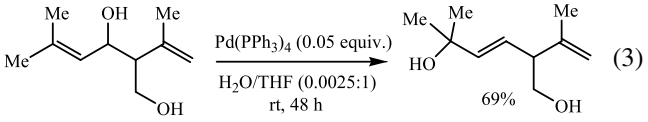


Scheme 1.



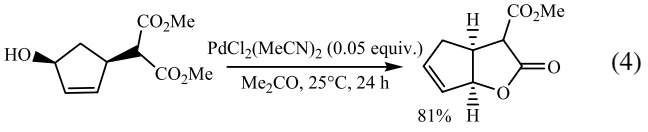
(2)

In contrast, η^3-allylpalladium intermediates are probably involved in the Pd^0-catalysed 1,3-allylic rearrangement depicted in Eq. 3,[18] and in the formation of 1-buten-3-ol from *E*- and *Z*-2-buten-1-ol mediated by the $Pd(acac)_2/PPh_3$ catalytic system at 80 °C.[7]



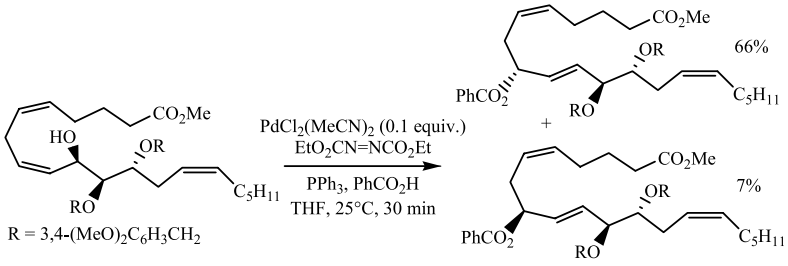
(3)

We suspect that the formation of the bicyclic lactone depicted in Eq. 4,[19], which requires a Pd^{II} catalyst,[20] occurs via the allylic transposition of the hydroxy group, followed by its intramolecular reaction with one of two ester groups.



(4)

Another type of Pd-catalysed rearrangement is the allylic Mitsunobu displacement disclosed by Falck et al. (Eq. 5), which would involve the in situ transformation of the hydroxy group into the Mitsunobu oxyphosphonium salt to afford an η^3-allylpalladium intermediate having the benzoate group as a ligand, the *cis*-transfer, of which to carbon provides the main final product.[21]



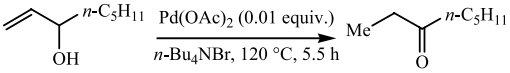
(5)

2.3. Isomerisation of unsaturated alcohols into carbonyl compounds

Although, the formation of 3-pentanone from 4-penten-3-ol over palladium black was disclosed as early as 1926 by Delaby,[22] the Pd-catalysed isomerisation of unsaturated alcohols into carbonyl compounds has been scarcely documented,[7,23–26] and was rather reported as an undesirable side reaction.[22,27–29] In 1972, it was observed that the treatment of vapours of primary unsaturated alcohols over palladium on carbon in the presence of small amounts of hydrogen gave saturated aldehydes, rather than saturated alcohols, the rate of the isomerisation decreasing with the increase of the distance between the double bond and the hydroxy group.[25] With secondary allylic alcohols as substrates, these experimental conditions led mainly to dehydratation products, while a palladium-on-polymer catalyst improved the isomerisation process.[25] Subsequently, the competition between isomerisation and hydrogenation of allylic alcohols over various supported palladium catalysts has been abundantly reported.[30]

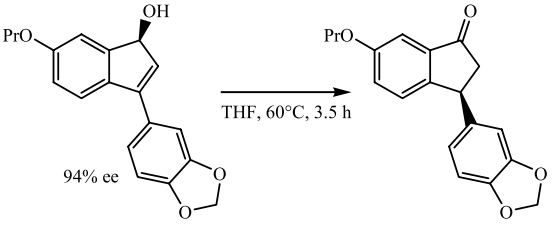
The isomerisation has also been observed when using homogeneous systems. At 80 °C, the $Pd(acac)_2/PPh_3$ catalytic system led mainly to 2-butanone from 1-buten-3-ol,[7] while the efficiency of $PdCl_2(PPh_3)_2$ for the isomerisation of 1-phenyl-3-buten-1,2-diol depends greatly on the nature of the solvent and on the reaction temperature, DMF at 150 °C affording quantitatively 1-hydroxy-1-phenylbutan-2-one.[23]

Recently, we reported an effective recyclable catalytic system, using $Pd(OAc)_2$ in molten tetrabutylammonium bromide, for the isomerisation of (homo)-allylic alcohols to ketones (Eq. 6),[31] and subsequent studies have indicated a catalysis by palladium nanoparticles.[32]



(6)

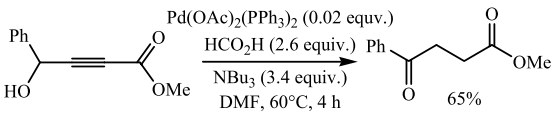
The stereospecific formal 1,3-hydrogen transfer depicted Eq. 7 was, at first, observed using a Pd^{II} catalyst and an organic base, but subsequently, it was discovered that simple heating with DABCO resulted in the same rearrangement.[33]



(7)

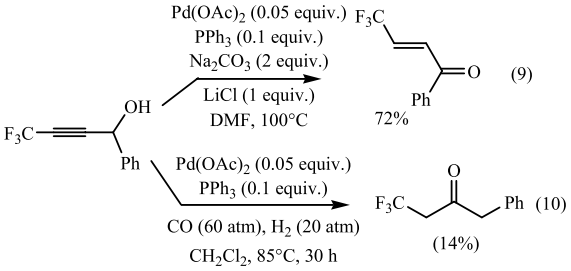
The Pd-catalysed hydrogenation of methyl 4-hydroxy-4-

phenyl-2-butynoate, using HCO_2H/NBu_3 as the hydrogen source, led to the corresponding γ-ketoester depicted Eq. 8.[34] This transformation involves semi-hydrogenation of the triple bond and isomerisation of the resulting allylic alcohol.



(8)

The isomerisation of secondary propargylic alcohols into the corresponding α,β-unsaturated ketones at 100 °C in the presence of palladium and sodium carbonate has been reported (Eq. 9).[35] This reaction, which probably involves the allenyl alcohol as intermediate,[36] could be induced by the basic medium, rather than the Pd catalyst,[36–41] although, the isomerisation of 3-(2-pyridyl)-2-propyn-1-ol to 3-(2-pyridyl) acrylaldehyde with $PdCl_2(PPh_3)_2/CuI$ in diethylamine at 80 °C occurred only in the presence of the metal catalysts.[42] Under carbonylation conditions, a different, unexpected and unexplained reaction leading to 4,4,4-trifluoro-1-phenylbutan-2-one took place from 4,4,4-trifluoro-1-phenylbut-2-yn-1-ol (Eq. 10).[43]



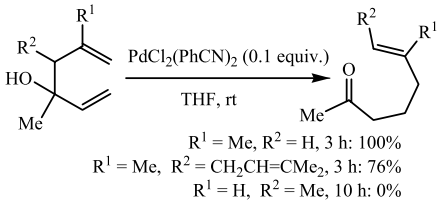
2.4. Racemisation of allenols

Bäckvall et al. have disclosed the racemisation of optically active allenols, via a bromopalladation–debromopalladation sequence, mediated with catalytic amounts of both $Pd(OAc)_2$ and LiBr (Scheme 2).[44]

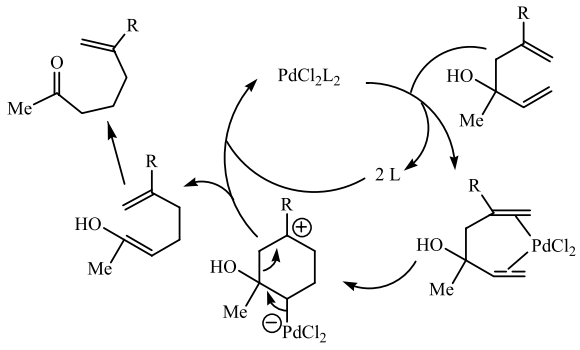
3. C–COH bond cleavage of tertiary alcohols

3.1. Acyclic alcohols

3.1.1. 1,5-Hexadien-3-ols. The Pd^{II}-catalysed oxy-Cope transposition of tertiary 1,5-hexadien-3-ols was first reported by Goré et al.[45] (Eq. 11), who have disclosed the beneficial effect[46] of a nitrile ligand on palladium^{II}, and that this [3,3] sigmatropic rearrangement requires a substituent on C-5, which stabilises the ionic intermediate (Scheme 3).[45,47,48]

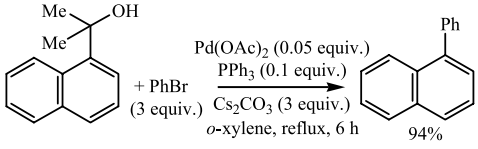


(11)



Scheme 3.

3.1.2. Aryl and heteroaryl methanols. Palladium catalyses the arylative C–C bond cleavage of tertiary benzylic alcohols (Eqs. 12 and 13),[50–52] leading to optically active binaphthyls in the presence of homochiral ligands (Eq. 14).[50,51] According to Miura et al.[51] the key step of the coupling is the β-carbon elimination from an alkoxypalladium intermediate, as shown in Scheme 4.



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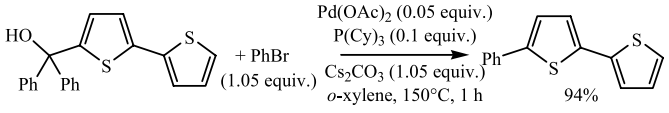

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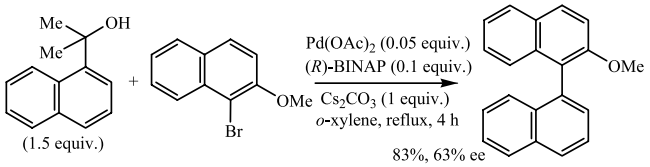
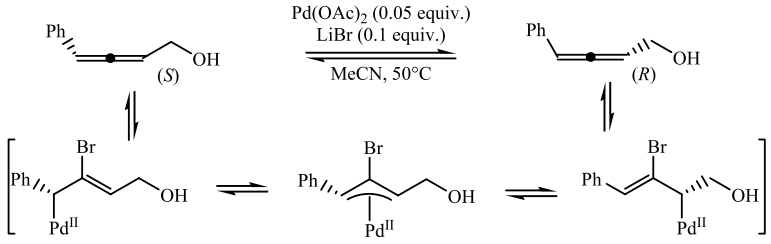
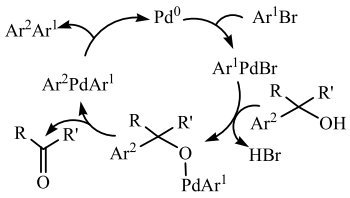


(14)

The Pd-catalysed reaction of (1-naphthyl)diphenylmethanol in refluxing xylene affords naphthalene with a reaction rate increased in the presence of 0.2 equiv of both Cs_2CO_3 and

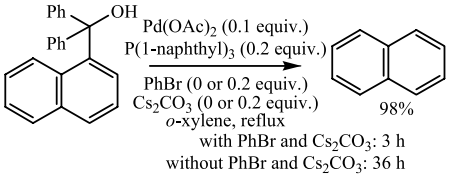


Scheme 2.

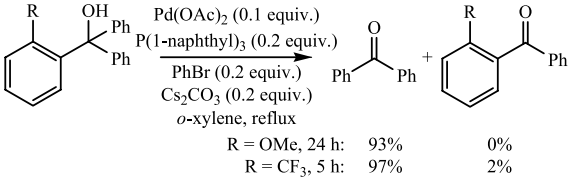


Scheme 4.

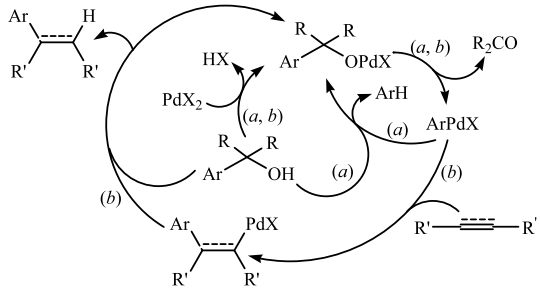
PhBr (Eq. 15). This methodology has been used for the efficient formation of ketones via the dehydroarylation of triarylmethanols (Eq. 16). These reactions were explained following Scheme 5-path a and, furthermore, the arylpalladium intermediates can react with unsaturated compounds to afford hydroarylated adducts (Scheme 5-path b; Eq. 17).[53]



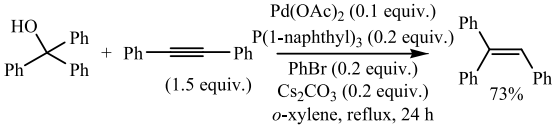
(15)



(16)

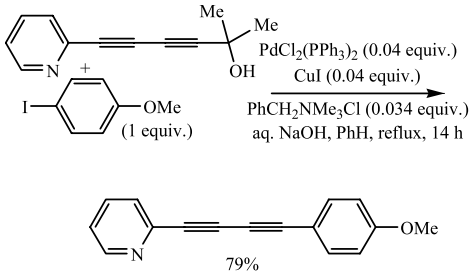


Scheme 5.

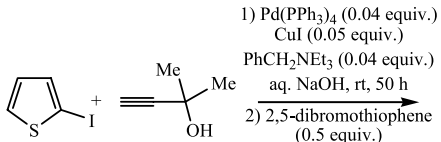


(17)

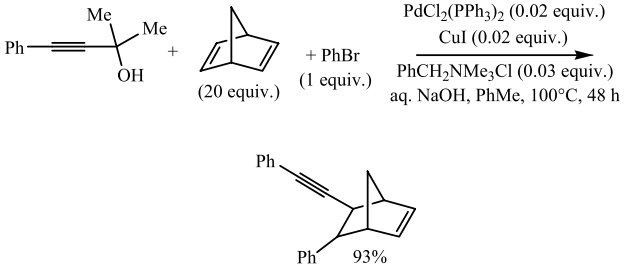
3.1.3. Propargylic alcohols. The Pd-catalysed reaction of tertiary propargylic alcohols with aryl halides, in a basic medium under phase-transfer conditions (Eq. 18),[54–56] involves the cleavage of the C–CR_2OH bond. Although this cleavage can be explained by a mechanism similar to that shown in Scheme 4, it should be noted that the base can mediate such a cleavage, with elimination of $R_2C{=}O$, in the absence of any metal catalyst.[57–60] The equivalence of tertiary propargylic alcohols with terminal acetylenes has been used for three-component coupling reactions (Eqs. 19 and 20).[61–64]



(18)

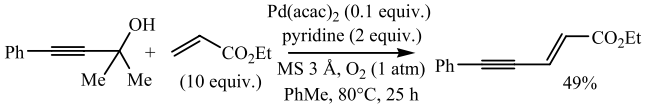


(19)



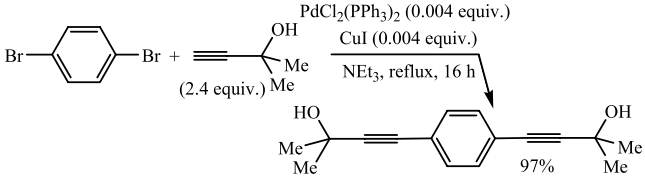
(20)

In a non-aqueous medium, Uemura et al. obtained conjugated enynes from the coupling between substituted tertiary propargylic alcohols and alkenes (Eq. 21); these couplings require the presence of the metal catalyst, oxygen and pyridine, and their efficiencies depend highly on the nature of the catalyst ($Pd(acac)_2 > Pd(OAc)_2 \gg PdCl_2$).[65,66]

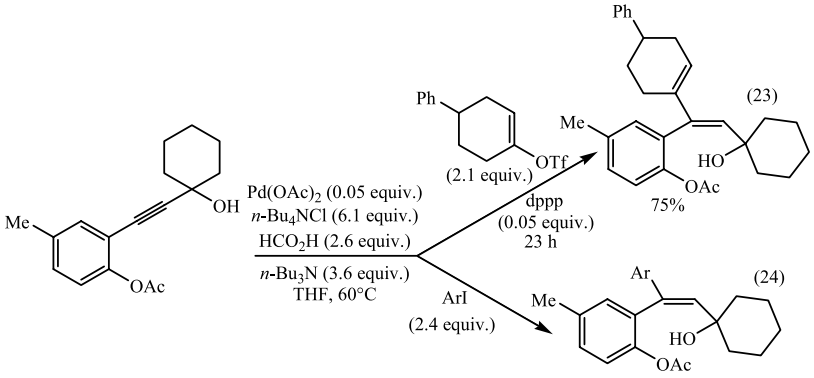


(21)

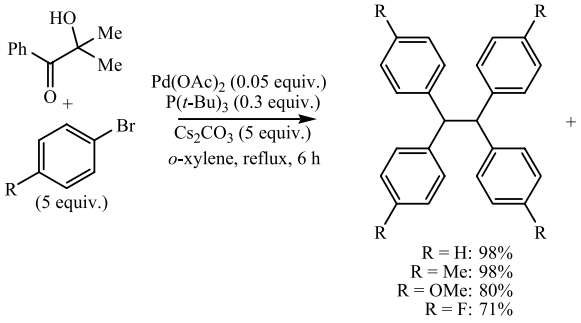
It is necessary to note that the cleavage reactions of tertiary propargylic alcohols under Pd catalysis are not general (Eqs. 22–24 for examples),[67–69] but require particular conditions such as those depicted in Eqs. 18–21.



(22)



3.1.4. α-Ketols. Successive C–C and C–H bond cleavages have been observed by Miura et al. in the course of the reaction of 2-hydroxy-2-propiophenone with aryl bromides (Eq. 25). According to the authors, the mechanism is not clear; the sequence illustrated in Scheme 6 is, nevertheless, in harmony with a set of experiments carried out using 1-hydroxy-1,1,3-triphenyl-2-propanone (Eq. 26), 1-benzoyl-1-hydroxycyclohexanone (Eq. 27) or benzil as substrates.[70]



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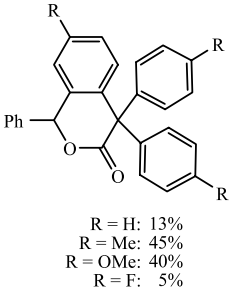
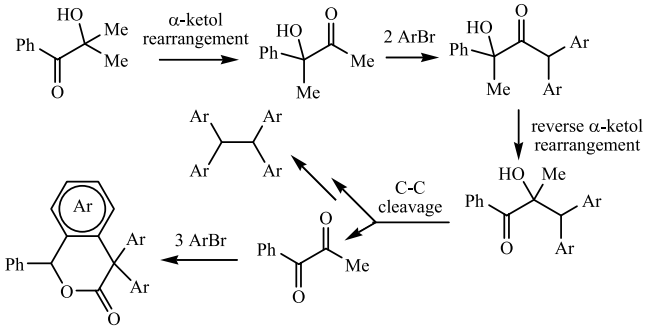
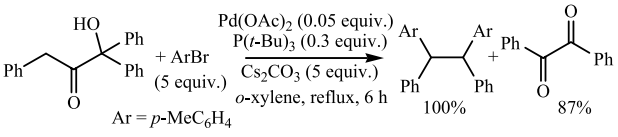
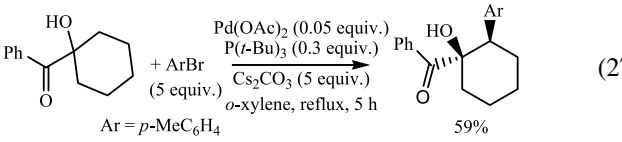




Scheme 6.



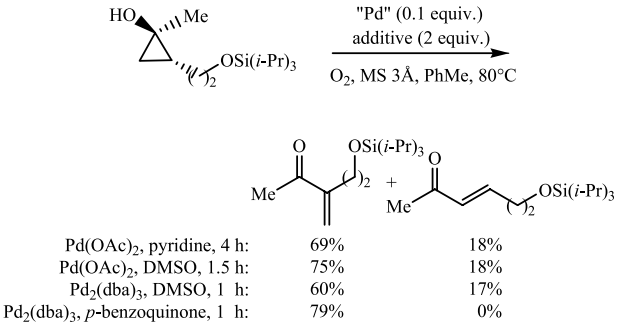
(26)



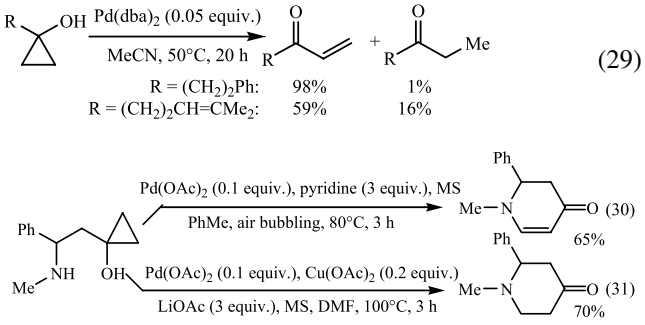
(27)

3.2. Cyclanols

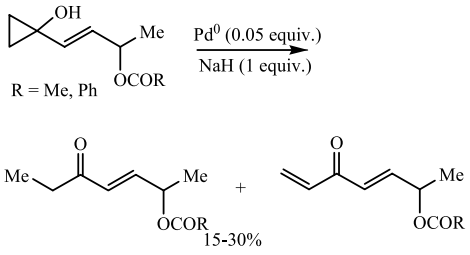
3.2.1. Cyclopropanols. The teams of Cha and Okumoto have independently described the ring cleavage of various tertiary cyclopropanols, affording enones. Both teams proposed the insertion of palladium into the O–H bond as the first step, but Cha et al. assumed that this insertion is achieved by Pd^{II} and they carried out the reactions in the presence of potential re-oxidants of Pd^0 (Eq. 28),[71] while the best results of Okumoto et al. were obtained with a Pd^0 catalyst in the absence of any additive (Eq. 29).[72] Using β-aminocyclopropanols as substrates, Brandi et al. took advantage of the transformation of cyclopropanols into enones to carry out domino reactions leading to either 2,3-dihydro-1*H*-pyridin-4-ones (Eq. 30) or tetrahydropyridin-4-ones (Eq. 31), the evolution of the enone intermediate towards the Wacker-type reaction (Eq. 30) or the aza-Michael addition (Eq. 31), depending on the reaction conditions.[73]



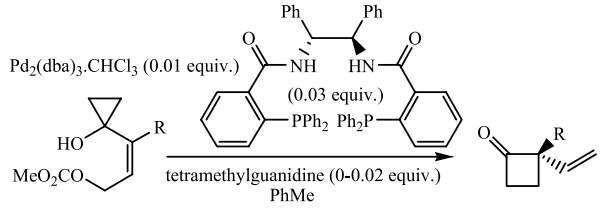
(28)



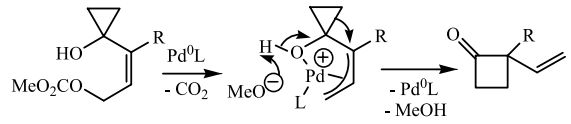
Although, de Meijere, Salaün and co-workers expected a C-3→C-4 ring expansion of esters of (*E*)-4-(1-hydroxycyclopropyl)-but-2-en-1-ol by treatment with a Pd^0 catalyst and 1 equiv of NaH, they only obtained polymers and low yields of a 1:1 mixture of conjugated enones and dienones (Eq. 32).[74] The formation of these ring-opened products is similar to Okumoto's results depicted above (Eq. 29) and reported ten years later.[72] In the absence of base, Salaün et al. observed that the use of the optically active (1-hydroxycyclopropyl) allylic carbonate led to the partially racemised enone and dienone, implying the reversible coordination of palladium to the allyl carbonate moiety.



Subsequently, Trost et al. obtained efficient asymmetric C-3→C-4 ring expansions of 1-(1-substituted-3-methoxycarbonyloxy-1-propenyl)cyclopropanols, in particular in the presence of catalytic amounts of tetramethylguanidine (Eq. 33).[75]

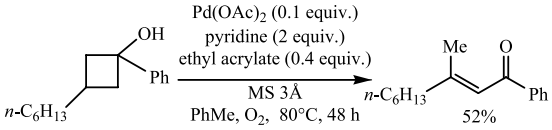


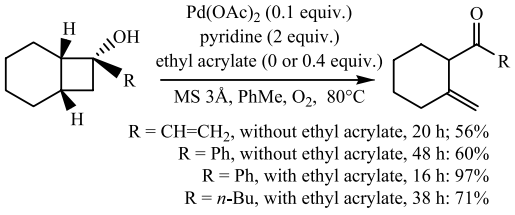
Having not cited the paper[74] of Salaün and co-workers, Trost et al. did not make a comparison between the two studies. In contrast to the teams of de Meijere and Salaün, Trost et al. used substrates having a disubstituted sp^2 carbon in the α-position of the cyclopropanol, and a cis-relationship between the cyclopropanoyl unit and the leaving group. Therefore, we suggest that the Wagner-Meerwein rearrangement[75] is promoted by this disubstitution, which provides a tertiary migration terminus, and also by the cis-relationship, which could facilitate the O–H bond cleavage, owing to the easier coordination of the hydroxy group to palladium, as illustrated in Scheme 7.

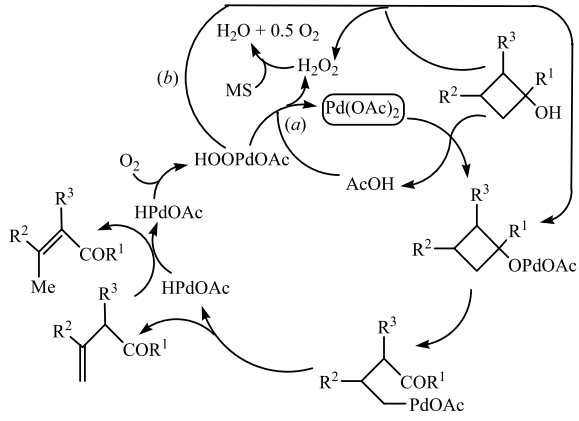


Scheme 7.

3.2.2. Cyclobutanols. The Pd-catalysed oxidative cleavage of *tert*-cyclobutanols can generate α,β- or β,γ-unsaturated ketones (Eqs. 34 and 35); ethyl acrylate, as additive, often increases the efficiency of the transformation, but its role remains unclear.[76,77] These reactions involve a C–C bond cleavage, an HPd elimination and the possible regeneration of the active species following paths a or *b* of Scheme 8;[66] the formation of Pd^0 from HPdOAc and its oxidation to Pd^{II} by oxygen under these experimental conditions is another possibility (see Refs. 1, 78 and 79 and Scheme 10 below).

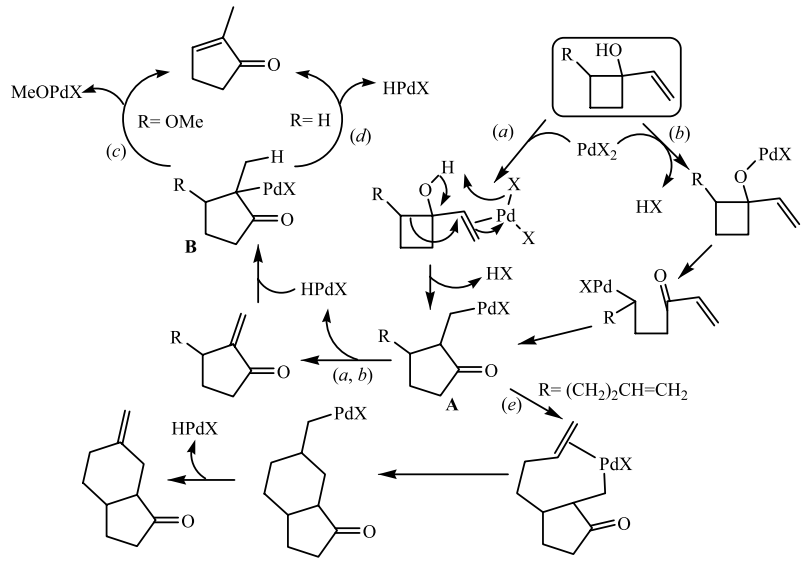




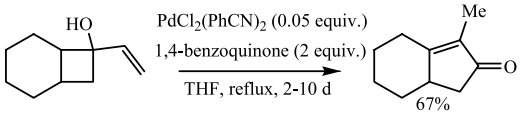


Scheme 8.

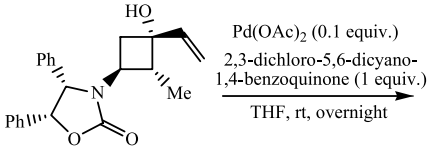
Instead of cleavage products, 1-vinyl-1-cyclobutanols can afford ring-expansion compounds, the recycling of the active Pd species being assumed by 1,4-benzoquinone (Eq. 36),[80,81] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Eq. 37),[82] oxygen (Eq. 38)[77] or $copper^{II}$ salts.[81,83] The first step of these reactions would be either the coordination of the double bond to palladium (Scheme 9, path a),[77,80,82] or the formation of an alkoxypalladium complex (Scheme 9, path b).[77] The same $PdCl_2$-catalysed ring expansion has been obtained from trimethylsilyl ethers of 1-vinyl-1-cyclobutanols,[84] the deprotection of the silyl ether being in situ Pd mediated.[85]



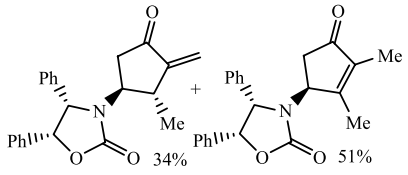
Scheme 9.

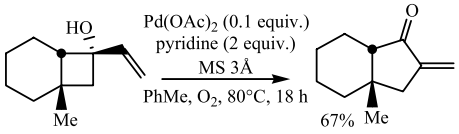


(36)



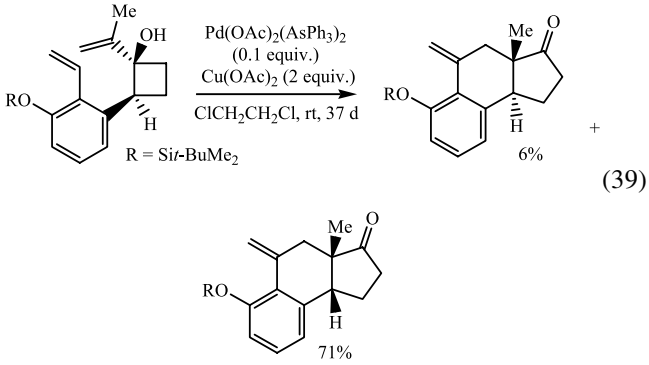
(37)





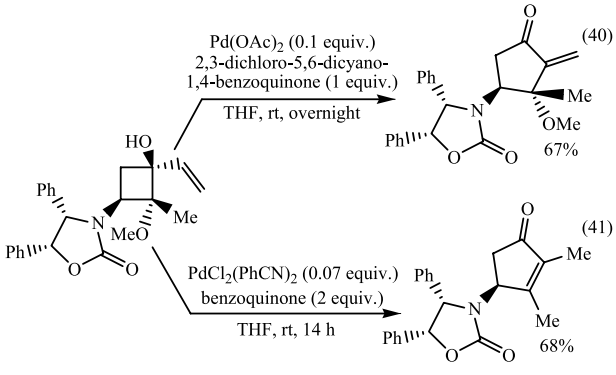
(38)

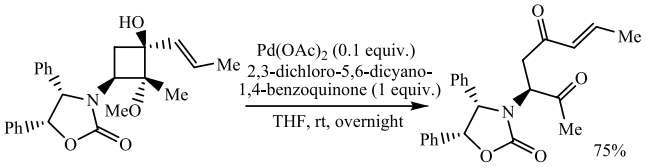
With 1-isopropenyl-1-cyclobutanols bearing a chain with a C=C double bond in a position suitable for coordination to the alkylpalladium intermediate **A** (Scheme 9), a cascade reaction can afford benzo- and naphthohydrindans as reported by Nemoto et al. using either stoichiometric amounts of Pd^{II},[86] or catalytic conditions (Scheme 9, path e; Eq. 39).[87]



(39)

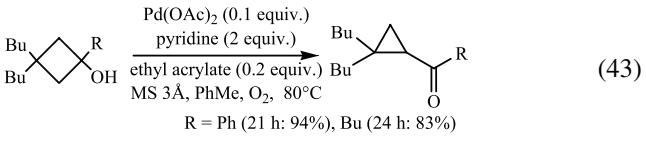
When the 1-vinyl-1-cyclobutanol is 2-substituted by a methoxy and a methyl group, the course of the reaction depends on the initial catalyst: $Pd(OAc)_2$ produces the desired ring-expansion compound (Eq. 40), while, with $PdCl_2(MeCN)_2$, the palladium intermediate **B** evolves towards the cyclopentenone through a β-MeO elimination instead of a β-H elimination (Scheme 9, path c instead of *d*; Eq. 41).[82] The exchange of the vinyl by the 1-propenyl group affords an acyclic diketone instead of the ring-expanded product (Eq. 42).[82]



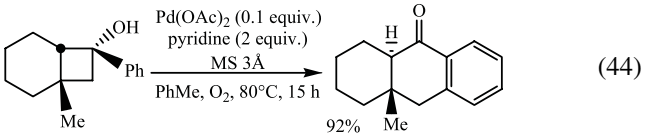


(42)

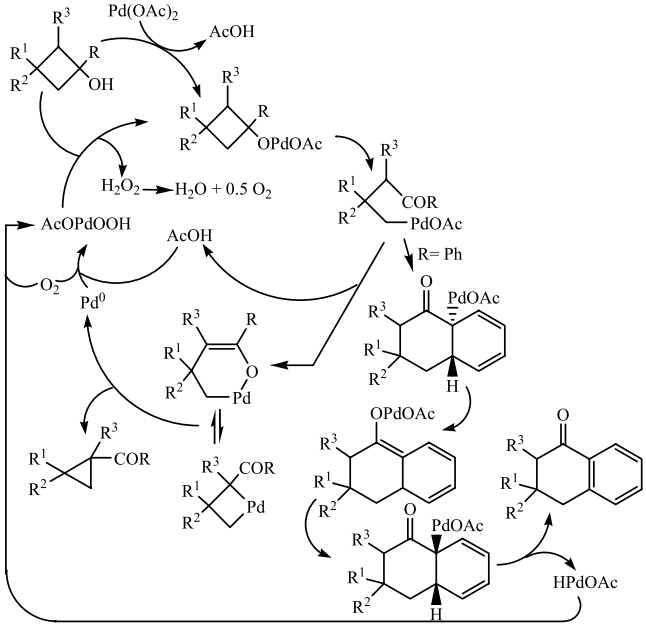
The alkylpalladium intermediates obtained from the C–C bond cleavage of 3-disubstituted *tert*-cyclobutanols have no available hydrogen for a β-H elimination; they suffer either a ring-contracting reaction (Eq. 43), or a ring-expansion process via an intramolecular reaction with a phenyl group (Eq. 44),[77] as shown in Scheme 10.[66,88]



(43)

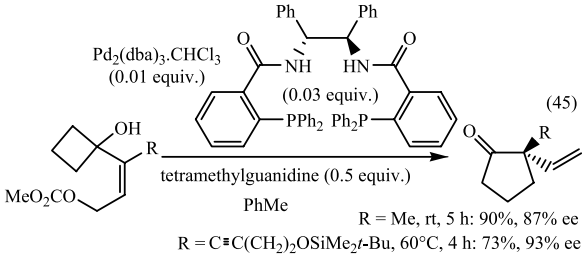


(44)



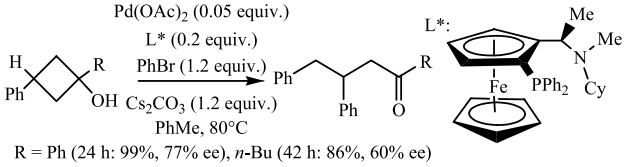
Scheme 10.

Using the procedure for the C-3→C-4 ring expansions of 1-(1-substituted-3-methoxycarbonyloxy-1-propenyl)cyclopropanols (Eq. 33), Trost et al. obtained Pd^0-catalysed efficient asymmetric C-4→C-5 ring expansions of 1-(1-substituted-3-methoxycarbonyloxy-1-propenyl)cyclobutanols (Eq. 45).[75]



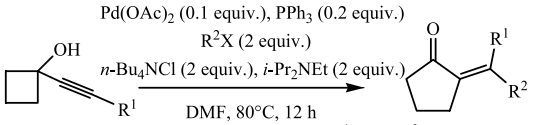
(45)

The reaction of *tert*-cyclobutanols with arylating, vinylating or allenylating reagents provides γ-substituted ketones.[89] Optically active adducts (Eq. 46)[90,91] and the kinetic resolution of racemic tertiary cyclobutanols[66,88,92] have been obtained in the presence of homochiral ligands.

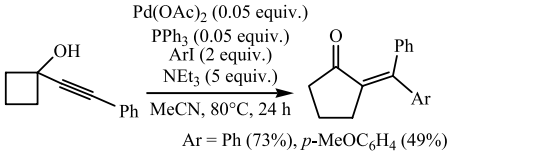


(46)

Larock et al. have synthesised 2-alkylidenecyclopentanones from the reaction between 1-(1-alkynyl)cyclobutanols and aryl iodides, vinyl iodides or triflates (Eq. 47), the use of phenyl triflate failing to produce the expected cyclopentanone.[93,94] Such a reaction with aryl iodides was subsequently rediscovered by Wu et al. (Eq. 48).[95,96] According to both teams, the cleavage of a C–C bond of the cyclobutane is subsequent to the carbopalladation of the triple bond (Scheme 11).[93–95]



(47)



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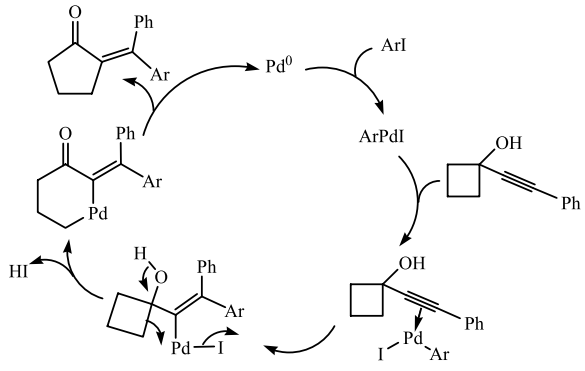
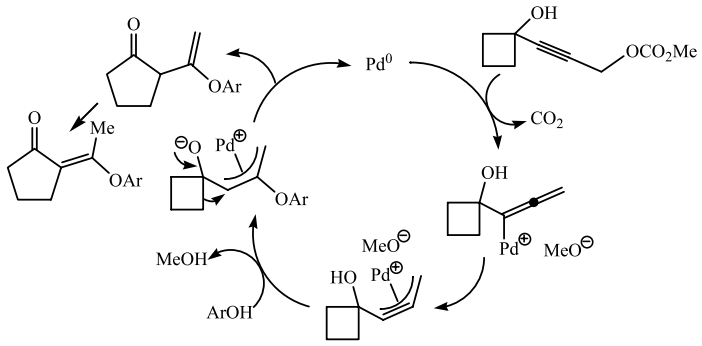
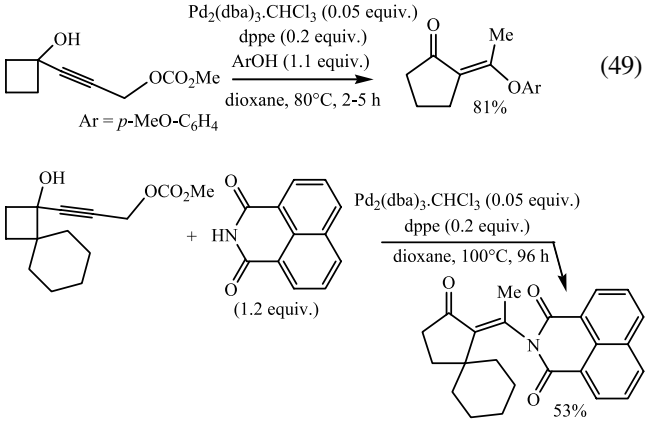


Scheme 11.



Scheme 12.

When the triple bond of the propargylic cyclobutanol is substituted by the CH_2OCO_2Me group, the reaction at 80 °C with phenols (Eq. 49)[97,98] or imides (Eq. 50)[98] occurs firstly at the level of the propargylic carbonate moiety, and is followed by the ring expansion (Scheme 12).[98] Such a domino reaction occurs also between *p*-methoxyphenol and the acetate or benzoate of 1-(3-hydroxy-1-propynyl)cyclobutanol-2-spirocyclohexane, provided that DBU is added into the reactive mixture (Eq. 51).[98] With 1-(3-bromo-1-propynyl)cyclobutanol-2-spirocyclohexane as substrate, the domino reaction is inefficient with *p*-methoxyphenol, but takes place with methanol, ethanol or benzyl alcohol, using catalytic amounts of the corresponding sodium alcoholates, and $Pd(PPh_3)_4$ rather than $Pd_2(dba)_3 \cdot CHCl_3$/dppe, as the catalyst (Eq. 52).[98]



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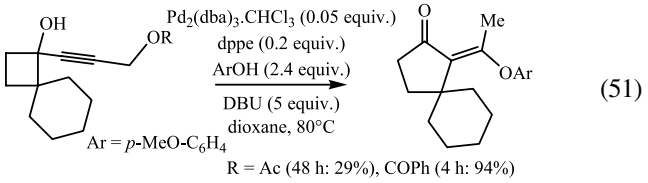
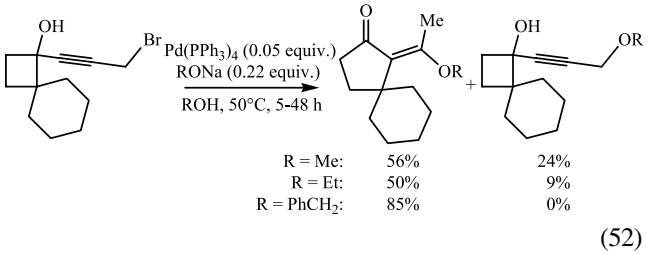
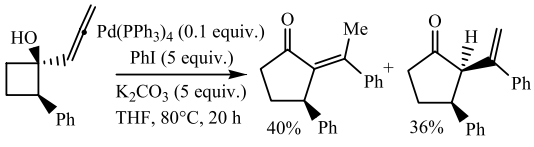


(51)

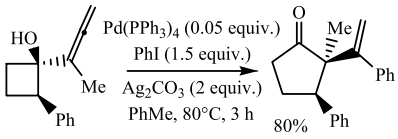


(52)

Yoshida et al. have synthesised α-substituted cyclopentanones (Eqs. 53 and 54) via the addition of in situ-formed arylpalladium^{II} complexes to the allene unit of allenylcyclobutanols. This addition leads to an η^3-allylpalladium intermediate, and its rearrangement affords the ring-expansion products (Scheme 13).[99–102] The intramolecular version of this domino reaction has also been studied (Eq. 55).[99] It should be noted that, after an analogous addition to the allenyl moiety of 3-hydroxy-3-(1,2-alkadienyl)-2-azetidinones, cleavage of the C–COH bond does not occur (see Eqs. 134 and 135 in Part C[3]).[103]



(53)



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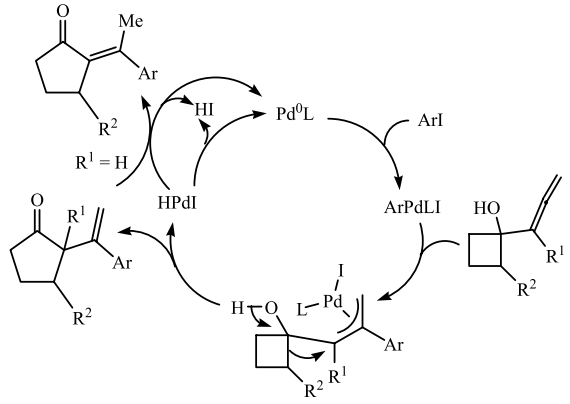
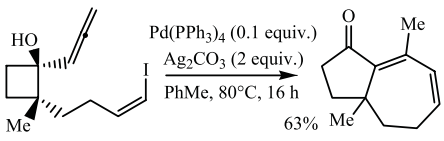
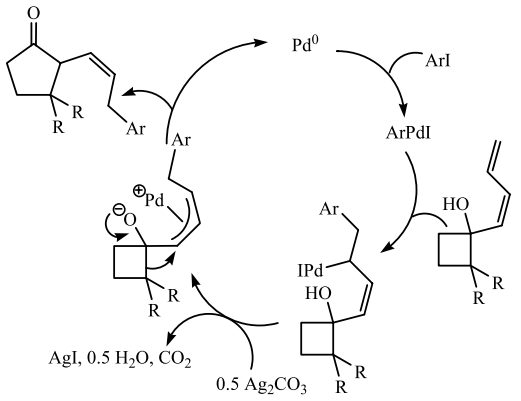


Scheme 13.



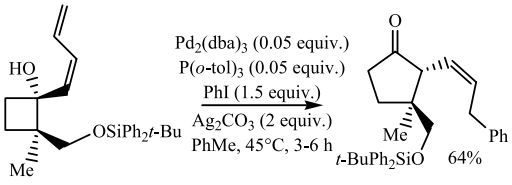
(55)

For the cascade ring-expansion process leading to (*Z*)-2-(3-aryl-1-propenyl)cyclopentanones from the reaction of (*Z*)-1-(1,3-butadienyl)cyclobutanols with aryl iodides (Eq. 56), Yoshida et al. have proposed the simplified mechanism depicted in Scheme 14, and suggested that the specificity of the reaction is chelation



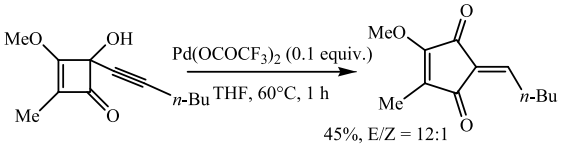
Scheme 14.

controlled through the coordination of the hydroxy group to palladium intermediates.[104]

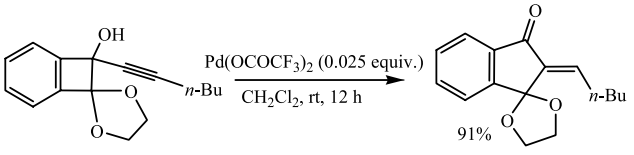


(56)

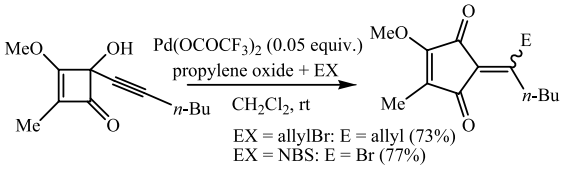
3.2.3. Cyclobutenols. Liebeskind et al. disclosed $Pd(OCOCF_3)_2$-catalysed ring expansions of 4-alkynyl-4-hydroxycyclobutenone systems, leading to 4-oxygenated 5-alkylidenecyclopentenones (Eq. 57) and 3-oxygenated 2-alkylideneindanones (Eq. 58).[105,106] The addition of propylene oxide to quench the in situ-produced $HOCOCF_3$ allows the trapping of the vinylic palladium intermediate with allyl bromide or NBS (Scheme 15), rather than with $HOCOCF_3$, and thus, affords the tetrasubstituted alkylidene adducts (Eq. 59).[105,107]



(57)

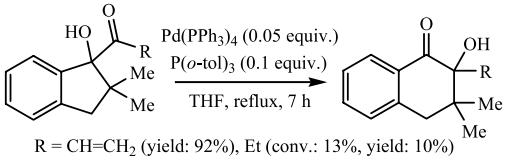


(58)



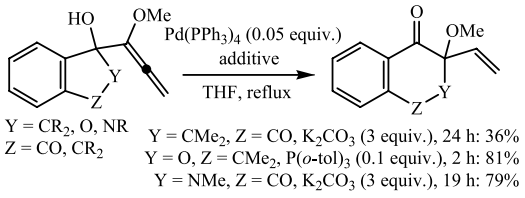
(59)

3.2.4. Other cyclanols. The ring expansion of 1-hydroxy-2,2-dialkyl-1-propenoylindans has been reported by Nagao et al. who have shown the importance of the C=C bond in the conjugated propenoyl moiety on the efficiency of the process, the reaction of 1-hydroxy-2,2-dialkyl-1-propanoylindans being sluggish (Eq. 60).[108,109]

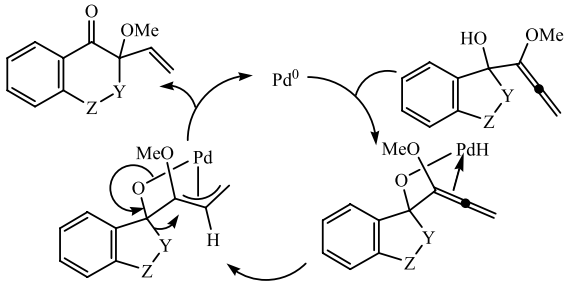


(60)

The ring expansion of hydroxy-methoxyallenyl compounds (Eq. 61), performed by Nagao et al. would occur from the η^3-allylpalladium obtained by the intramolecular hydropalladation of the allenyl moiety (Scheme 16).[110]

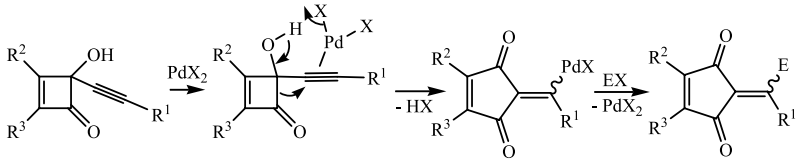


(61)

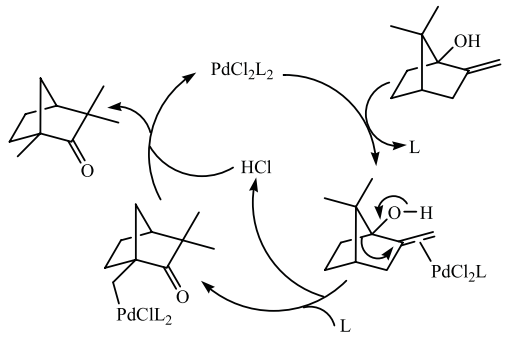


Scheme 16.

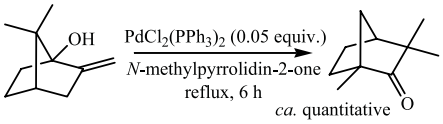
Martínez et al. disclosed the effective synthesis of fenchone, via the Wagner-Meerwein rearrangement of 7,7-dimethyl-2-methylenenorbornan-1-ol (Eq. 62). According to the authors, the initial formation of an η^2-palladium complex is the key step of this ring expansion (Scheme 17).[111]



Scheme 15.

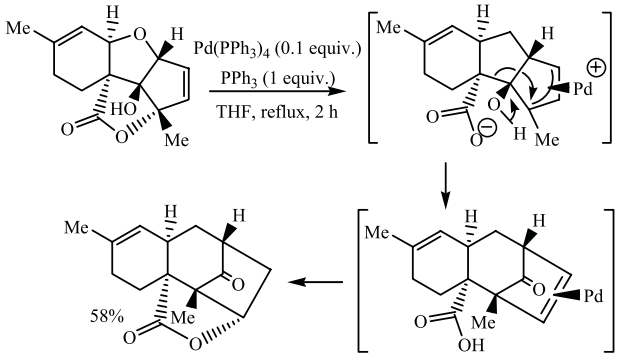


Scheme 17.



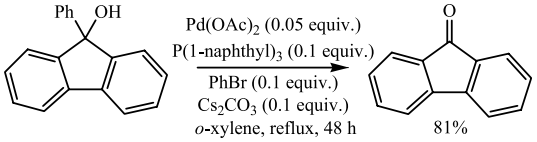
(62)

White et al. reported a Pd-assisted Cargill rearrangement,[112] which would occur from the η^3-allylpalladium intermediate obtained via cleavage of a lactone unit (Scheme 18).[113]

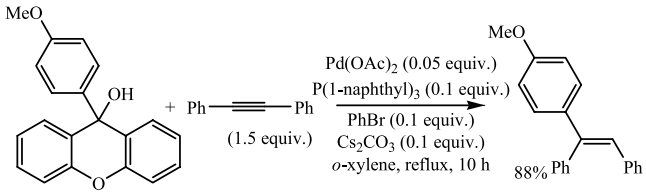


Scheme 18.

The dehydroarylation of triarylmethanols and the trapping of the arylpalladium intermediates summarised in Section 3.1.2. (Eqs. 15–17 and Scheme 5) has also been documented from (hetero)cyclanols of this type (Eqs. 63 and 64).[53]



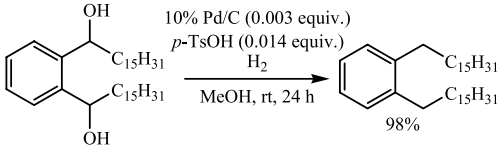
(63)



(64)

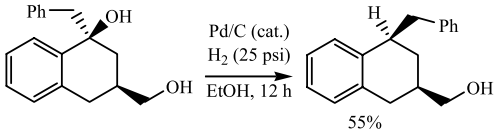
4. Hydrogenolysis

The heterogeneous Pd-catalysed cleavage of the C–OH bond of benzylic alcohols is a common reaction carried out under a hydrogen atmosphere using MeOH,[114–121] EtOH[122,123] or EtOAc[124,125] with, sometimes, the addition of a small amount of an acid (Eq. 65),[116,117,119,124,126] or using AcOH[126] and even aqueous HCl as solvent,[127] and with mainly Pd/C as catalyst, but also Pd/$CaCO_3$[123] or Pearlman's catalyst.[128] Other hydrogen sources such as formic acid have been used.[6,129]

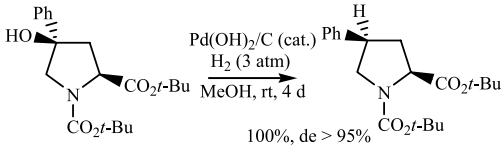


(65)

The hydrogenolysis proceeds usually with inversion at the carbon centre (Eqs. 66 and 67),[114,116,123,128] this inversion being sometimes incomplete.[115,117,124] From the report of McQuillin et al.[126] the mechanism of the inversion is tentatively depicted as illustrated in Scheme 19.

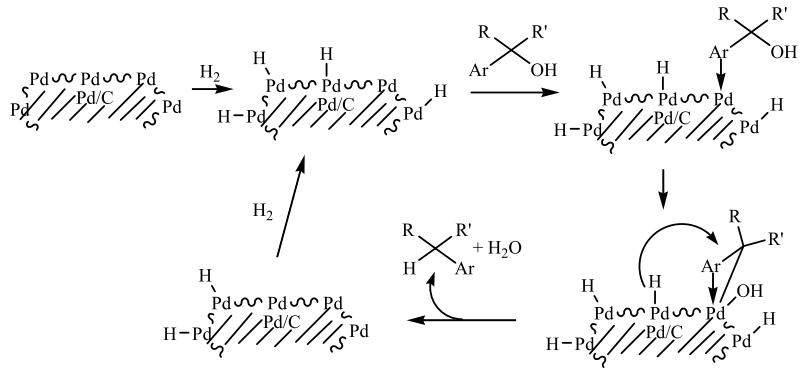


(66)



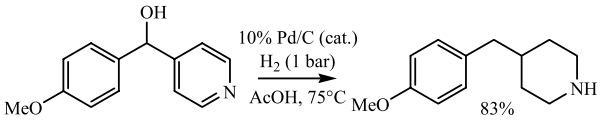
(67)

As the Pd/C-catalysed hydrogenolysis of benzylic alcohols is an efficient process, it can be difficult to stop the reduction of aryl ketones with Pd/C and hydrogen at the level of the



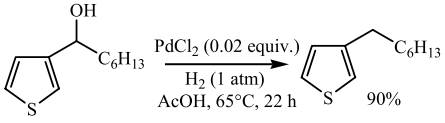
Scheme 19.

alcohol.[118,130–134] Besides, the hydrogenolysis of aryl(pyridin-2-yl)- and aryl(pyridin-4-yl)methanols can lead to the concomitant hydrogenation of the heteroaromatic ring (Eq. 68).[133]



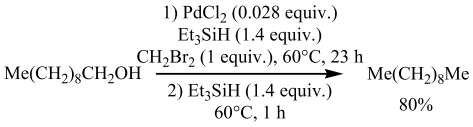
(68)

Various experimental conditions have been tested by Lemaire et al. for the Pd-catalysed hydrogenolysis of 3-(1-hydroxy)-heptylthiophene, and the best results have been obtained with $PdCl_2$ in acetic acid (Eq. 69).[135]



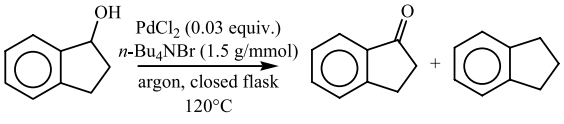
(69)

$PdCl_2$-catalysis has also been used for the one-pot conversion of alcohols to alkanes with triethylsilane and either iodomethane or dibromethane (Eq. 70). Under these conditions, the alcohol is transformed into the corresponding halide (Eq. 173 in Section 8.4), and the halide leads to the alkane.[136]



(70)

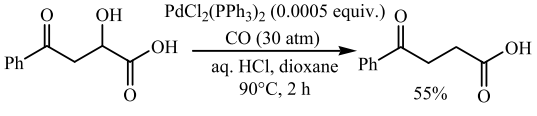
Since the Pd-catalysed dehydrogenation of benzylic alcohols produces the corresponding ketones, but also hydrogen, the hydrogenolysis of the starting material is sometimes a side reaction (Eq. 71).[137]



(71)

Allylic alcohols may be deoxygenated under the Pd-catalysed heterogeneous conditions used to hydrogenolyse the benzyl oxygen bond, but the double-bond saturation occurs along with the loss of oxygen.[138]

The hydrogen transfer, from H_2O/CO to γ-keto-α-hydroxycarboxylic acids to give γ-ketoacids, is catalysed by a combination of $PdCl_2(PPh_3)_2$ and hydrochloric acid (Eq. 72), but Toniolo and al. have demonstrated that the substrate is transformed in situ into the corresponding γ-keto-α-chlorocarboxylic acid. Therefore, this reaction involves, in fact, the hydrogenolysis of a C–Cl bond.[139]



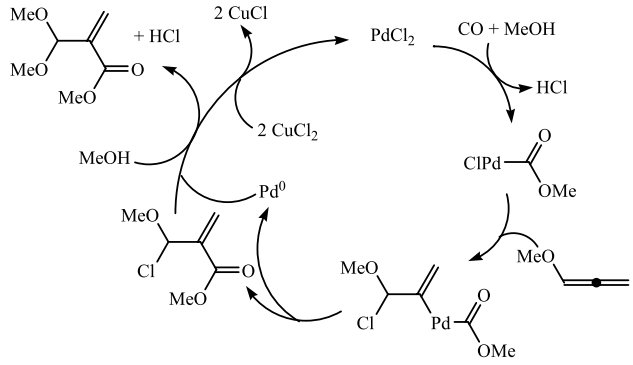
(72)

5. Alcoholysis

5.1. Organic halides

The formation of ethers from the Pd-catalysed alcoholysis of aryl halides has been summarised in Part C, Section 5.[3]

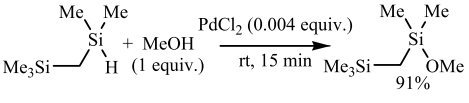
According to Trofimov et al. the $PdCl_2$-catalysed methoxycarbonylation of methoxyallene depicted in Scheme 20 involves the formation of a C–Cl bond and the substitution of the C–Cl carbon centre with MeOH.[140] As this reaction concerns an allylic C–Cl bond, we suspect the the corresponding η^3-allylpalladium complex as an intermediate.



Scheme 20.

5.2. Hydrosilanes

Pd^{II} compounds,[141,142] particularly $PdCl_2$ (Eq. 73 and 74),[143–145] and Pd/C (Eq. 75)[146–148] are commonly used to catalyse the alcoholysis of hydrosilanes. Using optically active organosilicon hydrides and various alcohols, Sommer et al. have shown that Pd/C led to the inversion of the stereogenic heteroatom, while Pd^0 in situ produced from $PdCl_2$ led to a racemic product, this racemisation being greatly reduced with NEt_3 as additive.[146]



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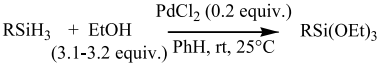
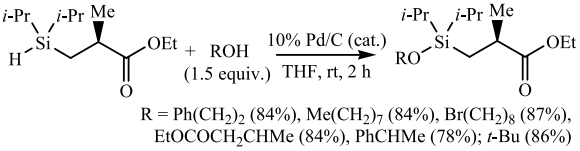


(74)



(75)

Recently, the $PdCl_2$-catalysed alcoholysis of unsaturated hydrosilanes has been carried out with norbornadiene as additive to trap the produced hydrogen,[149] and the silylation of sugars by $HSiMe_2t$-Bu and $HSiPh_3$ has been catalysed by palladium nanoparticles prepared by the reduction of PdX_2 (X=Cl, OAc) with $HSiMe_2t$-Bu, the selectivity depending greatly on the nature of X and on the temperature.[150]

5.3. Silyl ethers

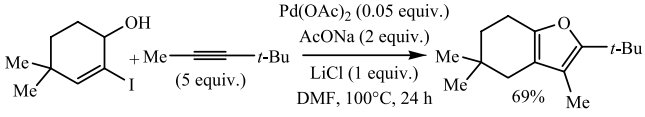
Prunet et al. have assumed that Pd/C catalyses the cleavage of alkyl triethylsilyl ethers in methanol or ethanol, even at room temperature, via the Pd-assisted transfer of the silyl group to the alcoholic solvent, and it was briefly mentioned that $Pd(OAc)_2$ as catalyst was less efficient, while the deprotection was very fast with $PdCl_2$.[151,152] This report[151] was in disagreement with a Pd/C-catalysed procedure, published virtually simultaneously by Sajiki et al., which required the presence of hydrogen.[153] Nevertheless, Rokach et al. have, subsequently, carried out the deprotection of alkyl triethylsilyl ethers (and also of alkyl tripropylsilyl ethers) with Pd/C in methanol without hydrogen, the reaction time being much longer than under a hydrogen atmosphere (4.5–73 h instead of 1.3–3.5 min); the same team has also deprotected selectively triethyl-, tripropyl-tributyl- and *t*-butyldimethylsilyl ethers in the presence of *t*-butyldiphenyl- and triisopropylsilyl ethers with Pd/C and hydrogen in methanol.[154] Complementary studies by Sajiki's team have shown a significant supplier-dependence on the catalyst activity of commercial Pd/C, and it was concluded that the cleavage of triethylsilyl ethers in the absence of hydrogen is an acid-catalysed alcoholysis, due to the acidity of some commercial Pd/C catalysts.[155–158]

5.4. Tetrahydropyranyl ethers

As described in Part C[3], the tetrahydropyranylation of alcohols is catalysed by solutions of $PdCl_2(MeCN)_2$ at room temperature (Eq. 86 in Part C).[159] Usually, the reverse reaction did not occur using an alcohol as solvent,[160] and the alcoholysis in the presence of Pd^{II} (Eqs. 212 and 213 in Part C)[161] could be particular cases or uncontrolled reactions.[162] Actually, the cleavage of a THP ether in methanol or ethanol has been observed with a few commercial Pd/C catalysts but, as for the above cleavage of silyl ethers, this was attributed to the acidity of these catalysts.[155,157,163]

5.5. Vinylpalladium complexes

The vinylpalladium intermediates formed from the Heck-type addition of hydroxyvinyl halides to internal alkynes can afford unsaturated heterocycles by ring closure (Eqs. 76 and 77).[165,166]



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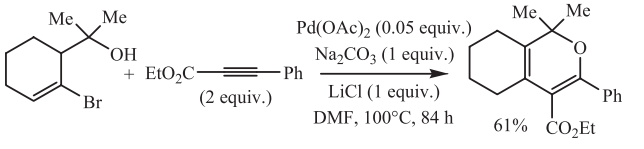
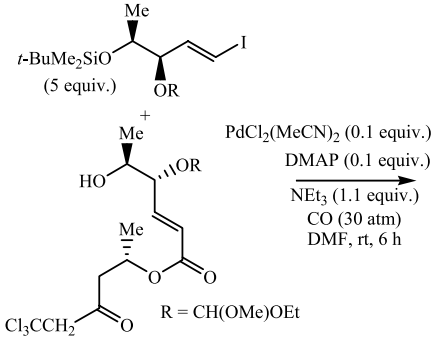


(77)

5.6. Acylpalladium complexes

The acylpalladium complexes are produced from a variety of processes, and the use of an alcohol as the solvent instead of an aprotic solvent may modify the course of a reaction in trapping the acylpalladium intermediate to afford the corresponding ester.[167–172] The synthesis of polyfunctionalised compounds by carbonylative esterification using two polyfunctionalised synthons has been exploited (Eq. 78),[173] and the intramolecular alcoholysis of a variety of acylpalladium intermediates has been intensively reported for cyclocarbonylations to produce carbonates, lactones, butenolides, oxazolidinones and cyclic oxamates;[164,174–192] the examples depicted in Eqs. 79–86 illustrate that various experimental conditions and substrates have been used. Instead of organic solvents, supercritical CO_2 has been used for the intramolecular carbonylation of 2-iodobenzyl alcohol,[193] whereas various ionic liquids and molten salts have been explored as solvents for the butoxycarbonylation of 4-bromoacetophenone, the best result being obtained in tetra-*n*-butylammonium bromide.[194]



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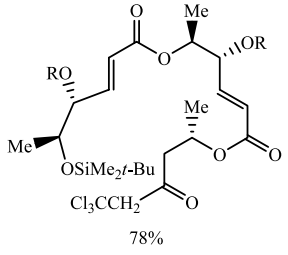

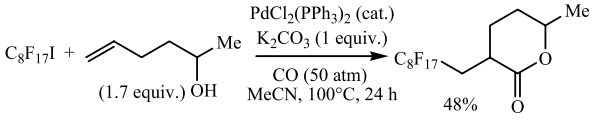

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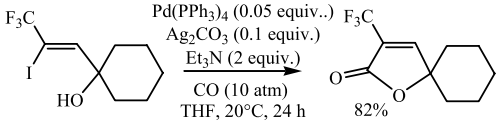

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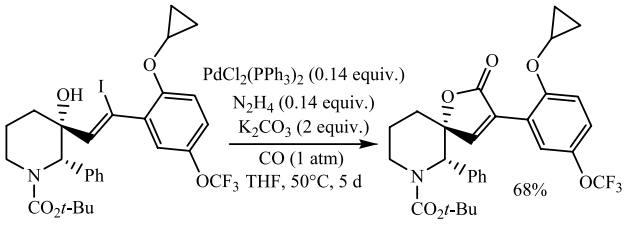

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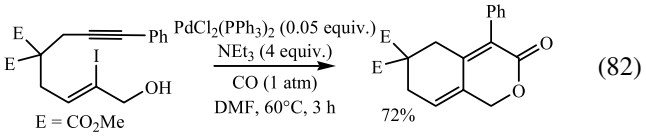

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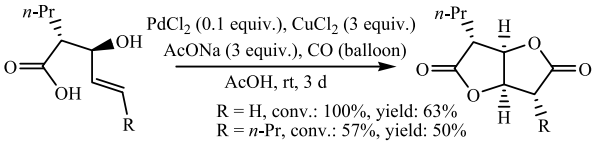

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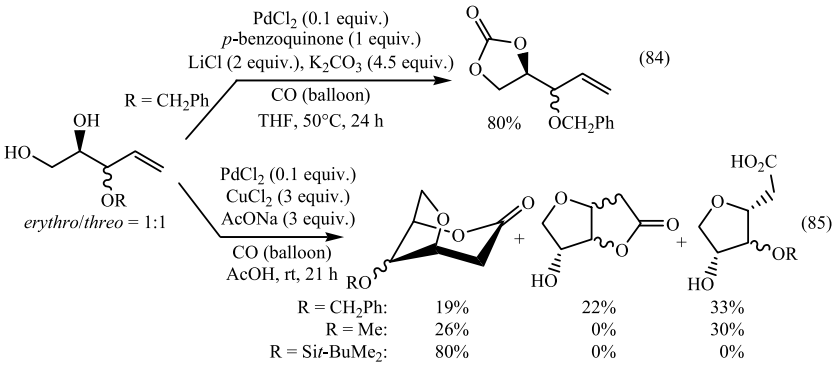

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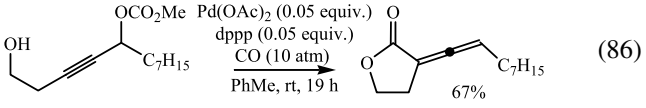
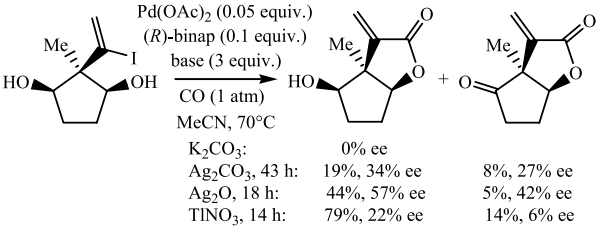


(86)

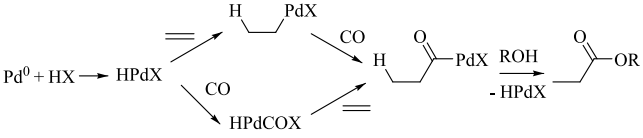
The mechanism of the alcoholysis of acylpalladium complexes is not obvious, as pointed out by Milstein,[195] and conflicting reaction pathways have been proposed, namely, direct attack of ROH or RO^- at the acyl carbon (outer-sphere attack),[196,197] or coordination of these species to the palladium atom as the prerequisite step to alcoholysis.[198] In fact, the mechanism could depend on the nature of the ligands and on the experimental conditions. An important role of the base could be the deprotonation of the hydroxyl to produce the corresponding alkoxide[196] and, in addition, the effect of the nature of the base on the efficiency of enantioselective cyclocarbonylations has been reported (Eq. 87).[199]



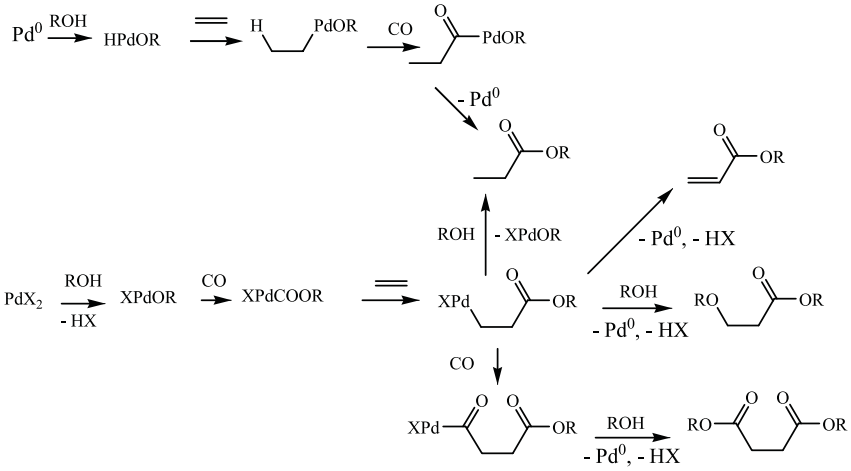
(87)

6. Carbonylation

The Pd-catalysed carbonylations of a mixture of an alcohol and an alkene can lead to various compounds, as summarised in Scheme 21. The mechanism of these reactions has led to numerous debates.[200] The reaction courses seem to be highly dependent on the nature of the catalytic system and the additives.[201] Furthermore, the alkoxycarbonylation of alkenes can, in fact, involve the alcoholysis of the acylpalladum intermediate, as depicted in Scheme 22[202] A variety of carbonylated products is also



Scheme 22.

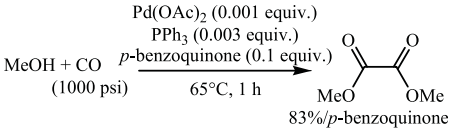


Scheme 21.

produced from the reaction of alcohols with CO and alkynes.[203,204] These intermolecular reactions between alcohols, alkenes or alkynes, and carbon monoxide have led to many reports and mechanistic proposals,[200,205] but this particular topic is out of the scope of the present review. Examples where the unsaturated carbon–carbon bond belongs to a hydroxylated compound have, however, been retained, these are presented in Sections 6.3–6.7.

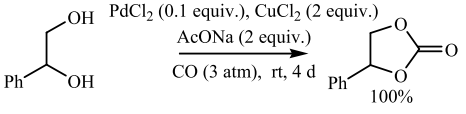
6.1. Alkanols

The Pd^{II}-catalysed carbonylation of saturated alcohols can provide dialkyl carbonates and oxalates (Eq. 88),[206–209] in some cases under electrosynthesis conditions,[210] or with alkyl nitrites associated to oxygen to regenerate the Pd^{II} catalyst.[211] The use of ionic liquids as solvents has been explored for the oxidative carbonylation of methanol to dimethyl carbonate.[212]



(88)

With a 1,2-diol such as 1-phenylethane-1,2-diol, the cyclic carbonate is effectively obtained under Pd^{II}-catalysed conditions and $CuCl_2$ as re-oxidant (Eq. 89), while ethylene glycol as substrate requires a stoichiometric amount of palladium chloride, probably because of the interaction of this diol with $CuCl_2$.[174] Subjecting β-aminoethanols to catalytic conditions may afford selectively oxazolidinones (Eq. 90),[174,184] a mixture of oxazolidinone and carbonate being obtained from 1-(*N*-phenylamino)propane-2,3-diol (Eq. 91).[174]



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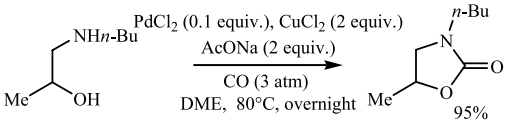

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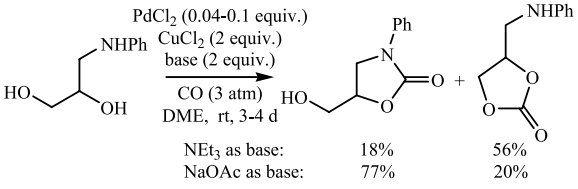
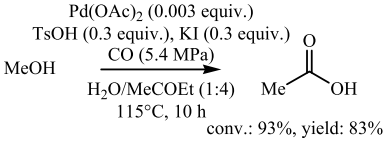


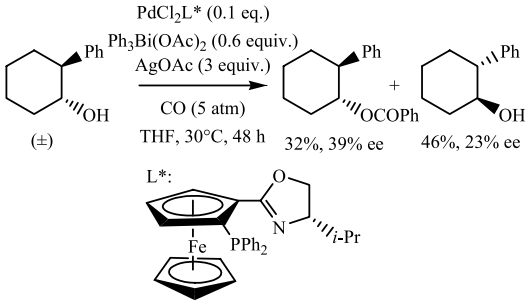
(91)

The formation of acetic acid from the Pd-catalysed carbonylation of methanol in an aqueous medium is promoted by iodides (Eq. 92). Methyl acetate can also be obtained, the selectivity depending on the reaction conditions.[213,214]



(92)

The use of carbon monoxide, a triphenylbismuth^{V} compound, silver acetate and a Pd^{II} catalyst in THF led to the benzoylation of secondary alcohols, a chiral ligand allowing the kinetic resolution of the alcohol and the enantioselective formation of the benzoate (Eq. 93).[215] The proposed mechanism involves $Pd(OAc)_2L^*$ as the active catalyst, and alcoholysis of a benzoylpalladium intermediate (Scheme 23),[215] but the Sigman and Stoltz Pd^{II}-catalysed oxidative kinetic resolution of alcohols[216] led us to suggest the alternative mechanism depicted in Scheme 24.



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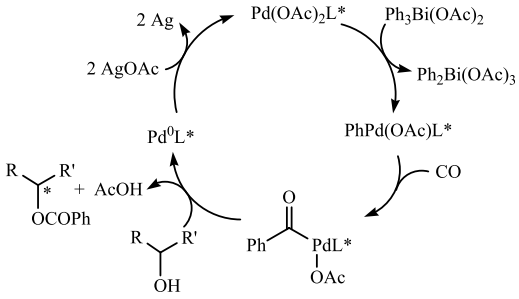
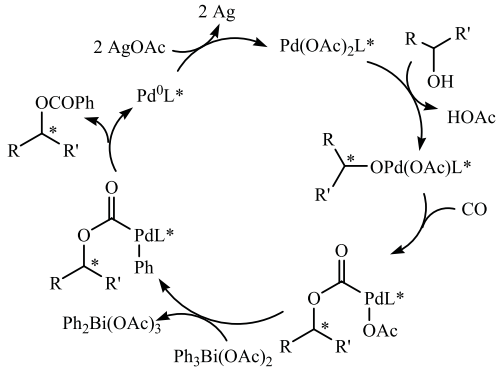


Scheme 23.

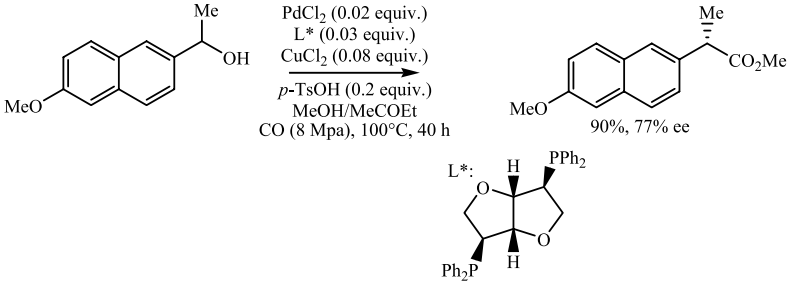


Scheme 24.

6.2. Aryl and heteroaryl methanols

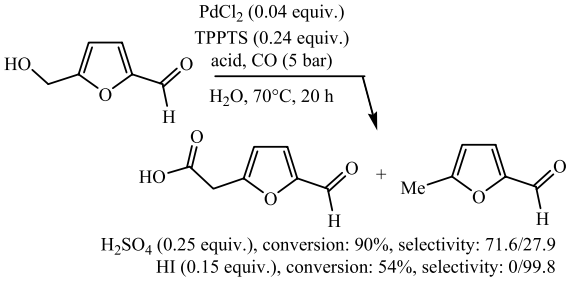
The carbonylation of benzyl alcohol, using catalytic amounts of hydrogen iodide and either a Pd^0 or Pd^{II} complex in an aqueous solvent, affords phenylacetic acid as the main product; a study of the mechanism of this reaction has led to the conclusion that the carbonylation occurs from benzyl iodide, which is produced in situ.[217] The synthesis of 2-arylpropionic acids via the carbonylation of 1-arylethanols using supported Pd catalysts in the presence of phosphine ligands, TsOH and LiCl would also involve the formation of 1-arylethyl chlorides as intermediates.[218]

With the aim of obtaining optically active naproxen, Yin et al. have carried out the carbonylation of 1-(6-methoxy-2-naphthyl)ethanol in the presence of a chiral ligand (Eq. 94).[219] The concomitant formation of traces of the non-branched compound, namely methyl 3-(6-methoxy-2-naphthyl)propanoate, leads us to suspect the occurrence of in situ dehydration of the substrate; in this way, the carbonylation would occur from 2-vinyl-6-methoxy-naphthalene. Such a reaction has also been studied by Henryon et al.[220]



(94)

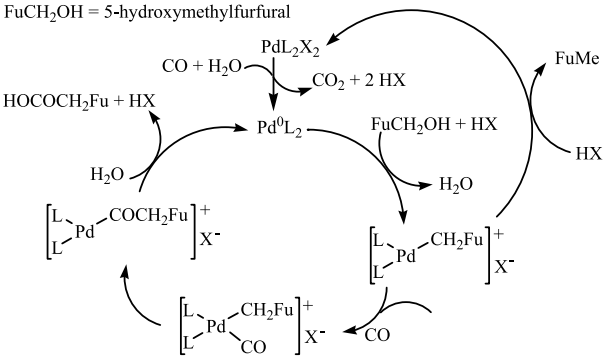
Sheldon et al. have obtained 5-formylfuran-2-acetic acid and/or 5-methylfurfural from 5-hydroxymethylfurfural using CO and a water-soluble Pd^{II} catalyst in an acidic aqueous medium, the reaction course depending on the acid employed (Eq. 95).[221] This process implies the cleavage of the C–OH bond of the substrate, that is, a reaction already reported from secondary alcohols and stoichiometric amounts of $PdCl_2(PhCN)_2$.[222] According to Sheldon et al.,[221] the catalytic cycle of their carbonylation is induced by Pd^0 (Scheme 25).[223] Thus, the proposed mechanistic scheme has some similarities with that of the carbonylation of allylic alcohols leading to unsaturated esters, which occurs via η^3-allylpalladium intermediates (see Section 6.3.).



(95)

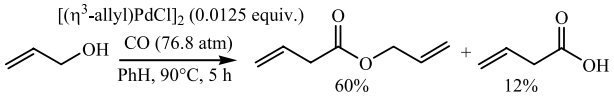
6.3. Allylic alcohols[224]

In 1964, Tsuji et al. reported the $PdCl_2$-catalysed carbonylation of allylic alcohols under various conditions (Eqs. 96–98); in the course of these reactions, the C–OH bond is cleaved and allylpalladium chloride complexes were proposed as intermediates.[225] In fact, the formation of ethyl 3-butenoate from the reaction of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ with CO and EtOH was already known[226] and, consequently,



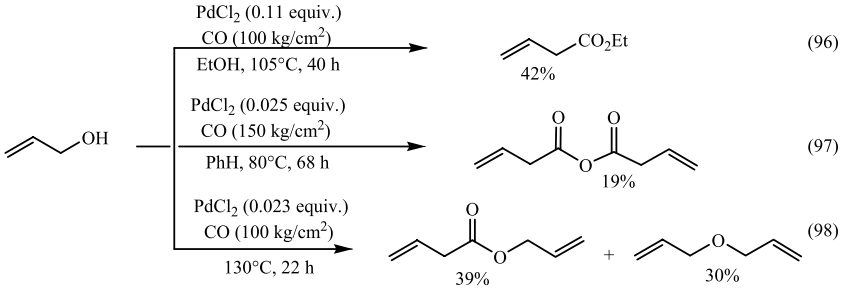
Scheme 25.

bis-(η^3-allylpalladium chloride) has also been used as a catalyst (Eq. 99), it being assumed that the presence of halide was essential.[227]

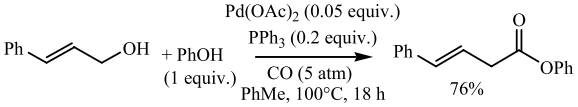


(99)

Such carbonylations of allylic alcohols have been subsequently catalysed not only with $PdCl_2$,[221,228,229] but also with supported $Pd(OAc)_2$[230] or $Pd(PPh_3)_4$[231] usually in association with an alkali-metal halide,[231] tin^{II} chloride,[232] tetrabutylphosphonium chloride[228,229] or a Brönsted



acid[221,230,233,234] and, sometimes, titanium^{IV} isopropoxide.[231] It has been proposed that, with hydrogen chloride as additive, the first reaction is between the substrate and the acid to afford water and the corresponding allylic chloride, this latter species reacting with palladium to give the corresponding η^3-allylpalladium complex.[230] In the presence of alcohols, phenol or thiophenol, the corresponding β,γ-unsaturated esters[232,233] or thioesters[234] are produced (Eqs. 100 and 101).



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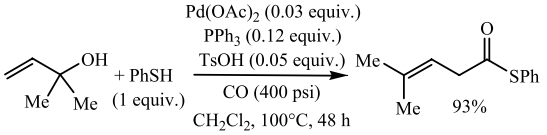
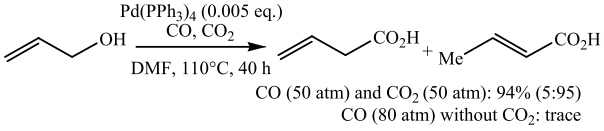


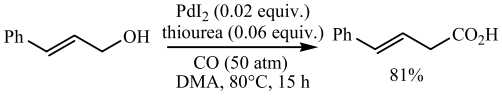
(101)

Yamamoto et al. have observed that carbon dioxide mediates the activation of allylic alcohols towards nucleophilic additions (see Eq. 98 in Part B[2]), and they have used this promoting effect to carry out their carbonylations (Eq. 102). The substrate would be transformed into the corresponding allylic hydrogen carbonate, that leads easily to the cationic η^3-allylpalladium complex, which reacts with CO to afford the unsaturated acids.[235]



(102)

A 3:1 mixture of PdI_2 and thiourea[236] catalyses effectively the carbonylation of a variety of allylic alcohols to afford the unsaturated acids or esters, depending on the solvent (Eqs. 103 and 104).[28]



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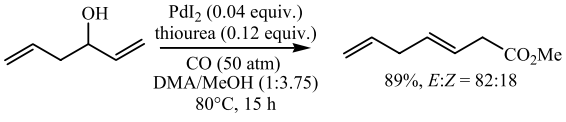
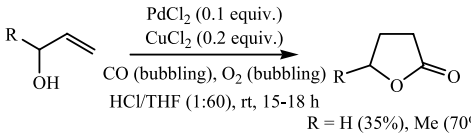


(104)

By bubbling both carbon monoxide and oxygen into acidic solutions of allylic alcohols containing catalytic amounts of both $PdCl_2$ and $CuCl_2$, Alper et al. have synthesised lactones (Eq. 105),[237] the addition of chiral ligands resulting in the enantioselective lactonisation of but-2-en-1-ol.[238] This Canadian team has also obtained γ-buyrolactones with a Pd^0 catalytic system, but at higher reaction temperatures and pressures, and only from terminal secondary or tertiary allylic alcohols (Eq. 106), allyl alcohol leading to crotonic acid (93% yield), while no reaction occurred with 3-penten-2-ol as substrate.[239] In contrast to the carbonylations illustrated in Eqs. 96–104, the lactonisations do not involve cleavage of the C–OH bond. For the two above lactonisation procedures, Alper et al. suggest the insertion of carbon monoxide into an alkoxypalladium complex.[238–240]



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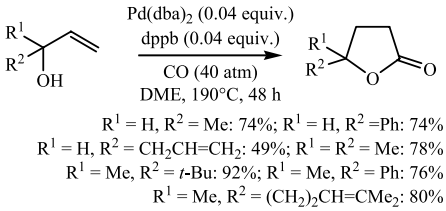
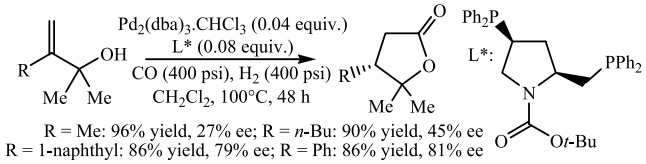


(106)

Alper et al. have also performed the carbonylation of β-substituted tertiary allylic alcohols, leading to optically active lactones, using an atmosphere of CO and H_2 and a chiral Pd catalyst (Eq. 107), a primary alcohol such as 2-phenyl-2-propen-1-ol being fully recovered under the experimental conditions.[241] According to the authors, the mechanism of this reaction is unclear; a hydridopalladium complex was nevertheless assumed to be the active species, because a hydride source was required to obtain an effective transformation.[242] The reaction of this complex with the double bond would be followed by insertion of CO and trapping of the resultant acylpalladium by the hydroxyl to produce the γ-butyrolactone (Scheme 26). Therefore, this reaction would be more relevant to those discussed in Section 5.6. Soon afterwards, Alper's team reported the cyclocarbonylation of β,γ-substituted primary or secondary allylic alcohols using again a CO/H_2 atmosphere (Eq. 108). This reaction, which was mediated by Pd^{II} and Pd^0 catalysts associated to dppb as ligand, was dependent on the structure of the substrate, the corresponding alkene or the β,γ-unsaturated carboxylic acid being formed in a few cases.[243]



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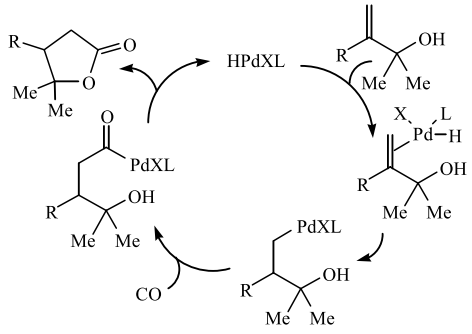
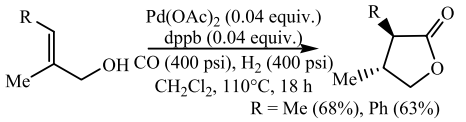
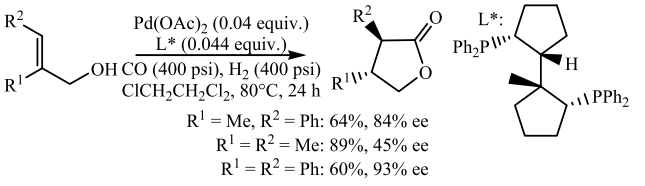


Scheme 26.



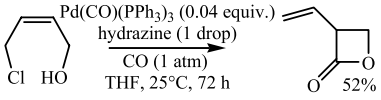
(108)

Subsequently, Zhang et al. using the CO/H_2 cyclocarbonylation methodology with new chiral ligands, observed that the formation of optically active lactones was efficient, not only from β-substituted tertiary allylic alcohols, but also, from β,γ-substituted primary allylic alcohols (Eq. 109).[244]

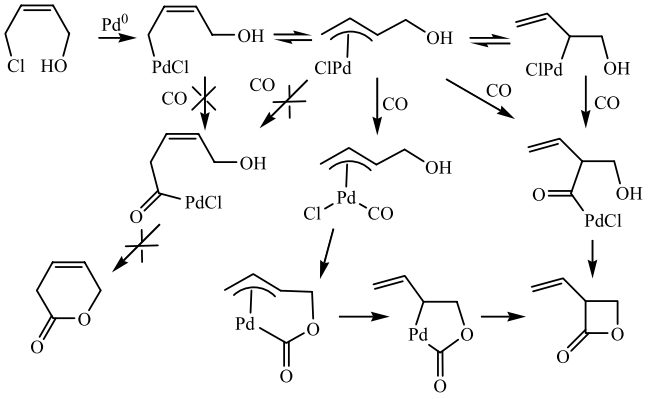


(109)

A rather intriguing mechanism concerns the carbonylation of (*Z*)-4-chloro-but-2-en-1-ol, which produces a β-lactone instead of the expected δ-lactone (Eq. 110).[175b] According to Stille et al.[175b] the first step is the insertion of palladium into the C–Cl bond, but this is not followed by reaction with CO. Carbon monoxide would react after the formation of the η^3-allylpalladium and two reactive pathways have been proposed, that is, either formation of a secondary, rather than a primary, C–COPd bond from this complex, followed by alcoholysis, or attack of the hydroxyl to a coordinated molecule of CO, to afford a five-membered palladacycle, leading to the lactone through the reductive elimination of palladium (Scheme 27).



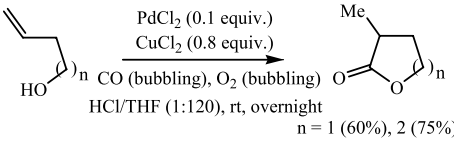
(110)



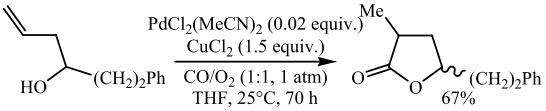
Scheme 27.

6.4. Other alkenols

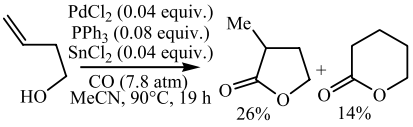
Using a procedure established for the carbonylation of allylic alcohols (Eq. 105), Alper et al. have obtained five- and six-membered ring lactones from unconjugated alkenols (Eq. 111).[240,245] In fact, the $PdCl_2$ catalyst led to γ-butyrolactones from homoallylic alcohols, even without HCl, provided that $CuCl_2$ was present in excess, as shown by Inomata et al. (Eq. 112)[246] using a procedure disclosed for the alkoxycarbonylation of terminal olefins,[247] while Norton et al. have briefly reported the formation of a mixture of γ- and δ-valerolactones from 3-buten-1-ol and the $PdCl_2/SnCl_2/2\ PPh_3$ catalytic system, without oxidant of palladium, but at a higher temperature and pressure of CO (Eq. 113).[248] This latter system has been used for the synthesis of ε-caprolactone from 4-penten-1-ol.[249]



(111)

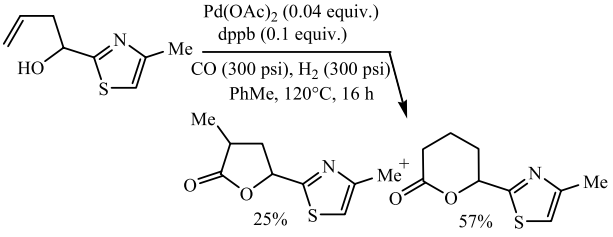


(112)



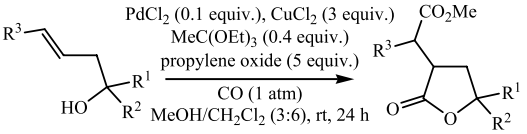
(113)

With the CO/H_2 method (see Section 6.3), Troisi et al. usually obtained a mixture of five- and six-membered lactones from heteroaryl homoallylic alcohols (Eq. 114); the ratio between the two heterocycles can be greatly dependent on the nature of the Pd ligands, but the use of chiral ligands did not provide appreciable enantiomeric enrichments of the new stereocentre.[250]



(114)

In MeOH containing an HCl quencher (*N*,*N*,*N*′-tetramethylurea or propylene oxide) and a dehydrating agent (ethyl orthoacetate) as additives, Tamaru et al. have performed dialkoxycarbonylations of primary, secondary and tertiary homoallylic alcohols, the regeneration of the catalyst being assumed by $CuCl_2$ (Eq. 115).[251,252] Subsequently, Inomata et al. also prepared α-[(methoxycarbonyl)methyl]-γ-butyrolactones in good yields, in the absence of such additives, but with CuCl and O_2 as the co-oxidants (Eq. 116).[246] An asymmetric procedure, the efficiency of which was greatly dependent on the nature of the Cu salt, was disclosed a few years later, the dialkoxycarbonylation of a primary homoallylic alcohol proceeding with a low enantioselectivity (Eq. 117).[253]



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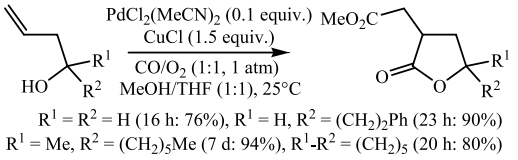
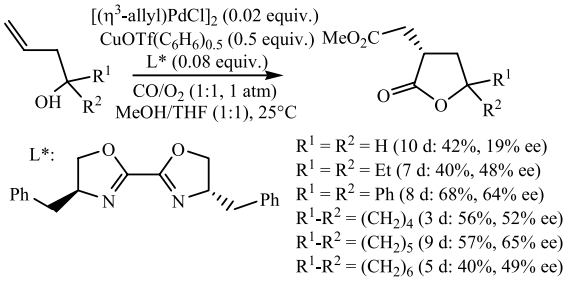
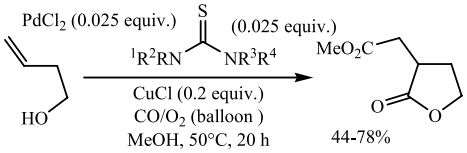


(116)



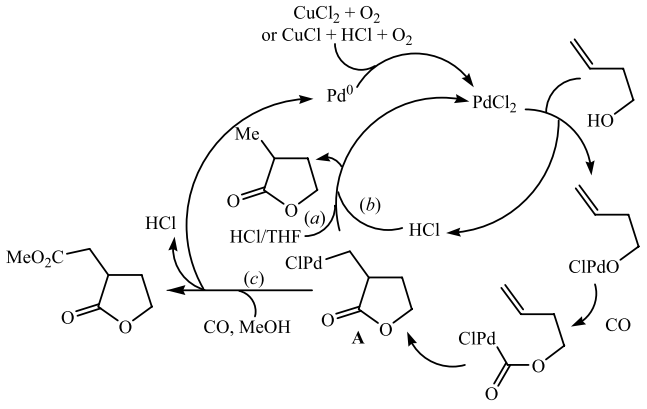
(117)

Recently, Dai et al. reported the dialkoxycarbonylation of 3-buten-1-ol with thiourea-based ligands of palladium, the yield depending on the substitution of the thiourea (Eq. 118).[254]



(118)

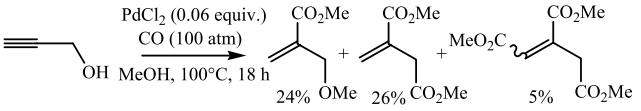
The different steps leading to mono- and dicarbonylation of homoallylic alcohols with $PdCl_2$ as catalyst are tentatively summarised in Scheme 28. According to the teams of Alper, Tamaru and Inomato, the cyclisation proceeds via alkoxypalladium and alkoxycarbonylpalladium intermediates.[245,251,253] The insertion of the latter species into the C=C bond would lead to the alkylpalladium complex **A**, which would be either hydrolysed by HCl (path a or b), or carbonylated and then methanolysed (path c). Nevertheless, the requirement of an oxidant to regenerate the catalyst, even for the monocarbonylation reaction, is rather surprising, because the protic cleavage of the alkyl-PdCl bond by HCl would give $PdCl_2$. We suspect that some Pd^0 is formed in situ from side reactions such as the oxidation of the hydroxy functionalities, and that the copper salt has other roles than just the regeneration of Pd^{II}. Copper chloride might form a new complex with $PdCl_2$, which may be bimetallic or anionic, and this could be a more active catalyst. Although, the absence of a β-H elimination at the level of **A** may be ascribed to a Pd coordinatively saturated by CO, the presence of an excess of halide ion may also contribute to the saturation of the Pd coordination, and a β-H elimination is then not so feasible. Furthermore, the Pd electron density increases with the coordination of halide ions, which results in the weakening of the C-Pd bond.[255,256]



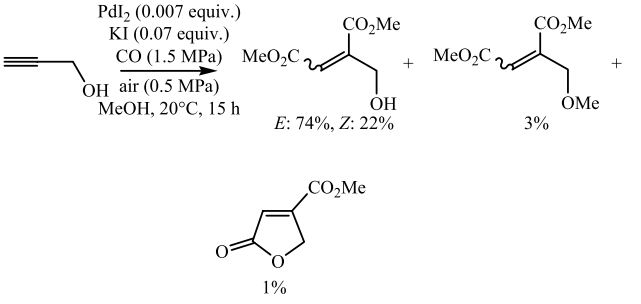
Scheme 28.

6.5. Propargylic alcohols

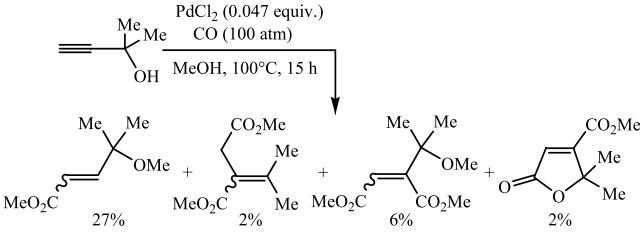
The products arising from the carbonylation of propargylic alcohols in methanol are very dependent on the substitution of the starting material and on the nature of the catalyst.[172,240,257–259] Thus, the products obtained from propargyl alcohol and 2-methyl-3-butyn-2-ol, respectively, by the teams of Tsuji (Eqs. 119 and 121)[260] and Chiusoli (Eqs. 120 and 122)[236,261,262] were quite different, and these differences are also apparent from the other examples collected in Table 1. Chiusoli's method involves catalysis by Pd^{II}, with regeneration of the active catalytic species by oxygen and iodic acid, and it was suspected that the β-lactone formed as the main product from 2-methyl-3-butyn-2-ol (Eq. 122)[261,262] is due to alkoxycarbonylation at the terminal carbon of the alkyne and cis-carbonylation at the internal carbon, followed by the trapping of the acylpalladium by the hydroxyl.



(119)

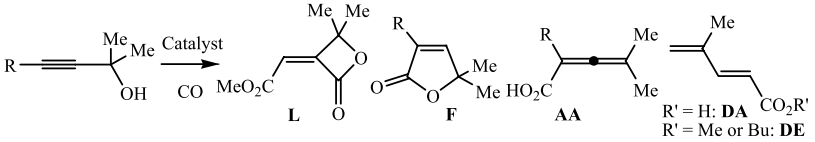


(120)

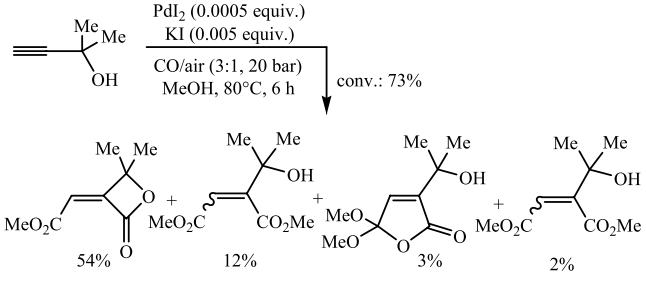


(121)

Table 1. Influence of the substitution and the experimental conditions on the carbonylation of tertiary propargylic alcohols

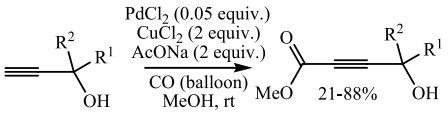


Entry	R	Catalytic system (equiv)	Conditions. additive (equiv)	**L** (%)	**F** (%)	**AA** (%)	**DA** (%)	**DE** (%)
1[261]	H	PdI_2 (0.0005)	CO/air (3:1, 20 bar), MeOH, 80 °C, 6 h. KI (0.005)	54				
2[239]	H	$Pd(dba)_2$ (0.04), dppb (0.04)	CO (20 atm), DME, 150 °C, 48 h		60			
3[263]	H	$Pd_2(dba)_3\cdot CHCl_3$ (0.04), dppb (0.08)	CO (600 psi), H_2 (200 psi), CH_2Cl_2, 95 °C, 36 h		98			
4[263]	*n*-Bu	$Pd_2(dba)_3\cdot CHCl_3$ (0.04), dppb (0.08)	CO (600 psi), H_2 (200 psi), CH_2Cl_2, 95 °C, 36 h		87			
5[263]	Ph	$Pd_2(dba)_3\cdot CHCl_3$ (0.04), dppb (0.08)	CO (600 psi), H_2 (200 psi), CH_2Cl_2, 95 °C, 36 h		97			
6[264]	H	$[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ (0.02)	CO (10 kg/cm^{-2}), THF, 50 °C, 3 h		2	10		
7[264]	*n*-Bu	$[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ (0.02)	CO (10 kg/cm^{-2}), THF, 50 °C, 1 h		16	76		
8[264]	Ph	$[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ (0.02)	CO (10 kg/cm^{-2}), THF, 50 °C, 3 h		84	0		
9[265]	H	$[(PCy_3)_2PdH(H_2O)]BF_4$ (0.012), dppb (0.012)	CO (20 atm), THF, 100 °C, 48 h. *p*-TsOH (0.024)				59	
10[265]	H	$[(PCy_3)_2PdH(H_2O)]BF_4$ (0.012), dppb (0.012)	CO (20 atm), THF/MeOH (0.2:5), 100 °C, 48 h. *p*-TsOH (0.024)					56
11[266]	H	$Pd(OAc)_2$ (0.02), dppb (0.012), PPh_3 (0.08)	CO (20 atm), THF, 100 °C, 48 h. HCO_2Bu (10), *p*-TsOH (0.08)					55



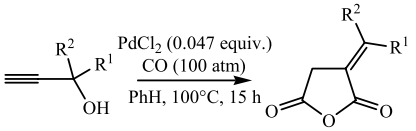
(122)

The above results contrast with those reported by Cacchi et al. who obtained 4-hydroxy-2-alkynoates from the treatment in MeOH of various secondary and tertiary propargylic alcohols with CO, $CuCl_2$, AcONa and catalytic amounts of $PdCl_2$ (Eq. 123),[34] that is, using Tsuji's alkoxycarbonylation method of terminal acetylenes.[203]



(123)

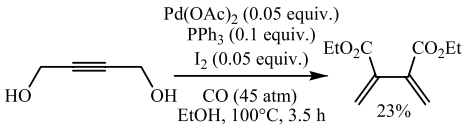
In carrying out the carbonylation in benzene instead of methanol, Tsuji et al. obtained anhydrides from secondary and tertiary propargylic alcohols (Eq. 124), whereas propargyl alcohol afforded resinous substances.[260]



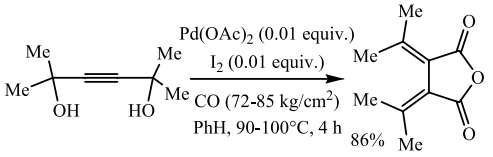
R^1 = H, R^2 = Et: 19%; R^1 = R^2 = Me: 42%

(124)

With methanol[265] or ethanol[267] as the solvent, 2-butyne-1,4-diols provide cross-conjugated diesters (Eq. 125) while, in benzene, the carbonylation affords mainly fulgides,[260] the best catalytic system being a 1:1 $Pd(OAc)_2/I_2$ mixture (Eq. 126).[268,269]

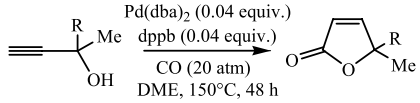


(125)



(126)

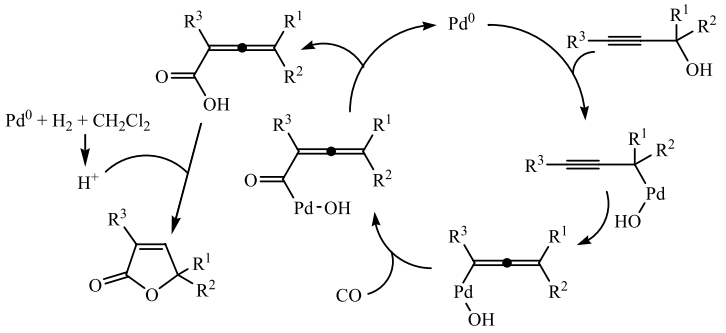
Using a Pd^0 procedure established for the carbonylation of secondary and tertiary allylic alcohols (Eq. 106), Alper et al. have obtained selectively 2(5*H*)-furanones from terminal tertiary propargylic alcohols (Eq. 127); a reaction course involving the insertion of carbon monoxide into the in situ-formed alkoxypalladium complex was proposed.[239]



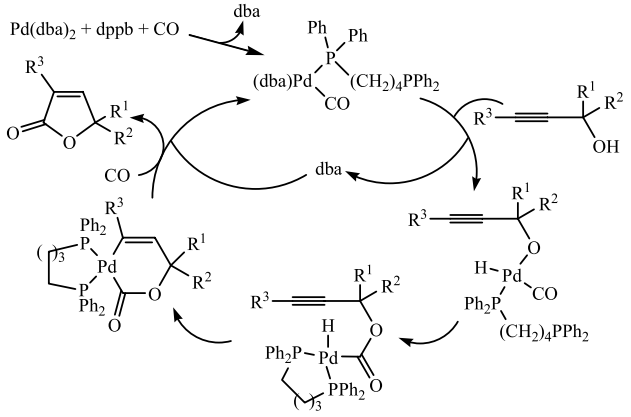
R = Me (60%), Et (70%), Ph (62%), $(CH_2)_2CH{=}CH_2$ (80%)

(127)

Secondary and tertiary propargylic alcohols have also been converted into 2(5*H*)-furanones by Alper's team using a Pd^0 catalytic system, but in methylene chloride and with both CO and H_2 pressure (Table 1, entries 3–5), these conditions improving, in particular, the reaction of non-terminal alkynols. According to the authors, the insertion of Pd^0 into the C–OH bond would mediate the transformation of the substrate to the corresponding 2,3-dienoic acid, the cyclisation, of which would be induced by traces of acid generated from the interaction between Pd^0, H_2 and CH_2Cl_2 (Scheme 29).[263] This mechanism remains, however, a

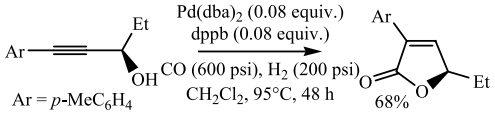


Scheme 29.

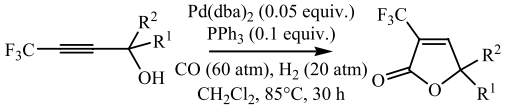


Scheme 30.

matter of debate because, under these conditions, Rossi et al. obtained the cyclocarbonylation of an optically active secondary propargylic alcohol, with retention of configuration, and 2.5% or less of racemisation (Eq. 128).[270] Consequently, Rossi et al. prefer to consider the insertion of a Pd–CO complex into the O–H bond (Scheme 30), that is, a reaction step previously proposed, in fact, by Alper et al.[239] A slightly modified Alper procedure has been used by Qing et al. for the cyclocarbonylation of trifluoromethyl propargylic alcohols (Eq. 129), but the method was successful only from tertiary alcohols.[43]



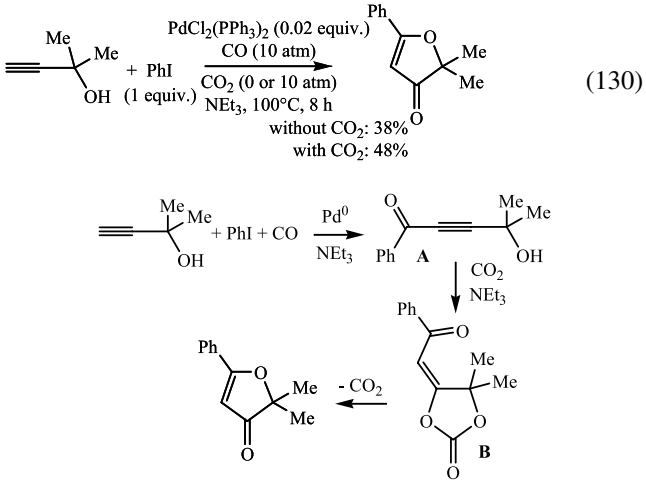
(128)



(129)

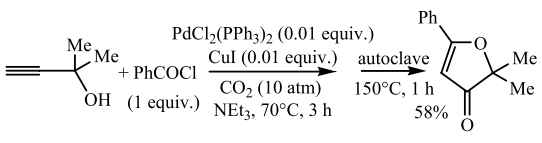
Nevertheless, the carbonylation of tertiary propargylic alcohols, catalysed by a cationic palladium^{II} complex, led also to 2(5*H*)-furanones in the absence of hydrogen, but 2,3-dienoic acids can be the main products (Table 1, entries 6–8); these acids are rapidly and quantitatively isomerised into the furanones on addition of a trace amount of acid such as *p*-toluenesulfonic acid.[264] Actually, Alper et al. obtained dienoic acids and esters using cationic or neutral palladium catalysts in association with catalytic amounts of both dppb and *p*-TsOH (Table 1, entries 9–11).[265,266]

In preparing 2,2-dimethyl-5-substituted-2*H*-furan-3-ones from 2-methyl-3-butyn-2-ol, carbon monoxide and aryl iodides or bromides, or β-bromostyrene or allyl acetate, Inoue et al. have observed that the reaction was under the influence of carbon dioxide (Eq. 130).[271,272] According to the authors, some CO_2 is present in the system, even when an atmosphere of CO is only used and, furthermore, they suspect the formation of CO_2 under their experimental conditions. The proposed reaction course, illustrated in Scheme 31, is supported by the isolation of the intermediates **A** and **B** and a study of their reactivity.[272] Moreover, previous studies from the same laboratory,[273] not cited in this report,[272] concern the Pd-catalysed synthesis of 2,2-dimethyl-5-pheny-2*H*-furan-3-one from 2-methyl-3-butyn-2-ol and benzoyl chloride (Eq. 131) with **A** and **B** as intermediates. Subsequent work by Kiji et al. is in agreement with these observations and proposals.[274] We suspect that the Pd^0-catalysed degradation of the carbonate into the 2*H*-furan-3-one at 100 °C in the presence of $Pd(PPh_3)_4$[272] involves an η^3-allylpalladium intermediate and the subsequent steps shown in Scheme 32.



(130)

Scheme 31.



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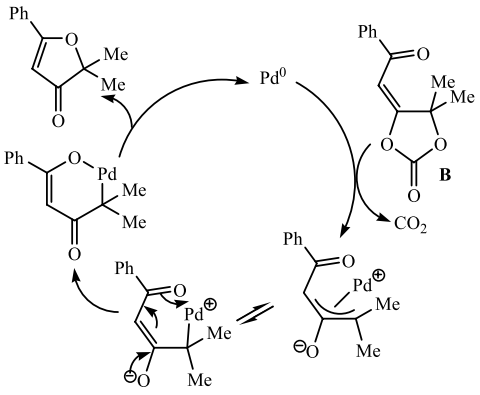
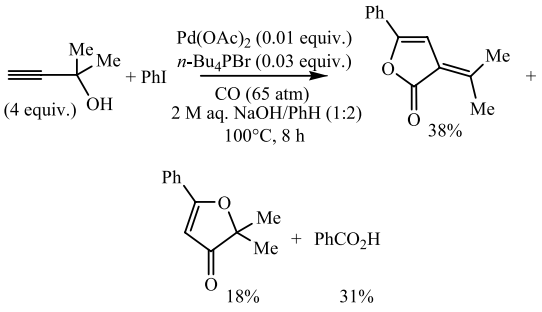


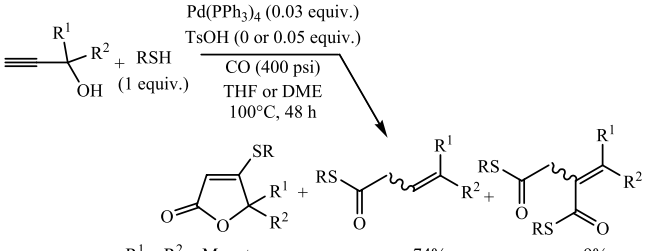
Scheme 32.

In sharp contrast with the results of the above carbonylation/phenylation of 2-methyl-3-butyn-2-ol carried out in a homogeneous NEt_3 solution (Eq. 130), the reaction in a biphasic system led to a mixture of 3-isopropylidene-5-phenyl-2*H*-furan-2-one, 2,2-dimethyl-5-pheny-2*H*-furan-3-one and benzoic acid (Eq. 132), the two furanones also being isolated on subjecting the acetylenic hydroxyketone **A** of Scheme 31 to such biphasic conditions.[274]



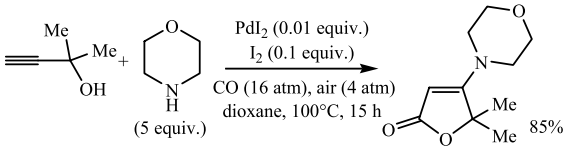
(132)

The carbonylation of propargylic alcohols with the concomitant formation of a C–S or C–N bond has been reported by the teams of Alper and Gabriele independently.[275–277] The Canadian team has disclosed the thiocarbonylation of a variety of propargylic alcohols with a selectivity very sensitive to the experimental conditions and to the substitution of the substrate (Eq. 133),[275] while the Italian team has used the PdI_2 methodology to synthesise 4-dialkylamino-5*H*-furan-2-ones (Eq. 134).[277]



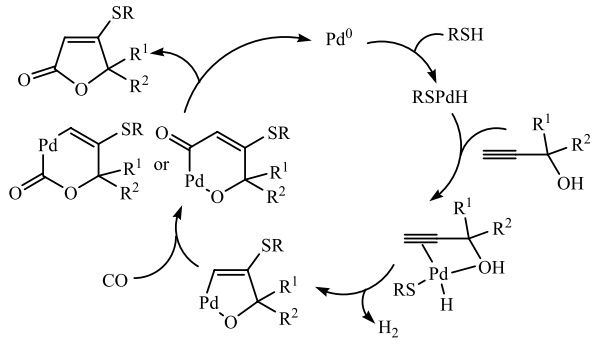
R = Ph in THF with TsOH	$R^1 = R^2 = Me$:	trace	74%	9%
	R^1-$R^2 = (CH_2)_5$:	13%	64%	trace
	$R^1 = H$, $R^2 = Me$:	10%	72%	4%
	$R^1 = Me$, $R^2 = Et$:	0%	63%	14%
R = Ph in DME without TsOH	$R^1 = R^2 = Me$:	67%	5%	4%
	R^1- $R^2 = (CH_2)_5$:	85%	trace	trace
	$R^1 = H$, $R^2 = Me$:	88%	trace	trace
	$R^1 = Me$, $R^2 = Et$:	70%	4%	4%
R = *n*-octyl, $R^1 = R^2 = Me$, in DME without TsOH:		74%	10%	0%

(133)



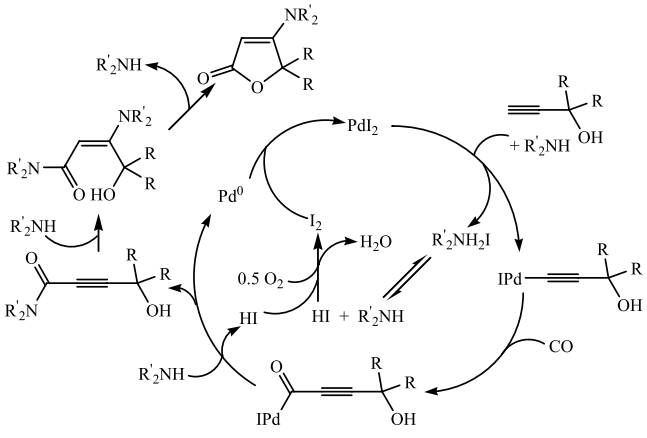
(134)

According to Alper et al., the formation of β-[aryl(or alkyl)thio]-α,β-unsaturated lactones (Eq. 133) involves the insertion of Pd^0 into the RS–H bond, the coordination of the propargylic alcohol to the aryl(or alkyl)thiopalladium complex and the formation of palladacycles (Scheme 33).[276]



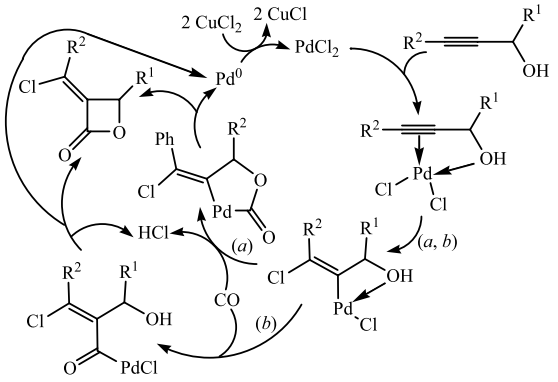
Scheme 33.

A careful study of this Italian domino reaction (Eq. 134) has led to deduction of the reaction course shown in Scheme 34, where (i) the Pd catalyst plays a role only in the formation of the 4-hydroxy-2-ynamide (which has been isolated), and (ii) the hydroxyl is not engaged in a step mediated by palladium.[277]

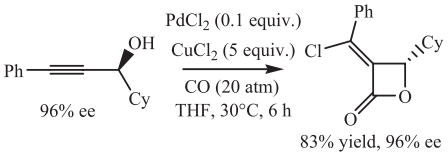


Scheme 34.

In the presence of an excess of $CuCl_2$, the teams of Ma and Xie have independently obtained (*Z*)-α-chloroalkylidene-β-lactones via the $PdCl_2$-catalysed cyclocarbonylation of propargylic alcohols (Eq. 135).[278–280] According to Ma et al. the reaction involves a *cis*-chloropalladation of the triple bond, and the insertion of CO into a Pd–Cl or Pd–O bond (Scheme 35, path a).[278] The trapping of an acylpalladium intermediate, as illustrated in Scheme 35, path b, was not considered.

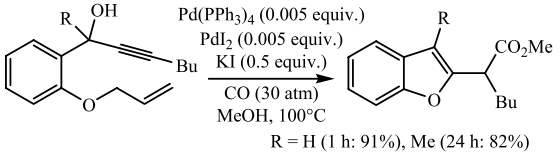


Scheme 35.



(135)

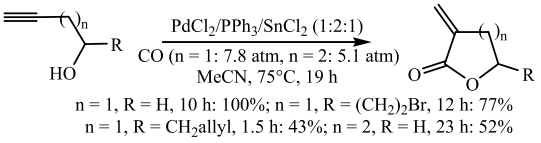
A surprising cascade reaction has been recently disclosed by Gabriele et al. using 1-(2-allyloxyphenyl)-2-yn-1-ols in MeOH, with a catalytic mixture of $Pd(PPh_3)_4$, PdI_2 and KI, under a pressure of CO (Eq. 136).[281] According to these authors, the process involves two sequential catalytic cycles, the first, with the Pd^0 catalyst, for the deprotection of the phenoxy group, and the second, with the Pd^{II} catalyst, for the heterocyclisation, the carbonylation and the cleavage of the C–OH bond via the formation of a η^3-allylpalladium complex (Scheme 36).



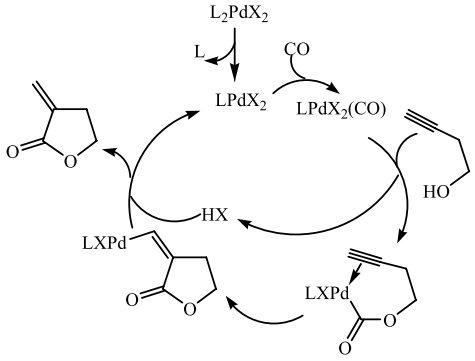
(136)

6.6. Other alkynols

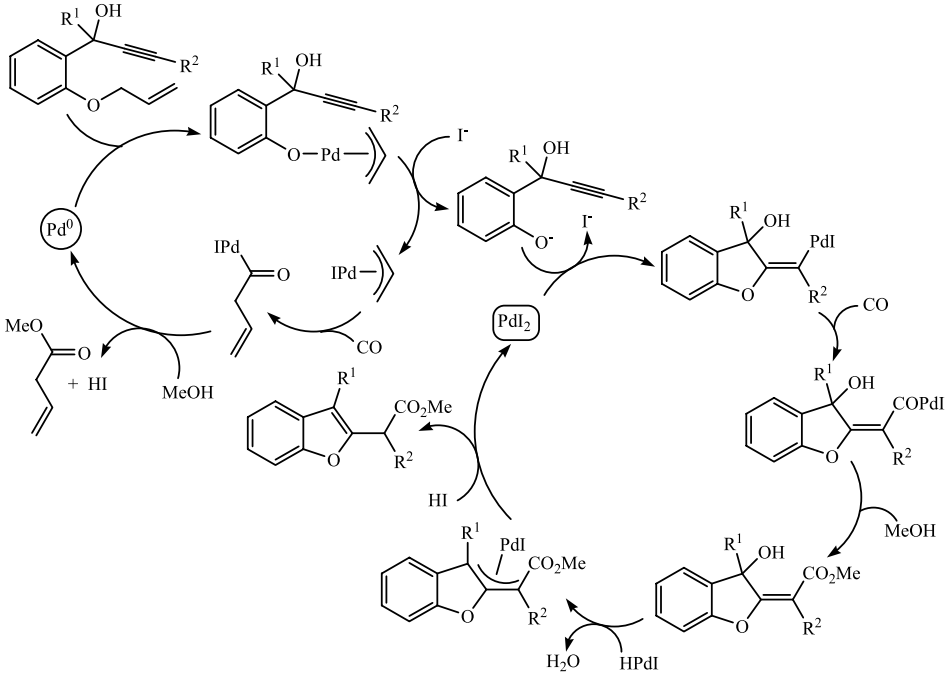
The synthesis of methylene lactones via the Pd-catalysed carbonylation of the appropriate acetylenic alcohols was first reported by Norton et al.[282–285] using, initially, a modified form of the $PdCl_2$/thiourea-catalysed methoxycarbonylation of acetylene (Chiusoli's method).[286] A better catalyst system, $PdCl_2/SnCl_2$/2 PPh_3, which was already disclosed for the carboalkoxylation of olefins[287] and acetylenes,[288] has been subsequently used; five- and six-membered ring lactones were obtained from terminal 1,3- and 1,4-acetylenic alcohols (Eq. 137), with an efficiency depending on the substitution of the substrate, the nature of the solvent and the concentrations.[248] According to Norton's team, the cis-addition of a carboalkoxypalladium intermediate to the triple bond affords a vinylpalladium species, which produces the lactone by protic cleavage (Scheme 37).[289–291]



(137)

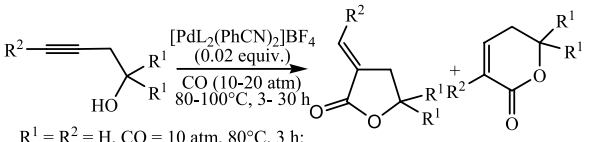


Scheme 37.



Scheme 36.

Using cationic palladium complexes for the cyclocarbonylation of homopropargylic alcohols, Inoue et al. have obtained lactones with a ratio of five- to six-membered rings depending greatly on the nature of the solvent: the six-membered ring lactones were mainly produced with cationic palladium complexes in MeCN (as with the neutral catalyst $PdCl_2$-$(PPh_3)_2$), while the methylene γ-lactones were the main products in DMF. Interestingly, the reaction catalysed by the cationic palladium complexes is not limited to terminal homopropargylic alcohols (Eq. 138), and the procedure in DMF led selectively to α-methylene-δ-valerolactone from 4-pentyn-1-ol, but with a declined yield.[292] According to the authors, the results in DMF could be explained as illustrated above in Scheme 37, while a palladium hydride would be involved in MeCN. The cis-addition of this complex to the acetylenic bond would be followed by the insertion of CO into the resultant alkenyl–Pd bond and, then, by intramolecular alcoholysis. Dupont et al. also suggest the carbonylation of the alkyne moiety as an intermediate step of the synthesis, in toluene or ionic liquids, of *exo*-α-methylene-β-, γ- and δ-lactones from the corresponding alkynols with $Pd(OAc)_2$/2-(diphenylphosphino)pyridine/*p*-toluenesulfonic acid as the catalytic system. These Dupont conditions were, in general, highly effective for the intramolecular alkoxycarbonylation of 3- and 4-alkyn-1-ols (Eq. 139), but yielded ≤5% of the *exo*-α-methylene-β-lactone from 1-methyl-2-butyn-1-ol.[293]



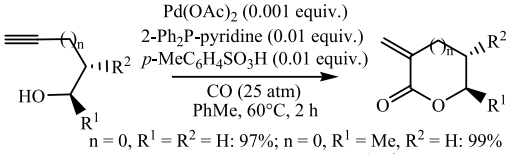
$R^1 = R^2 = H$, CO = 10 atm, 80°C, 3 h:

L_2 = dppb, MeCN:	6%	30%
L_2 = dppb, DMF:	35%	5%
L = PPh_3, DMF:	48%	0%

L = PPh_3, CO = 20 atm, 100°C, DMF:

$R^1 = R^2 = H$, 3 h:	49%	0%
R^1 = Me, R^2 = H, 20 h:	44%	1%
R^1 = H, R^2 = $SiMe_3$, 30 h:	61%	0%

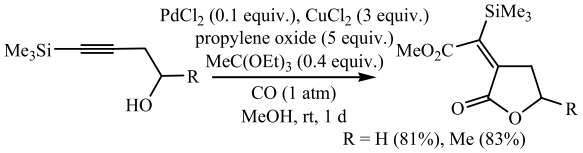
(138)



n = 0, $R^1 = R^2 = H$: 97%; n = 0, R^1 = Me, R^2 = H: 99%
n = 0, R^1–R^2 = C_4H_8: 99%
n = 1, $R^1 = R^2 = H$: 98%; n = 1, R^1–R^2 = C_4H_8: 50%

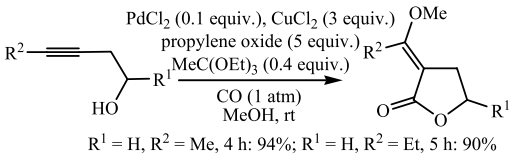
(139)

In applying their carbonylation method of homoallylic alcohols (Eq. 115) to 4-substituted 3-butyn-1-ols, apart from the use of methanol alone as the solvent, Tamaru et al. have observed a reaction course dramatically dependent on the type of the C-4 substituent: a dicarbonylation occurred with a trimethylsilyl group (Eq. 140), while methoxycarbonylation was obtained with an alkyl or aryl group (Eq. 141).[252]



R = H (81%), Me (83%)

(140)



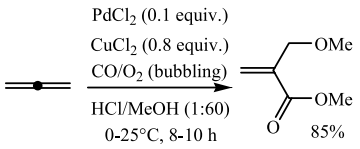
R^1 = H, R^2 = Me, 4 h: 94%; R^1 = H, R^2 = Et, 5 h: 90%
R^1 = Me, R^2 = Et, 6 h: 83%; R^1 = Me, R^2 = Ph, 18 h: 89%

(141)

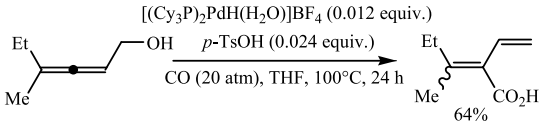
To close this Section, it is necessary to remember the formation of furan and pyran derivatives when 2-alkynylbenzyl alcohols are subjected to Chiusoli's PdI_2-based oxidative carbonylation methodology (Eqs. 174–176 in Part C[3]), the intramolecular alkoxypalladation preceding the carbonylation under these conditions.[4]

6.7. Allene and allenols

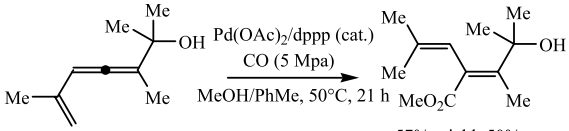
The alkoxy-alkoxycarbonylation of allene was reported by Alper et al. (Eq. 142),[294,295] and, using a cationic palladium complex, the same laboratory has obtained α-vinylacrylic acids from di- and trisubstituted primary α-allenic alcohols (Eq. 143).[296] These Alper procedures require the presence of an acid, and a mechanism has been proposed to explain the cleavage of the C–OH bond of α-allenic alcohols (Scheme 38).[296] With 2,3,6-trimethyl-hepta-3,4,6-trien-2-ol as the substrate and under different experimental conditions, the carbonylation can occur without such a cleavage (Eq. 144).[297]



(142)



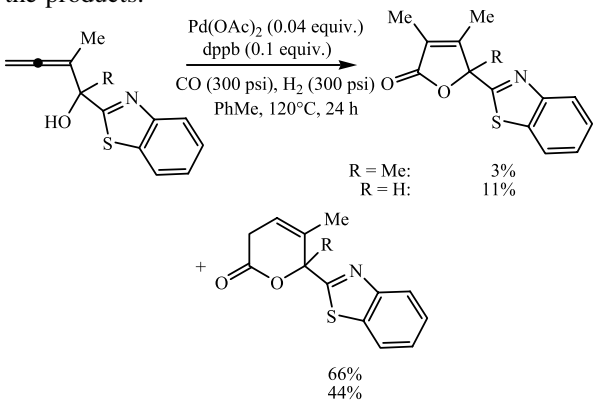
(143)



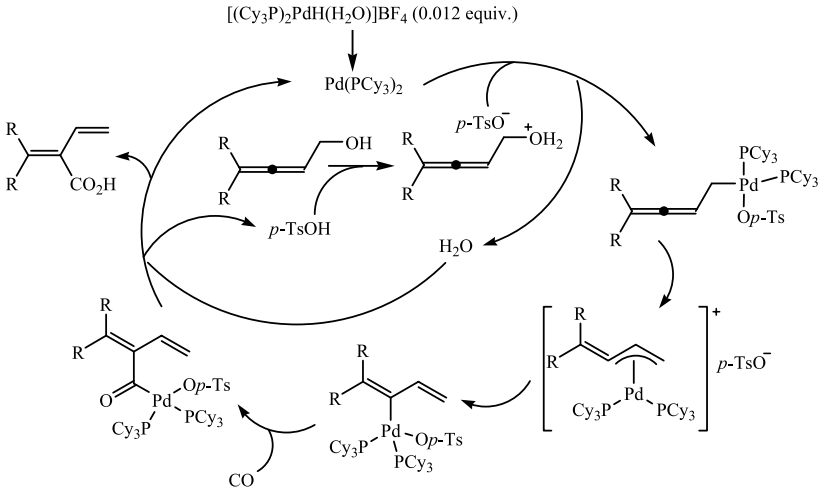
conv.: 57%, yield: 50%

(144)

With the CO/H_2 method (see Sections 6.3 and 6.4), Troisi et al. have obtained a mixture of five- and six-membered unsaturated lactones from heteroaryl allenyl alcohols (Eq. 145) with, as from homoallylic alcohols (Eq. 114), a strong influence of the nature of the ligands on the ratio of the products.[250]



(145)



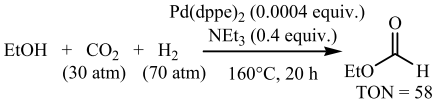
Scheme 38.

7. Reactions with carbon dioxide

The Pd-catalysed reactions of alcohols with the insertion of carbon dioxide requires, usually, a basic medium, because one step of the process is often the formation of the alcoholate; its reaction with CO_2 affords the corresponding carbonate anion, which evolves towards the final product via the Pd catalysis.

7.1. Alkanols

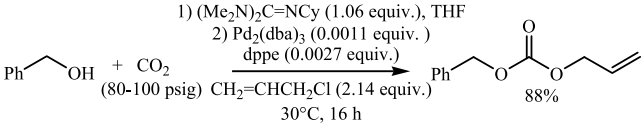
A pressure of both CO_2 and H_2, with a Pd catalyst and tertiary amines, led to the preparation of alkyl formates, for example, ethyl formate, from alkanols (Eq. 146).[298,299]



(146)

7.2. Benzyl alcohol

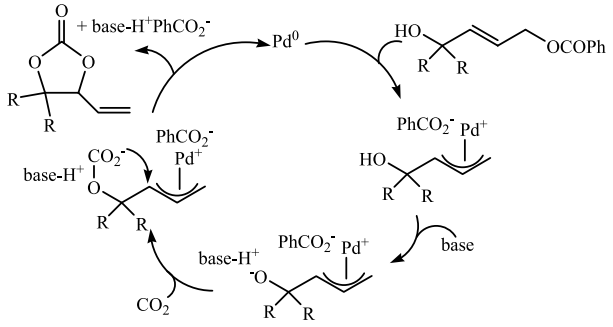
Benzyl alcohol reacts with carbon dioxide and allyl chloride, under basic conditions and Pd catalysis, to give benzyl allyl carbonate with a high turnover (Eq. 147). This reaction involves the formation of the $PhCH_2OCO_2^{-1}$ anion and its addition to the η^3-allylpalladium complex.[300]



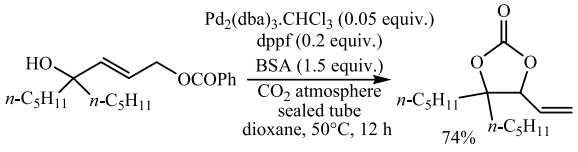
(147)

7.3. Allylic alcohols

Yoshida et al. reacting 1,1-dipentyl-4-benzoyloxy-2-buten-1-ol with CO_2 in a basic medium containing a Pd^0 catalyst, have obtained the corresponding cyclic carbonate with a fair yield (Eq. 148). The mechanism of this reaction is illustrated in Scheme 39.[301]

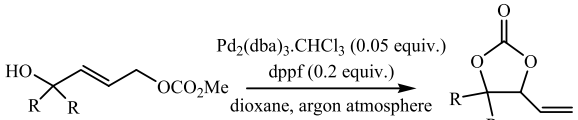


Scheme 39.



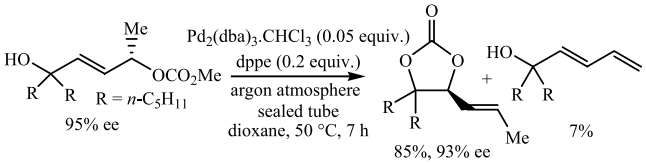
(148)

In addition, the same team has developed a Pd-catalysed cascade reaction involving a carbon dioxide elimination–fixation process from 1,1-disubstituted-4-methoxycarbonyloxy-2-buten-1-ols (Eq. 149).[301,302] The formation of the η^3-allylpalladium intermediate from these substrates delivers $MeOCO_2^-$, which leads to MeO^- and CO_2. Therefore, the required base and CO_2 are from an internal source. Furthermore, chirality transfer has succeeded from α-substituted allylic carbonates (Eq. 150).[301]



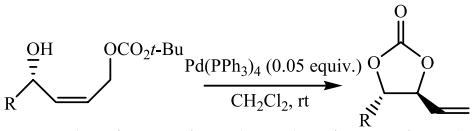
R = Et: 79%; R-R = $(CH_2)_4$: 60%; R-R = $(CH_2)_5$: 60%; R-R = $(CH_2)_6$: 77%

(149)



(150)

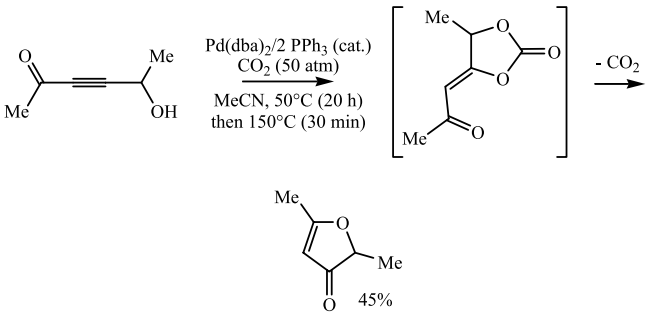
Shortly afterwards, Garcia et al. disclosed that such a carbon dioxide elimination-fixation process is not limited to tertiary alcohols, and can be efficiently carried out at room temperature in methylene chloride (Eq. 151).[303]



(151)

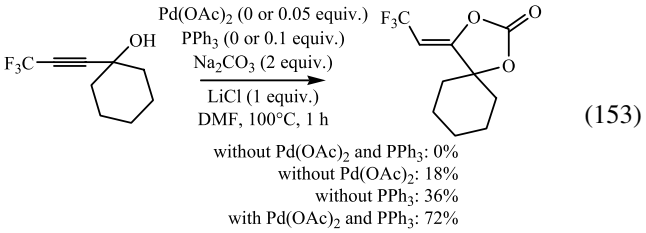
7.4. Propargylic alcohols

The reaction of propargylic alcohols with CO_2 and catalytic amounts of both K_2CO_3 and dibenzo-18-crown ether in *N*, *N*-dimethylacetamide can lead to α-alkylidene cyclic carbonates in the absence of a metal catalyst,[304] while the use of $PdCl_2$ or $Pd(OAc)_2$ as catalyst, in an ionic liquid, in the absence of base, led only to a black tar.[305] Nevertheless, the reaction of 5-hydroxy-3-hexyn-2-one with CO_2 required Pd^0 catalysis, the uncatalysed reaction in NEt_3 resulting in isomerisation into 3-hexen-2,5-dione. Under the Pd^0-catalysed conditions, 5-hydroxy-3-hexyn-2-one led, in fact, to 2,5-dimethyl-3(2*H*)furanone, carbon dioxide being eliminated from the intermediate carbonate (Eq. 152),[306] and the mechanism of this reaction has been discussed above with related examples (Eqs. 130 and 131, Schemes 31 and 32).



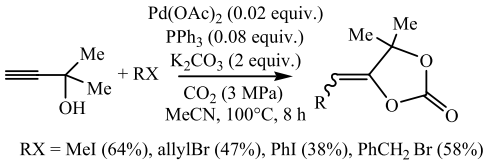
(152)

Sodium carbonate has been used, both as a base and as a carbon dioxide source, for the synthesis of cyclic carbonates from tertiary trifluoromethylated propargylic alcohols via a reaction, which required catalysis with either $Pd(OAc)_2$ or PPh_3, the best efficiency being obtained with both $Pd(OAc)_2$ and PPh_3 (Eq. 153).[35]

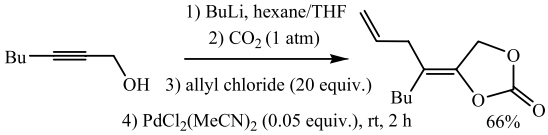


(153)

Actually, the Pd-catalysis carboxylations of propargylic alcoholates has been mainly used in association with the Heck-type coupling, using methyl iodide,[304] aryl halides,[304,307] β-bromostyrene,[307] allyl halides,[304,307,308] benzyl bromide[304] or allyl acetate[307] (Eqs. 154 and 155).

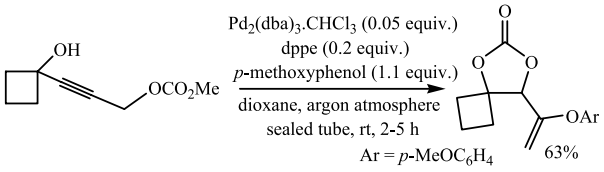


(154)

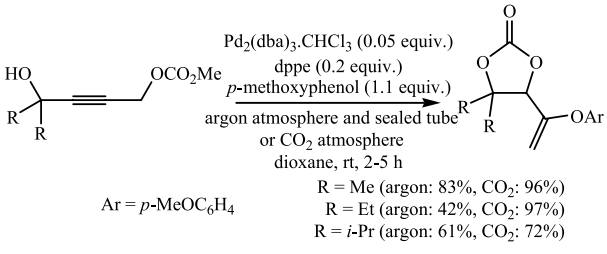


(155)

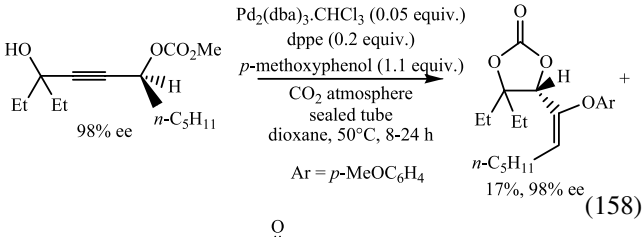
Yoshida et al. have applied their Pd-catalysed carbon dioxide elimination-fixation process[302] to the reaction of 4-methoxycarbonyloxy-2-butyn-1-ols with phenols (Eqs. 156 and 157);[309,310] the chirality transfer (Eq. 158)[311] as the induction of chirality by ligands (Eq. 159)[310] has been studied. These reactions were sometimes carried out under a CO_2 atmosphere to improve the process, and are sensitive to the experimental conditions (compare Eqs. 156–159 with Eqs. 49 and 50 above, and Eqs. 75–77 in Part C[3]). Besides, cyclic carbonates have been obtained under a CO_2 atmosphere from propargylic compounds, which contain non-CO_2-liberating groups (Eq. 160).[310]



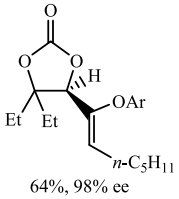
(156)

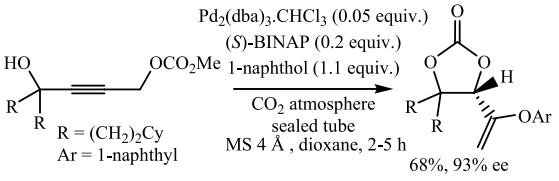


(157)

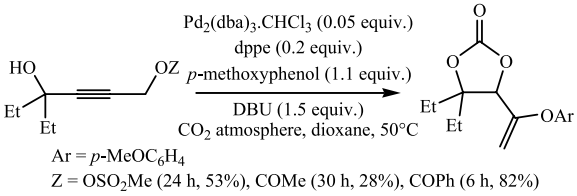


(158)



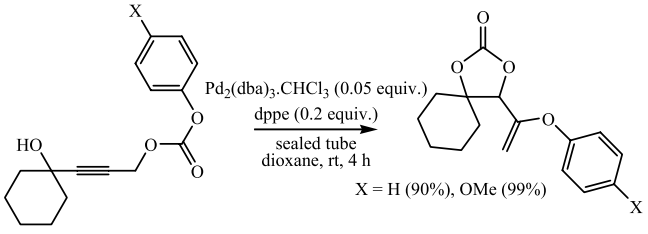


(159)



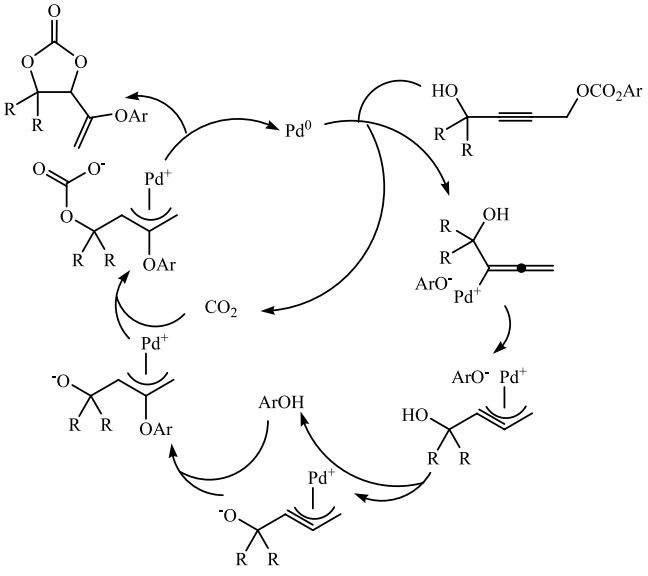
(160)

The same Japanese team has successfully applied their methodology to three-component decomposition/reconstruction reactions using 4-aryloxycarbonyloxy-2-butyn-1-ols as substrates (Eq. 161).[309,310]



(161)

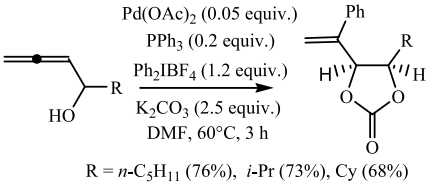
All of these Yoshida/Ihara reactions of propargylic compounds have a mechanism related to Scheme 40,[223] depicted for the cascade reaction of 4-aryloxycarbonyloxy-2-butyn-1-ols.



Scheme 40.

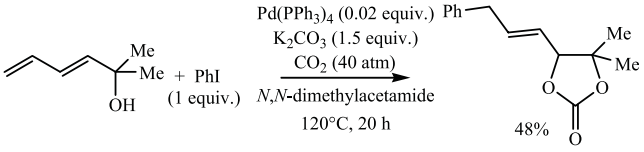
7.5. Dienols

Kang et al. have obtained cyclic carbonates from the Pd-catalysed arylation of alkyl-substituted α-allenic alcohols with diphenyliodonium tetrafluoroborate in the presence of K_2CO_3 (Eq. 162), in demonstrating the decisive role of the nature of the base and the *gem*-substituent of the hydroxyl on the course of the reaction (see Eqs. 41–43 in Part C[3]).[312]

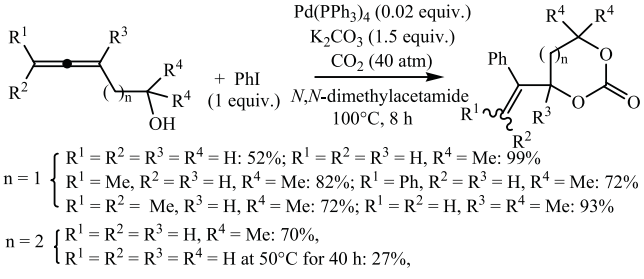


(162)

The Pd-catalysed addition of phenyl iodide to (*E*)-2-methyl-3,5-hexadien-2-ol under pressure of CO_2 led to (*E*)-4,4-dimethyl-5-(3-phenyl-1-propenyl)-1,3-dioxolan-2-one with a moderate yield (Eq. 163); this type of three-component reaction is usually more efficient with 1,2-dien-4(or 5)-ols as substrates (Eq. 164).[313] For these reactions, the addition of ArPdX to the substrate led to η^3-allylpalladium intermediates, which evolve towards the five- or six-membered carbonates, as illustrated in Schemes 39 and 40.



(163)

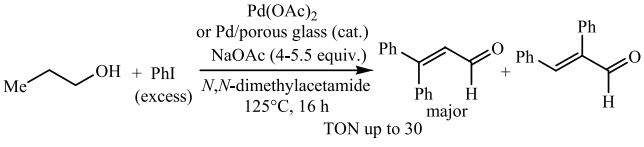


(164)

8. Other reactions

8.1. Arylation of alkanols

Straus et al. have disclosed the arylation of 1-propanol (Eq. 165) and 3-phenyl-1-propanol with phenyl iodide.[314] For these unusual reactions, PhI serves both as an oxidant and as a reactant. A quite complicated mechanism involving the insertion of palladium into a terminal hydrogen of a propyloxypalladium complex, leading to a palladaoxetane, and, then, to a phenyl-allyloxypalladium intermediate was suggested, the subsequent steps being rather different from those usually admitted for the Heck reaction of allylic alcohols.



(165)

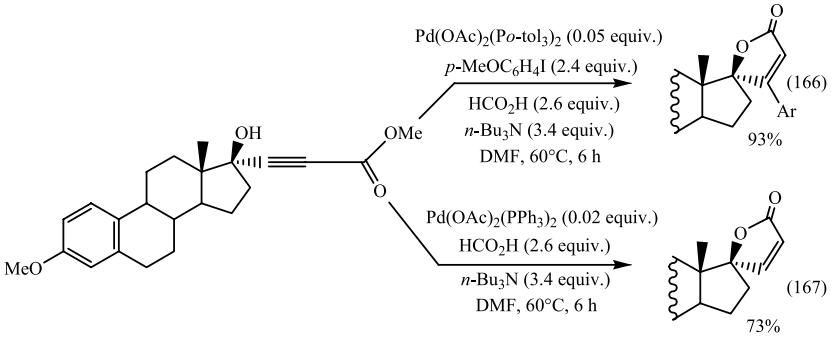
8.2. Disproportionation of benzylic and allylic alcohols

Various catalytic systems, for example, Pd/C in MeOH at room temperature,[6] solvent-free $Pd(acac)_2/PPh_3$ at 80 °C,[7]

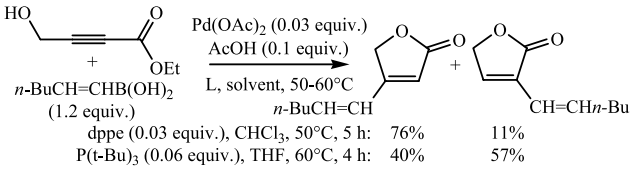
or $PdCl_2$ in molten n-Bu_4NBr[137] (Eq. 71), can act as disproportionation catalysts of allylic or benzylic alcohols.

8.3. Esterification

The formation of butenolides from either hydroarylation (Eq. 166) or semi-hydrogenation (Eq. 167) of methyl 4-hydroxy-2-alkynoates involves a transesterification, mediated perhaps by the Pd catalyst.[34]

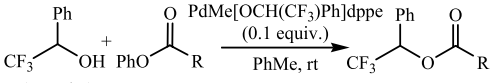


A similar in situ lactonisation has been recently, reported from the Pd-catalysed addition of aryl- and alkenylboronic acids to 4-hydroxy-2-alkynecarboxylates (Eq. 168).[315]

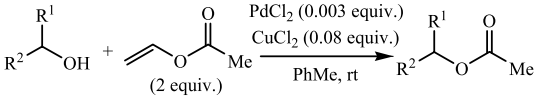


(168)

The palladium alkoxide complex, PdMe[OCH(CF_3)-Ph](dppe), catalysed the transesterification of aryl esters with 2,2,2-trifluoro-1-phenylethanol (Eq. 169), but was inefficient for the transesterification of butyl acetate with 2-methyl-1-propanol.[316] The acetylation of a variety of alcohols has been effectively performed with vinyl acetate and a catalytic mixture of $PdCl_2$ and $CuCl_2$ (Eq. 170);[317] this transesterification contrasts with the Pd^{II}-catalysed vinyl interchange between alcohols and vinyl ethers (see Eqs. 119–121 in Part C[3]).[5,318]



(169)

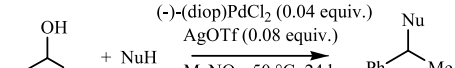


R^1 = Ph, R^2 = H, 3.5 h: 96%; R^1 = Ph, R^2 = Me, 9.5 h: 92%
R^1-R^2 = C_5H_{10}, 3.5 h: 89%; R^1 = PhCH=CH, R^2 = H, 4 h: 96%
R^1 = $HSCH_2$, R^2 = H, 3 h: 95%; R^1 = $C_6H_{13}SCH_2$, R^2 = H, 5 h: 58%

(170)

8.4. Thioetherification, amination and halogenation

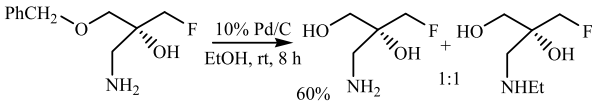
Abu-Omar's process of etherification of secondary benzyl alcohols, which involves the formation of the corresponding carbocation as intermediate (Scheme 46 in Part C[3]), has been extended to the reaction with thiols and electron-deficient anilines (Eq. 171).[319]



Nu = SPh (99%), SCH_2Ph (99%), $S(CH_2)_2OH$ (43%), Sn-Pr (99%), NHC_6F_5 (64%)

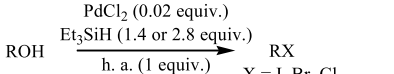
(171)

The reductive debenzylation of (2*R*)-3-amino-2-fluoro-methyl-3-benzyloxy-propan-2-ol, over Pd/C in ethanol, has been accompanied by some ethylation of the amino group (Eq. 172).[320]



(172)

The $PdCl_2$/Et_3SiH system, in association with halogenating agents, mediated the transformation of various alcohols into the corresponding halides (Eq. 173). The iodation of (+)-2-octanol occurred with inversion of configuration. According to Chatgilialoglu et al., the silyl ethers are formed prior to the appearance of the halides.[136]

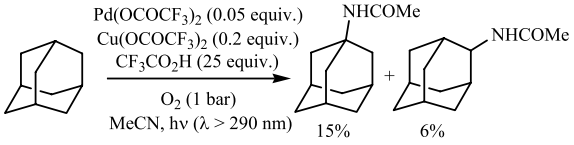


h. a. = MeI: R = CH_2Ph (98%), CH_2CH=CHPh (83%), t-Bu (98%), Cy (98%), $(CH_2)_9Me$ (90%)
h. a. = CH_2Br_2: R = CH_2Ph (98%), CH_2CH=CHPh (91%), t-Bu (98%), Cy (89%), $(CH_2)_9Me$ (81%)
h. a. = $(CCl_3)_2$: R = CH_2Ph (94%), CH_2CH=CHPh (86%), t-Bu (80%), Cy (80%), $(CH_2)_9Me$ (13%)

(173)

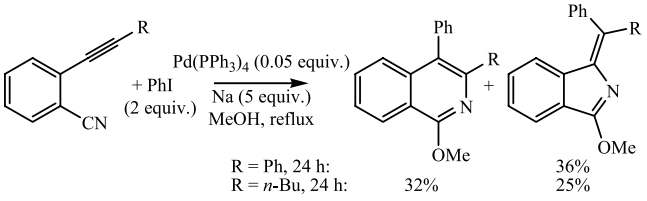
8.5. Reactions of hydroxy groups with C=N and C≡N bonds

8.5.1. With nitriles. The synthesis of amides by the addition of alcohols to nitriles, usually called the Ritter reaction, is generally conducted in a strongly acidic medium, which converts the alcohol into the corresponding carbonium ion.[321] This reaction has also been observed from oxygenated acetonitrile solutions of adamantane, with the association of $Pd(OCOCF_3)_2$ and $Cu(OCOCF_3)_2$ as the catalytic system, in the presence of CF_3CO_2H and UV light (Eq. 174), the adamantanols being produced in situ as intermediates,[322] and from tertiary alcohols under neutral conditions with the cationic complex $[PdMeCN)_2(PPh_3)_2](BF_4)_2$ as the catalyst.[323]



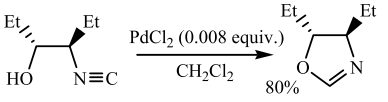
(174)

Wu et al. have synthesised isoquinoline and isoindole derivatives from the domino reaction between aryl iodides, 2-alkynylbenzonitriles and methanol (Eq. 175).[324] The proposed mechanism (Scheme 41) was similar to that illustrated with alkynylaldehydes as substrates (Scheme 42 in Part C[3]).[325]



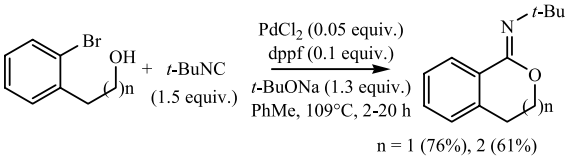
(175)

8.5.2. With isocyanides. 2-Oxazolines and 5,6-dihydro-4*H*-1,3-oxazine have been obtained via the Pd-catalysed intramolecular reaction of 3-hydroxyalkyl isocyanides (Eq. 176).[326,327]



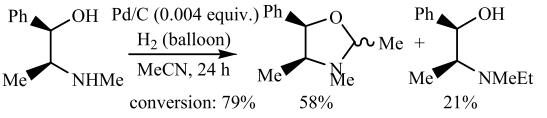
(176)

Having observed a Pd-catalysed three-component reaction leading to acyclic imidates from vinyl or aryl bromides, isocyanides and alcoholates,[328] Whitby et al. have extended the method to the synthesis of cyclic imidates using aryl bromides carrying a pendant alcohol group (Eq. 177).[329]

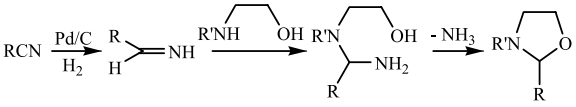


(177)

8.5.3. With imines. Nitriles under Pd-catalysed hydrogenation conditions are substitutes for aldehydes in the reaction with 1,2-aminoalcohols, leading to 1,3-oxazolidines (Eq. 178),[330] through a reaction, which would involve the trapping of the in situ-formed imine by the aminoalcohol (Scheme 42).[331,332]

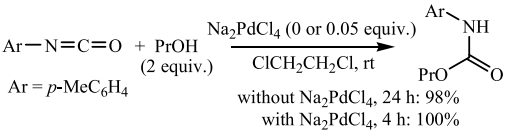


(178)



Scheme 42.

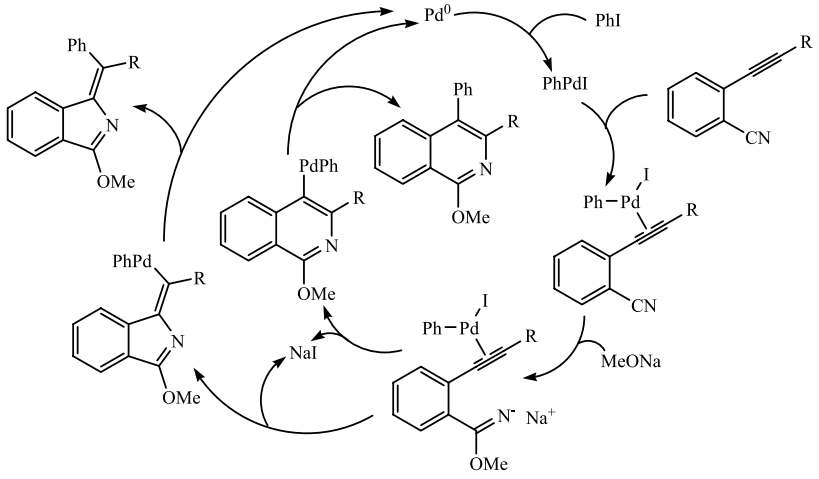
8.5.4. With isocyanates. The synthesis of carbamates from the treatment of isocyanates with alcohols does not require a metal catalyst,[333] but the presence of Na_2PdCl_4 increased the rate of the reaction, owing to its Lewis acid properties (Eq. 179).[334]



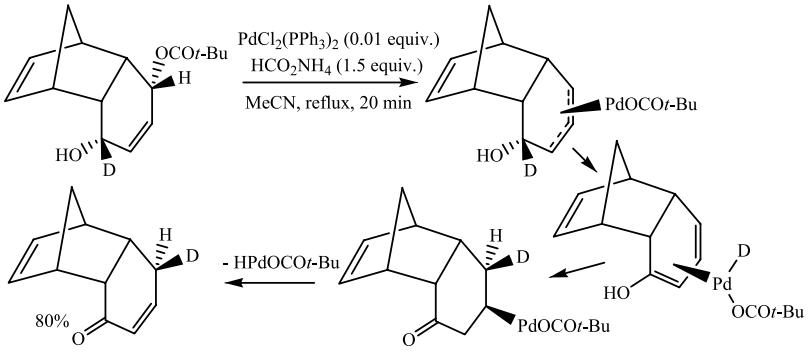
(179)

8.6. Miscellaneous elimination reactions

In contrast to allylic acetates, the Pd-catalysed formation of 1,3-dienes from allylic alcohols is not an usual reaction,[335] but is rather observed as a side reaction.[7,25] Cyclohexenones have nevertheless been effectively obtained from a variety of *cis*-cyclohex-2-en-1,4-diols and their monoprotected derivatives, in the presence of ammonium formate, using $PdCl_2(PPh_3)_2$ as catalyst in refluxing acetonitrile (Eq. 180) or dioxane,[336–338] through a suprafacial 1,4-hydrogen shift mediated by palladium, as demonstrated from deuterium labelling experiments.[337] These reactions have been explained as depicted in Scheme 43, but ammonium formate did not appear in this scheme, although, only traces of the cyclohexenone were obtained in its absence.[337] The role of

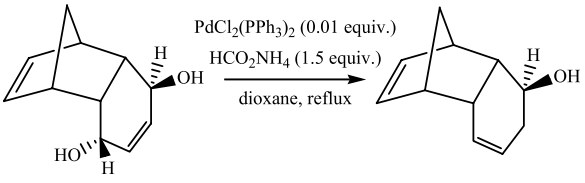


Scheme 41.

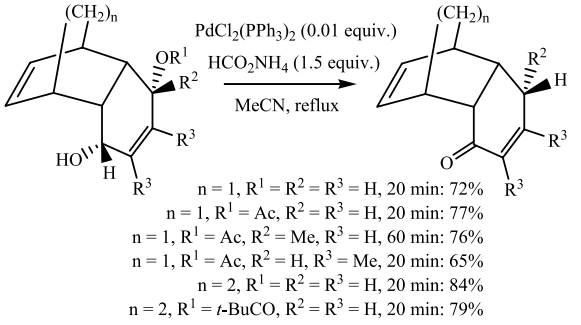


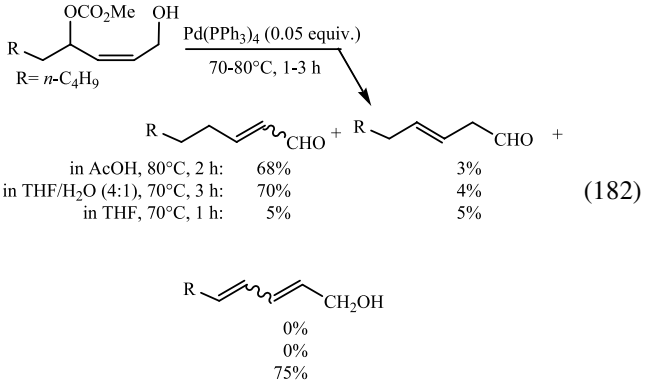
Scheme 43.

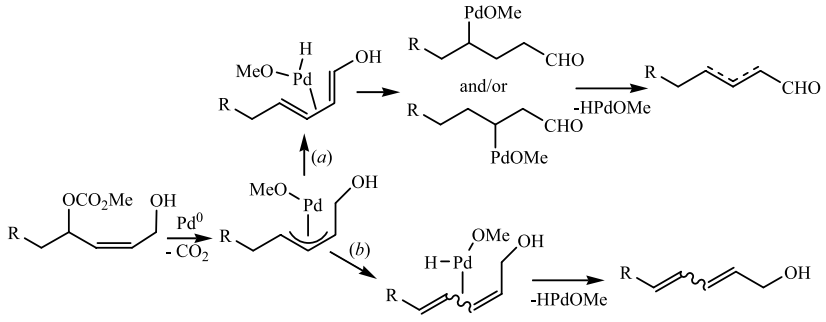
HCO_2NH_4 is not obvious since, in the presence of Pd catalysts, it usually removes hydrogenolytically the ester group of allylic esters.[339] The reaction would involve an η^3-allylpalladium intermediate, but the use of $Pd(PPh_3)_4$ as catalyst with or without HCO_2NH_4 produced, at the most, traces of the cyclohexenone; nevertheless, catalytic amounts of a mixture of $Pd(OAc)_2$ and PPh_3 with an excess of HCO_2NH_4 were efficient.[337] To have an effective formation of the cyclohexenone, the 1,4-oxygens have to be in an *endo*–cis relationship, but the starting material was unchanged when both hydroxy groups were protected.[337] Therefore, these elimination reactions under these experimental conditions are surprising. In contrast to the above results, the trans-1,4-dihydroxy substrate led to the corresponding β,γ-unsaturated *exo*-cyclohexenol (Eq. 181),[337] which was apparently generated by the conventional hydrogenolysis mechanism.[339,340]



The hydrogen migration has also been observed by Hanaoka et al. from primary allylic alcohols γ-substituted by a leaving group, this leading to unsaturated aldehydes (Eq. 182). For these elimination reactions, $Pd(PPh_3)_4$ was an efficient catalyst and HCO_2NH_4 was not used, but a protic solvent seems to be required, since anhydrous THF afforded mainly the 2,4-dien-1-ol (Eq. 182).[341] A mechanistic scheme, similar to that in Scheme 43, explains the formation of the aldehydes (Scheme 44, path a), the elimination of HPdOMe from the η^3-allylpalladium intermediate leading to the 2,4-dien-1-ol (Scheme 44, path b).

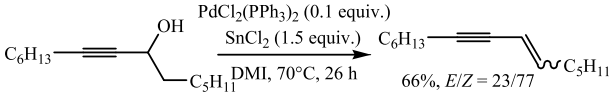




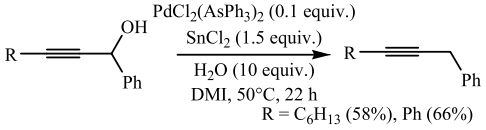


Scheme 44.

The Pd-catalysed dehydration of secondary propynyl alcohols with tin^{II} chloride (Eq. 183), which would involve an allenylpalladium intermediate, is highly dependent on the nature of both the solvent and the catalyst, efficient reactions being obtained in 1,3-dimethylimidazolidin-2-one with catalysis by $PdCl_2(PPh_3)_2$ or $PdCl_2(AsPh_3)_2$.[342] When the starting alcohol has no hydrogen in the α-position, the reaction in the presence of water led to propynes (Eq. 184), and 1-deuterio-1-phenyl-non-2-yne was produced from 1-phenyl-non-2-yn-1-ol and D_2O.[342]

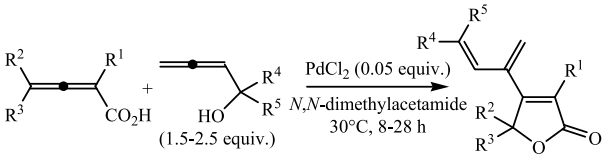


(183)

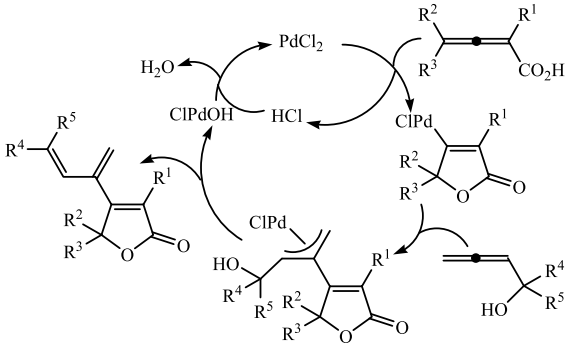


(184)

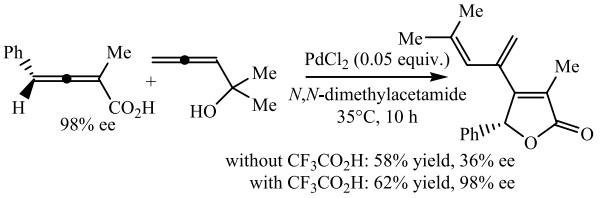
Ma et al. have established a coupling cyclisation protocol to synthesize 4-(1′,3′-dien-2′-yl)-2(5*H*)-furanone derivatives from the reaction of primary, secondary or tertiary 1,2-dien-3-ols with 2,3-allenoic acids (Eq. 185). An optically active allenoic acid afforded the corresponding adduct, without racemisation when trifluoroacetic acid was added to the mixture (Eq. 186). A possible mechanism has been proposed by the authors (Scheme 45).[343]



(185)

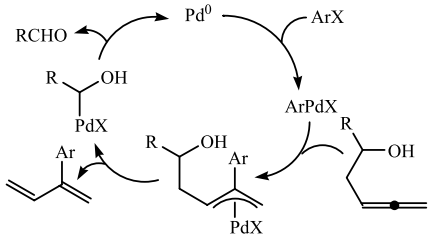


Scheme 45.

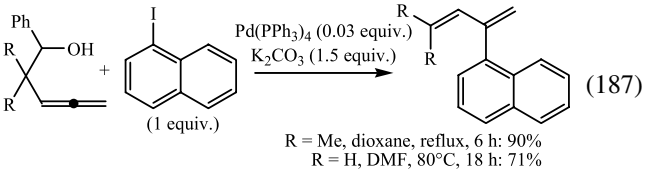


(186)

When 1,2-dien-5-ols are treated with aryl iodides or bromides under the experimental conditions proposed by Oh et al. (Eq. 187), the decarbopalladation of the η^3-allylpalladium intermediate occurs via a β-carbon elimination, which leads to the corresponding 2-arylated-1,3-diene (Scheme 46).[344]

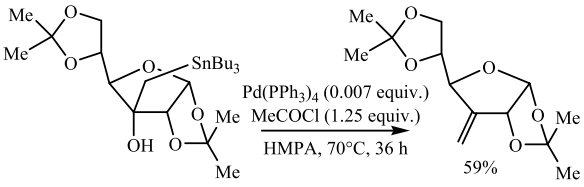


Scheme 46.



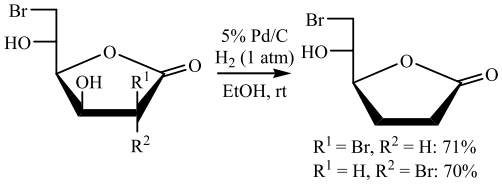
(187)

The formation of a C=C bond was obtained via an unclear mechanism from a β-hydroxyalkyltin compound using a stoichiometric amount of acetyl chloride and $Pd(PPh_3)_4$ as the catalyst (Eq. 188).[345]



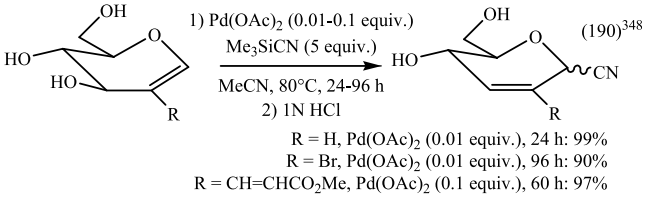
(188)

Taub et al. have obtained 3α-acetoxy-16β-acetyl-5β-androstane-11-one from the treatment of 3α-acetoxy-16α-hydroxy-17β-bromo-16β-acetyl-5β-androstane-11-one with hydrogen over supported palladium in aqueous methanol.[346] This process has been used by Pedersen et al. for the synthesis of 2,3-dideoxyaldono-1,4-lactones from 2-bromo-2-deoxyaldono-1,4-lactones having a hydroxy group at C-3 (Eq. 189); it has been proved that the corresponding 2,3-unsaturated lactones are intermediates, since they were isolated when the reactions were interrupted after 50% of the hydrogen was consumed.[347]

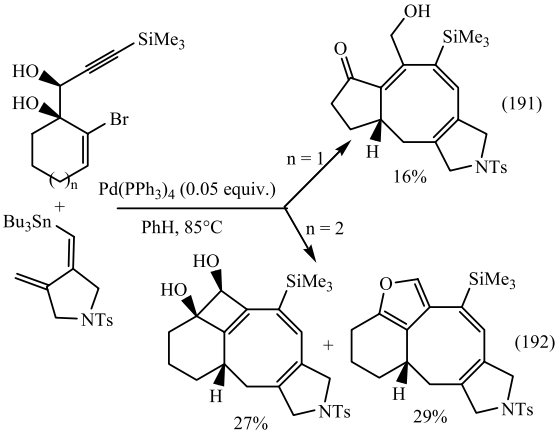


(189)

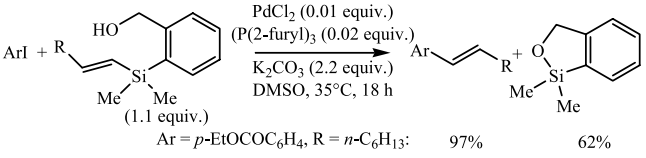
Unprotected glycosyl cyanides have been produced from the *C*-glycosidation of unprotected D-glycals with trimethylsilyl cyanide under Pd^{II} catalysis, followed by an acidic treatment (Eq. 190). The real cyanating agent would be hydrogen cyanide generated by the reaction of Me_3SiCN with a hydroxy group of the glycal, this HCN attacking the anomeric position activated by coordination of the double bond to Pd^{II}; the subsequent step would be the β-OH (or β-$OSiMe_3$) elimination, leading to the regeneration of an active Pd^{II} catalyst.[348] The absence of a reaction with $Pd(PPh_3)_4$ as catalyst is in agreement with such a mechanism, rather than with an η^3-allylpalladium intermediate. Thus, this process would imply the carbopalladation of the C=C bond of the heterocycle, that is, a reaction step analogous to the oxypalladation and aminopalladation of alkenes documented in Parts B and C.[2,3] Nevertheless, such a C–C bond formation seems to be restricted to the double bond of vinyl ethers, since no reaction was reported at the level of the unsaturated ester substituent (Eq. 190, R=CH=$CHCO_2Me$). Although it has been assumed that the alkoxysilanes produced in situ are cleaved by the acidic work up, some Pd^{II}-mediated cleavage is envisageable.[85,199,349]



Suffert et al. obtained complex polycycles (Eqs. 191 and 192) through cascade reactions involving an intramolecular Heck-type reaction with a triple bond, and then an intermolecular Stille reaction as the first steps (Scheme 47).[350,351]



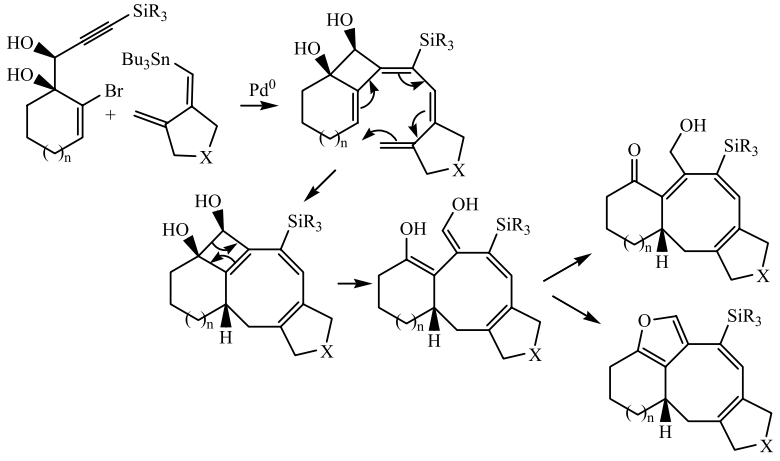
Tetraorganosilicon reagents have been obtained via the reaction of alkenyl- and aryl[2-(hydroxymethyl)phenyl] dimetylsilanes with aryl and alkenyl iodides (Eq. 193).[352]



(193)

9. Conclusions

Although, the topic of this series of reviews is certainly not covered comprehensively,[353] the strong diversity of reactions carried out from a large panel of hydroxylated compounds in the presence of palladium catalysts, under a variety of experimental conditions, which involved either Pd^0 or Pd^{II} species as the real catalysts, is exemplified. Sigman et al. have recently, noted that Pd^0 catalysis has dominated the landscape of catalyst development for the past several decades, while Pd^{II} catalysis was developed at a much slower pace and, from the recent published studies, they have concluded the renaissance of Pd^{II}-catalysed chemistry.[354] This series of reviews, which summarises a large number of Pd^{II}-catalysed reactions, could participate in this renaissance. In the context of Green Chemistry,[355] it



Scheme 47.

is particularly attractive to use alcohols, rather than chlorides, esters or carbonates, because these latter compounds are often produced from the corresponding alcohols and, in addition, their Pd-catalysed reactions do not usually answer to the atom economy requirement.

I would like to finish this series of reviews with a personal remark. For 25 years,[356] I have been involved in the area of palladium-mediated reactions, but I have to confess that I have been surprised by the number of references and the diversity of reactions, I have collected over the years, on the topic of the Pd-catalysed reactions of alcohols.

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Biographical sketch

Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Champagne-Ardenne and received his degrees (Doctorat de 3ème cycle—1972, Doctorat d'Etat—1976) for his work with Jean-Pierre Pète on photochemical rearrangements of α,β-epoxyketones and β-diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 as Stagiaire de Recherche and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with Elias J. Corey at Harvard University on natural product synthesis. On his return to Reims, he mainly studied the photoreactivity of η^3-allylpalladium complexes and anionic activation by supported reagents. In 1988, he was promoted to Directeur de Recherche CNRS. His research interests concentrate on transition metal-catalysis with particular emphasis on oxidations, asymmetric reactions and mechanisms. Since a few years, he is also involved in the valorisation of agricultural by-products and in the use of water and molten salts as solvents for Organic Synthesis.

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One catalyst for two distinct reactions: sequential asymmetric hetero Diels–Alder reaction and diethylzinc addition

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Abstract—This paper describes the successful development of a series of chiral zinc catalysts containing (*R*)-3,3′-Br_2-BINOL ligand and various diimine activators for enantioselective HDA reaction of Danishefsky's diene with aldehydes through a combinatorial approach, affording the corresponding 2,3-dihydro-4*H*-pyran-4-one derivatives in excellent yields and enantioselectivities. The application of this type of catalysts was also extended to the diethylzinc addition to the benzaldehyde, affording the corresponding secondary alcohol with up to 94.5% ee under optimized conditions. On the basis of these facts, the integration of two distinct enantioselective reactions, HDA and diethylzinc addition reactions, has been realized in one-pot with the promotion of a single chiral zinc catalyst in a sequential manner. The impact of diimine additive on the catalytic system of HDA reaction was also investigated by probing the nonlinear effect of reaction system. The positive nonlinear effect exhibited in the catalytic system could be attributed to the poor solubility of the heterochiral zinc species. On the basis of various experimental findings disclosed in this research, a possible mechanism for the asymmetric induction in the 3,3′-Br_2-BINOL/Zn/diimine catalyzed enantioselective HDA reaction of Danishefsky's diene with aldehydes was outlined.

1. Introduction

Organometallic catalysts are traditionally designed and optimized to promote a single reaction.[1] However, the increasing demand for expedient synthetic processes requires the development of more efficient organometallic catalysts that are capable of catalyzing multiple, mechanistically distinct reactions directly or by simple modification.[2] Asymmetric catalysis of organic reactions has provided a powerful strategy for amplification of chirality to get optically active compounds. So far there were only very few reports on the sequential catalysis of two distinct enantioselective reactions using a single chiral catalyst.[3] Therefore, integration of two or more reactions in one-pot with the promotion of a single catalyst is still a great challenge for chemists. As an effort to exemplify such a system,[4] herein, we demonstrate the ability of a single catalyst to promote two different reactions in one-pot through a sequential approach.

The enantioselective hetero-Diels–Alder (HDA) reaction of Danishefsky's diene with aldehydes represents one of the most important methods for the construction of optically active six-membered oxo heterocycles with extensive synthetic applications in natural or unnatural products.[5,6] Since the first HDA reaction of Danishefsky's diene and aldehydes was achieved with the catalysis of $ZnCl_2$,[7] various chiral Lewis acids, such as aluminum, boron, transition and lanthanide metal complexes, and so on, have been employed for this type of reaction.[5,6] However, the use of chiral zinc catalysts for this reaction has been less explored although the chiral zinc complexes of ligands **1**[8] and **2**[9] have been recently reported to be efficient catalysts for a variety of catalytic asymmetric reactions. The Lewis acid **3** obtained from the reaction of diethylzinc and 1,1′-bi-2-naphthol (BINOL) was reported by Yamamoto to catalyze the enantioselective cyclization of unsaturated aldehydes.[10] Very recently, Yamamoto's Zn–BINOL complex **3** was found to be an enantioselective catalyst for asymmetric Diels–Alder reaction of *N*-alkoxyacrylamides with cyclopentadiene or aza-Diels–Alder reaction of Danishefsky's diene with imines by Renaud and Whiting.[11] However, stoichiometric amount of Zn–BINOL complex was required in order to ensure an acceptable enantioselectivity and reactivity of the reactions. A successful application of catalytic amount of BINOLate–zinc complex as efficient chiral Lewis acid for HDA was reported in our previous communication.[12] The Zn–BINOLate complex (**4**) prepared in situ from the reaction of 3,3′-dibromo-1,1′-bi-2-naphthol

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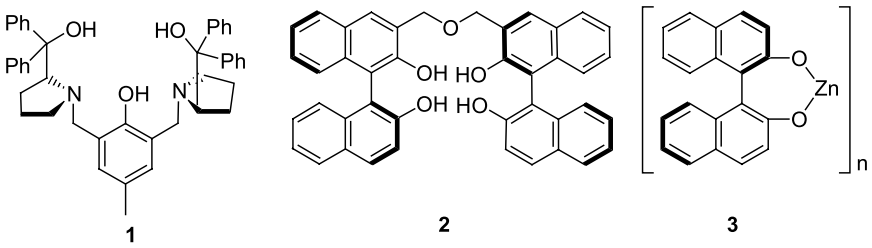
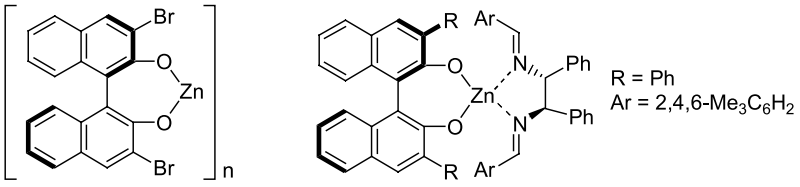
(3,3′-Br_2-BINOL) with Et_2Zn was found to be highly efficient for the catalysis of enantioselective reaction of Danishefsky's diene and aldehydes, affording 2-substituted 2,3-dihydro-4*H*-pyran-4-one in up to quantitative yield and 98% ee. Moreover, the asymmetric activation of 3,3′-Ph_2BINOL–Zn (**5**) complex with diimine has been found to be a useful strategy for achieving high efficiency and enantioselectivity in catalytic asymmetric diethylzinc addition to aldehydes.[13,14] Accordingly, if the enantioselective catalysis of HDA reaction can be realized with the catalysis of diimine-activated Zn–binolate complexes, it would be possible to carry out both HDA and diethylzinc addition reactions in one-pot with a single catalyst.



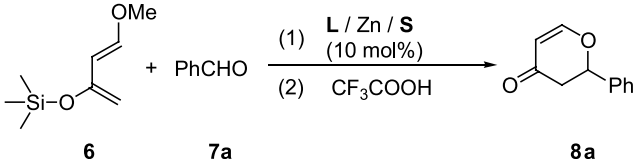
1 **2** **3**



4 **5**

2. Results and discussion

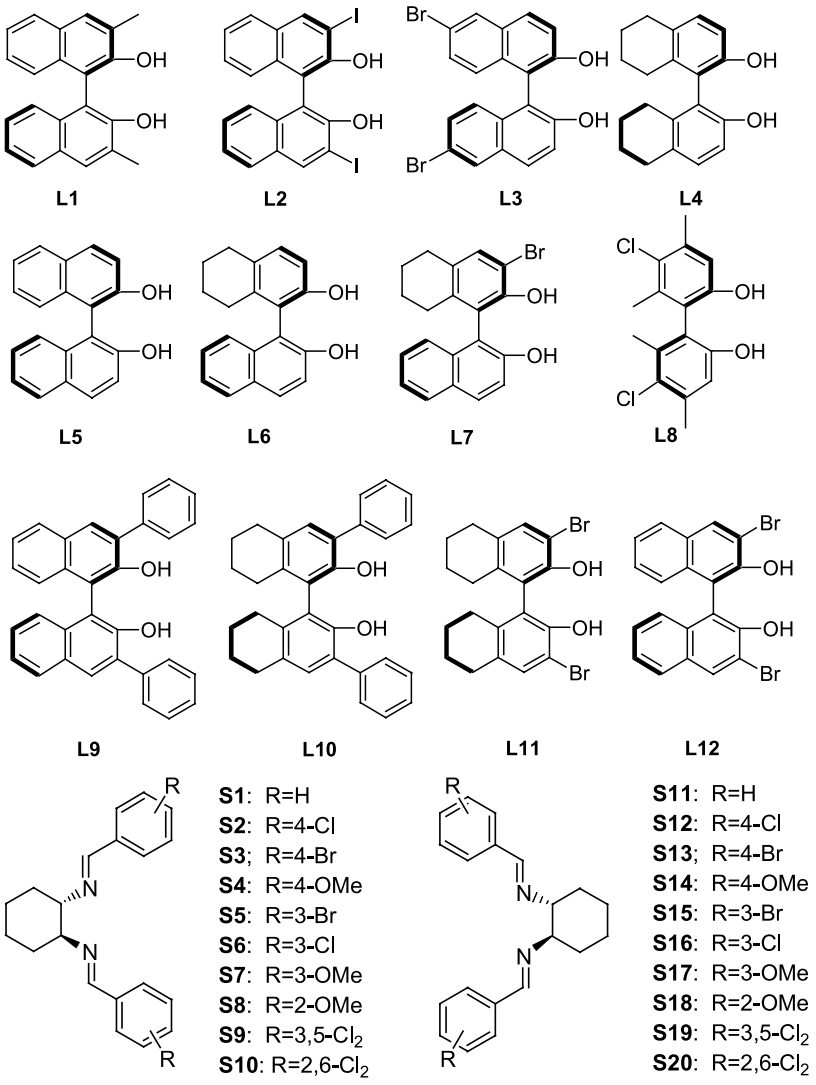
As an effort to explore the potential application of diimine-activated Zn–binolate complexes with the structures like **5** as catalysts for two distinct asymmetric reactions such as diethylzinc addition and hetero-Diels–Alder reaction, we first investigated the possibility of using this type of complexes for the promotion of hetero Diels–Alder (HDA) reaction of Danishefsky's diene (**6**) with benzaldehyde (**7a**).[5,6] The initial trials using complex **3** in combination with diimine **S1** (Scheme 1) as the catalyst for HDA reaction between **6** and **7a** (Eq. 1) showed that the reaction proceeded smoothly at 0 °C to give (*S*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one **8a** in 78% yield with moderate enantioselectivity (63.6%). This result prompted us to further improve the enantioselectivity of the reaction by tuning the steric and electronic features in the diol ligands and diimine activators through a combinatorial approach.[15] Accordingly, a library of chiral diol ligands including commercially available or easily prepared BINOL and biphenol derivatives (**L1**–**L12**) and a library of diimines (**S1**–**S20**) derived from enantiopure 1,2-diaminocyclohexane were created, respectively (Scheme 1). High throughput screening of the chiral Zn catalyst library with 240 members generated by combining the members of diol ligand (**L1**–**L12**) and diimine activator (**S1**–**S20**) libraries with Et_2Zn showed that all of the catalysts could promote the HDA reaction of **6** with **7a** at 0 °C to give the desired product **8a**. The results were summarized in Figure 1, which clearly demonstrated that the enantioselectivity and reactivity of the reaction were significantly influenced by both the electronic effect and steric hindrance of the substituents at 3,3′-positions of BINOL. The serious steric hindrance of phenyl groups at 3,3′-positions of BINOL (**L9**, **L10**) was found to be unfavorable for the reaction. Moreover, the absolute configuration of product was mainly controlled by the chirality of diol ligands, and the level of enantioselectivity of the reaction could be affected by the chirality and steric environment of diimine activators. The effect of binaphthyl backbone was not evident in the cases of **L4**–**6**. However, in the asymmetric induction of 3,3′-substituted BINOL derivatives, partially reduced binaphthyl ligands **L11**, **L10** are inferior to their parent ligands **L12** and **L9** in terms of both enantioselectivity and reactivity. Among the chiral diols screened for this reaction, (*S*)-3,3′-dibromo-1,1′-bi-2-naphthol (3,3′-Br_2-BINOL, **L12**) turns out to be the most efficient one in the presence of various diimines, affording the product in up to quantitative yield and 93.8% ee.



6 **7a** **8a**

(1)

The reaction catalyzed by the lead combinations (**L12** with **S2**–**3**, **S6**–**7**, **S10**–**S13**, **S15**, or **S20**) was further optimized by lowering the reaction temperature to −20 °C. It was found that **8a** could be obtained in up to 98.7% ee and quantitative yield with the catalysis of Zn complex of **L12**/**S13** or **L12**/**S20** combination (entries 8 and 10, Table 1). Accordingly, the optimized catalysts **L12**/Zn/**S2**, **L12**/Zn/**S7**, **L12**/Zn/**S13**, and **L12**/Zn/**S20** were submitted to the catalysis of the reactions of the Danishefsky's diene with a variety of aldehydes (**7a**–**k**) in order to examine their substrate scope adaptability. As shown in Table 2, the optimized catalysts were applicable for the promotion of HDA reaction of **6** with a variety of aldehydes **7a**–**k**, including aromatic and olefinic derivatives, to give corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones in excellent yields and enantioselectivities with the



Scheme 1. Libraries of chiral diol ligands (**L1**–**L12**) and diimine activators (**S1**–**S20**).

exception of the cases of aliphatic (entry 3) and sterically demanding aromatic aldehydes (entry 11). It is obvious that all these results obtained in the presence of diimine activators are comparable or even superior to those achieved by the catalysis of **4** in the absence of activator. Particularly, the reaction of cinnamic aldehyde (**7d**) catalyzed by various diimine activated **L12**/Zn catalysts (entry 4, Table 2) afforded the corresponding cycloadduct **8d** in 91–>99% yields with 94.4–96.4% ee's, which are significantly higher

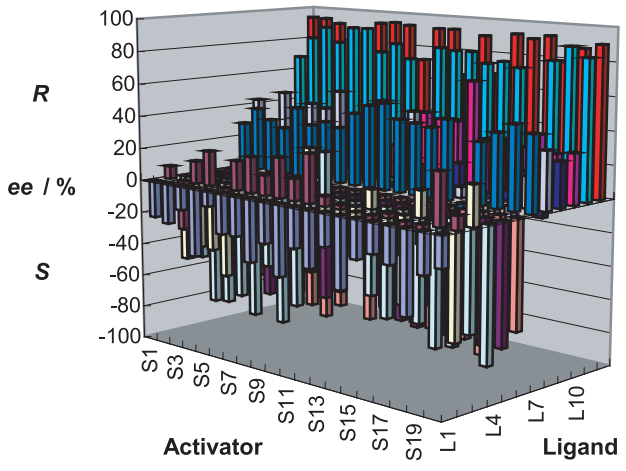


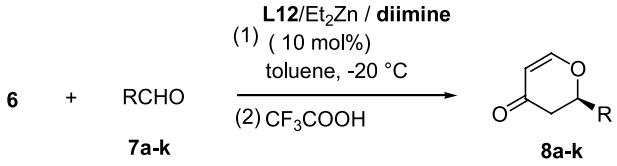
Figure 1. Screening of Zn catalyst library generated by assembling chiral diol ligands (**L1**–**L12**) and chiral diimine activators (**S1**–**S20**) with Zn for HDA reaction of **6** with **7a**.

Table 1. Enantioselective catalysis of the reaction between **6** and **7a** with the lead catalysts[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**L12**/Zn/**S2**	>99	98.6
2	**L12**/Zn/**S3**	>99	98.3
3	**L12**/Zn/**S6**	>99	97.9
4	**L12**/Zn/**S7**	93.8	98.6
5	**L12**/Zn/**S10**	96.9	97.2
6	**L12**/Zn/**S11**	>99	97.8
7	**L12**/Zn/**S12**	>99	98.2
8	**L12**/Zn/**S13**	>99	98.7
9	**L12**/Zn/**S15**	92.9	98.0
10	**L12**/Zn/**S20**	>99	98.7

[a] All of the reactions were carried out at −20 °C.
[b] Determined by HPLC with biphenyl as an internal standard.
[c] Enantiomeric excesses of product **8a** were determined by HPLC on Chiralcel OD column.

Table 2. The investigation of substrate scope for the reactions of Danishefsky's diene (**6**) with various aldehydes (**7a–k**) under the catalysis of optimized catalysts



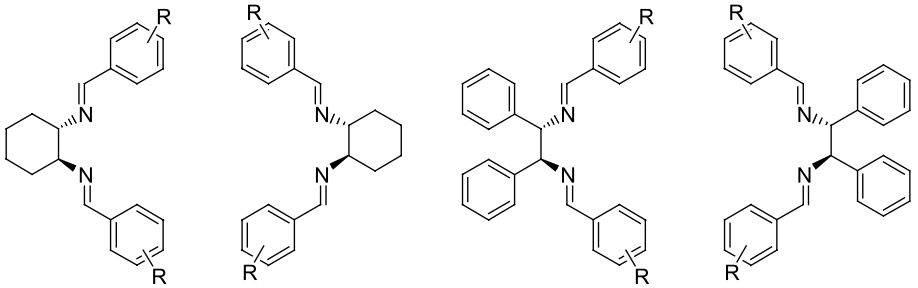
Entry	R in **7**	ee (%)[a]			
		L12/Zn/**S2**	**L12**/Zn/**S7**	**L12**/Zn/**S13**	**L12**/Zn/**S20**
1	Ph (**7a**)	98.6 (>99)	98.6 (93.8)	98.7 (>99)	98.7 (>99)
2	3-MeOPh (**7b**)	93.8 (>99)	92.7 (>99)	93.1 (>99)	88.4 (>99)
3	3-Ph(CH_2)$_2$ (**7c**)	58.8 (60.6)	56.6 (25.5)	51.8 (53.6)	43.7 (56.1)
4	*E*-Stylryl (**7d**)	96.4 (91.2)	96.4 (>99)	95.3 (>99)	94.4 (>99)
5	2-Furfuryl (**7e**)	95.7 (>99)	96.4 (>99)	90.4 (>99)	93.4 (>99)
6	4-NCPh (**7f**)	97.0 (>99)	95.7 (>99)	97.2 (>99)	96.2 (>99)
7	3-BrPh (**7g**)	98.0 (>99)	96.7 (>99)	96.3 (>99)	95.9 (>99)
8	3-ClPh (**7h**)	96.6 (>99)	54.5 (>99)	97.0 (>99)	70.1 (>99)
9	4-BrPh (**7i**)	96.6 (94.9)	96.6(>99)	95.8 (>99)	94.9 (>99)
10	4-ClPh (**7j**)	95.8 (81.3)	96.0 (91.4)	97.6 (92.8)	96.1 (>99)
11	2,6-Cl_2Ph (**7k**)	88.5 (>99)	82.7 (>99)	71.8 (>99)	83.5 (>99)

[a] Enantiomeric excesses of products were determined by HPLC on Chiralcel OD or Chiralpak AD column, and the data shown in parentheses are isolated yields.

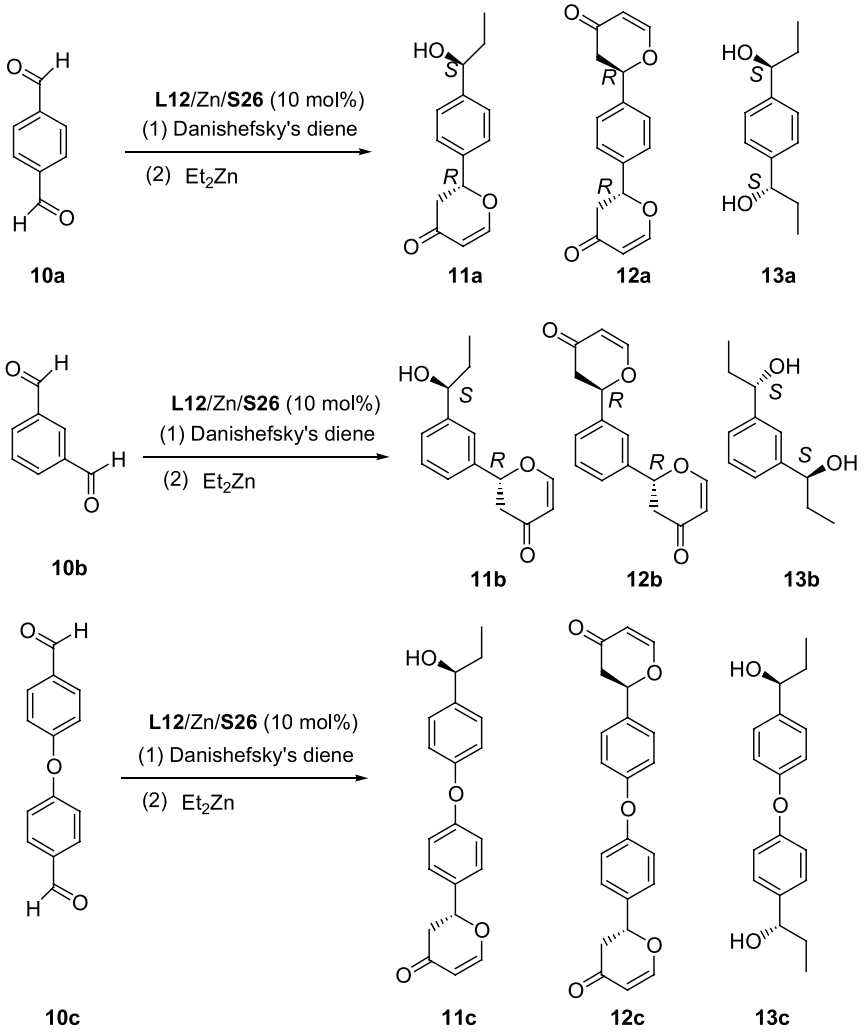
than those obtained with **L12**/Zn (**4**) (33% yield and 86.7% ee).[12]

With these leading results in hand, we switched our attention to the screening of highly efficient and enantioselective catalysts for diethylzinc addition to benzaldehyde by combining **L12** with a variety of diimine activators. The literature results showed that in the catalysis of diethylzinc addition to aldehydes, the steric hindrance of diimine activators were critical for getting maximum activation of BINOL-Zn catalyst.[13] Accordingly, a library of diimines with eight members (Scheme 2) was created by condensation of enantiopure 1,2-diphenylethylenediamine or 1,2-diaminocyclohexane with 2 equiv of 2,6-disubstituted or 2,4,6-trisubstituted benzaldehydes. A rapid screening of the chiral catalyst library composed of **L12** and the chiral activators shown in Scheme 2 for diethylzinc addition to benzaldehyde at 0 °C disclosed that **L12/S26** was the best combination, affording (*S*)-1-phenylpropanol ((*S*)-**9**) with 72% ee (Table 3). The enantioselectivity of the reaction could be improved to 94.5% at a lower reaction temperature (−20 °C) with the catalysis of **L12/S26**. Reexamination of **L12/S26** catalyst system for HDA reaction at −20 °C resulted in the formation of (*R*)-**5** with 97.4% ee and quantitative yield.

So far, we have discovered that catalyst (**L12**/Zn/**S26**) is highly efficient and enantioselective in both HDA reaction and diethyl zinc addition of benzaldehyde. This catalyst system has provided an excellent opportunity to conduct two asymmetric reactions in one-pot using a single catalyst. Thus, terephthalaldehyde **10a** was taken as a substrate for sequential asymmetric HDA reaction and diethylzinc addition to generate dihydropyranone and secondary alcohol moieties in one molecule (Scheme 3). The HDA reaction was first carried out in the presence of 10 mol% of **L12/S26** combined with 14 mol% of diethyl zinc for 30 h at −20 °C in toluene, and subsequently, 3 equiv of diethyl zinc was introduced directly to the reaction mixture for the second-step asymmetric addition under the same experimental conditions without workup of the first HDA reaction product. As shown in Table 4, the two asymmetric reactions proceeded efficiently and selectively to give product **11a** in 92% yield. It was found that the ee for the HDA reaction was 97.4%, and the de for the diethylzinc addition step was 95.0%, which were essentially identical to those obtained using benzaldehyde substrate. Similarly, the sequential asymmetric HDA reaction and diethylzinc addition of isophthalaldehyde **10b** using the same catalyst also demonstrated the excellent stereoselectivity for the formation of product **11b** (82% yield, entry 2, Table 4). The



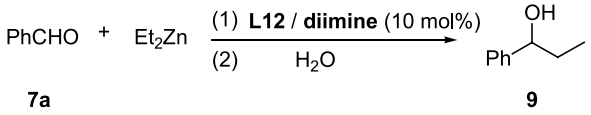
Scheme 2. A library of diimine activators for asymmetric diethylzinc addition to benzaldehyde.



Scheme 3. Sequential asymmetric catalysis of hetero Diels–Alder reaction and diethylzinc addition using a single catalyst.

configurations of two chiral centers formed through HDA and diethylzinc reactions in product **11a** and **11b** were tentatively assigned to be *R* and *S*, respectively, as shown in Scheme 3 on the basis of the results obtained using benzaldehyde as substrate mentioned above. The conversion and chemical selectivity for the first HDA step was found to be very high (monoadduct:diadduct > 96:4) in the reaction of **10a**. The high chemoselectivity of the first-step reaction is probably due to the fact that strong electron-withdrawing formyl group can make the dienophile more electrophilic to better interact with diene, and as a result to facilitate the first HDA reaction. After HDA reaction, the remaining second formyl group becomes much less reactive than the starting dialdehyde because of electron-donating property of α-dihydropyranyl moiety in the monoadduct. The significant decrease of chemoselectivity in the reaction of dialdehyde **10c** (entry 3, Table 4) further supports the explanation mentioned above, because the bridging oxygen atom between two benzaldehyde will block the electronic communication of two formyl groups in **10c**.

Table 3. Screening of activated catalysts for diethylzinc addition to benzaldehyde by combining **L12** with a variety of diimine activators



7a **9**

Entry	Diimine	Yield (%)[a]	ee (%)[b]	Configuration[c]
1	**S10**	>99	45.6	*S*
2	**S20**	>99	34.1	*S*
3	**S21**	91.2	48.1	*S*
4	**S22**	97.0	21.1	*R*
5	**S23**	75.5	45.7	*S*
6	**S24**	62.4	4.6	*S*
7	**S25**	76.3	14.2	*R*
8	**S26**	55.5	72.0	*S*

[a] Isolated yields.
[b] Determined with HPLC on Chiralcel OD column.
[c] Determined by comparison of the retention time with that of an authentic sample.

2.1. Mechanistic investigation of L12/Zn/diimine promoted HDA reaction

The search for nonlinear effects (NLE) in a given system has become a useful probe for analyzing the nature of the catalytic species or the nonreacting species involved in an asymmetric synthesis.[16] In our previous work, we have disclosed that there exists a very unusual and interesting NLE in the catalytic system with **L12**/Zn (Fig. 2a).[12] The

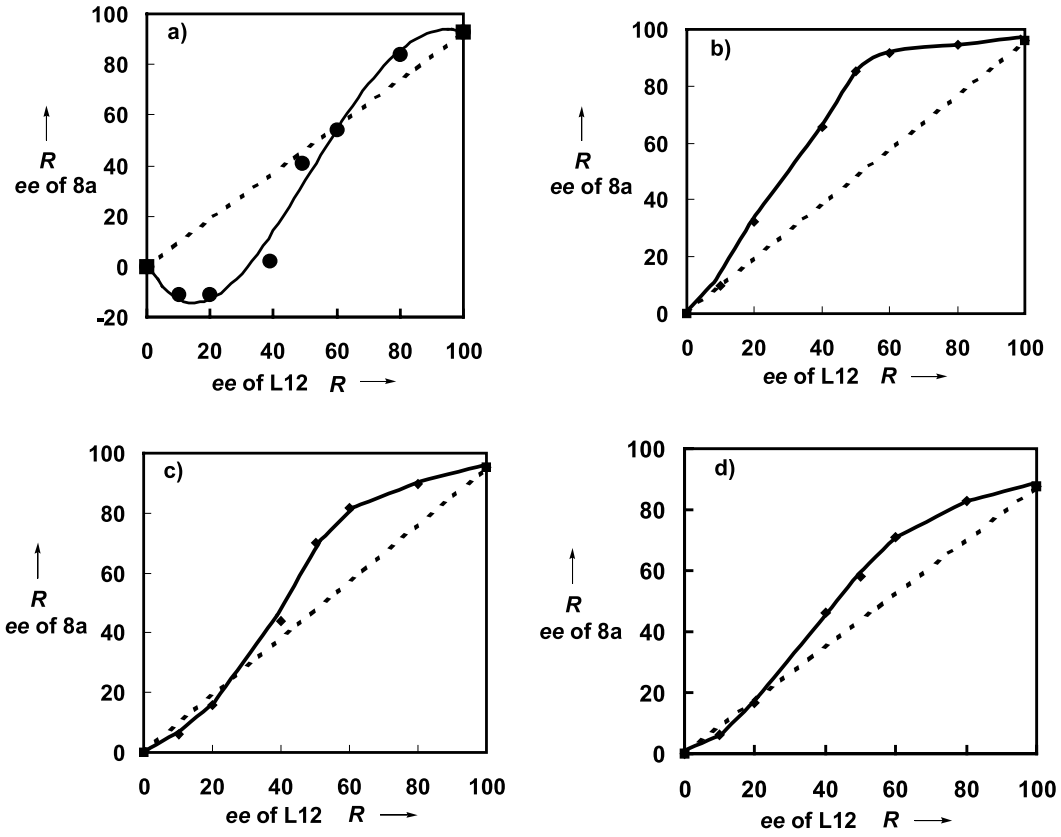
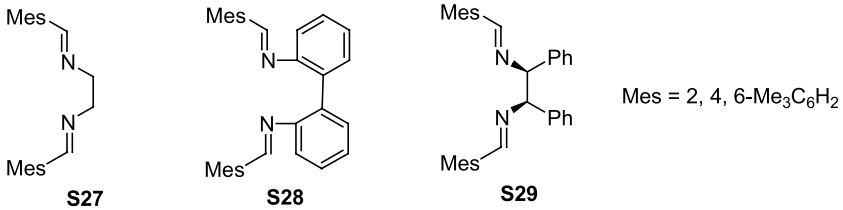


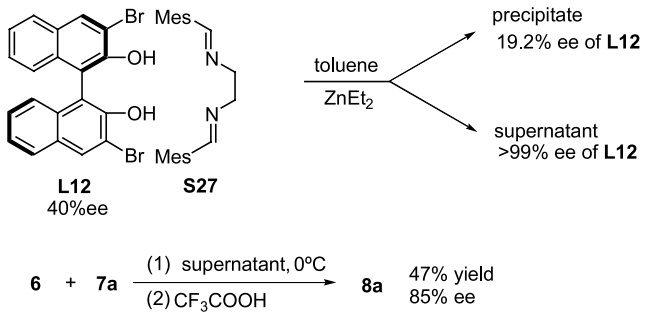
Figure 2. Enantioselectivity for the reaction of **6** with **7a** catalyzed by the Zn complexes of partially resolved (*R*)-**L12** in the absence (a), and in the presence of **S27** (b), **S28** (c) or **S29** (d). The broken lines indicate the expected values when the reactivity difference between (*R*)-**L12**/Zn/**diimine** and (*S*)-**L12**/Zn/**diimine** was not considered.

sign of product configuration was found to be dependent on the enantiopurity of **L12**, which implies that a variety of aggregated catalytic species might be involved in the catalytic system and the catalytic system may not be behaved in one particular model. The change of the catalytically active species might occur along with the variation of ligand enantiopurity. On the other hand, upon addition of achiral (**S27**–**28**) or *meso* (**S29**) diimines (Scheme 4) to the BINOLate-Zn catalyst system, the NLE patterns were dramatically changed in comparison with the case in the absence of diimine additive. These facts clearly indicated that the diimine additives indeed have some impact on the catalytic process. As shown in Figure 2c–d, when the ee value of **L12** was less than 20%, very week (−)-NLE could be observed in the presence of **S28** or **S29**. However, the catalytic systems demonstrated obvious (+)-NLE with the increase of enantiopurity of **L12**. This is apparently different from that observed by Walsh in the diethylzinc addition reaction, in which only linear relationship between the ee's of ligand and product was observed.[13c]

In order to further understand the origin of (+)-NLE observed in the present catalytic system, an experiment was carried out to isolate the precipitates formed during the catalyst preparation using 40% ee of **L12** in the presence of achiral diimine **S27** (Scheme 5). The enantiomeric excesses of **L12** in the isolated solids and in the supernatant were determined to be 19.2% and >99%, respectively, which implies that the enantiopurity of the catalytic species in the liquid phase of the reaction system could be significantly enriched due to the poor solubility of heterochiral zinc species. Employing this supernatant for the catalysis of the reaction between **6** and **7a** under the otherwise identical conditions afforded **8a** in 47% yield with 85% ee, which is higher than that obtained with in situ prepared catalyst using **S27** and **L12** having 40% ee. On the basis of these observations and the impact of diimine additives on the



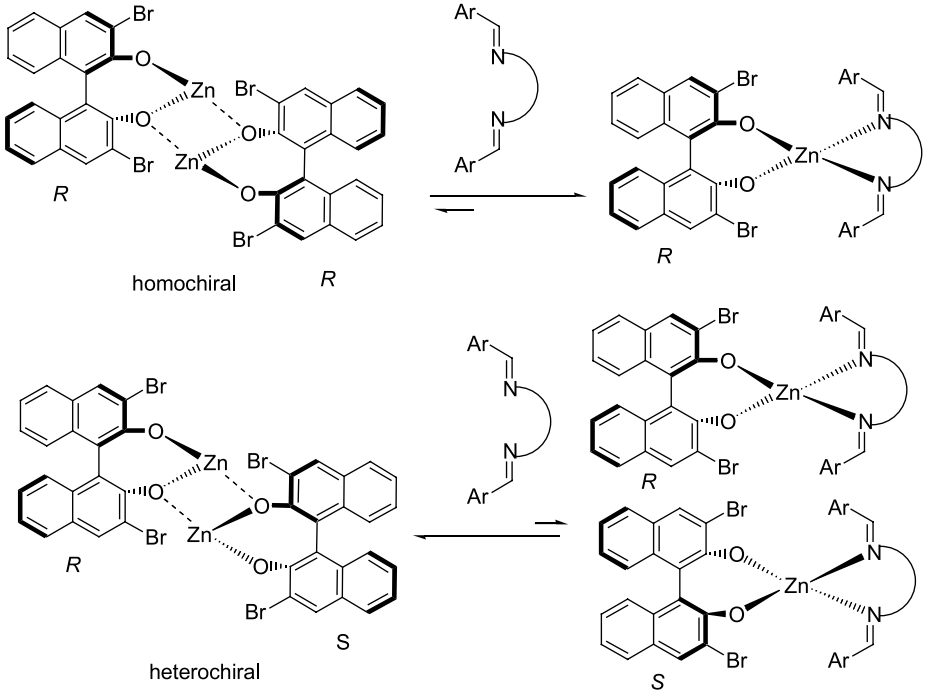
Scheme 4. Achiral and *meso*-diimine activators.



Scheme 5. Experimental probing the origin of (+)-NLE.

reaction, as well as the discovery by Walsh,[13c] we can conclude that the heterochirally aggregated Zn complexes might be much more stable than the homochiral species, and as a result, only trace amount of heterochiral aggregated Zn complexes in the reaction system could be dissociated by the coordination of diimine (Scheme 6). On the contrary, the homochiral species will be readily cleaved by the interaction with diimine to give the monomeric species that is responsible for the catalysis (Scheme 6).

As to the reaction pathway for the catalytic addition of Danishefsky's diene to aldehydes, two posibilities have been reported: Mukaiyama aldol condensation versus concerted [4+2] cycloaddition.[5,7,17] In our reaction system, ^{1}H NMR determination of primary reaction product before CF_3COOH treatment revealed that [4+2] cycloadduct were formed exclusively, which supported a concerted cycloaddition mechanism. The possible asymmetric induction pathway can be illustrated by using the schematic representation depicted in Figure 3 (the interaction pattern between catalyst and benzaldehyde was obtained by geometrical optimization using universal force field (UFF) implemented in GAUSSIAN 98) on the basis of experimental evidence disclosed above, the sense of asymmetric induction observed in the products, as well as the nonlinear effects in the catalytic systems. It can be assumed that the catalytically active species should be a monomeric zinc



Scheme 6. Interaction of homochiral and heterochiral dimeric zinc complexes with diimine additive.

Table 4. Sequential asymmetric reactions of dialdehydes in the presence of **L12**/Zn/**S26**[a]

Entry	Substrate	Et_2Zn (%)	Yield (%)[b]	ee (%)[c,d]	De (%)[d,e]
1	**10a**	14[c]+300[e]	**11a** (92)	**11a** (97.4)	**11a** (95.0)
			12a (<3)	**12a** (>99)	**12a** (96.9)
			13a (<3)	**13a** (nd)	**13a** (nd)
2	**10b**	14[c]+300[e]	**11b** (82)	**11b** (95.9)	**11b** (94.9)
			12b (6)	**12b** (>99)	**12b** (96.6)
			13b (10)	**13b** (nd)	**13b** (nd)
3	**10c**	14[c]+300[e]	**11c** (74)	**11c** (94.1)	**11c** (92)
			12c (17)	**12c** (>99)	**12c** (94.5)
			13c (8)	**13c** (nd)	**13c** (nd)

[a] All of the reactions were carried out at −20 °C in toluene with a molar ratio of dialdehyde: Danishefsky's diene:**L12**:**S26**=1:1.3:0.1:0.1.
[b] Isolated yields.
[c] For the first step HDA reaction.
[d] Determined by HPLC on Chiralcel OD or AD column. The de is the enantioselectivity of the second alkylation step.
[e] For diethylzinc addition.

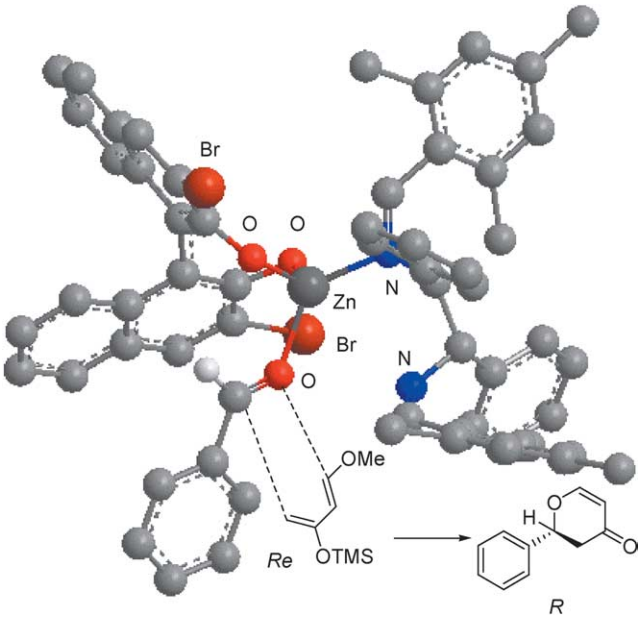


Figure 3. Schematic representation of the proposed asymmetric induction pathway for **L12**/Zn/diimine catalyzed enantioselective HDA reaction.

complex containing both binolate and diimine moieties. Upon the attaching of carbonyl group of aldehyde to the central zinc ion, one of the coordinated imino N will dissociate from zinc atom. Due to the steric shielding of naphthyl ring and bromo atom from the *Si* face of coordinated carbonyl group, the bound aldehyde is ready to accept the attack of Danishefsky's diene from *Re* face (Fig. 3) to give the product in *R* configuration.

3. Conclusion

In summary, a series of new type of chiral zinc catalysts containing (*R*)-3,3′-Br_2-BINOL ligand and diimine activators have been discovered based on the combinatorial approach, and were found to be highly efficient and enantioselective for HDA reaction of Danishefsky's diene with aldehydes, affording the corresponding 2,3-dihydro-4*H*-pyran-4-one derivatives in excellent yields and up to 98.7% ee. The application of this type of catalysts was also extended to the diethylzinc addition to the benzaldehyde, affording the corresponding secondary alcohol with up to 94.5% ee after optimization. On the basis of these facts, the integration of enantioselective HDA and diethylzinc addition reactions has been realized in one-pot with the promotion of a single chiral zinc catalyst in a sequential manner. The strategy described in the present work demonstrated the ability of a single catalyst to promote two distinct enantioselective reactions in one-pot, which might provide an important direction to the design of chiral catalysts for asymmetric synthesis. The impact of diimine additive on the catalytic system of HDA reaction was also investigated by probing the nonlinear effect of reaction system. The positive nonlinear effect exhibited in the catalytic system could be attributed to the poor solubility of the heterochiral zinc species. We hope these findings will be helpful for the further understanding of the asymmetric induction mechanism and design of new catalytic asymmetric reaction systems using activated Zn catalysts.

4. Experimental

4.1. General considerations

NMR spectra were recorded in deuteriochloroform on a Varian Mercury 300 (^{1}H 300 MHz; ^{13}C 75 MHz) spectrometer. Chemical shifts are reported in ppm relative to an internal standard: tetramethylsilane (0 ppm) for ^{1}H NMR and deuteriocholorform (77.0 ppm) for ^{13}C NMR. Coupling constants, *J*, are listed in Hertz. EI mass (70 ev) and ESI spectra were obtained on HP5989A and Mariner LC-TOF spectrometers, respectively. HRMS spectra were determined on a Kratos Concept instrument, Q-Tof micro instrument or APEXIII 7.0 TESLA FTMS. Elemental analysis was performed with an Elemental VARIO EL apparatus. Optical rotations were measured on a Perkin-Elmer 341 automatic polarimeter. Infrared spectra were obtained on a BIO-RAD FTS-185 Fourier transform spectrometer in KBr pellelts or neat. Liquid chromatographic analyses were conducted on a JASCO 1580 system. All the experiments sensitive to moisture or air were carried out under argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Dichloromethane, chloroform, and tetrachloromethane were freshly distilled from calcium hydride and THF, diethyl ether and toluene from sodium benzophenone ketyl.

4.2. Ligand library

All the members of ligand library were prepared according to the following literature methods: **L1**, **L2**, **L9**, **L10**, **L12**;[18] **L3**;[19] **L5**;[20] **L4**, **L6**;[6d] **L7**, **L8**;[21] **L11**.[22] The diimine activators **S1**–**S20** were prepared by simple condensation of tatarate salt of (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine, which was synthesized according to the procedure reported by Jacobsen[23] with corresponding aldehyde in methanol in the presence of K_2CO_3, and the following known diimines were characterized by comparing the analytical data with those reported in the literatures: **S1**, **S11**;[24] **S2**, **S10**, **S12**, **S20**;[25] **S3**, **S13**;[26] **S4**, **S14**;[27] **S8**, **S18**;[28] **S21**, **S22**;[29] **S23**, **S24**;[13a] **S25**, **S26**.[30] The achiral diimine activators **S27**–**28** were prepared by the condensation of 2,4,6-trimethylbenzaldehyde with corresponding diamines in refluxing toluene or methanol.[13c] Danishefsky's diene,[31] diethylzinc,[32] and dialdehyde **9c**[33] were prepared following the literature procedures.

4.2.1. (*R*,*R*)-*N*,*N*′-Di(3-bromobenzylidene)cyclohexane-1,2-diamine (S5) and (*S*,*S*)-*N*,*N*′-di(3-bromobenzylidene)-cyclohexane-1,2-diamine (S15). S5; $[\alpha]_D^{20}-268.2$ (*c* 0.4 in MeOH). **S15**; $[\alpha]_D^{20}+271.0$ (*c* 0.4 in MeOH); mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.13$ (s, 2H), 7.79 (t, $J=1.8$ Hz, 2H), 7.56–7.52 (m, 4H), 7.21–7.16 (m, 2H), 3.42–3.40 (m, 2H), 1.88–1.78 (m, 6H), 1.52–1.45 (m, 2H); FT-IR (KBr): $\nu=2927$, 2854, 1647, 1560, 1477, 1372, 1339, 1278, 1200, 1065, 939, 891, 794, 687 cm^{-1}; EI-MS (70 ev) (*m*/*z*): 448 (M^+, 2), 184 (100), 186 (94), 265 (37), 264 (29), 267 (25), 89 (20), 81 (16). Anal. Calcd for $C_{20}H_{20}Br_2N_2$: C,

53.66; H, 4.50; N, 6.25%. Found: C, 53.53; H, 4.63; N, 6.12%.

4.2.2. (*R*,*R*)-*N*,*N*′-Di(3-chlorobenzylidene)cyclohexane-1, 2-diamine (S6) and (*S*,*S*)-*N*,*N*′-di(3-chlorobenzylidene)-cyclohexane-1,2-diamine (S16). S6; $[\alpha]_D^{20}-300.9$ (*c* 0.4 in MeOH). **S16**; $[\alpha]_D^{20}+297.0$ (*c* 0.4 in MeOH); mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.14$ (s, 2H), 7.64 (t, $J=1.5$ Hz, 2H), 7.44–7.40 (m, 2H), 7.34–7.12 (m, 4H), 3.42–3.40 (m, 2H), 1.90–1.71 (m, 6H), 1.52–1.46 (m, 2H); FT-IR (KBr): $\nu=2931$, 2928, 1646, 1568, 1480, 1373, 1340, 1280, 1214, 1098, 1071, 939, 891, 796, 687, 426 cm^{-1}; EI-MS (70 ev) (*m*/*z*): 358 (M^+, 1), 140 (100), 186 (94), 142 (32), 221 (30), 220 (23), 138 (20), 89 (19). Anal. Calcd for $C_{20}H_{20}Cl_2N_2$: C, 66.86; H, 5.61; N, 7.79%. Found: C, 66.67; H, 5.72; N, 7.73%.

4.2.3. (*R*,*R*)-*N*,*N*′-Di(3-methoxybenzylidene)cyclohexane-1,2-diamine (S7) and (*S*,*S*)-*N*,*N*′-di(3-methoxybenzylidene)cyclohexane-1,2-diamine (S17). S7; $[\alpha]_D^{20}-306.2$ (*c* 0.5 in MeOH). **S17**; $[\alpha]_D^{20}+303.3$ (*c* 0.5 in MeOH); mp 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.24$ (s, 2H), 7.32–7.26 (m, 2H), 7.22–7.18 (m, 4H), 6.96–6.93 (m, 2H), 3.84 (s, 2H), 3.49–3.45 (m, 2H), 1.94–1.83 (m, 6H), 1.52–1.50 (m, 2H); FT-IR (KBr): $\nu=2936$, 2859, 1647, 1640, 1596, 1558, 1491, 1465, 1431, 1378, 1321, 1264, 1168, 1155, 1035, 802, 690, 429 cm^{-1}; EI-MS (70 ev) (*m*/*z*): 350 (M^+, 2), 136 (100), 135 (96), 134 (74), 217 (73), 214 (25), 186 (23), 121 (21). Anal. Calcd for $C_{22}H_{24}O_2N_2$: C, 75.40; H, 7.48; N, 7.99%. Found: C, 75.18; H, 7.53; N, 7.89%.

4.2.4. (*R*,*R*)-*N*,*N*′-Di(2-methoxybenzylidene)cyclohexane-1,2-diamine (S9) and (*S*,*S*)-*N*,*N*′-di(2-methoxybenzylidene)cyclohexane-1,2-diamine (S19). S9; $[\alpha]_D^{20}-250.8$ (*c* 0.4 in MeOH). **S19**; $[\alpha]_D^{20}+252.3$ (*c* 0.4 in MeOH); mp 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.08$ (s, 2H), 7.48 (d, $J=1.8$ Hz, 4H), 7.34 (t, $J=2.1$ Hz, 2H), 3.42–3.89 (m, 2H), 1.90–1.67 (m, 6H), 1.53–1.47 (m, 2H); FT-IR (KBr): $\nu=3092$, 3078, 2929, 2862, 2858, 1645, 1589, 1565, 1420, 1375, 1341, 1217, 1039, 862, 803, 604, 468 cm^{-1}; EI-MS (70 ev) (*m*/*z*): 426 (M^+, 0.4), 174 (100), 176 (62), 255 (62), 257 (33), 256 (30), 254 (29), 173 (26). Anal. Calcd for $C_{20}H_{18}Cl_4N_2$: C, 56.10; H, 4.24; N, 6.49%. Found: C, 56.13; H, 4.38; N, 6.49%.

4.3. High throughput screening of the chiral Zn catalyst library generated by assembling the member of diol ligand (L1–L12) and diimine activator (S1–S20) libraries with Zn for HDA reaction of Danishefsky's diene (7) with benzaldehyde (8a)

To each member of an array of 1.5 mL polypropylene microtubes were added 0.050 M toluene solution of **Lm** (0.01 mmol, 0.2 mL) and 0.050 M toluene solution of **Sn** (0.01 mmol, 0.2 mL), and then 1 M solution of Et_2Zn in hexane (0.012 mmol, 12 μL) was added. The mixtures were kept at room temperature for 0.5 h and then to each microtube freshly distilled benzaldehyde **8a** (10.6 mg, 0.10 mmol) was added. The microtubes were then set up in a cooling bath to maintain the temperature at 0 °C for 30 min, and finally Danishefsky's diene (17.2 mg, 0.1 mmol) was quickly added to each tube. The reaction was quenched by introducing 5 drops of trifluoroacetic acid after 24 h. Internal standard biphenyl (10 mg) in toluene and saturated sodium bicarbonate aqueous solution (0.5 mL) were added to the quenched mixture. The organic layer was separated and submitted to HPLC analysis for the determination of yields and enantiomeric excesses (ee). The yields were determined with a JASCO HPLC1500 with autosampler on Intersil CN-3 column: eluent hexane/2-propanol 97:3, flow rate = 0.5 mL/min; UV detection at $\lambda=254$ nm; t_R of biphenyl, 7.6 min (factor 1.000); t_R of benzaldehyde, 11.4 min (factor 1.208); t_R of 2-phenyl-2, 3-dihydro-4*H*-pyran-4-one, 23.0 min (factor 1.742). The enantiomeric excesses were determined by using the same HPLC analytical system on Chiralcel OD column: eluent hexane/2-propanol 90:10, flow rate = 1.0 mL/min; UV detection at $\lambda=254$ nm; $t_R=13.0$ min (*S* enantiomer), 15.2 min (*R* enantiomer). The results for the catalyst library screening were summarized in Figure 1.

4.3.1. A typical procedure for asymmetric catalysis of HDA reaction of Danishefsky's diene (6) with aldehydes (7) under optimized conditions. To a 1.5 mL polypropylene microtube were added 0.05 M toluene solution of **L12** (0.01 mmol, 0.2 mL), 0.050 M toluene solution of **S13** (0.01 mmol, 0.2 mL), and 1 M solution of Et_2Zn in hexane (0.014 mmol, 14 μL, 1 M in hexane). The mixture was kept at room temperature for 0.5 h and then freshly distilled benzaldehyde (**7a**) (10.6 mg, 0.10 mmol) was added. Danishefsky's diene (**6**) (34.4 mg, 0.2 mmol) was charged when the reaction temperature was kept constant at −20 °C. The reaction was quenched by introducing 10 drops of trifluoroacetic acid after 24 h. Saturated sodium bicarbonate aqueous solution (0.8 mL) was added to the quenched mixture. The aqueous layer was extracted with diethyl ether (3×15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silcal gel with hexane/ethyl acetate 4:1 as eluent to afford 17.4 mg (>99% yield) of (*R*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**8a**) as colorless oil with 98.7% ee; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 7.46 (d, $J=6.6$ Hz, 1H), 7.42–7.36 (m, 5H), 5.51 (dd, $J=$ 5.7, 1.2 Hz, 1H), 5.41 (dd, $J=14.18$, 3.4 Hz, 1H), 2.95–2.84 (m, 1H), 2.68–2.60 (m, 1H); FT-IR (neet): $\nu_{max}=3064$, 1676, 1596, 1402, 1272, 1228, 1210, 1040, 990, 934, 864, 826, 796, 760, 732, 720, 640, 612 cm^{-1}. The results were summarized in Table 1.

Following the optimized procedure described above, the scope of the substrate was investigated under the catalysis of **L12**/Zn/diimine. The results were shown in Table 2.

4.4. Procedure for screening of enantioselective catalysts for diethylzinc addition to benzaldehyde by combining L12 with a variety of diimine activators

To each member of an array of 1.5 mL polypropylene microtubes were added 0.10 M toluene solution of **L12** (0.02 mmol, 0.2 mL) and 0.10 M toluene solution of diimine activators (shown in Scheme 2) (0.02 mmol, 0.2 mL), then freshly distilled benzaldehyde (21.2 mg, 0.20 mmol) was added. The microtubes were then set up in a cooling bath to maintain the temperature at 0 °C for 30 min, and finally Et_2Zn (0.4 mL, 1 M in toluene, 0.4 mmol) was quickly added. After standing at 0 °C for

4 h, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the crude product was purified by flash chromatography on silica gel with EtOAc/hexane 1:7 as eluent to give 1-phenyl-1-propanol as a colorless liquid. Its enantiomeric excess was determined with HPLC on Chiralcel OD column: eluent hexane/2-propanol 98.5:1.5, flow rate = 1.0 mL/min; UV detection at $\lambda = 254$ nm; $t_R = 18.6$ min (*R* enantiomer), 22.9 min (*S* enantiomer). The results of screening were summarized in Table 3.

4.4.1. The optimized procedure for diethylzinc addition to benzaldehyde under the catalysis of L12/S26. To a 1.5 mL polypropylene microtubes were added 0.10 M toluene solution of **L12** (0.02 mmol, 0.2 mL), 0.10 M toluene solution of **S26** (0.02 mmol, 0.2 mL) and freshly distilled benzaldehyde (21.2 mg, 0.20 mmol) was added. Et_2Zn (0.4 mmol, 0.4 mL, 1 M in toluene) was introduced to the reaction system after the microtube was kept at −20 °C for 30 min. The reaction was continued for 24 h at −20 °C before it was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the crude product was purified by flash chromatography on silica gel with EtOAc/hexane 1:7 as eluent to give 1-phenyl-1-propanol 24.0 mg (87.6% yield, 94.5% ee (*S*)) as colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (t, 3H, $J = 7.8$ Hz), 1.65–1.84 (m, 2H), 1.88 (br s, 1H), 4.58 (t, 1H, $J = 7.5$ Hz), 7.23–7.38 (m, 5H).

4.5. General procedure for sequential asymmetric catalysis

All of the experiments were carried out under argon. Weighed amounts of chiral ligand **L12** (8.9 mg, 0.02 mmol) and chiral activator **S26** (9.4 mg, 0.02 mmol) were introduced into a 1.5 mL polypropylene microtube. Toluene (0.8 mL), Et_2Zn (0.28 mmol, 28 μL, 1 M in hexane) and aldehyde **10** (0.2 mmol) were added to the microtube in glove box with a microsyringe. The microtube was then set up in a cooling bath to maintain the temperature at −20 °C for 30 min, and finally Danishefsky's diene **6** (41.2 mg, 0.26 mmol) was quickly added. After agitation at −20 °C for 30 h, Et_2Zn (0.6 mmol, 0.2 mL, 3 M in toluene) was introduced to the reaction system. After the reaction was continued for additional 24 h, the microtube was opened and trifluoacetic acid was added to quench the reaction. The aqueous layer was neutralized with $NaHCO_3$ aqueous solution and extracted with ethyl acetate for three times. The combined organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography on silica gel with EtOAc/hexane 1:2 as eluent to give **11** as colorless oil.

4.5.1. Compound 11a. Yield 92%, 42.8 mg; $[\alpha]_D^{25} -110$ (*c* 2.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$ (d, $J = 6.0$ Hz, 1H), 7.40 (s, 4H), 5.53 (dd, $J = 6.0$, 1.2 Hz, 1H), 5.43 (dd, $J = 14.1$, 3.9 Hz, 1H), 4.65 (t, $J = 6.3$ Hz, 1H), 2.86–2.97 (m, 1H), 2.62–2.69 (m, 1H), 1.70–1.83 (m, 3H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 192.3, 163.3, 145.6, 136.7, 126.4, 126.1, 107.2, 80.8, 75.4, 43.1, 31.9, 10.0; MS (EI, 70 ev) (*m*/*z* %): 232 (2), 203 (61), 133 (100), 105 (41), 77 (25); HRMS: calcd for $C_{14}H_{16}O_3$: 232.1099; found: 232.1092. The enantiomeric excess and diastereoselectivity were determined by HPLC on Chiralcel OD column with hexane/isopropanol 80:20 as eluent, flow rate = 1.0 mL/min, $t_{R1} = 12.8$ min, $t_{R2} = 14.0$ min, $t_{R3} =$ 16.3 min, $t_{R4} = 18.1$ min.

4.5.2. Compound 12a. Yield 3%, 1.7 mg, >99% ee. Mp 170–172 °C; $[\alpha]_D^{20} -179$ (*c* 0.3 in $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.52$ (d, $J = 5.7$ Hz, 2H), 7.34 (s, 4H), 5.39 (d, $J = 13.5$ Hz, 2H), 5.24 (d, $J = 8.1$ Hz, 2H), 2.69–2.79 (m, 2H), 2.32 (d, $J = 12$ Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 191.3$, 173.7, 138.6, 126.6, 106.7, 79.8, 42.4; FT-IR (KBr): $\nu = 2971$, 1667, 1592, 1579, 1403, 1374, 1274, 1230, 1214, 1172, 1403, 976, 937, 841, 798 cm^{-1}; EI-MS *m*/*z* (relative intensity): 270 (M^+, 1.76), 130 (100), 241 (21.88), 128 (15.65), 131 (15.01), 115 (12.25), 171 (11.03), 182 (10.36); HRMS (EI): calcd for $C_{16}H_{14}O_4$: 270.0892; found: 270.0856. The enantiomeric excess and diastereoselectivity were determined by HPLC on Chiralcel OD column, hexane:isopropanol 65:35, flow rate = 1.0 mL/min, $t_{RR} = 26.88$ min; $t_{SS} = 21.72$ min; $t_{meso} =$ 23.93 min.

4.5.3. Compound 11b. Colorless oil, 38.2 mg, 95.0% ee, 95.0% de, 82% yield; $[\alpha]_D^{20} -90.5$ (*c* 1.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$ (d, $J = 6.0$ Hz, 1H), 7.28–7.40 (m, 4H), 5.53 (dd, $J = 5.7$, 1.2 Hz, 1H), 5.43 (dd, $J = 14.1$, 3.3 Hz, 1H), 4.64 (t, $J = 6.6$ Hz, 1H), 2.84–2.94 (m, 1H), 2.61–2.67 (m, 1H), 2.20 (s, 1H), 1.75–1.83 (m, 2H), 0.93 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 192.3, 163.3, 145.6, 137.9, 128.9, 126.6, 125.1, 123.7, 107.3, 81.1, 75.6, 43.3, 32.0, 10.1; FT-IR (neat): $\nu = 3423$, 2966, 2933, 2877, 2248, 1673, 1591, 1405, 1276, 1221, 1041, 991, 912, 799, 734, 706 cm^{-1}; EI-MS *m*/*z* (relative intensity): 232 (M^+, 5.57), 133 (100), 105 (55.59), 203 (48.46), 77 (29.04), 159 (23.18), 103 (19.04), 79 (16.59); HRMS (EI): calcd for $C_{14}H_{16}O_3$: 232.1099; found: 232.1103. The enantiomeric excess and diastereoselectivity were determined by HPLC on Chiralcel OD column, hexane:isopropanol 85:15, flow rate = 1.0 mL/min, $t_{R1} =$ 12.2 min, $t_{R2} = 13.1$ min, $t_{R3} = 15.8$ min, $t_{R4} = 30.9$ min.

4.5.4. Compound 12b. Yield 6%, 3.5 mg, >99% ee, 3% meso. Mp 118–120 °C; $[\alpha]_D^{20} -145$ (*c* 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.60$ (d, $J = 5.7$ Hz, 2H), 7.49 (s, 1H), 7.35 (s, 3H), 5.44 (dd, $J = 14.1$, 2.4 Hz, 2H), 5.30 (d, $J = 6.0$ Hz, 2H), 2.77–2.89 (m, 2H), 2.38 (d, $J =$ 14.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 191.4$, 163.8, 138.7, 128.8, 126.7, 124.7, 106.7, 80.0, 42.4; FT-IR (KBr): $\nu = 3070$, 3062, 2908, 1666, 1599, 1591, 1411, 1353, 1284, 1272, 1230, 1218, 1039, 994, 940, 796, 707 cm^{-1}; EI-MS *m*/*z* (relative intensity): 270 (M^+, 2.16), 149 (100), 130 (95.17), 129 (26.92), 171 (21.35), 182 (18.33), 128 (17.08), 131 (15.49); HRMS (EI): calcd for $C_{16}H_{14}O_4$: 270.0892; found: 270.08882; The enantiomeric excess and diastereoselectivity were determined by HPLC on Chiralcel AD column, hexane:isopropanol 80:20, flow rate = 1.0 mL/min, $t_{RR} = 19.82$ min; $t_{SS} = 28.74$ min; $t_{meso} = 21.00$ min.

4.5.5. Compound 11c. Colorless oil, 47.7 mg, 74% yield, 94.1% ee, 92.1% de; $[\alpha]_D^{20}-84.9$ (*c* 2.9 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.49$ (d, $J=6.3$ Hz, 1H), 7.36 (t, $J=8.4$ Hz, 4H), 7.03 (t, $J=7.8$ Hz, 4H), 5.54 (d, $J=5.7$ Hz, 1H), 5.39 (dd, $J=14.1$, 3.0 Hz, 1H), 4.61 (t, $J=6.6$ Hz, 1H), 2.98–2.88 (m, 1H), 2.69–2.62 (m, 1H), 2.25 (br s, 1H), 1.87–1.73 (m, 2H), 0.94 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=192.2$, 163.3, 158.0, 155.7, 140.1, 132.2, 127.8, 127.5, 119.1, 118.5, 107.2, 80.6, 75.4, 43.1, 31.9, 10.3; IR (neat): $\nu=3421$, 3062, 2966, 2932, 2876, 1674, 1599, 1504 1404, 1274, 1233, 1211, 1170, 1041, 987, 934, 837, 797 cm^{-1}; EI-MS *m/z* (relative intensity): 324 (M^+, 10.02), 257 (100), 225 (83.89), 211 (51.99), 295 (51.61), 49 (44.51), 84 (40.63), 77 (32.72); HRMS (EI): calcd for $C_{20}H_{20}O_4$: 324.1356; found: 324.1354. The enantiomeric excess and diastereoselectivity were determined by HPLC on Chiralcel OD column, hexane:isopropanol 80:20, flow rate = 1.0 mL/min, $t_{R1}=17.2$ min, $t_{R2}=19.3$ min, $t_{R3}=21.8$ min, $t_{R4}=24.5$ min.

4.5.6. Compound 12c. Colorless oil, 12.6 mg, 17% yield, >99% ee, 5% meso; $[\alpha]_D^{20}-128.0$ (*c* 1.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.49$ (d, $J=6.0$ Hz, 2H), 7.42–7.38 (m, 4H), 7.10–7.06 (m, 4H), 5.54 (dd, $J=6.0$, 0.9 Hz, 2H), 5.43 (dd, $J=14.1$, 3.3 Hz, 2H), 2.99–2.88 (m, 2H), 2.71–2.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=1192.1$, 163.2, 157.3, 132.8, 127.9, 119.1, 107.3, 80.6, 43.2; FT-IR (neat): $\nu=3071$, 1684, 1668, 1603, 1588, 1506, 1405, 1272, 1243, 1231, 1209, 1172, 1049, 1038, 988, 933, 836 cm^{-1}; EI-MS *m/z* (relative intensity): 362 (M^+, 1.0), 225 (100), 295 (75.39), 211 (66.18), 77 (21.25), 226 (17.05), 91 (16.33), 296 (15.26), 324 (15.15); HRMS (EI): calcd for $C_{22}H_{18}O_5$: 362.1149; found: 362.1144. The enantiomeric excess and diastereoselectivity were determined by HPLC on Chiralcel OD column, hexane:isopropanol 80:20, flow rate = 1.0 mL/min, $t_{RR}=22.3$ min; $t_{SS}=39.2$ min; $t_{meso}=28.1$ min.

4.6. Investigation of nonlinear effects

The examination of NLE was carried out following the similar procedure mentioned above at 0 °C with 10 mol% of **L12** with specified enantiopurity in the absence of or in the presence of achiral diimine activators (**S27–S29**). The enantiomeric excesses of the **L12** employed for the reaction were measured by HPLC on Chiralpak AD column (hexane/isopropanol 60:40, flow rate = 1.0 mL/min, $t_{R1}=13.9$ min (*R*), $t_{R2}=19.4$ min (*S*)) before they were submitted to the catalysis. The yields were determined with a JASCO HPLC1500 with autosampler on Intersil CN-3 column: eluent hexane/2-propanol 97:3, flow rate = 0.5 mL/min; UV detection at $\lambda=254$ nm; t_R of biphenyl, 7.6 min (factor 1.000); t_R of benzaldehyde, 11.4 min (factor 1.208); t_R of 2-phenyl-2, 3-dihydro-4*H*-pyran-4-one, 23.0 min (factor 1.742). The enantiomeric excesses were determined by using the same HPLC analytical system on Chiralcel OD column: eluent hexane/2-propanol 90:10, flow rate = 1.0 mL/min; UV detection at $\lambda=254$ nm; t_R 13.0 min (*S* enantiomer), 15.2 min (*R* enantiomer). The results were shown in Figure 2a–d.

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Synthesis and characterisation of *N*-1,10-phenanthrolin-5-ylalkylamides and their photosensitising heteroleptic Ru(II) complexes

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Abstract—In the context of our studies on ruthenium(II) complexes containing polyazaheterocyclic ligands as functionalised photosensitisers for singlet molecular oxygen generation in heterogeneous phase, we describe the synthesis and spectroscopic characterisation of different amide-functionalised *N*-1,10-phenanthrolin-5-ylalkylamides. These chelators are used to obtain heteroleptic $[Ru(phen)_2\mathbf{L}]^{2+}$ complexes, where **L** stands for 2-iodo-*N*-1,10-phenanthrolin-5-ylacetamide (5-iap), 4-oxo-4-(1,10-phenanthrolin-5-ylamino)butanoic acid (5-suap), 5-oxo-5-(1,10-phenanthrolin-5-ylamino)pentanoic acid (5-glap) and *tert*-butyl 4-oxo-4-(1,10-phenanthrolin-5-ylamino)butylcarbamate (BOC-5-ngap). The spectroscopic data, excited state lifetimes and quenching rate constants with O_2 (ca. 3.7×10^9 L mol^{-1} s^{-1}) of these novel complexes are also reported.

1. Introduction

Ruthenium(II) complexes with polyazaaromatic chelating ligands have been widely studied because of their unique spectroscopic, photochemical and redox properties.[1,2] Since 1959, when the luminescence of tris(2,2′-bipyridine)ruthenium(II), $[Ru(bpy)_3]^{2+}$, was described for the first time,[3] these structures have been used in many areas of chemistry, such as photonic and optoelectronic devices,[4] luminescent probes for micelles and other organised media,[5] artificial photonucleases and photochemical reporters of the rich DNA morphology,[6] development of therapeutic agents,[7] constituents of supramolecular edifices,[8] chemiluminescent analytical reagents[9] and luminescent indicator dyes for optochemical sensing,[10] to name just a few.

The variety of applications for these complexes does not end here: due to their microsecond excited state lifetimes and the diffusion-controlled O_2 quenching rate constants, they display a high quantum yield of singlet (molecular) oxygen, abbreviated $O_2(^1\Delta_g)$, production (Φ_Δ).[11,12] For instance, a Φ_Δ of 1.0 has been measured for tris(4,7-diphenyl-1,10-phenanthroline)ruthenium(II) in methanol solution.[12] Such reactive oxygen species, typically generated by electronic energy transfer from the triplet excited state of certain dyes (methylene blue, rose bengal, phenalenone, porphyrins,…),[13] are useful for photosensitised oxidation of organic compounds and fine chemicals synthesis,[14,15] molecular probing of microheterogeneous systems,[16] as the 'magic bullet' in photodynamic therapies (PDT)[17] and water disinfection.[18,19] For both synthetic and disinfection purposes, immobilisation of the photosensitising dye onto a solid support allows an easy removal after fulfilling its function.

The spectroscopic, photophysical and photochemical features of Ru(II) polypyridyl complexes may be finely tuned by a judicious molecular design of the heterocyclic chelating ligands in the co-ordination sphere. Moreover, introduction of different ligands around the metal centre (so-called heteroleptic complexes) provides an even finer tuning of their properties and allows introduction of suitable chemical groups for covalent attachment to functionalised solid supports.

In this work, we describe the synthesis of a family of *N*-1,10-phenanthrolin-5-ylalkylamide ligands (**L**) containing a spacer and an electrophilic or nucleophilic end group to tether the corresponding heteroleptic Ru(II) complex to either organic or inorganic polymer supports bearing the opposite chemical function. Phen (1,10-phenanthroline) has

Keywords: 1,10-Phenanthroline; Ruthenium(II) complexes; Polyazaheterocyclic ligands; Singlet oxygen; Photosensitisers.
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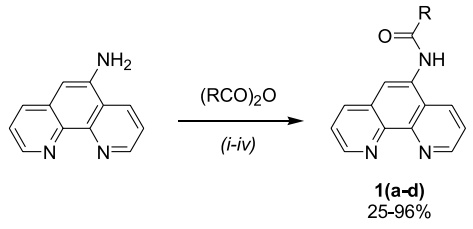
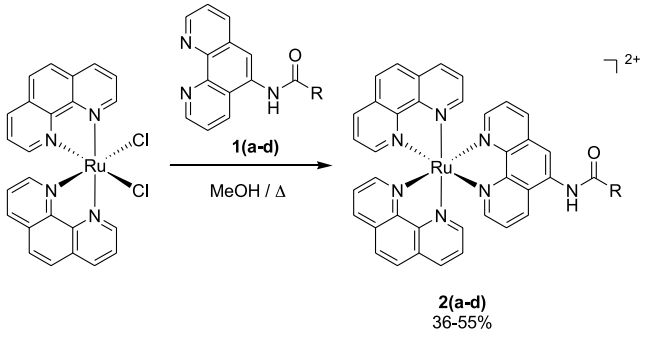
been selected as the ancillary ligand to maximise the emission lifetime and Φ_Δ of the sensitising dye.[11] Such molecular engineering aims to impart the immobilised $[Ru(phen)_2L]^{2+}$ complex the widest compatibility with the solvent (i.e., both aqueous and organic media) for water treatment[20] and synthetic purposes,[14] and to serve as oxygen-sensitive luminescent materials for optosensor development.[10,21,22]

While some work on chemical derivatisation of 1,10-phenanthrolin-5-amine (5-ap) has been reported for introducing long alkyl chains[23] or biomolecular labelling,[24–27] we have developed general procedures for the (difficult) acylation of 5-ap using carboxylic acid anhydrides. In this way, the functionalised phen ligands **1** were prepared (Scheme 1) and fully characterised by NMR, as well as their corresponding heteroleptic Ru(II) complexes **2** (Scheme 2).



Scheme 1. Conditions: (i) **1a**: $(ICH_2CO)_2O/CHCl_3/\Delta$; (ii) **1b**: $(COCH_2CH_2CH_2CO)O/PTSA/CHCl_3$; (iii) **1c**: $(COCH_2CH_2CH_2CO)O/PTSA/CHCl_3$; (iv) **1d**: (1) $ClCO_2Et/Et_3N$, (2) BOC-GABA-OH/$CHCl_3$.



Scheme 2.

In addition to their structural characterisation, the absorption and luminescence spectra, the emission lifetimes and the excited state quenching rate constants with dissolved oxygen have been determined for the novel sensitisers in acetonitrile solution. Proof of singlet oxygen generation in this solvent, using its phosphorescence at 1270 nm, is provided.

2. Results and discussion

The synthesis of the functionalised *N*-1,10-phenanthrolin-5-ylalkylamides (**1a–d**) is carried out by the reaction between 1,10-phenanthrolin-5-amine and different anhydrides either from commercial sources or prepared in situ, modifying some methods described in the literature[26,28,29] (Scheme 1). This reaction takes place with moderate to excellent yields (25–96%) (Table 1) and is a simple way to obtain such ligands in only one step. The usual low yields are related to steric hindrance to the approach of the electrophile due to the peri hydrogen atom in the 4-position. Actually, the highest chemical yield is obtained with the smallest carboxylic acid anhydride (iodoacetic), an improvement over the literature procedure.[24]

Table 1. Chemical yields of the synthesis of *N*-1,10-phenanthrolin-5-ylalkylamides (**1a–d**) and their corresponding heteroleptic Ru(II) complexes (**2a–d**)

R	Ligand	Yield (%)	Complex	Yield (%)
CH_2I	**1a**	96	**2a**	55
$(CH_2)_2CO_2H$	**1b**	25	**2b**	36
$(CH_2)_3CO_2H$	**1c**	43	**2c**	47
$(CH_2)_3NHCO_2C(CH_3)_3$	**1d**	42	**2d**	46

Protection of the ω-amino group with BOC is required to avoid competition in the amide formation step of phenanthroline **1d** (Scheme 1). Facile deprotection of the *tert*-butyloxycarbonyl moiety can be carried out with acetyl chloride in methanol.[30]

Once the functionalised phenanthrolines are prepared, they are used for the synthesis of heteroleptic ruthenium(II) complexes. The reaction of *cis*-dichloro-bis-(1,10-phenanthroline)ruthenium(II), $Ru(phen)_2Cl_2$, and the chelating ligands (**1a–d**) in methanol affords the complexes (**2a–d**) (Scheme 2) in moderate yields (36–55%) after repeated precipitation as PF_6^- salts (Table 1). The chemical composition and structure of these novel complexes has been confirmed by the usual spectroscopic methods (high-field ^1H and ^{13}C NMR, electrospray ionisation MS and elemental analysis).

The ^1H NMR signals are characteristic of the Ru(II) polypyridyl complexes, taking into account the combined effects on the chemical shifts of electronic σ-donation to the metal centre, π-back-bonding to the ligand and magnetic anisotropy of the heterocyclic rings.[31] The α,β and γ protons of the phenanthroline ring appear separately in the aromatic region ($\delta_\gamma > \delta_\alpha > \delta_\beta$).[5] The CH_2 singlet from the amide side chain is duplicated in the case of **2a**, and two signals are observed in 7:3 area ratio. A similar pattern appears in **2c**, where two of the three methylene groups display duplicate signals (3:2 area ratio). The NH proton is also observed twice for **2a** and **2c** in the same ratio described above. Duplication of some signals is observed also in the ^{13}C NMR spectra of those Ru(II) complexes, especially those corresponding to the carbonyl and the side chain methylene groups. As no signal duplication is observed in any of the free ligands, restricted rotation around the $C5_{phen}–N_{amide}$ bond could explain these experimental facts. The strong electron-withdrawing character of the metal complex increases the order of such single bond due to enhanced mesomeric effect of the aminocarbonyl group.

The base peak in the ESI mass spectra of these complexes corresponds to the $[M]^{2+}$ ion. In case of having a carboxylic acid moiety on the side chain, the $[M-H_2O]^{2+}$ ion is observed instead. No abundant fragments are detected together with the molecular ions.

Spectroscopic and photophysical data of the novel Ru(II) complexes (**2a**–**d**) have also been measured (Table 2). Their absorption spectra display bands in two regions, an intense one around 265 nm that may be ascribed to the ligand-centred π–π* transition, and a maximum that corresponds to the metal-to-ligand charge transfer (MLCT) d–π* transition at approximately 450 nm. Regardless the absorption maximum, all the complexes show strong emission peaking around 595 nm. Similar values have been reported for the homoleptic tris-phenanthroline complex.[2]

The excited state lifetimes (τ) of these novel photosensitisers were measured in N_2-saturated, air-equilibrated and O_2-purged acetonitrile solutions (Table 2). In the absence of dioxygen, the emission lifetimes of the heteroleptic Ru(II) complexes (**2a**–**d**) are ca. 700 ns, a value slightly lower than that of $[Ru(phen)_3]^{2+}$. Therefore, introduction of the amide group and functionalised side chain in the 5-position of the phen ligand does not perturb significantly the electronic features of the metal complex and provides a high efficiency of excited state quenching by O_2 (80% of the ^{3}MLCT states produced are deactivated by O_2 in the air-equilibrated solvent, Table 2). The sensitiser quenching rate constants (k_q) in acetonitrile can be determined from the observed (linear) Stern–Volmer relationships ($\tau_0/\tau = 1 + k_q\tau_0[O_2]$).[32] The calculated k_q values (Table 2) are close to 4×10^9 L mol^{-1} s^{-1}, a value near the diffusion control limit at room temperature. These photochemical parameters also make them highly suitable for luminescence oxygen sensing with fibre-optic probes.[10]

Moreover, we have confirmed the production of singlet (molecular) oxygen from the O_2 quenching of the excited state of the novel photosensitisers. Laser-flash illumination in the visible of an aerated acetonitrile solution of any of the Ru(II) complexes (**2a**–**d**) followed by time-resolved detection at 1270 nm (the characteristic $^1O_2$ phosphorescence maximum)[13] affords the typical decay kinetics and emission spectrum of $^1O_2$ (Fig. 1, $^1O_2$ generation by **2d** as a representative member of the family). The emission decay traces have to be fit to a biexponential function due to interference from the wide luminescence band of the photoexcited Ru(II) complex, which is not fully quenched by O_2 under air-saturated conditions.

3. Conclusions

The novel amido-functionalised Ru(II) complexes will allow us to prepare solid-supported photosensitisers containing the covalently bonded dye. Using easy straightforward synthetic procedures, we may attach the efficient $^1O_2$ generators to activated organic and inorganic polymer materials, such as polystyrene, silica gel or glass beads, for water/air disinfection, $^1O_2$-mediated photooxidation reactions or chemical optosensors. These fields are currently being explored in our laboratory.

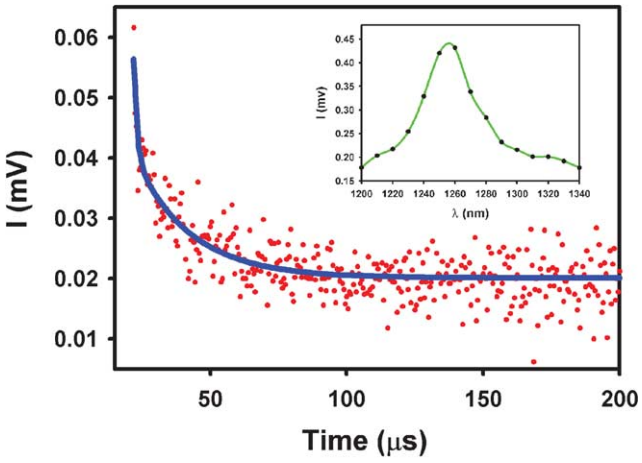


Figure 1. Decay of the emission signal at 1270 nm after laser-flash excitation of an air-equilibrated acetonitrile solution of photosensitising complex **2d**. The solid line through the experimental points represents the best fit to the function $I(t) = 0.02 + 0.0047\exp(-t/4.1) + 0.0148\exp(-t/21)$. Inset: emission spectrum recorded 2.5 μs after the laser pulse.

4. Experimental

4.1. General

All reagents were commercial grade and were used as received unless otherwise stated. 1,10-Phenanthrolin-5-amine (5-ap) was obtained from 5-nitro-1,10-phenanthroline (Aldrich) as previously described by Nasielski-Hinkens et al.[33] $Ru(phen)_2Cl_2$ was prepared according to the procedure reported by Sullivan et al.[34]

Melting points were measured with a Bibby-Sterilin apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at the UCM NMR Central Instrumentation Facilities on a Bruker AC-200 at 200 MHz for ^{1}H and 50 MHz for ^{13}C, or on a Bruker AMX-500 at 500 MHz for ^{1}H and 125 MHz for ^{13}C. $CDCl_3$, CD_3CN, MeOH-d_4 and

Table 2. Wavelengths of the absorption and emission maximums, ^{3}MLCT excited state lifetimes, O_2 quenching constants and fraction of triplets quenched by O_2 for the Ru(II) complexes (**2a**–**d**) in acetonitrile solution at 25 °C

Complex	λ_{abs}^{max} (nm)[a]	λ_{em}^{max} (nm)[a,b]	τ (N_2) (ns)[c]	τ (air) (ns)[c]	$\tau(O_2)$ (ns)[c]	$k_q\times10^{-9}$ (L mol^{-1} s^{-1})[d]	$P_{O_2}^T$ (air)[e]	$P_{O_2}^T$ (O_2)[e]
2a	263, 446	596	716	142	33	3.6	0.80	0.95
2b	262, 446	594	645	144	33	3.6	0.78	0.95
2c	263, 448	593	629	138	31	3.8	0.78	0.95
2d	263, 447	593	696	139	31	3.8	0.80	0.96

[a] Estimated uncertainty ±1 nm.
[b] Uncorrected for the instrument response function.
[c] Estimated uncertainty ±3%.
[d] From the Stern–Volmer lifetime quenching plot (see text); estimated uncertainty ±4%.
[e] Calculated from the equation: $P_{O_2}^T = 1 - (\tau/\tau_0)$.

DMSO-d_6 (Cambridge Isotope Laboratories) were used as solvents. The chemical shifts (δ_H and δ_C) are given from the residual $CHCl_3$ signal (7.26 and 77.0 ppm, respectively). Coupling constants (J) are given in Hz. Electron impact (EI) mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 250 °C. Electrospray ionisation (ESI) mass spectra were obtained on a Bruker Esquire-LC™ apparatus using 3500 V as ionisation voltage, N_2 as nebuliser gas and methanol as solvent. Both instruments belong to the UCM MS Central Instrumentation Facilities. TLC analyses and column chromatography were performed on silica gel $60F_{254}$ plates (Merck) and on silica gel 60 (Merck, 70–230 mesh), respectively.

UV–vis absorption spectra were recorded with a Varian Cary-3Bio spectrophotometer. Emission spectra were obtained with a Perkin-Elmer LS-5 spectrofluorometer at 25 °C and are uncorrected for the instrumental response. Emission lifetimes of the Ru(II) complexes were measured with an Edinburgh Instruments LP-900 laser kinetic spectrometer equipped with a frequency-doubled Nd:YAG laser (Minilite II, Continuum, USA) for excitation at 532 nm (15 mJ per 3 ns pulse) and a red-sensitive Hamamatsu R-928 photomultiplier. Decay traces were recorded at 595 nm through a 550 nm cut-off filter with a Tektronix TDS 340A digital oscilloscope, in N_2-saturated, air-equilibrated and O_2-purged photosensitiser solutions in spectroscopic-grade acetonitrile dried over 3 Å molecular sieves for more than one week. Measurements were carried out after purging the solution with the corresponding gas for at least 30 min. After transmission to a PII computer, the kinetic parameters were extracted by exponential non-linear least squares fitting to the experimental data using the original EI software. $^1O_2$ phosphorescence decay traces were recorded at 1270 nm with an Edinburgh Instruments EI-P N_2-cooled fast Ge diode.

4.2. Preparation of *N*-1,10-phenanthrolin-5-ylalkylamides, 1

4.2.1. Synthesis of phenanthrolines 1a, 1b and 1c. A mixture of 1,10-phenanthrolin-5-amine (195 mg, 1 mmol) and the corresponding anhydride (iodoacetic anhydride: 425 mg, 1.2 mmol; succinic anhydride: 500 mg, 5 mmol; glutaric anhydride: 685 mg, 6 mmol, for **1a**, **1b** and **1c**, respectively), was dissolved in 30 mL of anhydrous $CHCl_3$ at room temperature under argon. In the case of phenanthrolines **1b** and **1c**, *p*-toluensulfonic acid (PTSA, 38 mg, 0.2 mmol) was also added as catalyst.

After refluxing the reaction mixture for 2–3 days, an insoluble precipitate was observed. It was filtered, washed with chloroform and dried. Finally, the product was recristallised in the appropriate solvent.

4.2.1.1. 2-Iodo-*N*-1,10-phenanthrolin-5-ylacetamide, 5-iap, 1a. Filtration of reaction mixture afforded 349 mg (96%) of a yellow solid, mp 180 °C (with decomposition) ($CHCl_3$); δ_H (200 MHz, DMSO-d_6): 4.10 (s, 2H, CH_2), 8.06 (dd, 1H$_\beta$, J=8.2, 4.2 Hz), 8.10 (dd, 1H$_\beta$, J=8.2, 4.2 Hz), 8.42 (s, 1H), 8.88 (d, 1H$_\gamma$, J=8.2 Hz), 8.91 (d, 1H$_\gamma$, J=8.2 Hz), 9.16 (d, 1H$_\alpha$, J=4.2 Hz), 9.27 (d, 1H$_\alpha$, J=4.2 Hz), 10.73 (s, 1H, NH); δ_C (50 MHz, DMSO-d_6): 0.92 (CH_2), 118.93 (CH), 124.51, 124.86 (CH$_\beta$), 128.84, 132.40 (C), 133.53 (CH$_\gamma$), 138.25 (C), 140.56 (CH$_\gamma$), 141.16 (C), 146.73, 149.48 (CH$_\alpha$), 168.21 (CO); *m/z* (EI, 70 eV): 363 ($M^{+\cdot}$, 3), 236 ($M^{+\cdot}-I$, 100), 196 (5-NH_2phen$^{+\cdot}$+H, 83), 168 ($NHCOCH_2I^{+\cdot}$, 83), 127 ($I^{+\cdot}$, 63). Anal. Calcd for $C_{14}H_{10}IN_3O\cdot CHCl_3$: C, 37.34; H, 2.30; N, 8.71%, found: C, 37.13; H, 2.57; N, 9.15%.

4.2.1.2. 4-Oxo-4-(1,10-phenanthrolin-5-ylamino)butanoic acid, 5-suap, 1b. Precipitation of the crude product with methanol afforded 74 mg (25%) of a white solid, mp 188–190 °C (MeOH); δ_H (200 MHz, DMSO-d_6): 2.62 (t, 2H, J=6.2 Hz, CH_2), 2.79 (t, 2H, J=6.2 Hz, CH_2), 7.74 (dd, 1H$_\beta$, J=8.3, 4.3 Hz), 7.81 (dd, 1H$_\beta$, J=8.3, 4.3 Hz), 8.43 (dd, 1H$_\gamma$, J=8.3, 1.5 Hz), 8.65 (dd, 1H$_\gamma$, J=8.3, 1.5 Hz), 9.03 (dd, 1H$_\alpha$, J=4.3, 1.5 Hz), 9.12 (dd, 1H$_\alpha$, J=4.3, 1.5 Hz), 10.22 (s, 1H, NH), 12.25 (br s, 1H, CO_2H); δ_C (50 MHz, DMSO-d_6): 28.92, 30.63 (CH_2), 119.93 (CH), 122.72, 123.49 (CH$_\beta$), 124.69, 128.00 (C), 131.74 (CH$_\gamma$), 131.80 (C), 135.72 (CH$_\gamma$), 143.73, 145.74 (C), 149.23, 149.77 (CH$_\alpha$), 171.38 (CO_2H), 173.87 (NHCO); *m/z* (EI, 70 eV): 295 ($M^{+\cdot}$, 6), 277 ($M^{+\cdot}-H_2O$, 100), 249 ($M^{+\cdot}-HCO_2H$, 23), 195 (5-NH_2phen$^{+\cdot}$, 46). Anal. Calcd for $C_{16}H_{13}N_3O_3\cdot CH_3OH$: C, 62.38; H, 5.38; N, 12.84%, found: C, 62.08; H, 5.63; N, 12.44%.

4.2.1.3. 5-Oxo-5-(1,10-phenanthrolin-5-ylamino)pentanoic acid, 5-glap, 1c. Filtration of reaction mixture afforded 133 mg (43%) of a white solid, mp 233–235 °C ($CHCl_3$); δ_H (200 MHz, DMSO-d_6): 1.92 (q, 2H, J=7.3 Hz, CH_2), 2.38 (t, 2H, J=7.3 Hz, CH_2), 2.60 (t, 2H, J=7.3 Hz, CH_2), 7.75 (dd, 1H$_\beta$, J=8.3, 4.1 Hz), 7.83 (dd, 1H$_\beta$, J=8.3, 4.1 Hz), 8.19 (s, 1H), 8.46 (dd, 1H$_\gamma$, J=8.3, 1.6 Hz), 8.62 (dd, 1H$_\gamma$, J=8.3, 1.6 Hz), 9.04 (dd, 1H$_\alpha$, J=4.1, 1.6 Hz), 9.14 (dd, 1H$_\alpha$, J=4.1, 1.6 Hz), 10.14 (s, 1H, NH), 12.15 (br s, 1H, COOH); δ_C (50 MHz, DMSO-d_6): 20.52, 33.05, 34.98 (CH_2), 119.85 (CH), 122.83, 123.54 (CH$_\beta$), 124.63, 128.10 (C), 131.83, 136.06 (CH$_\gamma$), 143.20, 145.34 (C), 148.91, 149.65 (CH$_\alpha$), 171.96 (CO_2H), 174.15 (NHCO); *m/z* (ESI)=332 $[M+Na]^+$, 310 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N_3O_3\cdot CHCl_3$: C, 50.43; H, 3.76; N, 9.80%, found: C, 50.38; H, 4.06; N, 10.04%.

4.2.2. Synthesis of phenanthroline 1d. 1,10-Phenanthrolin-5-amine (195 mg, 1 mmol) was dissolved in 30 mL of $CHCl_3$ and cooled at 0 °C under argon with an ice-water bath. Triethylamine (405 mg, 4 mmol) and ethyl chloroformate (434 mg, 4 mmol) were then added and the reaction mixture was stirred at this temperature for 30 min. Then, 4-(*tert*-butyloxycarbonylamino)butyric acid (BOC-GABA-OH, 406 mg, 2 mmol) was added. The mixture was allowed to reach room temperature and refluxed for 4 days. The reaction progress was monitored by TLC.

The reaction mixture was treated with an aqueous HCl (pH 4) solution (2×25 mL), the organic layer was separated and washed successively with water (2×25 mL), Na_2CO_3-saturated aqueous solution (2×25 mL) and water (2×25 mL). Finally, it was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography using dichloromethane/acetone 1:2 (v/v) as the eluent.

4.2.2.1. *tert*-Butyl 4-oxo-4-(1,10-phenanthrolin-5-ylamino)butylcarbamate, BOC-5-ngap, 1d. Purification of the crude product by column chromatography afforded 160 mg (42%) of a yellow oil; δ_H (500 MHz, $CDCl_3$): 1.51 (s, 9H, $3CH_3$), 2.00 (m, 2H, CH_2), 2.71 (t, 2H, $J=6.4$ Hz, CH_2), 3.36 (c, 2H, $J=6.2$ Hz, CH_2), 5.20 (t, 1H, $J=6.2$ Hz, NH), 7.58 (dd, $1H_\beta$, $J=8.2$, 4.2 Hz), 7.67 (dd, $1H_\beta$, $J=8.2$, 4.2 Hz), 8.26 (dd, $1H_\gamma$, $J=8.2$, 0.9 Hz), 8.45 (s, 1H), 8.89 (dd, $1H_\gamma$, $J=8.2$, 0.9 Hz), 9.00 (dd, $1H_\alpha$, $J=4.2$, 0.9 Hz), 9.10 (dd, $1H_\alpha$, $J=4.2$, 0.9 Hz), 10.31 (s, 1H, NH); δ_C (50 MHz, $CDCl_3$): 26.57 (CH_2), 28.07 (CH_3), 33.87, 39.33 (CH_2), 79.21 (CMe_3), 119.39 (CH), 122.17, 122.91 (CH_β), 124.21, 127.82, 130.87 (C), 131.06, 135.51 (CH_γ), 143.38, 145.39 (C), 148.74, 149.15 (CH_α), 156.81 ($NHCO_2$), 172.98 (NHCO); *m/z* (EI, 70 eV) $=380$ ($M^{+\cdot}$, 6), 324 ([$M^{+\cdot}+H$]–$C(CH_3)_3$, 12), 307 ($M^{+\cdot}-OC(CH_3)_3$, 5), 195 (5-NH_2phen$^{+\cdot}$, 100). Anal. Calcd for $C_{21}H_{24}N_4O_3$: C, 66.30; H, 6.36; N,14.73%, found: C, 65.96; H, 6.31; N, 15.02%.

4.3. Preparation of [bis(1,10-phenanthroline)(*N*-1,10-phenanthrolin-5-ylalkylamide)]ruthenium(II) complexes, $[Ru(phen)_2(5\text{-}(N\text{-}COR)phen)](PF_6)_2$, 2: general procedure

A mixture of the corresponding *N*-1,10-phenanthrolin-5-ylalkylamide **1** (0.450 mmol) and *cis*-dichloro-bis(1,10-phenanthroline)ruthenium(II), $Ru(phen)_2Cl_2$ (200 mg, 0.375 mmol), was dissolved in 30 mL of methanol at room temperature under argon atmosphere. The reaction mixture was refluxed with stirring during 1–2 days. The evolution of the reaction was monitored by TLC. Then the mixture was concentrated at reduced pressure and 1 mL of a saturated ammonium hexafluorophosphate (Fluka) aqueous solution was added. Water was subsequently added to favour precipitation of the product, which was then filtered and washed with plenty of water. The complex was reprecipitated from a methanol/water mixture and finally dried under vacuum (40 °C, 0.1 Torr).

4.3.1. [Bis(1,10-phenanthroline)(2-iodo-*N*-1,10-phenanthrolin-5-ylacetamide)]ruthenium(II) bis(hexafluorophosphate), $[Ru(phen)_2(5\text{-}iap)](PF_6)_2$, 2a. Filtration of the product affords 230 mg (55%) of an orange solid; δ_H (500 MHz, CD_3CN): 4.12 (s, 0.6H, CH_2), 4.47 (s, 1.4H, CH_2), 7.60–7.71 (m, $6H_\beta$), 7.98–8.11 (m, $6H_\alpha$), 8.28 (s, 4H), 8.61–8.64 (m, $4H_\gamma$), 8.65–8.76 (m, $2H_\gamma$), 9.40 (s, 0.3H, NH), 9.45 (s, 0.7H, NH); δ_C (125 MHz, CD_3CN): 0.01, 0.57 (CH_2), 121.13, 121.89, 126.43, 126.88, 127.03, 127.07 (CH), 127.94 (C), 129.03 (CH), 131.53, 131.58, 131.99, 132.00 (C), 132.97, 133.25 (CH), 134.10, 134.40 (C), 137.32, 137.37, 137.78 (CH), 147.00, 148.87, 148.90, 148.92, 148.93, 149.37 (C), 153.23, 153.40, 153.92, 153.95, 154.03, 154.06, 154.08 (CH), 166.85 (CO), 168.69 (CO); *m/z* (ESI) $=412.5$ $[M]^{2+}$. Anal. Calcd for $[C_{38}H_{26}IN_7ORu](PF_6)_2$: C, 40.95; H, 2.35; N, 8.80%, found: C, 40.63; H, 2.41; N, 8.64%.

4.3.2. [Bis(1,10-phenanthroline)(4-oxo-4-(1,10-phenanthrolin-5-ylamino)butanoic acid)]ruthenium(II) bis(hexafluorophosphate), $[Ru(phen)_2(5\text{-}suap)](PF_6)_2$, 2b. Filtration of the product afforded 141 mg (36%) of an orange solid; δ_H (500 MHz, CD_3CN): 2.77 (t, 2H, $J=6.2$ Hz, CH_2), 2.92 (t, 2H, $J=6.2$ Hz, CH_2), 7.59 (dd, $1H_\beta$, $J=8.3$, 5.0 Hz), 7.62–7.69 (m, $5H_\beta$), 7.96 (d, $1H_\alpha$, $J=5.0$ Hz), 8.02–8.08 (m, $5H_\alpha$), 8.27 (s, 4H), 8.55 (d, $1H_\gamma$, $J=8.3$ Hz), 8.61–8.63 (m, $4H_\gamma$, 1H), 8.73 (d, $1H_\gamma$, $J=8.3$ Hz), 8.97 (s, 1H, NH); δ_C (125 MHz, CD_3CN): 29.14, 30.30 (CH_2), 119.70 (C), 125.68, 126.29, 126.36 (CH), 127.24 (C), 128.44 (CH), 131.19, 131.40, 131.42 (C), 132.63 (CH), 134.29 (C), 136.65, 137.18 (CH), 137.26, 146.18, 148.31, 148.34, 148.75 (C), 152.35, 153.32, 153.43, 153.47 (CH), 172.15 (CO), 173.63 (CO); *m/z* (ESI) $=369.5$ $[M-H_2O]^{2+}$. Anal. Calcd for $[C_{40}H_{29}N_7O_3Ru](PF_6)_2$: C, 45.90; H, 2.79; N, 9.37%, found: C, 45.54; H, 2.57; N, 9.23%.

4.3.3. [Bis(1,10-phenanthroline)(5-oxo-5-(1,10-phenanthrolin-5-ylamino)pentanoic acid)]ruthenium(II) bis(hexafluorophosphate), $[Ru(phen)_2(5\text{-}glap)](PF_6)_2$, 2c. Filtration of the product afforded 197 mg (47%) of a dark orange solid; δ_H (500 MHz, CD_3CN): 2.06 (q, 2H, $J=7.3$ Hz, CH_2), 2.47 (t, 0.6H, $J=7.3$ Hz, CH_2), 2.50 (t, 0.4H, $J=7.3$ Hz, CH_2), 2.68 (t, 0.6H, $J=7.3$ Hz, CH_2), 2.69 (t, 0.4H, $J=7.3$ Hz, CH_2), 7.59 (dd, $1H_\beta$, $J=8.3$, 5.2 Hz), 7.62–7.68 (m, $5H_\beta$), 7.96 (d, $1H_\alpha$, $J=5.2$ Hz), 8.02–8.09 (m, $5H_\alpha$), 8.28 (s, 4H), 8.54 (d, $1H_\gamma$, $J=8.3$ Hz), 8.61–8.64 (m, $4H_\gamma$, 1H), 8.74 (d, $1H_\gamma$, $J=8.3$ Hz), 8.95 (s, 0.6H, NH), 8.97 (s, 0.4H, NH); δ_C (125 MHz, CD_3CN): 20.84, 20.90 (CH_2), 32.98, 33.24 (CH_2), 35.99, 36.02 (CH_2), 119.86, 125.81, 126.34, 126.37 (CH), 126.45, 127.28 (C), 128.49 (CH), 131.18, 131.43, 131.44 (C), 132.89, 132.92 (CH), 134.34 (C), 136.64, 137.25 (CH), 146.15, 148.29, 148.33, 148.37, 148.71, 148.75, 152.32 (C), 152.36, 153.36, 153.40, 153.44, 153.49, 153.52 (CH), 172.86, 172.93 (CO), 173.87, 174.25 (CO); *m/z* (ESI) $=376.5$ $[M-H_2O]^{2+}$. Anal. Calcd for $[C_{41}H_{31}N_7O_3Ru](PF_6)_2$: C, 46.42; H, 2.95; N, 9.24%, found: C, 46.17; H, 3.23; N, 9.10%.

4.3.4. [Bis(1,10-phenanthroline)(*tert*-butyl 4-oxo-4-(1,10-phenanthrolin-5-ylamino)butylcarbamate)]ruthenium(II) bis(hexafluorophosphate), $[Ru(phen)_2(BOC\text{-}5\text{-}ngap)](PF_6)_2$, 2d. Filtration of the product afforded 195 mg (46%) of an orange-red solid; δ_H (500 MHz, CD_3CN): 1.91 (q, 2H, $J=7.1$ Hz, CH_2), 2.63 (t, 2H, $J=7.1$ Hz, CH_2), 3.21 (c, 2H, $J=6.4$ Hz, CH_2), 5.53 (br s, 1H, NH), 7.59 (dd, $1H_\beta$, $J=8.1$, 5.1 Hz), 7.62–7.67 (m, $5H_\beta$), 7.95 (dd, $1H_\alpha$, $J=5.1$, 0.7 Hz), 8.01–8.07 (m, $5H_\alpha$), 8.27 (s, 4H), 8.54 (d, $1H_\gamma$, $J=8.0$ Hz), 8.60–8.62 (m, $4H_\gamma$), 8.70 (s, 1H), 8.82 (d, $1H_\gamma$, $J=8.0$ Hz), 9.25 (broad s, 1H, NH); δ_C (125 MHz, CD_3CN): 26.53 (CH_2), 28.07 (CH_3), 34.23, 39.74 (CH_2), 78.92 (CMe_3), 117.72 (C), 125.61 (CH), 126.27 (C), 126.29 (CH), 126.37, 127.16 (C), 128.44 (CH), 131.23, 131.40 (C), 132.68 (CH), 134.48 (C), 136.58, 137.18 (CH), 146.05, 148.31, 148.34, 148.71 (C), 152.25, 153.32, 153.36, 153.40, 153.45 (CH), 157.08 ($NHCO_2$), 173.14 (NHCO); *m/z* (ESI) $=421$ $[M]^{2+}$. Anal. Calcd for $[C_{45}H_{40}N_8O_3Ru](PF_6)_2$: C 47.75, H 3.56, N 9.90%, found: C, 47.68; H, 3.90; N, 9.87%.

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Palladium catalyzed Suzuki cross-coupling reactions using *N*,*O*-bidentate ligands

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Abstract—Palladium-catalyzed Suzuki cross-coupling reactions employing Schiff-bases as ligands toward a series of substituted arylbromides and boronic acids were pursued. In the presence of a *N*,*O*-bidentate ligand, 2-[1-(2,4,6-trimethyl-phenylimino)-ethyl]-phenol **5**, the catalytic reactions could be carried out efficiently at room temperature with a wide array of arylbromides, even with electronically deactivated arenes. A deprotonated **5**, **5′**, chelated palladium acetate complex, [**5′**Pd(II)(OAc)(solv)] **8**, was proposed as a precursor of a genuine catalytically active species.

1. Introduction

For the past few decades, transition metal-mediated catalytic cross-coupling reactions are among the most powerful and convenient tools of modern organic synthesis.[1] Recently, the palladium-catalyzed Suzuki reactions, involving cross-coupling of aryl halides with aryl boronic acids, have emerged as the most important synthetic methods for the preparation of biaryl compounds.[2–7] As a result, many efforts have been devoted to the finding of even more efficient and selective methods in the synthesis of biaryls. For many years, phosphines have been the most commonly employed ligands for the reaction. Lately, *N*-heterocyclic carbenes (NHC) have been introduced as potentially effective ligands for Suzuki reactions.[8] Nevertheless, these types of ligands are normally either air/moisture sensitive or expensive, which places significant limits on their synthetic applications. Besides, these types of compounds are not ecological friendly. On the contrary, most of the *N*,*O*- or *N*,*N*-bidentate ligands are inexpensive, easy to access and stable.[9] Moreover, the process of the complexation of ligand with palladium is straightforward and their palladium complexes are found to be quite suitable for Suzuki cross-coupling reactions. Thereby, the practices of employing phosphine-free palladium catalysts in Suzuki cross-coupling reactions are of interest to many.[10] To our knowledge, only few work using Schiff base as ligand in Suzuki reaction has been reported.[11] In this work, we report some remarkable results of using several new types of *N*,*O*- or *N*,*N*-bidentate ligands in palladium-catalyzed Suzuki coupling reactions. The efficiency of these ligands are compared and discussed subsequently.

2. Results and discussion

Several *N*,*O*- or *N*,*N*-bidentate ligands, **1**–**6**, were prepared and screened for the $Pd(OAc)_2$ catalyzed Suzuki cross-coupling reactions (Fig.1).

Table 1 summarizes the reaction conditions and results of the Suzuki coupling reactions for 4-bromo-benzaldehyde and phenylboronic acid. As shown, the best result (90% in yield) was obtained for employing **5** as the ligand while the reaction was carried out at 25 °C for 50 min in K_3PO_4/THF system (entry 5). Judging from these data alone, **5** is a quite efficient ligand in this reaction condition. Obviously, the lower yield obtained by employing **6** as ligand is mainly due to its more sterically demanding isopropyl groups on arene (entry 6). It is interesting to see that there is no catalytic efficiency being observed by using (2,4,6-trimethyl-phenyl)-(1-pyridin-2-yl-ethylidene)-amine **1** as ligand at 25 °C in KF/THF system (entry 1). For comparison, the **1**-chelated palladium complex, **1**-$PdCl_2$, was synthesized from the reaction of **1** with another palladium source, $PdCl_2$. The same results were obtained. There is not detectable catalytic ability being observed for **1**-$PdCl_2$ in Suzuki–Miyaura coupling reaction. By contrast, in similar catalytic reactions a wide range of activities (from 0 to 99%) were reported for employing various

Keywords: Suzuki reaction; Palladium complex; Schiff-base; Bidentate ligand.
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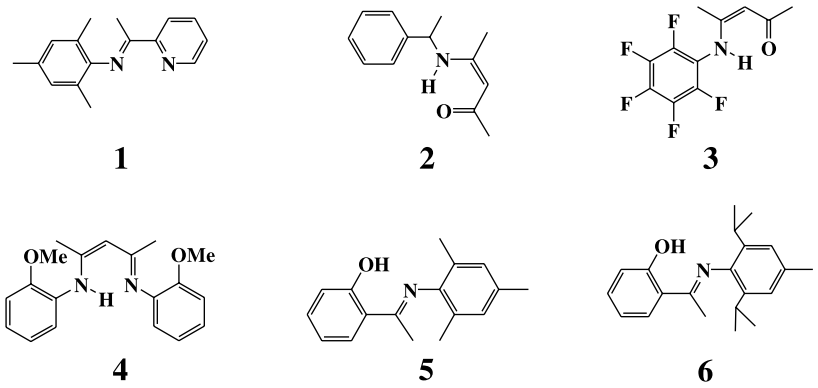
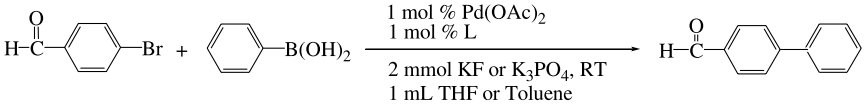


Figure 1. Some selected *N,N*- and *N,O*-bidentate ligands **1**–**6**.

Table 1. Suzuki coupling reactions of 4-bromo-benzaldehyde with phenylboronic acid employing ligands **1**–**6**



Entry[a]	Ligand	Base	Solvent	Time (min)	Conv. (%)[b]	Yield (%)[c]
1	**1**	K_3PO_4	Toluene	50	NR	NR
		K_3PO_4	THF	50	NR	NR
		KF	Toluene	50	NR	NR
		KF	THF	50	NR	NR
2	**2**	K_3PO_4	Toluene	50	57	50
		K_3PO_4	THF	50	73	65
		KF	Toluene	20	20	13
		KF	THF	50	86	85
3	**3**	K_3PO_4	Toluene	50	68	68
		K_3PO_4	THF	50	63	61
		KF	Toluene	190	16	6
		KF	THF	50	46	45
4	**4**	K_3PO_4	Toluene	20	33	25
		K_3PO_4	THF	20	0	0
		KF	Toluene	20	17	17
		KF	THF	350	87	86
5	**5**	K_3PO_4	Toluene	90	80	77
		K_3PO_4	THF	60	92	90
		KF	Toluene	20	22	10
		KF	THF	50	90	81
6	**6**	K_3PO_4	Toluene	50	44	39
		K_3PO_4	THF	50	65	63
		KF	Toluene	50	77	—[d]
				150	85	81
		KF	THF	50	72	70

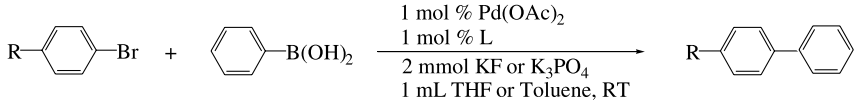
[a] Reaction conditions: 1.0 equiv of ArBr, 1.5 equiv of $Ar'B(OH)_2$.
[b] NMR yield.
[c] Isolated yield.
[d] Not isolated.

diazabutadienes at reaction temperature around 80 °C.[12] Lower efficiency were observed for reactions employing **2**, **3** or **4** as ligand than that of **5**. In summary, the catalytic efficiencies of these types of ligands are in the sequence of imine–phenol > ketimine > imine–pyridine. It implies that the catalytic efficiency is better while the ligand–metal bonding mode is a grouping of chelated oxide- and imine–palladium bonds.

In palladium-catalyzed cross-coupling reactions, it is generally accepted that better conversions are assured for aryl halides with electron-withdrawing rather than donating substituent.[13] The Suzuki coupling reactions were carried out and the reaction conditions and results were summarized in Table 2. Here, two bromobenzaldehydes having electron-donating substituents, –OMe and –Me were used as the bromide sources. As expected, low conversion rates were observed for all the $L/Pd(OAc)_2$ combinations.

Table 3 summarizes the results of the palladium-catalyzed Suzuki reactions for various substituted arylbromides and phenylboronic acids by employing **5** as ligand. Excellent yields were obtained for the reactions of arylbromides with electron-withdrawing groups at 25 °C for 50–120 min (entries 1, 2, 7, and 8). On the contrary, rather low yield was observed for arylbromide with electron-donating group at that temperature (entry 6). Yields might be improved while the reaction temperature was raised to 100 °C for

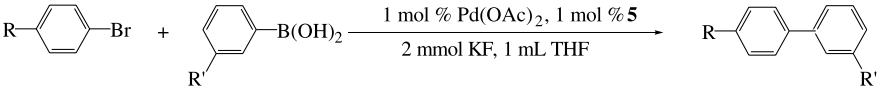
Table 2. Suzuki coupling reactions of 4-bromo-benzene derivatives with phenylboronic acid employing ligands **1–6**



Entry[a]	Ligand	R	Base	Solvent	Time (min)	Conv. (%)[b]	Yield (%)[c]
1	**2**	CH_3	KF	THF	20	13	—[d]
2					50	13	11
3	**3**	OCH_3	K_3PO_4	Toluene	50	7	—[d]
4	**4**	CH_3	KF	THF	50	22	—[d]
5					1210	50	48
6	**5**	CH_3	KF	THF	20	11	—[d]
7					50	20	—[d]
8					120	23	20
9	**6**	OCH_3	KF	Toluene	50	24	17

[a] Reaction conditions: 1.0 equiv of ArBr, 1.5 equiv of $Ar'B(OH)_2$.
[b] NMR yield.
[c] Isolated yield.
[d] Not isolated.

Table 3. Suzuki coupling reactions of substituted arylbromides and phenylboronic acids employing ligand **5**



Entry[a]	R	R′	Base/solvent	Time (min)	Conv. (%)[b]	Yield (%)[c]
1[d]	CHO	H	KF/THF	50	90	81
2[d]	$COCH_3$	H	KF/THF	50	92	90
3[e]	CH_3	H	KF/THF	120	23	20
4[e]	CH_3	H	KF/EtOH	120	77	68
5[e]	MeO	H	KF/CH_3CN	240	34	30
6[d]	MeO	H	KF/THF	720	10	—[f]
7[d]	CHO	NO_2	KF/THF	120	82	75
8[d]	$COCH_3$	NO_2	KF/THF	120	71	70
9[e]	CH_3	NO_2	KF/EtOH	120	87	83
10[e]	MeO	NO_2	KF/CH_3CN	360	40	33
11[e]	CHO	H	KF/EtOH	1440	10	—[f]

[a] Reaction conditions: 1.0 equiv of ArBr, 1.5 equiv of $Ar'B(OH)_2$.
[b] NMR yield.
[c] Isolated yield.
[d] The reaction was conducted at 25 °C.
[e] At 100 °C.
[f] Not isolated.

arylbromides with electron-donating group (entries 3, 5, and 10). Recently, a reductive process of Pd(II) to Pd(0) through the β-H elimination of the coordinated alkoxide ligand was proposed by Nolan et al.[8a] Nevertheless, there was no formation of acetaldehyde being observed by ^1H NMR while the reaction was performed in ethanol, $Pd(OAc)_2$, and **5** at 100 °C for 24 h (entries 4 and 9). Even though the β-H elimination process did not take place in this case, it indeed increases the solubility of the reactants and eventually speed up the reaction (entry 3 vs 4). Accidentally, the **5**/$Pd(OAc)_2$ catalytic system worked for aryl chlorides. About 10% conversion was observed for the reaction of 4-chlorobenzaldehyde with phenylboronic acid at 100 °C for 24 h employing **5**/$Pd(OAc)_2$ as catalyst.

A bis-**5**′-chelated palladium complex, **7**, was obtained while in an attempt to isolate the active species in the reaction. The orange crystals of **7** were grown in toluene at room temperature, then suitable crystals were sampled and subjected for X-ray crystal structural determination (Table 4). The ORTEP drawing of **7** are depicted in Figure 2. The bond angles for O(1)–Pd(1)–N(1),

Table 4. Crystal data of **7**

Formula	$C_{34}H_{36}N_2O_2Pd$
F_w	611.05
Crystal system	Monoclinic
Space group	*P*2(1)
a (Å)	15.987(3)
b (Å)	20.699(3)
c (Å)	8.9941(15)
β (°)	95.428(3)
V (Å^3)	2963.1(8)
Z	4
Density (calcd) (Mg/m^3)	1.370
λ (Mo K*α*) (Å)	0.71073
Absorption coefficient (mm^{-1})	0.658
F(000)	1264
Crystal size	0.60×0.35×0.21 mm^3
2*θ* Range (°)	2.35–26.03°
Reflections collected	16,492
Independent reflections	5790 [*R*(int)=0.0753]
Data/restraints/parameters	5790/0/355
*R*1 for significant reflections[a]	0.0578
*wR*2 for significant reflections[b]	0.1484
Go*F*[c]	0.962

[a] $R1=|\Sigma(|F_o|-|F_c|)/|\Sigma F_o||$.
[b] $wR2=\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$; $w=0.0993$ for **7**.
[c] $GoF=[\Sigma w(F_o^2-F_c^2)^2/(N_{rflns}-N_{params})]^{1/2}$.

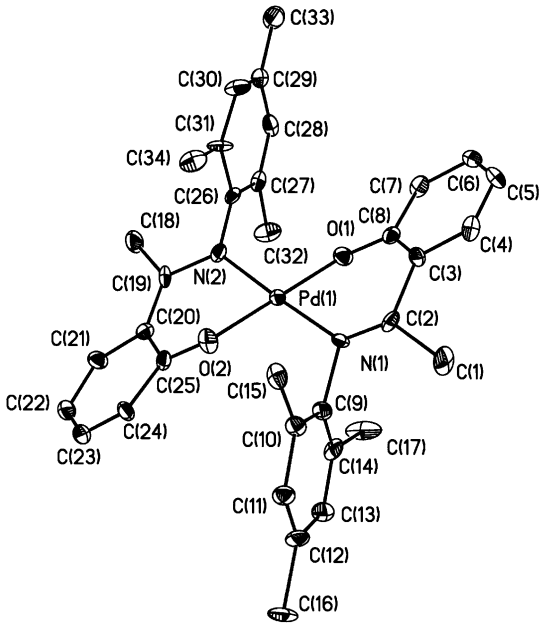


Figure 2. ORTEP drawing of **7** with the numbering. Some carbon and hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–O(1) 1.974(11); Pd(1)–O(2) 1.989(10); Pd(1)–N(1) 1.980(14); Pd(1)–N(2) 2.051(15); O(1)–C(8) 1.32(2); O(1)–C(25) 1.29(2); N(1)–C(2) 1.19(2); N(1)–C(9) 1.54(2); N(2)–C(26) 1.38(2); N(2)–C(19) 1.39(2); O(1)–Pd(1)–N(1) 88.1(5); O(1)–Pd(1)–O(2) 179.0(8); N(1)–Pd(1)–O(2) 92.6(6); O(1)–Pd(1)–N(2) 89.8(5); N(1)–Pd(1)–N(2) 177.8(7); O(2)–Pd(1)–N(2) 89.5(6); C(8)–O(1)–Pd(1) 121.3(11); O(25)–O(2)–Pd(1) 120.3(10).

N(1)–Pd(1)–O(2), O(1)–Pd(1)–N(2) and O(2)–Pd(1)–N(2) are 88.1(5)°, 92.6(6)°, 89.8(5)° and 89.5(6)°, respectively. Obviously, the Pd(II) metal center is a typical square planar environment with d^8 electron configuration. The bond lengths of Pd(1)–O(1), Pd(1)–O(2), Pd(1)–N(1) and Pd(1)–N(2) are 1.974(11), 1.989(10), 1.980(14), and 2.051(15), respectively. Interestingly, two oxides and two nitrogen atoms are trans to each other. This arrangement is believed due to the steric demand from two tri-methyl-phenyl rings rather than the reflection of the electronic effect.

Rather low efficiency was observed by employing **7** as the catalyst in Suzuki reaction than that of using the mixed **5**/$Pd(OAc)_2$ in situ. Apparently, **7** is not the genuine catalytically active species. It might be, at most, a precursor of a more reactive compound. Nevertheless, the catalytic process could be greatly improved while 1 equiv of $Pd(OAc)_2$ was added to **7**. It is believed that certain amount of **8**, **5**′Pd(OAc)(solv), was formed through the process of disproportionation and most of the catalytic reactivity was caused by this newly formed complex (Scheme 1). The efficiency is further improved by adding in additional amount of $Pd(OAc)_2$. By that, presumably more species **8** was formed via equilibrium. Nonetheless, the proposed complex **8** is still regarded as a precursor of the genuine catalytically active species, which might be a Pd(0) complex.

3. Conclusion

We have demonstrated the exceptional catalytic reactivity of a *N*,*O*-bidentate ligand, 2-[1-(2,4,6-trimethyl-phenyl-imino)-ethyl]-phenol **5**, in the palladium-catalyzed Suzuki cross-coupling reaction. These types of ligands are attractive alternatives to the conventional phosphine ligands. A deprotonated **5**, **5**′, chelated palladium acetate complex, [**5**′Pd(II)(OAc)(solv)] **8**, was proposed as a precursor of a genuine catalytically active species and which has been proposed from the ligand exchange reaction of **7** with $Pd(OAc)_2$.

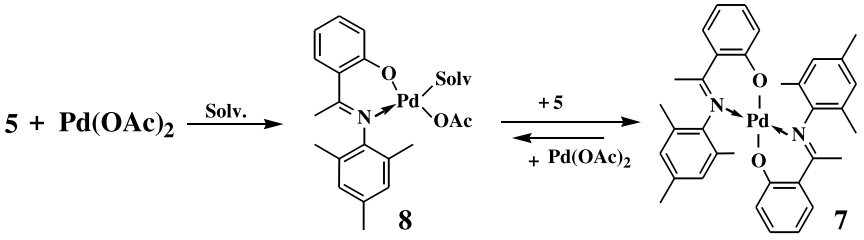
4. Experimental

4.1. General

All manipulations were carried out under a dry nitrogen atmosphere. All solvents including deuterated solvents were purified before use. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer with chemical shifts given in ppm from the internal TMS or center line of $CHCl_3$. Mass spectra were recorded on JOEL JMS-SX/SX 102A GC/MS/MS spectrometer. Microanalyses were performed using a Heraeus CHN-O-RAPID instrument.

4.1.1. Synthesis of (2,4,6-trimethyl-phenyl)-(1-pyridin-2-yl-ethylidene)-amine 1. 2-Acetylpyridine (12 mmol, 1.4 mL), 2,4,6-trimethylaniline (10 mmol, 1.4 mL), and benzenesulfonic acid (0.30 mL) were placed in a 100 mL round flask and was refluxed in absolute toluene (10 mL) for 36 h. After being cooled to room temperature, the orange extraction was dried over $MgSO_4$ and filtered. Removal of the solvent in vacuum afforded **1** as the desired light yellow oily product. Yield: 2.2 g (90%). ^1H NMR ($CDCl_3$, δ/ppm): 7.38–8.68 (m, 4H, Py), 6.88 (s, 2H, Ph), 2.88 (s, 3H, MeCN); 1.99 (s, 6H, Ph-*o*-Me), 2.18 (s, 3H, Ph-*p*-Me); Elemental Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.6; N, 11.75%. Found: C, 80.79; H, 7.61; N, 11.87%.

4.1.2. Synthesis of 4-(1-penyl-ethylamino)-pent-3-en-2-one 2. DL-α-Methyl benzylamine (0.1 mol, 12.1 g),



Scheme 1. The formation of a proposed catalyst precursor **8**.

2,4-pentanedione (0.1 mol, 10.0 g), and benzenesulfonic acid (0.30 mL) were placed in a 100 mL round flask and was refluxed in absolute toluene (10 mL) for 24 h. Removal of the solvent in vacuum afforded mixture. The resulting mixture was extracted by water and toluene. The organic extraction was recrystallized from hexane at 0 °C to afford a yellow solid **2** as the desired product. Yield: 18.29 g (90%). ^{1}H NMR ($CDCl_3$, δ/ppm): 11.24 (s, 1H, COH), 7.20–7.32 (m, 5H, Ph), 4.99 (s, 1H, CCHC), 4.66, 2.26 (m, 2H, PhCH), 2.04 (s, 1H, H(CO)C), 1.78 (s, 1H, NCHCH); ^{13}C NMR ($CDCl_3$, δ/ppm): 18.8 (PhCC), 125.2, 126.9, 128.1, 143.9 (Ph), 24.4 ($NCCH_3$), 28.5 ($O{=}CCH_3$), 32.7 (PhC), 95.5 (NC=CH), 162.3 (NC=C), 194.9 ($O{=}CCH_3$); MS (FAB, *m*/*z*): 203 (M^+).

4.1.3. Synthesis of 4-pentafluorophenylamino-pent-3-en-2-one 3. Pentafluoroaniline (0.02 mol, 3.6 g), 2,4-pentanedione (0.02 mol, 2.0 g), and benzenesulfonic acid (0.30 mL) were placed in a 100 mL round flask and was refluxed in absolute toluene (10 mL) for 24 h. Removal of the solvent in vacuum yielded mixture. The resulting mixture was extracted by water and toluene. The organic extraction was recrystallized from hexane at 0 °C to gave a desired yellow solid **3**. Yield: 3.88 g (25%). ^{1}H NMR ($CDCl_3$, δ/ppm): 2.15 (s, 1H, $H_3C(CO)CH$), 5.340 (s, 1H, $H_3C(CO)CH$), 1.86 (s, 1H, NCHCH(CO)); ^{13}C NMR ($CDCl_3$, δ/ppm): 136.4–144.8 (Ph), 18.6 ($NCCH_3$), 29.1 ($O{=}CCH_3$), 99.5 (NC=CH), 159.7 (NC=C) 197.9 ($O{=}CCH_3$); Elemental Anal. Calcd for $C_{11}H_8NOF_5$: C, 49.82; H, 3.04; N, 5.28%. Found: C, 49.55; H, 3.12; N, 4.98%.

4.1.4. Synthesis of 2-((2-methoxyphenyl)amino)-4-((2-methoxyphenyl)imino)-2-pentene 4. 2-Methoxyaniline (12.30 g, 100 mmol), 2,4-pentanedione (5.00 g, 50 mmol), and benzenesulfonic acid (0.30 mL) were placed in a 100 mL round flask and was refluxed in absolute toluene (30 mL) for 24 h. After being cooled to room temperature, volatile materials were removed under vacuum to give brown oil. Diethyl ether (100 mL) were then added and the resulting precipitate was extracted by CH_2Cl_2 (30 mL). The orange extraction was dried over $MgSO_4$, and filtered. Removal of the solvent in vacuum afforded a light yellow solid **4** as the targeted product. Yield: 3.88 g (25%). ^{1}H NMR ($CDCl_3$, δ/ppm): 12.20 (1H, s, N*H*), 6.99 (4H, d, J= 7.2 Hz, MeOArH), 6.86–6.88 (4H, m, ArH), 4.92 (1H, s, β-CH), 3.77 (6H, s, CH_3O), 1.98 (6H, s, α-CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ/ppm): 160.21 (C=N), 151.51 (MeOCCN), 135.61 (MeOCCN), 123.84, 123.29, 120.74, 111.68 (Ph), 98.16 (β-C), 55.98 (CH_3O), 21.39 (C=CHC); Elemental Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03%. Found: C, 72.66; H, 7.58; N, 8.40%.

4.1.5. Synthesis of 2-[1-(2,4,6-trimethyl-phenylimino)-ethyl]-phenol 5. 2-Hydroxyacetophenone (50 mmol, 6.0 mL), 2,4,6-trimethylaniline (50 mmol, 7.0 mL), and benzenesulfonic acid (0.30 mL) were placed in a 100 mL round flask and was refluxed in 1-butanol (50 mL) for 48 h. Removal of the solvent in vacuum afforded mixture. The mixture was purified by column chromatography (silica gel, ethyl acetate/hexane = 1:23). The organic extraction was recrystallized from hexane at 0 °C to gave a yellow solid **5**. Yield: 4.05 g (32%). ^{1}H NMR ($CDCl_3$, δ/ppm): 14.90 (s, 1H, OH), 7.61–7.65 (m, 1H, Ph), 7.33–7.42 (m, 1H, Ph); 7.01–7.05 (m, 1H, Ph), 6.85–6.89 (m, 3H, Ph), 2.30 (s, 3H, $C{=}NCH_3$), 2.16 (s, 6H, *o*-$PhCH_3$), 2.03 (s, 3H, *p*-$PhCH_3$); ^{13}C NMR ($CDCl_3$, δ/ppm): 171.90 (C=N), 162.33, 142.42, 133.67, 132.85, 128.75, 128.63, 127.35, 119.18, 118.15, 117.84 (Ph), 20.64 ($C{=}NCH_3$), 17.98 (*o*-$PhCH_3$), 16.71 (*p*-$PhCH_3$); MS (EI, *m*/*z*): 253 (M^+); Elemental Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53%. Found: C, 80.84; H, 7.64; N, 5.90%.

4.1.6. Synthesis of 2-[1-(2,6-diisopropyl-phenylimino)-ethyl]-phenol 6. 2-Hydroxyacetophenone (50 mmol, 6.0 mL), 2,6-diisopropylaniline (50 mmol, 9.4 mL), and benzenesulfonic acid (0.30 mL) were placed in a 100 mL round flask and was refluxed in 1-butanol (50 mL) for 48 h. Removal of the solvent in vacuum afforded **6**. The organic extraction was recrystallized from hexane at 0 °C to afford a yellow solid **6**. Yield: 4.43 g (32%). ^{1}H NMR ($CDCl_3$, δ/ppm): 7.65 (d, J=4 Hz, 1H, Ph), 7.39 (t, J=3 Hz, 1H, Ph), 7.19 (d, 1H, Ph), 7.07 (d, J=4 Hz, 1H, Ph), 6.93 (t, J= 2 Hz, 1H, Ph), 2.75–2.81 (m, 2H, $CH(CH_3)_2$), 2.20 (s, 3H, $C{=}NCH_3$), 1.13 (d, 6H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, δ/ppm): 172.22 (C=N), 162.42, 142.15, 138.14, 133.17, 128.93, 125.23, 123.27, 119.08, 118.36, 118.04 (Ph), 28.36 ($C{=}NCH_3$), 23.62 ($CH(CH_3)_2$), 22.78 ($CH(CH_3)_2$), 17.60 ($CH(CH_3)_2$); MS (EI, *m*/*z*): 295 (M^+); Elemental Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74%. Found: C, 81.48; H, 8.47; N, 4.64%.

4.1.7. Synthesis of $Pd(C_{17}H_{18}NO)_2$ 7. 2-[1-(2,4,6-Trimethyl-phenylimino)-ethyl]-phenol (2.0 mmol, 0.506 g) and palladium acetate (1.0 mmol, 0.224 g) were placed in a 100 mL round bottle, and removal of air in vacuum for 1 h. The mixture was then allowed to react in absolute THF (10 mL) at room temperature for 1 h. Removal of the solvent in vacuum afforded **7** as a brown solid product. Yield: 0.604 g (96%). ^{1}H NMR ($CDCl_3$, δ/ppm): 7.37 (q, J=2 Hz, 1H, Ph), 7.06 (m, J=8 Hz, 1H, Ph), 6.98 (s, 2H, Ph), 6.49 (m, J=8 Hz, 1H, Ph), 6.32 (d, J=2 Hz, 1H, Ph), 2.33 (s, 3H, *p*-$PhCH_3$), 2.32 (s, 6H, *o*-$PhCH_3$), 2.03 (s, 3H, $C{=}NCH_3$); MS (EI, *m*/*z*): 610 (M^+).

4.2. Exchanging procedure for the Suzuki coupling of aryl bromide

An oven-dried flask was evacuated and charged with complex **7** (3.05 mg, 0.5 mmol%), $Pd(OAc)_2$ (1.10 mg, 0.5 mmol%), the boronic acid (0.183 g, 1.0 mmol), 4-bromo-benzaldehyde (0.185 g, 1.0 mmol), KF (0.116 g, 2.0 mmol). Toluene (1 mL) was added and the mixture was stirred. After 50 min, 37% conversion was observed. Then, the conversion reached 81% after 7 days in reaction.

4.3. X-ray crystallographic studies

Suitable crystals of **7** were sealed in thin-walled glass capillaries under nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing (width of 0.3° per frame). The absorption correction was based on the symmetry equivalent reflections using SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences, and was

confirmed using the structure solution. The structure was solved by direct methods using a SHELXTL package. All non-H atoms were located from successive Fourier maps and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms.

5. Supplementary information available

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC no. 253791 for compound **7**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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Palladium-catalyzed aromatization of β-bromovinyl aldehydes with alkenes

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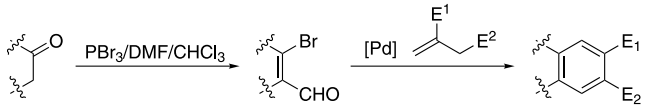
Abstract—β-Bromovinyl aldehydes, which are readily available from ketones and PBr_3/DMF/$CHCl_3$, are aromatized with suitably electron withdrawing group substituted alkenes in THF at 125 °C in the presence of a catalytic amount of a palladium catalyst along with a base.

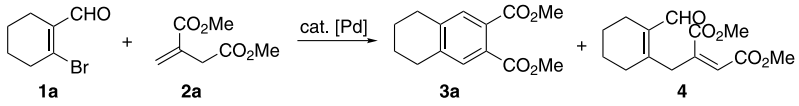
1. Introduction

Palladium-catalyzed annulation technology has been widely introduced as an useful synthetic tool for carbo- and heterocycles, which play an important role as a basic unit for the design of many pharmacologically and biologically active compounds.[1] As part of our continuing studies toward transition metal-catalyzed cyclization reactions, we recently reported on palladium-catalyzed synthesis of various cyclic compounds from *o*-halo aromatics.[2–6] Among them, in connection with this report, 2-bromobenzaldehydes were found to be cyclized with suitably functionalized alkenes in the presence of a palladium catalyst and a base via tandem Heck and intramolecular aldol reactions to give naphthalenes.[7] This protocol led us to extend to the reaction with β-bromovinyl aldehydes, which are readily prepared from ketones via the bromo analogue of Vilsmeier reaction (Scheme 1).[8] Herein, we report a successful palladium-catalyzed aromatization of β-bromovinyl aldehydes with alkenes via intrinsic tandem Heck and aldol reactions.



Scheme 1.

Table 1. Palladium-catalyzed aromatization of **1a** with **2a** under several conditions



Run	Pd catalysts	Bases	Temperature (°C)	Isolated yield (%)	
				3a	**4**
1	$Pd(OAc)_2/2PPh_3$	NaOAc	70	0	60
2	$Pd(OAc)_2/2PPh_3$	NaOAc	100	14	39
3	$Pd(OAc)_2/2PPh_3$	NaOAc	125	50	19
4	$PdCl_2(PPh_3)_2$	NaOAc	125	47	13
5	$Pd(OAc)_2/2PPh_3$	Et_3N	100	15	36
6	$Pd(OAc)_2/2PPh_3$	K_2CO_3	100	7	0
7	$PdCl_2(PPh_3)_2$	K_2CO_3	100	14	0

Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), palladium catalyst (0.05 mmol), base (3 mmol), THF (5 mL), for 20 h.

Keywords: Alkenes; Aromatization; β-Bromovinyl aldehydes; Heck–aldol reaction; Palladium catalyst.
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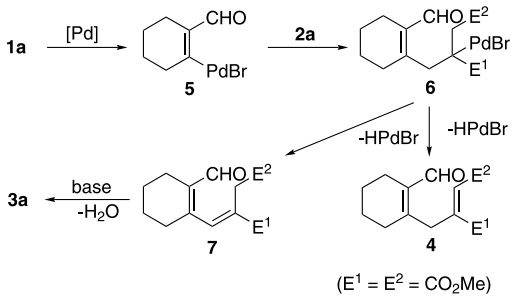
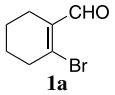
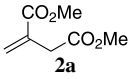
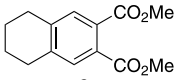
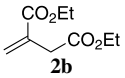
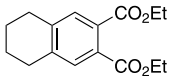
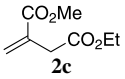
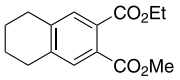
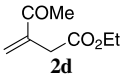
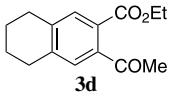
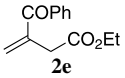
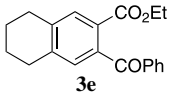
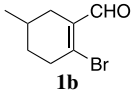
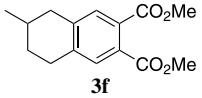
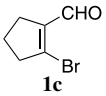
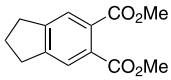
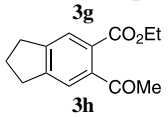
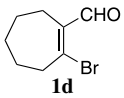
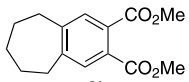
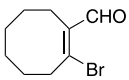
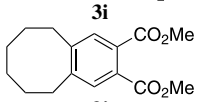
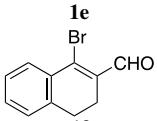
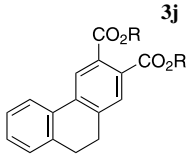
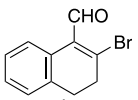
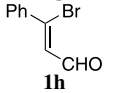
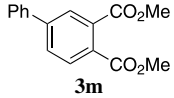


Scheme 2.

2. Results and discussion

Based on our recent report on palladium-catalyzed synthesis of naphthalenes from 2-bromobenzaldehydes and functionalized alkenes,[7] Table 1 shows several attempted results for the aromatization of 2-bromocyclohex-1-enecarbaldehyde (**1a**) with dimethyl itaconate (**2a**). Generally, treatment of equimolar amounts of **1a** and **2a** in THF in the presence of a catalytic amount of a palladium catalyst along with a base afforded dimethyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (**3a**) with concomitant formation of dimethyl

Table 2. Palladium-catalyzed aromatization of β-bromovinyl aldehydes **1** with alkenes **2**

β-Bromovinyl aldehydes **1**	Alkenes **2**	Products **3**[a]	Yield (%)
 **1a**	 **2a**	 **3a**	50
	 **2b**	 **3b**	50
	 **2c**	 **3c**	49
	 **2d**	 **3d**	60
	 **2e**	 **3e**	53
 **1b**	**2a**	 **3f**	49
 **1c**	**2a**	 **3g**	46
	2d	 **3h**	54
 **1d**	**2a**	 **3i**	55
 **1e**	**2a**	 **3j**	35
 **1f**	**2a**	 R = Me(**3k**)	46
	2b	R = Et(**3l**)	60
 **1g**	**2a**	**3k**	45
 **1h**	**2a**	 **3m**	21

Reaction conditions: **1** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), NaOAc (3 mmol), THF (5 mL), 125 °C, for 20 h.

[a] Although non-aromatized products like **4** are present in a small amount in several cases on GLC and TLC analyses, we did not focus our attention on the isolation of such non-aromatized products.

2-(2-formylcyclohex-1-enylmethyl)maleate (**4**). As has been depicted in our recent report,[7] it appears that precursor **7** for **3a** and **4** are produced, respectively, according to the direction of β-hydrogen elimination on alkylpalladium **6**, which is formed via vinylpalladium **5** by conventional Heck reaction between **1a** and **2a**. (Scheme 2). The reaction temperature was critical for the distribution of aromatized product **3a** and non-aromatized product **4** under $Pd(OAc)_2$ combined with PPh_3, higher reaction temperature resulting in preferential formation of **3a** (runs 1–3). Absolute formation of **4** was achieved with the reaction temperature 70 °C shown in run 1 of Table 1. However, the overall yield of both products did not show such a significant change. Similar yield and distribution of products were observed with $PdCl_2(PPh_3)_2$ comparing with $Pd(OAc)_2/2PPh_3$ catalytic system (runs 3 and 4). Among bases examined, Et_3N could be alternatively used under the employed conditions (runs 2 and 5), but the reaction did not proceed effectively with K_2CO_3 (runs 6 and 7).

Given the controlled conditions, the reactions of various β-bromovinyl aldehydes **1** and suitably electron withdrawing group substituted alkenes **2** were screened in order to investigate the reaction scope and several representative results are summarized in Table 2. From the reactions between **1a** and dialkyl itaconate (**2a–c**),[9] the corresponding dialkyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylates (**3a–c**) were produced in similar yields (49–50%). The reaction proceeds likewise with ethyl 3-butenoates (**2d** and **2e**)[10] having acyl group at position 3 to give the corresponding aromatized products (**3d** and **3e**). 2-Bromo-5-methylcyclohex-1-enecarbaldehyde (**1b**) reacts similarly with **2a** to give dimethyl 6-methyl-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (**3g**) in 49% yield. Several cyclic β-bromovinyl aldehydes (**1c–e**) were also reacted with **2a** and **2d**, the corresponding aromatized products (**3g–j**) being obtained in the range of 35–55% yields. However, lower reaction yield was observed with higher membered cyclic β-bromovinyl aldehyde **1e**. To test for the effect of the position of formyl group and bromide on cyclic β-bromovinyl aldehydes, **1f** and **1g** were employed. However, the aromatization took place similarly irrespective of the position. Performing the reaction of acyclic β-bromovinyl aldehyde **1h** with **1a** did not proceed satisfactorily toward aromatization compared with cyclic one.

In summary, it has been shown that β-bromovinyl aldehydes undergo an aromatization with various suitably electron withdrawing group substituted alkenes in the presence of a palladium catalyst and a base via domino Heck and aldol processes. We believe that the present reaction will work as an useful procedure for the synthesis of aromatics from ketones.

3. Experimental

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out via column (silica gel 60, 70–230 mesh, Merck) and thin layer (silica gel 60 GF_{254}, Merck) chromatography. β-Bromovinyl aldehydes **1**[8] and alkenes (**2c**,[9] **2d**,[10] and **2e**[10]) were prepared by the reported methods. Commercially available organic and inorganic compounds were used without further purification except for THF, which was distilled by known method before use.

3.1. Typical procedure for palladium-catalyzed aromatization of β-bromovinyl aldehydes with alkenes

A mixture of 2-bromocyclohex-1-enecarbaldehyde (**1a**) (0.189 g, 1 mmol), dimethyl itaconate (**2a**) (0.158 g, 1 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol) and NaOAc (0.246 g, 3 mmol) in THF (5 mL) was placed in a 50 mL pressure vessel. After the system was flushed with argon, the mixture was stirred at 125 °C for 20 h. The reaction mixture was passed through a short silica gel column (ethyl acetate) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin-layer chromatography (silica gel, ethyl acetate/hexane = 1:5) to give dimethyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (**3a**) (0.124 g, 50%) along with dimethyl 2-(2-formylcyclohex-1-enylmethyl)maleate (**4**) (0.051 g, 19%). The compounds prepared by the above procedure were characterized spectroscopically as shown below. **3a**, **3g**, **3k**, and **3m** are known.

3.1.1. Dimethyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (3a).[11] Oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79–1.82 (m, 4H), 2.78–2.81 (m, 4H), 3.88 (s, 6H), 7.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.82, 29.41, 52.59, 129.16, 129.89, 140.95, 168.44.

3.1.2. Dimethyl 2-(2-formylcyclohex-1-enylmethyl)maleate (4). Oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66–1.71 (m, 4H), 2.23–2.28 (m, 4H), 3.28 (s, 2H), 3.67 (s, 3H), 3.81 (s, 3H), 7.50 (s, 1H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.52, 21.99, 22.04, 30.98, 33.61, 52.57, 52.84, 129.49, 136.80, 140.55, 153.29, 166.64, 170.83, 192.48. Anal. Calcd for $C_{14}H_{18}O_5$: C 63.15; H 6.81. Found: C 62.94; H 6.75.

3.1.3. Diethyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (3b). Oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.04 Hz, 6H), 1.78–1.82 (m, 4H), 2.78–2.81 (m, 4H), 4.34 (q, J = 7.04 Hz, 4H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.53, 23.05, 29.63, 61.77, 129.60, 130.05, 141.01, 168.32. Anal. Calcd for $C_{14}H_{20}O_4$: C 69.54; H 7.30. Found: C 69.26; H 7.27.

3.1.4. 2-Ethyl 3-methyl 5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (3c). Oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3H), 1.78–1.80 (m, 4H), 2.78 (br s, 4H), 3.87 (s, 3H), 4.34 (q, J = 7.0 Hz, 2H), 7.40 (s, 1H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.51, 23.1 (×2), 29.6 (×2), 52.71, 61.75, 129.35, 129.58, 130.03, 130.08, 141.04, 141.08, 168.19, 168.74. Anal. Calcd for $C_{15}H_{18}O_4$: C 68.68; H 6.92. Found: C 68.49; H 6.81.

3.1.5. Ethyl 3-acetyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (3d). Oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 1.80–1.81 (m, 4H), 2.50 (s, 3H), 2.80 (s,

4H), 4.34 (q, J=7.0 Hz, 2H), 7.10 (s, 1H), 7.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.42, 23.08 (×2), 29.55, 29.80, 30.43, 61.79, 126.80, 127.76, 130.80, 139.99, 140.20, 142.02, 167.68, 203.37. Anal. Calcd for $C_{15}H_{18}O_3$: C 73.15; H 7.37. Found: C 72.81; H 7.28.

3.1.6. Ethyl 3-benzoyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (3e). Solid (hexane–chloroform); mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.0 Hz, 3H), 1.83–1.85 (m, 4H), 2.81–2.86 (m, 4H), 4.02 (q, J=7.0 Hz, 2H), 7.09 (s, 1H), 7.41 (t, J=7.5 Hz, 2H), 7.51–7.55 (m, 1H), 7.76–7.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 23.09, 23.16, 29.58, 29.85, 61.58, 126.91, 128.79, 128.84, 129.71, 131.24, 133.26, 137.95, 139.02, 139.39, 142.76, 166.58, 197.74. Anal. Calcd for $C_{20}H_{20}O_3$: C 77.90; H 6.54. Found: C 77.53; H 6.75.

3.1.7. Dimethyl 6-methyl-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylate (3f). Solid (hexane–chloroform); mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J=6.5 Hz, 3H), 1.34–1.44 (m, 1H), 1.81–1.94 (m, 2H), 2.37–2.44 (m, 1H), 2.80–2.88 (m, 3H), 3.88 (s, 6H), 7.41 (s, 1H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.00, 29.16, 29.38, 31.19, 38.16, 52.83 (×2), 129.35, 129.38, 129.86, 130.06, 140.77, 141.01, 168.73 (×2). Anal. Calcd for $C_{15}H_{18}O_4$: C 68.68; H 6.92. Found: C 68.43; H 7.15.

3.1.8. Dimethyl indan-5,6-dicarboxylate (3g). Solid (hexane–chloroform); mp 67–68 °C; (lit.[11] 68–69 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87–2.98 (m, 4H), 3.92 (s, 3H), 3.94 (s, 3H), 7.25–7.36 (m, 3H), 7.60 (s, 1H), 7.79–7.81 (m, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.09–2.16 (m, 2H), 2.95 (t, J=7.5 Hz, 4H), 3.88 (s, 6H), 7.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.47, 32.89, 52.70, 125.00, 130.46, 148.12, 168.73.

3.1.9. Ethyl 6-acetylindan-5,6-dicarboxylate (3h). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J=7.0 Hz, 3H), 2.09–2.16 (m, 2H), 2.51 (s, 3H), 2.95 (t, J=7.5 Hz, 4H), 4.34 (q, J=7.0 Hz, 2H), 7.25 (s, 1H), 7.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.42, 25.68, 30.55, 32.92, 33.21, 61.81, 122.82, 125.86, 127.84, 141.68, 147.01, 149.20, 167.80, 203.78. Anal. Calcd for $C_{14}H_{16}O_3$: C 72.39; H 6.94. Found: C 72.15; H 6.82.

3.1.10. Dimethyl 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2,3-dicarboxylate (3i). Solid (hexane–chloroform); mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61–1.66 (m, 4H), 1.82–1.88 (m, 2H), 2.82–2.85 (m, 4H), 3.88 (s, 6H), 7.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.07, 32.81, 36.75, 52.85, 129.88 (×2), 147.45, 168.69. Anal. Calcd for $C_{15}H_{18}O_4$: C 68.68; H 6.92. Found: C 68.36; H 7.09.

3.1.11. Dimethyl 5,6,7,8,9,10-hexahydrobenzocyclooctene-2,3-dicarboxylate (3j). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33–1.36 (m, 4H), 1.69–1.70 (m, 4H), 2.78–2.81 (m, 4H), 3.89 (s, 6H), 7.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.07, 32.18, 32.50, 52.83, 130.02, 130.12, 145.42, 168.75. Anal. Calcd for $C_{16}H_{20}O_4$: C 69.54; H 7.30. Found: C 69.64; H 7.36.

3.1.12. Dimethyl 9,10-dihydrophenanthrene-2,3-dicarboxylate (3k). Solid (hexane–chloroform); mp 82–83 °C (lit.[12] 84 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87–2.98 (m, 4H), 3.92 (s, 3H), 3.94 (s, 3H), 7.25–7.36 (m, 3H), 7.60 (s, 1H), 7.79–7.81 (m, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.04, 28.39, 52.33 (×2), 123.97, 124.39, 125.22, 126.98, 128.04, 128.48, 129.26, 129.96, 130.39, 132.33, 137.20, 140.24, 167.88, 168.21.

3.1.13. Diethyl 9,10-dihydrophenanthrene-2,3-dicarboxylate (3l). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J=7.0 Hz, 3H), 1.39 (t, J=7.0 Hz, 3H), 2.86–2.94 (m, 4H), 4.38 (q, J=7.0 Hz, 2H), 4.40 (q, J=7.0 Hz, 2H), 7.24–7.35 (m, 3H), 7.60 (s, 1H), 7.79–7.81 (m, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.59 (×2), 28.81, 29.13, 62.01, 62.05, 124.67, 124.71, 127.69, 128.75, 129.14, 129.15, 130.96, 131.38, 133.15, 137.66, 137.96, 140.79, 168.12, 168.28. Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06; H 6.21. Found: C 73.76; H 6.17.

3.1.14. Dimethyl 4-phenylphthalate (3m).[13] Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.94 (s, 3H), 7.41–7.49 (m, 3H), 7.60–7.62 (m, 2H), 7.74 (dd, J=2.0, 8.0 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.91 (d, J=1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.04, 53.13, 127.61, 127.77, 128.86, 129.42, 129.70, 130.11, 130.28, 133.46, 139.39, 144.75, 168.05, 168.74.

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Salt, concentration, and temperature effects on an asparagine-based, aqueous Diels–Alder cycloaddition

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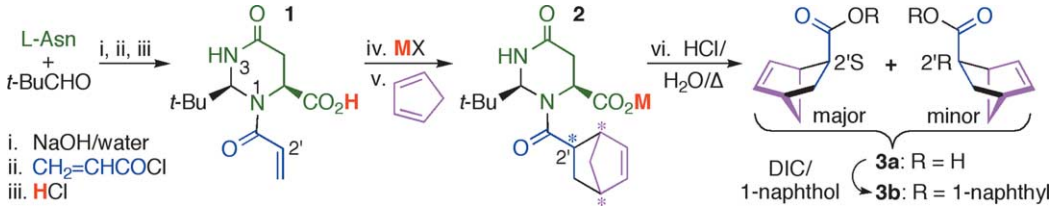
Abstract—Results are reported on the salt, concentration, and temperature effects in an aqueous, auxiliary-mediated asymmetric Diels–Alder cycloaddition. The auxiliaries were prepared under basic aqueous conditions from asparagine and trimethylacetaldehyde, and coupled to acryloyl chloride to generate dienophiles in one pot. Temperature and concentration modestly impacted cycloaddition stereochemistry. Experiments with a range of salts examined the speculation that complexation between the counterion of the auxiliary carboxylate and the dienophile carbonyl promotes the formation of the minor *endo* product, reducing cycloaddition diastereoselectivity for the *endo* products. The transformation was poorly selective for the carboxylic acid but gave moderate selectivities for several metallated carboxylates. The magnitude of the diastereoselectivity of the *endo* products was weakly dependent on carboxylate counterion and more strongly influenced by the basicity of the salt anion. Data presented suggest that Lewis acid catalysis reduces cycloaddition diastereoselectivity for the *endo* products.

1. Introduction

The Diels–Alder reaction is a powerful technique for assembling complex organic frameworks[2] and is a crucible for examining subtle electronic and steric effects.[3] Auxiliary-based methods for asymmetric Diels–Alder cycloadditions have received much attention but less has been disclosed on aqueous variants.[4,5] We recently reported preliminary results on such a reaction employing L-asparagine-derived pyrimidinones for chirality transmission (Scheme 1).[6] Among its notable features were the in situ auxiliary preparation using asparagine and aldehyde, the completion of the entire synthetic process in a two-pot sequence, and the compatibility of this system with ambient aqueous media. While experimentally simple and economical, this methodology suffered from moderate cycloaddition selectivity. We now report the results of salt, concentration, and temperature studies aimed at elucidating factors impacting cycloaddition stereochemistry.

2. Results and discussion

The present studies focused on investigating the possible participation of the metal counterion of the salt of **1** (generated by the addition of MX) in cycloaddition stereoselectivity.[7,8] Proton NMR and crystallography indicate that analogs of **1** maintain the carboxyl group at



Scheme 1. Aqueous, L-asparagine-based, auxiliary-mediated cycloaddition (*exo* products not shown).

Keywords: Diels–Alder; Cycloaddition; Aqueous; Salt effects; Auxiliary; Asymmetric.
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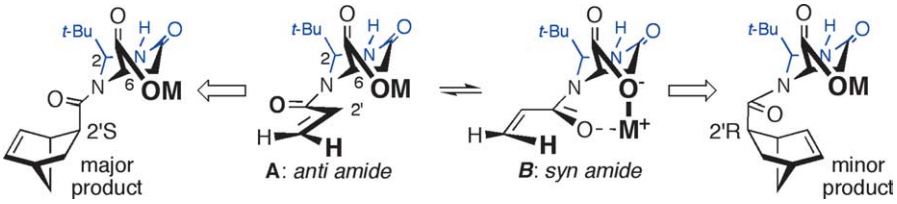


Figure 1. Dienophile conformations and their respective adducts with cyclopentadiene.

C6 and alkyl unit at C2 in pseudo-axial orientations[9] in order to minimize vicinal interactions with the amide unit.[10] Proton NMR of **1** in D_2O with 1.1 equiv $NaHCO_3$ at 25 °C indicated the presence of two major conformers in 4:1 ratio. We suspected these were the two *s-cis* amide rotomers (*anti*-amide **A** and *syn*-amide **B**; Fig. 1) since preliminary computational studies indicated that *s*-trans conformers are disfavored by congestion between the vinyl group and the pyrimidinone C2 and C6 substituents.[11] Assuming that the diene would react preferentially at the pi-face opposite to the sterically demanding pyrimidinone 2-*tert*-butyl and 6-carboxyl substituents, the observed major 2′*S*-*endo* cycloaddition product suggested that cycloadditions occurred primarily with *anti*-amide **A** conformer. We speculated that Lewis acid complexation between the carboxylate counterion (M) and the eneamide carbonyl of *syn*-amide **B** (a bidentate complexation as depicted below in Fig. 1) may electronically activate this dienophile conformer toward Diels–Alder cycloaddition. Catalysis of cycloadditions of the *syn*-amide **B** would increase the occurrence of the minor 2′*R*-*endo* cycloaddition product, thus leading to diminished *endo* selectivity for this transformation. Salt, concentration, and temperature studies were performed to examine this hypothesis and to survey for conditions that enhance cycloaddition stereoselectivity.

In these studies, acrylamide **1** was prepared, reacted with cyclopentadiene under specified conditions, and the resulting cycloadducts were analyzed as described below. Treatment of L-asparagine (10 g) with aqueous sodium hydroxide (2 M, 1 equiv) and trimethylacetaldehyde (1 equiv) at room temperature induced cyclocondensation. The resulting heterocycle was cooled to ice bath temperature and directly acylated upon treatment with solid sodium bicarbonate (1.5 equiv) and acryloyl chloride (1.3 equiv). Acrylamide **1** was precipitated upon acidification (10% HCl), filtered, washed with water, and evacuated overnight (0.1 mmHg) to yield a white amorphous solid in 55% yield. The individual cycloaddition stereoselectivity studies, which were conducted as specified below, resulted in 2-norbornene carboxylic acid cycloadducts **2**. The carboxylic acids (**3a**) were released from the pyrimidinone auxiliary upon aqueous acid exposure and heating (70 °C, 24 h), and were extractively isolated.[12] The dried CH_2Cl_2 solutions of **3a** were coupled to 1-naphthol (DIC/cat DMAP) to generate a mixture of UV active stereoisomeric esters (**3b**) for HPLC analysis. Individual isomer ratios of **3b** were determined by chiral stationary phase HPLC (Pirkle Type 1, 95% hexanes/isopropanol, 1 mL/min),[6] which exhibited baseline separated *endo* isomer signals (retention time = 16 and 18 min) that were widely separated from the *exo* isomer signals (retention time = 14 and 14.5 min; the *exo* isomers were only partially separated). The early eluting *endo* isomer (retention time = 16 min), which was the minor *endo* product in all preparations, was identified as the 2′*R*-enantiomer (Scheme 1; numbering is maintained for simplicity) based on coelution studies with the 1-naphthyl ester prepared from an authentic sample. In each case, integrated signals from the HPLC traces were used (uncorrected) to determine *endo* enantiomer ratios[13] and *endo*/*exo* diastereomer ratios. Minor experimental variations that were employed to examine salt, temperature, and concentration effects are described below.

2.1. Concentration effects on cycloaddition stereoselectivity

To begin these studies, concentration effects were examined to identify convenient and reproducible cycloaddition concentrations. The studies were conducted at 0.05, 0.10, 0.25, 0.50, 1.0 M acrylamide **1** (2.5 mmol scale) in satd $NaHCO_3$ solution and the results are presented in Table 1. These data indicate that concentrations at or below 0.25 M provide optimal selectivity. This may be due to species aggregation at higher concentrations of acrylamide, though this phenomenon was not investigated further. Based on these studies, succeeding reactions were conducted at 0.25 M acrylamide.

Table 1. Concentrations studies versus cycloaddition stereoselectivity

[Auxiliary] (M)	*endo* ee (%)[a]	*endo*/*exo*[a]
0.05	71.8 (±0.4)	24.9 (±1.3)
0.10	70.0 (±0.6)	23.7 (±0.7)
0.25	68.1 (±0.8)	27.2 (±2.3)
0.50	63.4 (±0.1)	20.9 (±0.3)
1.00	51.3 (±2.1)	20.4 (±0.4)

[a] Data are averages of triplicate experiments.

2.2. Temperature effects on cycloaddition stereoselectivity

For temperature studies, **1** (0.50 mmol) was added to satd $NaHCO_3$ solution (2 mL) at room temperature, cooled to the listed temperature (Table 2), and treated with

Table 2. Temperature effects (Scheme 1, Y = Na)

Entry	Temperature (°C)	Time (h)	*endo* ee (%)[a]	*endo*/*exo*[a]
1	−15[b]	148	59.2 (±0.6)	36.0 (±1.8)
2	0	72	71.3 (±0.7)	42.5 (±2.6)
3	7	48	71.8 (±0.6)	32.3 (±1.1)
4	14	36	69.7 (±0.2)	31.3 (±2.4)
5	23	24	68.3 (±0.1)	31.3 (±2.2)
6	35	12	66.6 (±0.2)	24.3 (±2.2)

[a] Data are averages of triplicate experiments.
[b] This sample congealed under these conditions.

cyclopentadiene. For preparations below room temperature, the diene was chilled upon contact with the cold interior surface of the reactor prior to exposure to **1**. After stirring for the time specified, the mixtures were processed to 1-naphthyl esters and analyzed by HPLC. The data from these preparations are presented in Table 2. It was found that lower temperatures gave greater selectivities as is normally found in DA reactions, except for entry 1, in which the cycloaddition was performed in a congealed mixture. There was concern that at the lower temperatures, the selectivity might be reduced due to aggregation effects, however, there was no significant reduction in selectivity for samples that remained dissolved at the tested temperatures.

2.3. Effect of sodium bicarbonate molar ratio on cycloaddition stereoselectivity

Next, we examined the selectivity as a function of molar equivalents of sodium bicarbonate (Table 3). These room temperature experiments were conducted as described above with varying amounts of sodium bicarbonate as listed. Because of the experimental consistency of the aforementioned trials and of these results, data presented below (except as indicated) were obtained from single preparations. The results of these experiments clearly indicate that the reaction requires a stoichiometric amount of bicarbonate, reaching the maximum diastereoselectivity for *endo* adducts at 1.0 equiv $NaHCO_3$. The correlation between the diastereoselectivity of the *endo* cycloadducts and bicarbonate molar proportion is highly linear up to 1 equiv (Fig. 2).

Table 3. Cycloaddition selectivity at various molar ratios of sodium bicarbonate (MX = $NaHCO_3$)

Entry	(MX/**1**) molar ratio	*endo* ee (%)	*endo*:*exo*
1	0.00	7.9	22:1
2	0.10	19.3	22:1
3	0.30	34.2	23.1
4	0.50	42.8	27:1
5	0.75	53.2	23:1
6	1.00	70.9	25:1
7	1.20	70.5	25:1
8	1.50	70.7	26:1
9	2.00	68.2	23:1
10	3.00	70.2	25:1

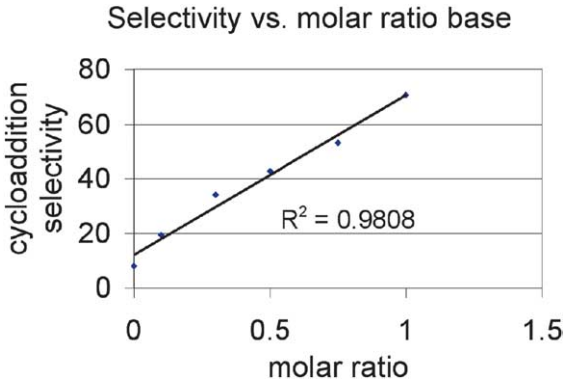


Figure 2. Cycloaddition *endo* selectivity versus sodium bicarbonate molar ratio.

Table 4. Salt influence on the Diels–Alder cycloaddition stereoselectivity (MX = salt in Scheme 1)

Entry	MX	*endo* ee (%)	*endo*:*exo*
1	None	7.9	22:1
2	NaCl	2.0	20:1
3	$BaCl_2$	4.7	20:1
4	LiOAc	62.8	23:1
5	NaOAc	64.5	24:1
6	CsOAc	61.9	23:1
7	$NaHCO_3$	70.7	26:1
8	Li_2CO_3	67.2	20.1
9	Na_2CO_3	67.0	19:1
10	K_2CO_3	67.4	31:1
11	Cs_2CO_3	67.9	30:1
12	$MgCO_3$	67.2	29:1
13	$CaCO_3$	64.9	34:1
14	LiOH	69.7	26:1
15	NaOH	67.5	23:1
16	KOH	66.5	24:1
17	$Ba(OH)_2$	60.2	28:1
18	NH_4OH	70.5	19:1
19	*n*-Bu_4NOH	64.9	26:1
20	MgO	66.5	24:1

2.4. Salt effects on cycloaddition stereoselectivity

Counterion experiments were conducted at room temperature in water using the alkali and alkaline earth salts listed in Table 4. In these studies acrylamide **1** was added to water containing the listed salt (1.5 equiv) and stirred for 1 h prior to the addition of cyclopentadiene. The mixtures were stirred overnight, processed, and analyzed routinely. Salts were selected to examine the impact of both cations and anions. As discussed above, cations that strongly complex to the carboxylate and eneamide carbonyl should exhibit decreased cycloaddition diastereoselectivity for *endo* isomers by enhancing the reactivity of the conformation that generates the minor product. Metal salts containing various anions with different basicities were employed to examine possible selectivity differences caused by metal association with the carboxylate, or carboxylic acid for salts with weakly basic anions, and the eneamide carbonyl. Thus, sodium was examined as the chloride, acetate, bicarbonate, carbonate, and hydroxide salts (Table 4, entries 2, 5, 7, 9, and 15, respectively). Selected other metal salts were also examined including transition metal salts that are presented in Table 5.

Several interesting trends emerged from these data. Poorly basic sodium and barium chloride (entries 2 and 3) exhibited

Table 5. Effect of the transition metal salts on the Diels–Alder cycloaddition reaction (Scheme 1, in water with salts listed)

Entry	MX	*endo* ee (%)	*endo*:*exo*
1	$NiCl_2$	2.7	21:1
2	$CoCl_2$	3.9	20:1
3	$BaCl_2$	4.7	20:1
4	$CuCl_2$	5.9	22:1
5	$ZnCl_2$	9.5	20:1
6	$Cu(OAc)_2$	40.4	30:1
7	$Zn(OAc)_2$	54.2	25:1
8	$Ni(OAc)_2$	56.5	25:1
9	$Mn(OAc)_2$	57.1	25:1
10	$Co(OAc)_2$	57.4	27:1
11	$Mn(OAc)_3$	36.4	29:1
12	$Ti(OAc)_4$	56.0	25:1

poor diastereoselectivities for *endo* isomer formation, while moderately basic lithium, sodium, and cesium acetates (entries 4–6) gave higher *endo* diastereoselectivities. Both of these salt series exhibited diastereoselectivities in narrow ranges of values. The alkali and alkaline earth carbonate entries 8–13 were also obtained in a small range of diastereoselectivities for *endo* adducts, which were slightly higher than the values obtained for the acetate salts. The alkali, alkaline earth, and ammonium hydroxides (entries 14–17, 18, and 19) exhibited a moderate range of selectivities (approximately 60–71% ee), which is suggestive of a modest cation effect. The calcium carbonate and barium hydroxide preparations (entries 13 and 17) exhibited the smallest selectivities in the carbonate and hydroxide series, respectively, which is supportive of a Lewis acid influence on these transformations (these trials were repeated to verify reproducibility). The tetrabutylammonium hydroxide salt (entry 19), which was expected to poorly activate the dienophile delivered lower *endo* diastereoselectivity, contrary to what was expected. Overall, these results suggest a modest impact of the salt cation on the cycloaddition *endo* diastereoselectivity.

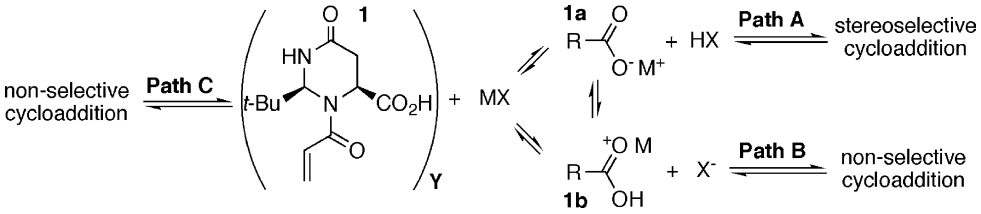
In contrast, anion effects appeared much stronger than cation effects. Thus, sodium salt entries 2, 5, 7, 9, and 15 (chloride, acetate, bicarbonate, carbonate, and hydroxide salts, respectively) were strongly affected by the anion. Generally, chloride salts gave poorly selective transformations while acetate salts gave much improved *endo* diastereoselectivities that varied little with cation (61.9–64.5%). Bicarbonate, carbonate, and hydroxide salts typically gave higher selectivities than acetate salts. The remainder of the salts tested exhibited similar behaviors relative to the magnitude of cation and anion impacts.

Several transition metal salts were also examined (Table 5). Weakly basic chloride salts (entries 1–5) exhibited comparable selectivities to their corresponding alkali and alkaline earth chlorides. Transition metal acetate salts (entries 6–12) exhibited a greater range of cycloaddition diastereoselectivities for *endo* products, and these were each smaller than the alkali acetate salts (entries 4–6 in Table 4). These results are consistent with the known propensities of these transition metals to chelate carbonyl groups and carboxylates in biomolecules such as peptides, hydroxamic acids, and siderophores.[14] Most striking is the smaller *endo* diastereoselectivity observed for the acetate salt of copper(II) (entry 6) relative to zinc(II), nickel(II), manganese(II), cobalt(II), manganese(III), and titanium(IV) (entries 7–12).

2.5. General discussion

Overall, these data indicate that salt cations influence the diastereoselectivity of the *endo* adducts only weakly compared to the effect of salt anions. Salts with weakly basic anions gave poor *endo* cycloaddition diastereoselectivities while salts with moderately to highly basic anions gave significantly enhanced *endo* cycloaddition diastereoselectivities. Cations derived from salts that generate dienophile carboxylates (bicarbonate, carbonate, and hydroxide) were associated with modest selectivity differences. Intermediately basic acetates gave *endo* diastereoselectivities between the extremes described above, though several showed a significant *endo* diastereoselectivity variance with different metals. Each of the transition metal acetate salts gave lower selectivities than the alkali and alkaline earth acetate salts, which is consistent with increased metal complexation with the eneamide carbonyl as suggested in the above model. This rationale for cycloaddition diastereoselectivity is further supported by the poor *endo* diastereoselectivities of oxophilic copper(II) and manganese(III) acetates, which are known to bind to carbonyls and complex strongly to carboxylate ions. It was somewhat surprising that titanium(IV) acetate, a metal that typically binds strongly to oxygen ligands, did not strongly influence the diastereoselectivity of *endo* adducts relative to other transition metal acetates. According to the data presented, the effectiveness of the metals in activating this Diels–Alder cycloaddition follows the order: $Mn^{+3} > Cu^{+2} > Zn^{+2} > Ti^{+4} \approx Ni^{+2} \approx Mn^{+2} \approx Co^{+2} >$ alkali metals-$\approx$alkaline earth metals, in good agreement with the empirical order given by Irvin and Williams ($Mn < Co < Ni < Cu > Zn$) for the bivalent ion complexation.[15a] Furthermore, the order of the activating ability of the transition metals reported here parallels the order of the binding strength of transition metals on a bidentate dienophile and Lewis acid dienophile activation reported by Otto and co-workers.[15b]

These results are consistent with a process in which the salt must form acrylamide carboxylate **1a** (Scheme 2, path A) for enhanced cycloaddition stereoselectivity. The weak influence of the alkali and alkaline earth metal cations in *endo* cycloaddition diastereoselectivity is likely due to strong water solvation about the metal, for which the eneamide carbonyl competes weakly.[5] The difficulty of overcoming metal ion hydration also extends to transition metals, though slightly less so, and is a significant problem associated with aqueous Lewis acid catalysis. Selectivity differences among salts with a common anion—particularly between alkali, alkaline earth, and transition metal acetate



Scheme 2. Cycloadditions from salt experiments (R=heterocycle acrylamide).

salts—are suggestive of differences in Lewis acid activation of the dienophile. Salts that do not form dienophile carboxylates undergo cycloadditions as weakly associated, metallated carboxylic acid **1b** (path B), or as free carboxylic acid **1**, which proceeds without significant Lewis acid dienophile activation (path C). The poor *endo* diastereoselectivity observed with weakly basic salts might be associated with cycloadditions with dienophile aggregates (Scheme 2, $Y>1$) that result from the poor solubility of the free carboxylic acid in water. Thus, the low selectivity of weakly basic salts may not correspond to the kinetic selectivities of monomeric acrylamide **1**. Intermediately basic acetate salts, which are expected to generate both metallated carboxylate **1a** and carboxylic acid **1**, gave intermediate selectivities, as anticipated for a product mixture generated from cycloadditions to both species.

These studies also examined for a correlation between *endo* diastereoselectivity and *endo*/*exo* ratios in the Diels–Alder cycloadditions.[16] According to the analysis, increased Lewis acid activation, which yields diminished *endo* diastereoselectivity, would lead to a concomitant increase in *endo*/*exo* ratios.[17] This correlation would not be expected to be dramatic since the *endo* selectivity data in Tables 4 and 5 suggest only a modest Lewis acid activation. Data from Table 4 do not indicate a strong correlation between the *endo* diastereoselectivity values and *endo*/*exo* ratios. Indeed, such a correlation, if present, is obscured by the variability of *endo*/*exo* ratios. However, the transition metal acetate salts in Table 5 routinely exhibited higher *endo*/*exo* selectivity ratios than the alkali or alkaline earth acetates (compare entries 4–6 in Table 4 with entries 6–12 in Table 5). Furthermore, the copper(II) and manganese(III) acetate salts (entries 6 and 11 in Table 5) each induced significantly less *endo* diastereoselectivity and higher *endo*/*exo* ratios than the other transition metal acetate salts tested (entries 7–10 and 12 in Table 5). Both of the aforementioned results are consistent with Lewis acid promotion of *endo*/*exo* ratios. Thus, while these results are subtle and additional studies are required to firmly establish trends, Lewis acid activation appears to be involved in this aqueous, auxiliary-mediated process, diminishing the *endo* diastereoselectivity in a salt-dependent manner, while simultaneously increasing the *endo*/*exo* selectivity in these preparations.[18]

3. Summary

Salt, concentration, and temperature influences on an aqueous, auxiliary-mediated Diels–Alder cycloaddition have been examined. The results of these studies suggest that the cycloaddition stereochemistry is reduced at higher concentration and temperature. These studies also indicate a strong correlation between cycloaddition stereoselectivity and salt anion basicity, and a modest impact associated with salt cation. The reported results suggest that the metals associated with the dienophile carboxylate are not strongly complexed with the eneamide carbonyl and thus, only weakly impart electronic activation to the dienophile eneamide. The limited impact of cation on the cycloaddition stereoselectivities reported here illustrates the challenges that remain to be addressed in exploiting Lewis acid catalysis in aqueous media. In this instance, Lewis acid activation appears to promote the formation of the minor *endo* diastereomer, thus leading to reduced *endo* diastereoselectivity and increased *endo*/*exo* ratios. Ongoing investigations on the origin of the selectivity of this process and approaches to enhance the cycloaddition stereoselectivity will be reported in due course.

4. Experimental

4.1. General methods

Proton and ^{13}C NMR spectra were recorded at 500 and 125 MHz (Varian Inova), respectively, in water-d_2 or $CDCl_3$ as indicated at 25 °C. Chemical shift values are reported in ppm with TMS as an internal reference. *J* values are given in Hz. Optical rotation was recorded on a Rudolph Autopol IV digital polarimeter at room temperature. Mass spectrometric data were recorded using Finnigan MAT95 mass spectrometer (CI+, 20 eV, reagent gas: CH_4). Kieselgel $60F_{254}$ silica gel TLC plates were used for monitoring reaction progress. Flash chromatography was performed using silica gel (Aldrich, 200–300 mesh) with ethyl acetate–hexanes gradients. Reactions were routinely effected in capped vials with magnetic stirring. Cyclopentadiene was fractionally distilled on the day of its use. All other chemicals were purchased from the Sigma-Aldrich Chemical Company (St. Louis, MO) and used without purification.

4.1.1. (2*S*,4*R*)-3-Acryloyl-2-*tert*-butyl-6-oxo-hexahydropyrimidine-4-carboxylic acid (1). Into a 100 mL flask was added (*S*)-asparagine monohydrate (7.51 g, 50 mmol) and aqueous NaOH (2.0 M, 1 equiv). The mixture was stirred 15 min and trimethylacetaldehyde (1 equiv) was added via syringe over 5 min. The mixture was stirred 4 h, treated with solid sodium bicarbonate (1.5 equiv), cooled in an ice bath, and acryloyl chloride (1.3 equiv) was added slowly (four portions over 1 h) to the vigorously stirred solution. Cooling and stirring were continued an additional 2 h, after which the mixture was treated with HCl (10%, 1.6 equiv) inducing precipitation of **1**. The product was filtered, washed with cold water, and dried overnight under high vacuum leaving behind **1** as an amorphous white power (55% yield). Mp=160 °C (dec); $[\alpha]_D^{25.6}$ −145.5° (c 0.015 g/cm^3, methanol); ^1H NMR (satd $NaHCO_3$ in D_2O): δ 0.98 (9H, s), 2.87 (dd, J=9.3, 18.1 Hz, 1H), 2.98 (dd, J=9.3, 3.9, 18.1 Hz, 1H), 4.75 (t, J=9.3 Hz, 1H), 5.69 (s, 1H), 5.82 (d, J=10.7 Hz, 1H), 6.23 (d, J=16.6 Hz, 1H), 6.55 (dd, J=10.7, 16.6 Hz, 1H); ^{13}C NMR (satd $NaHCO_3$ in D_2O): δ 25.7 (q), 31.5 (t), 39.2 (s), 55.5 (d), 69.5 (d), 128.2 (d), 130.1 (t), 170.2 (s), 172.9 (s), 176.9 (s); MS (*m*/*z*): 255 (16, $M^+ + 1$), 210 (16), 197 (90), 154 (38), 143 (88), 123 (36), 97 (44), 85 (45), 55 (100); IR (cm^{-1}): 2957, 1717, 1607, 1484, 1436, 1332, 1282, 1213, 1194, 1087, 1028, 975, 937. Anal. Calcd for $C_{12}H_{20}N_2O_5$ (monohydrate, as determined by a proton NMR integration study): C, 52.93; H, 7.40; N, 10.29. Found: C, 52.91; H, 7.16; N, 10.06.

4.1.2. General procedures for Diels–Alder cycloaddition (the synthesis of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (3a) as a mixture of stereoisomers). Chiral acrylamide **1** (1 mmol) was dissolved in an aqueous salt

or Lewis acid solution (1.5 equiv) and treated with cyclopentadiene (3 equiv) under specified conditions. The mixture was stirred for 24 h at room temperature (unless otherwise specified) and the reaction was quenched by heterogeneous removal of unreacted cyclopentadiene with ethyl acetate (2×5 mL). The aqueous layer was then treated with HCl (10%, 1.5 equiv), extracted with ethyl acetate (2× 5 mL), and dried over anhydrous sodium sulfate. Removal of solvent in vacuo left behind a slightly yellow solid (**2**; M=H) that exhibited a forest of signals in ^{1}H NMR (satd $NaHCO_3$ in D_2O) and was not further characterized. The solid was suspended in water (5 mL) and heated to 70 °C for 24 h. The resulting clear solution was extractively (ethyl acetate) processed as described above to yield **3a** as a colorless oil (54%). For spectral observation, an aliquot was removed from ethyl acetate extract and the major *endo* isomer was enriched via silica gel chromatography, which exhibited proton and carbon NMR signals that were identical to reported values of **3a**.[19] ^{1}H NMR ($CDCl_3$): δ 1.28 (br d, J=8.3 Hz, 1H), 1.40 (ddd, J=2.4, 4.4, 11.72 Hz, 1H), 1.45 (ddt, J=2.4, 8.3, 2.0 Hz, 1H), 1.92 (ddd, J=3.4, 9.3, 11.7 Hz, 1H), 2.92 (br s, 1H), 3.00 (dt, J=9.3, 3.9 Hz, 1H), 3.23 (br s, 1H), 6.00 (dd, J=2.9, 5.4 Hz, 1H), 6.21 (dd, J=3.4, 5.9 Hz, 1H), 10–12 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.1 (t), 42.5 (d), 43.3 (d), 45.7 (d), 49.7 (t), 132.4 (d), 137.9 (d), 181.4 (s).

4.1.3. Naphthalen-1-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate (3b, mixture of stereoisomers). The stereoisomeric mixture of carboxylic acid **3a** (34.5 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and treated with 1-naphthol (39.6 mg, 1.1 equiv), DMAP (7.6 mg, 25% mol) and DIC (34.7 mg, 1.1 equiv). After 6 h stirring, the mixture was washed with brine (2×1 mL), dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was flash chromatographed in a 5×0.5 cm plug of silica gel (5% ethyl acetate in hexanes) prior to stereochemical analysis by chiral phase HPLC (Regis Pirkle Type 1, RR; 95:5 hexanes/isopropanol, 1.0 mL/min). For analytical purposes the *endo* product was enriched by gradient normal phase chromatography (hexanes to 20% ethyl acetate/hexanes) to yield **3b** as a light yellow solid. Mp=56–58 °C; ^{1}H NMR ($CDCl_3$): δ 1.39 (br d, J=8.3 Hz, 1H), 1.54 (ddt, J=2.4, 8.3, 2.0 Hz, 1H), 1.64 (ddd, J=2.9, 3.9, 11.7 Hz, 1H), 2.07 (ddd, J=3.4, 9.3, 11.7 Hz, 1H), 2.99 (br s, 1H), 3.37 (dt, J=9.3, 3.9 Hz, 1H), 3.50 (br s, 1H), 6.17 (dd, J=2.9, 5.9 Hz, 1H), 6.30 (dd, J=2.9, 5.9 Hz, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.41 (t, J= 7.8 Hz, 1H), 7.47 (m, 2H), 7.68 (d, J=8.3 Hz, 1H), 7.82 (ddd, J=1.5, 2.5, 7.3 Hz, 1H), 7.87 (ddd, J=1.5, 2.4, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.4 (t), 42.6 (d), 43.7 (d), 46.1 (d), 49.8 (t), 117.9 (d), 121.1 (d), 125.3 (d), 125.6 (d), 126.2 (d), 126.3 (d), 126.9 (s), 127.9 (d), 132.3 (d), 134.6 (s), 138.3 (d), 146.7 (s), 173.1 (s); HRMS (*m*/*z*): Calcd for $C_{18}H_{16}O_2$ 264.115030, found 264.115050; MS (*m*/*z*): 264 (40), 144 (100), 121 (44), 115 (22), 93 (24), 55 (38); IR (cm^{-1}): 3062, 2962, 2942, 2871, 1749, 1595, 1388, 1338, 1258, 1224, 1127, 1106, 1013.

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Direct approaches to annulated indoles. A formal total synthesis of 0231B

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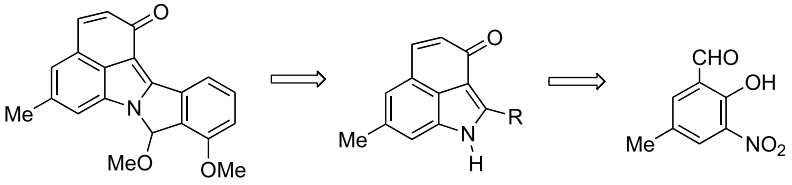
Abstract—An advanced intermediate in the Nakatsuka synthesis of 0231B was prepared using a fluoride-mediated indole formation in the key step. Both palladium-based approaches and hydride-based approaches failed to generate the indole.

1. Introduction

In 2001 the structure of 0231B (**1**), a novel inhibitor of 3a-hydroxysteroid dehydrogenase, was reported from *Streptomyces* sp. HKI0231.[1] Recently, Nakatsuka reported a clever synthesis of **1** utilizing a novel Friedel-Crafts alkylation reaction.[2] Because compounds that inhibit this enzyme may be useful leads for new anti-inflammatory agents, we developed a synthetic approach via **2** beginning with known aldehyde[3] **3**. We report herein a concise preparation of **2b**, a key intermediate in Nakatsuka's synthesis, from **3**.



In our first approach, we envisioned constructing a 2,3,4,6-tetrasubstituted indole from, which the enone moiety could be generated by way of an intramolecular aldol reaction. As a model system we decided to construct **2a**. As shown in Scheme 1, aldehyde **3**, prepared in one step from commercially available starting materials, underwent reductive acetylation (Pd/C, H_2, Ac_2O) followed by conversion of the phenol into a triflate to provide triflate **4** in 70% yield from **3**. Triflate **4** was subjected to a Sonogashira coupling using the method of Wang[4] to afford aldehyde **5** in 86% yield.

Attempts to convert acetylene **5** into an indole using palladium chloride (10 mol%) in boiling acetonitrile failed, despite close literature precedent.[5] Using different palladium catalysts was not effective. Both NMR and thin-layer chromatography indicated that a complex mixture of products had been produced. Base mediated indole formation methods (KH/NMP and *t*-BuOK/NMP) also failed.[6] Fortunately, treatment of acetylene **5** with tetrabutylammonium fluoride[7] in THF at reflux provided indole **6** in 67% yield. Surprisingly, acetylation of **6** using a variety of Lewis acids ($AlCl_3$, $SnCl_4$, Et_2AlCl) and acetylating agents (AcCl, Ac_2O, CH_3CN) afforded at best a 46% yield of keto aldehyde **7**.[8] This modest yield may be related to Lewis acid coordination to the aldehyde, which would be expected to attenuate the reactivity of the indole towards electrophiles. Steric hindrance from the phenyl group at C-2 may also have been a factor. Intramolecular aldol condensation using potassium *tert*-butoxide in THF at ambient temperature afforded enone **2a**; however, the aldol reaction was not reproducible upon scale up beyond

Keywords: Sonogashira coupling; Aldol condensation; 3,4,6-Trisubstituted indole.
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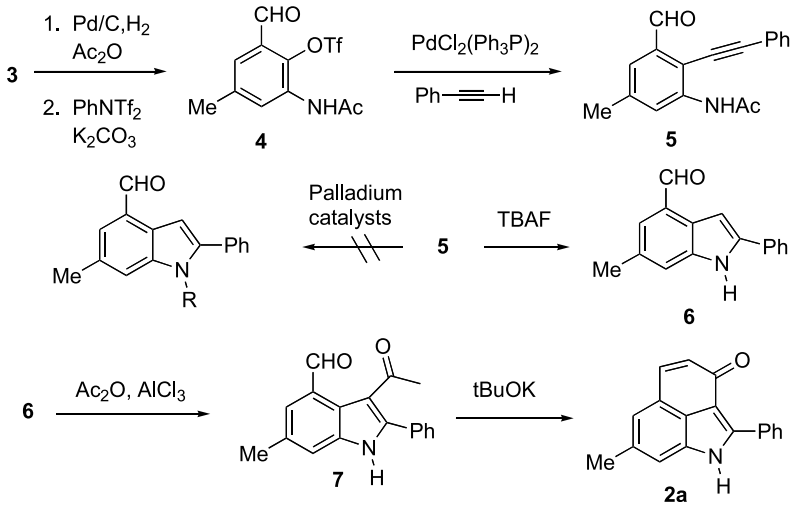
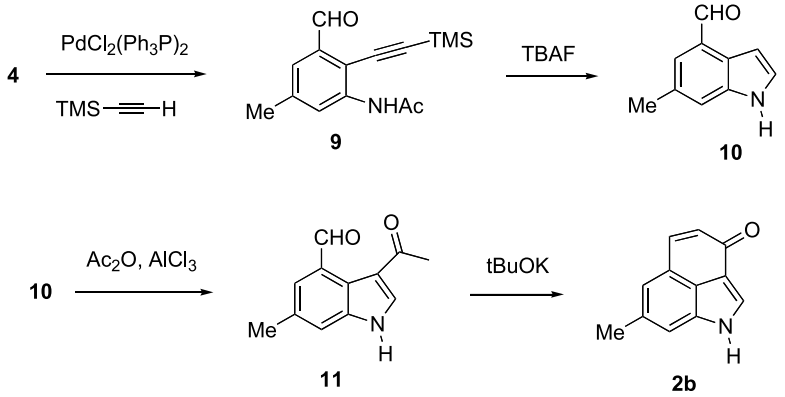


Scheme 1.



Scheme 2.

milligram amounts. The problems with reproducibility may be related to substitution at C-2, since indole keto aldehydes without a substituent at C-2 readily and reproducibly cyclize as shown in Scheme 2.

The modest yields in the acylation step and the problematic aldol step prompted us to evaluate the approach depicted in Scheme 2. The objective now became **2b**, an advanced intermediate in the Nakatsuka synthesis of 0231B. The synthesis of indole **2b** began with triflate **4**. This compound underwent a Sonogashira coupling with trimethylsilylacetylene (**8**) to provide acetylene **9** in 80% yield. Fluoride-mediated cyclization, desilylation and deacetylation occurred in a one-pot reaction and led to the conversion of **9** into indole **10** in 34% yield. In contrast to the reaction with indole **6**, acetylation of indole **10** at C-3 proceeded smoothly using acetic anhydride and aluminum chloride at sub ambient temperature. The resulting keto aldehyde **11** was produced in 72% yield. Aldol condensation using potassium *tert*-butoxide in THF afforded enone **2b** in 98% yield. In this case the aldol step was reproducible. The proton NMR and ^{13}C NMR of **2b** were identical to the literature spectra. Unfortunately, no melting point data was reported in the literature.

An advanced intermediate for the synthesis of **1** was synthesized in only six steps from **3**. This strategy should also be applicable to 3,4-annulated indoles such as the isonitrile-containing hapalindole alkaloids,[9] agroclavine[10] and abeo-ergoline.[11]

2. Experimental

2.1. General

2.1.1. 2-Acetylamino-6-formyl-4-methylphenyl trifluoromethanesulfonate (4). To a solution of phenol **3** (906 mg, 5.0 mmol) in 50 ml of ethyl acetate was added 10% Pd on charcoal (106 mg, 0.10 mmol) and acetic anhydride (2.4 ml, 25 mmol). The reaction mixture was stirred under a H_2 atmosphere at room temperature overnight. The solid was filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (715 mg, 74% yield), mp 124–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.17 (s, 1H), 9.34 (s, 1H), 8.35 (s, 1H), 7.81 (br, 1H), 6.99 (s, 1H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 168.7, 148.1, 129.6, 127.7, 127.2, 127.0, 119.5, 24.7, 20.8; MS (*m/z*): 193, 165, 152, 151, 150, 123, 105; HRMS: calcd for $C_{10}H_{11}NO_3$:

193.0739, found: 193.0741. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17%; H, 5.74%; N, 7.25. Found: C, 62.30%; H, 5.77%; N, 7.39%.

The product from reduction and acetylation (966 mg, 5.0 mmol), K_2CO_3 (898 mg, 6.5 mmol) and *N*-phenyltriflimide (1.96 g, 5.5 mmol) in 25 ml of THF were stirred at room temperature overnight. The solid was filtered and solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (1.54 g, 95% yield), mp 118–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.09 (s, 1H), 7.80 (br, 1H), 7.51 (s, 1H), 2.39 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.9, 169.1, 140.1, 138.1, 131.7, 131.2, 139.0, 127.7, 118.7 (q, J = 319 Hz), 24.0, 21.2; MS (*m*/*z*): 325, 193, 192, 176, 150, 122; HRMS: calcd for $C_{11}H_{10}F_3NO_5S$: 325.0232, found: 325.0237.

2.1.2. *N*-[3-Formyl-5-methyl-2-(phenylethynyl)phenyl acetamide (5). To a degassed solution of triflate **4** (650 mg, 2.0 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (12 mg, 0.06 mmol) and diisopropylethylamine (1.05 ml, 6.0 mmol) in 20 ml THF was added phenylacetylene (0.27 ml, 0.24 mmol) dropwise. The reaction mixture was stirred at 55 °C for 6 h. The solid was filtered and the filtrate was washed consecutively with saturated NH_4Cl and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:2) to give a yellow solid (477 mg, 86% yield), mp 145–146 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.52 (s, 1H), 8.54 (s, 1H), 8.07 (br, 1H), 7.56–7.59 (m, 2H), 7.50 (s, 1H), 7.42–7.44 (m, 3H), 2.44 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2, 168.5, 140.2, 139.6, 135.6, 131.5, 129.5, 128.8, 125.4, 123.3, 121.7, 112.5, 102.5, 80.6, 24.9, 21.8; MS (*m*/*z*): 277, 276, 249, 248, 247, 207, 206; HRMS: calcd for $C_{18}H_{15}NO_2$: 277.1103, found: 277.1107.

2.1.3. 2-Phenyl-6-methylindole-4-carboxaldehyde (6). A mixture of aldehyde **5** (139 mg, 0.50 mmol), 1 M TBAF (1.5 ml, 1.5 mmol) in 10 ml of THF was stirred at reflux for 1 h. Solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The ethyl acetate extract was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:2) to give a yellow solid (78 mg, 67% yield), mp 187–189 °C.

^{1}H NMR (300 MHz, DMSO-*d*): δ 10.15 (s, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.53 (s, 1H), 7.45–7.50 (m, 4H), 7.32–7.37 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*): δ 193.9, 141.3, 139.1, 132.4, 131.2, 129.7, 129.2, 128.7, 127.9, 126.0, 125.1, 118.4, 99.1, 21.7; MS (*m*/*z*): 235, 234, 207, 206, 204, 178, 103, 102; HRMS: calcd for $C_{16}H_{13}NO$: 235.0997, found: 235.1001. Anal. Calcd for $C_{16}H_{13}NO$: C, 71.68%; H, 5.57%; N, 5.95. Found: C, 81.39%; H, 5.68%; N, 5.99%.

2.1.4. 3-Acetyl-2-phenyl-6-methylindole-4-carboxaldehyde (7). To a suspension of $AlCl_3$ (415 mg, 1.5 mmol) in 12 ml dry CH_2Cl_2 was added acetyl anhydride (0.14 ml, 3.0 mmol) dropwise with ice water bath cooling. The reaction mixture was stirred at room temperature for 15 min before cooling to −20 °C. A solution of indole **7** (118 mg, 0.5 mmol) in 3 ml dry CH_2Cl_2 was added dropwise. The mixture was stirred at the same temperature for 1 h and quenched by slow addition of crushed ice. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, $NaHCO_3$, and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow oil (64 mg, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 9.12 (br, 1H), 7.57 (s, 1H), 7.49–7.51 (m, 2H), 7.40–7.43 (m, 3H), 7.36 (s, 1H), 2.27 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 193.4, 142.1, 137.0, 133.3, 132.0, 132.0, 129.8, 129.2, 129.1, 127.5, 122.1, 117.7, 117.2, 32.5, 21.5; MS (*m*/*z*): 277, 276, 249, 248, 235, 234, 205, 204, 191, 189, 179; HRMS: calcd for $C_{18}H_{15}NO_2$: 277.1103, found: 277.1107.

2.1.5. 7-Methyl-2-phenyl-1-benz[*c*,*d*]indol-3-(1*H*)-one (2a). A mixture of indole **7** (7 mg, 0.025 mmol), *t*-BuOK (14 mg, 0.125 mmol) in 5 ml of THF was stirred for 1 h. The solvent was removed and the residue was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (6 mg, 92%). The yield of this reaction when scaled up was highly variable.

Compound **2a** ^{1}H NMR (300 MHz, $CDCl_3$): 8.36 (s, 1H), 8.33 (s, 1H), 7.57–7.60 (d, J = 9.5 Hz 1H), 7.43–7.49 (m, 3H), 7.29–7.30 (m, 2H), 6.65–6.69 (d, J = 9.5 Hz, 1H), 2.51 (s, 3H); HRMS (ES) *m*/*z* calcd for $C_{18}H_{13}NO$: 259.0997, found: 259.0999.

2.1.6. *N*-[3-Formyl-5-methyl-2-(trimethylsilylethynyl) phenyl acetamide (9). To a degassed solution of triflate **4** (273 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (6 mg, 0.03 mmol) and diisopropylethylamine (0.63 ml, 3.0 mmol) in 20 ml of THF was added trimethylsilylacetylene **8** (0.31 ml, 2.2 mmol) dropwise. The reaction mixture was stirred at 55 °C for 5 h. The solid was filtered and the filtrate was washed consecutively with saturated NH_4Cl and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (191 mg, 80% yield), mp 119–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (s, 1H), 8.48 (s, 1H), 8.05 (br, 1H), 7.42 (s, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 0.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 168.4, 140.7, 140.3, 135.9, 124.9, 122.7, 112.4, 109.5, 96.2, 25.0, 22.0, 0.0; MS (*m*/*z*): 273, 272, 259, 258, 230, 217, 216, 202, 200, 172, 171; HRMS: calcd for $C_{15}H_{19}NO_2Si$: 273.1185, found: 273.1188.

2.1.7. 6-Methylindole-4-carboxaldehyde (10). A mixture of aldehyde **9** (190 mg, 0.80 mmol), 1 M TBAF (2.4 ml, 2.4 mmol) in 10 ml THF was stirred at reflux for 1 h. The solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The

ethyl acetate extract was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:2) to give a yellow solid (43 mg, 34% yield), mp 116–118 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.22 (s, 1H), 8.55 (br, 1H), 7.47 (s, 2H), 7.34–7.36 (m, 1H), 7.27–7.29 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.5, 137.2, 131.5, 129.2, 128.2, 127.2, 124.0, 117.8, 102.8, 21.5; MS (*m*/*z*): 160, 159, 158, 131, 130, 128, 103, 77; HRMS: calcd for $C_{10}H_9NO$: 159.0684, found: 159.0686.

2.1.8. 3-Acetyl-6-methylindole-4-carboxaldehyde (11). To a suspension of $AlCl_3$ (415 mg, 1.5 mmol) in 12 ml of dry CH_2Cl_2 was added acetyl anhydride (0.14 ml, 3.0 mmol) dropwise with ice water bath cooling. The reaction mixture was stirred at room temperature for 15 min before cooling to −20 °C. A solution of indole **10** (118 mg, 0.5 mmol) in 3 ml dry CH_2Cl_2 was added dropwise. The mixture was stirred at the same temperature for 1 h and quenched by slow addition of crushed ice. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, $NaHCO_3$, and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 3:1) to give a yellow solid (64 mg, 72% yield), mp 200–201 °C.

^{1}H NMR (300 MHz, acetone-*d*): δ 11.33 (s, 1H), 8.48 (br, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 2.48 (s, 3H), 2.54 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, acetone-*d*): δ 195.5, 192.1, 139.5, 137.1, 133.1, 130.4, 122.8, 122.1, 118.8, 117.5, 27.3, 20.5; MS (*m*/*z*): 201, 200, 173, 172, 158, 157, 155, 129; HRMS: calcd for $C_{12}H_{11}NO_2$: 201.0790, found: 201.0793.

2.1.9. 7-Methyl-1-benz[*c*,*d*]indol-3-(1*H*)-one (2b). A mixture of indole **11** (15 mg, 0.075 mmol), potassium *tert*-butoxide (25 mg, 0.225 mmol) in 5 ml of THF was stirred for 30 min. The solvent was removed and the residue was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (100% ethyl acetate) to give a yellow solid (13 mg, 98% yield), mp 178–180 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.45 (br, 1H), 8.12 (s, 1H), 7.71 (d, J = 9.5 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 6.73 (d, J = 9.4 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9, 138.9, 134.8, 133.8, 132.4, 131.8, 124.9, 124.1, 123.6, 116.1, 116.1, 22.2; MS (*m*/*z*): 183, 182, 154, 153, 126; HRMS: calcd for $C_{112}H_9NO$: 183.0684, found: 183.0687.

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Synthesis and conformational studies of amide-linked cyclic homooligomers of a thymidine-based nucleoside amino acid☆

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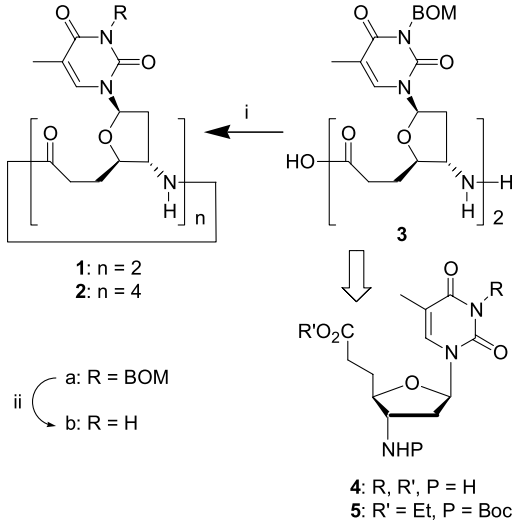
Abstract—Cyclic homooligomers of a thymidine-based nucleoside amino acid were synthesized from the linear dimer using BOP reagent in the presence of DIPEA under dilute conditions. Conformational analysis by NMR and constrained MD studies revealed that all the cyclic products had symmetrical structures. The NH and CO groups in these molecules point in opposite directions with near perpendicular orientation with respect to the plane of the macrocyclic ring having CO on the same side as the base.

1. Introduction

Cyclisation of linear biopolymers is widely used to constrain their conformational degrees of freedom and induce desirable structural biases permitting enhanced receptor selectivity and binding affinity with additional properties like decreased susceptibility to degradation in biological systems.[1] Cyclic DNAs and RNAs, for example, have been studied extensively for their unusual chemical and biological activities.[2] However, synthesis of such cyclic DNAs remains a challenging task,[3] thereby limiting exploratory studies, especially in discovering potential leads for drug discovery. It was envisaged that the replacement of the phosphodiester linkages with amide bonds would not only facilitate the assembly of such substrates using standard solid- or solution-phase peptide synthesis methods, but would also help to enhance their stability towards nucleases. Amide-linked oligonucleotides have been studied extensively for potential therapeutic applications involving antisense strategy.[4] However, their cyclic versions have remained largely unexplored. Herein, we report the synthesis and conformational studies of amide-linked cyclic homooligonucleotides **1** and **2**, which were prepared, as shown in Scheme 1, by cyclisation of the linear dimer **3** of the monomeric building block **4**,[4h] a thymidine-based nucleoside amino acid (Taa).



Scheme 1. Reagents and conditions: (i) BOP reagent, DIPEA, DMF, 0 °C to rt, 10 h; (ii) H_2, Pd-C (10%), THF–MeOH (1:1), rt, 0.5 h.

1.1. Synthesis of the cyclic homooligomers

The starting material for our synthesis was the fully protected monomer Taa **5a**.[5,6] While the *tert*-butoxycarbonyl (Boc) group was deprotected using TFA–CH_2Cl_2 (1:3), saponification of the ethyl ester was carried out with LiOH in dioxane–water (1:1). Reaction of Boc-Taa(BOM)-OH with H_2N-Taa(BOM)-OEt using the conventional solution phase method using *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) and 1-hydroxybenzotriazole (HOBt) as coupling agents in

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Keywords: Nucleoside amino acids; Cyclic DNAs; Cyclic RNAs; Cyclic peptides; Conformation; NMR.
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presence of *N*-methylmorpholine (NMM) in CH_3CN gave the protected dimer, Boc-[Taa(BOM)]$_2$-OMe in 75% yield. Saponification of the protected dimer was followed by Boc-deprotection under the conditions mentioned above to furnish the intermediate **3**, which was directly subjected to cyclisation using benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in amine-free DMF as solvent to furnish a mixture of products, **1a** and **2a**, in 16 and 28% yields, respectively. They were separated by standard silica gel column chromatography and hydrogenated using 10% Pd-C in THF–MeOH (1:1) to furnish the BOM-deprotected products **1b** and **2b** in quantitative yields. The purified products were fully characterized by spectroscopic methods before using them in the conformational studies.

All the products were characterized by positive ion electrospray ionization (ESI) mass spectra.[7] The spectra showed the expected $[M+Na]^+$ ion to confirm the molecular weight of the product, and sometimes $[2M+Na]^+$ ion was also found. Interestingly, the spectra of some of the products showed $[M+2Na]^{2+}$. Although, the *m*/*z* value of $[M+2Na]^{2+}$ ion matches with that of $[M+Na]^+$ ion of lower homologue, these ions were identified by isotopic distribution patterns and also by the mass differences between the ^{12}C and ^{13}C isotopic peaks, that is, a difference of 1 Da in the case of $[M+Na]^+$ ion and 0.5 Da in the case of $[M+2Na]^{2+}$ ion. Further the $[2M+Na]^+$ and $[M+2Na]^{2+}$ ions were confirmed by MS/MS, which resulted in the corresponding $[M+Na]^+$ ion in addition to the other characteristic fragment ions.[8]

1.2. Conformational analysis. NMR studies

The conformational analysis of **1a** and **2a** were carried out by NMR spectroscopy at 500 MHz. The studies were undertaken in 5–10 mM solution at 30 °C in $CDCl_3$ and DMSO-d_6 for **1a**, whereas structures of **2a**, due to its inadequate solubility in $CDCl_3$, were investigated in DMSO-d_6. The presence of only one set of peaks in **1a** and **2a** is consistent with a two and four fold symmetry, respectively, in the NMR time frame.

While extensive decoupling experiments and simulations of the spectra were used to obtain the couplings, the

Table 1. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (*J*, Hz) of **1a** ($CDCl_3$, 500 MHz, 30 °C)

Ring protons		Base protons[a]	
H1′	6.15 (t, *J*=6.9 Hz)	C5-Me	2.01 (s)
H2′	2.27 (ddd, *J*=6.2, 10.2, 14.3 Hz)	H6	7.14 (s)
H2″	1.71 (ddd, *J*=6.6, 7.6, 14.3 Hz)	H7	5.68 (d, *J*=10.2 Hz)
H3′	4.32 (dddd, *J*=6.6, 8.2, 8.3, 10.2 Hz)	H7′	5.47 (d, *J*=10.2 Hz)
H4′	3.55 (ddd, *J*=3.2, 8.2, 11.0 Hz)	H9	4.72 (d, *J*=11.6 Hz)
H5′	2.37 (dddd, *J*=1.8, 11.0, 12.2, 13.5 Hz)	H9′	4.70 (d, *J*=11.6 Hz)
H5″	2.07 (dddd, *J*=2.0, 3.2, 7.1, 13.5 Hz)	NH	6.55 (d, *J*=8.3 Hz)
H6′	2.33 (ddd, *J*=1.8, 7.1, 14.3 Hz)	Ph	7.29–7.40 (m)
H6″	2.03 (ddd, *J*=2.0, 12.2, 14.3 Hz)		

[a] H7,7′; H9,9′ and Ph protons are from BOM groups.

Table 2. ^{1}H NMR Chemical shifts (δ, ppm) and coupling constants (*J*, Hz) of **1a** (DMSO-d_6, 500 MHz, 30 °C)

Ring protons		Base protons[a]	
H1′	6.04 (t, *J*=6.4 Hz)	C5-Me	1.86 (s)
H2′	2.30 (ddd, *J*=5.7, 9.5, 13.7 Hz)	H6	7.52 (s)
H2″	1.99 (m)	H7	5.34 (d, *J*=9.8 Hz)
H3′	4.10 (m)	H7′	5.32 (d, *J*=9.8 Hz)
H4′	3.71 (ddd, *J*=3.5, 7.9, 10.0 Hz)	H9	4.58 (br s)
H5′	2.12 (m)	H9′	4.58 (br s)
H5″	1.95 (m)	NH	7.80 (d, *J*=7.8 Hz)
H6′	2.24 (m)	Ph	7.25–7.35 (m)
H6″	2.12 (m)		

[a] H7,7′; H9,9′ and Ph protons are from BOM groups.

Table 3. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (*J*, Hz) of **2a** (DMSO-d_6, 500 MHz, 30 °C)

Ring protons		Base protons[a]	
H1′	6.15 (t, *J*=6.7 Hz)	C5-Me	1.86 (s)
H2′	2.30 (ddd, *J*=14.2, 9.1, 5.7 Hz)	H6	7.57 (s)
H2″	2.15 (m)	H7	5.33 (d, *J*=9.8 Hz)
H3′	4.25 (m)	H7′	5.31 (d, *J*=9.8 Hz)
H4′	3.60 (ddd, *J*=8.6, 7.0, 4.2 Hz)	H9	4.58 (S)
H5″	1.95 (m)	H9′	4.58 (S)
H5′	1.86 (m)	NH	8.12 (d, *J*=8.0 Hz)
H6′	2.26 (ddd, *J*=5.8, 9.1, 14.9 Hz)	Ph	7.24–7.34 (m)
H6″	2.16 (m)		

[a] H7,7′; H9,9′ and Ph protons are from BOM groups.

assignments were carried out with the help of DQFCOSY experiments,[9] and ROESY experiments[10] provided the information on the proximity of protons. The spectral parameters are given in Tables 1–3. Some of the important long-range NOEs seen in the ROESY spectra of **1a** and **2a** are shown in Figures 1 and 3, respectively.

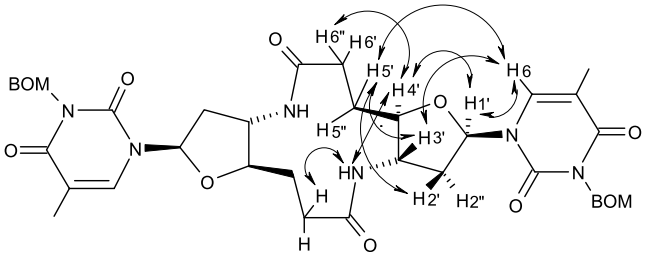

Figure 1. Schematic representation of some of the diagnostic long-range NOEs seen in the ROESY spectrum of **1a** in $CDCl_3$.

The conformational analysis of **1b** and **2b** could not be carried out due to line-broadening and overlapping signals both in $CDCl_3$ and DMSO-d_6, making it very difficult to derive the spectral parameters.

1.3. Conformational analysis of 1a

The spectral data of **1a** suggested that its 12-membered macrocyclic ring was very rigid. The vicinal couplings, $^3J_{H4'-H5'}=11.0$ Hz, $^3J_{H5'-H6''}=12.2$ Hz, $^3J_{H5''-H6''}=2.0$ Hz, $^3J_{H5'-H6'}=1.8$ Hz, $^3J_{H4'-H5''}=3.2$ Hz are consistent with values of about 60°and $-60°$ for C_4–C_5–C_6–CO and C_3–C_4–C_5–C_6, respectively. This is further supported by the NOE correlations H4′↔H6″ and H3′↔H5′ shown in Figure 1. The resulting structure had the NH and CO pointing approximately perpendicular to the plane of the macrocyclic ring with CO on the same side as the base. The information on the sugar pucker was derived with the help of PSUEROT programme,[11] which indicates that the sugar ring takes a single $^{O}_{4}T$ conformation[12] with $P=69.2$ and $\nu_{max}=39.6°$. In nucleosides $^{O}_{4}T$ pucker is in between the C2′ endo and C3′ endo sugar puckerings, which are the lowest energy conformations. The structure is consistent with the NOEs between H2′↔H5′, H1′↔H4′ and H3′↔H5′ (Fig. 1). The information on the orientation of the base was obtained from the distinct NOEs between the base proton, H6 and sugar protons. The presence of NOEs between H2′↔H6, H3′↔H6, and H5′↔H6 very clearly supported the presence of *anti* conformation of the base. Yet the NOE correlation H1′↔H6 implies a significant population of molecule with *syn* conformation. Such a situation is often encountered in nucleosides and nucleotides where both *syn* and *anti* conformations[12] are observed in solution.

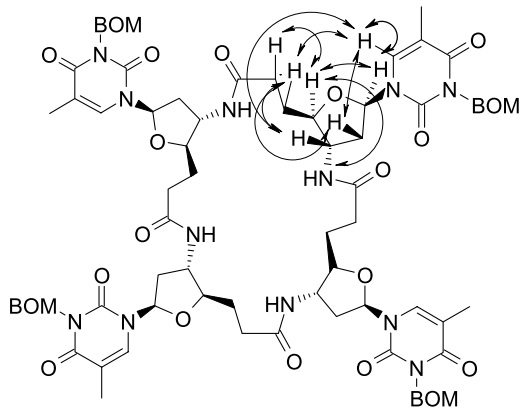

Figure 3. Schematic representation of some of the diagnostic long-range NOEs seen in the ROESY spectrum of **2a** in DMSO-d_6.

The cross-peak intensities in the ROESY spectra were used for obtaining the restraints in the molecular dynamics (MD) calculations[13] on **1a**. Molecular dynamics calculations were carried out using Sybyl 6.8 program on a Silicon Graphics O2 workstation. The Tripos force field, with default parameters, was used throughout the simulations. The detailed protocol of the MD calculations is provided in the Section 4. Figure 2 depicts the ensemble of the backbone-superimposed structures of the 20 samples, collected during 600 ps simulated annealing protocol, which clearly shows the proposed structure of the molecule. The average pair wise backbone RMSD for the structures is $0.24+0.15$ Å.[14]

1.4. Conformational analysis of 2a

For **2a**, though the chemical shift values were obtained from the DQFCOSY spectra, it was not possible to derive all the couplings due to spectral complexity and overlap. However, ROESY data showed NOEs (Fig. 3), which were similar to those for **1a**, suggesting a very similar structure for the tetramer.

Few of the couplings, which could be obtained, as well as weaker NOEs, point towards averaging of the spectral parameters, which may arise due to several other conformations contributing to the structure, due to the larger macrocyclic ring. The predominant structure, however, resembles that of **1a**. The NOEs between the base proton, H6 and the protons in the sugar ring, are consistent with the presence of both *syn* and *anti* conformation, with the latter being dominant.

Cyclic homooligomers of nucleoside amino acids constitute a new class of novel molecular entities that display interesting 3-D structures, reminiscent of the structures of peptide nanotubes. The NH and CO groups in these molecules point in opposite directions with near

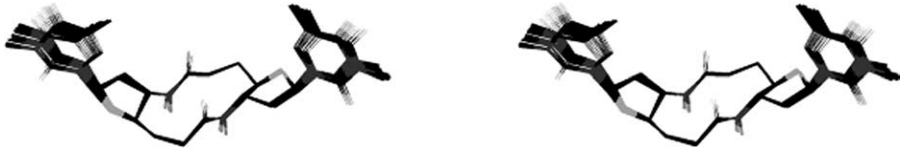

Figure 2. Stereo view of the 20 superimposed energy-minimized structures of **1a** sampled during 100 cycles of the 600 ps constrained MD simulations following the simulated annealing protocol. For clarity the protons (except amide protons) and the BOM groups are not shown.

perpendicular orientation with respect to the plane of the macrocyclic ring having CO on the same side as the base. This study will be useful in creating various de novo amide-linked cyclic homo- as well as heterooligomers using other nucleoside amino acids as well. The well-defined structures of these macrocyclic peptides will be useful to carry out investigations into many interesting molecular recognition processes, especially those involving base-pairing and may find many applications similar to those exhibited by cyclic DNAs and RNAs.

2. Experimental

2.1. General procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Melting points are uncorrected. IR spectra were recorded as KBr pellets on FT-IR. Mass spectra were obtained under liquid secondary ion mass spectrometric (LSIMS) and electrospray ionisation (ESI) techniques. Optical rotations were measured with a digital polarimeter.

2.2. Details of NMR studies

NMR spectra were recorded using a 500 MHz spectrometer at 30 °C with 5–10 mM solutions in appropriate solvents using TMS as internal standard and the solvent signals as secondary standards and the chemical shifts (δ) are shown in ppm. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded at 75 and 125 MHz with complete proton decoupling. The proton chemical shift assignments were carried out with the help of two-dimensional double quantum filtered correlation spectroscopy (DQFCOSY)[9] and nuclear Overhauser effect spectroscopy (NOESY)/rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments,[10] the later also provided the information on the proximity of protons. All the experiments were carried out in the phase sensitive mode.[15] The spectra were acquired with 2×256 or 2×192 free induction decays (FID) containing 8–16 transients with relaxation delays of 1.0–1.5 s. The ROESY experiments were performed with mixing time of 0.3 s and a spin-locking field of about 2.5 kHz was used. The two-dimensional data were processed with Gaussian apodization in both the dimensions.

2.3. Details of molecular dynamics studies

Molecular mechanics/dynamics calculations were carried out using Sybyl 6.8 program on a Silicon Graphics O2 workstation. The Tripos force field, with default parameters, was used throughout the simulations.

A dielectric constant of 47 Debye for DMSO solvent was used in all minimizations as well as in MD runs. Minimizations were done first with steepest decent, followed by conjugate gradient methods for a maximum of 2000 iterations each or RMS deviation of 0.005 kcal/mol, whichever was earlier. The energy-minimized structures were then subjected to MD studies. A number of inter atomic distance constraints (more than three bond away) were used in the MD studies that were derived from the rOe cross-peaks from the ROESY spectrum. Distance constraints have been obtained from 0.3 s mixing time ROESY experiments by using the volume integral and two-spin approximation. Force constant of 15 kcal/Å were applied in the form of flat bottom potential well with the lower and upper bounds obtained by subtracting and adding 10% to the distances obtained above. These constraints are given in Table 4.[13]

Table 4. NOE constraints used in MD simulation study of compound **1a**

S.no.	From	To	Upper bound	Lower bound
1	H2′	H6	2.713	2.220
2	H3′	H6	2.868	2.347
3	H5′	H6	3.425	2.802
4	H3′	H5′	2.860	2.340
5	H1′	H4′	2.496	2.042
6	NH	H4′	3.439	2.810

No H-bonding constraint was used. The energy-minimized structures were subjected to constrained MD simulations for duration of 600 ps using 100 cycles, each of 6 ps period, of the simulated annealing protocol. The atomic velocities were applied following Boltzmann distribution about the center of mass, to obtain a starting temperature of 700 K.[16]

After simulating for 1 ps at high temperature, the system temperature was reduced exponentially over a 5 ps period to reach a final temperature of 300 K. Structures were sampled after every five cycles, leading to an ensemble of total 20 structures. The sampled structures were energy-minimized without constraints, by using the above-mentioned protocol and the superimposed structures obtained by backbone alignment are shown in the paper, in Figure 2. To determine the backbone and the average pair-wise heavy atom RMSD, the structures were analyzed using the MOLMOL program.[14]

2.3.1. Synthesis of 5a. To a solution of Boc-Taa-OEt (**5b**, 1.21 g, 2.94 mmol) in CH_3CN (10 mL) at room temperature was added DBU (1.32 mL, 8.83 mmol) with stirring. After 5 min at the same temperature, BOM-Cl (0.61 mL, 4.41 mmol) was added to it and stirring continued for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 28–30% EtOAc in petroleum ether eluant) gave the desired compound **5a** (1.32 g, 85%) as a white semisolid. Data for **5a**: $R_f=0.4$ (silica gel, 30% EtOAc in

petroleum ether); $[\alpha]_D^{26}$ +42.1 (c=5.5 in $CHCl_3$); IR (neat) ν_{max} 3373, 2927, 1710, 1660, 1523 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5H, aromatic), 7.13 (s, 1H, H6), 6.16 (t, J=6.0 Hz, 1H, H1′), 5.48 (s, 2H, N–CH_2), 4.70 (m, 3H, BocNH and Ph–CH_2), 4.14 (q, J=7.15 Hz, 2H, ester CH_2), 3.98 (m, 1H), 3.72 (m, 1H), 2.50 (m, 2H), 2.25 (m, 2H), 2.15 (m, 2H), 1.95 (s, 3H, C5–CH_3) 1.45 (s, 9H, Boc), 1.26 (t, J=7.15 Hz, 3H, ester-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 163.1, 155.2, 150.7, 137.8, 133.6, 128.1, 127.4, 110.4, 84.3, 83.2, 79.9, 77.2, 72.1, 70.4, 60.4, 53.7, 38.1, 30.5, 28.5, 28.2, 14.0, 13.1; MS (LSIMS) m/z (%) 532 (16) $[M+H]^+$; HRMS (LSIMS) calcd for $C_{27}H_{37}N_3O_8Na$ 554.2478, found 554.2498.

2.3.2. Synthesis of 3. To a solution of **5a** (334 mg, 0.629 mmol) in dioxane–water (6 mL, 1:1) at 0 °C was added LiOH–H_2O (79.2 mg, 1.88 mmol) with stirring and the temperature was allowed to rise from 0 °C to room temperature over 3 h. Then the reaction mixture was neutralized by DOWEX 50×80–100 ion exchange acidic resin and filtered. The filtrate was concentrated in vacuo. The mixture was then diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to obtain the acid Boc-[Taa(BOM)]-OH.

In another round bottom flask, a solution of **5a** (341 mg, 0.692 mmol) in CH_2Cl_2 (4 mL) was taken. To this solution was added trifluoroacetic acid (1 mL) with stirring at 0 °C. Stirring was continued for 2 h as the temperature was allowed to rise slowly from 0 °C to room temperature. The reaction mixture was then concentrated in vacuo to give TFA [Taa(BOM)]-OEt.

The crude acid Boc-[Taa(BOM)]-OH was dissolved in CH_3CN (4 mL) and NMM (0.07 mL, 0.619 mmol) was added. Then it was sequentially treated with HOBT·H_2O (42.5 mg, 0.314 mmol) and TBTU (222 mg, 0.619 mmol) at room temperature. After 30 min, compound TFA [Taa(BOM)]-OEt dissolved in CH_3CN (4 mL) containing NMM (0.1 mL, 0.963 mmol) was added to the reaction mixture at room temperature. After being stirred for 12 h at room temperature, the reaction mixture was quenched with saturated aqueous NaH_2PO_4 solution and the solvent was evaporated under reduced pressure. The water phase was extracted with CH_2Cl_2, washed with water, brine, dried (Na_2SO_4), concentrated in vacuo. Purification by column chromatography (SiO_2, 1.8% MeOH in $CHCl_3$ as eluant) afforded the protected linear dimer Boc-[Taa(BOM)]$_2$-OEt (432 mg, 75%). Data for Boc-[Taa(BOM)]$_2$-OEt: R_f=0.45 (silica gel, 3% MeOH in $CHCl_3$); $[\alpha]_D^{26}$ +36.2 (c=1.9 in $CHCl_3$); IR (KBr) ν_{max} 3348, 2975, 1711, 1665, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.3–7.17 (m, 10H, aromatic), 7.08 (s, 2H, H6), 6.93 (d, J=7.15 Hz, 1H, N–H), 6.08 (m, 2H, H1′), 5.51 (d, J=7.15 Hz, 1H, BocNH), 5.41 (s, 4H, N–CH_2), 4.64 (s, 4H, Ph–CH_2), 4.19 (m, 1H), 4.1 (m, 2H), 3.95 (m, 1H), 3.72 (m, 2H), 2.5–2.4 (m, 2H), 2.38–2.08 (m, 10H), 1.97 (s, 3H, one of the C5-methyls), 1.95 (s, 3H, other C5–CH_3) 1.42 (s, 9H, Boc), 1.26 (t, J=7.15 Hz, 3H, ester-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.3, 163.1, 155.4, 150.7, 137.8, 133.8, 133.6, 128.1, 127.5, 110.5, 84.7, 84.4, 83, 80.1, 77.1, 72.1, 70.5, 60.5, 53.8, 52.4, 37.7, 32.4, 30.3, 29.1, 28.5, 28.2, 14.0, 13.1; MS (LSIMS) m/z (%) 918 (20) $[M+H]^+$; HRMS (LSIMS) calcd for $C_{47}H_{60}N_6O_{13}Na$ 939.4116, found 939.4089.

To a solution of Boc-[Taa(BOM)]$_2$-OEt (295 mg, 0.321 mmol) in dioxane–water (4 mL, 1:1) at 0 °C was added LiOH–H_2O (40.5 mg, 0.965 mmol) with stirring. Stirring was continued for 3 h as the temperature was allowed to rise slowly from 0 °C to room temperature. Then the reaction mixture was neutralized by DOWEX 50×80–100 ion exchange acidic resin and filtered. The filtrate was concentrated in vacuo. The mixture was then diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to obtain the acid Boc-[Taa(BOM)]$_2$-OH. The acid was dissolved in CH_2Cl_2 (3 mL) To this solution was added trifluoroacetic acid (0.75 mL) with stirring at 0 °C. Stirring was continued for 3 h as the temperature was allowed to rise slowly from 0 °C to room temperature. The reaction mixture was then concentrated in vacuum to give the TFA salt of the crude acid, **3**, which was used directly in the next step.

2.3.3. Synthesis of 1a and 2a. To the TFA salt of the crude acid **3** in amine free dry DMF (32.1 mL, 10^{-2} M) was added BOP reagent (156.5 mg, 0.353 mmol) at 0 °C and the reaction mixture was stirred for 15 min. This was followed by the slow addition of DIPEA (0.27 mL, 1.6 mmol) to the reaction mixture and stirring was continued for 10 h at room temperature. Evaporation of the DMF under reduced pressure gave a residue that was dissolved in CH_2Cl_2, washed with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated in vacuum. The crude was purified by column chromatography (SiO_2, 3.8–4.0% MeOH in $CHCl_3$ as eluant) to afford the cyclic dimer **1a** (39 mg, 16%) and the cyclic tetramer **2a** (139 mg, 28%) as solids. Data for **1a**: R_f=0.24 (silica gel, 7% MeOH in $CHCl_3$); $[\alpha]_D^{26}$ +17.5 (c=0.95 in $CHCl_3$); IR (KBr) ν_{max} 3291, 2924, 2854, 1713, 1650, 1547 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) see Table 1; ^1H NMR (DMSO-d_6, 500 MHz) see Table 2; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 163.1, 151.3, 137.1, 133.7, 128.6, 128.2, 111.7, 83.0, 82.4, 73.0, 71.0, 51.6, 39.0, 31.3, 29.6, 27.9, 13.2; MS (ESI) m/z (%) 793 (100) $[M+Na]^+$, 810 (20) $[M+K]^+$; HRMS (ESI) calcd for $C_{40}H_{46}N_6O_{10}Na$ 793.3173, found 793.3211. Data for **2a**: R_f=0.32 (silica gel, 7% MeOH in $CHCl_3$), $[\alpha]_D^{26}$ +30.6 (c=0.76 in $CHCl_3$), IR (KBr) ν_{max} 3296, 2924, 2854, 1713, 1650, 1547 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) see Table 3; ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 162.1, 150, 137.5, 135.1, 127.6, 126.8, 126.7, 108.6, 83.4, 81.9, 70.4, 69.7, 51.3, 35.6, 31.5, 28.4, 12.0; MS (ESI) m/z (%) 1563 (100) $[M+Na]^+$; HRMS (ESI) calcd for $C_{80}H_{92}N_{12}O_{20}Na$ 1562.6370, found 1562.6345.

2.3.4. Synthesis of 1b. To a solution of **1a** (30 mg, 0.038 mmol) in THF–MeOH (2 mL, 1:1) was added 10% Pd on C (10 mg). The mixture was hydrogenated under atmospheric pressure using of a H_2-filled balloon for 30 min. The reaction mixture was filtered through a short pad of Celite, and the filter cake was washed with MeOH. The filtrate and the washings were combined and concentrated in vacuum to get a quantitative yield of **1b** (20 mg). Data for **1b**: R_f=0.18 (silica gel, 20% MeOH in $CHCl_3$), $[\alpha]_D^{26}$ −21.9 (c=0.47 in DMSO), IR (KBr) ν_{Max}

3421, 1664, 1562 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H, NH of thymine), 8.24 (br s, 1H, CONH), 7.46 (s, 1H, H6), 6.06 (d, $J=6.6$ Hz, H1′), 3.91 (m, 1H, H3′), 3.77 (m, 1H, H4′), 2.35–1.92 (m, 6H), 1.79 (s, 3H, 5-Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.9, 163.6, 150.2, 136.0, 109.6, 82.4, 79.9, 52.2, 37.2, 30.5, 28.5, 11.9; MS (ESI) *m/z* (%) 553 (100) $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{30}N_6O_8Na$ 553.2022, found 553.2043.

2.3.5. Synthesis of 2b. Compound **2b** was synthesized from **2a** in quantitative yield following the same procedure described above for the synthesis of **1b**. Data for **2b**: $R_f=$ 0.17 (silica gel, 20% MeOH in $CHCl_3$), $[\alpha]_D^{26}$ +57.1 ($c=$ 0.24 in DMSO); IR (KBr) ν_{Max} 3434, 2927, 1700, 1551 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H, NH of thymine), 8.19 (d, $J=9.1$ Hz, 1H, CONH), 7.50 (s, 1H, H6), 6.10 (d, $J=6.9$ Hz, 1H, H1′), 4.23 (m, 1H, H3′), 3.55 (m, 1H, H4′), 2.33–1.86 (m, 6H), 1.81 (s, 3H, 5-Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.4, 163.6, 150.3, 136.1, 109.8, 82.9, 82.3, 51.8, 36.1, 32.0, 29.0, 11.9; MS (ESI) *m/z* (%) 1083 (20) $[M+Na]^+$; HRMS (ESI) calcd for $C_{48}H_{60}N_{12}O_{16}Na$ 1083.4147, found 1083.4190.

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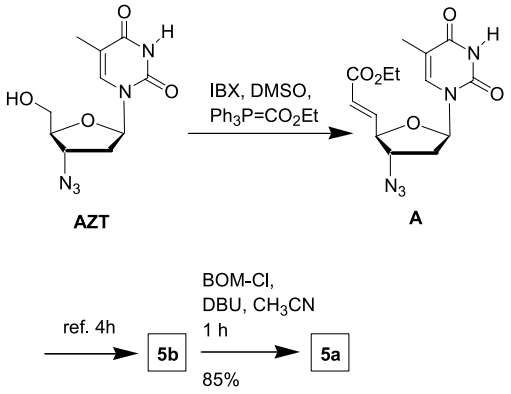
5. Compound **5a** was synthesized from **5b**, which was prepared from 3′-Azido-3′-deoxythymidine (AZT) by a slight modification of the reported procedure [Ref. 4h], in which the oxidation of AZT and olefination of the resulting aldehyde was accomplished in an one-pot process using iodoxybenzoic acid (IBX) in the presence of stabilized ylide, $Ph_3P=CHCO_2Et$ (Ref. 6). The resulting product **A** was then transformed into **5b**

following the earlier reported steps (Ref. 4h). Treatment of **5b** with BOM-Cl in the presence of DBU gave **5a** in 85% yield



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Highly efficient one-pot synthesis of 1-substituted-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles

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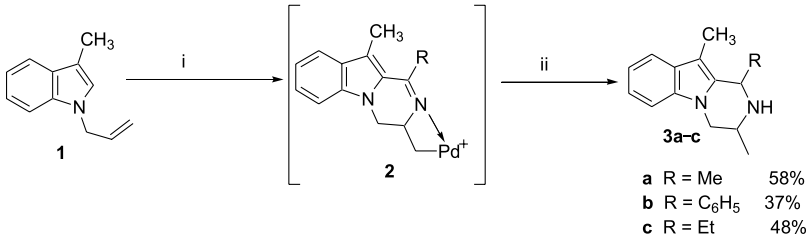
Abstract—A practical and general one-pot synthesis of 1-substituted-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles is described. The approach uses 2-(3-methyl-1*H*-indol-1-yl) ethylamine, benzotriazole and aldehydes in the presence of catalytic amount of acid catalysts ($AlCl_3$, $ZnCl_2$, $ZnBr_2$, *p*-TsOH, CH_3SO_3H) and proceeds in high yields via iminium cation intramolecular cyclization. The mechanism of the observed intramolecular cyclization reaction has been investigated theoretically by means of PM3 semiempirical method and results were consistent with the experimental results.

1. Introduction

Pyrazino[1,2-*a*]indoles are biologically active, demonstrating serotonin antagonistic,[1] thrombolytic,[2] antidepressant, anxiolitics,[3] central nervous system depressants,[4] anticonvulsants,[5] antihistaminic,[6] protein kinase C inhibitors,[7] 5-HT_{2A}, 5-HT_{2C} agonistic,[8–9] and selective imidazoline I_2 receptor ligands activities.[10] They are also found active in variety of cardiovascular diseases.[11] Therefore, versatile and widely applicable method for the synthesis of pyrazino[1,2-*a*]indoles are of considerable interest.

Many synthetic procedures exist for the synthesis of the pyrazino[1,2-*a*]indole nucleus,[6,12–14] however, there is only one report by Hegedus et al., which describes the synthesis of 1-substituted 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **3a–c** (three examples 37–58% yields) in two steps: (i) generation of palladium complex **2** by the reaction of 1-allyl-3-methyl-1-*H* indole **1** and nitriles in the presence of the strongly electrophilic complex Pd $(CH_3CN)_4(BF_4)_2$ (ii) reduction of palladium complex **2** with $NaBH_4$ to generate compounds **3a–c** (Scheme 1).[12] Reported methodologies for the synthesis of 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles suffer from several practical disadvantages such as the use of a costly catalyst, multi step synthesis, long reaction times, elevated temperatures, difficult to recover the solvent and moderate yields.

Recently, we described the synthesis of 2-substituted-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles in two steps by the cyclocondensation of 2-(3-methyl-1*H*-indol-1-1yl) ethylamine with benzotriazole and formaldehyde followed by nucleophilic substitution of the benzotriazolyl group to perform *N*-functionalization at 2-position.[15] In light of the rising interest in pyrazino[1,2-*a*]indole systems due to its medicinal importance,[1–11] we now describe a more general



Scheme 1. Reaction conditions (i) $Pd(CH_3CN)_4 \cdot (BF_4)_2$/RCN, rt; (ii) $NaBH_4$.

Keywords: Intramolecular cyclization; Benzotriazole; Lewis acid; Frontier molecular orbital.
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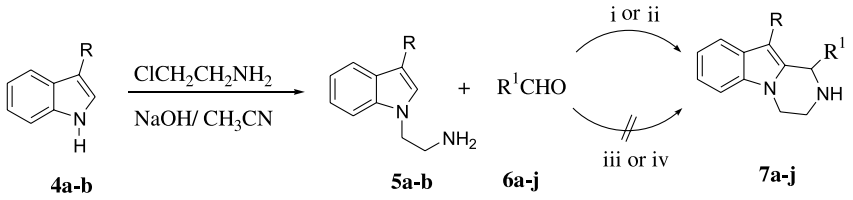


Scheme 2. BtH = Benzotriazole. Reaction conditions (i) **5b**: R = Me, BtH, Lewis acids ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) or CH_3SO_3H, CH_2Cl_2, 25 °C, 0.5–6 h; (ii) **5b**: R = Me, BtH, *p*-TsOH, benzene, reflux Dean–Stark trap, 6–8 h; (iii) **5a**: R = H, BtH, Lewis acids ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) CH_2Cl_2, 25 °C to reflux, 0.5–12 h, or *p*-TsOH, benzene, reflux, Dean–Stark trap, 6–8 h; (iv) **5a** (R = H), **5b** (R = Me) Lewis acids ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) CH_2Cl_2, 25 °C to reflux, 0.5–18 h or *p*-TsOH, benzene, reflux, Dean–Stark trap, 6–8 h.

and practical approach for the synthesis of novel 1-substituted-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **7a–i** at rt in one-pot in good to excellent yields.

2. Results and discussion

2.1. Synthesis

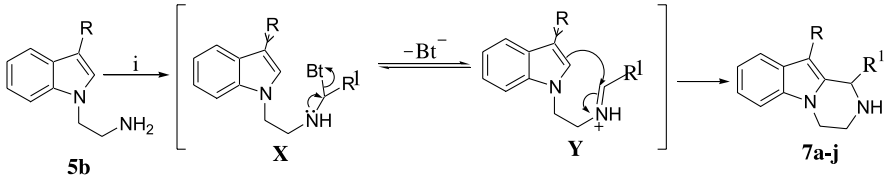
1-(2-Aminoethyl) indoles **5a–b** (**5a**, R = H; **5b**, R = Me) were obtained by the reaction of indole **4a** or 3-methyl indole **4b** with 2-chloroethylamine hydrochloride using the reported procedures.[15] 1-Substituted-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **7a–i** were obtained as racemic mixtures in high yields by the reaction of 2-(3-methyl-1*H*-indol-1-yl) ethylamine **5b** with benzotriazole and aldehydes **6a–i** in the presence of a catalytic amount of: (**A**) Lewis acid ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) or protic acid (CH_3SO_3H) at 25 °C in dichloromethane; (**B**) *p*-toluenesulphonic acid in a Dean–Stark trap (Scheme 2). A variety of Lewis acids ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) as well as protic acids (CH_3SO_3H, *p*-TsOH) under varied reaction conditions were screened and the results are summarized in Table 1. The reactions were more efficient in the presence of $AlCl_3$ and $ZnCl_2$ in dichloromethane. It is noteworthy that compounds **7a–i** isolated by method **A** and compounds **7a–g** obtained by method **B** were pure and directly used for the spectral analysis, however, compounds **7h–i** obtained by method **B** were purified by column chromatography. The structures of compounds **7a–i** are clearly supported by their ^1H, ^{13}C NMR spectra and microanalysis. The ^1H NMR spectra showed NC*H*-pyrazino singlet signal for **7a–i** at ~5.3 ppm and the presence of exchangeable N*H*-pyrazino was confirmed by deuterium exchange.

The reaction pathway is believed to involve the formation of transient intermediate **X** and subsequent generation of iminium cation **Y**, which undergoes intramolecular

Table 1. Intramolecular cyclization of amine **5b** with aldehydes catalyzed by different Lewis acids and protic acids

Entry	Compound	R^1	Catalyst[a]	Time (h)	Yields (%)[b]
1	**7a**	C_6H_5	$AlCl_3$	0.5	91
2	**7a**	C_6H_5	$ZnBr_2$	1.5	83
3	**7a**	C_6H_5	CH_3SO_3H	1.5	81
4	**7a**	C_6H_5	*p*-TsOH	7.5	79
5	**7b**	*p*-Me–C_6H_5	$AlCl_3$	1.0	84
6	**7b**	*p*-Me–C_6H_5	$ZnCl_2$	1.5	77
7	**7b**	*p*-Me–C_6H_5	CH_3SO_3H	1.5	80
8	**7b**	*p*-Me–C_6H_5	*p*-TsOH	6.5	78
9	**7c**	*p*-MeO–C_6H_5	$AlCl_3$	1.5	82
10	**7c**	*p*-MeO–C_6H_5	*p*-TsOH	6.5	77
11	**7d**	*p*-NO_2–C_6H_5	$AlCl_3$	0.5	88
12	**7d**	*p*-NO_2–C_6H_5	$ZnBr_2$	3.5	78
13	**7d**	*p*-NO_2–C_6H_5	CH_3SO_3H	1.8	77
14	**7e**	*p*-Cl–C_6H_5	$AlCl_3$	2.0	93
15	**7e**	*p*-Cl–C_6H_5	*p*-TsOH	6.5	81
16	**7e**	*p*-Cl–C_6H_5	CH_3SO_3H	1.8	80
17	**7e**	*p*-Cl–C_6H_5	$ZnBr_2$	2.0	77
18	**7f**	*p*-Br–C_6H_5	$AlCl_3$	2.0	93
19	**7f**	*p*-Br–C_6H_5	$ZnCl_2$	2.5	79
20	**7f**	*p*-Br–C_6H_5	CH_3SO_3H	2.5	82
21	**7g**	*p*-F–C_6H_5	$AlCl_3$	2.0	93
22	**7g**	*p*-F–C_6H_5	*p*-TsOH	6.5	80
23	**7g**	*p*-F–C_6H_5	$ZnCl_2$	3.5	78
24	**7h**	2-Pyr	$AlCl_3$	1.2	87
25	**7h**	2-Pyr	$ZnBr_2$	3.5	65
26	**7h**	2-Pyr	*p*-TsOH	7.5	77[c]
27	**7i**	2-Thie	$AlCl_3$	>4.0	88
28	**7i**	2-Thie	*p*-TsOH	7.5	78[c]
29	**7j**	*iso*-Propyl	$AlCl_3$	10	—[d]
30	**7j**	*iso*-Propyl	$ZnCl_2$	12	—[d]

[a] Reaction conditions for catalyst (i) $AlCl_3$, $ZnCl_2$, $ZnBr_2$ or CH_3SO_3H: CH_2Cl_2/25 °C; (ii) for *p*-TsOH, benzene/reflux using Dean–Stark trap.
[b] Isolated yield.
[c] Purified by column chromatography.
[d] The compound was not obtained.



Scheme 3. R = Me. R^1CHO, BtH, Lewis acids ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) or CH_3SO_3H, CH_2Cl_2, 25 °C.

cyclization to furnish **7a–i** (Scheme 3). Lewis ($AlCl_3$, $ZnCl_2$, $ZnBr_2$) or protic (CH_3SO_3H, *p*-TsOH) acid in catalytic amounts facilitate loss of benzotriazolyl anion from intermediate **X** to form iminium cation **Y**, which finally cyclizes with the loss of one proton to give cyclized compounds **7a–i**. However, the 3-position methyl group in **5b** appears to be essential because, without it, we failed to obtained cyclization. The presence of the 3-position methyl group activates the indole ring system, which facilitates the intramolecular cyclization via formation of tertiary carbocation whereas in case of non-substituted indole **5a**, decompostion occurred, which might be due to the proton loss or dimerization or polymerization via cationic processes. It is also noteworthy that when the reaction was carried out in the absence of benzotriazole, no cyclization product was obtained (Scheme 2).

For showing generality in the reaction we had carried one reaction in 10 gm scale using 2-(3-methyl-1*H*-indol-1-yl) ethylamine **5b** with benzotriazole and aldehydes **7e** in presence of catalytic amount of $AlCl_3$. In addition, mechanism of the observed intramolecular cyclization with indolethylamine (with or without methyl at 3-position) with various aromatic aldehydes **6a–j** containing electron releasing or electron-withdrawing group is also discussed.

2.2. Frontier molecular orbital analysis

To demonstrate the results obtained in the work, we used a simple approach of frontier molecular orbital (FMO)[16] based on the energy gap of HOMO and LUMO. The ineffective cyclization of 2-indol-1-yl-ethylamine **5a** can be explained through FMO analysis. It has been realized from the Figure 1 that the reactions are very much controlled by $E_{HOMO(amine)} - E_{LUMO(aldehyde)}$ energy gap, if we observe the reaction of both the amines **5a** and **5b** with an aldehyde **6a**, we find that the energy gap for **5b** and **6a** $\Delta E = 4.76$ eV is less than for **5a** and **6a** $\Delta E = 6.08$ eV revealing that the reaction between **5b** and **6a** must proceed at higher rate compared to **5a** and **6a**. Similarly, **5a** and **6b** $\Delta E = 6.13$ eV > **5b** and **6b** $\Delta E = 4.79$ eV, **5a** and **6i** $\Delta E = 7.95$ eV > **5b** and **6i** $\Delta E = 6.61$ eV, this reaction occurred

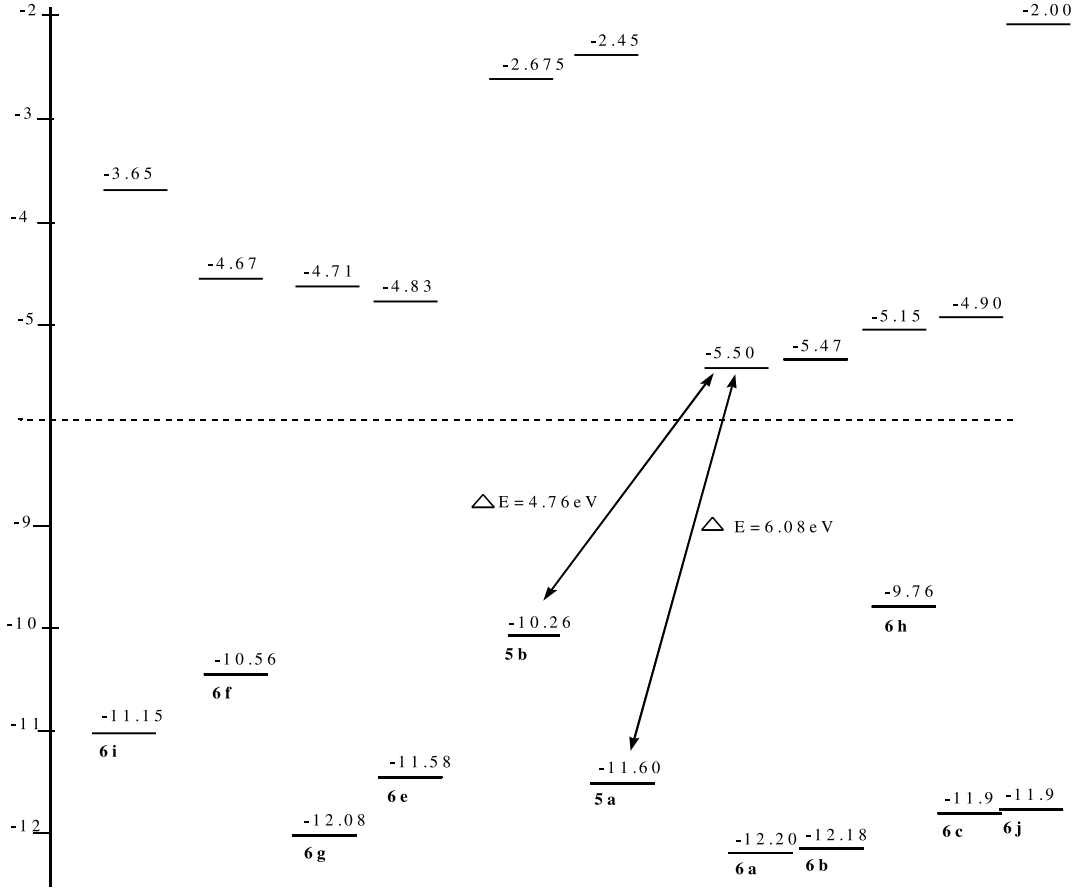


Figure 1. Frontier molecular orbitals of amines **5a–b** and aldehydes **6a–c** and **6e–j**. (**6d** structure is far from equilibrium).

with difficulty and took >4 h. Difference in the reactivity of **5b** and **5a** is mainly due to: (i) formation of stable tertiary carbocation; (ii) energy gap $E_{HOMO(amine)}-E_{LUMO(aldehyde)}$. In case of **5b**(with methyl group at 3 position) cyclization occurs via formation of stable tertiary carbocation, however, in case of nonsubstituted amine **5a** polymerization occurs via cationic processes. The data presented in the Table 1 showed that the reaction of **5b** with various aldehydes completed in different time periods. This observation can also be explained through same FMO model. The insertion of electron donating group such as –Me, –Cl, –F, –Br, and –OMe, at 4-phenyl ring of **6a–i** increased the energy gap and subsequently retarded the rate of reaction (Fig. 2). In general observed reaction rate followed the pattern **7a**>**7b**>**7h**>**7c**>**7e**>**7g**>**7f**>**7i**. However, cyclization was not achieved when the amine **5b** is condensed with aliphatic aldehyde **6j** and benzotriazole in the presence Lewis acid $AlCl_3$ or $ZnCl_2$, which is believed due to high-energy gap (Fig. 1).

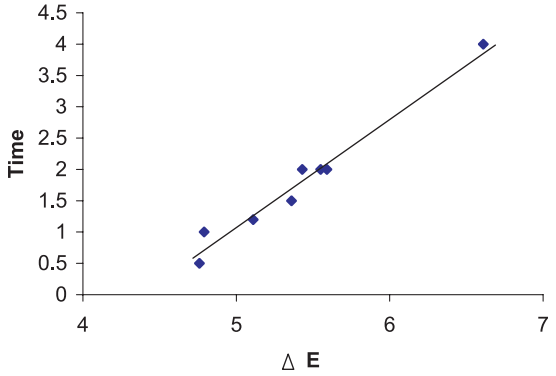


Figure 2. Plot between the reaction time and energy difference of frontier molecular orbitals for reaction of **5b** and aldehydes **6a–i** (ΔE=HOMO−LUMO).

3. Conclusion

The present studies have demonstrated the efficient one-pot access to 1-substituted-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **7a–i** from **5b** using benzotriazole, aldehydes **6a–i** and a catalytic amount of Lewis acids or protic acid via intramolecular cyclization. Semi empirical PM3 studies support the experimental results. The advantage of present work includes (i) use of cheap, easy to handle and commercially available material and catalyst; (ii) rt reaction conditions; (iii) short reaction time and high yields; (iv) no extra efforts for purification. Simple reaction conditions, high yields and high purity of the crude product make this methodology applicable for large-scale operations.

4. Experimental

All reagents used were AR grade. Melting points were determined using a Thomas Hoover melting point apparatus. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as internal references) unless otherwise stated. MS were recorded on Agluent 1100 ES-MS Karlsrhue Germany. Infrared spectra (υ_{max}) were recorded on Perkin Elmer FTIR spectrophotometer as thin films on KBr plates (for oils) or KBr discs (for solids). Column chromatography was performed on silica gel (230–400 mesh). Microanalyses were obtained with an Elemental Analysensysteme GmbH VarioEL V3.00 element analyser. The reactions were monitored by thin-layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} (Merck). All of the reactions were carried out under nitrogen atmosphere.

4.1. Synthesis of 1-substituted-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles 7a–j: general procedure

Method (*A*). To a mixture of 2-(3-methyl-1*H*-indol-1-yl) ethylamine (**5b**, 0.5 g, 2.9 mmol), an aldehyde (**6a–j**) (2.9 mmol), benzotriazole (0.342 g, 2.9 mmol), in the presence of catalytic amount of Lewis acid ($AlCl_3$ or $ZnCl_2$ or $ZnBr_2$) or protic acid (CH_3SO_3H) in dichloromethane (20 mL) was stirred at 25 °C for 0.5–8.0 h. (TLC monitoring) The reaction mixture was quenched with water and extracted with ethyl acetate (100 mL×3). The combined extract was washed with 1 N NaOH, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give solid compound **7a–j**. For microanalysis, compounds were recrystallized from ethyl acetate/hexanes.

Method (*B*). A mixture of 2-(3-methyl-1*H*-indol-1-yl) ethylamine (**5b**, 500 mg, 2.9 mmol), an aldehyde (**6a–j**) (2.9 mmol), benzotriazole (0.342 g, 2.9 mmol) in the presence of catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in benzene (30 mL), was heated under reflux for appropriate time (4–8 h). Water was azeotropically removed by using a Dean–Stark trap. The reaction was monitored by TLC. The solvent was removed under reduced pressure, and residue was then dissolved in ethyl acetate (100 mL), washed with 1 N NaOH solution (100 mL×2), brine solution and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure gave a residue, which was crystallized to give **7a–g** and compounds **7h–j** were purified using column chromatography with hexanes/ethyl acetate 6:1–2:1 as an eluent.

4.1.1. 10-Methyl-1-phenyl-1,2,3,4-tetrahydropyrazino-[1,2-*a*]indole 7a. (White needles from EtOAc/hexanes). Mp 122–124 °C; [Found: C, 82.38; H, 6.88; N, 10.59 $C_{18}H_{18}N_2$ requires C, 82.41; H, 6.92; N, 10.68%]; ν_{max} (KBr) 3315, 3055, 3043, 2956, 2920, 2880, 750, 677 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54–7.08 (9H, m, Ph, Ph), 5.37 (1H, s, H-1), 4.16–3.93 (2H, m, H-4), 3.34–3.14 (2H, m, H-3), 1.93 (1H, s, NH), 1.86 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 142.0, 135.8, 131.6, 130.5, 128.4, 127.5, 120.8, 119.2, 118.2, 108.4, 106.0, 100.2, 56.6, 42.7, 40.0, 8.4; LCMS *m*/*z* 263.5 (100, M+1).

4.1.2. 10-Methyl-1-(4-methylphenyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7b. Yellow oil; [Found: C, 82.73; H, 7.12; N, 10.24 $C_{19}H_{20}N_2$ requires C, 82.57; H, 7.29; N, 10.14%]; ν_{max} (KBr) 3313, 3051, 3043, 2955, 2926, 2875, 751, 676 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.52–7.10 (8H, m, Ph, Ph), 5.30 (1H, s, H-1), 4.03–3.96 (2H, m, H-4), 3.24–3.13 (2H, m, H-3), 2.39 (1H, s, NH); 2.31 (3H, s, CH_3), 1.85

(3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 139.0, 137.0, 135.7, 131.7, 129.0, 128.1, 124.3, 120.6, 119.5, 118.1, 108.3, 105.8, 56.2, 42.5, 39.8, 21.0, 8.4; LCMS *m/z* 275 (100%, M−1), 276 (20%, M), 277 (8%, M+1).

4.1.3. (4-Methoxyphenyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7c. (White needles from EtOAc/hexanes). Mp 126–128 °C; [Found: C, 77.72; H, 9.51; N, 9.54 $C_{19}H_{20}N_2O$ requires C, 78.00; H, 9.58; N, 9.58%]; ν_{max} (KBr) 3320, 3049, 3044, 2955, 2920, 2877, 1041, 742, 677 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.52–6.84 (8H, m, Ph, Ph), 5.33 (1H, s, H-1), 4.16–3.99 (2H, m, H-4), 3.79 (3H, s, OMe), 3.36–3.15 (2H, m, H-3), 1.86 (3H, s, CH_3), 1.66 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 150.9, 145.7, 143.2, 131.5, 130.9, 127.0, 119.6, 119.1, 118.6, 116.1, 108.3, 105.8, 58.2, 56.2, 42.5, 39.8, 8.4; LCMS *m/z* 293 (5%, M+1); 292 (30%, M); 291 (100%, M−1).

4.1.4. 1-(4-Nitrophenyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7d. (Yellow crystals from EtOAc/hexanes). Mp 112–114 °C; [Found: C, 70.31; H, 5.56; N, 13.45 $C_{18}H_{17}N_3O_2$ requires C, 70.34; H, 5.58; N, 13.67%]; ν_{max} (KBr) 3321, 3050, 3042, 2955, 2922, 2876, 1520, 1360, 750, 680 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.53–6.90 (8H, m, Ph, Ph); 5.31 (1H, s, H-1), 4.15–3.96 (2H, m, H-4), 3.30–3.15 (2H, m, H-3), 2.70 (3H, s, CH_3), 1.60 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 135.9, 132.4, 130.0, 129.3, 127.3, 125.7, 121.4, 119.5, 118.5, 117.0, 111.1, 109.0, 56.2, 42.7, 40.9, 8.4; LCMS *m/z* 307 (80%, M), 308 (20%, M+1), 185.2 (14%, M−122).

4.1.5. 1-(4-Chlorophenyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7e. (White needles from EtOAc/hexanes). Mp 110–111 °C; [Found: C, 72.52; H, 5.40; N, 9.21 $C_{18}H_{17}N_2Cl$ requires C, 72.80; H, 5.70; N, 9.40%]; ν_{max} (KBr) 3310, 3050, 3043, 2956, 2922, 2878, 1087, 760, 689 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54–7.11 (8H, m, Ph, Ph) 5.34 (1H, s, H-1), 4.15–3.96 (2H, m, H-4), 3.30–3.15 (2H, m, H-3), 1.88 (s, 4H, NH, CH_3); δ_C (100 MHz, $CDCl_3$) 158.7, 140.6, 136.3, 133.5, 131.1, 129.7, 128.6, 125.1, 121.0, 119.4, 118.3, 108.5, 55.7, 42.6, 39.8, 8.5; LCMS *m/z* 297.1 (50%, M+1), 295 (100%, M−1), 280.1 (7%, M−15), 186.2 (12%, M−110).

4.1.6. 1-(4-Bromophenyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7f. (White needles from EtOAc/hexanes). Mp 115–117 °C; [Found: C, 63.03; H, 5.25; N, 8.27 $C_{18}H_{17}N_2Br$ requires C, 63.30; H, 5.03; N, 8.21%]; ν_{max} (KBr) 3311, 3050, 3043, 2957, 2922, 2879, 760, 684 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54–7.11 (8H, m, Ph, Ph), 5.32 (1H, s, H-1), 4.10–3.90 (2H, m, H-4), 3.20–3.15 (2H, m, H-3), 1.80 (3H, s, CH_3), 1.26 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 141.0, 135.5, 133.1, 132.1, 131.6, 130.9, 130.0, 121.0, 119.3, 118.2, 108.5, 106.1, 55.7, 42.6, 39.7, 8.4; LCMS *m/z* 343.1 (45%, M+2), 341 (100%, M), 339 (65%, M−2).

4.1.7. 1-(4-Fluorophenyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7g. (White needles from EtOAc/hexanes). Mp 120–121 °C; [Found: C, 77.18; H, 5.86; N, 9.62 $C_{18}H_{17}N_2F$ requires C, 77.12; H, 6.11; N, 9.99%]; ν_{max} (KBr) 3311, 3049, 3043, 2957, 2921, 2879, 1200, 761, 683 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54–7.11 (8H, m, Ph, Ph), 5.32 (1H, s, H-1), 4.10–3.91 (2H, m, H-4), 3.27–3.15 (2H, m, H-3), 1.82 (4H, s, NH, CH_3); δ_C (100 MHz, $CDCl_3$) 164.2, 139.8, 139.5, 139.1, 132.8, 129.9, 120.9, 119.3, 118.2, 108.2, 102.4, 100.5, 55.8, 42.7, 39.9, 8.5; LCMS *m/z* 281.16 (76%, M+1), 282.18 (14%, M+2), 279.14 (100%, M−2).

4.1.8. 10-Methyl-1-pyridin-2-yl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7h. (White needles from EtOAc/hexanes). Mp 127–128 °C; [Found: C, 77.18; H, 6.34; N, 15.69 $C_{17}H_{17}N_3$ requires C, 77.54; H, 6.51; N, 15.96%]; ν_{max} (KBr) 3306, 3051, 3044, 2958, 2924, 2881, 1580, 1440, 748, 704 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.82–6.83 (8H, m, Ph, pyri), 5.19 (1H, s, H-1), 3.97–3.76 (2H, m, H-4), 3.15–3.03 (2H, m, H-3), 1.95 (3H, s, CH_3), 1.80 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 154.2, 148.4, 138.8, 137.5, 134.9, 130.8, 122.0, 120.7, 119.6, 119.1, 118.6, 111.1, 108.0, 54.2, 43.6, 41.5, 8.6; LCMS *m/z* 364 (40%, M+1).

4.1.9. 10-Methyl-1-thien-2-yl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole 7i. (Brown needles from EtOAc/hexanes). Mp 130–131 °C; [Found: C, 71.54; H, 5.98; N, 10.38; S, 11.87 $C_{16}H_{16}N_2S$ requires C, 71.60; H, 6.01; N, 10.44; S, 11.95%]; ν_{max} (KBr) 3320, 3059, 3043, 2966, 2922, 2888, 775, 650, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43–6.33 (7H, m, Ph, thien), 5.19 (1H, s, H-1), 3.87 (2H, m, H-4), 2.90 (2H, m, H-3), 2.20 (3H, s, CH_3), 1.90 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 139.5, 139.1, 138.1, 132.0, 127.5, 124.5, 121.0, 120.4, 119.5, 117.6, 108.1, 106.0, 54.2, 43.2, 40.5, 8.4; LCMS *m/z* 269 (25%, M+1).

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Soluble and insoluble polymeric 1,3-dithiane reagents for the synthesis of aldehydes from alkyl halides

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Abstract—Through the synthesis and study of model systems as proper dithiane derivatives, vinyl monomers and soluble copolymeric reagents containing 2-unsubstituted 1,3-dithiane rings, we attained the key synthon 1,3-dithiane-5-methanol. Through its reaction with commercial resins, new polymeric reagents useful for supported organic synthesis and combinatorial chemistry were developed. Exploiting the reactivity of position 2 in 1,3-dithiane rings, such polymeric reagents were employed in the production of aldehydes from alkyl halides through a process entirely free from unpleasant odors.

1. Introduction

In organic chemistry the great synthetic potentiality of sulfur(II) compounds such as thiols and dithiols, precursors of thioacetals or thioketals, is strongly handicapped by the very unpleasant odor of such materials. In previous papers[1–5] we have overcome this handicap through the fully odorless synthesis of polymeric reagents containing 1,3-propanedithiol or 2-substituted 1,3-dithiane functions, which were tested in the preparation of ketones from aldehydes and in the reduction of ketones, and proved effective for solid-phase synthesis exploitable in the field of combinatorial chemistry. The utility of thioacetal functions in the solid-phase synthesis is also reported as a way of protecting and anchoring the carbonyl function of methylarylketones to commercial aminomethyl polystyrene resins before carrying out transformations on the benzene ring.[6] Such a process requires, however, the unattractive handling of a 1,3-propanedithiol derivative to transform ketones into thioketals, and uses secondary amide bonds, not fully inert towards various reagents, for the immobilization of the thioketals on the commercial resin.

This work reports the functionalization of commercial chloromethylstyrene resins with the key synthon 1,3-dithiane-5-methanol (**6**) and their application to the production of aldehydes from alkyl halides, optimized through the synthesis of model molecules, proper vinyl monomers and soluble copolymeric reagents containing 2-unsubstituted 1,3-dithiane rings.

2. Results and discussion

The known 1,3-dithian-5-one[7] (**1**), obtainable from slightly odorous pure thioglycolic acid, having a reactive carbonyl group useful for the introduction of a linker in the position 5 of the 1,3-dithiane ring, the farthest from the thioacetalic carbon, appeared a reasonable precursor for the preparation of a synthon aimed to the functionalization of haloalkyl resins. Hence, **1** was prepared according to the literature,[7] reduced to the alcohol **2**,[8] and allowed to react with benzyl bromide obtaining in good yield from **1** the ether **3**, a model molecule of an umpoled thioacetal equivalent of methanal. The compound **3**, allowed to react first with *n*-butyllithium then with methanol-*d*, afforded the deuterated dithiane derivative **4** (Scheme 1), which showed the ^{1}H NMR spectrum corresponding to the substitution of the high-field proton at C(2) with deuterium, in full agreement with the known preferred equatorial deprotonation[9] and anomeric effect[10] in 1,3-dithianes. The obtained low yield (45.3%), probably due to a concomitant elimination reaction, made **2** an unacceptable synthon.

Wishing to find a reliable process for further spacing the ether linkage from sulfur atoms and preventing eliminations, we considered the 1,3-dithiane-5-methanol[11] (**6**) and accomplished its synthesis with an overall yield of 65% from **1**, through a Wittig reaction followed by hydrolysis and reduction with $NaBH_4$ of the enolether **5** (Scheme 2).

Keywords: Supported reagents; Umpolung reactions; 1,3-Dithianes; Aldehydes; Alkyl halides.
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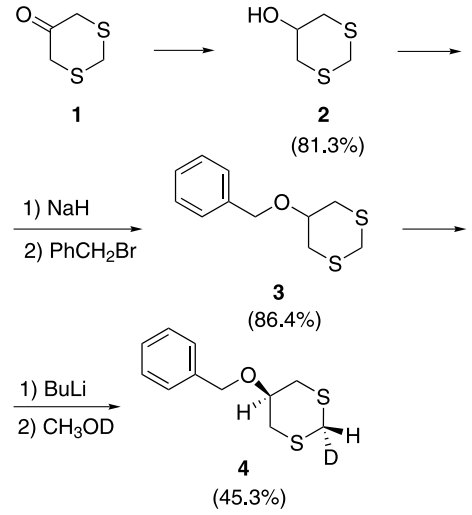
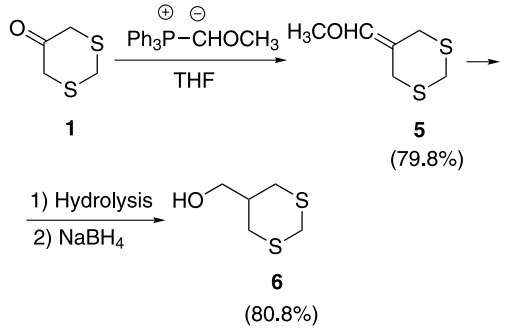
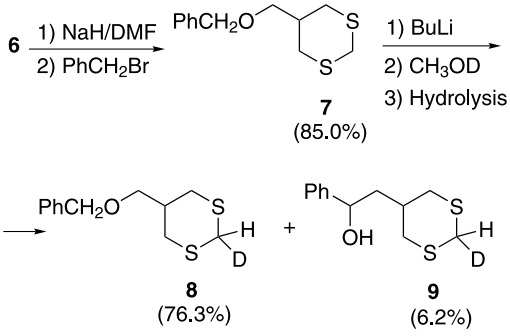


Scheme 1.



Scheme 2.

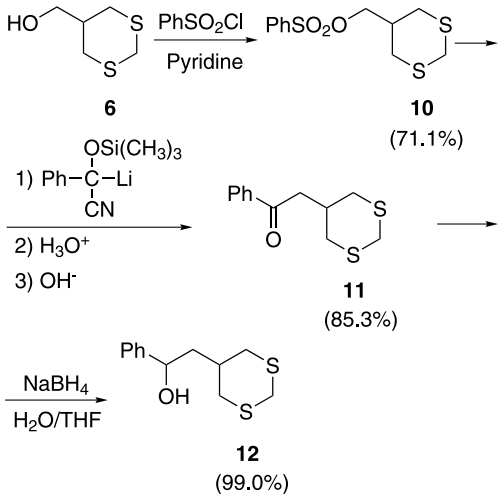
The alcohol **6** was submitted to several test reactions. It was transformed with benzyl bromide into the benzyl ether **7**, then lithiated and deuterated (Scheme 3). The process afforded after hydrolysis the expected **8** in 76.3% yield, together with **9** recovered in 6.2% yield.



Scheme 3.

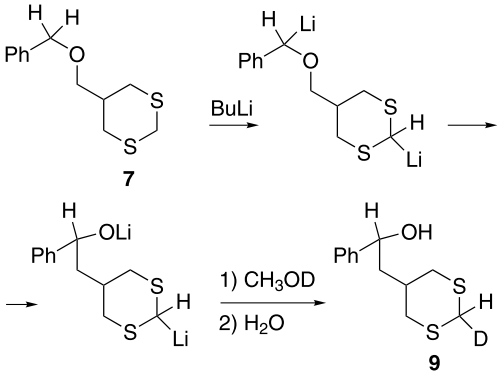
The structure of **9** was confirmed by preparing its non-deuterated analogue **12** from **6** through the ketone **11**, which was obtained from the benzenesulfonate ester **10** applying Hünig's umpolung procedure[12] of aromatic aldehydes (Scheme 4), then comparing the ^{1}H and ^{13}C NMR spectra of **9** and **12**.

The formation of **9** from **7** can be rationalized through a



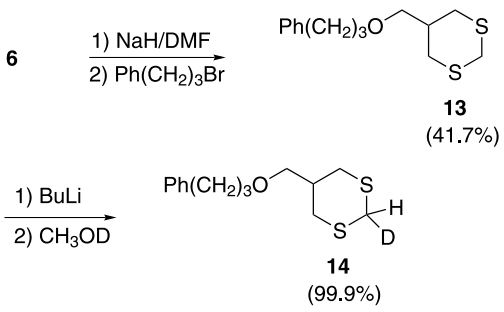
Scheme 4.

Wittig rearrangement of the benzylic ether[13] to the lithium alcoholate metallated at C(2), followed by deuteration with methanol-*d* and exchange H–D at the hydroxy group by addition of water (Scheme 5).



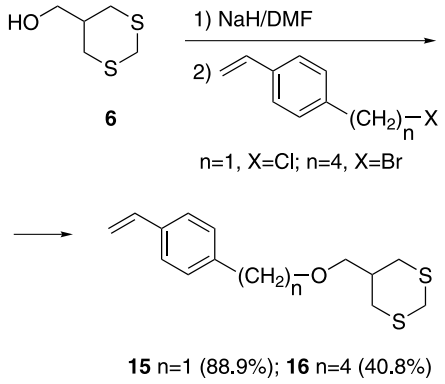
Scheme 5.

To avoid the presence of undesired products originating from the reactivity of the benzyl ether, **6** was transformed into the ether **13** with a chain of three methylene groups. After lithiation and deuteration **13** afforded **14** in quantitative yield (Scheme 6), proving that **6** is a good dithiane synthon for umpolung reactions, but the modest yield (41.7%) obtained in the synthesis of the model molecule **13** stimulated additional studies.



Scheme 6.

It appeared reasonable to synthesize new 1,3-dithiane vinyl monomers with or without a benzyl ether group by reacting **6** both with commercial (4-ethenylphenyl)chloromethane and with 1-bromo-4-(4-ethenylphenyl)butane[14] to reach monomeric then polymeric models and to test if the length of the spacer could affect the yield attained with 1-bromo-3-phenylpropane in the synthesis of **13**. The reactions reported in Scheme 7 gave the monomers **15** and **16**, respectively, confirming a good yield for **15** comparable with **7** and a modest yield for **16** comparable with **13**.



6

15 n=1 (88.9%); **16** n=4 (40.8%)

Scheme 7.

Under the conditions already used for the preparation of masked 1,3-propanedithiol linear copolymers,[1,2] **15** and **16** were copolymerized with styrene starting from feed molar ratios of dithiane monomer/styrene equal to 1:9 or 1:19, recording conversions higher than 95%. All the copolymers from **15** (**P1$_{15(1:9)}$**, **P1$_{15(1:19)}$**) and **16** (**P1$_{16(1:9)}$**, **P1$_{16(1:19)}$**) were recovered in the form of easily filtered powders after precipitation with methanol from their dioxane solutions. Such copolymers were tested in the transformation of 1-bromo-4-phenylbutane into the stable 5-phenylpentanal (**17a**), whose ^{1}H and ^{13}C NMR spectra are known[15] (Scheme 8).

The lithiation was found to cause a certain amount of cross-linking, as evidenced by the presence of variable percentages of gelatinous insoluble material together with the copolymeric products **P3**. The cross-linking was higher with copolymers more concentrated in dithiane units (1:9) and containing benzyl ether linkages. The use of the copolymeric reagent **P1$_{16(1:19)}$** with diluted dithiane units and without benzyl ether linkages gave a negligible cross-linking (Table 1). Since a low extent of side reactions is sufficient to produce a significant quantity of cross-linked material, the reported percentages of the insoluble fraction of **P3** was calculated on the assumption that the soluble and insoluble portions of **P3** had the same composition. The cleavage of the dithiane rings in **P3** with periodic acid or with mercury(II) perchlorate hydrate afforded the aldehyde **17a** (Table 1). Both soluble and insoluble portions of **P3** produced **17a**, but the yields of **17a** reported in the fifth column of the Table 1 refer only to the soluble one.

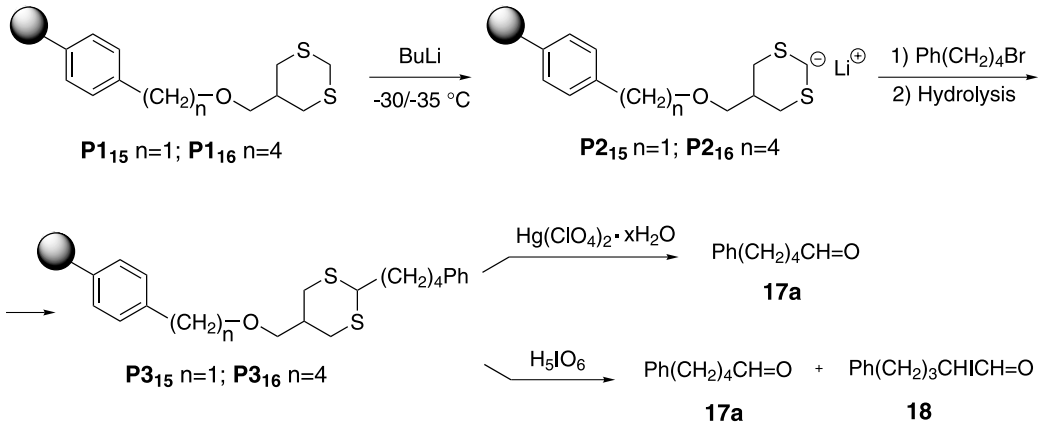
The reaction with mercury(II) perchlorate hydrate gave pure **17a** showing an aldehydic proton triplet at δ 9.74 in the ^{1}H NMR spectrum, while the reaction with periodic acid, besides **17a**, not unexpectedly[1] produced 5–10% of the iodine derivative **18**, showing an aldehydic proton doublet at δ 9.22, whose structure was deduced from the spectroscopic data compared with those of 2-iodohexadecanal[16] and other α-iodinated aldehydes.[17]

On the basis of the recorded yields, the best procedure for the obtainment of **17a** uses the model copolymeric reagent **P1$_{16(1:19)}$**, characterized by a low concentration of dithiane units and absence of benzyl ether linkages, and carries out the cleavage of the dithiane rings with mercury(II) perchlorate hydrate.

Under analogous conditions, the model copolymeric reagent **P1$_{15(1:19)}$** containing benzyl ether linkages gave yields only slightly lower than **P1$_{16(1:19)}$**, in spite of the Wittig rearrangements, which consumes *n*-butyllithium forming alcoholate and produces a significant cross-linking under lithiation.

Considering that the (4-ethenylphenyl)chloromethane, precursor of **P1$_{15}$**, is commercially available, and that the preparation of 1-bromo-4-(4-ethenylphenyl)butane, precursor of **P1$_{16}$**, is rather laborious and expensive, for most applications the recommended copolymeric reagent model is **P1$_{15}$** with a low concentration of dithiane units.

On this basis reagents for solid phase syntheses can be



P1$_{15}$ n=1; **P1$_{16}$** n=4

P2$_{15}$ n=1; **P2$_{16}$** n=4

P3$_{15}$ n=1; **P3$_{16}$** n=4

Scheme 8.

Table 1. Synthesis of the aldehyde **17a** from $\mathbf{P1_{15}}$ and $\mathbf{P1_{16}}$ with excess of 1-bromo-4-phenylbutane

Polymer **P1**	% Yield of insoluble **P3**	% Yield of soluble **P3**	Cleavage reagent	% Yield of **17a** from **P1**
$\mathbf{P1_{15(1:9)}}$	32.2	63.4	H_5IO_6	35.2
$\mathbf{P1_{15(1:19)}}$	11.5	86.2	H_5IO_6	40.1
$\mathbf{P1_{15(1:19)}}$	11.5	86.2	$Hg(ClO_4)_2 \cdot xH_2O$	56.6
$\mathbf{P1_{16(1:9)}}$	15.5	79.8	H_5IO_6	43.4
$\mathbf{P1_{16(1:19)}}$	0.7	98.9	$Hg(ClO_4)_2 \cdot xH_2O$	62.7

properly prepared by anchoring **6** to commercial resins of Merrifield type.

2.1. Solid phase synthesis of aldehydes using transformed Merrifield resins

We prepared cross-linked supports with a low concentration of well accessible 1,3-dithiane units and tested them in the synthesis of aldehydes from alkyl halides, anchoring **6** to the commercial Merrifield resin having a CH_2Cl loading of 0.8 mmol g^{-1} of resin, cross-linked with 1% divinylbenzene (DVB), which showed a good swelling in DMF and THF and a good reactivity towards the alkoxide ions. The nominal CH_2Cl group loading was checked by addition of excess of sodium methoxide and titration of the chloride ions with standard silver nitrate. The commercial resin **R0** was transformed into the active dithiane resin **R1** through the reaction with the sodium salt of **6** in the empirically optimized molar ratio 1:1.5, monitoring the process by the disappearing of the IR band at 1263 cm^{-1} (C–Cl) and the appearing of that at 1092 cm^{-1} (C–O) (Scheme 9).

The resin **R1**, allowed to react with excess *n*-butyllithium in analogy with a previous work,[3] quite likely underwent the Wittig rearrangement to a small extent, nevertheless, it turned red owing to the deprotonation of the dithiane ring (**R2**). The red colour persisted after washing the beads with anhydrous THF to remove the excess of base that could interfere with the successive alkylation step, and disappeared when an excess of alkyl halide was added to the mixture. From the alkylated resin **R3** the aldehyde was recovered by cleavage with mercury(II) perchlorate hydrate. Optimized conditions for preparative syntheses are as follows: 1,3-dithiane units in **R1**:*n*-butyllithium:alkyl halide molar ratios = 1:1.25:1.50; no washing of **R2** with anhydrous THF; lithiation time and temperature: 2 h between −30 and −35 °C. Shorter lithiation times as well as the use of **R0** with high chlorine loading decreased the yields of the aldehyde referred to the CH_2Cl units. No traces of double alkylation of the dithiane ring with formation of ketones were found in any experiment. Table 2 collects some characteristic data of the reaction performed. The yields of aldehyde in the last column refer to the CH_2Cl units in **R0**.

Table 2. Chemical modifications of the commercial resin **R0** and synthesis of aldehydes

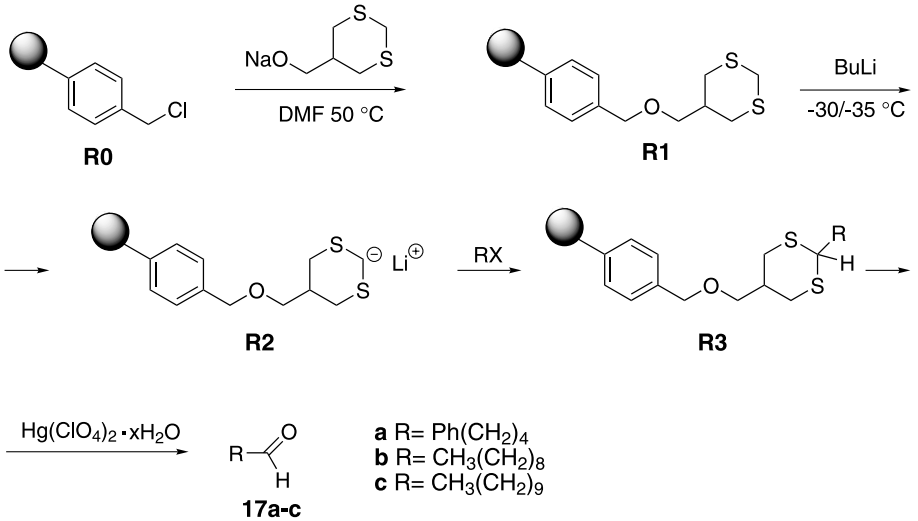
R0 (mmol Cl/g)[a]	**R1** (% yield from **R0**)	**R3** (% yield from **R1**)	RX	RCHO (% yield from **R0**)
0.822	96.7	98.3	$C_6H_5(CH_2)_4Br$	**17a** (61.3)
0.806	97.3	95.8	$CH_3(CH_2)_8Br$	**17b** (48.0)
0.806	98.1	97.2	$CH_3(CH_2)_9Br$	**17c** (57.3)

[a] Determined by titration.

3. Conclusions

We performed the synthesis of polymeric reagents endowed with thioacetal reactivity for supported organic reactions and combinatorial chemistry using commercial Merrifield resins and a proper 1,3-dithiane synthon, obtained through an odorless synthesis, unsubstituted at the position 2 and carrying at the position 5 a suitable alcoholic function for the formation of stable ether bonds.

After having examined and then discarded the 5-hydroxy-1, 3-dithiane (**2**) as a possible synthon, we prepared the fully



Scheme 9.

satisfactory 1,3-dithiane-5-methanol (**6**). Through synthesis and study of the model molecules and soluble copolymers **7**, **9**, **12**, **13**, **14**, **15**, **16**, $\mathbf{P1_{15}}$ and $\mathbf{P1_{16}}$, we demonstrated that **6** can be easily anchored to a polymeric material by forming benzyl ether or alkyl ether bridges with chloromethylphenyl or various ω-bromoalkylphenyl residues, respectively.

The presence of benzyl ether groups has the handicap of producing by treatment with *n*-butyllithium small amounts of alcoholate through the Wittig rearrangement, increasing the consumption of the lithium reagent. Nevertheless, materials that show such handicap, like those derived from the Merrifield resins, have the advantage of being prepared from commercial products, while those not containing benzyl ether groups and not undergoing the Wittig rearrangement, require rather laborious and expensive preparations and show only a slightly higher efficiency (compare $\mathbf{P1_{15}}$ and $\mathbf{P1_{16}}$ in the Table 1). For these reasons the use of reagents derived from commercial products has to be preferred for most applications.

The effectiveness of **6** for the preparation from commercial Merrifield resins of valuable polymeric reagents for solid-phase synthesis was demonstrated with the transformation of alkyl halides into aldehydes containing an additional carbon atom.

4. Experimental

4.1. General

Melting points were determined on a Leica Galen III hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance DPX 300 Spectrometer at 300 and 75.5 MHz, respectively, using TMS as internal standard and were assigned with the help of standard NOE-difference, COSY and HETCOR experiments. Mass spectra were obtained with a GC-MS Ion Trap Varian Saturn 2000 instrument (EI mode, filament current 10 μA). Infrared spectra were measured on a Perkin-Elmer 2000 FTIR spectrophotometer, using KBr discs. Commercial solvents and reagents were purchased from Aldrich unless otherwise stated. Petroleum ether refers to the fraction with boiling point 40–60 °C. Flash-chromatographic separations were performed on Merck Silica gel (0.040–0.063 mm). Commercial 90% (4-ethenylphenyl) chloromethane was crystallized twice from pentane at −70 °C and distilled at reduced pressure (99% pure by ^{1}H NMR). Commercial styrene was washed with a 5% NaOH aqueous solution, dried over KOH pellets and distilled under nitrogen at reduced pressure. Azobisisobutyronitrile (AIBN) was crystallized from methanol. Merrifield resins (particle size 200–400 mesh, 1% DVB, CH_2Cl loading of 0.8 mmol g^{-1}) were purchased from Fluka. The solvents for polymer syntheses and transformations were carefully dried, deoxygenated and distilled under nitrogen. 1,3-Dithiane-5-one (**1**)[7], 1,3-dithiane-5-ol (**2**),[8] 1-bromo-4-(4-ethenylphenyl)butane[14] and 1-bromo-4-phenylbutane[18] were prepared according to the literature.

4.1.1. 5-Methoxymethylene-1,3-dithiane (5). To a vigorously stirred suspension of commercial methoxymethyltriphenylphosphonium chloride (11.01 g, 32.1 mmol) in anhydrous THF (50 mL) potassium *t*-butoxide (3.49 g, 31.1 mmol) was rapidly added under nitrogen at room temperature. The ensuing dark red mixture was further stirred for 1 h, cooled to −25 °C and treated in 5 min under stirring with 1,3-dithian-5-one **1**[7] (1.71 g, 12.7 mmol) in THF (25 mL), further stirred at −20 to −25 °C for 8 h, then added with water (50 mL) and Et_2O (100 mL). The organic layer was separated, washed with water and dried (Na_2SO_4). Evaporation at reduced pressure left a dark oil, which was purified by flash-chromatography (petroleum ether/Et_2O 100:5) to afford **5** (1.65 g, 79.8%). Mp 85–86 °C (Et_2O/pentane, white needles). IR (KBr) ν_{max} cm^{-1}: 1666 (C=C), 1215, 1130 (C–O). ^{1}H NMR ($CDCl_3$) δ_H 3.29 (d, 2H, J= 0.6 Hz, 6-H, trans to OCH_3), 3.47 (d, 2H, J=0.6 Hz, 4-H, cis to OCH_3), 3.64 (s, 3H, OCH_3), 3.95 (s, 2H, 2-H), 6.08 (quintet, 1H, J=0.6 Hz, 1′-H). ^{13}C NMR ($CDCl_3$) δ_C 27.7 (4-C), 33.3 (6-C), 33.7 (2-C), 59.8 (OCH_3), 108.1 (5-C), 142.4 (1′-C). *m/z* (EI) 162 (M^+, 100%). Found: C, 44.20; H, 6.19. $C_6H_{10}OS_2$ requires: C, 44.41; H, 6.21.

4.1.2. 1,3-Dithiane-5-methanol (6). Compound **5** (2.03 g, 12.5 mmol) was dissolved in Et_2O (50 mL) and carefully added under nitrogen and magnetic stirring with 48% aqueous tetrafluoroboric acid at 0 °C (12 mL). After removal of the cooling bath, the homogeneous mixture was left 3 h at room temperature, washed with saturated aqueous solution of $NaHCO_3$, then with water and dried (Na_2SO_4). The elimination of the solvent at reduced pressure left a residue of crude aldehyde that was taken up into Et_2O (20 mL) and treated with $NaBH_4$ (0.30 g, 7.9 mmol) in water (4 mL). The two-phase mixture was stirred vigorously for 2 h, the organic layer was separated and the aqueous one extracted with Et_2O (5×5 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated at reduced pressure to afford **6** as an oil that soon crystallized. Recrystallization from Et_2O/pentane at −30 °C gave pure **6** as a white solid (1.52 g, 80.8%). Mp 60–61 °C. IR (KBr) ν_{max} cm^{-1}: 3391 (OH), 1062 (C–O). ^{1}H NMR (CD_3OD) δ_H 2.00 (m, 1H, 5′-H), 2.64 (dd, 2H, J_1=13.9 Hz, J_2=9.5 Hz, 4′-H_{axial}), 2.85–2.90 (m, 2H, 4′-$H_{equatorial}$), 3.56 (d, 2H, J=6.7 Hz, 1-H), 3.60 (dt, 1H, J_1=13.9 Hz, J_2=1.3 Hz, 2′-$H_{equatorial}$), 3.92 (d, 1H, J=13.9 Hz, 2′-H_{axial}). ^{13}C NMR (CD_3OD) δ_C 32.4 (2′-C), 32.6 (4′-C and 6′-C), 39.4 (5′-C), 66.1 (1-C). *m/z* (EI) 150 (M^+, 100%). Found: C, 39.91; H, 6.80. $C_5H_{10}OS_2$ requires: C, 39.97; H, 6.71.

4.2. Synthesis of dithianic ethers 3, 7, 13, 15 and 16

The appropriate solid alcohol **2** or **6** (4 mmol) was added at 0 °C under nitrogen to the suspension of pure NaH (from the commercial 60% dispersion in oil washed with 3×5 mL of dry Et_2O) in dry DMF (9.5 mL) and left to react for 2 h at room temperature. The mixture cooled to 0 °C was treated with the pure alkyl halide (molar ratio, alcohol:NaH:alkyl halide=1:1.2:0.9 unless otherwise stated) and stirred for 20 min at 0 °C and 6 h at room temperature. Water (30 mL) was then added, the organic products were extracted with pentane (3×30 mL), the combined organic layers were washed with water and dried (Na_2SO_4). Removal of the solvent at reduced pressure left a residue, which was

purified by flash-chromatography (petroleum ether/Et_2O 100:5).

4.2.1. 5-Phenylmethoxy-1,3-dithiane (3). Oil, 86.4%. IR (film) ν_{max} cm^{-1}: 1088, 1069 (C–O), 738, 727, 698 (benzene ring). ^1H NMR ($CDCl_3$) δ_H 2.72 (dd, 2H, J_1=13.9 Hz, J_2=10.1 Hz, 4-H_{axial}), 2.90–2.96 (m, 2H, 4-$H_{equatorial}$), 3.30 (dt, 1H, J_1=13.9 Hz, J_2=1.6 Hz, 2-$H_{equatorial}$), 3.72–3.79 (m, 1H, 5-H), 3.82 (d, 1H, J=13.9 Hz, 2-H_{axial}), 4.60 (s, 2H, 1′-H), 7.25–7.38 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 30.9 (2-C), 33.8 (4-C and 6-C), 70.6 (1′-C), 74.1 (5-C), 127.7, 127.9, 128.5 (protonated aromatic carbons), 137.9 (1″-C). *m/z* (EI) 226 (M^+, 31%). Found: C, 58.28; H, 6.19. $C_{11}H_{14}OS_2$ requires: C, 58.37; H, 6.23.

4.2.2. 5-Phenylmethoxymethyl-1,3-dithiane (7). Oil, 85.0%. IR (film) ν_{max} cm^{-1}: 1102 (C–O), 738, 719, 698 (benzene ring). ^1H NMR ($CDCl_3$) δ_H 2.25 (m, 1H, 5-H), 2.66 (dd, 2H, J_1=13.9 Hz, J_2=9.4 Hz, 4-H_{axial}), 2.84–2.91 (m, 2H, 4-$H_{equatorial}$), 3.49 (d, 2H, J=6.4 Hz, 1′-H), 3.55 (dt, 1H, J_1=13.9 Hz, J_2=1.5 Hz, 2-$H_{equatorial}$), 3.85 (d, 1H, J=13.9 Hz, 2-H_{axial}), 4.51 (s, 2H, 1″-H), 7.26–7.38 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 31.9 (2-C), 32.3 (4-C and 6-C), 35.7 (5-C), 73.1 (1′-C and 1″-C), 127.6, 127.7, 128.4 (protonated aromatic carbons), 138.1 (1‴-C). *m/z* (EI) 240 (M^+, 84%). Found: C, 60.07; H, 6.67. $C_{12}H_{16}OS_2$ requires: C, 59.96; H, 6.71.

4.2.3. 5-(3-Phenylpropoxy)methyl-1,3-dithiane (13). Oil, 41.7%. IR (film) ν_{max} cm^{-1}: 1115 (C–O), 747, 719, 700 (benzene ring). ^1H NMR ($CDCl_3$) δ_H 1.91 (m, 2H, 2″-H), 2.23 (m, 1H, 5-H), 2.65 (m, 4H, 4-H_{axial}+3″-H), 2.86 (m, 2H, 4-$H_{equatorial}$), 3.42 (d, 2H, J=6.5 Hz, 1′-H), 3.42 (t, 2H, J=6.3 Hz, 1″-H), 3.58 (dt, 1H, J_1=13.9 Hz, J_2=1.4 Hz, 2-$H_{equatorial}$), 3.85 (d, 1H, J=13.9 Hz, 2-H_{axial}), 7.16–7.30 (m, 5H aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 31.2 (2″-C), 31.9 (2-C), 32.26 (4-C and 6-C), 32.34 (3″-C), 35.6 (5-C), 70.3 (1″-C), 73.7 (1′-C), 125.8, 128.3, 128.5 (protonated aromatic carbons), 141.9 (1‴-C). *m/z* (EI) 268 (M^+, 100%). Found: C, 62.55; H, 7.47. $C_{14}H_{20}OS_2$ requires: C, 62.64; H, 7.51.

4.2.4. 5-(4-Ethenylphenyl)methoxymethyl-1,3-dithiane (15). (From **6**:NaH:(4-ethenylphenyl)chloromethane=1:1.20:1). Mp 62–63 °C (Et_2O/pentane, white solid), 88.9%. IR (KBr) ν_{max} cm^{-1}: 1125, 1109 (C–O), 994, 922 (CH_2=CH), 826 (benzene ring). ^1H NMR ($CDCl_3$) δ_H 2.24 (m, 1H, 5-H), 2.66 (dd, 2H, J_1=13.9 Hz, J_2=9.3 Hz, 4-H_{axial}), 2.84–2.90 (m, 2H, 4-$H_{equatorial}$), 3.48 (d, 2H, J=6.4 Hz, 1′-H), 3.57 (dt, 1H, J_1=13.9 Hz, J_2=1.2 Hz, 2-$H_{equatorial}$), 3.85 (d, 1H, J=13.9 Hz, 2-H_{axial}), 4.50 (s, 2H, 1″-H), 5.24 (dd, 1H, J_1=10.9 Hz, J_2=0.9 Hz, 2⁗-H_{cis}), 5.75 (dd, 1H, J_1=17.6 Hz, J_2=0.9 Hz, 2⁗-H_{trans}), 6.71 (dd, 2H, J_1=17.6 Hz, J_2=10.9 Hz, 1⁗-H), 7.26–7.29 (m, 2H, 2‴-H), 7.38–7.41 (m, 2H, 3‴-H). ^{13}C NMR ($CDCl_3$) δ_C 31.9 (2-C), 32.2 (4-C and 6-C), 35.7 (5-C), 72.9 (1″-C), 73.1 (1′-C), 113.9 (2⁗-C), 126.3 (3‴-C and 5‴-C), 127.8 (2‴-C and 6‴-C), 136.5 (1⁗-C), 137.1, 137.7 (quaternary aromatic carbons). Found: C, 63.21; H, 6.90. $C_{14}H_{18}OS_2$ requires: C, 63.11; H, 6.81.

4.2.5. 5-(4-(4-Ethenylphenyl)butoxy)methyl-1,3-dithiane (16). (From **6**:NaH:1-bromo-4-(4-ethenylphenyl)butane=1:1.4:1.4). Oil, 40.8%. IR (film) ν_{max} cm^{-1} 1118 (C–O), 991, 906 (CH_2=CH), 843 (benzene ring). ^1H NMR ($CDCl_3$) δ_H 1.57–1.71 (m, 4H, 2″-H and 3″-H), 2.18 (m, 1H, 5-H), 2.61 (t, 2H, J=7.4 Hz, 4″-H), 2.62 (dd, 2H, J_1=13.9 Hz, J_2=9.2 Hz, 4-H_{axial}), 2.84 (m, 2H, 4-$H_{equatorial}$), 3.40 (d, 2H, J=6.5 Hz, 1′-H), 3.42 (t, 2H, J=6.2 Hz, 1‴-H), 3.56 (dt, 1H, J_1=13.9 Hz, J_2=1.4 Hz, 2-$H_{equatorial}$), 3.84 (d, 1H, J=13.9 Hz, 2-H_{axial}), 5.18 (dd, 1H, J_1=10.9 Hz, J_2=1.0 Hz, 2⁗-H_{cis}), 5.69 (dd, 1H, J_1=17.6 Hz, J_2=1.0 Hz, 2⁗-H_{trans}), 6.69 (dd, 1H, J_1=17.6 Hz, J_2=10.9 Hz, 1⁗-H), 7.11–7.14 (m, 2H, 2‴-H), 7.31–7.34 (m, 2H, 3‴-H). ^{13}C NMR ($CDCl_3$) δ_C 27.9 (3″-C), 29.2 (2″-C), 31.9 (2-C), 32.2 (4-C and 6-C), 35.4 (4″-C), 35.6 (5-C), 71.0 (1‴-C), 73.7 (1′-C), 112.9 (2⁗-C), 126.2 (3‴-C and 5‴-C), 128.6 (2‴-C and 6‴-C), 135.2 (quaternary aromatic carbon), 136.7 (1⁗-C), 142.1 (quaternary aromatic carbon). Found: C, 66.26; H, 7.89. $C_{17}H_{24}OS_2$ requires: C, 66.18; H, 7.84.

4.3. Deuteration of dithianic ethers 3, 7 and 13

A 0.1 M solution of the proper ether **3**, **7** or **13** in dry THF (1.3 mmol) was treated under stirring with a 1.6 M hexane solution of *n*-butyllithium in the molar ratio 1:1.3 at −30 °C under nitrogen. The homogenous solution was stirred 40 min at −30 to −35 °C, then quenched with methanol-*d* (0.5 mL) and treated with saturated ammonium chloride (0.5 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (2×20 mL). The combined organic layers were dried (Na_2SO_4), evaporated and submitted to flash-chromatography (petroleum ether/Et_2O 100:5) to obtain the products **4**, **8** or **14**. After the recovery of the product **8**, the column, further eluted with Et_2O/methanol 100:5, afforded **9**, which was purified through a second flash-chromatography (petroleum ether/Et_2O 3:1) giving an oily product whose ^1H and ^{13}C NMR data in $CDCl_3$ were coincident with those of the non-deuterated derivative **12**, with the exception of the absence of the signal of 2′-$H_{equatorial}$ and the following variations concerning axial proton and carbon in the position 2′ δ_H 3.76 (br s); δ_C 31.4 (t, J_{13C-D}=22 Hz).

4.4. 2-(1,3-Dithian-5-yl)-1-phenylethanone (11)

Alcohol **6** (0.366 g, 2.44 mmol) was dissolved in dry pyridine (2 mL) and treated at −10 °C with benzenesulfonyl chloride (0.38 mL, 2.98 mmol). The mixture was stirred at −10 °C for 4 h, then treated with cold 2 M H_2SO_4 (50 mL) and ethyl acetate (20 mL). The organic layer was separated, washed with 2 M H_2SO_4, then three times with water and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue crystallized from absolute ethanol to afford the benzenesulfonate ester **10** as white needles (0.503 g, 71.1%. Mp 71–72 °C. IR (KBr) ν_{max} cm^{-1}: 1353, 1339, 1184, 1176 (S–O), 754, 744, 684 (benzene ring). Found C, 44.70; H, 4.80. $C_{11}H_{14}O_3S_3$ requires: C, 44.49; H, 4.86). A solution of diisopropylamine (0.27 mL, 1.93 mmol) in anhydrous THF (2 mL) was treated with a 1.66 M hexane solution of *n*-butyllithium (1.2 mL, 1.99 mmol) at −75 °C under nitrogen, stirred at the same temperature for 10 min and added with benzaldehyde *O*-trimethylsilyl cyanohydrin (0.398 g, 1.94 mmol) in dry THF (0.5 mL). The thick yellow suspension immediately formed after 10 min was treated with the solution of **10** (0.401 g,

1.38 mmol) in dry THF (0.5 mL). Stirring was continued 2 h at −60 °C, then the temperature was left to rise in 2 h from −60 to 0 °C. The orange solution was treated with 1 M HCl (20 mL) and methanol (10 mL), stirred overnight at room temperature and extracted with Et_2O (3×20 mL). The combined organic layers were washed twice with 1 M aqueous NaOH, three times with water and dried (Na_2SO_4). After elimination of the solvent at reduced pressure the residue, purified by flash-chromatography (petroleum ether/ethyl acetate 4:1), afforded the ketone **11** (0.281 g, 85.3%). Mp 137–138 °C (ethanol, white leaflets). IR (KBr) ν_{max} cm^{-1}: 1682 (C=O), 750, 734, 689 (benzene ring). ^1H NMR (DMSO-d_6) δ_H 2.45 (m, 1H, 5′-H), 2.70 (dd, 1H, J_1= 13.7 Hz, J_2=8.6 Hz, 4′-H_{axial}), 2.89 (ddd, 2H, J_1=13.7 Hz, J_2=2.7 Hz, J_3=1.0 Hz, 4′-$H_{equatorial}$), 3.25 (d, 2H, J= 6.5 Hz, 2′-H), 3.74 (dt, 1H, J_1=13.6 Hz, J_2=1.0 Hz, 2′-$H_{equatorial}$), 3.87 (d, 1H, J=13.6 Hz, 2′-H_{axial}), 7.51–8.00 (m, 5H, aromatic protons). ^{13}C NMR (DMSO-d_6) δ_C 30.3 (2′-C), 30.4 (5′-C), 33.5 (4′-C and 6′-C), 42.4 (2-C), 127.8 (3″-C and 5″-C), 128.7 (2″-C and 6″-C), 133.2 (4″-C), 136.7 (1″-C), 198.5 (CO). *m/z* (EI) 238 (M^+, 68%). Found C, 60.38; H, 6.01. $C_{12}H_{14}OS_2$ requires: C, 60.46; H, 5.92.

4.5. 2-(1,3-Dithian-5-yl)-1-phenylethanol (12)

Ketone **11** (0.063 g, 0.26 mmol) in THF (3 mL) was added to $NaBH_4$ (0.058 g, 1.5 mmol) in water (0.4 mL), then the mixture was vigorously stirred for 3 h and extracted with Et_2O (3×5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure to afford **12** (quantitative yield). Mp 72–74 °C (Et_2O/pentane at −30 °C, white solid). IR (KBr) ν_{max} cm^{-1}: 3548 (OH), 1059 (C–O), 754, 738, 699 (benzene ring). ^1H NMR ($CDCl_3$) δ_H 1.80–1.95 (m, 2H, 2-H), 2.10 (br s, 1H, OH), 2.15 (m, 1H, 5′-H), 2.54–2.65 (m, 2H, 6′-H and 4′-H), 2.84–2.93 (m, 2H, 6′-H and 4′-H), 3.58 (dt, 1H, J_1=13.8 Hz, J_2= 1.5 Hz, 2′-$H_{equatorial}$), 3.76 (d, 1H, J=13.8 Hz, 2′-H_{axial}), 4.78 (br m, 1H, 1-H), 7.26–7.36 (m, 5H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ_C 31.6 (2′-C), 31.7 (5′-C), 34.7 (4′-C or 6′-C), 35.7 (4′-C or 6′-C), 44.0 (2-C), 71.9 (1-C), 125.7, 127.8, 128.7 (protonated aromatic carbons), 144.5 (1″-C). Found C, 59.89; H, 6.66. $C_{12}H_{16}OS_2$ requires: C, 59.96; H, 6.71.

4.6. Copolymers $P1_{15}$ and $P1_{16}$

Monomer **15** or **16** and styrene (molar ratio 1:9 and 1:19) together with the calculated volume of deoxygenated dioxane to give 8.5 M solutions and AIBN (2% weight of the monomers) were introduced in a vial with a side arm and subjected to three freeze-pump-thaw cycles at −78 °C. After sealing and stirring the vial containing the homogenous solution was heated at 60 °C in a thermostatic bath for 72 h. The cooled viscous clear content of the vial was diluted with dioxane (5 mL per g of monomer charge) and slowly poured with vigorous stirring into methanol (15 times the volume of the dioxane solution). The powdery precipitate was filtered, washed with methanol and dried under vacuum at room temperature up to constant weight. Yields were always greater then 95% of the mass of the used monomers.

4.7. Copolymers $P3_{15}$ and $P3_{16}$

A solution of $\mathbf{P1_{15}}$ or $\mathbf{P1_{16}}$ in anhydrous THF (1.2 mmol of 1,3-dithiane units at 0.1 M concentration) mechanically stirred at −40 °C under nitrogen was treated with a 1.6 M solution of *n*-butyllithium in hexane and further stirred at −30 to −35 °C for 1 h, during which a marked increase of the viscosity was observed owing to the formation of **P2**. The mixture was treated with 1-bromo-4-phenylbutane (1,3-dithiane units:*n*-buthyllitium:1-bromo-4-phenylbutane= 1:1.25:1.50), stirred for 2 h while the temperature was left slowly to rise from −30 to −15 °C, then it was kept at −10 °C overnight. Water (50 mL) and dichloromethane (100 mL) were added and the layers allowed slowly to separate. The organic layer was cautiously removed, while the insoluble portion of cross-linked **P3** remained floating between the two phases, then additional extractions with dichloromethane (2×100 mL) were performed using the same precautions. The combined organic layers were washed with water, dried (Na_2SO_4) and the solvent was removed at reduced pressure. The crumbly residue of **P3** was taken up in the appropriate solvent [(toluene for $\mathbf{P3_{15(1:9)}}$ (0.10 g mL^{-1}) and $\mathbf{P3_{15(1:19)}}$ (0.14 g mL^{-1}); dioxane for $\mathbf{P3_{16(1:9)}}$ (0.08 g mL^{-1}) and $\mathbf{P3_{16(1:19)}}$ (0.16 g mL^{-1})] and slowly poured into methanol (20 times the volume of the solution). The powdery precipitate of **P3** was filtered, washed with methanol and pump-dried at room temperature to constant weight. From the remaining mixture of aqueous phase and cross-linked **P3** any residual dichloromethane was eliminated in vacuo, the insoluble material was filtered, washed thoroughly with water and methanol then pump-dried at room temperature to constant weight.

4.8. Reaction of P3 with mercury(II) perchlorate hydrate

A THF solution of polymer **P3** (0.55 mmol of 2-alkylated 1,3-dithiane units at 0.2 M concentration) was treated under nitrogen and magnetic stirring with a solution of mercury(II) perchlorate hydrate (1,3-dithiane units:mercury ions= 1:2.5, considering a minimum content of 42% metal in the used reagent) in THF (15 mL). The mixture was stirred 1 h at room temperature then $NaHCO_3$ (0.75 g, 8.9 mmol) was added in the minimum amount of water. Stirring was continued for 5 min, flash-chromatography silica gel (5 g) was added and most of the solvent removed at in vacuo. The obtained coarse powder was charged on a flash-chromatography column packed with pentane/Et_2O 100:5 (20 g of silica gel in a 20 mm diameter column) and **17a** was eluted with this eluent.

4.9. Reaction of P3 with periodic acid

A weighted amount of polymer **P3** (corresponding to 0.45 mmol of 2-alkylated 1,3-dithiane units) was dissolved in THF (4.5 mL) under nitrogen and magnetic stirring at 0 °C, and treated with a 0.40 M solution of periodic acid in THF (3.4 mL, 1.36 mmol). The cooling bath was removed and stirring continued at room temperature for 2 h. Et_2O (50 mL) was carefully added, the organic solution separated, washed with 1.6 M sodium sulfite solution, then with water and dried (Na_2SO_4). After removal of the solvent the flash-chromatography of the residue (pentane/acetone

100:5) afforded a mixture of **17a**[15] and **18** whose NMR spectra in $CDCl_3$ allowed to assign the following signals: ^{1}H NMR δ_H 4.38 (m, 1H, 2-H); 9.22 (d, 1H, $J=2.9$ Hz, 1-H). ^{13}C NMR δ_C 191.5 (1-C).

4.10. Resins R1

NaH (6.0 mmol, from a corresponding amount of a commercial 60% dispersion in mineral oil washed with 3×10 mL of dry Et_2O) was suspended under nitrogen in dry DMF (15 mL) and treated under magnetic stirring with **6** (0.820 g, 5.45 mmol). The mixture was further stirred for 3 h at room temperature, then added with the proper amount (corresponding to 3.60 mmol of chloromethyl groups) of resin **R0** and diluted with 15 mL of anhydrous DMF. After stirring for additional 6 h in an oil bath at 50 °C, the resin was filtered, washed with peroxide-free THF and extracted under magnetical stirring for 1 h with the same solvent (50 mL). After filtration, the washing with THF was repeated, then the resin was filtered and washed in turn with peroxide-free THF, methanol, water and again methanol. The collected resin was pump-dried at room temperature to constant weight: more than 97% of the expected amount of **R1** was always recovered.

4.11. Resins R3

Resin **R1** (an amount corresponding to 1.4 mmol of 1,3-dithiane units) was suspended under nitrogen in the minimum amount of anhydrous THF necessary to give an easy to stir slurry (0.13 g resin mL^{-1}), cooled to −60 °C and added with a 1.6 M solution of *n*-butyllithium in hexane. The temperature was raised rapidly to −35 °C and the suspension of the beads, which turned deep red owing to their transformation into **R2**, was magnetically stirred at −35 to −30 °C for 2 h. The pure alkyl halide (1-bromo-4-phenylbutane, or 1-bromononane, or 1-bromodecane) was then added (1,3-dithiane units:*n*-butyllithium:alkyl halide = 1:1.25:1.50), the temperature was left to rise to −15 °C in 1 h and the reaction mixture kept at −10 °C overnight. The pale yellow resin **R3** was filtered, washed with peroxide-free THF and magnetically stirred for 1 h with the same solvent. After filtration, this treatment was repeated once again and finally **R3** was filtered, washed in turn with peroxide-free THF, methanol, water, methanol and pump-dried at room temperature to constant weight.

4.12. Aldehydes 17a–c from resins R3

Resin **R3** (an amount corresponding to 0.4 mmol of 2-alkylated 1,3-dithiane units) was suspended in peroxide-free THF (0.27 g mL^{-1}) under nitrogen and added with a 0.5 M THF solution of mercury(II) perchlorate hydrate (1,3-dithiane units:mercury ions = 1:3, calculated on the basis of a 42% metal content in the salt). The mixture was stirred for 1 h at room temperature, then it was treated with a saturated aqueous solution of $NaHCO_3$ (1 mL). The heterogeneous mixture was extracted with Et_2O (5×5 mL), the organic layers were combined, the solvent was eliminated at reduced pressure and aldehydes **17a–c** were recovered from the residue by flash-chromatography (petroleum ether/Et_2O 100:5).

4.13. Determination of the chlorine loading in Merrifield resins R0

A weighted sample of **R0** (1 g) was suspended under nitrogen in dry DMF (12 mL) and added with solid sodium methoxide (CH_2Cl units:methoxide ion = 1:2.5). The mixture was stirred 6 h at 50 °C, then the resin was filtered and accurately washed with water (150 mL in small portions). The aqueous filtrate was made strongly acidic with 65% nitric acid (1 mL) and briefly boiled. After cooling, the chloride ions were determined according to Volhard procedure, correcting for a blank titration without resin sample.

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Diterpenoids from *Coprinus heptemerus*

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Abstract—Seven diterpenoids, isolated due to their ability to inhibit spore germination in the plant pathogenic fungus *Magnaporthe grisea*, were obtained from cultures of the basidiomycete *Coprinus heptemerus*. The structures of the compounds, named heptemerones A–G, were determined with spectroscopic techniques.

1. Introduction

The fungal plant pathogen *Magnaporthe grisea* is the infective agent causing the rice blast disease, which is an important menace in rice cultivating countries.[1] During a screening of fungal extracts for metabolites with activity against *M. grisea*, extracts of *Coprinus heptemerus* were found to inhibit germination of the conidia without interfering with mycelial growth.[2] The possibility to neutralize the pathogen by inhibiting the infection and not using traditional fungicides has the potential of being more selective and more environmentally safe, and the active principles were consequently isolated and characterised. Bioassay-guided fractionation yielded seven metabolites, all being new diterpenoids of which six are heterocyclic with either a furan or dihydrofuran ring. We propose the names heptemerones A–G for the new metabolites. Six of the isolated metabolites share their carbon skeleton with the guanacastepenes A–O, that recently were reported as metabolites of an unidentified endophytic fungus growing on the *Daphnopsis americana* tree in Costa Rica,[3,4] while the seventh has a secoguanacastepene skeleton with the C-1/C-14 bond broken. The structural diversity displayed by the guanacastepenes and their antibiotic activity[5] has attracted the interest of synthetic chemists, and an approach to a total synthesis was recently published.[6] In this paper, we report the isolation and the structure determination of the new metabolites, while their production and biological properties are reported elsewhere.[2]

Keywords: *Coprinus heptemerus*; Diterpenoids; Guanacastepene; Seco-guanacastepene; Inhibitors of conidial germination; Structure determination.
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2. Results and discussion

The structures of heptemerones A–G are shown in Figure 1, and the 1D NMR of the compounds are presented in Tables 1 and 2. The elucidation of the structures is based on high-resolution mass spectrometry and 2D NMR spectroscopy. The structures of the guanacastepenes were determined by X-ray crystallography, which allowed the determination of the absolute configuration of guanacastepenes E and L as their *p*-bromobenzoyl derivatives.[3,4] Although only the relative configurations were determined for the compounds reported here, the heptemerones A–G are shown with the same C-8 and C-11 configuration (the same carbon numbering system as reported for the guanacastepenes[3,4] is used, see Fig. 1). High resolution FABMS experiments suggested that heptemerone A (**1**) had the elemental composition $C_{25}H_{34}O_8$, and this was confirmed by the presence of 25 signals in the ^{13}C NMR spectrum and signals integrating for 34 protons in the ^{1}H NMR spectrum. Consequently, **1** has an unsaturation index of 9, and as the NMR data suggested the presence of four carbonyl groups and two carbon–carbon double bonds the compound should consist of three rings. The carbonyls were one ketone, one methyl ester, and two acetoxy groups. There were three isolated COSY spin systems, 5-H/6-H_2/7-H_2, 9-H_2/10-H_2 and 13-H/12-H/18-H/19(20)H_3, and these could be put together by the HMBC correlations from 16-H_3 (to C-3, C-7, C-8 and C-9) and from 17-H_3 (to C-1, C-10, C-11 and C-12). HMBC correlations from 5-H and 13-H to the corresponding acetoxy carbonyl group placed the acetoxy groups on C-5 and C-13, while HMBC correlations from 13-H as well as the methoxy protons revealed that C-14 is the ester carbonyl group. 5-H gives HMBC correlations also to C-3, C-4 and C-15, showing that the two carbon–carbon

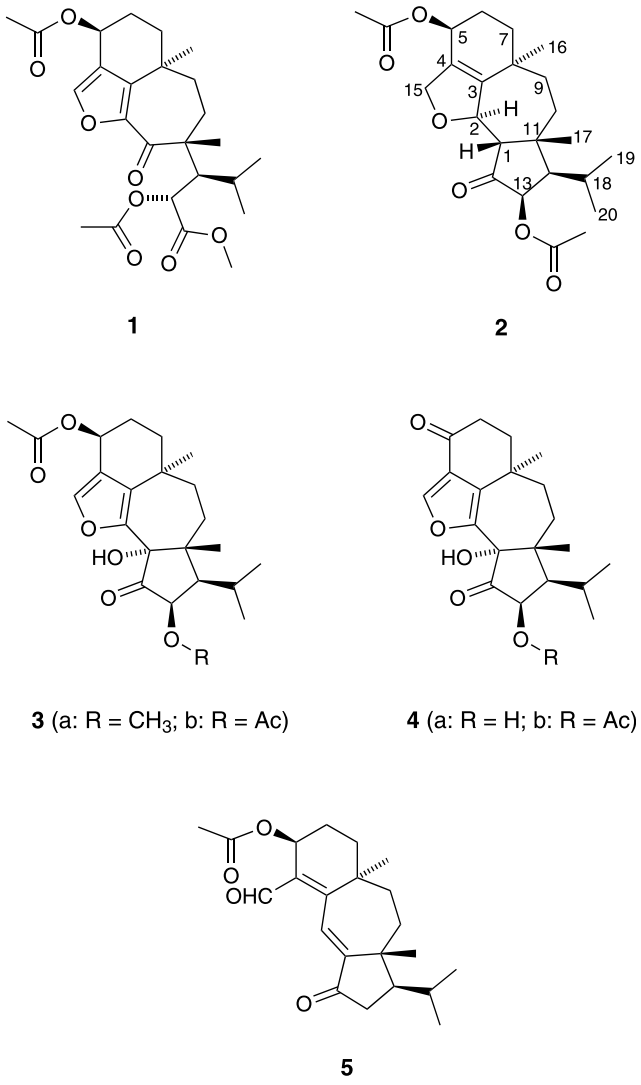

Figure 1.

double bonds are conjugated and closing the six-membered ring. All carbon atoms are now in place, and only C-1, C-2 (twice) and C-15 need to make additional bonds. One oxygen must also be inserted, and by closing the C-1/C-2 bond and thereby forming the seven-membered ring the only remaining alternative for the structure of heptemerone A is a oxygen bridge between C-2 and C-15. 15-H gives HMBC correlations to C-2, C-3 and C-4, but not to C-1, and the chemical shifts are in accordance with a furan ring conjugated with a ketone. In addition, the $^{1}J_{(C,H)}$ coupling constant for 15-H/C-15 is 205 Hz, which is expected for this position. The relative configuration of **1** was suggested by NOESY experiments (see Fig. 2). 16-H_3 correlate strongly with 6-Ha and 10-Ha while 17-H_3 correlate with 9-Ha and 10-Hb, indicating that the two methyl groups are on opposite sides of the molecule. As the J_{9a-10a} is 12.2 Hz, the two protons should have a dihedral angle of close to 0 or 180°, and the study of a Dreiding molecular model of the suggested stereostructure shows that it is almost 180°. Similarly, J_{6a-7a} is 14.4 Hz, and while 6-Ha is on the same side as 16-H_3, 7-Ha must be on the same side as 17-H_3. A NOESY correlation is consequently observed between 7-Ha and 9-Ha. 5-H, which gives NOESY correlations to 15-H, 6-Ha and 6-Hb, should be in the equatorial position, as judged by the small ^{1}H–^{1}H coupling constants observed. The lack of NOESY correlation between 16-H_3 and 5-H is thereby explainable. 18-H gives a strong NOESY correlation to 10-Ha, showing that the isopropyl group is positioned under the molecule, while 12-H is correlating to 17-H_3 and, weakly, to 10-Hb. 13-H, which gives a small ^{1}H–^{1}H coupling constant to 12-H and therefore should be nearly perpendicular to it, gives NOESY correlations to 12-H as well as to 19(20)-H_3, and although it is difficult to determine the relative configuration of this part of the molecule based on these observations, they do nevertheless support the structure for **1** shown in Figure 1.

While heptemerone B (**2**) only contains three carbonyl groups, as one ketone and two acetoxy groups, and one carbon–carbon double bond, the unsaturation index (8) given by the elemental composition determined by HRMS experiments ($C_{24}H_{34}O_6$) shows that it must contain an additional ring. Starting with the six-membered ring, this could be closed by a combination of the proton spin system 5-H/6-H_2/7-H_2, and the HMBC correlations from 16-H_3 to C-3, C-7, C-8 and C-9 as well as from 5-H to C-3, C-4 and C-15. The single carbon–carbon double bond is therefore part of this ring. Continuing with the seven-membered ring, this could be established by following the correlations from C-9 to C-10 (COSY correlations), to C-11 (HMBC correlations from 17-H_3 to C-1, C-10, C-11 and C-12), to C-1, and to C-2 (J_{1-2}=10.4 Hz). The HMBC correlations from 1-H to C-3 and from 2-H to C-3 and C-4 proves the connection between C-2 and C-3 and closes the ring. At 9.4 Hz, the ^{1}H–^{1}H coupling constant between 12-H and 13-H is large, and COSY as well as HMBC correlations show that the isopropyl group is attached to C-12. Both 1-H and 13-H give HMBC correlations to C-14, and the fact that 1-H also gives a clear HMBC correlation to C-13 closes the five-membered ring. The acetoxy groups can be positioned on C-5 and C-13, as discussed above. This leaves one oxygen atom and one ring to be accommodated, and the chemical shifts as well as COSY and HMBC correlations demonstrate that C-2 and C-15 are part of a dihydrofuran ring. The relative configuration of **2** in the index six/seven-ring system follows a similar reasoning as above, with NOESY correlations from 16-H_3 to 6-Ha and 10-Hb (see Fig. 2), although the signals for 9-Ha and 9-Hb overlapped in $CDCl_3$ and the corresponding correlation from 17-H_3 to the β-proton of C-9 was not observed. Nevertheless, the strong NOESY correlation between 10-Hb, which is axial and on the same side as 16-H_3, and 12-H, demonstrates the configuration of not only C-11 but also C-12 as shown in Figure 1. NOESY correlations between 1-H and 17-H_3 as well as between 2-H and 16-H_3 take care of both these stereocentre. Again, the small ^{1}H–^{1}H coupling constants for 5-H (not resolved but obviously small) and the observation that the 5-H gives NOESY correlations to both C-6 protons as well as to both C-15 protons reveal that it is equatorial and positioned on the same side of the molecule as 16-H_3.

For the furans heptemerone C (**3a**) and heptemerone D (**3b**), HRMS experiments suggested the elemental compositions $C_{23}H_{32}O_6$ and $C_{24}H_{32}O_7$ corresponding to the unsaturation

Table 1. ^{1}H (500 MHz) NMR data (δ; multiplicity; J) for heptemerones A (**1**), B (**2**), C (**3a**), D (**3b**), E (**4a**), F (**4b**) and G (**5**)

	1	**2**
H		
1	—	2.20; d, 10.4
2	—	4.99; dddd; 1.7, 1.7, 5.0, 10.4
5	5.82; ddd; 0.6, 1.2, 5.0	5.27; m
6a	2.26; dddd; 3.7, 5.0, 14.4, 15.4	2.00; m
6b	1.99; dddd; 1.2, 3.3, 3.4, 15.4	1.86; dddd; 1.4, 3.3, 3.4, 15.2
7a	1.82; ddd; 3.3, 13.4, 14.4	1.57; ddd; 3.1, 13.3, 14.5
7b	1.53; ddd; 3.4, 3.4, 13.4	1.43; m
9a	2.13; ddd; 1.7, 12.2, 14.4	1.43; m
9b	1.72; ddd; 1.3, 7.1, 14.4	1.43; m
10a	2.49; ddd; 1.3, 12.2, 15.3	1.92; ddd; 1.7, 7.2, 14.8
10b	2.43; ddd; 1.7, 7.1, 15.3	1.81; ddd; 1.9, 10.4, 14.8
12	3.37; dd; 1.2, 3.7	2.14; dd; 9.4, 10.8
13	5.50; d; 1.2	5.68; d; 9.4
15a	7.63; d; 0.6	4.59; dd; 5.0, 12.4
15b	—	4.43; dd; 1.0, 1.7; 12.4
16	1.21; s	1.06; s
17	1.17; s	1.03; s
18	1.78; dqq; 3.7, 6.7, 6.7	1.98; m
19	1.04; d; 6.7	0.90; d; 6.5
20	0.98; d; 6.7	1.07; d; 6.6
5-Ac	2.05; s	2.04; s
13-Ac	2.19; s	2.14; s
14-OMe	3.75; s	—

	3a	**3b**
H		
5	5.77; dd; 1.9, 3.8	5.76; ddd; 0.6, 1.8, 3.8
6a	2.01; m	2.03; m
6b	1.91; dddd; 1.9, 2.9, 3.7, 15.0	1.92; m
7a	1.75; ddd; 2.9, 13.4, 13.9	1.75; ddd; 2.6, 13.5, 13.8
7b	1.41; ddd; 3.1, 3.7, 13.9	1.42; ddd; 2.9, 3.5, 13.5
9a	1.83; ddd; 2.3, 12.8, 14.2	1.83; ddd; 1.7, 13.6, 14.4
9b	1.45; ddd; 1.8, 5.8, 14.2	1.48; ddd; 2.0, 5.9, 14.4
10a	2.52; ddd; 1.8, 12.8, 15.1	2.59; ddd; 2.0, 13.6, 14.8
10b	2.01; m	2.04; m
12	2.12; dd; 8.0, 10.6	2.36; dd; 9.1, 10.4
13	3.85; d; 8.0	5.92; d; 9.1
15	7.42; s	7.41; d; 0.6
16	1.29; s	1.29; s
17	0.88; s	0.85; s
18	2.08; m	1.94; m
19	1.01; d; 6.5	0.90; d; 6.4
20	1.08; d; 6.5	1.10; d; 6.6
5-Ac	2.02; s	2.00; s
13-Ac	—	2.14; s
13-OMe	3.65; s	—

	4a	**4b**	**5**
H			
2	—	—	7.23; s
5	—	—	5.61; s
6a	2.67; ddd; 4.9, 14.6, 17.9	2.69; ddd; 4.9, 14.6, 17.8	1.83; m
6b	2.48; ddd; 2.5, 3.8, 17.9	2.47; ddd; 2.5, 3.8, 17.8	1.83; m
7a	1.96; ddd; 3.8, 13.5, 14.6	1.96; m	1.81; m
7b	1.78; ddd; 2.5, 4.9, 13.5	1.78; ddd; 2.5, 4.9, 13.6	1.38; m
9a	1.87; ddd; 1.2, 13.6, 14.5	1.87; ddd; 1.3, 13.8, 14.5	1.77; m
9b	1.54; ddd; 1.7, 6.0, 14.5	1.56; ddd; 1.8, 6.1, 14.5	1.59; ddd; 1.6, 8.6, 14.2
10a	2.61; ddd; 1.7, 13.6, 14.8	2.61; ddd; 1.8, 13.8, 14.8	1.99; ddd; 2.3, 11.3, 12.2
10b	2.06; m	2.07; m	1.73; m
12	2.23; dd; 8.8, 10.7	2.40; dd; 9.3, 10.3	1.75; m
13	5.56; d; 8.8	5.90; d; 9.3	2.40; dd; 7.6, 18.5
13b	—	—	2.22; dd; 12.8, 18.5
15	7.96; s	7.94; s	9.73; s
16	1.39; s	1.41; s	1.06; s
17	0.88; s	0.88; s	1.02; s
18	2.09; m	1.94; m	1.82; m
19	1.14; d; 6.4	0.90; d; 6.4	1.01; d; 6.5
20	1.10; d; 6.6	1.11; d; 6.6	0.91; d; 6.5
5-Ac	—	—	1.93; s
13-Ac	—	2.15; s	—

The spectra were recorded in $CDCl_3$ (compounds **1**, **2**, **3a**, **3b**, **4a** and **4b**) and DMSO-d_6 at 100 °C (compound **5**) and the solvent signals (7.26 and 2.50 ppm, respectively) were used as reference. The coupling constants J are given in Hz.

Table 2. ^{13}C (125 MHz) NMR data (δ; multiplicity) for heptemerones A (**1**), B (**2**), C (**3a**), D (**3b**), E (**4a**), F (**4b**) and G (**5**)

	1	2	3a	3b	4a	4b	5
C							
1	193.9; s	66.4; d	79.7; s	79.3; s	79.6; s	79.1; s	149.5; s
2	145.4; s	80.6; d	146.5; s	145.7; s	147.9; s	147.7; s	125.5; d
3	137.1; s	147.0; s	128.7; s	129.0; s	131.4; s	131.4; s	161.1; s
4	121.8; s	128.2; s	120.9; s	120.8; s	123.3; s	123.2; s	133.2; s
5	62.4; d	63.6; d	63.0; d	63.0; d	194.9; d	195.2; d	63.0; d
6	25.4; t	25.5; t	25.7; t	25.6; t	35.8; t	35.8; t	23.3; t
7	33.5; t	34.3; t	34.8; t	34.6; s	39.3; t	39.4; t	31.4; t
8	33.6; s	33.7; s	32.2; s	32.2; s	32.3; s	32.3; s	38.4; s
9	35.8; t	35.7; t	36.8; t	36.7; t	36.3; t	36.5; i	35.9; t
10	26.5; t	33.8; t	27.8; t	27.5; t	26.7; t	26.6; t	32.2; t
11	54.6; s	43.8; s	46.4; s	46.8; s	46.5; s	46.5; s	45.9; s
12	26.8; d	55.9; d	52.1; d	50.2; d	51.6; d	50.2; d	48.1; d
13	71.4; d	73.2; d	80.1; d	72.7; d	72.0; d	72.6; d	39.4; t
14	171.9; s	210.4; s	208.8; s	204.1; s	210.4; s	203.8; s	202.9; s
15	146.5; d	74.7; t	141.0; d	141.4; d	143.9; d	143.9; d	189.9; d
16	26.8; q	22.8; q	25.6; q	25.5; q	24.4; q	24.2; q	24.4; q
17	24.1; q	22.1; q	15.7; q	15.2; q	15.4; q	15.1; q	19.6; q
18	29.7; d	25.6; d	25.2; d	25.6; d	25.4; d	25.6; d	27.0; d
19	24.2; q	23.3; q	23.9; q	23.7; q	24.4; q	23.7; q	23.2; q
20	20.3; q	22.7; q	23.3; q	23.2; q	23.3; q	23.2; q	21.1; q
5-OAc	170.7; s	170.7; s	170.7; s	170.7; s	—	—	168.7; s
	21.3; q	21.2; q	21.4; q	21.4; q	—	—	20.1; q
13-OAc	169.8; s	169.7; s	—	170.1; s	—	170.2; s	—
	20.9; q	20.7; q	—	20.8; q	—	20.8; q	—
13-OMe	—	—	60.3; q	—	—	—	—
14-OMe	52.4; q	—	—	—	—	—	—

The spectra were recorded in $CDCl_3$ (compounds **1**, **2**, **3a**, **3b**, **4a** and **4b**) and DMSO-d_6 at 100 °C (compound **5**) and the solvent signals (77.00 and 39.51 ppm, respectively) were used as reference. The multiplicities of the carbon signals were determined indirectly from HMQC experiments.

indexes 8 and 9, respectively. As **3b** contains one additional acetoxy group in addition to the keto function, the two carbon–carbon double bonds and the acetoxy group of **3a**, both **3a** and **3b** should consist of four rings. The spectroscopic evidence suggest that the northern, eastern and southern sides of **3a** and **3b** are very similar to those of heptemerone B (**2**) discussed above. The HMBC correlation from 17-H_3 revealed that C-1 is a tertiary alcohol, and the correlations from 13-H to both C-1 and C-14 close the five-membered ring and position the keto function on C-14. As with heptemerone A (**1**), the HMBC correlations from 5-H to C-3, C-4 and C-15 close the six-membered ring and show that the two carbon–carbon double bonds are conjugated. 15-H gives a HMBC correlation to C-2, but not to C-1, and the only way to put the structure together is with a furan ring as in **1**. The differences in the chemical shifts observed for **3a/3b** on the one hand and **1** on the other, can be explained by the fact that the furan in **1** is conjugated with the C-1 keto function. For **3a**, the presence of a methoxy group at C-13 is shown by the HMBC correlations from the methoxy protons to C-13 and from 13-H to the methoxy carbon, while the presence of an acetoxy substituent on C-13 in **3b** is shown by the HMBC correlations of 13-H and the acetoxy protons to the acetoxy carbonyl carbon. The determination of the relative configuration of **3a** and **3b** follows the same reasoning as for heptemerone B (**2**), and the corresponding NOESY correlations were also observed with **3a/3b** (see Fig. 2). The configuration of C-1 in **3a** was indicated by the NOESY correlation observed between 13-H and the 1-OH proton, appearing as a singlet at 2.43 ppm in the ^1H NMR spectra. This proton was not visible in the spectra of **3b** in $CDCl_3$, but the similarities between the relevant chemical shift in the two compounds support that they share the C-1 configuration. In addition, the opposite C-1 configuration in **3a** or **3b** would completely change the folding of the seven-membered ring and preclude the NOESY correlations observed between 17-H_3 and the axial 9-Ha.

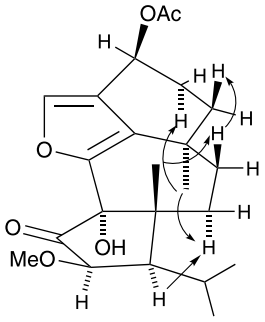

Figure 2. The general NOESY correlations that determine the relative configuration of the heptemerones. See the text for a detailed discussion of each compound.

Heptemerone E (**4a**) has the elemental composition $C_{20}H_{26}O_5$ and with two keto groups and two carbon–carbon double bonds the unsaturation index of 8 is fulfilled with four rings. HMBC correlations from 6-H_2 to C-4 and C-5, and from 15-H to C-2, C-3, C-4 and C-5, show that C-5 has been oxidised to a keto function that is conjugated with the furan ring. As discussed above, COSY correlations between 6-H_2 and 7-H_2 and HMBC correlations from 16-H_3 to C-3, C-7, C-8 and C-9 close the six-membered ring, and COSY correlations between 9-H_2 and 10-H_2 as well as HMBC correlations from 17-H_3 to C-1, C-10, C-11 and C-12 brings us to the third ^1H–^1H spin system consisting of 13-H, 12-H, 18-H and 19(20)-H_3. The HMBC correlations from 13-H to C-14 as well as C-1 close the five-membered ring. The $^1J_{(C,H)}$ coupling constant for 15-H/C-15 is 207 Hz, typical of

a furan system, and the remaining bond to close the seven-membered ring is the C-1/C-2 bond. Heptemerone F (**4b**) is simply the acetelylated derivative of **4a**, and the determination of its structure was made with the corresponding data as discussed above. The HMBC correlations between 13-H and the acetoxy protons to the acetoxy carbonyl carbon placed the acetoxy group on C-13. The relative configurations of C-8, C-11, C-12 and C-13 were determined with the NOESY correlations corresponding to those discussed above for **3a/3b** (see Fig. 2), and even if the 1-OH proton was not observed in the ^{1}H NMR spectrum the hydroxyl group must be present in order to facilitate the conformation that gives rise to the NOESY correlations and ^{1}H–^{1}H coupling constants observed.

The final product, heptemerone G (**5**), differs from the previously described compounds in lacking a heterocycle and containing an aldehyde function. The elemental composition of **5** is $C_{22}H_{30}O_4$ and with five double bonds (two carbon–carbon double bonds, an aldehyde, a ketone, and an acetoxy group) the compound should be tricyclic. However, the NMR spectra recorded at room temperature were not useful, as many of the signals were broadened. This was also reported for guanacastepene A, which is closely related to **5**, and it was found to be due to conformational flexibility in the C-9/C-10 bond.[4] By recording the spectra of **5** in DMSO-d_6 at 100 °C, sharper signals were obtained. HMBC correlations from 15-H to C-3, C-4 and C-5 show that the aldehyde is α,β-unsaturated, and COSY correlations from 5-H via 6-H_2 to 7-H_2 followed by HMBC correlations from 16-H_3 to C-3, C-7, C-8 and C-9 close the six-membered ring. The COSY correlations between 9-H_2 and 10-H_2, the HMBC correlations from 17-H_3 to C-1, C-10, C-11 and C-12, and the HMBC correlations from 13-H_2 to C-1, C-11, C-12 and C-14 close the five-membered ring. The remaining carbon C-2 must be part of the C-1/C-2 double bond, and the only remaining possibility is that it is additionally connected to C-3. 2-H consequently gives HMBC correlations to C-4, C-8, C-11 and C-14, in complete accordance with the suggested structure. NOESY correlations between 15-H and 2-H as well as 5-H are further supporting the structure. The stereostructure shown in Figure 1 is supported by the NOESY correlations from 16-H_3 to 9-Ha and 10-Ha, from 17-H_3 to 9-Hb, 10-Hb and 13-Hb, and from 13-Ha to 12-H (see Fig. 2). Heptemerone G (**5**) is therefore 5-*O*-acetyl-13-deacetoxy guanacastepene A.

3. Conclusion

The seven new diterpenoids heptemerones A–G possessing a secoguanacastepene (**1**) or guanacastepene (**2**, **3a**, **3b**, **4a**, **4b** and **5**) skeleton isolated from the basidiomycete *C. heptemerus* were characterised. They are potent inhibitors of the fungal germination of the plant pathogen *M. grisea*, with heptemerone G (**5**) being the most active with MICs starting at 1 μg/ml.[2] Growth of yeasts and bacteria was hardly affected, and the cytotoxic activities were moderate.[2] Only heptemerone D was phytotoxic.[2] A detailed description of the biological activities of the compounds reported here is given in Ref. 2.

4. Experimental

4.1. General

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded at room temperature with a Bruker DRX500 spectrometer with an inverse multinuclear 5 mm probehead equipped with a shielded gradient coil. The spectra were recorded in $CDCl_3$ and DMSO-d_6, and the solvent signals (7.26 and 77.0 ppm for $CDCl_3$, 2.50 and 39.51 ppm for DMSO-d_6) were used as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (J) in Hz. COSY, HMQC and HMBC experiments were recorded with gradient enhancements using sine shaped gradient pulses. For the 2D heteronuclear correlation spectroscopy the refocusing delays were optimised for $^1J_{CH}=145$ Hz and $^nJ_{CH}=10$ Hz. The raw data were transformed and the spectra were evaluated with the standard Bruker XWIN-NMR software (rev. 010101). HRMS spectra were recorded with a JEOL SX102 spectrometer (FAB ionisation) and a Micromass Q-TOF MICRO instrument (ES ionisation). UV and the IR spectra were recorded with a Perkin Elmer λ 16 and a Bruker IFS 48 spectrometer, and the optical rotations were measured with a Perkin-Elmer 141 polarimeter at 22 °C.

The fermentation of the producing organism is described in Ref. 2. The producing organism, *C. heptemerus* strain D99052, and is deposited in the culture collection of the LB Biotechnology, University of Kaiserslautern. The compounds were purified by solid phase extraction, silica gel chromatography with different mixtures of EtOAC and cyclohexane as eluent followed by preparative HPLC on RP-18 material with water:methanol. The isolation of the active compounds was carried out by bioassay-guided fractionation.

4.1.1. Heptemerone A (1). Obtained as a colourless oil. $[\alpha]_D^{20}$ −59 (*c* 0.6, $CHCl_3$); λ_{max} (ε) in MeOH: 281 nm (9500); ν_{max} (liquid film) 3440, 2960, 1740, 1650, 1450, 1370, 1235, 1135, 1045, 1015, 930, 900 and 605 cm^{-1}; *m/z* HRMS (FAB, M+H$^+$) found 463.2334, $C_{25}H_{35}O_8$ requires 463.2332 (mass error 0.4 ppm). See Table 1 for ^{1}H and ^{13}C NMR data. Strong COSY correlations were observed between 5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H as well as 18-H, and between 18-H and 19-H_3 and 20-H_3. Pertinent HMBC correlations were observed between 5-H and C-3, C-4, C-6, C-15 and 5-O_2CCH_3, between 13-H and C-11, C-12, C-14, C-18 and 13-O_2CCH_3, between 15-H and C-2, C-3 and C-4, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12, between 5-O_2CCH_3 and 5-O_2CCH_3, between 13-O_2CCH_3 and 13-O_2CCH_3, between 14-OCH_3 and C-14.

4.1.2. Heptemerone B (2). Obtained as a colourless oil. $[\alpha]_D^{20}$ +73 (*c* 0.5, $CHCl_3$); λ_{max} (ε) in MeOH: 301 nm (2300); ν_{max} (liquid film) 3450, 2935, 1740, 1630, 1450, 1370, 1230, 1125, 1055, 1020, 945 and 610 cm^{-1}; *m/z* HRMS (FAB, M+H$^+$) found 419.2426, $C_{24}H_{35}O_6$ requires 419.2434 (mass error 1.9 ppm). See Table 1 for ^{1}H and ^{13}C NMR data. Strong COSY correlations were observed between 1-H and 2-H, between 2-H and 15-H_2, between

5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H as well as 18-H, and between 18-H and 19-H_3 as well as 20-H_3. Pertinent HMBC correlations were observed between 1-H and C-2, C-3, C-11 and C-14, between 2-H and C-3, C-4, C-15 and C–C-11, between 5-H and C-3, C-4, C-6, C-15 and 5-O_2CCH_3, between 13-H and C-11, C-12, C-14, C-18 and 13-O_2CCH_3, between 15-H_2 and C-2, C-3, C-4 and C-5, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12, between 5-O_2CCH_3 and 5-O_2CCH_3, between 13-O_2CCH_3 and 13-O_2CCH_3.

4.1.3. Heptemerone C (3a). Obtained as a colourless oil. $[\alpha]_D^{20}$ +23 (*c* 0.6, $CHCl_3$); λ_{max} (ε) in MeOH: 214 nm (5000); ν_{max} (liquid film) 3435, 2955, 1735, 1635, 1450, 1375, 1245, 1130, 1100, 1045, 1015, 960, 795 and 610 cm^{-1}; *m/z* HRMS (ES, $M+H^+$) found 405.2261, $C_{23}H_{33}O_6$ requires 405.2277 (mass error 3.9 ppm). See Table 1 for ^1H and ^{13}C NMR data. Strong COSY correlations were observed between 5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H as well as 18-H, and between 18-H and 19-H_3 as well as 20-H_3. Pertinent HMBC correlations were observed between 5-H and C-3, C-4, C-6, C-15 and 5-O_2CCH_3, between 13-H and C-1, C-11, C-12, C-14, C-18 and 13-OCH_3, between 15-H and C-2, C-3, C-4 and C-5, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12, between 5-O_2CCH_3 and 5-O_2CCH_3, between 13-OCH_3 and 13-C.

4.1.4. Heptemerone D (3b). Obtained as a colourless oil. $[\alpha]_D^{20}$ +71 (*c* 0.6, $CHCl_3$); λ_{max} (ε) in MeOH: 214 nm (5300); ν_{max} (liquid film) 3430, 2925, 1770, 1730, 1450, 1370, 1245, 1130, 1020, 960, 910, 875, 820, 790 and 610 cm^{-1}; *m/z* HRMS (FAB, $M+H^+$) found 433.2212, $C_{24}H_{33}O_7$ requires 433.2226 (mass error 3.2 ppm). See Table 1 for ^1H and ^{13}C NMR data. Strong COSY correlations were observed between 5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H as well as 18-H, and between 18-H and 19-H_3 as well as 20-H_3. Pertinent HMBC correlations were observed between 5-H and C-3, C-4, C-6, C-15 and 5-O_2CCH_3, between 13-H and C-1, C-11, C-12, C-14, C-18 and 13-O_2CCH_3, between 15-H and C-2, C-3, C-4 and C-5, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12, between 5-O_2CCH_3 and 5-O_2CCH_3, between 13-O_2CCH_3 and 13-O_2CCH_3.

4.1.5. Heptemerone E (4a). Obtained as a colourless oil. $[\alpha]_D^{20}$ +42 (*c* 0.6, $CHCl_3$); λ_{max} (ε) in MeOH: 281 nm (1700); ν_{max} (liquid film) 3425, 2955, 1755, 1680, 1605, 1540, 1455, 1380, 1235, 1140, 1115, 1075, 1040, 960, 910, 870, 815 and 615 cm^{-1}; *m/z* HRMS (FAB, $M+H^+$) found 347.1859, $C_{20}H_{27}O_5$ requires 347.1858 (mass error 0.3 ppm). See Table 1 for ^1H and ^{13}C NMR data. Strong COSY correlations were observed between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H as well as 18-H, and between 18-H and 19-H_3 as well as 20-H_3. Pertinent HMBC correlations were observed between 6-H_2 and C-4 and C-5, between 13-H and C-1, C-11, C-12, C-14, and C-18, between 15-H and C-2, C-3, C-4 and C-5, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12.

4.1.6. Heptemerone F (4b). Obtained as a colourless oil. $[\alpha]_D^{20}$ +99 (*c* 0.6, $CHCl_3$); λ_{max} (ε) in MeOH: 276 nm (1500); ν_{max} (liquid film) 3425, 2960, 1750, 1690, 1605, 1540, 1455, 1370, 1230, 1145, 1020, 950, 910, 875, 790, 655, 615 and 530 cm^{-1}; *m/z* HRMS (FAB, $M+H^+$) found 389.1964, $C_{22}H_{29}O_6$ requires 389.1964 (mass error 0.0 ppm). See Table 1 for ^1H and ^{13}C NMR data. Strong COSY correlations were observed between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H as well as 18-H, and between 18-H and 19-H_3 as well as 20-H_3. Pertinent HMBC correlations were observed between 6-H_2 and C-4 and C-5, between 13-H and C-1, C-11, C-12, C-14, C-18 and 13-O_2CCH_3, between 15-H and C-2, C-3, C-4 and C-5, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12, between 13-O_2CCH_3 and 13-O_2CCH_3.

4.1.7. Heptemerone G (5). Obtained as a colourless oil. $[\alpha]_D^{20}$ +12 (*c* 0.6, $CHCl_3$); λ_{max} (ε) in MeOH: 281 nm (5500); ν_{max} (liquid film) 3430, 2960, 1735, 1680, 1455, 1370, 1235, 1175, 1020 and 605 cm^{-1}; *m/z* HRMS (ES, $M+H^+$) found 359.2221, $C_{22}H_{31}O_4$ requires 359.2222 (mass error 0.3 ppm). See Table 1 for ^1H and ^{13}C NMR data. Strong COSY correlations were observed between 5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 10-H_2, between 12-H and 13-H_2 as well as 18-H, and between 18-H and 19-H_3 as well as 20-H_3. Pertinent HMBC correlations were observed between 2-H and C-1, C-4, C-8, C-11 and C-14, between 5-H and C-3, C-4, C-6, C-15 and 5-O_2CCH_3, between 13-H_2 and C-11, C-12 and C-14, between 15-H and C-4 and C-5, between 16-H_3 and C-3, C-7, C-8 and C-9, between 17-H_3 and C-1, C-10, C-11 and C-12, between 5-O_2CCH_3 and 5-O_2CCH_3.

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Electrophilic substitution reactions of trisheteroarylmethanes: an efficient strategy to develop novel synthons for organic synthesis

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Abstract—Trisheteroarylmethanes are interesting molecules for the construction of three dimensionally complex systems. From this vantage point, we studied electrophilic substitution reactions on tris-2-thienylmethane and tris-2-furylmethane. During the bromination reaction, we have isolated the tris-bromosubstituted tris-2-thienylmethane in the former case and brominated furanones in the latter case, which may be of synthetic and biological importance.

1. Introduction

Symmetric tris-heteroaromatics are a fascinating group of molecules from the vantage point of their transformation to a number of valuable three dimensional network systems. The reactivity of tris-thienylmethane was previously investigated to some extent, but it covers only the chemistry on the central carbon atom.[1] The generation and investigations on tris-2-thienyl and tris-3-thienyl methyl radicals by Mangini et al.[2] and the isolation of the dimers by Nakayama et al.[3] are noteworthy in this context. In addition, the corresponding cations and anions were also investigated in detail and used for various applications.[4] Although the structure and the chemistry of tris-2-thienylmethyl radicals and ions have been well established, the reactivity and functionalization of the parent tris-2-thienylmethane via electrophilic substitution reactions has not been studied in detail.

Symmetric furans like bis-furylmethanes and tris-furylmethanes can be considered as potential synthons for multidimensional elaboration of methane, which cannot be achieved by conventional methods. Bis-furylmethanes are useful as flavour agents and are important in the perfume industry[5] and bis-furfuryldiamines have been used as monomers and cross-linking agents in polymer manufacturing.[6] The bis-furylmethanes are found to be a good substrate for cycloaddition reactions with oxyallyl cations.[7] Although tris-furylmethanes have been known for sometime[8–10] there has been no effort on the functionalization of these systems. Therefore, it was of interest to investigate their electrophilic reactions with the perception that such reactions will lead to products that can be further transformed to valuable three dimensional network systems. Both tris-2-thienylmethane **1** and tris-2-furylmethane **2** required for our studies were prepared by the condensation reaction of thiophene/furan with the corresponding aldehydes in the presence of P_2O_5 using benzene as solvent.[11] The results of our studies of a number of reactions viz., acetylation, formylation and bromination on tris-2-thienylmethane and tris-2-furylmethane are reported here.

2. Results and discussion

2.1. Electrophilic substitution reactions

2.1.1. Friedel–Crafts reaction. Friedel–Crafts acylation reaction of thiophene generally proceeds in good yield under controlled conditions. Usually α-substitution is observed in acylation reactions but substitution occurs at β-position when the α-positions are blocked.[12] In order to explore the reactivity of tris-2-thienylmethane in Friedel–Crafts reaction, it was reacted with acetyl chloride in the presence of $AlCl_3$. Tris-acetylated product **3** was formed exclusively as a viscous pale brown liquid in 86% yield (Scheme 1).

The structure of compound **3** was established by means of spectroscopic analysis. The IR spectrum of **3** exhibited a

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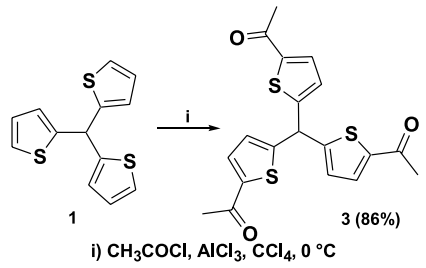
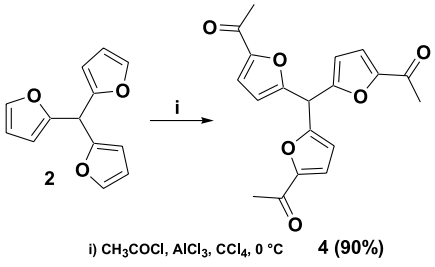


Scheme 1.

sharp signal at 1660 cm^{-1} corresponding to the carbonyl group absorption. In the ^1H NMR spectrum, the methyl group resonated as a singlet at δ 2.51. The central proton appeared as a singlet at δ 6.08 while the protons attached to the thiophene rings were discernible as two sets of doublets at δ 6.97 (J=3.8 Hz) and 7.54 (J=3.8 Hz). The ^{13}C NMR spectrum also supported the assigned structure. Signals due to the methyl carbons, the central carbon and the carbonyl group appeared at δ 26.3, 43.6 and 190.0, respectively.

In view of the well known susceptibility of furan to electrophilic substitution reactions,[13] we attempted Friedel–Crafts reaction on tris-2-furylmethane. When it was treated with acetyl chloride and aluminium chloride in CCl_4 the product **4** was obtained in 90% yield (Scheme 2).



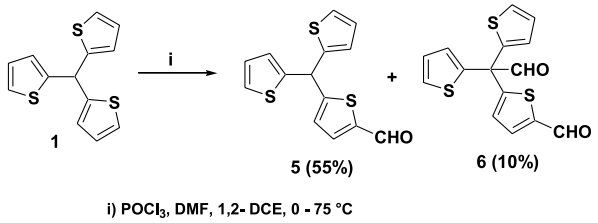
Scheme 2.

Compound **4** exhibited structural features analogous to that of **3**.

2.1.2. Formylation. Formylated heteroaromatic systems are potential synthons for a variety of chemical transformations. Kurata et al. reported the formylation of tris-2-thienylmethane using BuLi and DMF in the presence of TMEDA.[14]

We were interested in the reactivity of tris-2-thienylmethane towards the classical Vilsmeier formylation. When tris-2-thienylmethane was treated with DMF and $POCl_3$ at 0 °C, two products were obtained. Compound **5**, with one of the thiophene rings formylated, was observed as the major product along with small quantities of compound **6** in which the central carbon is also substituted with a formyl group (Scheme 3).

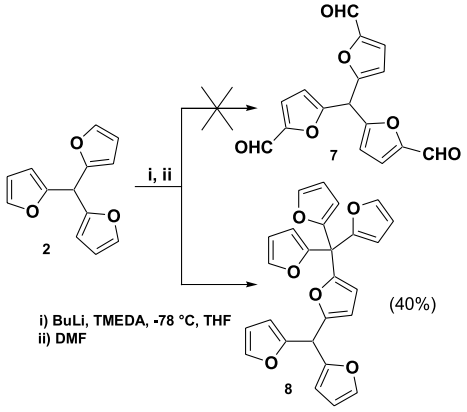
The structures of **5** and **6** were established on the basis of routine spectral analysis. The IR spectrum of **5** exhibited a sharp signal at 1729 cm^{-1} corresponding to the formyl group. In the IR spectrum of **6** the carbonyl stretching was seen at 1725 cm^{-1}. The characteristic signal (δ 5.52) corresponding to the central proton was absent in the ^1H NMR spectrum of **6**, indicating substitution at the central



Scheme 3.

carbon. Two aldehydic protons were discernible in the form of very closely spaced singlets at δ 9.93 and 9.98. In the ^{13}C NMR spectrum, the carbon at the center was seen at δ 50.0, appearing at a lower field than that in the case of tris-(2-thienyl)methane **1**, because of the attachment of the formyl group. The two carbonyl carbons were observed separately at δ 182.5 and 189.8.

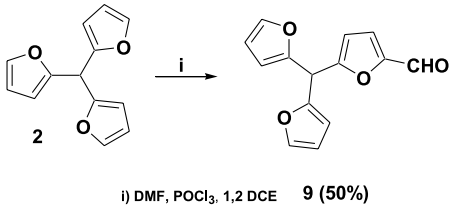
Adopting the procedure of Kurata et al. we tried to functionalize all the furan rings of tris-2-furylmethane. Surprisingly, however, the product obtained was not the formylated one but the dimer of tris-2-furylmethane, **8** in 40% yield, as a very pale yellow liquid (Scheme 4).[15]



Scheme 4.

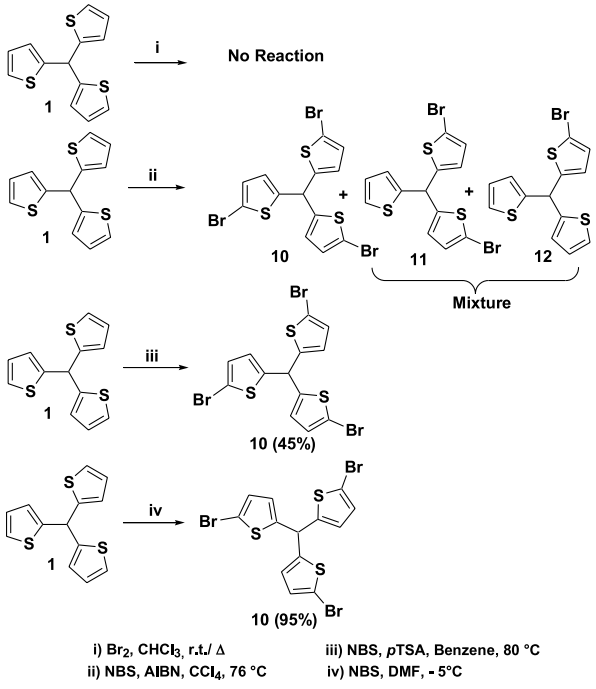
Since the Vilsmeier formylation reaction of furan is well known,[16] we performed it on tris-2-furylmethane. When tris-2-furylmethane was treated with the reagent prepared in situ from DMF and $POCl_3$ at 0 °C, monoaldehyde of tris-2-furylmethane **9** was formed in 50% yield. It was observed that even in the presence of excess reagents, only the monoadduct **9** was obtained (Scheme 5).

2.1.3. Bromination reaction. Various methods are available for the preparation of 2-mono and 2,5-dihalosubstituted thiophenes.[17] With the objective to employ tris-2-thienylmethane **1** as the core for dendrimer synthesis, we studied



Scheme 5.

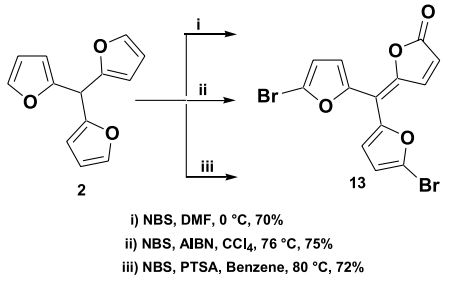
halogenation reactions of the same under various conditions. In an initial attempt, tris-2-thienylmethane **1** was treated with Br_2 in $CHCl_3$ at rt. Since no product was formed, the reaction was carried out under reflux conditions, which also did not produce the desired product. It was then decided to resort to other brominating agents and NBS was selected. In an experiment with NBS using AIBN as the radical initiator, an inseparable mixture of mono-, bis- and tris-bromo derivatives of tris-2-thienylmethane **1** was formed. In a modified procedure, tris-2-thienylmethane **1** in refluxing benzene was treated with NBS in the presence of *p*-TSA; this reaction afforded tris-(5-bromo-2-thienyl)-methane **10** in 45% yield. In order to improve the yield of **10**, another strategy was employed, wherein, to a stirred solution of tris-2-thienylmethane **1** in DMF at −5 °C, a solution of NBS in DMF was added slowly. The reaction afforded tris-(5-bromo-2-thienyl)methane **10** in 95% yield (Scheme 6).



Scheme 6.

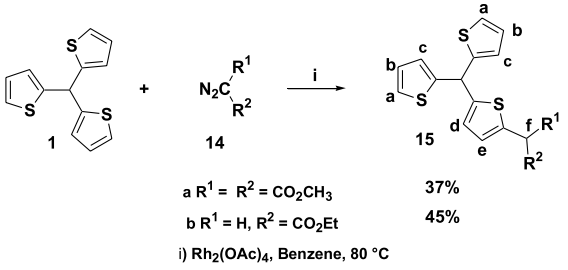
Furan is known to react with halogens vigorously and in most instances polymeric material is formed. Keegstra et al. reported the preparation of 2-bromofuran under controlled conditions by the treatment of furan with Br_2 and DMF.[18] With the objective of crafting some dendritic architectures of tris-2-furylmethane **2**, via the bromo derivatives, we attempted to its bromination reactions. Various conditions were employed, which include: (i) NBS in DMF; (ii) NBS in presence of catalytic amount of *p*-TSA and (iii) NBS in presence of AIBN. A polymer of tris-2-furylmethane was the only product formed in a Br_2/DMF experiment. All other methods mentioned above yielded the butenolide **13** as the only product (Scheme 7).

The structure of **13** was assigned by using spectroscopic techniques. The IR spectrum exhibited a sharp absorption peak at 1763 cm^{-1} characteristic of a lactone carbonyl group. In the ^1H NMR spectrum, the central proton of tris-2-furylmethane was absent and the doublet at δ 6.29 (J= 5.4 Hz) was attributed to the proton α- to the lactone carbonyl group. The protons β- to the lactone moiety resonated at δ 8.01 (J=5.4 Hz) as a doublet. The ^{13}C NMR spectral data was also in agreement with the assigned structure. The lactone carbonyl was discernible at δ 168.4. Presumably due to the extended conjugation the resonance signal of the central carbon was shifted downfield to δ 53.0; the corresponding signal in **2** appears at 39.1 (Scheme 7).



Scheme 7.

2.1.4. Reaction with electrophilic carbenes. Thiophenium ylides, obtained from the reaction between thiophene and carbenes, on subsequent rearrangement yield 2-substituted thiophene.[19] In order to exploit the reactivity of electrophilic carbenes towards tris-2-thienylmethane **1**, some reactions with cyclic as well as acyclic carbenes were performed. In a typical experiment, tris-2-thienylmethane **1** and the carbene precursor were taken in benzene to which rhodium(II) acetate was added under reflux conditions. In the case of acyclic carbenes, the reaction afforded products **15a**,**b** with only one of the rings participating in the reaction (Scheme 8).

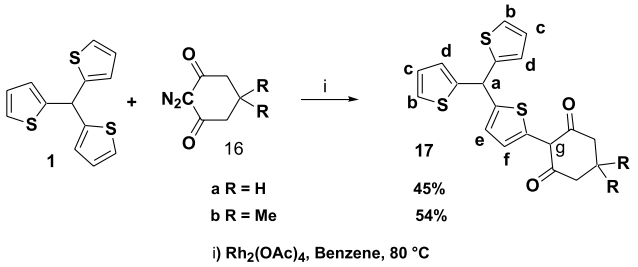


Scheme 8.

The structure of the compound **15a** was ascertained by spectral analysis. The IR spectrum exhibited a sharp absorption peak at 1738 cm^{-1}corresponding to the carbonyl group. In the ^1H NMR spectrum, protons of the two carbomethoxy groups appeared at δ 3.76 as a singlet (6H). The signal due to the resonance of proton **f** was seen at δ 4.81. The central proton appeared as a broad singlet at δ 6.03 while proton **e** was discernible at δ 6.77 (J=3.4 Hz) as a doublet. Protons **b** and **d** resonated together as a multiplet centered at δ 7.19. Protons labelled **a** were seen as a multiplet around δ 7.50. Satisfactory ^{13}C NMR and HRMS values were also obtained for these compounds.

The structure of **15b** was also ascertained on the basis of spectral analysis. The IR spectrum exhibited a sharp absorption peak at 1740 cm^{-1} corresponding to the carbonyl group. In the ^1H NMR spectrum protons of the carboethoxy group appeared at δ 1.26 as a triplet (3H) and around δ 3.46 as a multiplet (2H). The signal due to the resonance of proton **f** was seen at δ 4.14. Satisfactory ^{13}C NMR and HRMS values were also obtained for these compounds.

Similar reactivity pattern was observed with cyclic carbenes **16a**,**b** also affording products **17a**,**b** (Scheme 9).



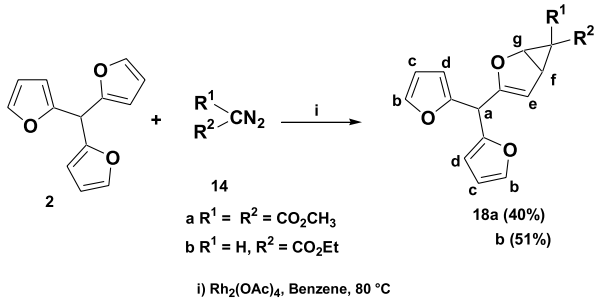
Scheme 9.

The structure of the compound **17a** was elucidated on the basis of spectral analysis. A sharp peak displayed at 1740 cm^{-1} was attributed to the carbonyl absorption. In the ^1H NMR spectrum of **17a**, the methylene protons were seen together as a multiplet centered at δ 2.01. The proton labelled **g** and the central proton labelled **a** were discernible as two separate singlets at δ 4.20 and δ 6.05. The signal due to protons **e** and **f** were seen at δ 6.56 as a doublet (J= 3.4 Hz) and at δ 6.81 as a broad singlet. Protons **c** and **d** were together seen centered at δ 6.91 as a multiplet and the protons labelled **b** were discernible at δ 7.18 (m). In the ^{13}C NMR spectrum, the carbonyl peak appeared at δ 192.4. HRMS value was also in accordance with the assigned structure. The structure of **17b** was also assigned on the basis of spectral analysis. The IR spectrum exhibited a sharp absorption peak at 1722 cm^{-1}corresponding to the carbonyl group. In the ^1H NMR spectrum, the methyl protons were appeared at δ 1.26 as a singlet (6H) and the methylene protons were discernible as two singlets at δ 2.20 (2H) and δ 2.51 (2H). The signal due to the resonance of proton **g** was seen at δ 4.25. Satisfactory ^{13}C NMR and HRMS values were also obtained for these compounds.

Furans also react with diazo compounds in the presence of metal catalysts such as Rh(II) and Cu(II), forming cyclopropane derivatives, which in turn could rearrange according to the reaction conditions employed.[20]

In order to explore the reactivity of **2** towards electrophilic carbenes, some reactions were carried out with cyclic and acyclic carbenes in the presence of Rh(II) acetate as catalyst. It was observed that, with acyclic carbenes, cyclopropanation took place only at one of the furan rings of the tris-2-furylmethane system yielding the products **18a** and **18b** (Scheme 10).

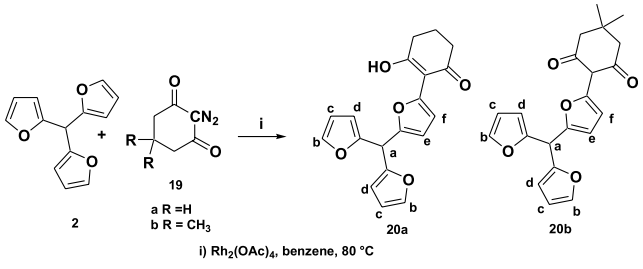
The structure elucidation of the products was based on spectroscopic analysis. The IR spectrum exhibited a sharp



Scheme 10.

signal at 1738 cm^{-1} corresponding to the ester carbonyl. In the ^1H NMR spectrum of **18a**, the two methoxy signals were seen as singlets at δ 3.77 and 3.83. Proton **g** was seen as a doublet at δ 3.61 (J=8.9 Hz) while the signal due to proton **a** was seen as a multiplet centered at δ 5.85. Proton **f** and **e** manifested doublet of a doublet at δ 6.54 (J_1=2.1 Hz, J_2= 6.2 Hz) and δ 6.80 (J_1=1.8 Hz, J_2=6.0 Hz) as two separate sets of double doublets. Furan protons were seen centered at δ 6.43 (m), 6.60 (d, J=3.3 Hz), 7.34 (s) and 7.42 (s). In the case of **18b**, the three methyl protons of carboethoxy group were seen as a triplet at δ 1.26. The methylene protons were appeared as a quartet at δ 4.10 (2H, J=7.1 Hz). The cyclopropyl proton was discernible at δ 1.06 (1H) as a multiplet. Proton **g** was appeared as a doublet at δ 4.83 (J= 4.8 Hz, 1H) whereas **f** was seen at δ 2.75 as a multiplet (1H). The central proton labelled **a** was appeared at δ 5.20 (s, 1H). Furan protons were seen centered at 6.10 (d, J=3.12 Hz, 2H), 6.33 (m, 2H), 7.34 (s, 2H). Satisfactory ^{13}C NMR and HRMS values were also obtained.

Similarly the cyclic carbenes **19a** and **19b** on reaction with **2** under usual conditions afforded the rearranged products **20a** and **20b**, respectively (Scheme 11). It is noteworthy that the former was isolated exclusively in the enol form.



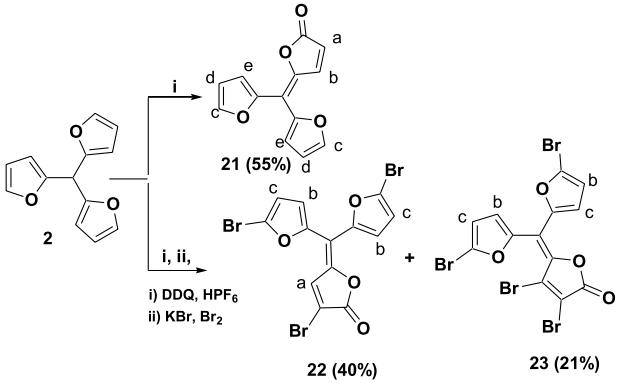
Scheme 11.

The structure of **20a** was elucidated by spectroscopic analysis. The IR spectrum exhibited a broad absorption at 3407 cm^{-1} showing the presence of –OH group; carbonyl absorption was seen at 1722 cm^{-1}. In the ^1H NMR spectrum, the central proton **a** appeared as a singlet at δ 5.52. Protons labelled **b**, **c** and **d** were seen at δ 6.13 (d, J= 3.0 Hz), 6.32 (m) and 7.37 (s). The protons **e** and **f** were seen as doublets at δ 6.21 (J=3.3 Hz) and 6.95 (J=3.3 Hz), respectively. The –OH proton resonated at δ 9.18 (D_2O exchangeable). Satisfactory ^{13}C NMR and HRMS data were also obtained for compound **20a**.

Compound **20b** was also characterized by the usual spectroscopic techniques. In the IR spectrum, the peak at 1725 cm^{-1} is attributed to the carbonyl functionality. In the ^1H NMR spectrum, the singlet at δ 4.31 corresponds to the methine proton in the cyclohexan-1,3-dione ring whereas the singlet at δ 5.01 was attributed to the proton **a**. In the ^{13}C NMR spectrum, the signal due to the carbonyl functionality was seen at δ 204.5. HRMS data was also in good agreement with the structure assigned.

2.2. Attempts towards the functionalization of the central carbon

Asao and co-workers have prepared various substituted tris-azulenylmethyl cations, employing DDQ as the hydride abstracting agent.[21] Against this literature precedence, attempts were made to synthesize the tris-2-furylmethyl cation using DDQ as the hydride abstracting agent. Conceivably the cation, in turn, could be used for the generation of the corresponding radical. Adopting a similar experimental procedure to that employed by Asao's group for the abstraction of hydride, tris-2-furylmethane **2** was stirred in dichloromethane with DDQ for 30 min. Surprisingly, the compound underwent oxidation to give the lactone **21**, instead of delivering the expected cation. In another strategy, **2** was treated with DDQ and then with potassium bromide and bromine. In this case the reaction afforded the bromoderivatives of butenolide, **22** and **23**, instead of the expected bromoderivative (Scheme 12).



Scheme 12.

Compound **21** was characterized by spectroscopic analysis. The IR spectrum exhibited a sharp peak at 1784 cm^{-1}, characteristic of lactone carbonyl absorption. In the ^1H NMR spectrum the proton α- to the lactone carbonyl was discernible as a doublet at δ 6.23 ($J=5.4$ Hz) and another doublet that appeared at δ 8.00 ($J=5.4$ Hz) was assigned to the β-proton. In the ^{13}C NMR spectrum, the carbonyl peak was seen at δ 168.2 and all other signals were in accordance with the assigned structure.

The structure of compound **22** was ascertained using the usual spectroscopic techniques. Its IR spectrum showed the lactone carbonyl absorption at 1763 cm^{-1}. In the ^1H NMR spectrum, the single proton at β-position, on the lactone ring resonated at δ 8.08 as a singlet. The ^{13}C NMR spectrum of **22** also supported the assigned structure. The characteristic

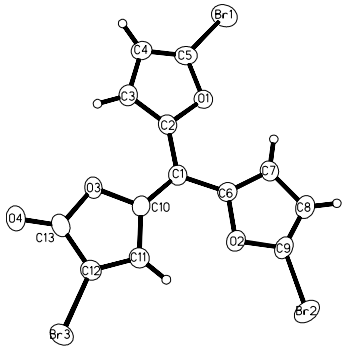


Figure 1.

lactone carbonyl was seen at δ 163.0. Conclusive proof for the structure of **22** was obtained by single crystal X-ray analysis (Fig. 1).

The structure of compound **23** was also established on the basis of spectroscopic data. The lactone carbonyl gave a sharp absorption peak at 1761 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum the signal due to the central proton was absent and in ^{13}C NMR spectrum the lactone carbonyl appeared at δ 168.2.

It is worthy of mention that lactones such as **22** and **23** are synthetically important molecules since bromosubstituted butenolides have been used extensively in Pd-catalyzed coupling reactions.[22] The swarming motility of *S. liquefaciens* MG1, a bacteria, was shown to be inhibited by halogenated furanones produced by the benthic marine microalga *Delisea pulchra*.[23,24] These compounds have the additional feature that they contain two bromofuran rings, which are very difficult to synthesise by usual methods.

3. Conclusion

In conclusion, we have unravelled the reactivity of tris-theinylmethane **1** and tris-2-furylmethane **2** toward a number of electrophilic reagents. Friedel–Crafts reaction of **1** and **2** afforded tris-acetylated compound while formylation gave only the monoadduct. Bromination of **1** with NBS afforded tris-brominated product while that of **2** under different conditions afforded butenolide with two bromofuran substituents. Reaction with electrophilic carbenes yielded α-substituted products. Similarly attempts toward the synthesis of tris-2-furylmethyl bromide resulted in some interesting and potentially useful furanone derivatives.

4. Experimental

4.1. General

All reactions were conducted in oven-dried glassware under an atmosphere of argon with magnetic stirring. NMR spectra were recorded on Bruker 300 MHz FT NMR spectrometer with samples dissolved in $CDCl_3$. Chemical shifts are reported in δ (ppm) relative to Me_4Si (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal standards. Abbreviations for

NMR multiplicities are as follows: s, singlet; d, doublet; m, multiplet; dd, doublet of doublet and br s, broad singlet. Coupling constants *J* are reported in Hertz (Hz). IR spectra were recorded on Bomem MB Series FT-IR spectrophotometer; absorbencies are reported in cm^{-1}. High-resolution mass spectra were recorded in EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer.

4.2. General procedure for the preparation of 1 and 2

To a stirred solution of thiophen/furan2-carbaldehyde (1 mmol) and thiophene/furan (2.2 mmol) in benzene (20 mL) was added P_2O_5 (15 g) in small portions. After stirring for 6 h, the crude tarry material was removed by filtration and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh, hexane) to afford tris-(2-thienyl)methane **1** (33%) (lit. yield is 33%)/tris-2-furylmethane **2** (20%). The former is obtained as a colorless crystalline solid. Mp 52–53 °C (lit. Mp 50–51 °C)[11] and the latter as a colourless viscous liquid.

4.2.1. Compound 3. To a solution of $AlCl_3$ (252 mg, 1.8 mmol) in CCl_4 (5 mL) was added CH_3COCl (148 mg, 1.8 mmol) slowly at 0 °C over 5 min. Compound **1** (100 mg, 0.38 mmol) in CCl_4 (5 mL) was added dropwise to the reagent prepared as mentioned above. After stirring for further 30 min, the reaction mixture was allowed to stand overnight and then poured into crushed ice. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (20% ethylacetate in hexane) to afford pure **3** (127 mg, 86%) as a viscous pale brown liquid. IR (Neat) ν_{max}: 1660, 1580, 1445, 1364, 1276, 1073, 1026, 932 cm^{-1}. ^1H NMR δ 2.51 (s, 9H), 6.08 (s, 1H), 6.97 (d, $J=3.8$ Hz, 3H), 7.54 (d, $J=3.8$ Hz, 3H). ^{13}C NMR δ 26.3, 43.6, 127.4, 132.1, 144.2, 153.0, 190.0. HRMS-EI: calcd for $C_{19}H_{16}O_3S_3$: 388.0261, found: 388.0269.

4.2.2. Compound 4. The compound **4** was synthesized using the same procedure as mentioned above (142 mg, 90%). IR (neat) ν_{max}: 1662, 1520, 1440, 1360, 1275, 1070, 1024, 930 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 9H), 5.74 (s, 1H), 6.37 (d, $J=3.4$ Hz, 3H), 7.12 (d, $J=3.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 39.6, 111.0, 117.9, 152.8, 153.6, 185.9. HRMS-EI: calcd for $C_{19}H_{16}O_6$: 340.0947, found: 340.0948.

4.2.3. Compounds 5 and 6. To a stirred solution of DMF (161 mg, 1.52 mmol) in 1,2-dichloroethane (3 mL) was added $POCl_3$ (232 mg, 1.52 mmol) at 0 °C. Compound **1** (100 mg, 0.38 mmol) in 1,2-dichloroethane (3 mL) was introduced to the reaction mixture and stirred at rt for 2 h. It was then refluxed for further 2 h, cooled and poured into crushed ice. After neutralization with sodium acetate the compound was extracted using dichloromethane (2× 50 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was removed on a rotary evaporator. The crude product was purified by column chromatography on silica gel (5% ethylacetate in hexane) to afford **5** (60 mg, 55%) as a viscous yellow liquid. Further elution with 10% ethylacetate in hexane afforded **6** (12 mg, 10%) as a viscous red liquid.

Compound **5**. IR (neat) ν_{max}: 1729, 1604, 1465, 1439, 1264, 1228, 1042 cm^{-1}. ^1H NMR δ 5.89 (s, 1H), 6.94–6.96 (m, 4H), 7.02 (d, $J=3.7$ Hz, 1H), 7.22–7.24 (m, 2H), 7.60 (d, $J=3.8$ Hz, 1H), 10.12 (s, 1H). ^{13}C NMR δ 43.5, 51.2, 125.8, 126.1, 127.0, 128.0, 135.9, 143.6, 155.9, 182.3. HRMS-EI: calcd for $C_{14}H_{10}OS_3$: 289.9894, found: 289.9890.

Compound **6**. IR (neat) ν_{max}: 1725, 1665, 1522, 1444, 1221, 1053, 797 cm^{-1}. ^1H NMR δ 6.99 (d, $J=3.5$ Hz, 2H), 7.04–7.07 (m, 2H), 7.11 (d, $J=3.9$ Hz, 1H), 7.37 (d, $J=5.1$ Hz, 2H), 7.68 (d, $J=3.9$ Hz, 1H), 9.93 (s, 1H), 9.98 (s, 1H). ^{13}C NMR δ 50.0, 127.1, 128.4, 129.2, 135.1, 142.7, 182.5, 189.8. HRMS-EI: calcd for $C_{15}H_{10}O_2S_3$: 317.9843, found: 317.9884.

4.2.4. Compound 9. To a stirred solution of DMF (99 mg, 0.93 mmol) in 1,2-dichloroethane (3 mL) was added $POCl_3$ (143 mg, 0.93 mmol) at 0 °C, and stirred for 5 min. Compound **2** (50 mg, 0.23 mmol) in 1,2-dichloroethane (3 mL) was introduced into the reaction mixture and processed as described earlier to afford **9** (28 mg, 50%) as a yellow viscous liquid. IR (neat) ν_{max}: 1729, 1603, 1460, 1435, 1260, 1222, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 1H), 6.09 (d, $J=3.2$ Hz, 2H), 6.33–6.34 (m, 3H), 7.16 (d, $J=3.5$ Hz, 1H), 7.37 (m, 2H), 9.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 108.0, 110.5, 121.0, 142.4, 150.4, 152.7, 158.5, 177.2. HRMS-EI: calcd for $C_{14}H_{10}O_4$: 242.0579, found: 242.0576.

4.2.5. Compound 10. (a) To a stirred solution of **1** (50 mg, 0.19 mmol) in DMF (2 mL) at −5 °C, was added NBS (135 mg, 0.76 mmol) in DMF (3 mL) and stirred for further 5 min. The reaction mixture was poured into crushed ice and the product was extracted using ethylacetate (2×20 mL). The organic layers were combined, dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane) to afford **10** (90 mg, 95%) as a colourless crystalline solid. Mp 72–74 °C.

(b) To a stirred solution of **1** (50 mg, 0.19 mmol) and 10 mol % of PTSA in benzene (5 mL) was added NBS (135 mg, 0.76 mmol) and stirred for further 30 min at 80 °C. The solvent was removed in vacuo and the crude product was purified by column chromatography as mentioned above to afford **10** (43 mg, 45%) as a colourless crystalline solid. Mp 72–74 °C. IR (KBr) ν_{max}: 3101, 2917, 2362, 1744, 1538, 1441, 1218, 1057, 971, 800, 702, 508 cm^{-1}. ^1H NMR δ 5.71 (s, 1H), 6.66 (d, $J=3.7$ Hz, 3H), 6.87 (d, $J=3.7$ Hz, 3H). ^{13}C NMR δ 43.3, 112.3, 126.8, 129.6, 146.8. HRMS-EI: calcd for $C_{13}H_7S_3Br_3$: 495.7259, found: 495.7274.

4.2.6. Compound 13. (a) To a stirred solution of **2** (50 mg, 0.23 mmol) in DMF (2 mL), was added NBS (143 mg, 0.92 mmol) and stirred for further 30 min. The product was extracted with ethylacetate (2×20 mL), washed with sodium thiosulphate solution, dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (100–200 mesh, 5% ethylacetate in hexane), to afford **13** (63 mg, 70%) in the form of a red crystalline solid. Mp 170–172 °C.

(b) To a stirred solution of **2** (50 mg, 0.23 mmol) and

10 mol% of AIBN, in CCl_4 (5 mL) was added NBS (143 mg, 0.92 mmol) and stirred for further 30 min. The solvent was removed in vacuo and the reaction mixture was purified by column chromatography as described earlier to afford **13** (68 mg, 75%) as a red crystalline solid. Mp 170–172 °C.

(c) To a stirred solution of **2** (50 mg, 0.23 mmol) and 10 mol% of *p*-TSA, in benzene (5 mL) was added NBS (143 mg, 0.92 mmol) and stirred for further 30 min. The solvent was removed in vacuo and the reaction mixture was purified by column chromatography as described earlier to afford **13** (65 mg, 72%) in the form of a red crystalline solid. Mp 170–172 °C. IR (KBr) ν_{max}: 1763, 1472, 1457, 1352, 1240, 1210, 1139, 1117, 1035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, $J=5.4$ Hz, 1H), 6.50 (m, 2H), 6.79 (d, $J=3.5$ Hz, 1H), 7.12 (d, $J=3.5$ Hz, 1H), 8.01 (d, $J=5.4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.0, 114.0, 114.6, 117.7, 119.1, 119.4, 120.6, 124.1, 124.5, 143.0, 164.2, 168.4. HRMS-EI: calcd for $C_{13}H_6Br_2O_4$: 383.8633, found: 383.8634.

4.3. General procedure for compounds 15a, 15b, 17a, 17b, 18a, 18b and 20a, 20b

To a stirred solution of **1/2** (50 mg, 1 equiv) and diazocompound (3 equiv) in benzene (5 mL) was added 2 mol % of Rh(II) acetate under argon and stirred for 12 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (100–200 mesh, hexane/ethylacetate mixtures) to afford compounds **15a**, **15b**, **17a**, **17b**, **18a**, **18b** and **20a**, **20b**.

4.3.1. Compound 15a. Viscous orange liquid, 30 mg, 40%. IR (neat) ν_{max}: 1738, 1594, 1439, 1243, 1166, 1027 cm^{-1}. ^1H NMR δ 3.76 (s, 6H), 4.81 (s, 1H), 6.03 (s, 1H), 6.77 (d, $J=3.4$ Hz, 1H), 7.18–7.20 (m, 5H), 7.50 (br s, 2H). ^{13}C NMR δ 42.6, 52.8, 53.0, 118.3, 124.8, 125.9, 126.5, 126.6, 126.7, 127.4, 146.7, 148.2, 167.4. HRMS-EI: calcd for $C_{18}H_{16}O_4S_3$: 392.0211, found: 392.0313.

4.3.2. Compound 15b. Viscous yellow liquid, 30 mg, 45%. IR (neat) ν_{max}: 1740, 1599, 1518, 1430, 1240, 1164, 1025 cm^{-1}. ^1H NMR δ 1.25–1.27 (m, 3H), 2.96–2.98 (m, 1H), 3.45–3.48 (m, 1H), 4.10–4.17 (m, 2H), 5.45 (s, 1H), 5.72 (s, 1H), 6.89–6.92 (m, 4H), 7.20 (d, $J=4.7$ Hz, 3H). ^{13}C NMR δ 14.3, 33.5, 38.5, 42.7, 60.8, 124.7, 125.5, 125.8, 126.0, 126.2, 126.5, 126.7, 126.8, 133.6, 144.6, 144.7, 148.0, 173.0. HRMS-EI: calcd for $C_{17}H_{16}O_2S_3$: 348.0312, found: 348.0324.

4.3.3. Compound 17a. Pink crystalline solid, 31 mg, 45%. Mp 136–138 °C. IR (KBr) ν_{max}: 1740, 1599, 1518, 1430, 1240, 1164, 1025 cm^{-1}. ^1H NMR δ 2.01 (s, 6H), 4.20 (s, 1H), 6.05 (s, 1H), 6.56 (d, $J=3.4$ Hz, 1H), 6.81 (br s, 1H), 6.89–6.92 (m, 4H), 7.17–7.19 (m, 2H). ^{13}C NMR δ 24.1, 42.8, 113.5, 124.8, 125.8, 126.1, 128.6, 192.4. HRMS-EI: calcd for $C_{19}H_{16}O_2S_3$: 372.0312, found: 372.0320.

4.3.4. Compound 17b. Pink crystalline solid, 44 mg, 54%. Mp 150–152 °C. IR (KBr) ν_{max}: 1722, 1604, 1377, 1243, 1166, 1027 cm^{-1}. ^1H NMR δ 1.08 (s, 6H), 2.20 (s, 2H), 2.51 (s, 2H), 4.25 (s, 1H), 6.86 (s, 1H), 7.15–7.17 (m, 5H), 7.35 (d, $J=7.4$ Hz, 1H), 7.38 (s, 2H). ^{13}C NMR δ 28.4, 30.8, 52.5, 53.3, 68.1, 125.0, 126.9, 127.7, 127.8, 136.6, 137.6, 143.6, 203.8. HRMS-EI: calcd for $C_{21}H_{20}O_2S_3$: 400.0625, found: 400.0630.

4.3.5. Compound 18a. Orange viscous liquid, 32 mg, 40%. IR (neat) ν_{max}: 1738, 1594, 1439, 1243, 1166, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.61 (d, $J=8.9$ Hz, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 5.83–5.87 (m, 1H), 6.40–6.44 (m, 2H), 6.53–6.56 (dd, $J_1=2.1$ Hz, $J_2=6.2$ Hz, 1H), 6.60 (d, $J=3.3$ Hz, 1H), 6.80 (dd, $J_1=1.8$ Hz, $J_2=6.0$ Hz, 1H), 7.34 (s, 2H), 7.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.0, 51.7, 52.8, 53.0, 56.5, 78.2, 107.5, 108.7, 109.5, 110.8, 134.3, 140.6, 149.8, 151.2, 157.5, 166.3, 166.7. HRMS-EI: calcd for $C_{18}H_{16}O_4S_3$: 392.0211, found: 392.0213.

4.3.6. Compound 18b. Viscous yellow liquid, 35 mg, 51%. IR (neat) ν_{max}: 1740, 1599, 1518, 1430, 1240, 1164, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06–1.07 (m, 1H), 1.26 (s, 3H), 2.73–2.77 (m, 1H), 4.07–4.14 (q, $J=7.1$ Hz, 2H), 4.83 (d, $J=4.8$ Hz, 1H), 4.98 (s, 1H), 5.20 (s, 1H), 6.10 (d, $J=3.12$ Hz, 2H), 6.30–6.35 (m, 2H), 7.34 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.2, 31.8, 38.4, 60.4, 67.2, 103.3, 107.3, 108.9, 109.4, 110.3, 112.0, 127.6, 141.9, 142.3, 150.8, 157.3. HRMS-EI: calcd for $C_{17}H_{16}O_5$: 300.0998, found: 300.1012.

4.3.7. Compound 20a. Pink crystalline solid, 45 mg, 60%. Mp 156–158 °C. IR (KBr) ν_{max}: 3407, 1722, 1650, 1624, 1594, 1548, 1383, 1336, 1171, 1135, 1012 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.96–2.03 (m, 2H), 2.41–2.46 (m, 2H), 2.57–2.61 (m, 2H), 5.52 (s, 1H), 6.13 (d, $J=3.0$ Hz, 2H), 6.21 (d, $J=3.3$ Hz, 1H), 6.32–6.33 (m, 2H), 6.95 (d, $J=3.3$ Hz, 1H), 7.37 (s, 2H), 9.18 (1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 29.7, 37.5, 38.7, 107.54, 109.0, 109.8, 110.5, 142.2, 147.7, 151.2, 171.6, 194.5. HRMS-EI: calcd for $C_{19}H_{16}O_5$: 324.0998, found: 324.1008.

4.3.8. Compound 20b. Pink crystalline solid, 44 mg, 54%. Mp 138–140 °C. IR (KBr) ν_{max}: 1725, 1652, 1630, 1598, 1550, 1390, 1340, 1180, 1140 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.11 (s, 3H), 2.20 (s, 2H), 2.35 (s, 2H), 4.31 (s, 1H), 5.01 (s, 1H), 6.10–6.14 (m, 2H), 6.30 (br s, 3H), 6.60 (m, 1H), 7.38 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 30.5, 39.8, 53.0, 67.5, 106.3, 109.3, 113.2, 141.5, 153.6, 153.9, 204.5. HRMS-EI: calcd for $C_{21}H_{20}O_5$: 352.1310, found: 352.1306.

4.3.9. Compound 21. To a stirred solution of **2** (50 mg, 0.23 mmol) in dichloromethane (5 mL) was added DDQ (80 mg, 0.35 mmol) followed by aqueous HPF_6 (1 mL) and stirred for 10 min at rt. The solid formed was filtered and dried. The crude product was purified by column chromatography on silica gel (10% ethylacetate in hexane) to afford **21** (29 mg, 55%) as a yellow crystalline solid. Mp 110–112 °C. IR (KBr) ν_{max}: 1784, 1759, 1609, 1470, 1230, 1156, 1115, 1022 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, $J=5.4$ Hz, 1H), 6.54–6.59 (m, 2H), 6.79 (d, $J=3.3$ Hz, 1H), 7.14 (d, $J=3.3$ Hz, 1H), 7.57 (br s, 2H), 8.00 (d, $J=5.4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 106.1, 112.0, 112.6, 115.2, 117.0, 118.3, 143.3, 144.0,

168.2. HRMS-EI: calcd for $C_{15}H_8O_4$: 228.0422, found: 228.0429.

4.3.10. Compounds 22 and 23. To a stirred solution of **2** (50 mg, 0.23 mmol) in dichloromethane (5 mL) was added DDQ (80 mg, 0.35 mmol) followed by aqueous HPF_6 (1 mL) and stirred for 10 min at rt. The solid formed was filtered, dried and used for further reaction without purification. To a stirred solution of the salt dissolved in dichloromethane (5 mL) was added KBr (63 mg, 0.46 mmol) and Br_2 (73 mg, 0.46 mmol). After stirring the reaction mixture for further 30 min, the solvent was removed and the crude products were purified by column chromatography on silica gel (5% ethylacetate in hexane) to afford **22** (42 mg, 40%) as a red crystalline solid. Mp 164–166 °C. On further elution with 10% ethylacetate in hexane afforded **23** (26 mg, 21%) as a viscous red liquid.

Compound **22**: IR (KBr) ν_{max}: 1763, 1457, 1348, 1244, 1210, 1035, 982 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (dd, $J_1=3.5$ Hz, $J_2=5.1$ Hz, 2H), 6.82 (d, $J=3.5$ Hz, 1H), 7.10 (d, $J=3.6$ Hz, 1H), 8.08 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.2, 114.7, 118.2, 119.7, 124.6, 124.9, 140.7, 147.9, 148.3, 163.0. HRMS-EI: calcd for $C_{13}H_5Br_3O_4$ (M+3): 464.7738, found: (M+3): 464.7729. The single crystal X-ray data of this compound has been deposited in the Cambridge Crystallographic Centre and was allocated the reference no. CCDC 266763.

Compound **23**. IR (neat) ν_{max}: 1784, 1760, 1537, 1485, 1336, 1300, 1233, 1166 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.39 (d, $J=5.4$ Hz, 1H), 6.50 (d, $J=6.1$ Hz, 2H), 7.66 (d, $J=5.4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.9, 105.9, 106.3, 117.4, 121.5, 142.1, 161.3, 168.2. HRMS-EI: calcd for $C_{13}H_4Br_4O_4$ (M+4): 543.6843, found: (M+4) 543.6839.

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Conjugate addition of indoles to α,β-unsaturated ketones using $Cu(OTf)_2$ immobilized in ionic liquids☆

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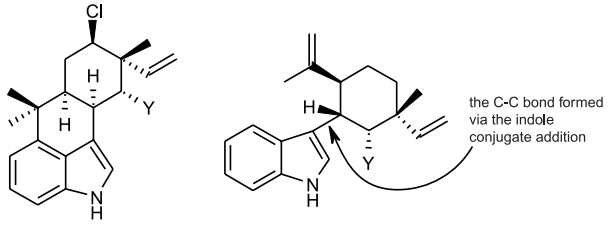
Abstract—Indoles undergo smooth conjugate addition with α,β-unsaturated ketones in the presence of 10 mol% copper(II) triflate immobilized in air and moisture stable [bmim]BF_4 ionic liquid under mild conditions to afford the corresponding conjugate addition products in high to quantitative yields. The recovery of $Cu(OTf)_2$ is facilitated by the ionic liquid. The recovered catalyst was reused four to five times with consistent activity.

1. Introduction

The conjugate addition of indoles to α,β-unsaturated ketones constitutes a key reaction in the total synthesis of complex natural products such as hapalindole.[1,2] The hapalindole alkaloids were isolated from the blue-green algae *Hapalosiphon fontinalis*. They exhibit potent antibacterial and antimycotic activity.



Hapalindole A: Y = NC
Hapalindole B: Y = NCS

Hapalindole C: Y = NC
Hapalindole D: Y = NCS

Consequently, numerous methods have been reported for the conjugate addition of indoles to electron-deficient olefins through the activation of enones or nitro alkenes by Lewis acids.[2,3] Asymmetric versions of conjugate additions of indoles to α,β-unsaturated ketones have also been reported using chiral Lewis acid catalysts to produce enantiomerically enriched indole derivatives.[4] Typically, conjugate addition reactions are performed under the influence of strong bases such as alkali metal alkoxides or hydroxides.[5] The strong basic conditions often lead to a number of undesirable side reactions such as aldol cyclizations, ester solvolysis, base induced rearrangements such as retro-Claisen or retro-Michael reactions and polymerization reactions. Subsequently, Lewis acids have been found to catalyze conjugate addition reactions under mild conditions.[6,7] However, most of the catalysts cannot be recovered and reused because they decompose under the quenching conditions. Furthermore, many of these methods often involve the use of strong acids, which always demand aqueous work-up for catalyst separation, recycling and disposal. Since indoles and their derivatives have become increasingly useful and important in the field of pharmaceuticals, the development of simple, efficient, and environmentally benign approaches are desirable.

Room temperature ionic liquids (RTLs) have been used as 'green' solvents and possess unique properties such as wide temperature liquid range, air and moisture stability, high solubilizing properties, immiscibility with a number of organic solvents, negligible vapour pressure and ease of recyclability.[8] Particularly, 1,3-dialkylimidazolium based ionic liquids are being used as green solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[9] They are referred to as 'designer solvents' as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to the imidazole moiety. These structural variations offer flexibility to the chemist to devise

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Keywords: Ionic liquids (ILs); α,β-Unsaturated ketones; $Cu(OTf)_2$; 3-Substituted indole derivatives.
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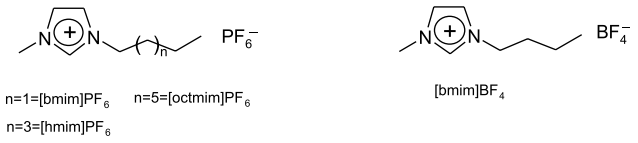


Figure 1.

idealized solvents, catering to the needs of any particular process (Fig. 1).

The high polarity and ability to solubilize both organic and inorganic compounds of ionic liquids can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.[10]

2. Results and discussion

As part of our ongoing programme in developing new synthetic methodologies[11] and in view of the emerging importance of ionic liquids as green solvents in organic reactions, we report herein the use of ionic liquids as recyclable solvents for the conjugate addition of indoles to α,β-unsaturated ketones to produce 3-substituted indole derivatives in high to quantitative yields under mild conditions (Scheme 1).

Accordingly, treatment of indole with methyl vinyl ketone in the presence of 10 mo1% copper(II) triflate immobilized in [bmim]BF_4 resulted in the formation of 4-(3-indolyl)-2-butanone **3a** in 90% yield. The reaction proceeded efficiently at room temperature with high 1,4-selectivity and complete conversion of the reaction takes place in a short period of time (3.5 h). The product obtained was isolated by simple extraction with diethyl ether. The ionic liquid was further washed with ether and reused several times without further purification. Encouraged by the results obtained with indole and methyl vinyl ketone, we turned our attention to various substituted indoles and electron-deficient alkenes. Interestingly, numerous cyclic enones and chalcones underwent 1,4-addition with a range of indoles under the reaction conditions to afford the corresponding 3-alkylated indoles. The yields are generally high to quantitative in a few hours. In a similar way to enones, other electron-deficient alkenes such as *trans*-β-nitrostyrene also afforded the conjugate addition product in excellent yield (Table 1, entry: **o**). In the absence of catalyst, the reactions did not proceed after a long reaction time (10–15 h). Interestingly, no by-products arising from 1,2-addition or bis-addition were observed. Compared to conventional solvents, enhanced reaction rates and improved yields are notable features observed using the $Cu(OTf)_2$–[bmim]BF_4 catalytic system. The reactivity of copper(II) triflate in various solvents has been studied in the reaction of 2-methylindole and cyclopentenone and the results are summarized in Table 2.

In further experiments, the reactivity of various indoles and enones were studied in both hydrophobic [bmim]PF_6 and hydrophilic [bmim]BF_4 ionic liquids. Among them, [bmim]BF_4 was found to be superior in terms of conversion and reaction rates (Table 2, runs **1** and **2**). The recovered ionic liquid containing copper(II) triflate was reused five times without loss of activity, and even after the fourth cycle, the product **3e** was obtained with similar yield and purity as that obtained in the first cycle. Commercially available ionic liquids were used in this study. The purity of [bmim]BF_4 ionic liquid is >97.0% (NMR). The use of ionic liquids as the reaction medium for this transformation helps to recycle the catalyst thereby making the process quite simple, more convenient and environmentally friendly.

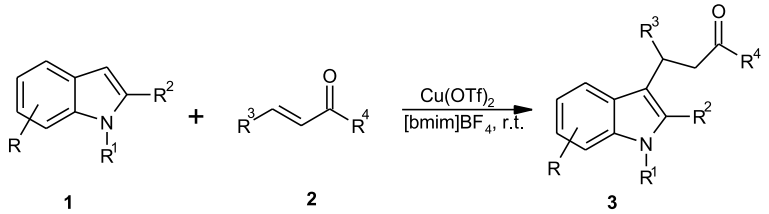
3. Conclusion

In summary, we describe a mild, clean and efficient protocol for the conjugate addition of indoles to α,β-unsaturated ketones using $Cu(OTf)_2$–[bmim]BF_4 as a novel and recyclable catalytic system. The enones show enhanced reactivity in ionic liquids thereby reducing the reaction times and improving the yield significantly. The simple experimental procedure combined with ease of recovery and reuse of this novel reaction medium is expected to contribute to the development of a green strategy for the conjugate addition reaction.

4. Experimental

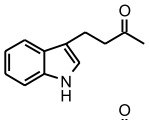
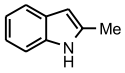
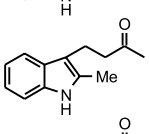
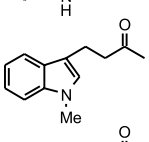
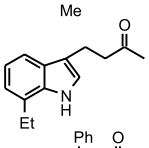
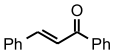
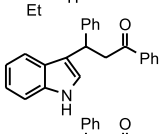
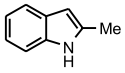
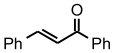
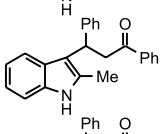
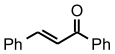
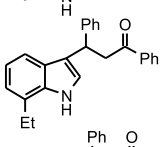
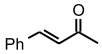
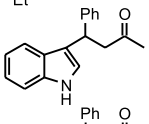
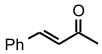
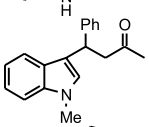
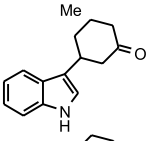
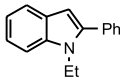
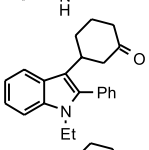
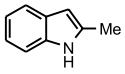
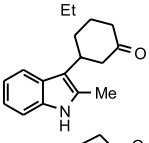
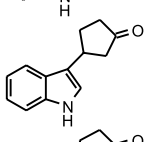
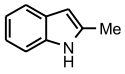
4.1. General methods

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectro-photometer using KBr optics. ^1H NMR and ^{13}C NMR spectra were recorded on Gemini 200 and Bruker Avance 300 MHz spectrometers in $CDCl_3$ using TMS as internal standard, with chemical shifts being given in ppm with respect to internal TMS and *J* values quoted in Hz. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All commercial reagents were used without purification. All reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel 60 F_{254} pre-coated glass plates, which were visualized with UV



Scheme 1.

Table 1. $Cu(OTf)_2$-catalysed conjugate addition of indoles to enones using $[bmim]BF_4$

Entry	Indole	Enone	Product[a]	Time (h)	Yield (%)[b]
a				3.5	90
b				3.0	93
c				4.0	91
d				3.5	90
e				4.5	85
f				2.0	95
g				4.0	87
h				4.0	89
i				5.0	86
j				6.0	82
k				4.0	88
l				4.5	87
m				5.0	85
n				4.5	89
o				4.0	90

[a] All the products were characterized by ^1H NMR, IR, mass spectra.
[b] Isolated and unoptimized yields.

Table 2. Reactivity of 10 mol% $Cu(OTf)_2$ in various solvents for the condensation of 2-methylindole with cyclopentenone[a]

Run	Reaction medium	Time (h)	Yield (%)
1	[bmim]BF_4	4.5	89
2	[bmim]PF_6	5.0	83
3	CH_3CN	8.5	68
4	CH_3OH	7.0	71
5	CH_2Cl_2	8.5	65

[a] Reactions were carried out in 1 mmol scale.

light and then developed by using iodine mixed with silica gel 60–120 mesh.

4.2. General procedure for the conjugate addition of indoles to α,β-unsaturated compounds

A mixture of α,β-unsaturated compound (1 mmol), indole (1 mmol) and 10 mol% $Cu(OTf)_2$ in 1-butyl-3-methyl imidazolium tetrafluoroborate (3 mL) was stirred at ambient temperature for the appropriate time (as shown in the Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined ether layers were concentrated in vacuo and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane to afford the pure 1,4-adduct. All known compounds were characterized by ^{1}H NMR, IR, mass spectra and their spectroscopic data identical to that reported in the literature.[2,3] The new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra and HRMS.

4.3. Physical and spectroscopic data for all the new compounds

4.3.1. Compound 3d. Pale yellow solid, mp 94–96 °C; IR (KBr): ν 3344, 3051, 2922, 2853, 1706, 1638, 1443, 1322, 1206, 1098, 923, 857, 737, 648 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, J=7.0 Hz), 2.10 (s, 3H), 2.78–2.90 (m, 4H), 3.05 (t, 2H, J=7.0 Hz), 6.93–7.18 (m, 3H), 7.40 (d, 1H, J=7.5 Hz), 7.92 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 19.4, 23.9, 29.9, 44.0, 115.5, 116.3, 119.5, 120.5, 121.0, 126.5, 126.8, 135.0, 208.9; EIMS *m*/*z* (%): 215 (M^+29), 187 (26), 158 (93), 130 (100), 103 (20), 89 (14), 77 (18), 63 (12), 51 (28), 43 (31); HRMS: calcd for $C_{14}H_{18}NO$ ($M+H^+$) 216.1388, found 216.1384.

4.3.2. Compound 3g. White solid, mp 125–126 °C; IR (KBr): ν 3367, 3057, 2964, 2847, 1665, 1593, 1491, 1443, 1356, 1277, 1098, 745, 692 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=6.0 Hz), 2.78 (q, 2H, J=7.0 Hz), 3.65–3.86 (m, 2H), 5.05 (t, 1H, J=7.0 Hz), 6.80 (s, 1H), 6.90 (d, 2H, J=4.2 Hz), 7.10–7.55 (m, 9H), 7.92 (d, 3H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 23.8, 38.3, 45.1, 117.2, 119.6, 120.5, 121.3, 126.2, 126.4, 126.7, 127.8 (2C), 128.0 (2C), 128.3 (2C), 128.5 (2C), 128.9, 133.0, 135.4, 137.0, 144.2, 198.6; FABMS *m*/*z* (%): 353 (M^+12), 234 (100), 219 (12), 204 (15), 154 (10), 145 (12), 130 (10), 121 (10), 109 (10), 109 (18), 105 (57), 95 (38), 83 (41), 69 (60), 55 (35); HRMS: calcd for $C_{25}H_{23}NONa$ ($M+Na^+$) 376.1677, found 376.1678.

4.3.3. Compound 3k. White solid, mp 142–143 °C; IR (KBr): ν 3387, 3041, 2931, 2861, 1698, 1458, 1339, 1222, 1064, 937, 964, 746, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.5 Hz), 1.60–1.80 (m, 1H), 1.98–2.20 (m, 3H), 2.30–2.50 (m, 3H), 2.95– 3.08 (m, 2H), 4.00 (q, 2H, J=7.5 Hz), 7.08–7.23 (m, 2H), 7.38 (d, 3H, J=8.0, Hz), 7.48 (dd, 3H, J=8.0, 2.0 Hz), 7.78 (1H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 25.8, 32.0, 37.4, 38.4, 41.3, 48.4, 109.9, 115.3, 119.0, 119.7, 121.4, 126.0, 128.5 (3C), 130.6 (2C), 132.1, 136.0, 136.9, 211.3; FABMS *m*/*z* (%): 317 (M^+100), 274 (10), 260 (27), 246 (12), 234 (10), 217 (15), 204 (11), 154 (10), 136 (12), 107 (15), 95 (10), 69 (18), 55 (20); HRMS: calcd for $C_{22}H_{24}NO$ ($M+H^+$) 318.1857, found 318.1846.

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Straightforward enantioselective synthesis of (+)-ancistrofuran

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Abstract—This paper reports the straightforward enantioselective synthesis of (+)-ancistrofuran starting from a readily available enantiopure building block. A stereofacial directed diastereoselective addition of an organocerate for the installation of the required stereogenic center served as the key step. In addition, the efficient conversion of an intermediate hydroxy aldehyde to the one-carbon homologated cyanide was developed. The sequence was achieved by the mild formation of a cyanohydrin and the subsequent one-pot two-step Barton–McCombie double deoxygenation of the hydroxyl groups.

1. Introduction

Baker and co-workers[1] isolated and identified ancistrofuran (**1**, Fig. 1) as the major component in the defensive repellent secretion used by the termite *Ancistrotermes cavithorax* major soldiers against their common ant predators. Several racemic syntheses of ancistrofuran have been reported.[2–5] The only enantioselective synthesis was reported by Mori and co-workers.[6]

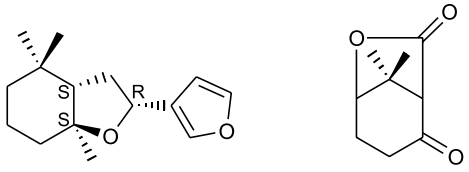
We recently developed a concise synthetic pathway to chiral, non-racemic oxo lactone **2** (8,8-dimethyl-6-oxabicyclo[3.2.1]octan-2,7-one) for the synthesis of karahana lactone.[7] In an effort to both probe the synthetic utility of this potentially useful chiral building block and to develop an efficient new synthetic route to (+)-ancistrofuran, we designed an approach to this furanosesquiterpene. The key steps utilize a stereofacial directed diastereoselective addition of a methylcerium dichloride, and the conversion of an intermediate hydroxy aldehyde to the one-carbon homologated cyanide using the formation of a cyanohydrin, followed by a double deoxygenation sequence of the hydroxyl groups.

2. Results and discussion

As shown in Scheme 1, fully stereoselective addition of methylcerium dichloride[8] to (1*S*,5*S*)-8,8-dimethyl-2-oxo-6-oxabicyclo[3.2.1]octan-7-one, (+)-**2**, gave hydroxy lactone (+)-**3** in 89% yield, and protection of the created tertiary alcohol with MOMCl (chloromethyl methyl ether) in the presence of *i*-Pr_2NEt[9] afforded (−)-**4** (92% yield). The required stereochemistry of the addition was actually established in the next step. Attempts to reduce the lactone moiety in **4** to the corresponding aldehyde (lactol) using 1.2 equiv of DIBAL (diisobutylaluminum hydride) under various conditions proved futile, giving a mixture of diol and unreacted starting material, due to the uncontrolable over-reduction. So, the desired product was obtained in two steps.

Convenient reduction of **4** with $LiAlH_4$ (lithium aluminum hydride) gave the diol (+)-**5** in 98% yield and selective oxidation of the primary alcohol function in **5** with sodium hypochlorite, mediated by TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy)[10] afforded hydroxy aldehyde (+)-**6** in 78% yield. X-ray crystallography analysis[11] carried out on the nicely crystalline diol (+)-**5** indirectly proved the proposed stereostructure for (+)-**3** (Fig. 2).

As depicted in our synthetic plan, elaboration of aldehyde (+)-**6** to compound (+)-**8** next required deoxygenation of



(+)-ancistrofuran (**1**) **2**

Figure 1.

Keywords: Ancistrofuran; Natural products; Enantioselective synthesis; One-carbon homologation.
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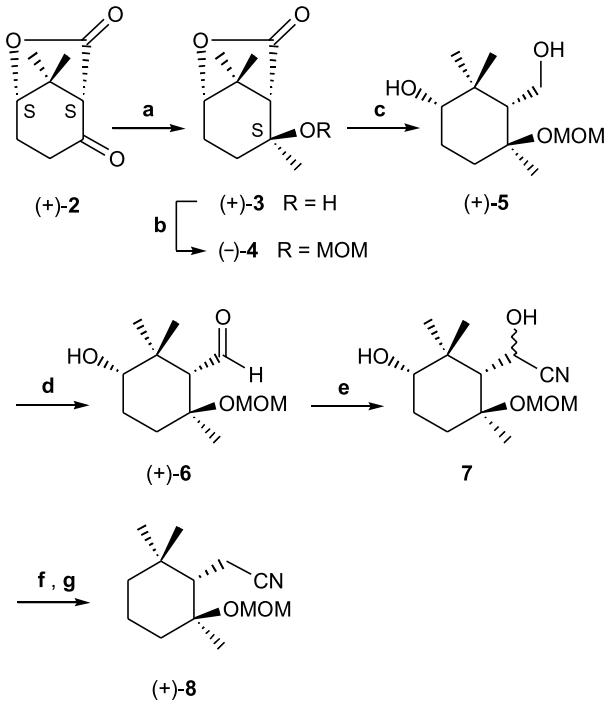


Scheme 1. Reagents and conditions: (a) dried $CeCl_3$ (3 equiv), MeLi (3 equiv), THF, 12 h, −78 °C to rt, 89%; (b) MOMCl (7 equiv), *i*-Pr_2NEt (7.7 equiv), CH_2Cl_2, 48 h, rt, 92%; (c) $LiAlH_4$ (2 equiv), Et_2O, 3 h, rt, 98%; (d) TEMPO (0.07 equiv), KBr (0.15 equiv), $Bu_4N^+Cl^-$ (0.06 equiv), NaOCl (2.6 equiv), $NaHCO_3$/brine, CH_2Cl_2, 0 °C, 78%; (e) KCN (25 equiv), AcOH (32.5 equiv), EtOH, 12 h, rt, 80%; (f) PhOCSCl (4 equiv), DMAP (8 equiv), CH_2Cl_2, 12 h, rt, then (g) Bu_3SnH (4 equiv), cat. AIBN, toluene, 1 h, reflux, 60% two steps.

the hydroxyl substituent and conversion of the aldehyde function to the one-carbon homologated cyanide. This could be conveniently combined without resorting to specific additional steps, with the aid of a cyanohydrin. Thus, the cyanohydrin **7** was prepared from aldehyde (+)-**6** (KCN, AcOH) as a mixture of diastereomers in 80% yield. Barton–McCombie[12] double deoxygenation of the two hydroxyl moieties of **7** was achieved in an one-pot two-step process via the corresponding thionocarbonate ester derivatives which were reduced smoothly with tri-*n*-butyltin to provide the target molecule (+)-**8** in 60% yield for the two steps.

With the desired nitrile (+)-**8** in hand, the introduction of the furan group was addressed using 3-lithiofuran[13] (Scheme 2).

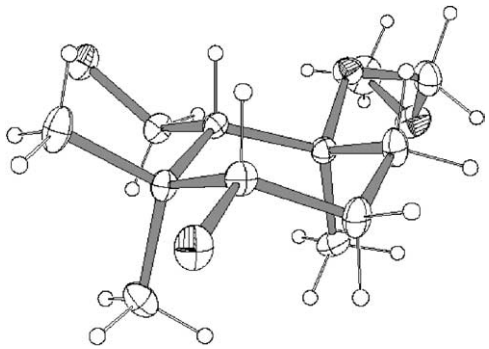
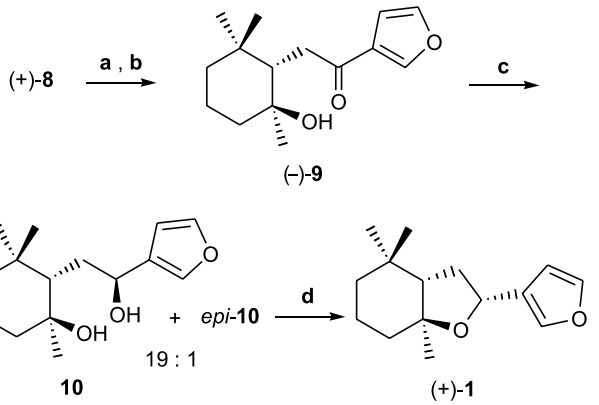


Figure 2. ORTEP view of (+)-**5**.



Scheme 2. Reagents and conditions: (a) (i) 3-bromofuran (3 equiv), *n*-BuLi (3 equiv), Et_2O, −78 °C, 30 min; (ii) hexane (hexane/ether=4:1), (+)-**8**, −78 to −45 °C, then −45 °C, 15 h; (b) 35% aq HCl (4.4 equiv), MeOH, 12 h, rt, 56% two steps; (c) $LiHBEt_3$ (2 equiv), THF, 12 h, −78 °C to rt, 95%; (d) *p*-TsCl (4 equiv), pyridine, 72 h, rt, 75%.

The main shortcoming of the use of 3-lithiofuran as a precursor is that very low temperatures must be maintained throughout the reaction. Indeed, temperatures exceeding −40 °C during the course of reagent generation and use result in isomerisation to the more thermodynamically stable 2-lithiofuran.[14] Unfortunately, in the present work, the addition reaction upon (+)-**8** was sluggish at low temperature. As a result, reactions were rigorously conducted at −45 °C so that the addition process was over in a few hours, while minimizing isomerisation. While studying the nucleophilic addition, we also observed that solvent effects were crucial for the outcome of the reaction. Due to the acidity of the hydrogens in the α-carbon atom, enolisable nitriles such as (+)-**8** may be deprotonated by organolithium reagents if the latter are employed in polar solvents.[15] Effectively, in our attempts, the addition of 3 equiv of 3-lithiofuran[16] to nitrile (+)-**8** in ether as a solvent and subsequent acidification (HCl, MeOH) afforded the expected hydroxy ketone (−)-**9** in only 24% yield after 15 h at −45 °C, a substantial amount of the deprotected starting material (ca. 35%) being recovered.[17] Following the same conditions, reaction performed in hexane–ether (4/1) gave complete conversion, and afforded pure (−)-**9** in 56% yield after column chromatography. At this stage conversion of (−)-**9** into (+)-**1** was carried out according to the procedure developed by Baker and co-workers for the synthesis of racemic **1**.[4,5] The crystalline hydroxy ketone (−)-**9** was reduced with lithium triethylhydroborate to give diol **10**, contaminated with ca. 5% of its epimer at the newly generated chiral center. Treatment of **10** with *p*-toluenesulfonyl chloride in pyridine gave crude **1**, which was purified by silica gel column chromatography, then preparative HPLC (see Section 4), to give pure (+)-ancistrofuran (**1**) whose IR and ^1H NMR spectroscopic data were identical with those reported.[6] The high optical purity of (+)-**1** (ee>98%) was verified by analytical chiral HPLC [(*S*,*S*)-Whelk-O1, 250×4.6 mm; solvent: *n*-hexane–isopropanol (95/5), 1 mL/min].

3. Conclusions

To sum up, we presented a straightforward enantioselective

synthesis of (+)-ancistrofuran with the aid of a provisional hydroxyl group, a diastereofacial selectivity and a specific homologation sequence as the key steps. The target molecule was prepared from a versatile enantiopure building block by an 11-step sequence in 12.5% overall yield. We believe that our strategy compares favourably with the one described[6] as far as number of steps, stereoselectivity and chemical yields are concerned. In addition, the enantiomer (−)-ancistrofuran can be synthesized from the available *ent*-**2**[7] following the reaction sequence detailed above.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz. Infrared spectra were measured as films or KBr pellets on an FT-IR spectrometer. Optical rotations were measured on a digital polarimeter at 25 °C with a Na lamp. Melting points were uncorrected. Routine monitoring of reactions was performed using Merck Silica gel 60 F254, aluminum supported TLC plates. Column chromatography was performed with Silica gel 60 (230–400 mesh) and gradients pentane/ether as eluent, unless otherwise stated. Microanalyzes were performed at our University. Unless otherwise stated, the solutions were dried over magnesium sulfate and evaporated in a rotary evaporator under reduced pressure.

4.1.1. (1*S*,2*S*,5*S*)-2-Hydroxy-2,8,8-trimethyl-6-oxabicyclo[3.2.1]octan-7-one ((+)-3). Finely crushed Cerium(III) chloride heptahydrate (8.65 g, 23.2 mmol) was placed in a 500 mL three-necked flask containing a stirring bar and evacuated (ca. 0.1 Torr). The apparatus was heated at 80 °C for 4 h, then the temperature was increased slowly to 140 °C and maintained 5 h. The white solid was cooled to rt, the apparatus was blanketed with argon, THF (26 mL) was added and the mixture was stirred for 12 h. A 1.5 M solution of methyllithium (15.5 mL, 23.2 mmol) was added dropwise at −78 °C to the resulting mixture. After 1 h at −78 °C, a solution of (+)-**2** (1.30 g, 7.73 mmol) in THF (10 mL) was added dropwise and the reaction mixture was allowed to rise to rt. After 12 h the reaction mixture was diluted with ether, poured in an aqueous solution of NH_4Cl and extracted with ether. The organic extracts were combined, washed with brine, dried, filtered and concentrated. Purification by column chromatography afforded 1.27 g (89% yield) of pure alcohol (+)-**3** as white crystals; mp=95 °C. $[\alpha]_D^{25}$ +29.0 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3397, 1763, 1148, 1054 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (br d, *J*=4.7 Hz, 1H), 2.13 (br s, 1H), 2.07 (dddd, *J*=14.5, 11.6, 7.4, 0.6 Hz, 1H), 1.94 (s, OH), 1.87–1.77 (m, 1H), 1.72–1.65 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9 (C), 85.5 (CH), 70.4 (C), 59.5 (CH), 42.2 (C), 31.9 (CH_2), 30.6 (CH_3), 27.9 (CH_3), 22.1 (CH_2), 21.5 (CH_3). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.75. Found: C, 64.88; H, 8.79.

4.1.2. (1*S*,2*S*,5*S*)-2-Methoxymethoxy-2,8,8-trimethyl-6-oxabicyclo[3.2.1]octan-7-one ((−)-4). To a stirred solution of (+)-**3** (1.20 g, 6.51 mmol) in CH_2Cl_2 (25 mL) was added at 0 °C, diisopropyl ethylamine (8.75 mL, 50.2 mmol) and chloromethyl methyl ether (3.50 mL, 46.1 mmol). After 48 h at rt, the reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with water. The aqueous washes were back-extracted and the combined organic layers were successively washed with 1 M HCl, saturated solution of $NaHCO_3$ and brine. The organic layer was dried, filtered and concentrated to afford after purification by column chromatography 1.37 g (92% yield) of pure (−)-**4** as a solid; mp=77 °C. $[\alpha]_D^{25}$ −14.2 (*c* 1.0, $CHCl_3$). IR (KBr): ν 1766, 1153, 1048 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 and 4.53 (AB, *J*=7.2 Hz, 2H), 4.24 (br d, *J*=4.5 Hz, 1H), 3.32 (s, 3H), 2.26 (br s, 1H), 2.05–1.76 (m, 3H), 1.55 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4 (C), 90.9 (CH_2), 85.2 (CH), 75.2 (C), 57.4 (CH), 55.6 (CH_3), 42.0 (C), 30.1 (CH_2), 28.0 (CH_3), 25.3 (CH_3), 22.2 (CH_2), 21.2 (CH_3). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.99; H, 8.81.

4.1.3. (1*S*,3*R*,4*S*)-3-Hydroxymethyl-4-methoxymethoxy-2,2,4-trimethyl-cyclohexanol ((+)-5). A solution of (−)-**4** (1.20 g, 5.26 mmol) in dry ether (30 mL) was slowly added at 0 °C to a stirred slurry solution of $LiAlH_4$ (400 mg, 10.5 mmol) in dry ether (10 mL). The reaction mixture was allowed to rise to rt. After 3 h, Celite (10 g) and $Na_2SO_4\cdot 10H_2O$ (10 g) were added and the solution was stirred for a further 1 h. The mixture was filtered through a pad of $MgSO_4$ and concentrated. Column chromatography of the residue afforded 1.20 g (98% yield) of pure diol (+)-**5** as white crystals; mp=86 °C. $[\alpha]_D^{25}$ +8.4 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3391, 1141, 1069 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.70 and 4.63 (AB, *J*=7.4 Hz, 2H), 3.82 and 3.67 (br ABX, *J*=11.0, 6.8 Hz, 2H), 3.31 (s, 3H), 3.30 (partially overlapped m, 1H), 1.93–1.72 (m, 2H), 1.66–1.51 (m, 2H), 1.46–1.38 (m, 1H), 1.33 (s, 3H), 1.12 (s, 3H), 0.80 (br s, 3H). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.35; H, 10.38.

4.1.4. (1*S*,3*S*,6*S*)-3-Hydroxy-6-methoxymethoxy-2,2,6-trimethyl-cyclohexanecarbaldehyde ((+)-6). To a stirred solution of (+)-**5** (400 mg, 1.72 mmol) and 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO, 29 mg, 0.127 mmol) in CH_2Cl_2 (20 mL) was added a saturated aqueous solution of sodium bicarbonate (4 mL) containing potassium bromide (30 mg, 0.252 mmol) and tetrabutylammonium chloride (29 mg, 0.104 mmol). To this cooled (0 °C) and well stirred mixture was added dropwise 2 mL of aqueous solution made of sodium hypochlorite (solution containing ca. 9.6% chlorine, 2.75 mL, 4.47 mmol), a saturated sodium bicarbonate solution (5 mL) and brine (11 mL). This solution (2 mL) was added every hour until the total consumption of the starting material monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried, filtered and concentrated. Purification by silica gel column chromatography afforded 309 mg (78% yield) of pure aldehyde (+)-**6** as an oil. $[\alpha]_D^{25}$ +43.0 (*c* 1.0, $CHCl_3$). IR (film): ν 3384, 2829, 1713, 1157 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (d, *J*=4.9 Hz, 1H), 4.74 and 4.62 (AB, *J*=7.3 Hz, 2H), 3.48 (br dd, *J*=5.8, 3.1 Hz, 1H), 3.34 (s, 3H), 2.33 (d, *J*=4.9 Hz, 1H), 2.06 (ddt, *J*=13.0, 9.6,

3.0 Hz, 1H), 1.88 (ddd, $J=13.8$, 10.4, 3.6 Hz, 1H), 1.29 (s, 3H), 1.15 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.1 (CH), 89.9 (CH_2), 75.7 (C), 74.4 (CH), 65.2 (CH), 55.3 (CH_3), 38.1 (C), 31.5 (CH_2), 28.4 (CH_3), 26.2 (CH_2), 24.1 (CH_3), 22.2 (CH_3). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.86; H, 9.59.

4.1.5. Hydroxy-(3-hydroxy-6-methoxymethoxy-2,2,6-trimethyl-cyclohexyl)-acetonitrile (7). This reaction must be done in a well-ventilated hood. To a stirred suspension of potassium cyanide (10.6 g, 163 mmol) in absolute ethanol (50 mL) was added dropwise glacial acetic acid (12.1 mL, 212 mmol) under an argon atmosphere. After 1.5 h, a solution of (+)-**6** (1.50 g, 6.51 mmol) in absolute ethanol (18 mL) was added dropwise at 0 °C, and the solution was stirred at rt for 12 h. The reaction mixture was diluted with ether, poured into water and extracted with ether. The combined extracts were washed with brine, dried, filtered and concentrated. Purification by column chromatography gave 1.34 g (80% yield) of an inseparable mixture (1:2) of diastereomers **7**. IR (film): ν 3406, 2241, 1143, 1050 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89–4.82 (m, 1H, major and minor), 4.75 and 4.65 (AB, $J=7.2$ Hz, 2H, minor), 4.74 and 4.66 (AB, $J=7.5$ Hz, 2H, major), 3.32 (s, 3H, major and minor), 3.32 (m, 1H, major and minor), 1.90–1.42 (m, 5H, major and minor), 1.52 (s, 3H, minor), 1.50 (s, 3H, major), 1.20 (s, 3H, minor), 1.19 (s, 6H, major), 1.02 (s, 3H, minor).

4.1.6. ((1*S*,2*S*)-2-Methoxymethoxy-2,6,6-trimethyl-cyclohexyl)-acetonitrile ((+)-8). To a stirred solution of cyanohydrin **7** (1.26 g, 4.90 mmol) in CH_2Cl_2 (40 mL) was added at 0 °C DMAP (4.80 g, 39.2 mmol) and phenyl chlorothionoformate (2.70 mL, 19.5 mmol) under an argon atmosphere. After 12 h at rt, the reaction mixture was poured into water and extracted with ether. The combined organic extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue afforded 2.30 g of a diastereomeric mixture of phenoxythiocarbonyl ester. To a stirred solution of ester (2.30 g, 4.34 mmol) in toluene (30 mL) was added tri-*n*-butyltin hydride (4.60 mL, 17.1 mmol) and a catalytic amount of AIBN in toluene (20 mL) under an argon atmosphere. The reaction mixture was stirred under reflux for 1 h, cooled and concentrated. The resulting oily residue was purified by silica gel column chromatography to give 663 mg of pure (+)-**8** (60% yield for the two steps). $[\alpha]_D^{25}$ +4.7 (*c* 1.0, $CHCl_3$). IR (film): ν 2253, 1246, 1167, 1054 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (s, 2H), 3.37 (s, 3H), 2.61 and 2.24 (ABX, $J=17.2$, 7.0, 4.7 Hz, 2H), 1.84 (m, 2H), 1.65–1.24 (m, 5H), 1.16 (s, 3H), 1.08 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.4 (C), 89.9 (CH_2), 78.2 (C), 55.4 (CH_3), 52.3 (CH), 41.0 (CH_2), 38.3 (CH_2), 35.2 (C), 33.0 (CH_3), 21.1 (CH_3), 19.7 (CH_3), 19.6 (CH_2), 12.9 (CH_2). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.60; H, 10.27.

4.1.7. 1-Furan-3-yl-2-((1*S*,2*S*)-2-hydroxy-2,6,6-trimethyl-cyclohexyl)-ethanone ((−)-9). To a solution of 3-bromofuran (223 μL, 2.48 mmol) in ether (3 mL) was added dropwise, at −78 °C, *n*-BuLi (1.6 M solution in hexanes, 1.55 mL, 2.48 mmol) under an argon atmosphere and the resulting solution was stirred at −78 °C for 1.5 h. Hexane (3.5 mL) was added at −78 °C and the mixture was stirred for 10 min before addition of a solution of (+)-**8** (184 mg, 0.82 mmol) in hexane (7 mL). The mixture was allowed to rise slowly to −45 °C and maintained at the same temperature over 15 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and the aqueous phase was extracted with AcOEt. The combined extracts were washed with water, dried, filtered and concentrated. To the crude residue in absolute MeOH (10 mL) was added concentrated HCl solution (35% wt in water, 0.35 mL) at 0 °C. The solution was allowed to rise to rt and then stirred overnight. The reaction mixture was diluted in ether, poured into a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried, filtered and concentrated. Column chromatography of the residue gave 115 mg (56% yield for the two steps) of compound (−)-**9** as a white solid; mp=94 °C. $[\alpha]_D^{25}$ −10.3 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3383, 1703, 1169 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.41 (br t, $J=$ 1.7 Hz, 1H), 6.76 (br dd, $J=1.7$, 0.7 Hz, 1H), 2.90 and 2.76 (ABX, $J=16.8$, 5.8, 4.7 Hz, 2H), 2.11 (br t, $J=5.2$ Hz, 1H), 1.83–1.75 (m, 1H), 1.61–1.20 (m, 5H), 1.14 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.5 (C), 147.0 (CH), 144.1 (CH), 127.7 (C), 108.8 (CH), 73.0 (C), 51.9 (CH), 43.3 (CH_2), 41.1 (CH_2), 37.1 (CH_2), 35.2 (C), 32.5 (CH_3), 22.5 (CH_3), 21.3 (CH_3), 20.5 (CH_2). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.21; H, 8.89.

4.1.8. (1*S*,2*S*)-2-((*S*)-2-Furan-3-yl-2-hydroxy-ethyl)-1,3,3-trimethyl-cyclohexanol (10). To a stirred solution of (−)-**9** (100 mg, 0.40 mmol) in THF (15 mL), a 1 M THF solution of lithium triethylhydridoborate (800 μL, 0.80 mmol) was added dropwise at −78 °C under an argon atmosphere. The reaction mixture was stirred for a further 3 h at −78 °C, then allowed to rise to rt. After 12 h, the solution was poured into water and extracted with ether. The organic extracts were combined, washed with brine, dried, filtered and concentrated. Purification by column chromatography of the residue afforded 96 mg (95% yield) of **10** contaminated with ca. 5% of its epimer. This mixture was used in the next steps without further purification. IR (film): ν 3362, 1158, 1029, 890 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 2H), 6.34 (br t, $J=1.3$ Hz, 1H), 4.99 (dd, $J=6.8$, 4.3 Hz, 1H), 2.02–1.73 (m, 3H), 1.58–1.30 (m, 6H), 1.23 (s, 3H), 0.81 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.9 (CH), 139.0 (CH), 129.5 (C), 109.0 (CH), 73.6 (C), 65.9 (CH), 50.0 (CH), 44.1 (CH_2), 41.8 (CH_2), 35.0 (CH_2), 33.9 (CH_3), 32.8 (C), 23.5 (CH_3), 21.4 (CH_3), 20.3 (CH_2).

4.1.9. (2*R*,3a*S*,7a*S*)-2-Furan-3-yl-4,4,7a-trimethyl-octahydro-benzofuran, ancistrofuran ((+)-1). *p*-Toluenesulfonyl chloride (275 mg, 1.44 mmol) was added to a solution of **10** (91 mg, 0.36 mmol) in pyridine (6 mL) at 0 °C and the mixture was allowed to rise to rt. After stirring for 3 days, the reaction mixture was poured into water and extracted with ether. The combined organic extracts were washed with 1 M HCl, saturated $NaHCO_3$, brine, dried and concentrated. The oily residue was purified by column chromatography followed by preparative high performance liquid chromatography (CHIRALCEL-OJ, 250×10 mm; solvent: *n*-hexane–isopropanol (90/10), 4.5 mL/min;

detection at 230 nm) to give 63 mg (75% yield) of pure (+)-**1**. $[\alpha]_D^{25}$ +8.1 (*c* 1, $CHCl_3$). IR (film): ν 1162, 1038, 991 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 2H), 6.37 (m, 1H), 4.91 (dd, $J=9.2$, 6.9 Hz, 1H), 2.19 (ddd, $J=$ 11.7, 6.7, 5.4 Hz, 1H), 1.97–1.32 (m, 7H), 1.24–1.16 (m, 1H), 1.13 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1 (CH), 138.8 (CH), 129.3 (C), 109.1 (CH), 81.0 (C), 71.6 (CH), 57.4 (CH), 40.8 (CH_2), 39.1 (CH_2), 33.2 (CH_3), 32.9 (CH_2), 31.4 (C), 23.4 (CH_3), 21.3 (CH_2), 20.4 (CH_3). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.09; H, 9.43.

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Pyranosylmagellanicus a novel structural class of polyhalogenated acetogenins from *Ptilonia magellanica*

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Abstract—Three naturally occurring pyranosyl-like polyhalogenated metabolites **1–3** as well as their likely biogenetic precursor, the linear compound **4**, have been isolated from the red alga *Ptilonia magellanica*. They are the first compounds within the genus that incorporate chlorine in their network. Compound **3** have structural features reminiscent of the universal chemical signal AI-2 (autoinducer-2) for bacterial communication.

1. Introduction

The significant antimicrobial activity of the extract of several species of red alga of the Bonnemaisoniaceae family led to the discovery of fimbrolides from *Delisea pulchra*.[1–3] They are halogenated furanones structurally similar to bacterial *N*-acyl homoserine lactone (AHLs or autoinducer-I), a family of small diffusible intercellular signaling molecules found in nature as key regulators of the community behavior of a number of genera of Proteobacteria, in a process commonly termed quorum sensing (QS) and that gram-negative bacteria use to coordinate cell population density-dependent control of gene expression.[4] Additionally, furanones possess AHL-antagonistic activity, interfering with AHL-regulated processes by competition for the binding site on the receptor proteins,[5] inhibiting QS in biofilm bacteria,[6] swarming motility,[7] and defending *D. pulchra* against extensive bacterial colonization by regulating expression of the virulence factor required for infection.[8,9]

In spite of the significant research carried out with naturally occurring furanones from *D. pulchra* little additional work to find new related naturally occurring metabolites was pursued since 1997.[10,11] This prompted us to search for novel compounds from the scarcely studied genus *Ptilonia* within the Bonnemaisoniaceae family. While *P. australasica* was rich in polybrominated acyclic and cyclic γ-pyrone derivatives,[12] *Ptilonia magellanica* from the Kergelen Islands yielded solely a linear polybrominated acetate,[13] these two being the only studied species of the genus. *P. magellanica*, like *D. pulchra*, stave off colonization by common epiphytes, which colonize other alga in the immediate area. Because of our interest in benthic organisms from the Chilean coasts[14–18] we decided to study *P. magellanica* collected at the Strait of Magellan, and now we report on three polyhalogenated pyranosyl-like acetogenins and an acyclic polyhalogenated enone.

2. Results and discussion

Pyranosylmagellanicus A–C, **1–3**, Figure 1, are polyhalogenated pyranosyl-like hemiacetal that represent a new

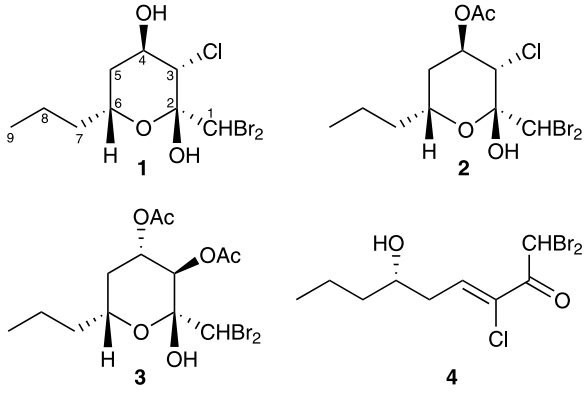

Figure 1. Pyranosylmagellanicus A–C, **1–3**, and **4**.

Keywords: Marine halogenated acetogenins; Red algae; Ptilonia.
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structural class of acetogenins, being the first compounds within the genus that incorporate chlorine in their network.

From the crude extract of *P. magellanica* compounds **1–4** were obtained after flash chromatography followed by HPLC. Compound **1** was obtained as an oil whose EIMS spectrum showed peaks at *m/z* 347/349/351/353, with relative intensities suggestive of two bromine atoms and one chlorine, which correspond to the empirical formula $C_9H_{14}O_2ClBr_2$ $[M-OH]^+$ (HREIMS). Absorptions for hydroxyl groups at 3480 and 3154 cm^{-1} were observed in their IR spectrum.

The ^{13}C NMR and DEPT spectra of **1** (Table 1), showed the presence of nine carbon signals assigned to $1CH_3$, $3CH_2$, 4CH, and one quaternary carbon bearing oxygen. The following ^1H NMR signals: four protons geminal to heteroatom [δ 5.85 (s), δ 4.32 (d, $J=2.9$ Hz), δ 4.24 (br s) and δ 4.20 (m)]; six methylene protons at δ between 1.95–1.38; two hydroxylic protons [δ 4.47 (s), δ 3.63 (d, $J=7.9$ Hz)] interchangeable with D_2O and a terminal methyl group [δ 0.92 (t, 7.2)] coupled to an adjacent methylene account for all of the 15 protons of **1**.

A COSY experiment established the connectivities H-3–H_3-9. The chemical shifts of C-4 (δ 70.4) and C-6 (δ 66.8) indicate that these carbons bear oxygen. The acetylation of **1** gave a monoacetate derivative suggesting the remaining hydroxyl group was tertiary. The absence of other insaturations in the IR spectrum combined with the ^{13}C NMR signal at 96.8 ppm indicates that the remaining oxygen atom must form part of a hemiacetalic ring, which agrees with the degree of unsaturation given by the molecular formula. The remaining heteroatoms, a chlorine, and two bromine, were attached to C-3 (δ_H 4.32d, δ_C 55.2) and C-1 (δ_H 5.85s, δ_C 51.9), respectively.

The regiochemistry of the halogens was corroborated by the MS of **1**, which showed a peak at *m/z* 199/201/203 corresponding to the fragment $[O{\equiv}C{-}CHBr_2]^+$. The hemiacetalic carbon C-2 was confirmed by the HMBC correlations 2-*OH*/C-1, C-2, C-3, which also secured the linkage C-1–C-2. All these data support the structure proposed for **1**.

The ^1H NMR data for **2** are very similar to those of **1**. The most significant difference was the proton chemical shift of H-4. This was observed at δ 4.24 for **1** and appeared at δ 5.18 in compound **2**. This variation together with the methyl signal at δ 2.12 ppm indicates that **2** is the acetate derivative of **1**. Acetylation of **1** gave **2** both having identical NMR data.

Compound **3** was a colorless oil. Their ^1H and ^{13}C NMR spectra showed signals for two acetate groups. This compound contains the same C-4–C-9 fragment as **2**. H-3 and C-3 chemical shifts (δ_H 5.47 ppm, δ_C 70.0 ppm) indicate that the chlorine atom at C-3 in **2** has been replaced by an acetate group.

The relative stereochemistry of compounds **1–3** was assigned on the basis of a NOESY experiment, coupling constants, and molecular mechanics calculations, Figure 2. The NOEs observed between the respective H-6 of **1** and **2** with their corresponding hydroxylic protons established a syn periplanar relationship. This, crossed with the NOEs observed between the remaining methines bearing heteroatom, allowed the whole stereochemistry of both **1** and **2** to be established. The large coupling constants measured for H-3, H-4, and H-6 of **3** are compatible with the NOEs depicted in Figure 2. The minimized structures **1–3** (Fig. 2) are consistent with the observed NOEs. The comparison of the well-resolved *J*-values of the selected protons of these compounds with the theoretical coupling constants given by the program[19] proved to be in good agreement.

Compound **4** was isolated as a colorless oil. The EIMS spectrum showed peaks at *m/z* 346/348/350/352, with relative intensities suggestive of two bromine and one chlorine atoms, which correspond to the empirical formula

Table 1. ^1H and ^{13}C NMR Data of compounds **1–4** [500 MHz, δ ppm, (*J*) Hz, $CDCl_3$]

#	**1**		**2**		**3**		**4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	5.85s	51.9	5.91 (s)	53.1	5.59s	49.3	6.66s	38.4
2	—	96.8	—	95.8	—	96.6	—	181.0
3	4.32 (d, 2.9)	55.2	4.34 (d, 2.6)	53.4	5.47 (dd, 1.7, 9.6)	70.0	—	127.9
4	4.24 br s	70.4	5.18, ddd (2.6, 2.9, 2.9)	71.0	5.27 (ddd, 5.0, 9.6, 11.5)	70.4	7.39 (dd, 7.0, 7.0)	142.5
5	*β*: 1.63m	31.6	*β*: 1.60m	29.0	*β*: 2.16 (ddd, 2.7, 5.0, 12.7)	36.1	*a*: 2.56m	37.8
	α: 1.95 (ddd, 3.1, 12.3, 12.3)		*α*: 1.98 (ddd, 3.3, 12.0, 12.0)		*α*: 1.48m		*b*: 2.64m	
6	4.20m	66.8	4.20m	67.1	4.03 (dddd, 2.2, 4.5, 10.0, 10.0)	69.1	3.89m	70.0
7	*a*: 1.49m	37.2	*a*: 1.40m	37.1	*a*: 1.38m	36.7	*a*: 1.50m	39.7
	b: 1.62m		*b*: 1.58m		*b*: 1.60m		*b*: 1.50m	
8	*a*: 1.38m	18.5	*a*: 1.30m	18.4	*a*: 1.40m	18.5	*a*: 1.39m	18.7
	b: 1.50m		*b*: 1.56m		*b*: 1.48m		*b*: 1.50m	
9	0.92 (t, 7.2)	13.9	0.91 (t, 7.2)	13.8	0.92 (t, 7.2)	13.9	0.95 (t, 7.1)	13.9
3 C=O	—	—	—	—	—	169.5	—	—
3 CH_3	—	—	—	—	2.10s	20.8	—	—
4 C=O	—	—	—	169.7	—	170.3	—	—
4 CH_3	—	—	2.12s	21.1	2.00s	20.9	—	—
2 OH	4.47s	—	3.54s	—	3.17 (d, 1.7)	—	—	—
4 OH	3.63 (d, 7.9)	—	—	—	—	—	—	—

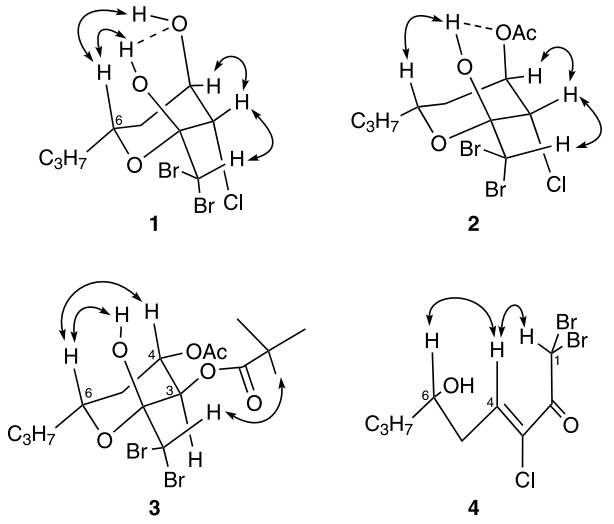

Figure 2. Selected NOEs of **1**–**4**.

$C_9H_{13}O_2ClBr_2$ $[M]^+$ (HREIMS). Absorption for hydroxyl and carbonyl groups at 3389 and 1701 cm^{-1}, respectively, were observed in the IR spectrum. Its ^{13}C NMR and DEPT spectra (Table 1) showed the presence of nine carbon signals assigned to $1CH_3$, $3CH_2$, 3CH (one olefinic and two geminal to heteroatom) and two quaternary carbons (one olefinic and one carbonyl). The two degrees of unsaturation given by the molecular formula indicate that **4** is acyclic.

Compound **4** has an identical carbon atom number and halogen pattern to **1**–**3** suggesting an open form of the pyrane ring for the backbone of **4**. A COSY experiment established the connectivities H-4–H3-9. The HMBC correlation H-4/C-2, C-3 allowed connecting C-3 bearing chlorine (δ 123.9) with C-2. Thus, the remaining carbon attached to two bromine atoms must be linked to C-2. The regiochemistry of the halogens was confirmed by the MS of **4**, which showed the base peak at *m/z* 175/177 corresponding to fragment $[O{\equiv}C{-}CCl{=}CHC_5H_{11}O]^+$.

The relative stereochemistry at C-6 and the geometry of the double bond were established by NOESY experiments. The NOE effect observed between H-4 and H-1, and H-6 established the *Z* geometry of the double bond, and an **S* configuration for C-6. This completes the structure and stereochemistry of the enone as depicted in **4**. On standing **4** converts to **5**, suggesting that **4** may be the biogenetic precursor of the cyclic acetogenins **1**–**3**, Figure 3. Attempts to determine the absolute configuration of **1** using the Mosher method were unsuccessful due to the lack of reactivity toward MTPA.

At least two types of signaling molecules are widespread and have been extensively studied: the *N*-acylhomoserine lactones (AHLs) commonly used by Gram-negative

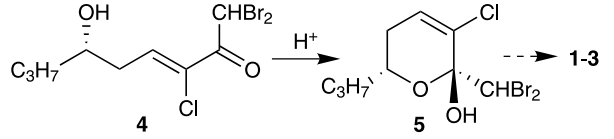

Figure 3. Possible biogenetic pathway for **1**–**3**.

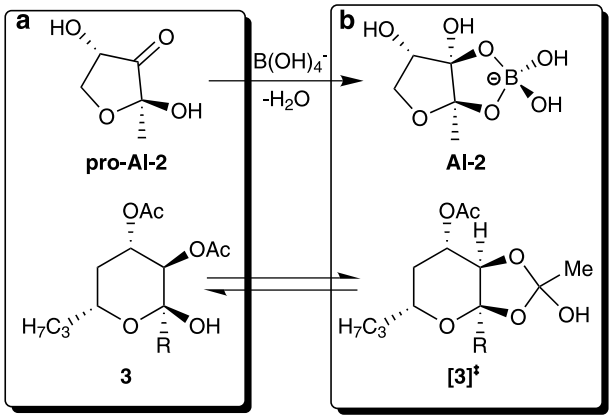

Figure 4. Structural and stereochemical analogy of the pairs pro-AI-2/**3** and AI-2/**3**‡.

bacteria, and peptide pheromones generally used by Gram-positive bacteria.[20]

Gram-positive bacteria, such as *V. harveyi*, have evolved an alternative quorum-sensing mechanism involving two independent autoinducers, one of which is the AHL (AI-1) and the other chemical signal, autoinducer-2 (AI-2), is a furanosyl borate diester molecule (Fig. 4). While AHLs are used for intraspecies communication, AI-2 has been proposed to act as a universal chemical signal for interspecies communication,[21] allowing this microorganism to sense and respond to cells of differing species.

Higher organisms have developed mechanisms that enable them to detect and respond to AHL messaging systems in order to prevent or limit infection. An example, as stated above, is the alga *D. pulchra*, which produces furane lactones to specifically interfere with AHL-mediated QS-systems.[5] Pyranosylmagellanicus, for instance **3**, Figure 4, that conserve the key stereocenters of pro-AI-2/AI-2, (box a), or even a likely intermediate **3**,‡ which is reminiscent of AI-2, (box b), encourage speculations about if these compounds may serve as autoinducer agonist or antagonist.

Naturally occurring metabolites that are structural and stereochemically related to AI-2 add attractiveness as potential interesting biological and biomedical compounds since QS has received much attention as a novel target for drug design.[22] We are now pursuing raw material for new tasks.

3. Experimental

3.1. General procedures

Optical rotations were measured on a Perkin-Elmer model 343 Plus polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin-Elmer 1650/FTIR spectrometer. ^1H and ^{13}C NMR, HSQC, HMBC, COSY, and NOESY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR. Two-dimensional NMR spectra were obtained with the standard Bruker software. EIMS and HRMS data were taken on a Micromass Autospec

spectrometer. HPLC separations were performed with a Hewlett Packard 1050 (Jaigel-Sil semipreparative column, 10 μ, 20×250 mm) with hexane–EtOAc mixtures. Merck Si gels 7734 and 7729 were used in column chromatography. The spray reagent for TLC was H_2SO_4–H_2O–AcOH (1/4/20).

3.2. Biological material

P. magellanica (Montagne) J Agardh 1852, was collected by SCUBA diving off Strait of Magellan (Chile).

3.3. Extraction and isolation

Air-dried samples (636 g) were extracted with petroleum ether at room temperature, and were concentrated to give a dark residue (1.4 g), which was chromatographed by flash chromatography on silica gel. The fraction eluted with hexane–EtOAc (92/8) (381 mg) was further separated on HPLC to give compounds **1** (4.2 mg), **2** (5.0 mg) and **4** (4.5 mg). From the fraction eluted with hexane–EtOAc (70/30) (381 mg) compound **3** (2.7 mg) was obtained after purification on HPLC.

3.3.1. Compound 1. Colorless oil; $[\alpha]_D^{25}$ +2 (*c* 1.5, CH_2Cl_2); IR ν_{max} (film) 3480; 3154; 2954; 1443; 1072; 861; 708 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 347/349/351/353 $[M-OH]^+$ (<1, <1, <1, <1), 321/323/325/237 $[M-C_3H_7]^+$ (<1, <1, <1, <1), 303/305/307/309 $[M-C_3H_7-H_2O]^+$ (<1, 2, 1, <1), 294/296/298/300 $[C_4H_5O_3Br_2Cl]^+$ (2, 4, 3, <1), 271/273/275 (6, 13, 6), 199/201/203 $[C_2HOBr_2]^+$ (4, 7, 3), 130/132 (100, 34); HREIMS 348.8993 (calcd for $C_9H_{14}O_2^{35}Cl^{79}Br^{81}Br$, 348.9019), 322.8459 (calcd for $C_6H_8O_3^{35}Cl^{79}Br^{81}Br$, 322.8499), 304.8348 (calcd for $C_6H_6O_2^{37}Cl^{79}Br_2$, 304.8393), 297.8233 (calcd for $C_4H_5O_3^{37}Cl^{79}Br^{81}Br$, 297.8243), 198.8467 (calcd for $C_2HO^{79}Br_2$, 198.8394).

3.3.2. Compound 2. Colorless oil; $[\alpha]_D^{25}$ +2 (*c* 2.0, CH_2Cl_2); IR ν_{max} (film) 3436; 2942; 1736; 1366; 1243; 1049 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$, see Table 1; EIMS *m/z* 346/348/350/352 $[M-HOAc]^+$ (<1, 1, <1, <1), 329/331/333/335 $[M-HOAc-OH]^+$ (<1, <1, <1, <1), 199/201/203 $[C_2HOBr_2]^+$ (4, 7, 3), 130/131 $[C_7H_{11}Cl]^+$ (100, 31).; HREIMS 345.8914 (calcd for $C_9H_{13}O_2^{35}Cl^{79}Br_2$, 345.8971), 330.8923 (calcd for $C_9H_{12}O^{35}Cl^{79}Br^{81}Br$, 330.8875), 198.8428 (calcd for $C_2HO^{79}Br_2$, 198.8394), 130.0587 (calcd for $C_7H_{11}^{35}Cl$, 130.0549).

3.3.3. Compound 3. Colorless oil; $[\alpha]_D^{25}$ +6 (*c* 0.24, CH_2Cl_2); IR ν_{max} (film) 3344; 2954; 1738; 1368; 1252; 1055 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 413/415/417 $[M-OH]^+$ (<1, <1, <1), 353/355/357 $[M-AcOH-OH]^+$ (<1, <1, <1), 327/329/331 $[M-AcOH-C_3H_7]^+$ (<1, <1, <1), 267/269/271 $[M-2AcOH-C_3H_7]^+$ (<1, 1, <1), 259 (1), 217 (1), 154 (41), 112 (100); HREIMS 412.9546 (calcd for $C_{13}H_{15}O_5^{79}Br_2$, 412.9599), 352.9350 (calcd for $C_{11}H_{15}O_3^{79}Br_2$, 352.9388).

3.3.4. Compound 4. Colorless oil; $[\alpha]_D^{25}$ −8 (*c* 0.24, CH_2Cl_2); IR ν_{max} (film) 3389; 2931; 1701; 1607; 1261; 1114; 1014 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 346/348/350/352 $[M]^+$ (<1, <1, <1, <1), 329/331/333/335 $[M-OH]^+$ (<1, 1, 1, <1), 303/305/307/309 $[M-C_3H_7]^+$ (<1, 2, 2, <1), 274/276/278/280 (16, 36, 24, 5), 195/197/199 (68, 90, 2), 175/177 $[C_8H_{12}O_2Cl]^+$ (100, 32); HREIMS 349.8957 (calcd for $C_9H_{13}O_2^{37}Cl^{79}Br^{81}Br$, 349.8920), 328.9023 (calcd for $C_9H_{12}O^{35}Cl^{79}Br_2$, 328.8943), 302.8458 (calcd for $C_6H_6O_2^{35}Cl^{79}Br_2$ 302.8423), 177.0447 (calcd for $C_8H_{12}O_2^{37}Cl$, 177.0496).

3.3.5. Compound 5. ^1H ($CDCl_3$) δ 0.94 (t, 7.4), 1.40–1.70 (m), 2.18 (ddd, 2.9, 6.1, 9.3), 4.05 (m), 6.03 (s), 6.22 (dd, 3.2, 5.6); EIMS *m/z* 346/348/350/352 $[M]^+$ (<1, <1, <1, <1), 329/331/333/335 $[M-OH]^+$ (<1, 1, <1, <1), 303/305/307/309 $[M-C_3H_7]^+$ (<1, 2, 2, <1), 274/276/278/280 (9, 22, 15, 3), 195/197/199 (37, 47, 12), 175/177 $[C_8H_{12}O_2Cl]^+$ (100, 32); HREIMS 345.8939 (calcd for $C_9H_{13}O_2^{37}Cl^{79}Br_2$, 345.8971), 328.9037 (calcd for $C_9H_{12}O^{35}Cl^{79}Br_2$, 328.8943), 177.0447 (calcd for $C_8H_{12}O_2^{37}Cl$, 177.0496).

3.4. Acetylation of 1

A solution of compound **1** (2.0 mg) in dry C_5H_5N (0.4 mL) was treated with Ac_2O (0.5 mL), stirred at room temperature for 16 h, and then poured into 5% aqueous HCl and extracted with CH_2Cl_2 and brine, dried (Na_2SO_4) and concentrated affording **2** (1.2 mg).

Acknowledgements

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Structure based design of simplified analogues of insect kinins

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Abstract—Based on a receptor interaction model, simplified analogues of insect kinins were prepared. The compounds were templated on a conformationally restricted amino piperidinone carboxylate scaffold. The conformation of the analogues was studied by NMR and the biological activity of the compounds was tested in a bio-assay.

1. Introduction

Insect neuropeptides control essential physiological processes such as maturation, water balance, pheromone production and metamorphosis.[1] Natural insect neuropeptides are readily degraded by peptidases; however, neuropeptide analogues, which could resist peptidase degradation would be attractive leads in the development of new insect control agents.

Design of such analogues requires knowledge of the chemical and conformational features of the neuropeptides. Earlier structure-activity studies have shown that the generalised pentapeptide sequence Phe-Xaa-Xbb-Trp-Gly-NH_2 (Xaa = Tyr, Phe, His, Ser or Asn, and Xbb = Ala, Ser or Pro) is present at the C-terminus of a number of insect neuropeptides, which are controlling diuretic and myotropic activity in cockroaches and crickets.[2] Within this active core pentapeptide, the aromatic residues Phe[1] and Trp[4] are both critical for myotropic and diuretic activity as was revealed by an alanine replacement scan. Moreover, by means of NMR and molecular dynamics analysis, a cis-Pro type VI β-turn has been shown to be involved in an active *cyclo*(Ala-Phe-Phe-Pro-Trp-Gly) insect kinin peptide analog centered around the Phe-Phe-Pro-Trp moiety. The possible presence of this turn conformation in the receptor bound state was further corroborated via the synthesis and biological screening of tetrazole containing analogues of these kinins which are known to mimic cis-peptide bonds. Similar, conclusions were obtained using a 4-aminopyroglutamate as a cis-peptide bond inducer.[3]

A receptor interaction model was presented in which it was assumed that the type VI β-turn over residues 1–4 places the side-chains of Phe and Trp on the same side of the structure where they can interact as a continuous aromatic surface with the Malpighian tubule receptor. On the other hand, the side-chains of Phe and Pro lie on the opposite face away from the receptor explaining why these positions are tolerant of considerable modification in the unconstrained structures described above.

Based on this structural information, a small library of 'pseudotetrapeptides' was designed containing the basic features assumed to be important for receptor binding (minimalistic approach): these are the cis-peptide bonds of the type VI β-turn and the side-chains of the Phe and Trp amino acids important for myotropic and/or diuretic activity (Fig. 1), the N-terminal amine function and the C-terminal carboxylate (as well as the glycine amide) were omitted in this approach. We assumed the beta turn properties of the systems could be imposed by means of a turn mimicking amino piperidinone carboxylate system (APC).[4] The side-chains of this APC system (which replaces the residues 2 and 3 in the parent peptide) are of no major importance since according to the receptor model these are diverted away from the receptor. Hence we chose one of the most simple APC systems available (Fig. 1). Phe and Trp side-chains were introduced as simple phenylalkylamides and indolylalkyl amides. Different tether lengths were chosen and also

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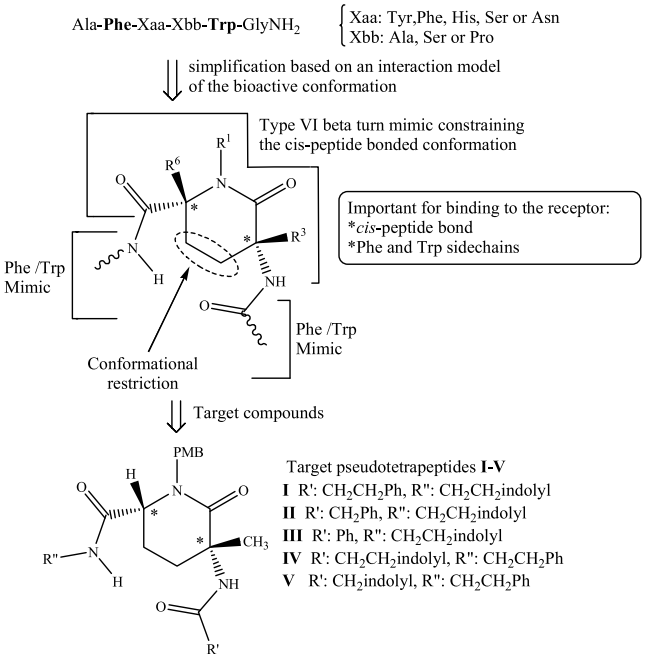


Figure 1. Design approach towards simplified insect kinin analogues.

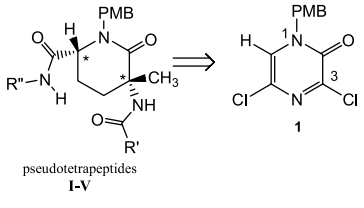
the position of the side-chains (N- or C-terminus) was varied. Compounds of this type, incorporating a β-turn mimic, are of course also interesting candidates for more general broad screening, especially in view of the major importance of the Phe and Trp amino acids in biological processes.

2. Results and discussion

In the following subsections, we will first describe our synthetic approach towards the target analogues **I–V** and discuss structural features of models **I** and **IV** by analysis of the NMR spectra. Finally, a bioassay performed on some of the analogues will be presented.

2.1. Insect kinin analogue synthesis

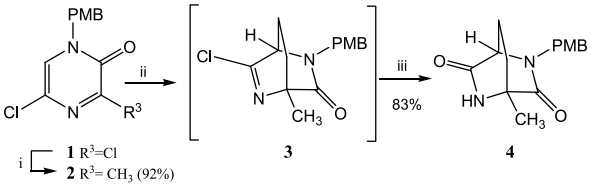
The target compounds **I–V** can be brought back to a 3,5-dichloropyrazinone **1** using chemistry previously developed in our laboratory (Scheme 1).[4] Key steps in the synthesis are a Diels–Alder reaction and a selective methanolysis as will be discussed further.



Scheme 1. Pyrazinone **1** as a precursor for compounds **I–V**.

2.1.1. Synthesis of the APC precursor.

2.1.1.1. Diels–Alder reaction and hydrolysis of the adduct: introduction of the conformational restriction of the APC system. The initially required *N*-(*p*-methoxybenzyl) pyrazinone **1** (Scheme 2) was generated using our



Scheme 2. Generation of bislactam **4**. Reagents and conditions: (i) $(CH_3)_4Sn$, toluene, 110 °C, tetrakis; (ii) ethene (35 atm), 145 °C, toluene, 4 h; (iii) air moisture.

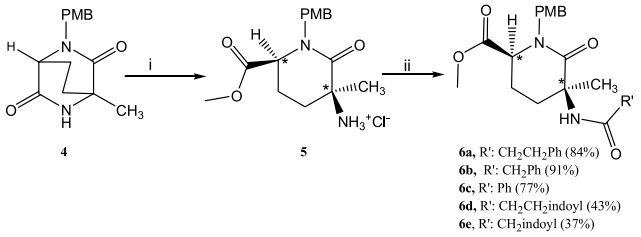
established procedure via cyclisation of 2-[*N*-(4-methoxybenzyl) amino] acetonitrile (in the form of an HCl salt) with oxalyl chloride.[5] The PMB group by now has become the standard protective group for the lactam function in this type of precursors. According to our design approach, the substituent R^3 is believed to be of minor importance for activity, so we have chosen to introduce the easily accessible methyl group at this position.

The 3-methyl analogue **2** was obtained through catalytic cross-coupling of 3,5-dichloro-2(1*H*)-pyrazinone **1** with tetramethyltin using the procedure described before.[6]

The 2(1*H*)-pyrazinone **2** underwent Diels–Alder addition with ethene[7] to produce the imidoyl chloride **3**, which was converted into the bis (lactam) **4** via hydrolysis (Scheme 2). In this reaction step, both the conformational restriction and the cis-relationship of the amine and the carboxylate of the target APC system are imposed.

2.1.2. Conversion of the APC precursor into tetrapeptide analogues.

2.1.2.1. Methanolysis of the bicyclic lactam systems. Introduction of the side-chains of both Phe and Trp occurs in the next steps in the synthesis. Different combinations of alkylphenyl and alkylindolyl amides were envisaged both for the N- and the C-terminus of the APC scaffold. To do so, the bislactam system **4** firstly was selectively converted into the HCl salt **5** using a selective methanolysis reaction via treatment with an HCl–saturated methanol solution for 12 h (Scheme 3).[8] The ammonium chloride salt was trapped as the corresponding amide by dissolving the evaporated residue **5** from the methanolysis in dichloromethane and adding an acyl chloride R′COCl (3 equiv) and Et_3N (4 equiv) under an inert atmosphere. After stirring for 16 h at room temperature, the reaction mixture was purified by column chromatography (silica gel, 10% MeOH/CH_2Cl_2 as eluent) to yield the *N*-acylated products **6a–c** (Scheme 3).



Scheme 3. Reagents and conditions: (i) MeOH/HCl, rt, 16 h; (ii) R′COCl (3 equiv), Et_3N (4 equiv), DCM, rt, 16 h or $R'CO_2H$ (1 equiv), DIEA (5 equiv), CH_3CN, TBTU (1.2 equiv), rt, 4 h.

For the synthesis of compound **6d** with the Trp side-chain mimick, we first activated indol-3-yl propionic acid as its OBt ester by treating it with TBTU and DIEA in CH_3CN. To this solution, product **5** was added. Compound **6d** was isolated in a moderate yield of 43%. The lower yield is due to the recyclisation of the ammonium chloride salt **5** to the bicyclic **4** because the OBt ester in this case reacts slower than the corresponding acyl chlorides used for the preparation of **6a–c**. Using the same conditions as for **6d**, product **6e** was obtained in 37% yield.

2.1.2.2. Hydrolysis of the ester function and subsequent coupling reaction with amines: addition of the fourth amino acid mimicking residue. Direct conversion of the methyl ester **6a** to the target compound **I** with amines proved to be impossible (we tried to do the substitution with different amines under reflux conditions in methanol or pyridine). In order to further functionalise the C-terminus of these compounds, we first needed to convert them into the corresponding acids.

The conversion of **6** into the corresponding acids **7** was successfully effected using LiI in dry pyridine for 16 h at 115 °C (the more standard ester hydrolysis methods using KOH or NaOH in water/methanol mixtures failed in this case). Upon completion of the reaction, the pH of the reaction mixture was adjusted to 2 by adding a dilute HCl solution. After extraction, the acids **7** were further purified by chromatography on silica gel.

The obtained derivatives **7** were activated with TBTU in dry DMF and reacted with different amines again representing side-chains of Phe or Trp. After stirring these mixtures for 16 h at room temperature, the products were extracted several times with dichloromethane and purified by column chromatography to yield the final target compounds **I–V** (Scheme 4).

2.2. NMR analysis of model systems I and IV

NMR techniques were used to study the solution conformation of pseudotetrapeptides **I** and **IV** in $CDCl_3$. The analysis was performed using one dimensional NOE-diff experiments and two-dimensional COSY- and NOESY-techniques.

An APC system can in theory adopt two conformations A or B (Fig. 2). The actual conformation in solution depends on the substitution pattern of the APC system.

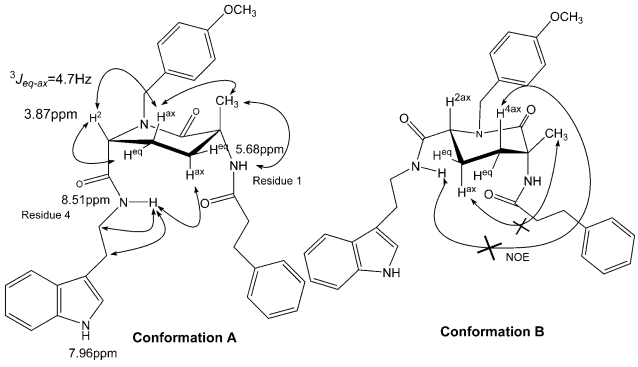


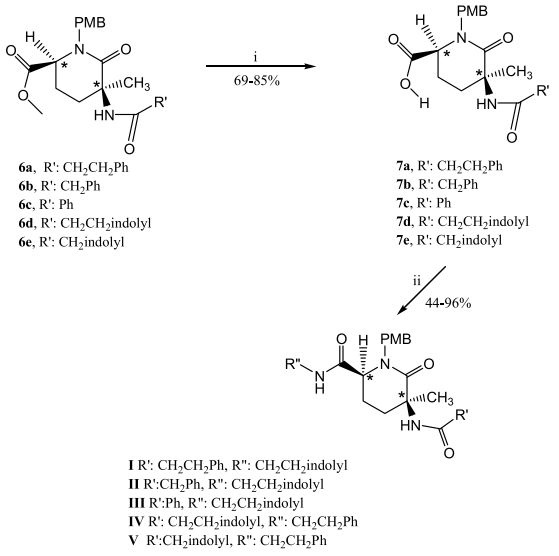
Figure 2. Observed through-space NOE's for pseudopeptide **I**.

In pseudopeptide **I**, the proton H^2 can be identified as the doublet at δ 3.87, which couples with both H^3 protons. One ^3J coupling constant is 4.7 Hz; the other H^3 coupling constant is not resolved in the 1D spectrum though it can be observed in the COSY spectrum. The axial protons H^3 and H^4 can be distinguished from the equatorial ones because they show broader multiplets due to the larger axial–axial coupling constants present in their spectrum. The axial H^3 proton shows a coupling in the NOESY spectrum with the methyl group and with H^2.

Based on the NOE-effect between the NH–amide proton at δ 8.51 and the axial proton H^4, it can be concluded that the conformation A of this pseudotetrapeptide prevails in solution and not conformation B (Fig. 2). The other NOE-effects in Figure 2 (as seen in the NOESY spectrum) are in agreement with the proposed conformation.

The chemical shift of the N*H*CH_2 amide proton shows a temperature dependence of −4.6 ppb/K indicating that it is not completely solvent exposed. This partial solvent shielding could be explained by the fact that a hydrogen bond is present in this structure as would be expected with a turn inducing APC scaffold.[4] However, the shielding is not complete and probably this hydrogen bonded conformation is in equilibrium with other non-hydrogen bonded conformations.

A similar analysis was performed for peptide **IV**. According to our NMR data the peptide **IV** adopts the same conformation as in the case of pseudopeptide **I**. Also in this case the temperature dependence of the chemical shift of the N*H*CH_2 amide proton of −4.7 ppb/K shows partial solvent shielding of this proton.



Scheme 4. Reagents and conditions: (i) LiI, dry pyridine, 115 °C, 16 h; (ii) TBTU, amine, dry DMF, rt.

2.3. Fluid secretion assay

In order to check whether the systems were suitable analogues (in structure and function) of the insect kinins,

biological testing of the products was performed. The exact details of the assay are discussed elsewhere.[1]

The most common way to analyse the rate of fluid secretion by Malpighian tubules (i.e., insect excretory organs) is the 'Ramsay assay'. Tubules are dissected and incubated in vitro in a physiological Ringer solution and the secretory tubule terminal is inserted in a drop of paraffin oil. A small droplet of liquid secretion is then easily visualised (appearing in the oil) and measured under a microscope (diameter can be measured and droplet volume can be calculated) after a given time interval (Schematic representation in Fig. 3).

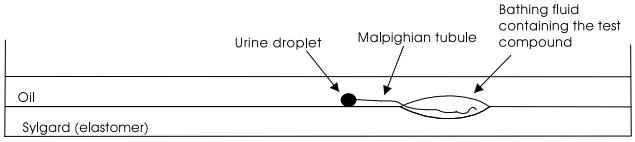


Figure 3. Schematic representation of the diuretic assay system.

All analogues were tested in the assay using 10 μM solutions (Fig. 4).[9] At first sight, all compounds seem to slightly increase the fluid secretion by the tubules compared to the secretion in the absence of analogue (basal level). A paired *t*-test however, reveals that the observed increase is only significant in the case of compounds **I**, **II** and **III**. In compound **IV** the side-chains of the N- and C-terminus were exchanged and, therefore, it shows less resemblance to the natural peptide than the other compounds.

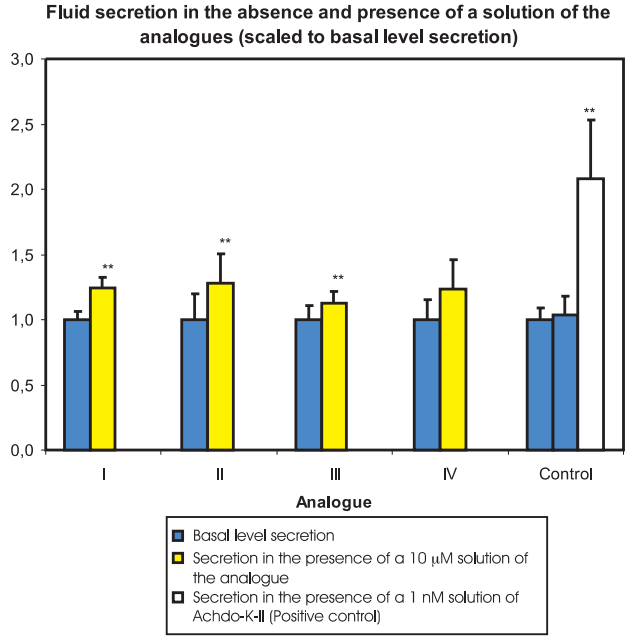


Figure 4. Diuretic assay: tubular fluid secretion in the absence (control; basal level) or presence of the analogues. Values marked with ** are significantly different from the basal level of secretion according to a paired *t*-test. As a positive test Achdo-K-II was added to the control sample.

The stimulation caused by compounds **I**, **II** and **III** should be considered very modest, this can be shown by adding a positive control (Achdo-K-II), which almost doubles the secretion. The fact however, that some stimulation is observed with the analogues is most probably due to meeting the minimal requirements for receptor-binding, which was the initial goal of this project.[10] Hence the APC system is an appropriate scaffold for stabilising the cis-peptide bond and for directing the side-chains of Phe and Trp towards the receptor surface as was stated in the receptor binding model. However, oversimplification of the parent system results in poor bioactivity.

3. Conclusion

In this paper, design and synthesis of simplified insect kinin analogues incorporating APC scaffolds was described. In the target pseudopeptides **I–V** the side-chains important for receptor binding were retained as well as the global beta turn conformation of the peptide backbone. We have shown that these simplified analogues are recognised by the receptor, for which they were developed. A similar minimalistic approach can be applied to other peptides, of which the bioactive conformation is established.

4. Experimental

4.1. General

All melting points are uncorrected, and were measured on an Electrothermal IA 9000 Digital melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 1720 Fourier transform spectrometer. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra and a Kratos MS 50TC instrument using DS90 data system for exact mass measurements performed in the EI mode at a resolution of 10.000. APCI and ESI spectra were recorded on a Thermo Finnigan LCQ Advantage mass spectrometer. For NMR spectra (δ, ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. Analytical and preparative thin-layer chromatography; TLC plates were performed on Alugram Sil G/UV_{254}. Column chromatography was carried out using 70–230 mesh silica gel 60 (E. M. Merck) as the stationary phase.

4.2. Synthesis

4.2.1. Synthesis of 2-(1*H*)-pyrazinones 1 and 2. For the preparation of 3,5-dichloro-2(1*H*)-pyrazinone **1** and its functionalisation to pyrazinone **2**, see Refs. 4 and 7.

5-Chloro-1-(4-methoxybenzyl)-3-methyl-2(1H)-pyrazinone **2**. Yield: 92%; mp 92 °C (EtOH); IR (KBr) cm^{-1}: 1652 (s, CO), 1599 (s, C=N); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.26 (d, $J=8$ Hz, 2H, H-2′+H-6′), 7.06 (s, 1H, H-6), 6.90 (d, $J=8$ Hz, 2H, H-3′+H-5′), 4.98 (s, 2H, N–CH_2 of PMB), 3.82 (s, 3H, O–CH_3), 2.49 (s, 3H, 3-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm):160.0 (CO), 158.7 (C–OCH_3 (PMB)), 155.4 (C-3), 130.7 (C-2′+C-6′), 126.6 (C-*ipso* PMB), 126.0 (C-5), 124.3 (C-6), 115.0 (C-3′+C-5′), 55.7 (O–CH_3), 52.3 (N–CH_2 of PMB), 21.3 (CH_3); EIMS *m/z* (%): 264 (M^+, 34), 121 ($CH_3OC_6H_4CH_2^+$, 100); HRMS: Calcd for $C_{13}H_{13}ClN_2O_2$: 264.0664; found: 264.0665.

4.2.2. Diels–Alder reaction and hydrolysis of the adduct: introduction of the conformational restriction in the APC system.

4.2.2.1. Synthesis of adduct 4. Pyrazinone **2** (1 mmol) is dissolved in 20 mL of toluene and the solution is transferred to a stainless steel bomb. The mixture is heated under ethene pressure (35 atm) at 145 °C for 4 h. Upon cooling and removal of ethene, the solvent is evaporated under reduced pressure. The imidoyl chloride intermediate is further hydrolised to the desired compound **4** by stirring it for 16 h in toluene open to air moisture. This compound is further purified by column chromatography (silica gel, MeOH–CH_2Cl_2 5/95).

5-(4-Methoxybenzyl)-1-methyl-2,5-diazabicyclo [2.2.2] octane-3,6-dione **4**. Yield: 83%; mp 156 °C (EtOH); IR (KBr) cm^{-1}: 3270 (w, NH), 1685 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.18 (d, $J=8$ Hz, 2H, H-2′+H-6′), 7.17 (s, 1H, NH), 6.85 (d, $J=8$ Hz, 2H, H-3′+H-5′), 4.72 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 4.29 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.79 (s, 3H, O–CH_3), 3.87 (br s, 1H, H-4), 1.83–1.75 (m, 4H, CH_2CH_2), 1.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 172.2 (CO), 171.2 (CO), 159.4 (C–OCH_3 (PMB)), 129.5 (C-2′+C-6′), 128.3 (C-*ipso* PMB), 114.2 (C-3′+C-5′), 59.0 (C-4), 58.1 (C-1), 55.2 (O–CH_3), 47.9 (N–CH_2 of PMB), 32.4 (CH_2–C1), 24.7 (CH_2–C4), 18.1 (CH_3); EIMS *m/z* (%): 274 ($M^{+\cdot}$, 92), 153 ($M^{+\cdot}-CH_3OPhCH_2$, 42), 121 ($CH_3OC_6H_4CH_2^+$, 100); HRMS: Calcd for $C_{15}H_{18}N_2O_3$: 274.1317; found: 274.1319.

4.2.2.2. Conversion of the bislactam into APC analogues. *a. Methanolysis reaction*. The bislactam **4** (0.5 mmol) was stirred in 10 mL of HCl–saturated methanol under an inert atmosphere for 16 h. Then methanol and HCl were evaporated to afford the amino piperidinone as the hydrochloride salt **5**. This crude product is used in step b without further purification.

b. Trapping the amine (Method A) (**6a–c**). The hydrochloride salt of the amino piperidinone **5** (0.7 mmol) was dissolved in CH_2Cl_2 and the acid chloride (2.1 mmol) was added followed by Et_3N (2.8 mmol). The reaction mixture was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel using 5% EtOAc–CH_2Cl_2 as eluent to afford **6a–c**.

(Method B) (**6d–e**). A solution of indol-3-yl propionic acid (or indole-3-acetic acid) (0.48 mmol) in CH_3CN (3 mL) was treated with DIEA (0.72 mmol), ammonium chloride salt **5** (0.58 mmol) and TBTU (0.58 mmol). The reaction mixture was stirred at room temperature for 18 h. After filtration, the filtrate was evaporated and purified by preparative thin-layer chromatography (silica gel) using EtOAc as eluent to give **6d–e**.

(2S,5S*) Methyl 1-(4-methoxybenzyl)-5-methyl-6-oxo-5[(3-phenylpropanoyl) amino]-2-piperidinecarboxylate* **6a**. Yield: 84%; Method A; mp 103 °C (EtOH); IR (KBr) cm^{-1}: 3310 (w, NH), 1740 (s, CO), 1623 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.29–7.16 (m, 5H, Ph-H), 7.09 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.84 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.57 (s, 1H, NH), 5.37 (d, $J=15$ Hz, 1H, N–CH_2 of PMB), 3.94 (br d, $J=4$ Hz, 1H, H-2), 3.79 (s, 3H, O–CH_3), 3.74 (s, 3H, CH_3 of ester), 3.63 (d, $J=15$ Hz, 1H, N–CH_2 of PMB), 2.94 (t, $J=7$ Hz, 2H, CH_2–CO), 2.68–2.64 (m, 1H, CH_2CH_2), 2.49–2.45 (m, 2H, CH_2-Ph), 2.08–2.02 (m, 3H, CH_2CH_2), 1.55 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 173.7 (CO), 172.1 (CO), 172.0 (CO), 159.6 (C–OCH_3 (PMB)), 141.2 (C-*ipso* Ph), 129.9 (C-2′+C-6′), 128.5, 128.3, 126.5 (CH-Ph), 128.2 (C-*ipso* PMB), 114.5 (C-3′+C-5′), 58.4 (C-2), 56.8 (C-5), 55.2 (O–CH_3), 53.1 (CH_3 of ester), 49.8 (N–CH_2 of PMB), 39.3 (CH_2–CO), 32.0 (CH_2-Ph), 30.2 (C-4), 25.1 (CH_3), 23.4 (C-3); EIMS *m/z* (%): 438 ($M^{+\cdot}$, 30), 289 ($M^{+\cdot}-NHCOCH_2CH_2Ph$, 17), 261 ($M^{+\cdot}-CH_3$–CO–$NCH_2PhOCH_3$, 100); HRMS: Calcd for $C_{25}H_{30}N_2O_5$: 438.2147; found: 438.2154.

(2S,5S*) Methyl 1-(4-methoxybenzyl)-5-methyl-6-oxo-5-(phenacylamino)-2-piperidinecarboxylate* **6b**. Yield: 91%; Method A; mp oil; IR (NaCl) cm^{-1}: 3350 (w, NH), 1739 (s, CO), 1647 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.36–7.25 (m, 5H, Ph-H), 7.07 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.83 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.59 (s, 1H, NH), 5.36 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.93 (br d, $J=5$ Hz, 1H, H-2), 3.78 (s, 3H, O–CH_3), 3.74 (s, 3H, CH_3 of ester), 3.61 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.52 (s, 2H, CH_2-Ph), 2.64 (br d, $J=14$ Hz, 1H, H-4eq), 2.16–1.99 (m, 3H, CH_2CH_2), 1.54 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm):173.1 (CO), 171.6 (CO), 170.4 (CO), 159.2 (C–OCH_3 (PMB)), 135.0 (C-*ipso* Ph), 129.5 (C-2′+C-6′), 129.2, 128.8, 127.0 (CH-Ph), 128.1 (C-*ipso* PMB), 114.1 (C-3′+C-5′), 58.0 (C-2), 56.8 (C-5), 55.2 (O–CH_3), 52.6 (CH_3 of ester), 49.4 (N–CH_2 of PMB), 44.4 (CH_2-Ph), 29.8 (C-4), 24.7 (CH_3), 23.0 (C-3); EIMS *m/z* (%): 424 ($M^{+\cdot}$, 35), 289 ($M^{+\cdot}-CH_3OC_6H_4CH_2$–$CH_3$, 30), 261 ($M^{+\cdot}-CH_3OPhCH_2$–$CO_2CH_3$, 100); HRMS: Calcd for $C_{24}H_{28}N_2O_5$: 424.1994; found: 424.1998.

(2S,5S*) Methyl 5-benzoylamino-1-(4-methoxybenzyl)-5-methyl-6-oxo-2-piperidinecarboxylate* **6c**. Yield: 77%; Method A; mp oil; IR (NaCl) cm^{-1}: 3393 (w, NH), 1739 (s, CO), 1646 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.94 (s, 1H, NH), 7.75 (d, $J=7$ Hz, 2H, *ortho* Ph), 7.43 (t, $J=7$ Hz, 1H, *para* Ph), 7.33 (t, $J=7$ Hz, 2H, *meta* Ph), 7.09 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.81 (d, $J=8$ Hz, 2H, H-3′+H-5′), 5.39 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.97 (br d, $J=4$ Hz, 1H, H-2), 3.72 (s, 3H, O–CH_3), 3.70 (s, H, CH_3 of ester), 3.66 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 2.77 (br d, $J=13$ Hz, 1H, CH_2CH_2), 2.23 (td, $J=13$, 5 Hz, 1H, CH_2CH_2), 2.08–1.86 (m, 2H, CH_2CH_2), 1.68 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 173.5 (CO), 171.5 (CO), 166.7 (CO), 159.3 (C–OCH_3 (PMB)), 134.9 (C-*ipso* Ph), 131.3, 128.5, 127.0 (CH-Ph), 129.5 (C-2′+C-6′), 127.9 (C-*ipso* PMB), 114.2 (C-3′+C-5′), 58.2 (C-2), 57.1 (C-5), 55.2 (O–CH_3), 52.6 (CH_3 of ester), 49.5 (CH_2 of PMB), 29.8 (C-4), 24.7 (CH_3), 23.0 (C-3); EIMS *m/z* (%): 410 ($M^{+\cdot}$, 25), 289 ($M^{+\cdot}-CH_3OPhCH_2$, 23), 121 ($CH_3OC_6H_4CH_2^+$, 86); HRMS: Calcd for $C_{23}H_{26}N_2O_5$: 410.1827; found: 410.1841.

(2S,5S*) Methyl 5-(3-1H-indol-3-yl-propionylamino)-1-(4-methoxybenzyl)-5-methyl-6-oxo-2-piperidine-carboxylate* **6d**. Yield: 43%; Method B; mp 90 °C (EtOH); IR (KBr) cm^{-1}: 3301 (w, NH), 1740 (s, CO), 1640 (s, CO); ^1H NMR

($CDCl_3$, 400 MHz, ppm): 8.54 (br s, 1H, NH-ind), 7.58 (d, $J=7$ Hz, 1H, H-4″i), 7.32 (d, $J=7$ Hz, 1H, H-7″i), 7.15 (t, $J=7$ Hz, 1H, H-6″i), 7.08 (d, $J=8$ Hz, 2H, H-2′+H-6′), 7.07 (t, $J=7$ Hz, 1H, H-5″i), 6.98 (s, 1H, H-2″i), 6.83 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.56 (s, 1H, NH), 5.39 (d, $J=15$ Hz, 1H, N–CH_2 of PMB), 3.95 (br d, $J=4$ Hz, 1H, H-2), 3.77 (s, 3H, O–CH_3), 3.73 (s, 3H, CH_3 of ester), 3.66 (d, $J=15$ Hz, 1H, N–CH_2 of PMB), 3.07 (t, $J=7$ Hz, 2H, CH_2-ind), 2.57–2.55 (m, 3H, H-4eq+CH_2–CO), 2.12–2.00 (m, 3H, CH_2CH_2), 1.53 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 173.1 (CO), 172.2 (CO), 171.5 (CO), 159.1 (C–OCH_3 (PMB)), 136.3 (C-7a″i), 129.4 (C-2′+C-6′), 128.1 (C-3a″i), 127.1 (C-*ipso* PMB), 121.7, 121.6 (C-2″i+C-6″i), 118.9 (C-5″i), 118.6 (C-4″i), 114.7 (C-3″i), 114.1 (C-3′+C-5′), 111.0 (C-7″i), 57.9 (C-2), 56.5 (C-5), 55.1 (O–CH_3), 52.5 (CH_3 of ester), 49.3 (N–CH_2 of PMB), 37.7 (CH_2–CO), 29.9 (C-4), 24.7 (CH_3), 22.9 (C-3), 21.0 (CH_2-ind); EIMS *m/z* (%): 477 ($M^{+\cdot}$, 57), 445 ($M^{+\cdot}-OCH_3$, 16), 261 ($M^{+\cdot}-OCH_3$–$NHCH_2CH_2$indole, 58); HRMS: Calcd for $C_{27}H_{31}N_3O_5$: 477.2244; found: 477.2263.

(2S,5S*) Methyl 5-(2-1H-indol-3-yl-acetylamino)-1-(4-methoxybenzyl)-5-methyl-6-oxo-2-piperidine carboxylate* **6e**. Yield: 37%; Method B; mp oil; IR (NaCl) cm^{-1}: 3311 (w, NH), 1741 (s, CO), 1642 (s, CO); ^1H NMR (C_6D_6, 400 MHz, ppm): 9.27 (s, 1H, NH-ind), 7.74 (dd, $J=6$, 2 Hz, 1H, H-4″i), 7.38 (dd, $J=6$, 2 Hz, 1H, H-7″i), 7.21–7.17 (m, 2H, H-5″i+H-6″i), 6.99 (s, 1H, NH), 6.97 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.81 (br d, $J=2$ Hz, 1H, H-2″i), 6.70 (d, $J=8$ Hz, 2H, H-3′+H-5′), 5.55 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.75 (br d, $J=5$ Hz, 1H, H-2), 3.67 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.62 (s, 2H, CH_2–CO), 3.37 (s, 3H, CH_3 of ester), 3.30 (s, 3H, O–CH_3), 2.44 (td(ddd), $J=12$ Hz, 1H, H-4ax), 2.36 (br d, $J=14$ Hz, 1H, H-4eq), 1.82 (br d, $J=14$ Hz, 1H, H-3eq), 1.53–1.51 (m, 1H, H-3ax), 1.40 (s, 3H, CH_3); ^{13}C NMR (C_6D_6, 100 MHz, ppm): 173.9 (CO), 172.0 (CO), 171.9 (CO), 160.2 (C–OCH_3 (PMB)), 137.7 (C-7a″i), 130.2 (C-3a″i), 129.5 (C-2′+C-6′), 128.3 (C-*ipso* PMB), 125.0 (C-2″i), 122.5, 120.1 (C-6″i+C-5″i), 119.6 (C-4″i), 114.9 (C-3′+C-5′), 112.5 (C-7″i), 109.5 (C-3″i), 58.9 (C-2), 57.1 (C-5), 55.3 (O–CH_3), 52.6 (CH_3 of ester), 50.4 (N–CH_2 of PMB), 34.9 (CH_2–CO), 31.1 (C-4), 25.4 (CH_3), 23.7 (C-3); EIMS *m/z* (%): 463 ($M^{+\cdot}$, 34), 307 ($M^{+\cdot}-COCH_2$indol, 18); 261 ($M^{+\cdot}-NHCOCH_2$indol–OCH_3, 18); HRMS: Calcd for $C_{26}H_{29}N_3O_5$: 463.2096; found: 463.2107.

4.3. General procedure for the deprotection of the ester compounds

Ester compound **6** (0.63 mmol) and anhydrous lithium iodide (1.9 mmol) in 10 mL of dry pyridine was refluxed for 16 h under argon. After cooling to room temperature the solution was adjusted to pH=2 by slowly adding dilute HCl solution. The residue was extracted with EtOAc (3×). The combined organics layers were dried over magnesium sulphate and evaporated under reduced pressure. The crude product was subjected to column chromatography on silica gel using 5% MeOH/CH_2Cl_2 as eluent to give the corresponding acid compound **7**.

(2S,5S*) 1-(4-Methoxybenzyl)-5-methyl-6-oxo 5 [(3-phenyl-propanoyl) amino]- piperidine-2-carboxylic acid* **7a**. Yield: 72%; mp 78 °C (EtOH); IR (KBr) cm^{-1}: 3288 (w, NH), 1648 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm, 55 °C): 8.66[11] (br s, 1H, OH), 7.14–7.06 (m, 7H, Ph-H+ (H-2′+H-6′)), 6.70 (d, $J=7$ Hz, 2H, H-3′+H-5′), 6.20 (br s, 1H, NH), 5.50 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.85 (br d, $J=4$ Hz, 1H, H-2), 3.69 (s, 3H, O–CH_3), 3.60 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 2.89–2.88 (m, 2H, CH_2-Ph), 2.55–2.30 (m, 2H, CH_2–CO), 2.42–2.32 (m, 1H, CH_2CH_2), 2.19–2.15 (m, 1H, CH_2CH_2), 1.99–1.89 (m, 1H, CH_2CH_2), 1.81–1.76 (m, 1H, CH_2CH_2), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm, 55 °C): 172.5 (CO), 171.7 (CO), 158.7 (C–OCH_3 (PMB)), 140.7 (C-*ipso* Ph), 129.2 (C-2′+C-6′), 128.3 (C-*ipso* PMB), 129.2, 128.3, 126.0 (CH-Ph), 113.8 (C-3′+C-5′), 59.5 (C-2), 56.0 (C-5), 55.1 (O–CH_3), 49.3 (N–CH_2 of PMB), 38.0 (CH_2–CO), 31.3 (CH_2-Ph), 30.3 (C-4), 25.3 (CH_3), 23.3 (C-3); EIMS *m/z* (%): 424 ($M^{+\cdot}$, 3), 406 ($M^{+\cdot}-H_2O$, 6), 380 ($M^{+\cdot}-CO_2H$, 2); HRMS: Calcd for $C_{24}H_{28}N_2O_5$: 424.1993; found: 424.1998.

(2S,5S*) 1-(4-Methoxybenzyl)-5-methyl-6-oxo-5-(phen-acylamino) piperidine-2-carboxylic acid* **7b**. Yield: 82%; mp 113 °C (EtOH); IR (KBr) cm^{-1}: 3259 (w, NH), 1725 (s, CO), 1649 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.32–7.19 (m, 5H, Ph-H), 7.14 (d, $J=8$ Hz, 2H, H-2′+H-6′), 7.06 (br s, 1H, NH), 6.83 (d, $J=8$ Hz, 2H, H-3′+H-5′), 5.52 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.98 (br d, $J=5$ Hz, 1H, H-2), 3.82 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.78 (s, 3H, O–CH_3), 3.50 (s, 2H, CH_2-Ph), 2.45 (td(ddd), $J=14$ Hz, 1H, CH_2CH_2), 2.24 (br d, $J=14$ Hz, 1H, CH_2CH_2), 1.87 (tdd(dddd), $J=14$, 4 Hz, 1H, CH_2CH_2), 1.65 (br d, $J=14$ Hz, 1H, CH_2CH_2), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 172.9 (CO), 172.2 (CO), 171.8 (CO), 159.3 (C–OCH_3 (PMB)), 134.6 (C-*ipso* Ph), 129.7 (C-2′+C-6′), 129.3, 128.8, 127.1 (CH-Ph), 128.2 (C-*ipso* PMB), 114.6 (C-3′+C-5′), 60.3 (C-2), 58.7 (C-5), 55.2 (O–CH_3), 49.6 (N–CH_2 of PMB), 42.7 (CH_2-Ph), 30.8 (C-4), 25.1 (CH_3), 23.0 (C-3); EIMS *m/z* (%): 410 ($M^{+\cdot}$), 396 ($M^{+\cdot}-CH_3$, 18), 121 ($CH_3OC_6H_4CH_2^+$, 100); HRMS: Calcd for $C_{23}H_{26}N_2O_5$: 410.1841; found: 410.1841.

(2S,5S*) 5-Benzoylamino-1-(4-methoxybenzyl)-5-methyl-6-oxo-piperidine-2-carboxylic acid* **7c**. Yield: 69%; mp 84 °C (EtOH); IR (KBr) cm^{-1}: 1730 (s, CO), 1635 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 7.80 (d, $J=7$ Hz, 2H, *ortho* Ph), 7.50 (t, $J=7$ Hz, 1H, *para* Ph), 7.43 (t, $J=7$ Hz, 2H, *meta* Ph), 7.17 (d, $J=8$ Hz, 2H, H-2′+H-6′), 7.14 (br s, 1H, NH), 6.86 (d, $J=8$ Hz, 2H, H-3′+H-5′), 5.46 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 4.10 (br d, $J=5$ Hz, 1H, H-2), 3.79 (s, 3H, O–CH_3), 3.72 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 2.55 (br t(dd), $J=16$ Hz,1H, H-4ax), 2.22 (br d, $J=16$ Hz,1H, H-3eq), 2.06–1.94 (m, 2H, H-4eq+H-3ax), 1.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm):172.9 (CO), 171.3 (CO), 167.8 (CO–NH), 159.4 (C–OCH_3 (PMB)), 132.9 (C-*ipso* Ph), 132.3, 128.6, 127.3 (CH-Ph), 129.8 (C-2′+C-6′), 127.9 (C-*ipso* PMB), 114.2 (C-3′+C-5′), 59.6 (C-2), 56.2 (C-5), 55.2 (O–CH_3), 49.5 (N–CH_2 of PMB), 30.9 (C-4), 25.5 (CH_3), 23.1 (C-3); EIMS *m/z* (%): 396 ($M^{+\cdot}$, 4), 352 ($M^{+\cdot}-CO_2H$, 2), 121 ($CH_3OC_6H_4CH_2^+$, 100); HRMS: Calcd for $C_{22}H_{24}N_2O_5$: 396.1685; found: 396.1700.

(2S,5S*) 5-(3-1H-Indol-3-yl-propionylamino)-1-(4-meth-oxybenzyl)-5-methyl-6-oxo-piperidine-2-carboxylic acid*

7d. Yield: 85%; mp 64 °C; IR (KBr) cm^{-1}: 3350 (w, NH), 1634 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 8.04 (br s, 1H, NH-ind), 7.57 (d, $J=7$ Hz, 1H, H-4″i), 7.34 (d, $J=7$ Hz, 1H, H-7″i), 7.19 (t, $J=7$ Hz, 2H, H-5″i+H-6″i), 7.13 (d, $J=8$ Hz, 2H, H-2′+H-6′), 7.06 (s, 1H, H-2″i), 6.83 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.18 (s, 1H, NH), 5.39 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 4.07 (br d, $J=5$ Hz, 1H, H-2), 3.78 (s, 3H, O–CH_3), 3.73 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.12–3.08 (m, 2H, CH_2-ind), 2.64–2.58 (m, 2H, CH_2–CO), 2.34–1.61 (m, 4H, CH_2CH_2), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 173.1 (CO), 172.2 (CO), 171.5 (CO), 159.1 (C–OCH_3 (PMB)), 134.6 (C-7a″i), 129.4 (C-2′+C-6′), 127.8, 127.1 (C-3a″i+C-*ipso* PMB), 121.7, 121.6 (C-6″i+C-2″i), 119.1 (C-5″i), 118.6 (C-4″i), 114.2 (C-3′+C-5′), 111.2 (C-7″i), 109.1 (C-3″i), 57.9 (C-2), 56.5 (C-5), 55.2 (O–CH_3), 49.4 (N–CH_2 of PMB), 37.7 (CH_2–CO), 29.9 (C-4), 24.7 (CH_3), 22.9 (C-3), 21.0 (CH_2-ind); EIMS *m/z* (%): 463 ($M^{+\cdot}$, 10), 445 ($M^{+\cdot}-H_2O$, 11), 130 (indolCH_2^+, 49); HRMS: Calcd for $C_{26}H_{29}N_3O_5$: 463.2107; found: 463.2116.

(2S,5S*) 5-(2-1H-Indol-3-yl-acetylamino)-1-(4-methoxybenzyl)-5-methyl-6-oxo-piperidine-2-carboxylic acid* **7e**. Yield: 75%; mp 104 °C (EtOH); IR (KBr) cm^{-1}: 3389 (w, NH), 1730 (s, CO), 1638 (s, CO); ^1H NMR ($CDCl_3$, 300 MHz, ppm): 9.60 (br s, 1H, OH), 8.73 (s, 1H, NH-ind), 7.56 (d, $J=7$ Hz, 1H, H-4″i), 7.49 (d, $J=7$ Hz, 1H, H-7″i), 7.29 (d, $J=7$ Hz, 2H, H-5″i+H-6″i), 7.09 (d, $J=8$ Hz, 1H, H-2′+H-6′), 7.01 (s, 1H, NH), 6.92 (s, 1H, H-2″i), 6.80 (d, $J=8$ Hz, 1H, H-3′+H-5′), 5.47 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.98 (br s, 1H, H-2), 3.82 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.74 (s, 3H, O–CH_3), 3.57 (s, 2H, CH_2–CO), 2.41 (br t(dd), $J=17$ Hz, 1H, CH_2CH_2), 2.18 (br d, $J=17$ Hz, 1H, CH_2CH_2), 1.87 (br t(dd), $J=16$ Hz, 1H, CH_2CH_2), 1.53 (br d, $J=17$ Hz, 1H, CH_2CH_2), 1.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 173.1 (CO), 172.8 (CO), 159.7 (C–OCH_3 (PMB)), 137.4 (C-7a″i), 130.1 (C-3a″i), 128.2 (C-2′+C-6′), 124.6 (C-2″i), 122.9, 120.4 (C-6″i+C-5″i), 119.0 (C-4″i), 114.6 (C-3′+C-5′), 111.9 (C-7″i), 108.3 (C-3″i), 59.8 (C-2), 56.0 (C-5), 55.6 (O–CH_3), 50.0 (N–CH_2 of PMB), 33.3 (CH_2–CO), 31.3 (C-4), 25.5 (CH_3), 23.4 (C-3); CIMS *m/z* (%): 450 (MH^+), 432 (MH^+-H_2O, 9), 404 (MH^+-CO_2H, 4), 275 (MH^+-COCH_2indol–H_2O, 100).

4.4. Amide formation: addition of the fourth amino acid mimicking residue

General procedure: to a solution of acid compound **7** (0.35 mmol) in 10 mL of dry DMF at room temperature, TBTU (0.14 mmol) was added followed by the corresponding amine (1.05 mmol). The reaction mixture was stirred for 16 h at room temperature. After extraction with ethyl acetate (3×25 mL), the combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure. Chromatographic separation of the residue on a silica gel column eluting with a dichloromethane/ethyl acetate mixture gave the target compounds **I**–**V**.

(2S,5S*) 1-(4-Methoxybenzyl)-5-methyl-6-oxo-5-[(3-phenylpropionyl) amino]-piperidine-2-carboxylic acid [-2(1H-indol-3-yl) ethyl]-amide* **I**. Yield: 96%; mp 120 °C (EtOH); IR (KBr) cm^{-1}: 3276 (w, NH), 1639 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 8.52 (t, $J=5$ Hz, 1H, NH–CO–C2), 7.95 (s, 1H, NH-ind), 7.69 (d, $J=8$ Hz, 1H, H-4″i), 7.32 (d, $J=8$ Hz, 1H, H-7″i), 7.24–7.18 (m, 5H, Ph-H), 7.14 (t, $J=7$ Hz, 1H, H-6″i or H-5″i), 7.10–7.06 (m, 2H, H-2″i+H-6″i or H-5″i), 7.05 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.79 (d, $J=8$ Hz, 2H, H-3′+H-5′), 5.68 (s, 1H, NH-C5), 5.29 (d, $J=15$ Hz, 1H, N–CH_2 of PMB), 3.86 (br d, $J=6$ Hz, 1H, H-2), 3.76 (s, 3H, O–CH_3), 3.71–3.64 (m, 2H, CH_2–NH), 3.30 (d, $J=15$ Hz, 1H, N–CH_2 of PMB), 3.11 (t, $J=2$ Hz, 2H, CH_2-ind), 2.96 (t, $J=2$ Hz, 2H, CH_2-Ph), 2.62–2.54 (m, 1H, CH_2–CO), 2.48–2.41 (m, 1H, CH_2–CO), 2.35 (td(ddd), $J=14$, 4 Hz, 1H, H-4ax), 2.03 (br d, $J=14$ Hz, 1H, H-3eq), 1.87 (tdd(dddd), $J=14$, 6, 4 Hz, 1H, H-3ax), 1.44 (br d, $J=14$ Hz, 1H, H-4eq), 1.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 171.7 (CO), 171.1 (CO), 170.6 (CO), 159.1 (C–OCH_3 (PMB)), 140.5 (C-*ipso* Ph), 136.2 (C-7a″i), 129.7 (C-2′+C-6′), 128.6 (C-3a″i), 127.6 (C-*ipso* PMB), 128.5, 128.3, 126.3 (CH-Ph), 122.0 (C-6i″), 121.0 (C-2″i), 119.3, 119.0 (C-4i″+C-5i″), 114.8 (C-3′+C-5′), 113.5 (C-7″i), 110.9 (C-3″i), 60.9 (C-2), 55.3 (C-5), 55.2 (O–CH_3), 48.9 (N–CH_2 of PMB), 40.0 (CH_2–NH), 37.8 (CH_2–CO), 31.3 (CH_2-Ph), 30.4 (C-4), 25.4 (CH_3), 24.8 (CH_2-ind), 23.1 (C-3); EIMS *m/z* (%): 566 ($M^{+\cdot}$, 20), 424 ($M^{+\cdot}-CH_2CH_2$indol, 58), 143 (CH_2CH_2indole, 55); HRMS: Calcd for $C_{34}H_{38}N_4O_4$: 566.2893; found: 566.2910.

(2S,5S*) 1-(4-Methoxybenzyl)-5-methyl-6-oxo-5-(phenacylamino) piperidine-2-carboxylic acid {2-(1H-indol-3-yl)-ethyl}-amide* **II**. Yield: 44%; mp 213 °C (EtOH); IR (KBr, cm^{-1}): 3439 (w, NH), 1634 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 8.45 (t, $J=5$ Hz, 1H, NH–CH_2), 8.10 (s, 1H, NH-ind), 7.62 (d, $J=7$ Hz, 1H, H-4″i), 7.31 (d, $J=7$ Hz, 1H, H-7″i), 7.28–7.24 (m, 5H, Ph-H), 7.13 (t, $J=7$ Hz, 1H, H-6″i), 7.09 (t, $J=7$ Hz, 1H, H-5″i), 7.01 (d, $J=9$ Hz, 2H, H-2′+H-6′), 7.00 (br s, 1H, H-2″i), 6.76 (d, $J=9$ Hz, 2H, H-3′+H-5′), 5.82 (s, 1H, NH-C5), 5.26 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.85 (br d, $J=6$ Hz, 1H, H-2), 3.73 (s, 3H, O–CH_3), 3.65 (m, 2H, CH_2–NH), 3.52 (s, 2H, CH_2-Ph), 3.30 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.04 (t, $J=8$ Hz, 2H, CH_2-ind), 2.31 (td(ddd), $J=14$, 3 Hz, 1H, H-4ax), 1.99 (br d, $J=14$ Hz, 1H, H-3eq), 1.83 (tdd(dddd), $J=14$, 6, 3 Hz, 1H, H-3ax), 1.41 (br d, $J=14$ Hz, 1H, H-4eq), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 171.0 (CO), 170.7 (CO), 170.6 (CO), 159.1 (C–OCH_3 (PMB)), 136.3 (C-*ipso* Ph), 134.5 (C-7a″i), 129.5 (C-2′+C-6′), 129.4, 128.9, 127.3 (CH-Ph), 128.5 (C-*ipso* PMB), 127.6 (C-3a″i), 122.1 (C-6″i), 121.7 (C-2″i), 119.1 (C-5″i), 118.9 (C-4″i), 114.0 (C-3′+C-5′), 113.1 (C-3″i), 110.9 (C-7″i), 60.3 (C-2), 55.3 (C-5), 55.0 (O–CH_3), 49.0 (N–CH_2 of PMB), 43.2 (CH_2–NH), 30.2 (CH_2-Ph), 25.2 (C-4), 24.6 (CH_3); 23.0 (C-3), 20.9 (CH_2-ind); EIMS *m/z* (%): 553 ($M^{+\cdot}$, 3), 410 ($M^{+\cdot}-CH_2CH_2$indol, 31), 365 ($M^{+\cdot}-NHCH_2CH_2$indol–OCH_3, 5), 121 ($CH_3OPhCH_2^+$, 100); HRMS: Calcd for $C_{33}H_{36}N_4O_4$: 552.2736; found: 552.2746.

(2S,5S*) 5-Benzoylamino-1-(4-methoxybenzyl)-5-methyl-6-oxo-piperidine-2-carboxylic acid {2-(1H-indol-3-yl)-ethyl}-amide* **III**. Yield: 58%; mp 215 °C (EtOH); IR (KBr) cm^{-1}: 3286 (w, NH), 1638 (s, CO); ^1H NMR ($CDCl_3$, 400 MHz, ppm): 8.45 (t, $J=5$ Hz, 1H, NH–CH_2), 8.20 (s, 1H, NH-ind), 7.76 (d, $J=7$ Hz, 2H, *ortho* Ph), 7.63 (d, $J=7$ Hz, 1H, H-4″i), 7.50 (t, $J=7$ Hz, 1H, *para* Ph),

7.43 (t, $J=7$ Hz, 2H, *meta* Ph), 7.25 (d, $J=7$ Hz, 1H, H-7″i), 7.14 (t, $J=7$ Hz, 1H, H-6″i), 7.09–7.04 (m, 4H, H-2′+H-6′+H-5″i+H-2″i), 6.79 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.49 (s, 1H, NH-C5), 5.25 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.85 (br d, $J=6$ Hz, 1H, H-2), 3.73 (s, 3H, O–CH_3), 3.70 (q, $J=7$ Hz, 2H, CH_2–NH), 3.31 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.04 (td, $J=7$ Hz, 2H, CH_2-ind), 2.32 (td(ddd), $J=14$ Hz, 3 Hz, 1H, H-4ax), 1.97 (br d, $J=14$ Hz, 1H, H-3eq), 1.88 (tdd(dddd), $J=14$ Hz, 3 Hz, 1H, H-3ax), 1.41 (br d, $J=14$ Hz, 1H, H-4eq), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 171.1 (CO), 170.7 (CO), 170.6 (CO), 159.1 (C–OCH_3 (PMB)), 136.3, 133.5 (C-*ipso* Ph +C-7a″i), 131.9, 128.5, 127.1 (CH-Ph), 129.6 (C-2′+C-6′), 128.7 (C-3a″i), 127.7 (C-*ipso* PMB), 121.8 (C-2″i), 121.1 (C-6″i), 119.8 (C-4″i), 118.6 (C-5″i), 114.2 (C-3′+C-5′), 113.4 (C-3″i), 111.0 (C-7″i), 61.0 (C-2), 55.7 (C-5), 55.2 (O–CH_3), 49.0 (N–CH_2 of PMB), 40.1 (CH_2–NH), 30.3 (C-4), 25.6 (CH_3), 24.7 (CH_2-ind), 23.1 (C-3); EIMS *m/z* (%): 538 ($M^{+\cdot}$, 4), 396 ($M^{+\cdot}-CH_2CH_2$indole, 31), 351 ($M^{+\cdot}-NHCOCH_2CH_2$indole, 5); HRMS: Calcd for $C_{32}H_{34}N_4O_4$: 538.2580; found: 538.2585.

(2S,5S*) 5-(3-1H-Indol-3-yl-propionylamino)-1-(4-methoxybenzyl)-5-methyl-6-oxo-piperidine-2-carboxylic acid phenethyl-amide* **IV**. Yield: 50%; mp 130 °C (EtOH); IR (KBr) cm^{-}: 3280 (w, NH), 1640 (s, CO); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm, 328 K): 8.48 (t, $J=5$ Hz, 1H, NH–CO–C2), 8.31 (br s, 1H, NH-ind), 7.56 (d, $J=7$ Hz, 1H, H-4i″), 7.36 (d, $J=7$ Hz, 1H, H-7″i), 7.26–7.23 (m, 5H, Ph-H), 7.16 (t, $J=7$ Hz, 1H, H-6″i), 7.08 (t, $J=7$ Hz, 1H, H-5″i), 7.05 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.95 (br d, $J=2$ Hz, 1H, H-2″i), 6.78 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.08 (s, 1H, NH-C5), 5.28 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.84 (br d, $J=6$ Hz, 1H, H-2), 3.74 (s, 3H, O–CH_3), 3.60 (q, $J=13$ Hz, 2H, CH_2–NH), 3.31 (d, $J=14$ Hz, 1H, N–CH_2 of PMB), 3.05 (t, $J=7$ Hz, 2H, CH_2-ind), 2.95 (q, $J=13$ Hz, CH_2-Ph), 2.48 (dt, $J=7$, 2 Hz, 2H, CH_2–CO), 2.25 (td(ddd), $J=14$, 3 Hz, 1H, H-4ax), 1.92 (br d, $J=14$ Hz, 1H, H-3eq), 1.79 (tdd(dddd), $J=14$, 6, 3 Hz, 1H, H-3ax), 1.32 (br d, $J=14$ Hz, 1H, H-4eq), 1.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm, 328 K): 172.2 (CO), 171.1 (CO), 170.9 (CO), 159.1 (C–OCH_3 (PMB)), 139.1 (C-7a″i), 135.3 (C-*ipso* Ph), 129.4 (C-2′+C-6′), 128.5 (C-3a″i), 128.8, 128.3, 126.1 (CH-Ph), 127.0 (C-*ipso* PMB), 121.9 (C-6″i), 121.8 (C-2″i), 119.1 (C-5″i), 118.4 (C-4″i), 114.4 (C-3″i), 114.0 (C-3′+C-5′), 111.3 (C-7″i), 61.0 (C-2), 55.1 (C-5), 55.0 (O–CH_3), 49.0 (N–CH_2 of PMB), 40.7 (CH_2–NH), 36.5 (CH_2–CO), 34.9 (CH_2-Ph), 30.3 (C-4), 25.1 (CH_3), 22.9 (C-3), 20.6 (CH_2-ind); EIMS *m/z* (%): 566 ($M^{+\cdot}$, 20), 418 ($M^{+\cdot}-NHCOCH_2CH_2Ph$, 19); HRMS: Calcd for $C_{34}H_{38}N_4O_4$: 566.2893; found: 566.2921.

(2S,5S*) 5-(2-1H-Indol-3-yl-acetylamino)-1-(4-methoxybenzyl)-5-methyl-6-oxo-piperidine-2-carboxylic acid phenethyl-amide* **V**. Yield: 43%; mp 201 °C (EtOH); IR (KBr) cm^{-1}: 3280 (w, NH), 1640 (s, CO); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 8.53 (t, $J=5$ Hz, 1H, NH–CH_2), 8.35 (s, 1H, NH-ind), 7.65 (d, $J=7$ Hz, 1H, H-4″i), 7.39 (d, $J=7$ Hz, 1H, H-7″i), 7.29–7.15 (m, 8H, Ph-H+H-6″i+H-5″i+H-2″i), 7.09 (d, $J=8$ Hz, 2H, H-2′+H-6′), 6.80 (d, $J=8$ Hz, 2H, H-3′+H-5′), 6.04 (s, 1H, NH-C5), 5.33 (d, $J=13$ Hz, 1H, N–CH_2 of PMB), 3.85 (br d, $J=6$ Hz, 1H, H-2), 3.75 (s, 3H, O–CH_3), 3.73 (2×d, $J=13$ Hz, 2H, CH_2–CO), 3.67–3.54 (m, 2H, CH_2–NH), 3.36 (d, $J=13$ Hz, 1H, N–CH_2 of PMB), 2.94 (dt, $J=7$ Hz, 2H, CH_2-Ph), 2.35 (td(ddd), $J=14$, 3 Hz, 1H, H-4ax), 1.95 (br d, $J=14$ Hz, 1H, H-3eq), 1.83 (tdd(dddd), $J=14$, 6, 3 Hz, 1H, H-3ax), 1.42 (br d, $J=14$ Hz, 1H, H-4eq), 1.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 171.2 (CO), 171.1 (CO), 170.7 (CO), 159.1 (C–OCH_3 (PMB)), 139.2 (C-*ipso* Ph), 136.4 (C-7a″i), 129.7 (C-2′+C-6′), 128.9, 128.3, 126.1 (CH-Ph), 128.6 (C-3a″i), 126.9 (C-*ipso* PMB), 123.8, 122.6, 120.1, 118.7 (CH-ind), 114.0 (C-3′+C-5′), 111.0 (C-7″i), 108.6 (C-3″i), 61.0 (C-2), 55.3 (C-5), 55.2 (O–CH_3), 49.0 (N–CH_2 of PMB), 40.7 (CH_2-Ph), 35.0 (CH_2–NH), 33.3 (CH_2–CO), 30.3 (C-4), 25.2 (CH_3), 23.0 (C-3); EIMS *m/z* (%): 552 ($M^{+\cdot}$, 20), 396 ($M^{+\cdot}-COCH_2$indole, 28), 121 ($CH_3OPhCH_2^+$, 100); HRMS: Calcd for $C_{33}H_{36}N_4O_4$: 552.2736; found: 552.2742.

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9. Actual concentrations: 8571, 9.05 μM; 8587, 9.29 μM; 8588, 8.83 μM; 8514, 9.71 μM. All compounds were tested as racemates.
10. We assume the diuretic effect is due to stimulation of the same receptors the natural peptides bind to.
11. Broad signals probably due to aggregation effects.

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Comparison of 'classic' ^{99m}Tc–DTPA, ^{99m}Tc(CO)$_3$–DTPA and ^{99m}Tc(CO)$_2$(NO)–DTPA

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Abstract—Diethylenetriamine pentaacetic acid (DTPA) was labeled with ^{99m}Tc in three different ways, resulting in 'classic' ^{99m}Tc–DTPA, ^{99m}Tc(CO)$_3$–DTPA and ^{99m}Tc(CO)$_2$(NO)–DTPA. The biodistribution of the formed DTPA-complexes was studied in mice with a special emphasis on the behavior of the novel tricarbonyl and dicarbonyl-nitrosyl complexes, which was clearly differing from that of 'classic' ^{99m}Tc–DTPA. The conversion of a Tc-tricarbonyl complex to a Tc-dicarbonyl-nitrosyl complex using NO^+ reagents offers a synthetic tool for preparing a novel class of ^{99m}Tc labeled compounds.

1. Introduction

A few years ago, Alberto et al. developed a convenient high-yield synthesis for ^{99m}Tc-tricarbonyl complexes.[1] A large number of such complexes has been reported since then and the access to this kind of technetium chemistry became even easier with the introduction of the IsoLink™ kit (Tyco-Mallinckrodt, Petten, The Netherlands). ^{99m}Tc(I)-complexes with a Tc(CO)$_3$-moiety show particular characteristics as compared to 'classic' Tc-compounds.[2–6] First clinical studies using Tc-tricarbonyl labeled biomolecules also revealed the potential clinical usefulness of such ^{99m}Tc-complexes.[7] However, for only a limited number of ^{99m}Tc-tricarbonyl complexes with simple chelators (not attached to a biomolecule) biological properties have been reported.[8–11]

Recently, this kind of bioorganometallic complex chemistry has been extended to dicarbonyl-nitrosyl complexes with a M(CO)$_2$(NO)-moiety (M=Re, Tc), which can be prepared starting from Re- or Tc-tricarbonyl complexes.[12] The introduction of a charged NO^+ group instead of a neutral CO group changes the charge of the formed Tc-dicarbonyl-nitrosyl complexes by +1 as compared to the original corresponding Tc-tricarbonyl compounds. Also the electronic properties of the Tc-nitrosyl complex differ, as NO^+ is a stronger π-acceptor, but a weaker σ-donor as compared to the isoelectronic CO.[13] To our knowledge, no reports about the biological properties of this new class of ^{99m}Tc(CO)$_2$(NO)-complexes have been published to date.

The chelating agent diethylenetriamine pentaacetic acid (DTPA) is a ligand known to form Tc-tricarbonyl and Tc-dicarbonyl-nitrosyl complexes.[14,15] The distance between the available oxo- and nitrogen heteroatoms is ideal, resulting in two five-membered rings when the radiometal is attached to the ligand.[16] Moreover, also the 'classic' ^{99m}Tc–DTPA-complex is well known, made by reduction of $^{99m}TcO_4^-$ with stannous ions in the presence of DTPA and used as a renal imaging radiopharmaceutical.[17] This made DTPA the ligand of choice to study the different Tc-cores mentioned above.

In the present study, we have compared the labeling and biodistribution characteristics in mice of the three different ^{99m}Tc–DTPA complexes: the 'classic' nuclear imaging agent ^{99m}Tc–DTPA (**1**), ^{99m}Tc(CO)$_3$–DTPA (**2**) and ^{99m}Tc(CO)$_2$(NO)–DTPA (**3**). Biodistribution experiments with complexes containing the same chelating ligand, but different Tc-cores, might provide the best insight in the influence of changes at the Tc-center on biological properties. A special emphasis was put on the novel tricarbonyl and dicarbonyl-nitrosyl complexes to investigate the potential of these ^{99m}Tc-complexes as clinically useful radiopharmaceuticals.

2. Results

Radiochemistry. ^{99m}Tc(CO)$_3$–DTPA (**2**) was obtained in similarly high yields (>98%) as 'classic' ^{99m}Tc–DTPA (**1**). Reversed phase high pressure liquid chromatography (RP-HPLC) showed the peak of (**1**) at a retention time (t_R) of

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3.5 min, while the more lipophilic (**2**) showed up at a t_R of 11.5 min (Fig. 1). In the same HPLC-system, $[^{99m}TcO_4]^-$ and the ^{99m}Tc-tricarbonyl precursor (**4**) had a t_R of 4.5 and 6.5 min, respectively. As shown in the HPLC-chromatograms of the unpurified reaction mixtures, none of these starting or intermediary ^{99m}Tc-compounds was present in any of the ^{99m}Tc–DTPA preparations.

The formation of $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) in water using $NOHSO_4$ afforded only moderate to poor yields and not a single, well-defined product. The conversion with $NOBF_4$ in CH_2Cl_2 or acetonitrile gave better results, but disadvantages were the time consuming procedure (including a complete change from saline to the organic solvent) and the overall lower yield as compared to the model complexes of rhenium with picolinic acid and iminodiacetic acid.[12,14]

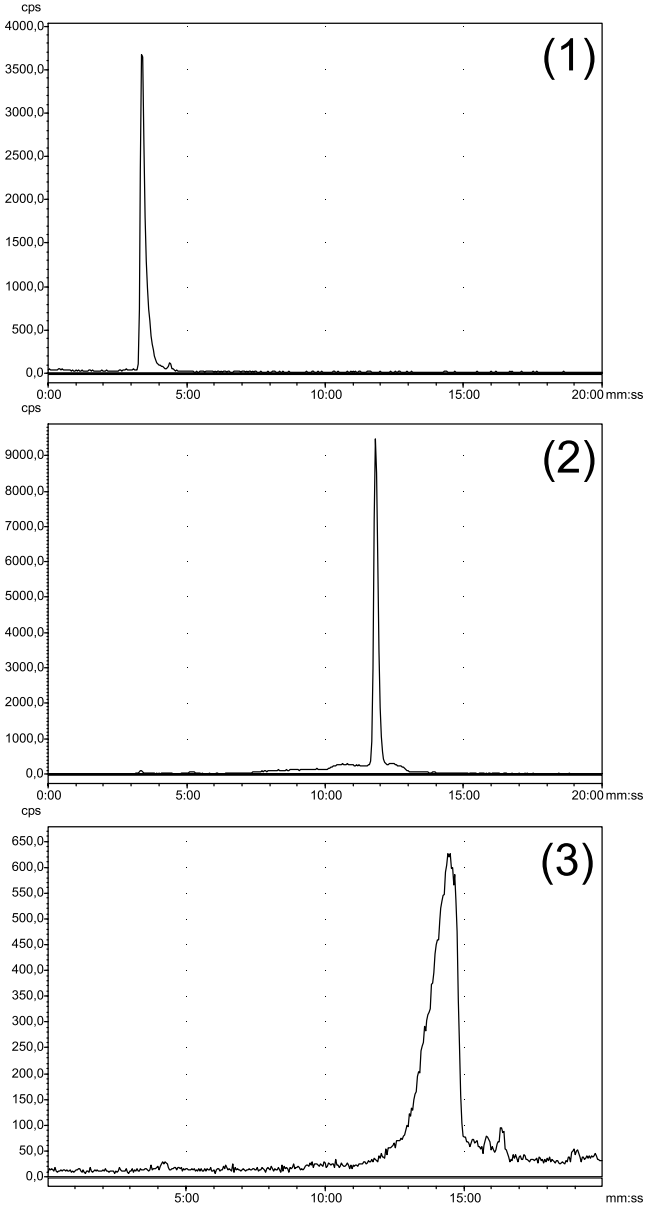

Figure 1. Reversed phase HPLC-analysis of the unpurified reaction mixtures of 'classic' ^{99m}Tc–DTPA (**1**), $^{99m}Tc(CO)_3$–DTPA (**2**), and $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) (X-Terra RP-18 column, gradient elution from 0.1% trifluoroacetic acid in water to 0.1% trifluoroacetic acid in acetonitrile in 20 min; flow rate 1 ml/min).

A novel strategy to solve this problem was the application of a two-layer system with water and CH_2Cl_2 for the conversion. $NOHSO_4$ was covered with CH_2Cl_2 and an aqueous solution containing $^{99m}Tc(CO)_3$–DTPA (**2**) was directly applied on top of it as second layer. Complex (**2**) was able to switch over to the organic layer and reacted with $NOHSO_4$, while $^{99m}TcO_4^-$ and inorganic salts remained in the aqueous layer. In this system, $NOHSO_4$ acts as suitable source of NO^+, whereas in direct contact with water it spontaneously releases brown gases (NO_2) in a vigorous reaction. $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) was obtained almost pure from the organic layer, but the yields were quite low. Mass spectral analysis of the isolated compound by LC-MS supported the formation of a $Tc(CO)_2(NO)$–DTPA complex. The detected mass of 576.90 Da corresponds with the theoretical value of 577.02 Da. Kryptofix 2.2.2 (377.26 Da) was added to the mobile phase and served as lock mass for accurate mass determination (Fig. 2). The conversion to (**3**) was completed after 4–5 h. For practical reasons the reaction was allowed to proceed overnight.

A second new strategy to form $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) was the isolation of the $^{99m}Tc(CO)_3$-precursor (**4**) in acetonitrile by RP-HPLC and adding this solution to a mixture of DTPA and $NOHSO_4$ (solid). This is the fastest of the three methods, but the yields were varying from 60 to 89%. RP-HPLC analysis showed the main peak of the intended complex at a retention time of 14.2 min and smaller peaks of yet unidentified ^{99m}Tc-compounds in the region 16 min (Fig. 1). For biodistribution experiments the main peak was isolated by RP-HPLC.

Stability tests. Stability tests of (**3**) have been performed in acetonitrile, CH_2Cl_2, water, phosphate buffer (0.025 M, pH=7.4) and blood plasma. Complex (**3**) was almost unchanged in the organic solvents CH_2Cl_2 and acetonitrile after 24 h. In water and phosphate buffer only a limited degradation of $^{99m}Tc(CO)_2(NO)$–DTPA was detected after 24 h After incubation in blood plasma analysis using size exclusion HPLC (SEC-HPLC, Superdex™ column, phosphate buffer as mobile phase) showed a peak at a retention time of 12–15 min in case of $^{99m}Tc(CO)_2(NO)$–DTPA, which was not observed for any of the two other ^{99m}Tc–DTPA-complexes. In aqueous solution, complexes (**2**) and (**3**) eluted at 31–32 min as well-defined peaks, showing almost identical SEC-HPLC chromatograms. In a control experiment, ^{99m}Tc-labeled albumin eluted also at a comparable retention time of 12–15 min, strongly suggesting a rapid and pronounced binding of the radionuclide or the intact complex to plasma proteins in case of $^{99m}Tc(CO)_2(NO)$–DTPA.

As serum proteins contain essentially cysteine and histidine as competing coordination sites,[8] the stability of $^{99m}Tc(CO)_2(NO)$–DTPA against an excess of histidine and cysteine was tested ('histidine and cysteine challenge'). Complex (**3**) remained unchanged under these conditions after 30 min, 1, 2, and 20 h and formation of a $^{99m}Tc(CO)_2(NO)$-species with histidine or cysteine was not observed. The histidine complex $[^{99m}Tc(CO)_2(NO)(HIS)]^+$ was

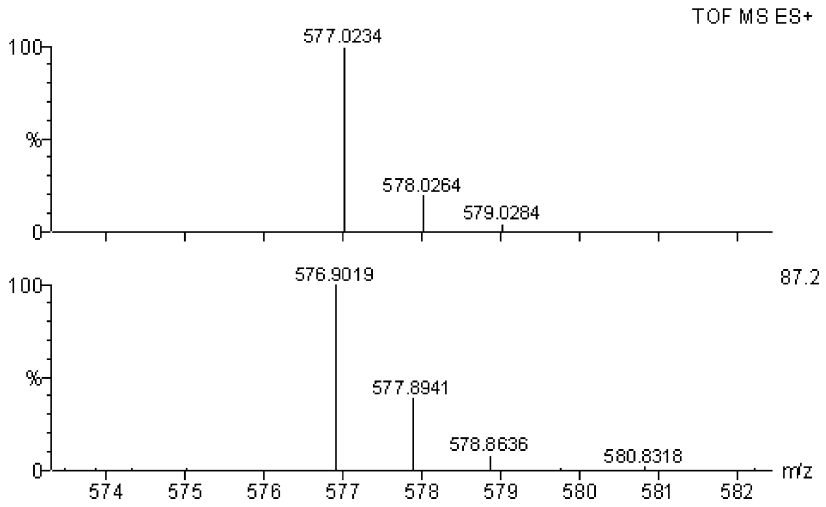

Figure 2. Calculated (a) and detected (b) mass spectrum of the isolated complex $^{99m}Tc(CO)_2(NO)$–DTPA obtained by LC-MS (ES^+).

synthesized as reference compound (retention time of 12.5 min on RP-HPLC) and also analyzed by LC-MS. The detected mass of 340.01 Da corresponds with the theoretical value of 339.96 Da.

Biological characteristics. The results of the biodistribution experiments for selected organs are shown in Table 1. As expected, 'classic' ^{99m}Tc–DTPA (**1**) was excreted rapidly via the renal system, while the Tc-tricarbonyl complex $^{99m}Tc(CO)_3$–DTPA (**2**) was retained longer in the body. The blood activity for these two agents was almost equal after 10 min, but higher for (**2**) after 65 min. Complex (**2**) showed a higher liver uptake, in line with its less polar nature as seen by RP-HPLC. Activity in heart and stomach did not differ significantly and for lungs and intestines only a slight increase of activity was detected for the Tc-tricarbonyl complex.

Table 1. Biodistribution data for 'classic' ^{99m}Tc–DTPA, $^{99m}Tc(CO)_3$–DTPA, $^{99m}Tc(CO)_2(NO)$–DTPA for selected organs (±SD) at 10 and 65 min (three–five mice for each tracer at each time point)

	Tc–DTPA	$Tc(CO)_3$–DTPA	$Tc(CO)_2(NO)$–DTPA
% of ID	10 min	10 min	10 min
Kidneys	7.52 (±2.16)	7.81 (±3.35)	10.00 (±1.24)
Urine	32.35 (±4.19)	13.20 (±3.44)	3.56 (±2.14)
Liver	2.84 (±0.28)	5.31 (±0.48)	17.40 (±1.17)
Intestines	3.23 (±0.36)	4.59 (±1.14)	8.04 (±0.90)
Lungs	0.87 (±0.09)	1.49 (±0.30)	2.90 (±0.60)
Heart	0.28 (±0.02)	0.3 (±0.08)	0.98 (±0.08)
Stomach	0.60 (±0.06)	0.71 (±0.10)	0.77 (±0.07)
Brain	0.07 (±0.02)	0.07 (±0.02)	0.42 (±0.09)
Blood	17.83 (±1.77)	18.57 (±1.10)	64.42 (±1.52)
	Tc–DTPA	$Tc(CO)_3$–DTPA	$Tc(CO)_2(NO)$–DTPA
% of ID/g	10 min	10 min	10 min
Kidneys	10.47 (±2.99)	12.14 (±4.84)	17.07 (±1.33)
Liver	1.08 (±0.07)	2.22 (±0.12)	8.26 (±1.14)
Blood	4.57 (±0.15)	5.57 (±0.50)	22.76 (±1.14)
	Tc–DTPA	$Tc(CO)_3$–DTPA	$Tc(CO)_2(NO)$–DTPA
% of ID	65 min	65 min	65 min
Kidneys	1.25 (±0.19)	2.25 (±0.17)	6.53 (±0.97)
Urine	85.63 (±4.71)	57.38 (6.01)	12.52 (1.07)
Liver	0.63 (±0.07)	3.16 (±0.85)	20.56 (±3.83)
Intestines	0.83 (±0.08)	4.68 (±1.95)	6.40 (±0.73)
Lungs	0.11 (±0.02)	0.52 (±0.13)	2.43 (±0.33)
Heart	0.03 (±0.00)	0.14 (±0.01)	0.81 (±0.05)
Stomach	0.17 (±0.05)	0.32 (±0.19)	0.70 (±0.10)
Brain	0.02 (±0.01)	0.07 (±0.04)	0.24 (±0.05)
Blood	2.62 (±0.72)	8.18 (±0.67)	48.39 (±2.86)
	Tc–DTPA	$Tc(CO)_3$–DTPA	$Tc(CO)_2(NO)$–DTPA
% of ID/g	65 min	65 min	65 min
Kidneys	1.77 (±0.27)	3.61 (±0.53)	10.72 (±1.49)
Liver	0.25 (±0.04)	1.38 (±0.32)	9.47 (±1.22)
Blood	0.48 (±0.04)	2.53 (±0.25)	16.11 (±1.71)

The introduction of a NO^+ group instead of a CO group changed the characteristics of the formed complex drastically. $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) had the lowest excretion rate via kidneys/urine after 10 and 65 min, but the highest liver uptake of the three compounds. Even more remarkable was its surprisingly high blood level. Blood activity of the nitrosyl complex (**3**) was more than threefold higher than that of (**1**) and (**2**) after 10 min. After 65 min still 48.4% of the activity remained in the blood, while most of (**1**) and (**2**) had already been excreted. Also the detected activity in lungs, heart and intestines was higher in case of the Tc–NO complex.

3. Discussion

The preparation of ^{99m}Tc–DTPA (**1**) and $^{99m}Tc(CO)_3$–DTPA (**2**) is straightforward and suitable for practical use. A synthesis of $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) in either of the three ways described above is more time consuming and includes at least one reaction step in an organic solvent, which should be avoided in a potential clinical application.

The exact position of the $Tc(CO)_3$- and $Tc(CO)_2(NO)$-core in the DTPA-complexes (**2**) and (**3**) was not determined in the present study. The distances between the available heteroatoms in the DTPA-molecule are suitable for the formation of different isomeric complexes. Trump et al. suggested a labeling via two carboxylic acid groups and one amine as most likely for their $Tc(CO)_3$(DTPA)-folate compound, but also a complexation via two amines and one acid group or via the three amines of the DTPA-

backbone cannot be excluded.[15] The charge of the Tc-tricarbonyl and Tc-dicarbonyl-nitrosyl complexes with DTPA would be different, depending on how the respective Tc-core binds to the ligand. However, the overall charge of all these potential DTPA-complexes under physiological conditions is negative in any case, since DTPA comprises additional carboxylate groups that do not coordinate, but contribute to the charge. X-ray structure analysis of the corresponding non-radioactive Re-complexes would be a possibility for determination of the exact position of the Tc-core in these complexes.

The differences in biodistribution of the three complexes ^{99m}Tc–DTPA (**1**), ^{99m}Tc(CO)$_3$–DTPA (**2**), and ^{99m}Tc(CO)$_2$(NO)–DTPA (**3**) are significant. There was a tendency in the biological behavior that corresponded with the polarity of the compound as seen in RP-HPLC-measurements, with (**1**) as the most polar and (**3**) as the most lipophilic compound. As expected, the most polar 'classic' ^{99m}Tc–DTPA is excreted rapidly via the kidneys and has a low overall uptake in all other organs. Labeling DTPA with a Tc(CO)$_3$-core makes the compound more lipophilic and leads to a decreased excretion rate, a slightly higher liver uptake and a longer retention in blood. The most significant changes, however, were observed after the introduction of a nitrosyl group instead of one carbonyl group in the Tc-tricarbonyl core. The liver uptake is significantly increased, while the excretion via the kidneys drops to a negligible level as compared to the 'classic' ^{99m}Tc–DTPA. Even after 1 h, the major part of the injected activity is detected in the blood. The slightly higher uptake in all other organs (including the brain), may also reflect the high blood activity instead of a real organ uptake. As in all three cases DTPA was the ligand of choice, the changes at the Tc-center must be responsible for the different characteristics of the complexes.

As a control, we also determined the biodistribution of the ^{99m}Tc(CO)$_2$(NO)-precursor itself (without DTPA as ligand) and found values approximately in the same range as for complex (**3**) (Fig. 3). More specifically, after injection of the ^{99m}Tc(CO)$_2$(NO)-precursor the activity is retained to a high degree in the plasma (41.4% at 65 min p.i. vs 48.4% for complex **3**) and excreted slowly and partially to the urine (17.3% at 65 min p.i. vs 12.5% for **3**). The significant retention of complex (**3**) in blood corresponds well with the high protein binding seen in size exclusion chromatography. However, it remains unclear whether this high protein binding reflects a binding of the ^{99m}Tc(CO)$_2$(NO)-core to plasma proteins after transchelation (shift of the ^{99m}Tc(CO)$_2$(NO)-core from DTPA to a macromolecular component of the plasma) or if DTPA remains—maybe only partially—bound to the Tc center, with binding of the complex or part of it to plasma proteins. The fact that in competition experiments with an excess of histidine or cysteine the ^{99m}Tc(CO)$_2$(NO)–DTPA complex remains intact tends to favor the latter hypothesis. The behavior of complex (**3**) and the ^{99m}Tc(CO)$_2$(NO)-precursor in vivo suggest that the presence of the NO-group might be responsible for a high affinity of these complexes for plama proteins.

In addition, in several experiments with tridentate Re(CO)$_2$(NO)-complexes we never detected a loss of the NO-group (the NO-band in the IR-spectrum was always present between 1700 and 1810 cm^{-1}), meaning that the M(CO)$_2$(NO)-core (M=Tc, Re) as such is stable.[18]

4. Conclusion

We synthesized three different DTPA-complexes, that is, 'classic' ^{99m}Tc–DTPA (**1**), ^{99m}Tc(CO)$_3$–DTPA (**2**), and ^{99m}Tc(CO)$_2$(NO)–DTPA (**3**) and studied their characteristics in biodistribution experiments in mice. The preparation of (**1**) and (**2**) was straightforward, while the synthesis of (**3**) was more elaborate. The new method using a two-layer system ('method B') was mainly developed to obtain pure (**3**), but the yields were low. The alternative method using HPLC-purification to isolate the ^{99m}Tc(CO)$_2$(NO)-precursor in acetonitrile ('method C') was chosen to obtain larger amounts of (**3**) in a relatively short time, but the yields were varying. Complexes (**1**), (**2**), and (**3**) showed clearly different physical and biological characteristics as compared to each other and these differences can only be attributed to the modifications at the Tc-center. The results show that the influence of a modified Tc-core on a certain ligand gives the opportunity to affect its biological behavior directly.

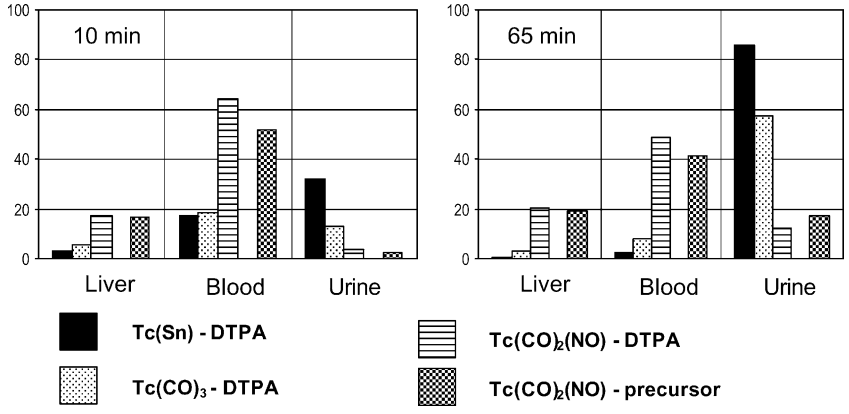

Figure 3. Biodistribution of the complexes ^{99m}Tc–DTPA, ^{99m}Tc(CO)$_3$–DTPA, ^{99m}Tc(CO)$_2$(NO)–DTPA in mice (n=3 or 4) in comparison with that of the ^{99m}Tc(CO)$_2$(NO)-precursor complex for selected organs (in % of I.D. 10 and 65 min p.i.).

The conversion of a Tc-tricarbonyl core to a Tc-dicarbonyl-nitrosyl core using NO^+ reagents offers a new synthetic tool for bioorganometallic chemistry. Studies with other ligands than DTPA are necessary to further explore the usefulness of ^{99m}Tc-dicarbonyl-nitrosyl complexes for clinical applications. There are different examples of stable mono-, bi- and tridentate non-radioactive $Re(CO)_2(NO)$-complexes.[12,14,18–21] Using one of the above described procedures, the successful preparation of the corresponding ^{99m}Tc-analogs or other new $^{99m}Tc(CO)_2(NO)$-complexes should be well feasible. The 'nitrosyl-approach' is a general method that allows the preparation of a novel class of ^{99m}Tc-labeled compounds.

5. Experimental

Analytical methods. The ^{99m}Tc-complexes were analyzed by reversed phase HPLC (X-Terra RP-18 column 4.6 mm×250 mm; Waters, Brussels, Belgium; gradient elution from 0.1% trifluoroacetic acid in water to 0.1% trifluoroacetic acid in acetonitrile in 20 min; flow rate 1 ml/min). Their mass was determined using LC-MS (Waters separation module, XTerra MS C18 column 50 mm×2.1 mm, 3-inch NaI(Tl) radiation detector, Micromass LCT mass spectrometer and MassLynx software, Waters-Micromass, Manchester, UK). The column was eluted at a flow rate of 300 µl/min with gradient mixtures of water and acetonitrile (linear gradient from 0% acetonitrile at 0 min to 100% at 20 min). A solution of 0.01% Kryptofix 2.2.2 (377.26 Da) in CH_3CN–H_2O (50/50) was added to the mobile phase at a flow rate of 1 µl/min and served as lock mass for accurate mass determination. Activity in organs and tissues was measured using a Wallac 1480 WIZARD 3' automatic gamma counter (Perkin-Elmer, Boston, USA).

Radiochemistry. Diethylenetriamine pentaacetic acid (DTPA) (Aldrich, Milwaukee, Wisconsin, USA) and nitrosyl tetrafluoroborate ($NOBF_4$) (Fluka, Bornem, Belgium) were purchased commercially.

The Tc-tricarbonyl precursor $[^{99m}Tc(CO)_3(H_2O)_3]^+$ (**4**) was synthesized directly from a solution of $[^{99m}TcO_4]^-$ (eluate from a commercially available Ultratechnekow FM ^{99m}Tc-generator; Tyco-Mallinckrodt, Petten, The Netherlands) using a mixture of $NaBH_4$, Na_2CO_3, K–Na-tartrate and CO-gas[1] or an IsoLink™ kit (Tyco-Mallinckrodt). Activities up to 1850 MBq in 1 ml saline were used for the carbonylation reaction.

'Classic' ^{99m}Tc–DTPA (**1**) was prepared by addition of generator eluate (400–800 MBq) to a home made labeling kit (containing 10 mg $CaNa_3$DTPA and 0.5 mg $SnCl_2\cdot 2H_2O$) and incubation for 5 min at room temperature.

$^{99m}Tc(CO)_3$–DTPA (**2**) was obtained in a reaction of 1 mg DTPA with 200 µl of a stock solution of precursor (**4**). The solution was adjusted to pH 10 with 1 M NaOH and heated for 10 min at 80 °C. After cooling to room temperature the reaction mixture was analyzed by RP-HPLC. The yield of complex (**2**) was 98%.

$^{99m}Tc(CO)_2(NO)$–DTPA (**3**). *Method A*. A solution of complex (**2**) was evaporated to dryness at 40 °C in a N_2 stream. The residue was mixed with 1 mg $NOBF_4$ in 1 ml CH_2Cl_2 and the mixture was stirred for 4 h at room temperature, yielding >70% of complex (**3**). For biodistribution experiments product (**3**) was purified by RP-HPLC.

Method B. $NOHSO_4$ (2 mg) was covered with 0.6 ml CH_2Cl_2 and 0.2 ml of an aqueous solution containing complex (**2**) was added on top of the organic layer. After addition of 40 µl acetonitrile the vial was stored overnight at room temperature. RP-HPLC analysis of the organic layer showed the presence of almost exclusively product (**3**), while the aqueous layer also contained the starting material (**2**) and $^{99m}TcO_4^-$. Removal of the aqueous layer with a pipette and separation of the organic layer from undissolved $NOHSO_4$ was an efficient purification method. CH_2Cl_2 was then removed in a N_2-stream and the residue redissolved in 0.9% saline solution, affording pure complex (**3**) in low yields.

Method C. The ^{99m}Tc-tricarbonyl precusor (**4**) was isolated using RP-HPLC with acetonitrile as mobile phase. The solution was transferred into a nitrogen flushed vial containing 1 mg DTPA and 5 mg $NOHSO_4$ (solid). HPLC analysis after 1 h showed the presence of complex (**3**) in yields varying from 60 to 89%.

Stability in plasma. $^{99m}Tc(CO)_3$–DTPA (**2**) was isolated by size-exclusion HPLC using a Superdex™ Peptide 10/300 GL column (Amersham Biosciences, Roosendaal, The Netherlands) with phosphate buffer as mobile phase (0.025 M, pH 7.4, flow rate 0.5 ml/min). $^{99m}Tc(CO)_2(NO)$–DTPA (**3**) was isolated by RP-HPLC (Waters X-Terra RP-18 column 4.6 mm×250 mm; gradient elution from 0.1% trifluoroacetic acid in water to a mixture of 75% of 0.1% trifluoroacetic acid in water and 25% of 0.1% trifluoroacetic acid in acetonitrile in 5 min, then pure acetonitrile; flow rate 1 ml/min). The solution was evaporated almost to dryness using a N_2-stream, 0.5 ml saline solution was added and the volume again reduced in a N_2-stream (15 min at 40 °C in a water bath).

An aliquot of 0.5 ml of a solution containing one of the isolated DTPA-complexes (**2**) or (**3**) was added to 2 ml human plasma (obtained from human blood, centrifuged at 3000 rpm for 10 min). After incubation for 1, 3 or 24 h at room temperature, the mixture was analyzed by size exclusion HPLC.

Cysteine and histidine challenge experiments. Aliquots of 50 µl solution containing the isolated $^{99m}Tc(CO)_2(NO)$ (DTPA)-complex were added to 500 µl of 10^{-2} M cysteine or histidine solutions in phosphate buffered saline (PBS pH 7.4). The solutions were incubated at 37 °C and analyzed by RP-HPLC after 30 min, 1, 2, and 20 h.

Animal studies. Biodistribution experiments were performed in compliance with national laws related to the conduct of animal experimentation and with the approval of the institutional ethical committee.

Each compound was studied in six normal male NMRI mice (body mass 27–43 g) by injecting a ^{99m}Tc-activity of

approximately 40 kBq/mouse via a tail vein. Three mice were sacrificed at 10 min p.i., the other three at 65 min p.i. and the organs and body parts were dissected and weighed. The activity in the dissected organs and body parts was measured using a gamma counter. Results are expressed as percentage of injected dose (% of ID) and percentage of injected dose per gram (% of ID/g) for selected organs. For calculation of total blood radioactivity, blood mass was assumed to be 7% of the body mass.[22]

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Intramolecular charge-transfer-induced chemiluminescent decomposition of 1,2-dioxetanes bearing a phenylmethanide anion

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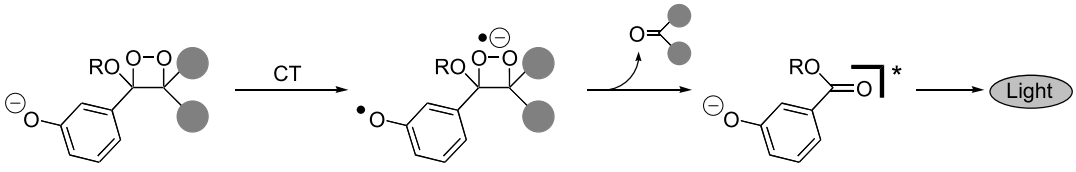
Abstract—Dioxetanes (**1**) bearing a phenyl moiety substituted with a methylene or methine having an electron-withdrawing group(s) (–CH_2-Ew or –CH(X)-Ew) and dioxetane (**2**) bearing a 3-(1-cyanoethenyl)phenyl group were synthesized. Treatment of dioxetanes (**1**) with tetrabutylammonium fluoride (TBAF) caused their decomposition with accompanying emission of light with maximum wavelength at 530–758 nm. The Michael addition of a bis(methoxycarbonyl)methanide anion to dioxetane (**2**) produced initially an unstable dioxetane bearing a phenylmethanide anion, decomposition of which gave light with maximum wavelength at 710–740 nm. Intramolecular cyclopropanation without decomposition of the dioxetane ring took place concurrently for the Michael reaction-induced decomposition of **2** with the bis(methoxycarbonyl)chloromethanide anion.

1. Introduction

Dioxetanes substituted with an aromatic electron donor such as an arenoxide anion (aryl-O^-) undergo intramolecular charge-transfer (CT)-induced decomposition with accompanying luminescence (Scheme 1).[1–4] The phenomenon has received much attention from the viewpoints of mechanistic interests related to bioluminescence and application to chemiluminescent bioassays, and extensive research efforts have been made to elucidate the chemiexcitation pathways as well as to develop efficient chemiluminescent systems.[5–7] However, there has been little known of dioxetanes bearing a carbanion such as an arenemethanide anion (aryl-C^-) instead of the arenoxide anion (aryl-O^-), though an arenemethanide anion would play the role of electron donor similarly to an arenoxide anion for the intramolecular CT-induced chemiluminescent decomposition. One advantage of such type of chemiluminescent substrate would be that a phenylmethanide anion can be generated not only by proton-abstraction from a benzylic methylene or methine but also by conjugate addition of an anion to an ethenylphenyl moiety (Scheme 2).

This situation stimulated us to design a stable dioxetane, which can be easily transformed into an unstable dioxetane bearing a phenylmethanide anion. Thus-designed were dioxetanes bearing a phenyl moiety substituted with a methylene or methine having electron-withdrawing group(s) (–CH_2-Ew or –C*H*(X)-Ew) and their 3-(1-cyanoethenyl)phenyl-analog. We report here the synthesis of these dioxetanes and their chemiluminescent decomposition induced by various bases such tetrabutylammonium fluoride (TBAF), and bis(methoxycarbonyl)methanide anions.[8,9]



Scheme 1.

Keywords: Dioxetane; Chemiluminescence; Carbanion; Michael addition; Cyclopropanation.
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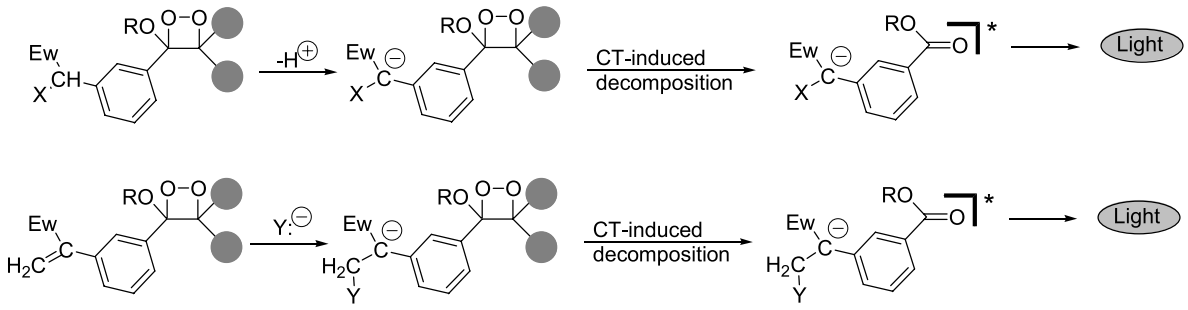
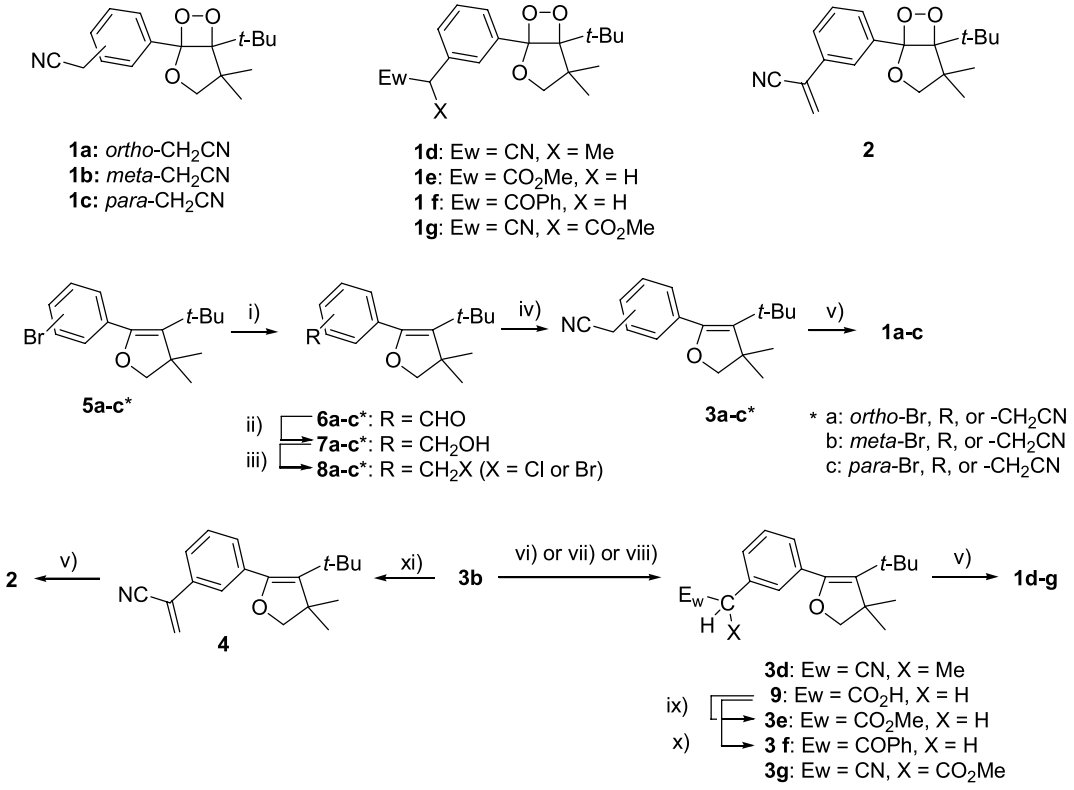


Scheme 2.

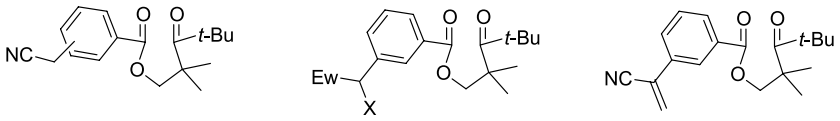
2. Results and discussion

2.1. Synthesis of 1,2-dioxetanes

Dioxetanes realized were 1-aryl-5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptanes (**1**),[10,11] the aryl moiety of which was substituted with a cyanomethyl group at the *ortho*-(**a**), *meta*-(**b**), or *para*-position (**c**). Bicyclic dioxetanes bearing a 3-(1-cyanoethyl)phenyl (**1d**), 3-(methoxycarbonylmethyl)phenyl (**1e**), 3-(benzoylmethyl)phenyl (**1f**), 3-[cyano(methoxycarbonyl)methyl]phenyl (**1g**) or 3-(1-cyanoethenyl)phenyl (**2**) were also realized. Synthesis of these dioxetanes was effectively attained by means of singlet oxygenation of the corresponding dihydrofurans (**3a**–**g** to **4**). Dihydrofurans (**3a**–**g** to **4**) were synthesized from 5-bromophenyl-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (**5a**–**5c**)[12] in several steps, as shown in Scheme 3. For example, 3-bromophenyl in (**5b**) easily underwent metal–halogen exchange reaction with butyllithium in THF to give a lithio derivative, to which *N*-methylformanilide added to afford formylphenyl derivative (**6b**). Reduction of (**6b**) with $NaBH_4$, followed by halogenation with CBr_4/PPh_3/THF, gave 3-(bromomethyl)phenyl-derivative (**8b**), which was, in turn, converted to the desired dihydrofuran bearing a 3-(cyanomethyl)phenyl moiety (**3b**) on treatment with NaCN. Dihydrofurans (**3a**, **3c**) were synthesized in a similar manner to the case of **3b**. The other dihydrofurans were prepared from 3-(cyanomethyl)phenyl-derivative (**3b**) as a key precursor. Methylation of the benzylic position in **3b** with MeI/NaH gave 3-(1-cyanoethyl)phenyl-dihydrofuran (**3d**). Hydrolysis of the nitrile group in **3b** gave 3-(carboxymethyl)phenyl-dihydrofuran (**9**), which was successively esterified into 3-(methoxycarboxylmethyl)-phenyl-derivative (**3e**). Lithiation of **9** with butyllithium followed by treatment with benzoyl chloride afforded 3-(benzoylmethyl)phenyl-dihydrofuran (**3f**). 3-[Cyano-(methoxycarbonyl)methyl]phenyl-dihydrofuran (**3g**) was synthesized by the Claisen condensation of **3b** with dimethyl



Scheme 3. Reagents: (i) BuLi/PhNMeCHO; (ii) $NaBH_4$; (iii) TsCl/DMAP or CBr_4/PPh_3; (iv) NaCN/TBA-HS; (v) O_2/TPP/*hv*; (vi) NaH/MeI; (vii) NaOH; (viii) NaH/$CO(OMe)_2$; (ix) $NaHCO_3$/MeI; (x) BuLi/PhCOCl; (xi) K_2CO_3/$(CHO)_n$/TBA-HS.



Scheme 4.

carbonate. Dihydrofuran bearing a 3-(1-cyanoethenyl)phenyl (**4**) was synthesized by the base-catalyzed condensation of **3b** with paraformaldehyde.

Singlet oxygenation of dihydrofurans (**3a**–**3g** to **4**) to the corresponding dioxetanes (**1a**–**1g** to **2**) was easily attained by the irradiation of a solution of dihydrofuran (**3a**–**3g** to **4**) and a catalytic amount of tetraphenylporphin (TPP) in CH_2Cl_2 with a 940 W Na lamp under O_2 atmosphere at $-78\sim0$ °C. All dioxetanes synthesized here except **2** were fairly stable thermally at room temperature, though they decomposed to give the corresponding ketoesters (**10a**–**10g**, **11**) exclusively in refluxing *p*-xylene (Scheme 4). On the other hand, dioxetane bearing a 3-(1-cyanoethenyl)phenyl moiety (**2**) polymerized gradually on standing for a long period at room temperature.

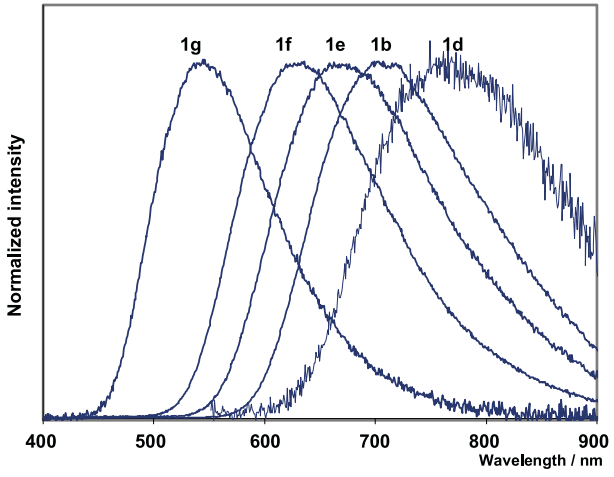


Figure 1. Chemiluminescene spectra for TBAF-induced decomposition of dioxetanes (**1b**, **1d**–**1g**) in DMSO.

2.2. Base-induced chemiluminescent decomposition of 1,2-dioxetanes bearing a phenyl moiety substituted with a methyl having an electron-withdrawing group

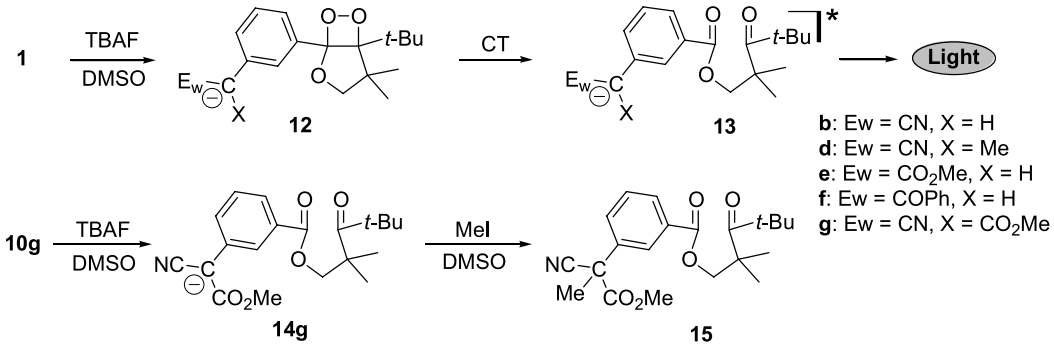
When a solution of dioxetane bearing a *meta*-(cyanomethyl) phenyl group (**1b**) in DMSO (1×10^{-4} mol dm^{-3}, 1 mL) was added to a solution of tetrabutylammonium fluoride (TBAF)[13,14] in DMSO (0.1 mol dm^{-3}, 2 mL) at 25 °C, **1b** decomposed rapidly to emit flash crimson light (maximum wavelength: $\lambda_{max}^{CL}=702$ nm, chemiluminescence efficiency: $\Phi^{CL}=3.3\times10^{-5}$).[15,16] The fresh spent reaction mixture was confirmed to include keto ester (**10b**) exclusively. Dioxetane bearing an *ortho*-(cyanomethyl)phenyl group (**1a**) and its *para*-isomer (**1c**) decomposed also easily to give the corresponding keto esters (**10a**) and (**10c**), though they gave little light. Such phenomenon has been observed as 'odd/even' relationship for dioxetanes bearing a phenoxide anion, among which the *meta*-oxidophenyl-isomer (odd-pattern) gives light in far higher yield than the *ortho*-oxidophenyl- and *para*-oxidophenyl isomer (even-pattern).[7,17–19]

Similarly to the case of **1b**, the other dioxetanes (**1d**–**1g**) bearing a phenyl substituted with a 3-methyl bearing an electron-withdrawing group(s) underwent the TBAF-induced decomposition in DMSO to afford light as shown in Figure 1. The chemiluminescent properties, namely, λ_{max}^{CL}, $t_{1/2}$ (half-life of chemiluminescent decomposition), k^{DICT} (rate constant of chemiluminescent decomposition: $k^{DICT}=\log_e 2/t_{1/2}$), Φ^{CL}, are summarized together with those for **1b** in Table 1. It is noteworthy that, dioxetane bearing a 3-(1-cyanoethyl)phenyl (**1d**) displayed light with λ_{max}^{CL} at 56 nm longer region than that for **1b**, while dioxetane bearing a 3-[cyano(methoxycarbonyl)methyl]phenyl (**1g**) exhibited chemiluminescence with prominent efficiency Φ^{CL}, though with far slower decomposition rate (rate constant: k^{DICT}) and far shorter λ_{max}^{CL} than those for the others (**1b**, **1d**–**1f**). It was confirmed that dioxetanes (**1d**–**1g**) were transformed exclusively into the corresponding keto ester (**10d**–**10g**) for TBAF-induced decomposition. However, fluorescence of

Table 1. TBAF-induced chemiluminescent decomposition of dioxetanes (**1b**, **1d**–**1g**) in DMSO[a]

Dioxetane (**1**)			λ_{max}^{CL}/nm	$t_{1/2}$/s	k^{DICT}/s^{-1}	Φ^{CL} [b]	pK_a of CH_2(X)Ew[c]	HOMO energy[d]/ev
	Ew	X						
1b	–CN	H	702	<0.02	>35	3.3×10^{-5}	25	−2.58
1d	–CN	Me	758	<0.05	>14	2.0×10^{-6}	—	−2.58
1e	–CO_2Me	H	666	0.42	1.7	4.0×10^{-5}	24.5	−2.88
1f	–COPh	H	622	0.43	1.6	4.4×10^{-4}	19	−2.99
1g	–CN	–CO_2Me	530	2300	3.0×10^{-4}	5.7×10^{-3}	9	−3.61

[a] A solution of a dioxetane (**1**) in DMSO (1×10^{-4} mol dm^{-3}, 1 mL) was added to a solution of TBAF in DMSO (0.1 mol dm^{-3}, 2 mL) at 25 °C.
[b] Chemiluminescent yields (Φ^{CL}) were based on the reported value for TBAF-induced chemiluminescent decomposition of 3-(2′-spiroadamantane)-4-methoxy-4-(3′-*tert*-butyldimethylsiloxy)phenyl-1,2-dioxetane in DMSO: $\Phi^{CL}=0.29$ (Ref. 16).
[c] pK_a of the corresponding parent carbon acid, CH_2(X)Ew (Ref. 21).
[d] Based on an AM1 MO calculation for model phenymethanides, PhC$^-$(X)Ew as a model of respective dioxetanes (**12**).



Scheme 5.

these spent reaction mixtures for dioxetane (**1**) was unfortunately not observed except that for dioxetane **1g**. The authentic keto ester (**10g**), prepared by thermolysis of **1g**, showed fluorescence with maximum wavelength (λ_{max}^{fl}), which coincided with λ_{max}^{CL} of **1g** in TBAF/DMSO, and its efficiency (Φ^{fl}) was estimated to be 0.018.[20] Furthermore, when a solution of keto ester (**10g**) in TBAF/DMSO was treated with methyl iodide, a methylation to an intermediary benzylic anion (**14g**) took place to give product (**15**) in 77% yield (Scheme 5). These facts reveal that the emitter produced from **1g** in TBAF/DMSO is undoubtedly a carbanion of **10g**, namely **13g**. Hence, the singlet-chemiexcitation efficiency ($\Phi_S = \Phi^{CL}/\Phi^{fl}$) is estimated to be 0.32 for the TBAF-induced decomposition of dioxetane (**1g**) in DMSO. The emitters would be the corresponding benzylic carbanions of keto esters (**13b**, **13d–13f**) also for the chemiluminescent decomposition of the other dioxetanes (**1b**, **1d–1f**), though little fluorescence was observed even for the authentic keto esters (**10b**, **10d–10f**) in TBAF/DMSO.

Chemiluminescent decomposition did not occur for all dioxetanes (**1a–1g**), when TBAF was absent in DMSO, while it took place easily on treatment with *tert*-BuOK as well as with TBAF. Considering this fact and that phenylmethanide anion (**13**) would be an emitter, it is reasonable to assume that proton-abstraction from **1** with TBAF generates an unstable dioxetane **12** bearing a phenymethanide anion, from which the intramolecular CT occurs to induce decomposition of the dioxetane producing excited carbanion **13** of keto ester by the mechanism similar to the case of a dioxetane bearing an arenoxide anion.[5–7] It is worth to point out that the singlet-chemiexcitation efficiency compares favorably with the value for dioxetanes bearing a *meta*-phenoxide anion, as observed for dioxetane (**1g**).[5–7]

In analogy with the CT-induced decomposition of a dioxetane bearing an arenoxide anion, it is inferring that chemiluminescent decomposition of dioxetane (**12**) bearing a phenylmethanide anion produced from **1** occurs the more easily, as the phenylmethanide anion becomes the less stable and the more easily oxidized. This idea is apparently consistent with the fact that the rate of chemiluminescent decomposition (k^{DICT}) increases in the order of **1g**<**1f**<**1e**<**1b** (**1d**) (Table 1). Considering the order of acidity for the parent carbon acids,[21] namely $CH_2(CN)CO_2Me \gg CH_3COPh > CH_3CO_2Me > CH_3CN$ (Table 1), the acidity of a benzylic position for **1** is presumed to decrease in the order of **1g**>**1f**>**1e**>**1b** (**1d**), so that stability of their conjugate carbanions decreases in the same order as illustrated in Figure 2. A similar tendency was observed also in the relationship between $\log_e k^{DICT}$ and HOMO energy estimated by an AM1 MO calculation for model phenymethanides, $PhC^-(X)Ew$ (Fig. 2).

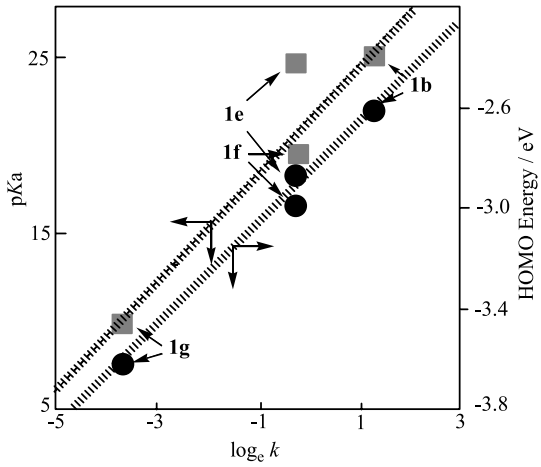
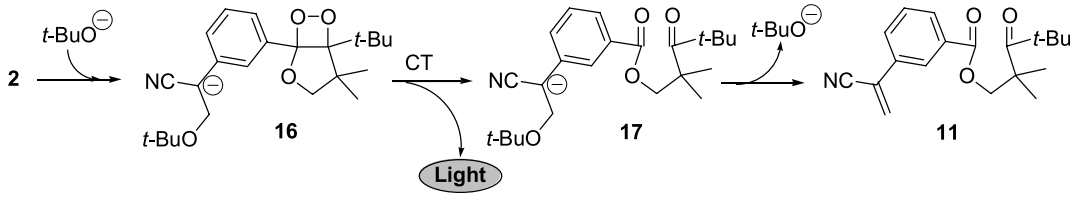


Figure 2. Relationship of $\log_e k^{DICT}$ for TBAF-induced decomposition of **1** with pK_a of parent carbon acids, X-CH_2-Ew and with HOMO energy of Ph-CH^-(X)-Ew.

2.3. Chemiluminescent decomposition of a dioxetane bearing a 3-(1-cyanoethenyl)phenyl moiety induced by the conjugate addition of a nucleophile

As described in the previous section, 3-(1-cyanoethyl) phenyl-substituted dioxetane (**1d**) underwent chemiluminescent decomposition through an intermediary dioxetane bearing a phenylmethanide anion (**12d**). Such type of phenylmethanide anion would be generated by the conjugate addition of a nucleophile to a (1-cyanoethenyl)-phenyl moiety. Thus, we attempted to react dioxetane (**2**) bearing a 3-(1-cyanoethenyl)phenyl group with the *tert*-BuO^- anion as a preliminary experiment. When dioxetane (**2**) was treated with 18-crown-6 ether complex of *tert*-BuOK in benzene, emission of light (λ_{max}^{CL}=706 nm) was observed, though the spent reaction mixture was found to include little product due to the conjugate addition of *tert*-BuO^-, but only 14% of keto ester (**11**) along with a complex mixture (Scheme 6). These results suggest for *tert*-BuO^--induced decomposition of **2** that dioxetane (**16**) bearing a phenylmethanide anion produced initially might



Scheme 6.

decompose to an excited keto ester (**17**), from which the *tert*-BuO$^-$ anion is eliminated to afford keto ester (**11**) after the emission of light (Scheme 6), though the intermediacy of neither **16** nor **17** was clear.

The next examination was to react dioxetane (**2**) with an anion of dimethyl methylmalonate, namely, 1,1-bis(methoxycarbonyl)ethanide anion (**18a**), which would add irreversibly to an electron-deficient olefin. An anion of ester (**18a**) (1.0×10^{-1} mol dm^{-3}) was prepared by dissolving malonate (**18a**) together with an equimolar amount of 18-crown-6 ether and *tert*-BuOK in benzene: the abbreviation [K⊂(18-crown-6)]$^+$(**18a**)$^-$ is used here for this anionic system. When a solution of a dioxetane (**2**) in benzene (1.0×10^{-3} mol dm^{-3}, 1 mL) was added to a solution of [K⊂(18-crown-6)]$^+$(**18a**)$^-$ in benzene (1.0×10^{-1} mol dm^{-3}, 2 mL) at 25 °C, dioxetane (**2**) decomposed rapidly to emit flash crimson light ($\lambda_{max}^{CL}=740$ nm, $\Phi^{CL}=5.6\times10^{-6}$) as shown in Figure 3. The maximum wavelength of chemiluminescence (λ_{max}^{CL}) was between that for dioxetane (**1b**) and that for dioxetane (**1d**) (Table1).

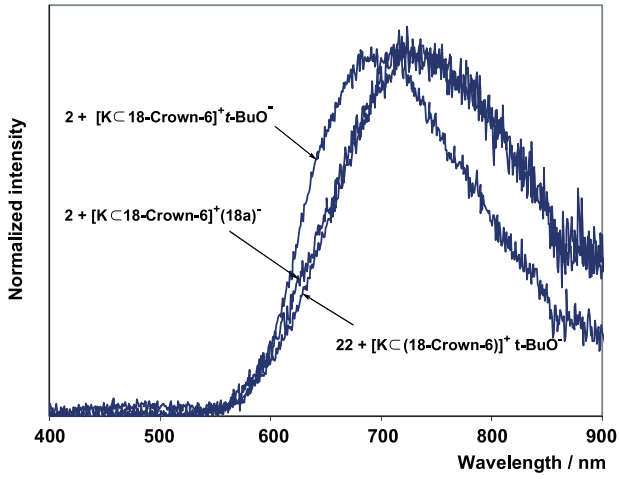
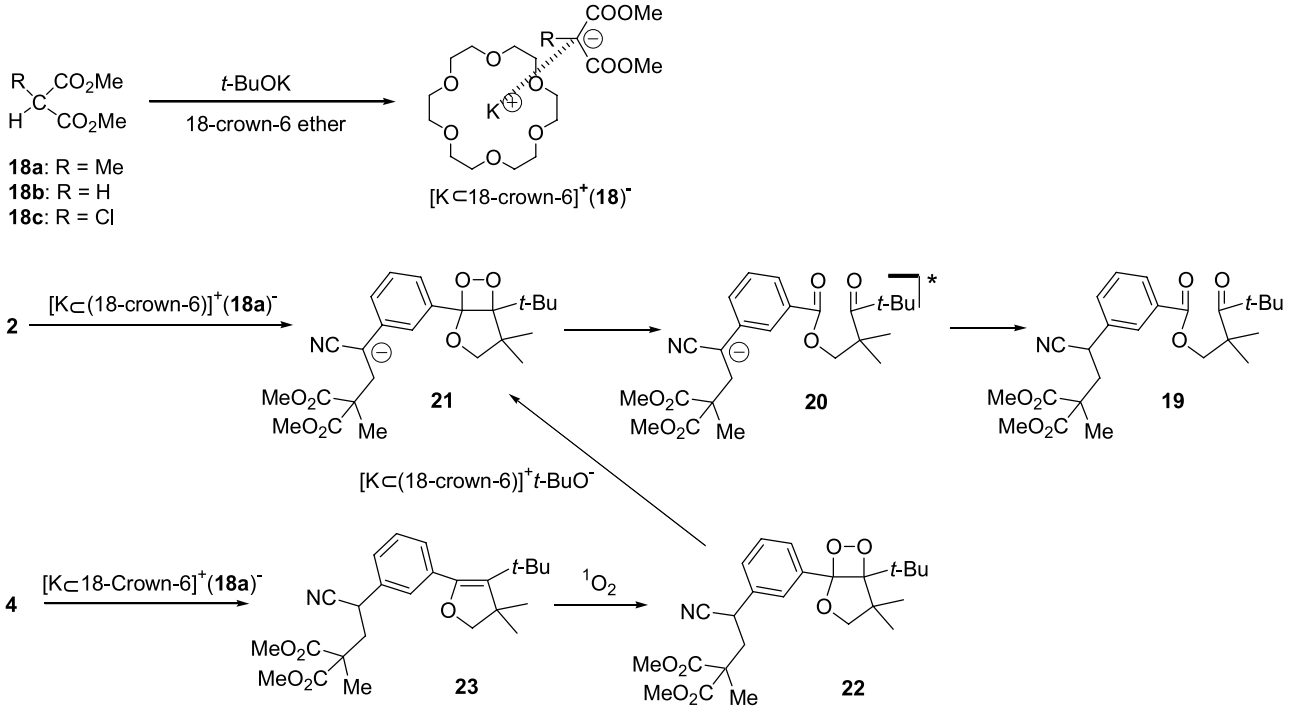


Figure 3. Chemiluminescene spectra for base-induced decomposition of dioxetane (**2**) and (**22**) in benzene.

The spent reaction mixture of **2** with [K⊂18-crown-6]$^+$(**18a**)$^-$ after neutralization gave exclusively keto ester (**19**). The result suggested that the emitter was carbanion (**20**), which was produced from an unstable Michael adduct, namely, dioxetane bearing a phenylmethanide anion (**21**). Thus, we synthesized authentic dioxetane (**22**), which was a neutral form of **21**, as a reference: the singlet oxygenation of dihydrofuran (**23**), which was prepared from dihydrofuran (**4**) and an anion of **18a**, gave **22** in high yield. On treatment with [K⊂(18-crown-6)]$^+$*t*-BuO$^-$ in benzene (1.0×10^{-1} mol dm^{-3}, 2 mL) at 25 °C, dioxetane (**22**) (1.0×10^{-3} mol dm^{-3}, 1 mL) decomposed rapidly to emit light with



Scheme 7.

chemiluminescent properties: $\lambda_{max}^{CL}=740$ nm, $\Phi^{CL}=5.7\times10^{-6}$, and the rate constant $k^{DICT}=8.1\ s^{-1}$.[22] Keto ester (**19**) was also obtained from the neutralized spent reaction mixture exclusively. These results are in good agreement with those for the decomposition of **2** with [K⊂18-crown-6]$^+$(**18a**)$^-$. Therefore, anionic dioxetane (**21**) is undoubtedly produced as an intermediate for the chemiluminescent decomposition of **2** induced by [K⊂18-crown-6]$^+$(**18a**)$^-$ (Scheme 7).

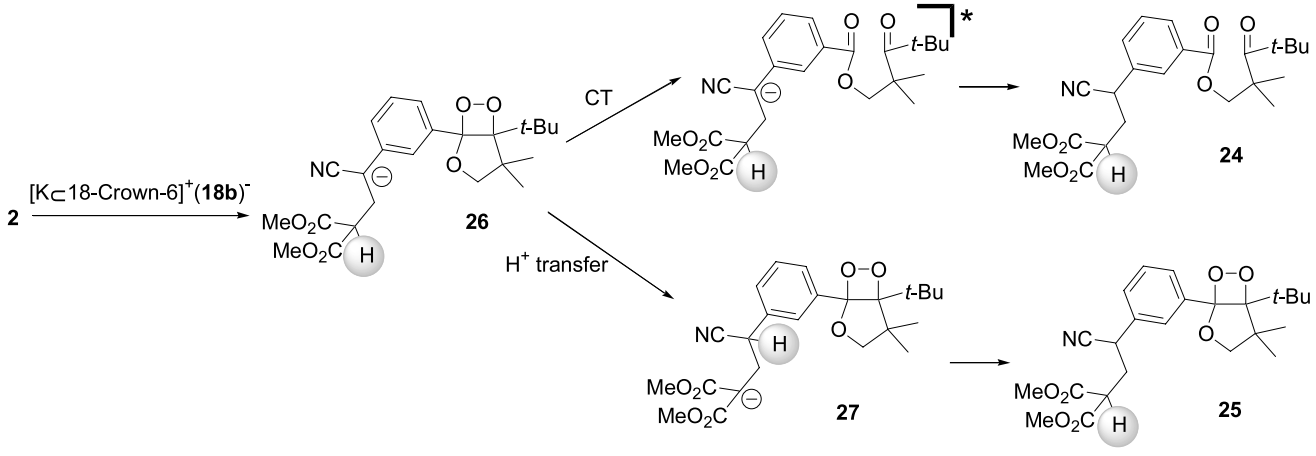
When dioxetane (**2**) was treated with a solution of bis(methoxycarbonyl)methanide complex (**18b**), [K⊂18-crown-6]$^+$(**18b**)$^-$, in benzene, **2** decomposed also to display crimson light ($\lambda_{max}=737$ nm, $\Phi^{CL}=1.5\times10^{-6}$) as in the case of anion (**18a**)$^-$ (Scheme 8). The spent reaction mixture gave the expected product **24** (39% yield), derived from the Michael addition of anion (**18b**)$^-$ to **2** followed by the CT-induced decomposition, and dioxetane (**25**) (28% yield), produced only by the Michael addition of (**18b**)$^-$ to **2**. The formation of dioxetane (**25**) reveals that a considerable quantity of initially-produced phenylmethanide anion (**26**) would change into a more stable anion (**27**) without causing the CT-induced decomposition to **24**. This means surely that the change of the phenylmethanide anion (**26**) into a bis(methoxycarbonyl)methanide anion (**27**) takes place as rapidly as the CT-induced decomposition of **26**, and should explain the fact that the chemiluminescent efficiency was considerably lower for the triggering with the (**18b**)$^-$ anion than for that with the (**18a**)$^-$ anion.

The results described above suggest a possibility that, when an intermediary phenylmethanide anion such as **26** undergoes another reaction competing with the intramolecular CT-induced chemiluminescent decomposition, its rate can be estimated by examining the chemiluminescent decomposition rate for the system of dioxetane (**2**), if the stoichiometry of products is clear and accurate. Thus, we attempted further to examine a reaction of dioxetane (**2**) that leads both to the CT-induced decomposition and a competitive reaction to extinguish it without causing the decay of the dioxetane ring.

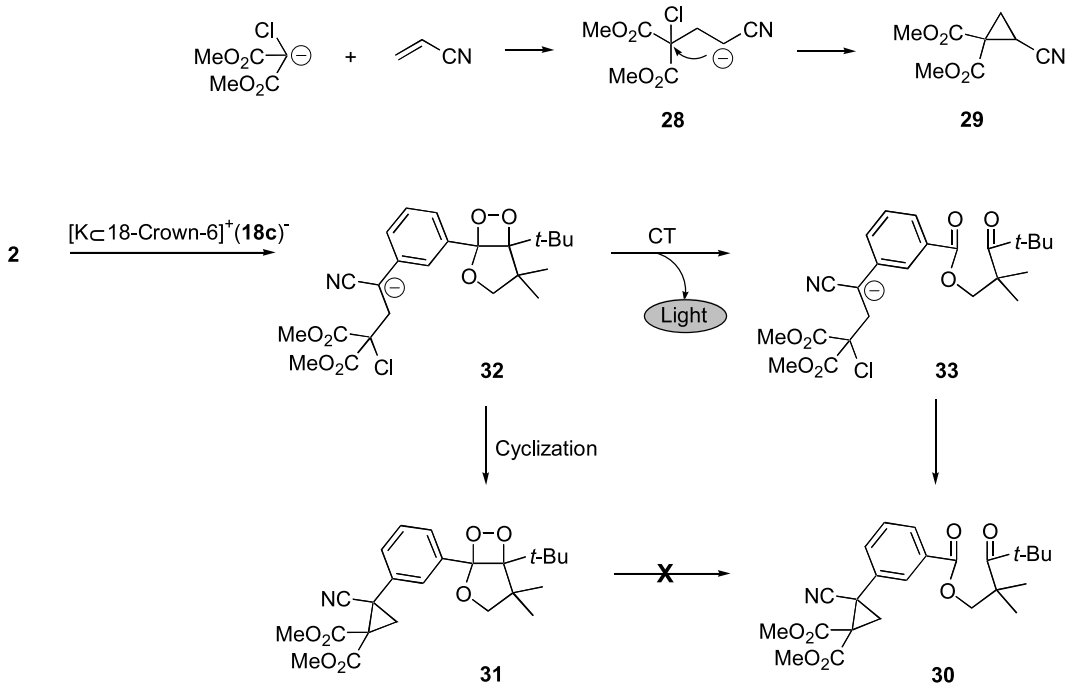
Dimethyl chloromalonate (**18c**) has been reported to undergo base-induced reaction with an α,β-unsaturated nitrile to give a cyclopropanedicarboxylate.[23,24] The reaction proceeds through the Michael addition of (**18c**)$^-$ to acrylonitrile giving an intermediary carbanion (**28**), whose intramolecular nucleophilic attack to an adjacent carbon bearing a chlorine furnishes a cyclopropanedicarboxylate (**29**). One mechanistically interesting point of this cyclopropanation is that the intramolecular nucleophilic attack of (**18c**)$^-$ should be more rapid than the quenching of the anion by protonation, since the reaction proceeds effectively even under weak basic conditions where anion (**28**) is hardly expected to form from a conjugate acid of **28**.

Thus, we carried out the reaction of dioxetane (**2**) with an anion of dimethyl chloromalonate, namely, bis(methoxycarbonyl)chloromethanide anion (**18c**). When **2** was treated with an anion of dimethyl chloromalonate (**18c**), [K⊂18-crown-6]$^+$(**18c**)$^-$, in benzene, emission of crimson light ($\lambda_{max}=710$ nm, $\Phi^{CL}=2.4\times10^{-6}$) was observed. After neutralization, the spent reaction mixture afforded ester (**30**) of a benzoic acid bearing a cyclopropyl group at the 3-position (71% yield) together with a cyclopropane derivative (**31**), in which the dioxetane ring remained intact (29% yield) (Scheme 9).

Dioxetane (**31**) was stable and hardly decomposed into ketoester (**30**) under the conditions similar to the case of **2** with [K⊂18-crown-6]$^+$(**18c**)$^-$. Therefore, a reasonable explanation of the formation of **30** is that an intermediary phenylmethanide anion **32**, produced by the Michael addition of an anion of **18c** to **2**, undergoes the CT-induced decomposition into phenylmethanide anion (**33**) with accompanying light, and, thereafter, **33** is transformed into a cyclopropane **30** through intramolecular cyclization. According to this explanation, the ratio of (rate for CT-induced decomposition of **32**) versus (rate for the reaction of **32** leading to a dioxetane **31**) equals the product ratio of **30** to **31**. Thus, the rate for intramolecular cyclopropanation of **32** is estimated roughly to be $k=3.3\ s^{-1}$, since the rate for CT-induced decomposition of **32** is presumably not so much different from the rate for the case of **22** with [K⊂18-crown-6]$^+$*t*-BuO$^-$.



Scheme 8.



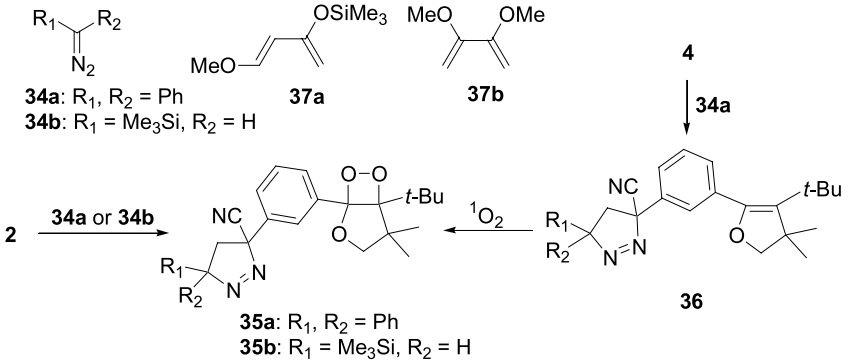
Scheme 9.

2.4. 1,3-Dipolar cycloaddition of diazomethanes to the (1-cyanoethenyl)phenyl moiety attached to a dioxetane ring

The results described earlier show a possibility that the chemiluminescent decomposition of dioxetane (**2**) induced by the conjugate addition of an anion provides a new probe to know a feature of an intramolecular reaction competing with the CT-induced chemiluminescent decomposition of an intermediary dioxetane. Thus, we dared finally to apply dioxetane (**2**) to a pericyclic reaction such as 1,3-dipolar cycloaddition and Diels–Alder reaction, which proceeds generally by a concerted mechanism and not by a stepwise ionic mechanism. 1,3-Dipoles chosen here were diphenyldiazomethane (**34a**) and trimethylsilyldiazomethane (**34b**). When dioxetane (**2**) was treated with diazomethane (**34a**) in CH_3CN at room temperature, 1,3-dipolar addition proceeded smoothly and completed within 120 min to afford dihydropyrazole (**35a**) without accompanying decomposition of the dioxetane ring. Adduct (**35a**) was synthesized also by the singlet oxygenation of dihydrofuran (**36**), which was prepared by the 1,3-dipolar addition of **34a** to **4**. The reaction of **2** with **34b** proceeded similarly to give dihydropyrazole (**35b**). These results are consistent with an idea that the reaction of **2** with **34** proceeds presumably by the concerted mechanism. On the other hand, Diels–Alder reaction of dioxetane (**2**) with a diene such as Danishefsky's diene (**37a**) and 2,3-dimethoxy-1,3-butadiene (**37b**) took place sluggishly at room temperature, though these dienes are well known to be very reactive to various dienophiles (Scheme 10).

3. Conclusion

Dioxetanes (**1**) bearing a phenyl moiety substituted with a methyl having an electron-withdrawing group(s) (–C*H*$_2$-Ew or –C*H*(X)-Ew) were effectively triggered with a base such as fluoride to decompose rapidly with accompanying emission of light ranging in color from yellow to crimson. The base-induced reaction of dioxetane (**1**) was clarified to proceed through dioxetanes bearing a phenymethanide anion, from which the intramolecular CT causes chemiluminescent decomposition of the dioxetane. The rate of



Scheme 10.

CT-induced decomposition for dioxetanes (**1**) in TBAF/DMSO was found to relate with the acidity of the parent carbon acids (CH_2(X)-Ew). This relationship provides a possibility to estimate the acidity of carbon acids by the use of chemiluminescent decomposition of dioxetanes.

Dioxetane (**2**) bearing a 3-(1-cyanoethenyl)phenyl group underwent the Michael addition of a bis(methoxycarbonyl)methanide anion to generate unstable dioxetane bearing a phenylmethanide anion, which decomposed with accompanying emission of light. When bis(methoxycarbonyl)-methanide anion or bis(methoxycarbonyl) chloromethanide anion was used, the CT-induced decomposition of an intermediary dioxetane competed with the intramolecular proton transfer or cyclopropanation. These findings suggest that the chemiluminescent properties, especially the rate, for the Michael addition-induced decomposition of **2** should become a probe to know the features of the intramolecular reactions, which occur concurrently.

4. Experimental

4.1. General

Melting points were measured with a Yanako MP-S3 melting point apparatus and are uncorrected. IR spectra were taken on a JASCO FT/IR-300 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX-400 and JEOL EPC-500 spectrometer. Mass spectra were obtained by using JEOL JMS-AX-505H, JEOL JMS-T-100LC mass spectrometers. Reagents were purchased from Aldrich, Tokyo Chemical Industries, Wako Pure Chemical Industries, and/or Kanto Chemical Industries. Column chromatography was carried out with silica gel, unless otherwise stated.

4.1.1. 4-*tert*-Butyl-5-(3-formylphenyl)-3,3-dimethyl-2,3-dihydrofuran (6b): typical procedure. BuLi (1.61 M in hexane, 30.1 mL, 48.5 mmol) was added to a solution of 5-(3-bromophenyl)-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (**5b**)[12] (14.3 g, 46.2 mmol) in THF (100 mL) at −78 °C under nitrogen atmosphere and was stirred for 30 min. To the solution, *N*-methylformanilide (6.27 mL, 50.8 mmol) was added and was stirred for 30 min. The reaction mixture was poured into 1 N HCl and then extracted with ethyl acetate (AcOEt). The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1/4) to give 11.5 g of **6b** as a pale yellow oil in 96.3% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.35 (s, 6H), 3.90 (s, 2H), 7.51 (t, J=7.6 Hz, 1H), 7.57 (d with fine coupling, J=7.6 Hz, 1H), 7.82 (s with fine coupling, 1H), 7.84 (d with fine coupling, J=7.6 Hz, 1H), 10.0 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.3, 32.5, 32.6, 47.3, 83.2, 127.0, 128.6, 129.2, 131.3, 135.9, 136.1, 137.3, 148.4, 192.0 ppm. IR (liquid film): 2959, 2868, 2723, 1702 cm^{-1}. Mass (*m*/*z*, %): 259 (M^++1, 14), 258 (M^+, 69), 244 (81), 243 (100), 187 (78), 159 (38), 133 (95). HRMS (ESI): 281.1538, calcd for $C_{17}H_{22}O_2Na$ ($M+Na^+$) 281.1518.

Similarly to the case of **6b**, 4-*tert*-butyl-5-(2-formylphenyl)-3,3-dimethyl-2,3-dihydrofuran (**6a**) was synthesized from 2-bromphenyl isomer (**5a**) as a yellow oil in 90.1% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.01 (s, 9H), 1.38 (s, 6H), 3.94 (s, 2H), 7.38 (d with fine coupling, J=7.6 Hz, 1H), 7.48 (t, J=7.6 Hz, 1H), 7.58 (td, J=7.6, 1.3 Hz, 1H), 7.95 (dd, J=7.6, 1.3 Hz, 1H), 10.2 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.2, 32.3, 32.5, 47.5, 83.4, 126.7, 128.9, 129.5, 131.5, 133.4, 134.4, 139.4, 145.0, 192.0 ppm. IR (liquid film): 2959, 2868, 2745, 1699 cm^{-1}. Mass (*m*/*z*, %): 258 (M^+, 17), 243 (38), 202 (18), 201 (100), 187 (45), 171 (25), 159 (28), 149 (40), 133 (45), 105 (30), 85 (27), 77 (26), 57 (44). HRMS (ESI): 281.1525, calcd for $C_{17}H_{22}O_2Na$ ($M+Na^+$) 281.1518.

Similarly to the case of **6b**, 4-*tert*-butyl-5-(4-formylphenyl)-3,3-dimethyl-2,3-dihydrofuran (**6c**) was synthesized from 4-bromphenyl isomer (**5c**) as a colorless columns, melted at 41.6–42.2 °C (from hexane) in 78.4% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.05 (s, 9H), 1.35 (s, 6H), 3.90 (s, 2H), 7.48 (d, J=8.2 Hz, 2H), 7.86 (d, J=8.2 Hz, 2H), 10.0 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.2, 32.4, 32.5, 47.4, 83.3, 127.1, 129.2, 130.6, 135.8, 142.6, 148.5, 191.9 ppm. IR (KBr): 2962, 2865, 1696 cm^{-1}. Mass (*m*/*z*, %): 258 (M^+, 18), 244 (18), 243 (100), 187 (33), 133 (40), 105 (12), 57 (16).

4.1.2. 4-*tert*-Butyl-5-[3-(hydroxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (7b): typical procedure. $NaBH_4$ (870 mg, 23.0 mmol) was added to a solution of 4-*tert*-butyl-5-(3-formylphenyl)-3,3-dimethyl-2,3-dihydrofuran (**6b**) (11.8 g, 45.6 mmol) in CH_2Cl_2 (100 mL) at 0 °C under nitrogen atmosphere. To the solution MeOH (10 mL) was added and stirred for 30 min. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1/4) to give 11.4 g of **7b** as a colorless oil in 96.0% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.05 (s, 9H), 1.34 (s, 6H), 3.87 (s, 2H), 4.69 (s, 2H), 7.21–7.25 (m, 1H), 7.29–7.34 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 32.4, 32.6, 47.1, 64.8, 83.0, 125.7, 126.4, 127.9, 128.1, 128.9, 136.1, 140.5, 149.6 ppm. IR (liquid film): 3415, 2957, 2869, 1653 cm^{-1}. Mass (*m*/*z*, %): 260 (M^+, 20), 246 (17), 245 (100), 243 (23), 171 (19), 135 (45). HRMS (ESI): 283.1662, calcd for $C_{17}H_{24}O_2Na$ ($M+Na^+$) 283.1674.

Similarly to the case of **7b**, 4-*tert*-butyl-5-[2-(hydroxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**7a**) was synthesized from 2-formylphenyl isomer (**6a**) as a colorless granules, melted at 59.3–60.0 °C (from hexane–CH_2Cl_2) in 97.1% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.37 (s, 6H), 2.65 (t, J=6.5 Hz, 1H), 3.89 (s, 2H), 4.60 (broad s, 2H), 7.27–7.38 (m, 3H), 7.42 (d, J=7.6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.1, 32.1, 32.5, 47.1, 64.2, 82.8, 127.3, 127.3, 128.7, 129.0, 131.0, 134.7, 139.9, 147.7 ppm. IR (KBr): 3475, 2957, 2872, 1647 cm^{-1}. Mass (*m*/*z*, %): 261 (M^++1, 11), 260 (M^+, 56), 246 (20), 245 (100), 227 (26), 173 (46), 171 (72), 135 (66), 133 (27), 57 (20). HRMS (ESI): 283.1665, calcd for $C_{17}H_{24}O_2Na$ ($M+Na^+$) 283.1674.

Similarly to the case of **7b**, 4-*tert*-butyl-5-[4-(hydroxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**7c**) was synthesized from 4-formylphenyl isomer (**6c**) as a colorless columns melted at 56.1–57.0 °C (from hexane) in 96.6% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.33 (s, 6H), 1.66 (t, J=6.0 Hz, 1H), 3.87 (s, 2H), 4.70 (d, J=6.0 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.4, 32.4, 32.6, 47.2, 65.1, 83.1, 125.9, 126.4, 130.1, 135.6, 140.6, 149.8 ppm. IR (KBr): 3272, 2957, 2867, 1648 cm^{-1}. Mass (*m*/*z*, %): 260 (M^+, 20), 246 (18), 245 (100), 243 (18), 171 (25), 135 (30), 77 (11), 57 (17). HRMS (ESI): 283.1671, calcd for $C_{17}H_{24}O_2Na$ ($M+Na^+$) 283.1674.

4.1.3. 4-*tert*-Butyl-5-[2-(chloromethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (8a). 4-(*N*,*N*-Dimethylamino)-pyridine (DMAP) (382 mg, 3.13 mmol) and *p*-toluenesulfonyl chloride (TsCl) (658 mg, 3.45 mmol) were added to a solution of 4-*tert*-butyl-5-[2-(hydroxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**7a**) (739 mg, 2.84 mmol) in THF (5 mL) at room temperature under nitrogen atmosphere and refluxed for 6 h. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (9/1) to give 411 mg of **8a** as a pale yellow oil in 51.8% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.36 (s, 6H), 3.88 (s, 2H), 4.65 (broad s, 2H), 7.23–7.30 (m, 2H), 7.36 (ddd, J=7.6, 7.1, 2.0 Hz, 1H), 7.50 (d, J=7.6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.2, 32.1, 32.6, 43.6, 47.2, 83.0, 127.6, 127.7, 129.0, 129.5, 130.8, 135.1, 136.3, 147.0 ppm. IR (liquid film): 2957, 2867, 1648 cm^{-1}. Mass (20 eV, *m*/*z*, %): 280 (M^+, 9), 278 (M^+, 32), 265 (33), 264 (13), 263 (100), 171 (29), 57 (13). HRMS (ESI): 303.1316, calcd for $C_{17}H_{23}ClONa$ ($M+Na^+$) 303.1306 and 301.1341, calcd for $C_{17}H_{23}ClONa$ ($M+Na^+$) 301.1335.

4.1.4. 5-[3-(Bromomethyl)phenyl]-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (8b); typical procedure. CBr_4 (3.94 g, 11.8 mmol) was added to a solution of PPh_3 (3.65 g, 13.9 mmol) and 4-*tert*-butyl-5-[3(-hydroxymethyl)-phenyl]-3,3-dimethyl-2,3-dihydrofuran (**7b**) (3.03 g, 11.6 mmol) in THF (30 mL) at room temperature under nitrogen atmosphere and stirred for 50 min. The reaction mixture was poured into satd aq NaCl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1/9) to give 3.55 g of **8b** as a pale yellow oil in 94.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.34 (s, 6H), 3.87 (s, 2H), 4.48 (s, 2H), 7.23 (d with fine coupling, J=7.2 Hz, 1H), 7.28–7.36 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 32.4, 32.6, 33.2, 47.2, 83.1, 126.1, 128.2, 128.5, 129.8, 130.5, 136.6, 137.2, 149.1 ppm. IR (liquid film): 2958, 2867, 1653, 1597 cm^{-1}. Mass (*m*/*z*, %): 324 (M^+, 17), 322 (M^+, 17), 310 (18), 309 (100), 308 (17), 307 (97), 243 (25), 228 (38), 199 (44), 197 (44), 172 (16), 171 (23), 90 (22), 57 (50). HRMS (ESI): 345.0841, calcd for $C_{17}H_{23}BrONa$ ($M+Na^+$) 345.0830 and 347.0819, calcd for $C_{17}H_{23}BrONa$ ($M+Na^+$) 347.0810.

Similarly to the case of **8b**, 4-*tert*-butyl-5-[4-(bromomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**8c**) was synthesized from 4-(hydroxymethyl)phenyl isomer (**7c**) as pale yellow oil and crude product was used to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.33 (s, 6H), 3.87 (s, 2H), 4.49 (s, 2H), 7.27 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.4, 32.4, 32.6, 33.2, 47.2, 83.1, 126.2, 128.6, 130.3, 136.4, 137.5, 149.3 ppm. IR (liquid film): 2957, 2868, 1651 cm^{-1}. Mass (*m*/*z*, %): 324 (M^+, 20), 322 (M^+, 21), 310 (17), 309 (99), 308 (19), 307 (100), 263 (26), 243 (32), 228 (20), 199 (25), 197 (24), 171 (43), 118 (27), 90 (29), 57 (72).

4.1.5. 4-*tert*-Butyl-5-[3-(cyanomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (3a); typical procedure. A solution of 5-[3-(bromomethyl)phenyl]-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (**8b**) (3.81 g, 11.8 mmol), NaCN (804 mg, 16.4 mmol) and tetra-*n*-butylammonium hydrogen sulfate (804 mg, 2.37 mmol) in THF–H_2O (5/1) (36 mL) was stirred under nitrogen atmosphere at refluxing temperature for 28 h. The reaction mixture was poured into satd aq NaCl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1/9) to give 2.43 g of **3a** as a colorless oil in 76.4% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.34 (s, 6H), 3.76 (s, 2H), 3.88 (s, 2H), 7.26–7.31 (m, 3H), 7.35 (t, J=7.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 23.5, 27.4, 32.5, 32.6, 47.3, 83.2, 117.6, 126.3, 127.4, 128.6, 129.2, 129.4, 129.6, 137.2, 148.8 ppm. IR (liquid film): 2957, 2869, 2251 cm^{-1}. Mass (*m*/*z*, %): 269 (M^+, 11), 255 (16), 254 (100), 144 (42), 116 (16), 57 (14). HRMS (ESI): 292.1663, calcd for $C_{18}H_{23}NONa$ ($M+Na^+$) 292.1677.

Similarly to the case of **3b**, 4-*tert*-butyl-5-[2-(cyanomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**3a**) was synthesized from 2-(chloromethyl)phenyl isomer (**8a**) as a colorless oil in 78.9% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.36 (s, 6H), 3.78 (s, 2H), 3.88 (s, 2H), 7.28–7.41 (m, 3H), 7.50 (d, J=7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.2, 27.3, 32.1, 32.6, 47.3, 83.1, 117.8, 127.5, 127.9, 128.0, 129.2, 129.2, 131.1, 135.0, 146.8 ppm. IR (liquid film): 2958, 2869, 2250 cm^{-1}. Mass (*m*/*z*, %): 269 (M^+, 19), 255 (17), 254 (100), 198 (40), 171 (19), 144 (30), 130 (60), 91 (66), 57 (30). HRMS (ESI): 292.1675, calcd for $C_{18}H_{23}NONa$ ($M+Na^+$) 292.1677.

Similarly to the case of **3b**, 4-*tert*-butyl-5-[4-(cyanomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**3c**) was synthesized from 4-(bromomethyl)phenyl isomer (**8c**) as pale yellow plates, melted at 68.7–69.1 °C (from hexane–CH_2Cl_2) in 62.0% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.33 (s, 6H), 3.76 (s, 2H), 3.87 (s, 2H), 7.28–7.34 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.4, 27.3, 32.4, 32.6, 47.2, 83.1, 117.7, 126.3, 127.4, 129.6, 130.7, 136.2, 149.0 ppm. IR (KBr): 2959, 2924, 2869, 2250 cm^{-1}. Mass (*m*/*z*, %): 269 (M^+, 18), 255 (20), 254 (100), 171 (11), 144 (41), 116 (13), 57 (22). HRMS (ESI): 292.1662, calcd for $C_{18}H_{23}NONa$ ($M+Na^+$) 292.1677.

4.1.6. 4-*tert*-Butyl-5-[3-(1-cyanoethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (3d). A solution of

4-*tert*-butyl-5-[3-(cyanomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**3b**) (497 mg, 1.84 mmol) in dry THF (2.5 mL) was added to a suspension of NaH (60% in oil, 74.9 mg, 1.87 mmol) in dry THF (2.5 mL) under nitrogen atmosphere at 0 °C. To the solution MeI (0.13 mL, 2.09 mmol) was added and stirred at room temperature for 2 h. The reaction mixture was poured into saturated aq NH_4Cl and extracted with AcOEt. The organic layer was washed with saturated aq NaCl, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel with hexane–AcOEt (9/1) to give 337 mg of **3d** as a pale yellow oil in 64.5% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.34 (s, 6H), 1.64 (d, J=7.3 Hz, 3H), 3.88 (s, 2H), 3.90 (q, J=7.3 Hz, 1H), 7.25–7.38 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.5, 27.3, 31.1, 32.4, 32.5, 47.2, 83.2, 121.4, 126.3, 126.4, 128.2, 128.7, 129.6, 136.6, 137.2, 149.1 ppm. IR (liquid film): 2957, 2870, 2243 cm^{-1}. Mass (*m*/*z*, %): 283 (M^+, 11), 268 (63), 243 (26), 228 (26), 159 (15), 158 (100), 57 (55). HRMS (ESI): 306.1804, calcd for $C_{19}H_{25}NONa$ ($M+Na^+$) 306.1834.

4.1.7. 4-*tert*-Butyl-5-[3-(carboxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (9). 4-*tert*-butyl-5-[3-(cyanomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**3b**) (8.52 g, 31.6 mmol) was added to a solution of NaOH (6.31 g, 158 mmol) in EtOH (80 mL) and H_2O (8 mL) and refluxed for 2 h. The reaction mixture was poured into 1 N HCl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–hexane (1/1) to give 8.44 g of **9** as a colorless leaflets melted at 95.5–96.1 °C (from hexane–CH_2Cl_2) in 97.4% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.03 (s 9H), 1.33 (s, 6H), 3.64 (s, 2H), 3.87 (s, 2H), 7.20–7.25 (m, 3H), 7.29 (t, J=7.3 Hz, 1H ppm). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.4, 32.4, 32.5, 40.9, 47.2, 83.1, 126.0, 128.1, 128.8, 129.0, 130.9, 132.8, 136.5, 149.6. 177.3 ppm. IR (KBr): 2983, 2955, 2916, 2869, 1711 cm^{-1}. Mass (*m*/*z*, %): 288 (M^+, 18), 274 (19), 273 (100), 171 (14), 163 (35), 57 (16). HRMS (ESI, negative): 287.1629, calcd for $C_{18}H_{23}O_3$ 287.1647.

4.1.8. 4-*tert*-Butyl-5-[3-(methoxycarbonylmethyl)-phenyl]-3,3-dimethyl-2,3-dihydrofuan (3e). $NaHCO_3$ (512 mg, 6.09 mmol) was added to a solution of 4-*tert*-butyl-5-[3-(carboxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**9**) (1.17 g, 4.06 mmol) in dry DMF (10 mL) at room temperature under nitrogen atmosphere and stirred for 20 min. To the solution methyl iodide (0.51 mL, 8.19 mmol) was added and stirred overnight. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1/4) to give 1.10 g of **3e** as a colorless oil in 89.7% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s 9H), 1.33 (s, 6H), 3.62 (s, 2H), 3.67 (s, 3H), 3.87 (s, 2H), 7.18–7.30 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 32.4, 32.6, 41.1, 47.2, 51.9, 83.1, 125.8, 128.0, 128.5, 128.8, 130.7, 133.4, 136.3, 149.7, 171.6 ppm. IR (liquid film): 2955, 2870, 1742 cm^{-1}. Mass (*m*/*z*, %): 302 (M^+, 18), 288 (20), 287 (100), 177 (46), 171 (29), 57 (25). HRMS (ESI): 325.1787, calcd for $C_{19}H_{26}O_3Na$ ($M+Na^+$) 325.1780.

4.1.9. 4-*tert*-Butyl-5-[3-(benzoylmethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (3f). A solution of 4-*tert*-butyl-5-[3-(carboxymethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**9**) (304 mg, 1.05 mmol) in dry THF (2 mL) was added dropwise over 10 min to a solution of butyllithium (1.62 M in hexane, 1.35 mL, 2.19 mmol) in dry THF (1.5 mL) at −78 °C under nitrogen atmosphere and was stirred for 30 min. Benzoyl chloride (0.13 mL, 1.12 mmol) was added to the solution and stirred for 1 h. The reaction mixture was poured into 1 N HCl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1/9) to give 96 mg of **3f** as a yellow oil in 26.2% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.99 (s, 9H), 1.32 (s, 6H), 3.86 (s, 2H), 4.27 (s, 2H), 7.17 (d, J=7.6 Hz, 1H), 7.21 (s, 1H), 7.21 (d, J=7.6 Hz, 1H), 7.28 (t, J=7.6 Hz, 1H), 7.43 (t, J=7.4 Hz, 2H), 7.53 (t with fine coupling, J=7.4 Hz, 1H), 7.98 (d, J=7.4 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.4, 32.3, 32.5, 45.5, 47.1, 83.1, 125.8, 128.2, 128.3, 128.6, 128.6, 129.0, 131.0, 133.0, 134.1, 136.5, 136.5, 149.7, 197.4 ppm. IR (liquid film): 2957, 2869, 1720, 1683 cm^{-1}. Mass (*m*/*z*, %): 348 (M^+, 22), 334 (27), 333 (100), 277 (17), 223 (38), 105 (67), 91 (13), 77 (27), 57 (29). HRMS (ESI): 371.1987, calcd for $C_{24}H_{28}O_2Na$ ($M+Na^+$) 371.1987.

4.1.10. 4-*tert*-Butyl-5-{3-[cyano(methoxycarbonyl) methyl]phenyl}-3,3-dimethyl-2,3-dihydrofuran (3g). A solution of 4-*tert*-butyl-5-[3-(cyanomethy)lphenyl]-3,3-dimethyl-2,3-dihydrofuran (**3b**) (511 mg, 1.90 mmol) and dimethyl carbonate (0.24 mL, 2.85 mmol) in toluene (4 mL) was added dropwise over 5 min to a suspension of NaH (60% in oil, 161 mg, 4.03 mmol) in toluene (4 mL) under nitrogen atmosphere and stirred for 1 h. The reaction mixture was poured into 1 N HCl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1/9) to give 582 mg of **3g** as a pale orange oil in 93.7% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.03 (s, 9H), 1.34 (s, 6H), 3.79 (s, 3H), 3.88 (s, 2H), 4.73 (s, 1H), 7.34 (d with fine coupling, J=7.1 Hz, 1H), 7.37–7.45 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.4, 32.5, 32.6, 43.4, 47.3, 53.9, 83.2, 115.3, 126.7, 127.4, 128.8, 129.2, 129.5, 130.7, 137.3, 148.6, 165.1 ppm. IR (liquid film): 2957, 2869, 2252, 1753 cm^{-1}. Mass (*m*/*z*, %): 327 (M^+, 13), 313 (21), 312 (100), 202 (42), 115 (10), 57 (56), 55 (11). HRMS (ESI): 350.1725, calcd for $C_{20}H_{25}NO_3Na$ ($M+Na^+$) 350.1732.

4.1.11. 4-*tert*-Butyl-5-[3-(1-cyanoethenyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (4). A solution of 4-*tert*-butyl-5-[3-(cyanomethyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**3b**) (521 mg, 1.93 mmol), paraformaldehyde (87.8 mg, 2.92 mmol), K_2CO_3 (429 mg, 3.10 mmol) and Bu_4NI (14.7 mg, 0.0398 mmol) in toluene (10 mL) was stirred under nitrogen atmosphere at 80 °C for 15 min. The reaction mixture was poured into satd aq NaCl and then extracted with AcOEt. The organic layer was washed with

satd aq NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel with hexane–AcOEt (9/1) to give 441 mg of (**4**) as a yellow oil in 81.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.05 (s, 9H), 1.35 (s, 6H), 3.89 (s, 2H), 6.12 (s, 1H), 6.35 (s, 1H), 7.35 (d with fine coupling, J=7.6 Hz, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.52 (s with fine coupling, 1H), 7.56 (d with fine coupling, J=7.6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.4, 32.5, 32.6, 47.3, 83.2, 117.6, 122.7, 125.4, 126.7, 127.1, 128.3, 128.6, 131.5, 132.0, 137.2, 148.8 ppm. IR (liquid film): 2957, 2868, 2228 cm^{-1}. Mass (*m*/*z*, %): 281 (M^+, 20), 267 (22), 266 (100), 210 (19), 156 (69), 128 (22), 101 (12), 57 (64). HRMS (ESI): 304.1654, calcd for $C_{19}H_{23}NONa$ ($M+Na^+$) 304.1677.

4.1.12. 4-*tert*-Butyl-5-{3-[1-cyano-3,3-bis(methoxycarbonyl)butyl]pheny}-3,3-dimethyl-2,3-dihydrofuran (23). Dimethyl methylmalonate (**18a**) (203 mg, 1.39 mmol) was added to 18-crown-6 (331 mg, 1.25 mmol) and *tert*-BuOK (1.0 M in THF, 1.2 mL, 1.20 mmol) in dry toluene (15 mL) at room temperature under nitrogen atmosphere. To the solution 4-*tert*-butyl-5-[3-(1-cyanoethenyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**4**) (339 mg, 1.20 mmol) in dry toluene (5 mL) was added at room temperature under nitrogen atmosphere and stirred for 8 min. The reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel with hexane–ethyl ether (3/1) to give 272 mg of **23** as a colorless viscous oil in 52.8% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.04 (s, 9H), 1.34 (s, 6H), 1.57 (s, 3H), 2.35 (dd, J=14.6, 3.7 Hz, 1H), 2.50 (dd, J=14.6, 10.3 Hz, 1H), 3.77 (s, 6H), 3.88 (s, 2H), 4.04 (dd, J=10.3, 3.7 Hz, 1H), 7.25–7.38 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.9, 27.4, 27.4, 32.4, 32.6, 33.2, 42.1, 47.3, 52.8, 52.9, 52.9, 83.2, 120.4, 126.5, 127.0, 128.7, 128.8, 129.9, 136.0, 137.3, 149.0, 171.3, 171.6 ppm. IR (liquid film): 2956, 2870, 2243, 1734 cm^{-1}. Mass (*m*/*z*, %): 427 (M^+, 17), 413 (31), 412 (100), 410 (10), 302 (11), 266 (13), 236 (12), 57 (12). HRMS (ESI): 450.2257, calcd for $C_{25}H_{33}NO_5Na$ ($M+Na^+$) 450.2256.

4.1.13. 4-*tert*-Butyl-5-[3-(3-cyano-4,5-dihydro-5,5-diphenyl-3*H*-pyrazole-3-yl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (36a). A solution of (diphenyl)diazomethane (1.0 mmol: prepared from benzophenone hydrazone and mercury oxide in hexane and ethanol in the presence of catalytic amount of EtONa and used crude product) in acetonitrile (1.0 mL) was added to a solution of 4-*tert*-butyl-5-[3-(1-cyanoethenyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**4**) (184 mg, 0.65 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (2.5 mg) in acetonitlile (2 mL) at room temperature under nitrogen atmosphere and stirred for 3.5 h. The reaction mixture was concentrated in vacuo and chromatographed on silica gel with hexane–AcOEt (10/1–5/1) to give 298 mg of **36a** as colorless viscous oil in 96.0% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.90 (s, 9H), 1.31 (s, 3H), 1.31 (s, 3H), 2.45 (d, J=6.2 Hz, 1H), 2.62 (d, J=6.2 Hz, 1H), 3.84 (s 2H), 6.97–7.16 (m, 8H), 7.18 (s with fine coupling, 1H), 7.28 (d with fine coupling, J=7.3 Hz, 1H), 7.35–7.40 (m, 2H), 7.58–7.62 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.6, 27.3, 27.3, 27.4, 32.3, 32.6, 47.0, 47.1, 83.1, 121.3, 126.1, 127.2, 127.5, 127.8, 127.8, 128.3, 128.8, 129.1, 129.2, 129.3, 129.7, 132.4, 136.6, 138.0, 141.1, 149.1 ppm. IR (liquid film): 2957, 2868, 2233, 1652 cm^{-1}. Mass (*m*/*z*, %): 475 (M^+, trace), 447 (22), 433 (37), 432 (100), 376 (16), 322 (20). HRMS (ESI): 470.2455, calcd for $C_{32}H_{33}NONa$ ($M-N_2+Na^+$) 470.2460.

4.2. Synthesis of bicyclic dioxetanes (1): general procedure

A solution of 5-aryl-4-*tert*-butyl-3,3-dimethyl-2,3-dihydrofuran (**3**) (100–300 mg) and tetraphenylporphin (TPP) (ca.1 mg) in CH_2Cl_2 (10 mL) was irradiated externally with 940 W Na lamp under oxygen atmosphere at 0 °C for 1–2 h, except the case of dihydrofuran (**4**), singlet oxygenation of which was carried out at −78 °C. The photolysate was concentrated in vacuo. The residue was chromatographed on silica gel to give the corresponding 5-*tert*-butyl-1-aryl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]-heptane (**1**).

4.2.1. 5-*tert*-Butyl-1-[3-(cyanomethyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1b). Pale yellow granules melted at 99.8–100.6 °C (from hexane–CH_2Cl_2), 88.9% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.98 (s, 9H), 1.16 (s, 3H), 1.39 (s, 3H), 3.79 (s, 2H), 3.83 (d, J=8.2 Hz, 1H), 4.59 (broad d, J=8.2 Hz, 1H), 7.39 (d, J=7.6 Hz, 1H), 7.44 (t, J=7.6 Hz, 1H), 7.59 (broad s, 1H), 7.62 (d, J=7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 18.5, 23.7, 25.2, 26.8, 36.7, 45.7, 80.3, 104.9, 116.2, 117.4, 127.8, 128.1, 128.7, 128.9, 129.7, 137.1 ppm. IR (KBr): 3000, 2966, 2902, 2251 cm^{-1}. Mass (20 eV, *m*/*z*, %): 302 (M^++1, 2), 269 (7), 246 (15), 244 (40), 218 (52), 216 (23), 162 (48), 144 (89), 125 (11), 111 (14), 97 (12), 85 (66), 57 (100), 56 (39). HRMS (ESI): 324.1587, calcd for $C_{18}H_{23}NO_3Na$ ($M+Na^+$) 324.1576. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.86; H, 8.08; N, 4.73.

4.2.2. 5-*tert*-Butyl-1-[2-(cyanomethyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1a). Pale yellow columns melted at 98.3–99.0 °C (from hexane–CH_2Cl_2), 94.8% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.98 (s, 9H), 1.22 (s, 3H), 1.44 (s, 3H), 3.89 (d, J=8.3 Hz, 1H), 3.98 (d, J=18.8 z, 1H), 4.29 (d, J=18.8 Hz, 1H), 4.57 (d, J=8.3 Hz, 1H), 7.38–7.48 (m, 2H), 7.58 (d, J=7.3 Hz, 1H), 7.86 (d, J=7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.3, 23.1, 25.8, 26.4, 36.7, 45.5, 80.2, 106.0, 117.3, 118.1, 127.7, 129.2, 130.3, 130.5, 131.3, 133.4 ppm. IR (KBr): 2978, 2905, 2251 cm^{-1}. Mass (20 eV, *m*/*z*, %): 301 (M^+, 1), 269 (7), 254 (11), 246 (36), 244 (50), 218 (34), 216 (27), 163 (11), 162 (100), 145 (13), 144 (86), 134 (14), 85 (32), 57 (69), 56 (17). HRMS (ESI): 324.1583, calcd for $C_{18}H_{23}NO_3Na$ ($M+Na^+$) 324.1576.

4.2.3. 5-*tert*-Butyl-1-(4-cyanomethyl)phenyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1c). Pale yellow granules melted at 69.3–70.2 °C (from hexane–CH_2Cl_2), 80.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (s, 9H), 1.16 (s, 3H), 1.38 (s, 3H), 3.79 (s, 2H), 3.83 (d, J=8.1 Hz, 1H), 4.58 (d, J=8.1 Hz, 1H), 7.37 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 18.4, 23.4, 25.0, 26.7, 36.6, 45.6, 80.2, 104.9,

116.3, 117.5, 127.5, 129.1, 131.3, 136.0 ppm. IR (KBr): 2969, 2897, 2251 cm^{-1}. Mass (20 eV, *m/z*, %): 302 (M^+ + 1, 1), 269 (2), 246 (13), 244 (56), 216 (19), 177 (21), 162 (24), 145 (11), 144 (100), 85 (79), 57 (73), 56 (24). HRMS (ESI): 324.1584, calcd for $C_{18}H_{23}NO_3Na$ ($M+Na^+$) 324.1576.

4.2.4. 5-*tert*-Butyl-1-[3-(1-cyanoethyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1d). Pale yellow plates melted at 134.7–135.5 °C (from hexane–CH_2Cl_2), 78.6% yield. ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (s, 9H), 1.16 (s, 3H), 1.39 (s, 3H), 1.64 (d, $J=7.3$ Hz, 3H), 3.84 (d, $J=8.1$ Hz, 1H), 3.95 (q, $J=7.3$ Hz, 1H), 4.59 (d, $J=8.1$ Hz, 1H), 7.40–7.46 (m, 2H), 7.59–7.62 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4, 21.3, 21.5, 25.1, 26.7, 31.2, 31.3, 36.7, 45.6, 80.2, 80.3, 104.9, 116.3, 121.2, 126.8, 126.9, 127.7, 127.8, 128.1, 128.2, 128.8, 136.8, 136.9, 137.1 ppm. IR (KBr): 2992, 2966, 2890, 2242 cm^{-1}. Mass (20 eV, *m/z*, %): 283 (M^+-32, 4), 260 (15), 258 (33), 232 (57), 230 (26), 177 (12), 176 (63), 159 (11), 158 (100), 85 (38), 57 (72). HRMS (ESI): 338.1752, calcd for $C_{19}H_{25}NO_3Na$ ($M+Na^+$) 338.1732.

4.2.5. 5-*tert*-Butyl-1-[3-(methoxycarbonylmethyl)-phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1e). Pale yellow oil, 85.6% yield. ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (s 9H), 1.16 (s, 3H), 1.38 (s, 3H), 3.66 (s, 2H), 3.67 (s, 3H), 3.82 (d, $J=8.1$ Hz, 1H), 4.59 (broad d, $J=8.1$ Hz, 1H), 7.30 (d with fine coupling, $J=7.6$ Hz, 1H), 7.35 (dd, $J=7.8$, 7.6 Hz, 1H), 7.52–7.56 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.5, 25.1, 26.7, 36.7, 41.1, 45.6, 52.0, 80.2, 104.8, 116.5, 127.1, 128.1, 129.3, 130.3, 133.7, 136.2, 171.6 ppm. IR (liquid film): 2962, 2896, 1740 cm^{-1}. Mass (20 eV, *m/z*, %): 334 (M^+, trace), 302 (trace), 277 (18), 195 (13), 178 (10), 177 (100), 57 (12). HRMS (ESR): 357.1686, calcd for $C_{19}H_{26}O_5Na$ ($M+Na^+$) 357.1678.

4.2.6. 5-*tert*-Butyl-1-[3-(benzoylmethyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1f). Pale yellow granules, melted at 110.0–110.9 °C (from hexane–CH_2Cl_2), 90.2% yield. ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.92 (s, 9H), 1.14 (s, 3H), 1.35 (s, 3H), 3.81 (d, $J=8.2$ Hz, 1H), 4.32 (s, 2H), 4.57 (d, $J=8.2$ Hz, 1H), 7.30 (d, $J=7.6$ Hz, 1H), 7.36 (dd, $J=8.2$, 7.6 Hz, 1H), 7.44 (dd, $J=8.3$, 7.3 Hz, 2H), 7.51–7.57 (m, 3H), 7.99 (d with fine coupling, $J=$ 8.3 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.5, 25.1, 26.7, 36.6, 45.5, 45.6, 80.2, 104.9, 116.6, 126.9, 128.2, 128.6, 128.6, 129.5, 130.5, 133.2, 134.3, 136.3, 136.5, 197.2 ppm. IR (KBr): 2971, 2906, 1688 cm^{-1}. Mass (20 eV, *m/z*, %): 348 (M^+-32, 1), 323 (20), 241 (21), 224 (17), 223 (100), 105 (24). HRMS (ESI): 403.1894, calcd for $C_{24}H_{28}O_4Na$ ($M+Na^+$) 403.1885.

4.2.7. 5-*tert*-Butyl-1-[3-cyano(methoxycarbonyl)methyl-phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (1g). Pale yellow oil in 88.9% yield (1:1 mixture of diastereoisomers). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.96 (s, 9H), 1.17 (s, 3H), 1.38 (s, 1.5H), 1.39 (s, 1.5H), 3.78 (s, 1.5H), 3.79 (s, 1.5H), 3.85 (d, $J=8.2$ Hz, 1H), 4.59 (d, $J=$ 8.2 Hz, 1H), 4.78 (s, 1H), 7.45–7.55 (m, 2H), 7.65–7.76 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4, 25.1, 26.7, 36.7, 43.4, 45.6, 54.0, 80.3, 80.3, 105.0, 115.2, 115.2, 116.0, 128.2, 128.2, 128.9, 128.9, 129.0, 129.0, 129.3, 129.3, 129.6, 137.4, 137.4, 165.1, 165.1 ppm. IR (liquid film): 2962, 2898, 2254, 1753 cm^{-1}. Mass (20 eV, *m/z*, %): 360 (M^+ + 1, 1), 327 (4), 304 (12), 302 (26), 287 (29), 276 (63), 274 (23), 220 (63), 203 (11), 202 (100), 85 (43), 57 (69), 56 (23). HRMS (ESI): 382.1626, calcd for $C_{20}H_{25}NO_5Na$ ($M+Na^+$) 382.1630.

4.2.8. 5-*tert*-Butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (2). Pale yellow granules melted at 123.3–124.0 °C (from hexane–CH_2Cl_2), 89.7% yield. ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.98 (s, 9H), 1.17 (s, 3H), 1.39 (s, 3H), 3.85 (d, $J=8.2$ Hz, 1H), 4.60 (d, $J=8.2$ Hz, 1H), 6.16 (s, 1H), 6.38 (s, 1H), 7.48 (t, $J=7.8$ Hz, 1H), 7.64 (d with fine coupling, $J=7.8$ Hz, 1H), 7.68 (d with fine coupling, $J=7.8$ Hz, 1H), 7.86 (s with fine coupling, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4, 25.1, 26.8, 36.7, 45.6, 80.3, 105.0, 116.2, 117.4, 122.6, 125.5, 127.0, 128.7, 128.8, 129.8, 132.2, 137.1 ppm. IR (KBr): 2998, 2959, 2902, 2226 cm^{-1}. Mass (20 eV, *m/z*, %): 281 (M^+-32, 8), 258 (22), 256 (33), 230 (40), 228 (26), 174 (41), 157 (13), 156 (100), 85 (40), 57 (75). HRMS (ESI): 336.1593, calcd for $C_{19}H_{23}NO_3Na$ ($M+Na^+$) 336.1576. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.52; H, 7.80; N, 4.17.

4.2.9. 5-*tert*-Butyl-1-{3-[1-cyano-3,3-bis(methoxycarbonyl)butyl]phenyl}-4,4-dimethyl-2,6,7-trioxabicyclo-[3.2.0]heptane (22). Pale yellow oil, 82.8% yield (1:1 mixture of diastereoisomers). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (s, 4.5H), 0.97 (s, 4.5H), 1.16 (s, 3H), 1.39 (s, 1.5H), 1.40 (s, 1.5H), 1.57 (s, 1.5H), 1.57 (s, 1.5H), 2.32 (dd, $J=$ 14.5, 3.5 Hz, 0.5H), 2.35 (dd, $J=14.5$, 3.5 Hz, 0.5H), 2.49 (dd, $J=14.5$, 7.6 Hz, 0.5H), 2.52 (dd, $J=14.5$, 7.6 Hz, 0.5H), 3.77 (broad s, 6H), 3.84 (d, $J=8.1$ Hz, 0.5H), 3.84 (d, $J=8.1$ Hz, 0.5H), 4.04–4.12 (m, 1H), 4.59 (d, $J=8.1$ Hz, 1H), 7.42–7.46 (m, 2H), 7.57–7.68 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4, 18.4, 20.8, 20.9, 25.1, 26.7, 33.2, 33.3, 36.7, 41.9, 42.1, 45.6, 52.8, 52.8, 52.9, 52.9, 80.2, 80.3, 105.0, 116.2, 120.2, 120.2, 127.3, 127.3, 128.3, 128.3, 128.4, 128.4, 128.8, 128.9, 136.1, 136.2, 137.2, 171.2, 171.2, 171.5, 171.5 ppm. IR (liquid film): 2958, 2898, 2243, 1731 cm^{-1}. Mass (20 eV, *m/z*, %): 427 (M^+- 32, 6), 320 (24), 303 (18), 302 (100), 57 (10). HRMS (ESI): 482.2143, calcd for $C_{25}H_{33}NO_7Na$ ($M+Na^+$) 482.2155.

4.2.10. 5-*tert*-Butyl-1-[3-(3-cyano-4,5-dihydro-5,5-diphenyl-3*H*-pyrazol-3-yl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (35a). Pale yellow granules melted at 151.0–153.0 °C (from MeOH–CH_2Cl_2), 99.3% yield (45:55 mixture of diastereoisomers). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.81 (s, 4.95H), 0.87 (s. 4.05H), 1.13 (s, 1.65H), 1.13 (s, 1.35H), 1.32 (s, 1.35H), 1.33 (s, 1.65H), 2.48 (d, $J=6.2$ Hz, 0.55H), 2.49 (d, $J=6.2$ Hz, 0.45H), 2.62 (d, $J=6.2$ Hz, 0.45H), 2.65 (d, $J=6.2$ Hz, 0.55H), 3.78 (d, $J=8.2$ Hz, 0.55H), 3.82 (d, $J=8.2$ Hz, 0.45H), 4.54 (d, $J=8.2$ Hz, 0.55H), 4.56 (d, $J=8.2$ Hz, 0.45H), 6.98–7.11 (m, 5H), 7.18–7.41 (m, 5.55H), 7.48 (d, $J=7.8$ Hz, 0.45H), 7.53–7.62 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4 (CH_3), 24.7, 24.9, 25.0, 25.0, 26.7, 26.8, 27.4, 36.5, 36.5, 45.5, 46.9, 47.2, 80.1, 80.2, 104.9, 104.9, 116.2, 116.3, 121.1, 121.1, 126.5, 127.2, 127.2, 127.7, 127.8, 127.8, 128.0, 128.4, 128.4, 128.4,

128.8, 128.9, 129.0, 129.1, 129.5, 129.6, 129.6, 132.7, 136.4, 136.5, 137.9, 138.0, 141.0 ppm. IR (KBr): 2968, 2894, 2234 cm^{-1}. Mass (*m/z*, %): 479 (M^+-N_2, 3), 452 (8), 339 (16), 338 (15), 323 (26), 322 (100), 321 (21), 312 (14), 295 (16), 294 (22), 293 (68), 217 (11), 216 (14), 165 (22), 141 (51), 57 (42). HRMS (ESI): 502.2352, calcd for $C_{32}H_{33}NO_3Na$ ($M-N_2+Na^+$) 502.2358.

4.3. Thermolysis of bicyclic dioxetanes (1a–1g); general procedure

A solution of 5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane bearing a substituted phenyl (**1**) (30 mg) in *p*-xylene (5 mL) was stirred under nitrogen atmosphere for 2 h at 140 °. After cooling, the reaction mixture was concentrated in vacuo. ^1H NMR Spectral analysis showed that the residue included the desired ester (**10**) exclusively. Chromatographic purification [silica gel/AcOEt–hexane (1/4)] of the residue gave the corresponding 2,2,4,4-tetramethyl-3-oxopentyl benzoate (**10**).

4.3.1. 2-(Cyanomethyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10a). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.28 (s, 9H), 1.40 (s, 6H), 4.23 (s, 2H), 4.39 (s, 2H), 7.41 (td, $J=7.3$, 2.0 Hz, 1H), 7.54–7.62 (m, 2H), 7.95 (d with fine coupling, $J=7.3$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.0, 23.5, 28.1, 45.8, 49.0, 72.3, 117.8, 128.1, 128.3, 130.1, 131.1, 132.2, 133.1, 165.9, 215.8 ppm. IR (liquid film): 2979, 2246, 1714, 1681 cm^{-1}. Mass (20 eV, *m/z*, %): 301 (M^+, 1), 246 (35), 244 (45), 218 (31), 216 (28), 163 (11), 162 (100), 145 (14), 144 (94), 85 (18), 57 (56), 56 (13). HRMS (ESI): 324.1533, calcd for $C_{18}H_{23}NO_3Na$ ($M+Na^+$) 324.1576.

4.3.2. 3-(Cyanomethyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10b). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.39 (s, 6H), 3.79 (s, 2H), 4.41 (s, 2H), 7.46 (t, $J=7.8$ Hz, 1H), 7.55 (d with fine coupling, $J=7.8$ Hz, 1H), 7.92–7.95 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 23.5, 23.7, 28.2, 45.9, 49.2, 72.4, 117.1, 128.9, 129.1, 129.3, 130.3, 131.0, 132.2, 165.3, 215.7 ppm. IR (liquid film): 2972, 2874, 2250, 1721, 1685 cm^{-1}. Mass (20 eV, *m/z*, %): 302 ($M^+ +1$, trace), 246 (13), 244 (35), 218 (43), 216 (31), 162 (48), 145 (11), 144 (100) 85 (46), 57 (85), 56 (32). HRMS (ESI): 324.1581, calcd for $C_{18}H_{23}NO_3Na$ ($M+Na^+$) 324.1576.

4.3.3. 4-(Cyanomethyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10c). Colorless needles, melted at 66.1–66.5 °C (from hexane–ether). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.28 (s, 9H), 1.39 (s, 6H), 3.81 (s, 2H), 4.41 (s, 2H), 7.41 (d, $J=8.4$ Hz, 2H), 7.99 (d, $J=8.4$ Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 23.7, 23.7, 28.2, 45.9, 49.2, 72.2, 117.0, 127.9, 129.9, 130.2, 134.8, 165.4, 215.7 ppm. IR (KBr): 2978, 2929, 2873, 2246, 1719, 1683 cm^{-1}. Mass (20 eV, *m/z*, %): 246 (M^+-55, 14), 244 (M^+, 46), 216 (13), 162 (24), 145 (11), 144 (100), 85 (46), 57 (59), 56 (23). HRMS (ESI): 324.1530, calcd for $C_{18}H_{23}NO_3Na$ ($M+Na^+$) 324.1576.

4.3.4. 3-(1-Cyanoethyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10d). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.39 (s, 3H), 1.40 (s, 3H), 1.66 (d, $J=7.3$ Hz, 3H), 3.95 (q, $J=7.3$ Hz, 1H), 4.42 (s, 2H), 7.47 (t, $J=7.8$ Hz, 1H), 7.58 (d with fine coupling, $J=7.8$ Hz, 1H), 7.93 (d with fine coupling, $J=7.8$ Hz, 1H), 7.96 (s with fine coupling, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.3, 23.6, 23.7, 28.1, 31.1, 45.9, 49.1, 72.4, 121.0, 127.8, 129.2, 129.4, 131.0, 131.2, 137.5, 165.5, 215.9 ppm. IR (liquid film): 2980, 2875, 2243, 1722, 1686 cm^{-1}. Mass (20 eV, *m/z*, %): 316 ($M^+ +1$, 2), 260 (12), 258 (26), 232 (36), 230 (20), 177 (12), 176 (48), 159 (11), 158 (100), 85 (25), 57 (59). HRMS (ESI): 338.1737, calcd for $C_{19}H_{25}NO_3Na$ ($M+Na^+$) 338.1732.

4.3.5. 3-(Methoxycarbonylmethyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10e). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.28 (s, 9H), 1.38 (s, 6H), 3.66 (s, 2H), 3.70 (s, 3H), 4.41 (s, 2H), 7.39 (t, $J=7.8$ Hz, 1H), 7.48 (d, $J=7.8$ Hz, 1H), 7.86–7.90 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 23.8, 28.2, 40.9, 45.9, 49.2, 52.2, 72.1, 128.2, 128.6, 130.3, 130.3, 133.8, 134.3, 165.9, 171.3, 215.7 ppm. IR (liquid film): 2958, 2874, 1741, 1722, 1686 cm^{-1}. Mass (20 eV, *m/z*, %): 334 (M^+, trace), 277 (18), 195 (16), 178 (11), 177 (100), 57 (11). HRMS (ESI): 357.1673, calcd for $C_{19}H_{26}O_5Na$ ($M+Na^+$) 357.1678.

4.3.6. 3-(Benzoylmethyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10f). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.27 (s, 9H), 1.37 (s, 6H), 4.33 (s, 2H), 4.40 (s, 2H), 7.39 (t, $J=7.6$ Hz, 1H), 7.44–7.50 (m, 3H), 7.58 (t with fine coupling, $J=7.4$ Hz, 1H), 7.85–7.90 (m, 2H), 7.98–8.03 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 23.8, 28.2, 45.1, 45.9, 49.2, 72.1, 128.0, 128.4, 128.6, 128.7, 130.3, 130.6, 133.3, 134.2, 134.8, 136.3, 165.9, 196.7, 215.8 ppm. IR (liquid film): 2973, 2873, 1721, 1684 cm^{-1}. Mass (20 eV, *m/z*, %): 381 ($M^+ +1$, trace), 323 (17), 241 (22), 224 (17), 223 (100), 105 (35), 57 (10). HRMS (ESI): 403.1873, calcd for $C_{24}H_{28}O_4Na$ ($M+Na^+$) 403.1885.

4.3.7. 3-[Cyano(methoxycarbonyl)methyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (10g). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.40 (s, 3H), 1.40 (s, 3H), 3.82 (s, 3H), 4.41 (s, 2H), 4.79 (s, 1H), 7.51 (t, $J=7.8$ Hz, 1H), 7.68 (d with fine coupling, $J=7.8$ Hz, 1H), 8.01 (d with fine coupling, $J=7.8$ Hz, 1H), 8.06 (s with fine coupling, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 23.7, 28.2, 43.3, 45.9, 49.2, 54.1, 72.5, 114.9, 129.0, 129.5, 130.3, 130.3, 131.3, 132.2, 164.8, 165.0, 215.7 ppm. IR (liquid film): 2960, 2252, 1754, 1723, 1685 cm^{-1}. Mass (20 eV, *m/z*, %): 360 ($M^+ +1$, trace), 304 (11), 302 (28), 277 (12), 276 (66), 274 (20), 220 (74), 203 (12), 202 (100), 85 (38), 57 (71), 56 (25). HRMS (ESI): 382.1609, calcd for $C_{20}H_{25}NO_5Na$ ($M+Na^+$) 382.1630.

4.3.8. 3-(1-Cyanoethenyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (11). A solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (**2**) (17.5 mg, 0.056 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (3 mg) in *p*-xylene (1.5 mL) was stirred under nitrogen atmosphere for 8 h at 120 °C. After cooling, the reaction mixture was concentrated in vacuo and chromatographed on silica gel with hexane–AcOEt (5/1) to give 10.5 mg of **11** as colorless oil in 60.0%

yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.40 (s, 6H), 4.42 (s, 2H), 6.18 (s, 1H), 6.40 (s, 1H), 7.51 (t, J= 7.8 Hz, 1H), 7.79 (d with fine coupling, J=7.8 Hz, 1H), 8.00 (d with fine coupling, J=7.8 Hz, 1H), 8.21 (s with fine coupling, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 28.2, 45.9, 49.2, 72.5, 117.2, 122.2, 126.5, 129.1, 129.2, 130.2, 130.6, 131.0, 132.7, 165.2, 215.6 ppm. IR (liquid film): 2972, 2875, 2229, 1724, 1685 cm^{-1}. Mass (20 eV, *m/z*, %): 256 (M^+-57, 14), 230 (15), 228 (16), 174 (28), 157 (14), 156 (100), 128 (17), 101 (11), 85 (21), 57 (69). HRMS (ESI): 336.1578, calcd for $C_{19}H_{23}NO_3Na$ ($M+Na^+$) 336.1576.

4.4. Chemiluminescence measurement: general procedure

Chemiluminescence were measured using a Hitachi FP-750 spectrometer and/or Hamamatsu Photonics PMA-11 multi-channel detector.

Freshly prepared solution (2 mL) of TBAF (1.0×10^{-1} mol/L) in DMSO was transferred to a quartz cell ($10\times10\times$ 50 mm) and the latter placed into the spectrometer, which was thermostated with stirring at 25 °C. After 3–5 min, a solution of the dioxetane in DMSO (1.0×10^{-3} mol/L or 1.0×10^{-4} mol/L 1 mL) was added by means of a syringe with immediate starting of measurement. The intensity of the light emission time-course was recorded and processed according to first-order kinetics. The total light emission was estimated by comparing it with that of an adamantylidene dioxetane, whose chemiluminescent efficiency Φ^{CL} has been reported to be 0.29 and was used here as standard[16].

Chemiluminescence measurement using a 18-crown-6 ether complex of *tert*-BuOK or potassium bis(methoxycarbonyl) methanide as a base was carried out in benzene similarly to the case of TBAF/DMSO. Complex of 18-crown-6 ether with a base was prepared in benzene as follows.

[K⊂(18-crown-6)]$^+$t-BuO$^-$: *tert*-BuOK (1 M in THF, 1.10 mL, 1.10 mmol) was added to a solution of 18-crown-6 ether (294 mg, 1.11 mmol) in benzene (30 mL) at room temperature under nitrogen atmosphere, and stirred for 10 min.

[K⊂(18-crown-6)]$^+$(**18a**)$^-$: *tert*-BuOK (1 M in THF, 1.10 mL, 1.10 mmol) was added to a solution of 18-crown-6 ether (291 mg, 1.10 mmol) and dimethyl methylmalonate, $CH_3CH(CO_2CH_3)_2$ (**18a**) (0.16 mL, 1.2 mmol) in benzene (30 mL) and stirred at room temperature under nitrogen atmosphere for 10 min.

[K⊂(18-crown-6)]$^+$(**18b**)$^-$: *tert*-BuOK (1 M in THF, 1.10 mL, 1.10 mmol) was added to a solution of 18-crown-6 ether (291 mg, 1.10 mmol), and dimethyl malonate, $CH_2(CO_2CH_3)_2$ (**18b**), (0.12 mL, 1.2 mmol) in benzene (30 mL) and stirred at room temperature under nitrogen atmosphere for 10 min.

[K⊂(18-crown-6)]$^+$(**18c**)$^-$: dimethyl chloromalonate, $ClCH(CO_2CH_3)_2$ (**18c**), (0.077 mL) was added to a solution of 18-crown-6 (148 mg, 0.56 mmol), and *tert*-BuOK (1 M in THF, 0.55 mL, 0.55 mmol) in benzene (4.4 mL) and stirred at room temperature under nitrogen atmosphere for 10 min.

4.5. Isolation of ketoesters (10) from the spent reaction mixture after chemiluminescent decomposition of dioxetanes (1): typical procedure

A solution of TBAF (1 M in THF, 0.1 mL) in DMSO (0.9 mL) was added to a solution of the dioxetane (**1g**) (20 mg) in DMSO (3 mL) at room temperature under nitrogen atmosphere. After stirring for 1 h, H_2O (1 mL) was added to the solution, and then, the reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. ^{1}H NMR spectral analysis showed that the residue was comprised of ketoester (**10g**) without detectable amount of other products. The residue was purified by column chromatograpy on silica gel with AcOEt–hexane (1/4) to give the corresponding ketoester (**10g**) as a colorless oil in 78.6% yield.

4.5.1. 3-[1-Cyano-1-(methoxycarbonyl)ethyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (15). TBAF (1 M in THF, 0.5 mL) was added to a solution of 3-[cyano(methoxycarbonyl)methyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (**10g**) (82.9 mg, 0.231 mmol) in DMSO (2 mL) at room temperature under nitrogen atmosphere. After 5 min, MeI (0.05 mL, 0.80 mmol) was added to the solution. After stirring for 5 min, the reaction mixture was poured into satd aq NH_4Cl and extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1/4) to give **15** as a colorless oil in 76.6% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.40 (s, 3H), 1.40 (s, 3H), 1.98 (s, 3H), 3.80 (s, 3H), 4.41 (s, 2H), 7.50 (t, J= 7.8 Hz, 1H), 7.75 (ddd, J=7.8, 2.1, 1.2 Hz, 1H), 7.99 (d with fine coupling, J=7.8 Hz, 1H), 8.13 (s with fine coupling, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.6, 23.7, 24.8, 28.1, 45.9, 47.9, 49.1, 54.1, 72.6, 118.9, 126.8, 129.4, 130.0, 130.4, 131.2, 136.1, 165.2, 168.0, 215.8 ppm. IR (liquid film): 2962, 2875, 2246, 1751, 1724, 1686, cm^{-1}. Mass (20 eV, *m/z*, %): 374 (M^++1, trace), 316 (25), 318 (10), 290 (56), 288 (15), 234 (71), 217 (14), 216 (100), 85 (23), 57 (42). HRMS (ESI): 396.1798, calcd for $C_{21}H_{27}NO_5Na$ ($M+Na^+$) 396.1787.

4.5.2. Chemiluminescent decomposition of a dioxetane (2) with [K⊂(18-crown-6)]$^+$*t*-BuO$^-$: isolation of 3-(1-cyanoethenyl)benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (11). To a solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo-[3.2.0]heptane (**2**) (31.4 mg, 0.10 mmol) in benzene (1 mL), a solution of [K⊂(18-crown-6)]$^+$*t*-BuO$^-$ (3 mL, 0.1 mmol) in benzene was added with a syringe at 25 °C under nitrogen atmosphere for 1 min, during which emission of orange light was observed. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Chromatographic purification (silica gel) of the residue with hexane–AcOEt (4/1–1/1) gave **11** in 14% yield.

4.5.3. Chemiluminescent decomposition of a dioxetane (2) with $[K\subset 18\text{-crown-6}]^+(18a)^-$: isolation of 3-[1-cyano-3,3-bis(methoxycarbonyl)butyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (19). To a solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (**2**) (31.4 mg, 0.10 mmol) in benzene (1 mL), a solution of $[K\subset(18\text{-crown-6})]^+(\mathbf{18a})^-$ (3 mL, 0.10 mmol) in benzene was added with a syringe at 25 °C under nitrogen atmosphere for 1 min, during which emission of crimson light was observed. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. ^{1}H NMR spectrum of the residue showed that 3-[1-cyano-3,3-bis(methoxycarbonyl)butyl]benzoic acid 2,2,4,4-tetramethyl-3-oxo-pentyl ester (**19**) was produced exclusively. Chromatographic purification of the residue on silica gel with CH_2Cl_2:hexane–AcOEt (4/5/1) gave **19** as a pale yellow oil in 39.1% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.40 (s, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 2.36 (dd, J=14.7, 3.7 Hz, 1H), 2.50 (dd, J=14.7, 10.1 Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 4.12 (dd, J=10.1, 3.7 Hz, 1H), 4.41 (s, 2H), 7.47 (t, J=7.8 Hz, 1H), 7.61 (broad d, J=7.8 Hz, 1H), 7.94 (broad d, J=7.8 Hz, 1H), 8.01 (broad s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.9, 23.6, 23.7, 28.1, 33.1, 42.0, 45.9, 49.1, 52.7, 52.9, 52.9, 72.4, 120.0, 128.4, 129.4, 129.4, 131.1, 131.8, 136.8, 165.4, 171.2, 171.4, 215.9 ppm. IR (liquid film): 2956, 2875, 2242, 1730, 1686 cm^{-1}. Mass (20 eV, *m/z*, %): 402 (M^+-57, 11), 376 (12), 320 (27), 303 (19), 302 (100), 270 (9), 57 (17). HRMS (ESI): 482.2143, calcd for $C_{25}H_{33}NO_7Na$ ($M+Na^+$) 482.2155.

4.5.4. Chemiluminescent decomposition of a dioxetane (2) with $[K\subset 18\text{-crown-6}]^+(18b)^-$: isolation of 3-[1-cyano-3,3-bis(methoxycarbonyl)propyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (24) and 5-*tert*-butyl-1-{3-[1-cyano-3,3-bis(methoxycarbonyl)propyl]-phenyl}-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (25). To a solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)-phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (**2**) (31.4 mg, 0.10 mmol) in benzene (1 mL), a solution of $[K\subset(18\text{-crown-6})]^+(\mathbf{18b})^-$ (3 mL, 0.1 mmol) in benzene was added with a syringe at 25 °C under nitrogen atmosphere for 1 min, during which emission of red light was observed. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. ^{1}H NMR spectrum of the residue showed that 3-[1-cyano-3,3-bis(methoxycarbonyl)propyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (**24**) (39%) was produced along with 5-*tert*-butyl-1-{3-[1-cyano-3,3-bis(methoxycarbonyl) propyl]phenyl}-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (**25**) (28%). Chromatographic purification of the residue with hexane–AcOEt (4/1–1/1) gave **24** as a colorless viscous oil in 26.9% yield and **25** as a colorless oil in 16.2% yield.

Compound **24**. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.29 (s, 9H), 1.40 (s, 3H), 1.40 (s, 3H), 2.48 (t, J=7.8 Hz, 2H), 3.57 (t, J=7.8 Hz, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 4.04 (t, J=7.8 Hz, 1H), 4.41 (s, 2H), 7.48 (t, J=7.8 Hz, 1H), 7.57 (d with fine coupling, J=7.8 Hz, 1H), 7.93–7.98 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.6, 23.7, 28.1, 34.4, 34.9, 45.9, 48.9, 49.1, 53.0, 53.0, 72.5, 119.2, 128.5, 129.6, 129.7, 131.3, 131.8, 135.1, 165.3, 168.3, 168.4, 215.9 ppm. IR (liquid film): 2958, 2875, 2243, 1734, 1685 cm^{-1}. Mass (20 eV, *m/z*, %): 414 (M^+-31, 1), 388 (7), 306 (23), 289 (33), 288 (100), 256 (17), 165 (21), 133 (35), 113 (68), 85 (27), 57 (64). HRMS (ESI): 468.2002, calcd for $C_{24}H_{31}NO_7Na$ ($M+Na^+$) 468.1998.

Compound **25** (1:1 mixture of diastereisomers). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.97 (s, 4.5H), 0.97 (s, 4.5H), 1.16 (s, 3H), 1.38 (s, 1.5H), 1.39 (s, 1.5H), 2.43–2.50 (m, 2H), 3.50–3.57 (m, 1H), 3.75 (s, 1.5H), 3.75 (s, 1.5H), 3.78 (s, 1.5H), 3.79 (s, 1.5H), 3.84 (d, J=8.3 Hz, 0.5H), 3.84 (d, J=8.3 Hz, 0.5H), 4.00–4.05 (m, 1H), 4.59 (d, J=8.3 Hz, 1H), 7.40–7.48 (m, 2H), 7.58–7.66 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4, 25.1, 26.7, 34.3, 34.4, 35.1, 35.1, 36.7, 45.6, 48.9, 53.0, 53.0, 80.3, 80.3, 105.0, 116.2, 119.4, 119.4, 127.4, 128.5, 128.5, 128.7, 128.7, 129.0, 134.3, 134.4, 137.4, 137.4, 168.4, 168.4, 168.5, 168.5 ppm. IR (liquid film): 2960, 2892, 2243, 1736 cm^{-1}. Mass (20 eV, *m/z*, %): 445 (M^+, trace), 413 (3), 373 (21), 306 (11), 289 (19), 288 (100), 143 (12), 113 (21), 85 (11), 57 (45). HRMS (ESI): 468.1983, calcd for $C_{24}H_{31}NO_7Na$ ($M+Na^+$) 468.1998.

4.5.5. Chemiluminescent decomposition of a dioxetane (2) with $[K\subset 18\text{-crown-6}]^+(18c)^-$: isolation of 3-[1-cyano-2,2-bis(methoxycarbonyl)cyclopropyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (30) and 1-{3-[1-cyano-2,2-bis(methoxycarbonyl)cyclopropyl]phenyl}-5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo-[3.2.0]heptane (31). To a solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo-[3.2.0]heptane (**2**) (31.4 mg, 0.10 mmol) in benzene (1 mL), a solution of $[K\subset(18\text{-crown-6})]^+(\mathbf{18c})^-$ (3 mL, 0.1 mmol) in benzene was added by means of a syringe at 25 °C under nitrogen atmosphere for 1 min, during which emission of red light was observed. The reaction mixture was poured into satd aq NH_4Cl and then extracted with AcOEt. The organic layer was washed with satd aq NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. ^{1}H NMR spectrum of the residue showed that 3-[1-cyano-2,2-bis(methoxycarbonyl)cyclopropyl]benzoic acid 2,2,4,4-tetramethyl-3-oxopentyl ester (**30**) (71%) and was produced along with 1-{3-[1-cyano-2,2-bis(methoxycarbonyl)propyl]phenyl}-5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo-[3.2.0]heptane (**31**) (29%). Chromatographic purification of the residue on silica gel with hexane–AcOEt (4/1–1/1) gave **30** as a colorless viscous oil in 52% yield and **31** as a colorless oil in 23% yield.

Compound **30**. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.30 (s, 9H), 1.39 (s, 3H), 1.40 (s, 3H), 2.41 (t, J=6.2 Hz, 1H), 2.58 (d, J=6.2 Hz, 1H), 3.39 (s, 3H), 3.92 (s, 3H), 4.40 (s, 2H), 7.45 (t, J=7.8 Hz, 1H), 7.63 (d with fine coupling, J=7.8 Hz, 1H), 7.94–7.98 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 22.8, 23.6, 23.7, 27.5, 28.1, 41.9, 45.9, 49.1, 53.1, 53.7, 72.5, 117.7, 129.1, 129.7, 130.4, 130.8, 131.2, 133.5, 164.1, 165.1, 165.7, 215.8 ppm. IR (liquid film): 2958, 2875, 2240, 1746, 1731, 1685 cm^{-1}. Mass (20 eV, *m/z*, %): 386 (M^+-57, 17), 360 (23), 305 (14), 304 (74),

287 (16), 286 (100), 272 (12), 57 (14). HRMS (ESI): 466.1828, calcd for $C_{24}H_{31}NO_7Na$ ($M+Na^+$) 466.1842.

Compound **31** (1:1 mixture of diastereoisomers). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.96 (s, 9H), 1.16 (s, 3H), 1.37 (s, 1.5H), 1.39 (s, 1.5H), 2.38 (d, $J=6.1$ Hz, 0.5H), 2.39 (d, $J=6.1$ Hz, 0.5H), 2.58 (d, $J=6.1$ Hz, 0.5H), 2.59 (d, $J=6.1$ Hz, 0.5H), 3.36 (s, 3H), 3.83 (d, $J=8.2$ Hz, 1H), 3.91 (s, 1.5H), 3.91 (s, 1.5H), 4.58 (d, $J=8.2$ Hz, 1H), 7.38–7.46 (m, 2H), 7.60–7.72 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 18.4, 18.4, 22.8, 22.9, 25.0, 25.1, 26.7, 26.7, 27.7, 27.8, 36.6, 41.9, 41.9, 45.6, 53.0, 53.1, 53.7, 80.2, 80.3, 105.0, 116.0, 116.0, 117.8, 117.9, 128.4, 128.5, 128.9, 129.4, 129.5, 129.8, 130.1, 130.5, 130.5, 137.0, 137.1, 164.1, 164.1, 165.9 ppm. IR (liquid film): 2961, 2241, 1743 cm^{-1}. Mass (20 eV, *m/z*, %): 411 (M^+-32, 2), 386 (14), 360 (23), 327 (11), 305 (13), 304 (70), 287 (19), 286 (100), 272 (12), 57 (17). HRMS (ESI): 466.1828, calcd for $C_{24}H_{29}NO_7Na$ ($M+Na^+$) 466.1842.

4.5.6. 5-*tert*-Butyl-1-[3-(3-cyano-4,5-dihydro-5,5-diphenyl-3*H*-pyrazole-3-yl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (35a). A solution of (diphenyl)diazomethane (0.50 mmol: prepared from benzophenone hydrazone and HgO in hexane–ethanol in the presence of catalytic amount of EtONa and used crude product) in acetonitrile (0.5 mL) was added to a solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (**2**) (92 mg, 0.29 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (2 mg) in acetonitlile (3 mL) at room temperature under nitrogen atmosphere and stirred for 2 h. The reaction mixture was concentrated in vacuo and chromatographed on silica gel with hexane–AcOEt (10/1–5/1) to give 142 mg of **35a** as pale yellow granules in 95.2% yield (45:55 mixture of diastereoisomers).

4.5.7. 5-*tert*-Butyl-1-[3-(3-cyano-4,5-dihydro-5-trimethylsilyl-3*H*-pyrazole-3-yl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane (35b). A solution of (trimethylsilyl)diazomethane (2.0 M in hexane, 1 mL, 2 mmol) was added to a solution of 5-*tert*-butyl-1-[3-(1-cyanoethenyl)phenyl]-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]-heptane (**2**) (52.4 mg, 0.17 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (2 mg) in acetonitlile (2 mL) at room temperature under nitrogen atmosphere and stirred for 1.5 h. The reaction mixture was concentrated in vacuo and chromatographed on silica gel with hexane–AcOEt (10/1–5/1) to give 41.4 mg of **35b** as colorless viscous oil in 58.0% yield (1:1 mixture of diastereoisomers). ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.22 (s, 4.5H), 0.23 (s. 4.5H), 0.57 (dd, $J=10.7$, 5.8 Hz, 0.5H), 0.59 (dd, $J=10.7$, 5.8 Hz, 0.5H), 0.96 (s, 9H), 1.16 (s, 3H), 1.39 (s, 3H), 1.59 (dd, $J=5.8$, 4.6 Hz, 0.5H), 1.60 (dd, $J=5.8$, 4.6 Hz, 0.5H), 1.66 (dd, $J=10.7$, 4.6 Hz, 0.5H), 1.69 (dd, $J=10.7$, 4.6 Hz, 0.5H), 3.83 (d, $J=8.1$ Hz, 1H), 4.58 (d, $J=8.1$ Hz, 1H), 7.35–7.43 (m, 2H), 7.49–7.55 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C −2.08, 17.5, 18.4, 19.9, 20.2, 21.4, 21.5, 25.0, 25.1, 26.7, 36.7, 45.6, 80.2, 80.2, 104.9, 104.9, 116.3, 116.3, 121.7, 121.8, 125.1, 125.4, 127.1, 127.2, 127.4, 127.4, 128.4, 136.7, 137.6, 137.7 ppm. IR (liquid film): 2961, 2897, 2232 cm^{-1}. Mass (*m/z*, %): 399 (M^+-N_2, 3), 343 (20), 342 (15), 314 (10), 260 (21), 259 (19), 244 (13), 243 (32), 242 (100), 169 (30), 73 (38), 57 (46). HRMS (ESI): 422.2116, calcd for $C_{23}H_{33}NO_3SiNa$ ($M-N_2+Na^+$) 422.2127.

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A convenient and efficient ring-opening reaction of aziridines with acetylenes and synthesis of dihydropyrroles

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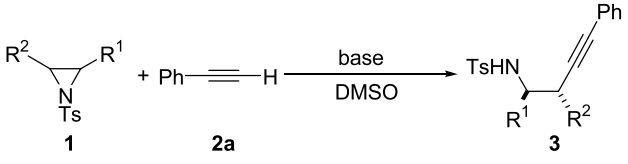
Abstract—In the presence of ^{t}BuOK, reaction of acetylenes with *N*-Ts substituted aziridines derived from both cyclic and acyclic alkenes at room temperature gave rise to homopropargylamines in good to high yields and in high regioselectivity. Not only Ph- and Me_3Si-substituted acetylenes but also acetylene itself was suitable reagents. Treatment of ring-opening products with I_2 and AgOAc in the presence of K_2CO_3 provided dihydropyrroles in high yields. One-pot synthesis of dihydropyrroles was also realized by the reaction of aziridines and phenylacetylene in the presence of NaH followed by the treatment with I_2 and AgOAc.

1. Introduction

Aziridines are widely used as intermediates in organic synthesis.[1] Many transformations of aziridines have well been documented. Among them, ring-opening reactions of aziridines with nucleophiles provide a useful protocol, and many reagents have recently been developed to realize the opening of aziridine ring. However, the most often used reagents are those O-,[2] S-,[3] and N-[4] nucleophiles; only a few examples were reported using carbon nucleophiles, such as Grignard reagents, organolithiums, Wittig reagents, cuprates and malonates, in the ring-opening reaction of aziridines, although these transformations are more important because a new carbon–carbon bond is formed.[5] Besides, some limitations were also reported when carbon nucleophiles were the reagent. For example, only aziridines derived from acyclic alkenes gave good results when alkynyllithiums were used.[6] During the course of studies on the ring-opening reactions of aziridines,[7] we developed an effective alkynylation of aziridines using CuOTf as catalyst.[8] But the reaction needed 2 equiv of BuLi as base and it also suffered from the long reaction time. Besides, acetylene was not suitable reagent. All of these limit its use in organic synthesis. To overcome such limitations, further studies were made. Herein we reported a simple, convenient and efficient alkynylation of aziridines using acetylene and phenyl acetylene in the presence of base as well as the synthesis of dihydropyrroles using these ring-opening products.

2. Results and discussions

Considering the acidity of acetylene group, the effect of a variety of bases on the reaction of aziridine **1** and phenylacetylene **2a** in DMSO was investigated initially (Eq. 1). The results are compiled in Table 1.



1 **2a** **3** (1)

As shown in Table 1, the property of base has a crucial influence on the yield of products and reaction time. The yield increased when basicity of base was enhanced from Cs_2CO_3, NaOH, KOH to NaH (entries 1–4). When Cs_2CO_3 was used as base aziridine **1a** was recovered fully (entry 1). Corresponding homopropargyl amine was obtained in low yield employing NaOH or KOH as base and aziridine **1a** could not be consumed completely (entries 2 and 3). When NaH was used as base the reaction gave the corresponding product in 71% yield (entry 4), which increased further to

Keywords: Alkynylation; Aziridine; Ring-opening; Cyclization; Dihydropyrrole.
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Table 1. Effect of bases on the ring-opening reaction of aziridine **1a** with phenylacetylene **2a**[a]

Entry	Substrate, R^1, R^2	Base (mol%)	Time (h)	Yield (%)[b]
1	**1a**, $-(CH_2)_4-$	Cs_2CO_3 (200)	5	NR[c]
2	**1a**, $-(CH_2)_4-$	NaOH (150)	5	9
3	**1a**, $-(CH_2)_4-$	KOH (150)	5	46
4	**1a**, $-(CH_2)_4-$	NaH (150)	5	71
5	**1a**, $-(CH_2)_4-$	NaH (200)	1.5[d]	87
6	**1a**, $-(CH_2)_4-$	$CsOH\cdot H_2O$ (200)	3[d]	73
7	**1a**, $-(CH_2)_4-$	$n$$Bu_4NOH$ (50)	12	NR[c]
8	**1c**,$-(CH_2)_5-$	NaH (200)	1[d]	74
9	**1e**, n-C_6H_{13}, H	NaH (200)	0.5[d]	45
10	**1e**, n-C_6H_{13}, H	$NaOCH_3$ (150)	0.5	12
11	**1e**, n-C_6H_{13}, H	^{i}PrONa (150)	0.5	63
12	**1e**, n-C_6H_{13}, H	^{t}BuONa (150)	0.5	68
13	**1e**, n-C_6H_{13}, H	^{t}BuOK (150)	0.5	95
14	**1e**, n-C_6H_{13}, H	^{t}BuOK (150)	0.5[d]	87

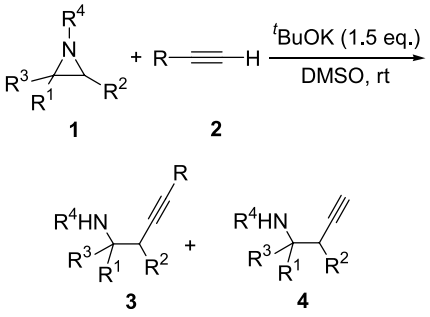
[a] Reactions proceeded with molecular ratio of **1**:**2a**=1:1.5 at room temperature.
[b] Isolated yields based on aziridine **1**.
[c] No reaction.
[d] 4 Å molecular sieves was added.

87% if molecular sieves was added (entry 5). Quaternary ammonium hydroxide and CsOH were also tested. No reaction occurred using Bu_4NOH (entry 7) while product **3a** was provided in 73% yield using CsOH as base and 4 Å MS as additives (entry 6).

The effect of solvent was also studied. When Et_2O, THF or toluene was used as solvent, no reaction took place and starting material was recovered. In DMF or CH_3CN aziridines **1a** disappeared but only unknown byproducts were provided.

Sodium hydride showed its superior in yield when aziridines **1a** and **1c** derived from cyclic alkenes were used (entries 5 and 8), low yield of product was given when the aziridine **1e** derived from acyclic alkene (entry 9). Thus, further screen of bases using **1e** was carried out. It was found that corresponding homopropargylamine **3e** was provided in 12% yield using $NaOCH_3$ as base (entry 10). However, the yield dramatically increased to 63 and 68% when more basic ^{i}PrONa and ^{t}BuONa was used, respectively, (entries 11 and 12). Further, great improvement of yield from 68 to 95% was observed when ^{t}BuOK instead of ^{t}BuONa was used (entry 13). It differs from the reaction using NaH as base, molecular sieves had no effect when ^{t}BuOK was used as base (entry 13 vs entry 14 and entry 4 vs entry 5).

To demonstrate the usefulness of this base-mediated ring-opening reaction of aziridines with alkynes, many kinds of aziridines **1** as well as Ph- and Me_3Si-substituted acetylenes **2** were tested (Eq. 2) and the results are shown in Table 2.



(2)

It can be seen from Table 2 that in the presence of stoichiometric amount of ^{t}BuOK, the reaction of aziridines **1** with alkynes completed within 0.5–2.5 h to provide the corresponding ring-opening product **3** in high yields. As previously observed in CuOTf promoted reaction,[8] the reaction was completely anti stereoselective. Besides, the attack of acetylenes to aziridines is highly regioselective. All reactions for aziridines derived from terminal alkenes gave only one regioisomer arising from terminal attack, even for phenyl aziridine **1h** (entry 8), while in CuOTf

Table 2. Ring-opening reaction of aziridines **1** with acetylenes **2** in the presence of ^{t}BuOK[a]

Entry	Substrate, R^1, R^2, R^3 and R^4	Alkyne, R	Product	Time (h)	Yield (%)[b]
1	**1a**, $-(CH_2)_4-$, H, Ts	**2a**, Ph	**3a**	1.5	85
2	**1b**, $-(CH_2)_3-$, H, Ts	**2a**, Ph	**3b**	2.5	77[c]
3	**1c**, $-(CH_2)_5-$, H, Ts	**2a**, Ph	**3c**	1.5	74[c]
4	**1d**, $-(CH_2)_4-$, H, SO_2Ph	**2a**, Ph	**3d**	1	73
5	**1e**, n-C_6H_{13}, H, H, Ts	**2a**, Ph	**3e**	0.5	95
6	**1f**, i-C_3H_7, H, H, Ts	**2a**, Ph	**3f**	1	84
7	**1g**, t-C_4H_9, H, H, Ts	**2a**, Ph	**3g**	1	67
8	**1h**, Ph, H, H, Ts	**2a**, Ph	**3h**	1.5	85
9	**1i**, n-C_5H_{11}, H, Me, Ts	**2a**, Ph	**3i**	1.5	92
10	**1j**, $-(CH_2)_4-$, H, COPh	**2a**, Ph	**3j**	1	29
11	**1k**, $-(CH_2)_4-$, H, Bn	**2a**, Ph	—	—	—
12	**1a**, $-(CH_2)_4-$, H, Ts	**2b**, Me_3Si	**4a**	1	83
13	**1e**, n-C_6H_{13}, H, H, Ts	**2b**, Me_3Si	**4e**	0.5	98

[a] Reactions run with molecular ratio of **1**:**2**:base=1:1.5:1.5.
[b] Isolated yield based on aziridine.
[c] NaH (200 mol%) was used.

promoted reaction, phenyl aziridine gave two regioisomers arising from the benzylic and terminal attack.[8] Many kind of aziridines, derived both from cyclic and acyclic alkenes including terminal disubstituted alkenes **1i** (entry 9) are suitable substrate. However, the choice of substituent on the nitrogen atom of aziridines is important. For example, *N*-COPh aziridine **1j** gave low yield of product (entry 10) while no reaction took place for *N*-Bn aziridine **1k** (entry 11), but *N*-SO_2Ph aziridine **1d** delivered good yield of product (entry 4). It seems from these results that the presence of electron-withdrawing substituents on nitrogen is necessary. It is worthwhile to point out that for aziridine **1c** corresponding product **3c** was provided in 74% yield (entry 3) while in the CuOTf catalyzed reaction only trace product was obtained when **1c** was substrate. Trimethylsilyl substituted acetylene is also a suitable reagent, but the product was desilylated product **4** (entries 9 and 10, Table 2).

Acetylene is a commercially available chemical. It is also one of the cheapest carbon sources. The addition of acetylene to carbonyl compound is one general method to form carbon–carbon bond.[9] However, no ring-opening reaction of aziridine with acetylene was reported. Based on the success of alkynylation of activated aziridines in the presence of base, we tried to use acetylene as nucleophile. Under above reaction condition, reaction of aziridines **1** with acetylene **2c** was carried out (Eq. 2, R = H) and the results are given in Table 3.

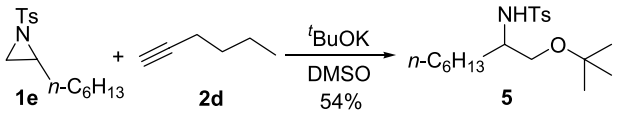
Table 3. Ring-opening reaction of aziridines **1** with acetylene **2c** using ^{t}BuOK as base[a]

Entry	Substrate, R^1, R^2, R^3 and R^4	Product	Time (h)	Yield (%)[b]
1	**1a**, $-(CH_2)_4-$, H, Ts	**4a**	0.5	87
2	**1b**, $-(CH_2)_3-$, H, Ts	**4b**	0.5	82
3	**1c**, $-(CH_2)_5-$, H, Ts	**4c**	2	55
4	**1d**, $-(CH_2)_4-$, H, SO_2Ph	**4d**	1	76
5	**1e**, *n*-C_6H_{13}, H, H, Ts	**4e**	0.5	78
6	**1f**, *i*-C_3H_7, H, H, Ts	**4f**	2	71
7	**1g**, *t*-C_4H_9, H, H, Ts	**4g**	0.5	61
8	**1h**, Ph, H, H, Ts	**4h**	0.5	77
9	**1i**, *n*-C_5H_{11}, H, Me, Ts	**4i**	0.5	67
10	**1m**, *n*-$C_{16}H_{33}$, H, H, Ts	**4m**	0.5	63

[a] Reactions run in DMSO with molecular ratio of **1**:^{t}BuOK = 1:1.5.
[b] Isolated yield based on aziridine.

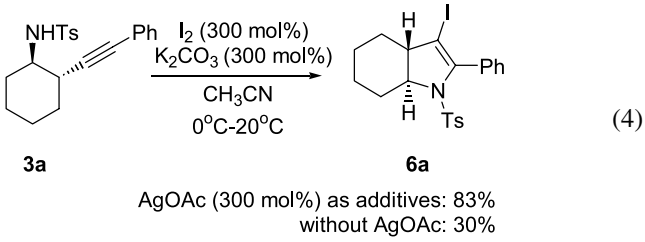
From Table 3, it can be seen that the ring-opening of aziridine **1** with acetylene proceeded smoothly in DMSO and various homopropargylamines **4** were afforded in good yields by the reaction of aziridine **1** with acetylide generated in situ. It is the same as that in the reactions with phenylacetylene and trimethylsilylacetylene, all tested aziridines derived both from cyclic and acyclic alkenes including terminal disubstituted alkenes gave expected products. One of advantages using acetylene is that the products still contain terminal acetylene group, thus provide an opportunity to convert it to other products.[9]

However, reaction of aziridine **1e** and 1-hexnye **2d** failed to yield the expected product; instead, only product **5** resulting from attack of *tert*-butoxide on less substituted carbon of aziridines was separated (Eq. 3).

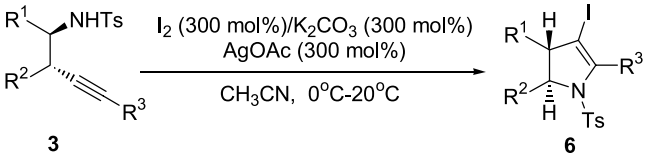


(3)

Dihydropyrroles are useful intermediates in natural products synthesis. Recently, Knigh and co-workers reported a simple procedure for the synthesis of dihydropyrroles from iodo-cyclization of homopropargylamines.[10] Obviously, such kind of homopropargylamines in turn can be produced from the ring-opening reaction of aziridines and alkynes. Under the reaction condition reported by Knigh and co-workers,[10] homopropargylic sulfonamide **3a** underwent smooth 5-*endo-dig* cyclization upon exposure to excess iodine in acetonitrile containing potassium carbonate affording 4-iodo-2,3-dihydropyrrole **6a** in 30% yield (Eq. 4). To improve the yield of product, the modification of reaction condition was made. It was found that the yield of dihydropyrrole increase to 83% from 30% when 300 mol% of AgOAc was added (Eq. 4). Under this reaction condition, iodocyclization of several homopropargylamines **3** derived from our base-mediated and CuOTf-catalyzed[8] ring-opening of aziridines to dihydropyrroles proceeded (Eq. 5, Table 4).



(4)



(5)

It is showed in Table 4 that all reactions gave desired products in good yields. When the amount of I_2, and AgOAc decreased to 150 mol%, the reaction still provided the product in good yield (entry 4). Many kinds of homopropargylamines, including those from ring-opening reaction of hexynes and aziridines (entry 6) and

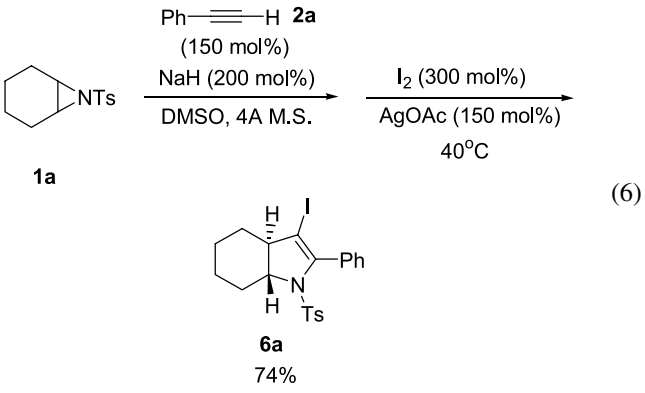
Table 4. Synthesis of dihydropyrroles **7** from cyclization of homopropargylamines **3**[a]

Entry	Substrate, R^1, R^2, R^3	Time (h)	Product	Yield (%)[b]
1	**3a**, $-(CH_2)_4-$, Ph	20	**6a**	30[c]
2	**3a**, $-(CH_2)_4-$, Ph	3	**6a**	83
3	**3n**, *n*-C_4H_9, H, Ph	12	**6n**	78
4	**3d**, *n*-C_4H_9, H, Ph	24	**6n**	56[d]
5	**3e**, *n*-C_6H_{13}, H, Ph	15	**6e**	76
6	**3o**, *n*-C_6H_{13}, H, *n*-C_4H_9,	16	**6o**	73
7	**3h**, Ph, H, Ph	18	**6h**	69
8	**3p**, Bn, H, Ph	15	**6p**	87

[a] The reaction condition is showed in Eq. 6.
[b] Isolated product based on homopropargyl amine.
[c] No AgOAc was added.
[d] The amount of I_2, and AgOAc were 150 mol%.

phenylacetylene and benzylaziridine (entry 8) are suitable substrates. However, homopropargylamine derived from the reaction of acetylene and aziridines gave an unstable product with uncertain reason.

It is interesting that dihydropyrroles can be provided in one-pot reaction manner. When 300 mol% of I_2 and 150 mol% of AgOAc were added to the reaction mixture of aziridines **1a** and phenylacetylene **2a**, dihydropyrrole **6a** was separated in 74% yield (Eq. 6).



(6)

In conclusion, a base-mediated ring-opening reaction of aziridines and a variety of acetylenes was developed in a simple and convenient way. Homopropargyl amines were provided in high yields and in high regioselectivity. The use of acetylene extends the utility of reaction. Besides, the reaction has the advantages of wider range of substrates and better regioselectivity over that catalyzed by CuOTf.[8] Based upon it, a facile preparation of dihydropyrroles was realized, even in a one-pot manner. The investigations on the extension of the reaction to other substrates and on the asymmetric version of the reaction are in progress in our laboratory.

3. Experimental

3.1. General experimental conditions

All reactions were performed under an atmosphere of dry argon using oven-dried glassware. Solvents were distilled under an atmosphere of dry argon before use. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Brucker AM-300 (300 MHz) spectrometer, and the chemical shifts were referenced to $CHCl_3$ (δ 7.27) in $CDCl_3$. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. IR spectra were measured in cm^{-1}.

3.2. General procedure for ring-opening reaction of aziridines 1 with acetylenes 2a and 2b in the presence of ^{t}BuOK

To a stirred solution of ^{t}BuOK (0.375 mmol) in DMSO (2.0 mL) was added acetylenes **2a** or **2b** (0.375 mmol) and aziridine **1** (0.25 mmol) successively under argon. The reaction mixture was stirred at room temperature until the substrate was completely consumed (monitored by TLC). Then reaction mixture was quenched with 5 mL of 1 N HCl aqueous solution. The resulting mixture was poured into diethyl ether (60 mL), and washed with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) solution. The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the crude product was purified by flash column chromatography on silica gel to provide corresponding homopropargyl amine.

3.3. General procedure for ring-opening reaction of aziridines 1 with acetylene 2c using ^{t}BuOK as base

A stirred solution of ^{t}BuOK (0.375 mmol) in DMSO (3.0 mL) was saturated with acetylene **2c** by bubbling for 30 min, then aziridine **1** (0.25 mmol) was added under argon. The reaction mixture was stirred at room temperature till complete consumption of substrate (monitored by TLC). Then reaction mixture was quenched carefully with 5 mL of 1 N HCl aqueous solution. The resulting mixture was poured into diethyl ether (60 mL), and washed with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) solution. The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the crude product was purified by flash column chromatography on silica gel to provide corresponding homopropargyl amine.

3.3.1. *N*-(2-Phenyl-1-ynyl-cyclohexyl)-4-methyl-benzenesulfonamide (3a).[8] White solid; mp 118–120 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.24–1.27 (m, 4H), 1.46–1.69 (m, 2H), 1.99–2.05 (m, 1H), 2.24–2.28 (m, 1H), 2.31 (s, 3H), 2.41–2.49 (m, 1H), 3.02–3.12 (m, 1H), 4.81 (d, J=5.4 Hz, 1H), 7.11 (d, J=8.1 Hz, 2H), 7.12–7.29 (m, 5H), 7.75 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.77, 21.39, 22.16, 25.87, 27.55, 33.90, 52.22, 83.29, 84.93, 123.09, 126.95, 127.89, 128.14, 129.55, 131.55, 137.99, 143.21; IR (film) $\tilde{\nu}$=3286, 2248, 1599, 1320, 1165 cm^{-1}; EI-MS *m/z* (%): 353 (M^+, 1.48), 198 (35), 155 (23), 115 (35), 91 (100). Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.35; H, 6.56; N, 3.96. Found: C, 71.42; H, 6.57; N: 3.80.

3.3.2. *N*-(2-Phenyl-1-ynyl-cyclopentyl)-4-methyl-benzenesulfonamide (3b).[8] White solid; mp 111–113 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.45–1.53 (m, 1H), 1.68–1.75 (m, 3H), 2.04–2.15 (m, 2H), 2.32 (s, 3H), 2.69–2.74 (m, 1H), 3.52–3.56 (m, 1H), 4.80 (d, J=6.0 Hz, 1H), 7.20 (d, J=8.1 Hz, 2H), 7.23–7.29 (m, 5H), 7.78–7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.38, 21.93, 30.77, 32.64, 37.79, 60.94, 81.93, 90.39, 123.32, 127.15, 127.67, 128.02, 129.53, 131.49, 137.24, 143.19; IR (film) $\tilde{\nu}$=3269, 1489, 1320, 1149 cm^{-1}; EI-MS *m/z* (%): 339 ($(M+1)^+$, 1.31), 184 (46), 168 (100), 115 (48), 91 (67). Anal. Calcd for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13. Found: C: 71.08; H, 6.51; N: 3.80.

3.3.3. *N*-(2-Phenyl-1-ynyl-cycloheptyl)-4-methyl-benzenesulfonamide (3c). White solid; mp 71–73 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.47–2.02 (m, 10H), 2.29 (s, 3H), 2.76–2.90 (m, 1H), 3.40–3.46 (m, 1H), 5.43 (d, J=6.9 Hz, 1H), 7.12 (d, J=7.8 Hz, 2H), 7.25 (s, 5H), 7.79 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.34, 22.26, 24.49, 27.58, 29.40, 32.74, 38.19, 58.32, 82.77, 91.18, 123.28, 127.02, 127.62, 127.95, 129.43, 131.41, 137.16, 142.97; IR (film) $\tilde{\nu}$=3273, 1598, 1322, 1162 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_2S$: C, 71.90; H, 6.86; N, 3.81. Found: C, 71.99; H, 6.86; N, 3.52.

3.3.4. *N*-(2-Phenyl-1-ynyl-cyclohexyl)-benzenesulfonamide (3d).[8] White solid; mp 146–148 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.21–1.69 (m, 6H), 1.99–2.05 (m, 1H), 2.23–2.27 (m, 1H), 2.42–2.50 (m, 1H), 3.07–3.13 (m, 1H), 4.88 (d, J=5.4 Hz, 1H), 7.24–7.47 (m, 8H), 7.87–7.89 (m, 2H); IR (film) $\tilde{\nu}$=3253, 1491, 1322, 1161 cm^{-1}; EI-MS *m/z* (%): 339 (M^+, 0.59), 141 (27), 115 (29), 77 (100). Anal. Calcd for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13. Found: C: 70.56; H, 6.35; N: 3.94.

3.3.5. 1-Phenyl-4-*N*-(*p*-toluenesulfonyl)aminodecyne-1 (3e).[8] White solid; mp 63–65 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.85 (t, J=6.9 Hz, 3H), 1.17–1.29 (m, 8H), 1.52–1.62 (m, 2H), 2.41 (s, 3H), 2.50 (d, J=4.8 Hz, 2H), 3.37–3.45 (m, 1H), 4.67 (d, J=9.0 Hz, 1H), 7.26–7.38 (m, 7H), 7.78 (d, J=8.1 Hz, 2H); IR (film) $\tilde{\nu}$=3279, 1599, 1327, 1162 cm^{-1}; EI-MS *m/z* (%): 268 ($(M-115)^+$, 100), 269 (21), 155 (43), 115 (21), 91 (49). Anal. Calcd for $C_{23}H_{29}NO_2S$: C, 72.02; H, 7.62; N, 3.65. Found: C, 72.19; H, 7.64; N: 3.45.

3.3.6. 1-Phenyl-5-methyl-4-*N*-(*p*-toluenesulfonyl)aminohexyne-1 (3f). White solid; mp 101–102 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.88 (d, J=3.0 Hz, 3H), 0.90 (d, J=3.0 Hz, 3H), 1.97–2.04 (m, 1H), 2.39 (s, 3H), 2.43–2.58 (m, 2H), 3.14–3.23 (m, 1H), 4.85–4.88 (m, 1H), 7.24–7.36 (m, 7H), 7.77–7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=18.09, 19.09, 21.49, 23.36, 31.03, 57.63, 83.21, 84.95, 123.05, 127.02, 127.98, 128.19, 129.60, 131.57, 137.86, 143.27; IR (film) $\tilde{\nu}$=3298, 1599, 1315, 1163 cm^{-1}; EI-MS *m/z* (%): 341 (M^+, 0.31), 226 (100), 155 (52), 115 (22), 91 (57); HRMS: Anal. Calcd for $C_{20}H_{24}NO_2S$ (M+H): 342.1509. Found: 342.1522.

3.3.7. 1-Phenyl-5,5-dimethyl-4-*N*-(*p*-toluenesulfonyl) aminohexyne-1 (3g).[8] White solid; mp 122–124 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.98 (s, 9H), 2.28–2.36 (m, 1H), 2.39 (s, 3H), 2.49–2.56 (m, 1H), 3.16–3.23 (m, 1H), 4.89 (d, J=10.5 Hz, 1H), 7.24–7.35 (m, 7H), 7.79 (d, J=8.1 Hz, 2H); IR (film) $\tilde{\nu}$=3298, 1598, 1316, 1151 cm^{-1}; EI-MS *m/z* (%): 355 (M^+, 0.03), 240 (100), 155 (35), 115 (21), 91 (39). Anal. Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.77; H, 7.09; N: 3.87.

3.3.8. 1,4-Diphenyl-4-*N*-(*p*-toluenesulfonyl)aminobutyne-1 (3h). White solid; mp 117–119 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=2.36 (s, 3H), 2.83 (dd, J=1.5, 6.0 Hz, 2H), 4.55 (dd, J=6.6, 12.9 Hz, 1H), 5.19 (d, J=6.0 Hz, 1H), 7.14 (d, J=8.1 Hz, 2H), 7.19–7.32 (m, 10H), 7.63 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.38, 28.39, 56.27, 83.82, 84.59, 122.80, 126.51, 127.03, 127.65, 128.02, 128.11, 128.30, 129.36, 131.53, 137.09, 139.54, 143.13; IR (film) $\tilde{\nu}$=3271, 1598, 1320, 1160 cm^{-1}; EI-MS *m/z* (%): 375 (M^+, 1.04), 260 (76), 155 (48), 115 (22), 91 (100). Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.31; H, 5.65; N, 3.61.

3.3.9. 1-Phenyl-4-methyl-4-*N*-(*p*-toluenesulfonyl)aminononyne-1 (3i). White solid; mp 71–73 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.86 (t, J=6.3 Hz, 3H), 1.16–1.32 (m, 9H), 1.52–1.74 (m, 2H), 2.39 (s, 3H), 2.59 (dd, J=16.8, 19.2 Hz, 2H), 4.94 (s, 1H), 7.22–7.26 (m, 2H), 7.28–7.30 (m, 3H), 7.33–7.38 (m, 2H), 7.80 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.89, 21.32, 22.39, 23.09, 23.98, 31.78, 39.90, 58.79, 83.37, 85.58, 123.20, 126.84, 127.74, 128.05, 129.29, 131.44, 140.16, 142.72; IR (film) $\tilde{\nu}$=3277, 1598, 1323, 1158 cm^{-1}; EI-MS *m/z* (%): 268 ($(M-115)^+$, 100), 155 (41), 115 (20), 91 (58). Anal. Calcd for $C_{23}H_{29}NO_2S$: C, 72.02; H, 7.62; N, 3.65. Found: C, 71.90; H, 7.68; N, 3.38.

3.3.10. *N*-(2-Phenyl-1-ynyl-cyclohexyl)-benzoylamide (3j). White solid; mp 201–203 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.23–1.41 (m, 3H), 1.45–1.85 (m, 3H), 2.05–2.16 (m, 1H), 2.25–2.30 (m, 1H), 2.56–2.64 (m, 1H), 4.07–4.10 (m, 1H), 6.23 (d, J=7.5 Hz, 1H), 7.20–7.33 (m, 5H), 7.38–7.50 (m, 3H), 7.79 (d, J=7.2 Hz, 2H); IR (film) $\tilde{\nu}$=3307, 2937, 1613, 1551 cm^{-1}; EI-MS *m/z* (%): 303 (M^+, 2.17), 183 (11), 182 (74), 105 (100), 77 (61). Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 82.88; H, 6.91; N, 4.54.

3.3.11. *N*-(2-Acetenyl-cyclohexyl)-4-methyl-benzenesulfonamide (4a). White solid; mp 107–109 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.12–1.46 (m, 4H), 1.59–1.63 (m, 2H), 1.91–1.95 (m, 2H), 2.05–2.08 (m, 1H), 2.25–2.31 (m, 1H), 2.42 (s, 3H), 3.03–3.11 (m, 1H), 5.16 (d, J=6.0 Hz, 1H), 7.29 (d, J=7.8 Hz, 2H), 7.80 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.46, 23.45, 23.71, 30.63, 32.17, 34.92, 55.92, 70.58, 84.57, 127.22, 129.40, 137.46, 143.14; IR (film) $\tilde{\nu}$=3269, 1597, 1323, 1157 cm^{-1}; EI-MS *m/z* (%): 277 (M^+, 2.47), 155 (47), 122 (97), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found: C, 64.86; H, 6.84; N, 4.80.

3.3.12. 4-*N*-(*p*-Toluenesulfonyl)aminodecyne-1 (4e). White solid; mp 48–50 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.84 (t, J=7.2 Hz, 3H), 1.05–1.22 (m, 8H), 1.45–1.54 (m, 2H), 1.96–1.98 (m, 1H), 2.27–2.29 (m, 2H), 2.43 (s, 3H), 3.29–3.36 (m, 1H), 4.83 (d, J=8.7 Hz, 1H), 7.29 (d, J=8.1 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.99, 21.44, 22.41, 24.98, 25.35, 28.67, 31.52, 33.82, 51.70, 71.30, 79.51, 126.96, 129.56, 137.88, 143.28; IR (film) $\tilde{\nu}$=3265, 2118, 1919, 1598, 1164 cm^{-1}; EI-MS *m/z* (%): 268 ($(M-39)^+$, 95), 222 (13), 155 (100), 91 (95). Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.17; H, 8.25; N, 4.26.

3.3.13. *N*-(2-Acetenyl-cyclopentyl)-4-methyl-benzenesulfonamide (4b). ^{1}H NMR ($CDCl_3$/TMS) δ=1.37–1.46 (m, 1H), 1.61–1.71 (m, 3H), 1.92–2.01 (m, 3H), 2.43 (s, 3H), 2.52–2.59 (m, 1H), 3.47–3.56 (m, 1H), 5.32 (d, J=6.9 Hz, 1H), 7.30 (d, J=7.8 Hz, 2H), 7.80 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 21.49, 21.87, 30.53, 32.25, 37.02, 60.73, 69.83, 85.04, 127.21, 129.56, 137.21, 143.33; IR (film) $\tilde{\nu}$=3278, 1599, 1158 cm^{-1}; EI-MS *m/z* (%): 263 (M^+, 2.15), 234 (12), 155 (47), 108 (31), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.60; H, 6.52; N, 5.13.

3.3.14. *N*-(2-Acetenyl-cycloheptyl)-4-methyl-benzenesulfonamide (4c). ^{1}H NMR ($CDCl_3$/TMS) δ=1.46–1.74 (m, 9H), 1.91–1.99 (m, 2H), 2.43 (s, 3H), 2.55–2.61 (m, 1H), 3.32–3.39 (m, 1H), 5.02 (d, J=6.0 Hz, 1H), 7.29 (d, J=7.8 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.51, 22.24, 24.29, 27.46, 29.25, 32.42, 37.48, 58.17, 70.83, 85.59, 127.30, 129.48, 137.26, 143.26; IR (film) $\tilde{\nu}$=3281, 1918, 1599, 1158 cm^{-1}; EI-MS

m/z (%): 291 (M^+, 0.77), 210 (13), 155 (48), 136 (40), 91 (100). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.73; H, 7.10; N, 4.57.

3.3.15. *N*-(2-Acetenyl-cyclohexyl)-benzenesulfonamide (4d). ^{1}H NMR ($CDCl_3$/TMS) δ=1.15–1.42 (m, 4H), 1.59–1.65 (m, 2H), 1.85 (d, J=2.4 Hz, 1H), 1.90–1.96 (m, 1H), 2.07–2.11 (m, 1H), 2.23–2.29 (m, 1H), 3.05–3.11 (m, 1H), 5.11 (d, J=5.1 Hz, 1H), 7.48–7.59 (m, 3H), 7.91–7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=23.62, 23.84, 30.91, 32.56, 35.09, 56.21, 70.54, 84.47, 127.21, 128.81, 132.44, 140.48; IR (film) $\tilde{\nu}$=3264, 1585, 1156 cm^{-1}; EI-MS *m/z* (%): 263 (M^+, 1.13), 141 (46), 122 (77), 77 (100). Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.49; N, 5.28.

3.3.16. 5-Methyl-4-*N*-(*p*-toluenesulfonyl)aminohexyne-1 (4f). ^{1}H NMR ($CDCl_3$/TMS) δ=0.83 (d, J=5.1 Hz, 3H), 0.85 (d, J=5.4 Hz, 3H), 1.83–1.97 (m, 2H), 2.15–2.24 (m, 1H), 2.28–2.37 (m, 1H), 2.42 (s, 3H), 3.05–3.14 (m, 1H), 5.01 (d, J=9.3 Hz, 1H), 7.29 (d, J=8.1 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=17.87, 19.14, 21.45, 22.52, 30.57, 57.23, 71.14, 79.58, 126.97, 129.54, 137.80, 143.25; IR (film) $\tilde{\nu}$=3275, 2121, 1924, 1600, 1164 cm^{-1}; EI-MS *m/z* (%): 226 ($(M-39)^+$, 50), 222 (29), 155 (72), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.45; H, 6.96; N, 5.12.

3.3.17. 5,5-Dimethyl-4-*N*-(*p*-toluenesulfonyl)aminohexyne-1 (4g). ^{1}H NMR ($CDCl_3$/TMS) δ=0.92 (s, 9H), 1.93 (t, J=2.7 Hz, 1H), 2.07–2.16 (m, 1H), 2.24–2.32 (m, 1H), 2.43 (s, 3H), 3.08–3.14 (m, 1H), 5.11 (d, J=10.2 Hz, 1H), 7.29 (d, J=8.1 Hz, 2H), 7.79 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.24, 21.47, 26.79, 35.52, 59.22, 72.17, 80.38, 127.04, 129.48, 138.14, 143.18; IR (film) $\tilde{\nu}$=3274, 2123, 1599, 1157 cm^{-1}; EI-MS *m/z* (%): 280 ($(M+1)^+$, 0.64), 240 (29), 222 (57), 155 (86), 91 (100), 57 (12). Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.32; H, 7.31; N, 4.82.

3.3.18. 4-Phenyl-4-*N*-(*p*-toluenesulfonyl)aminobutyne-1 (4h). ^{1}H NMR ($CDCl_3$/TMS) δ=1.93 (t, J=2.7 Hz, 1H), 2.35 (s, 3H), 2.60 (dd, J=2.7, 6.0 Hz, 2H), 4.49 (dd, J=6.3, 13.8 Hz, 1H), 5.72 (d, J=7.5 Hz, 1H), 7.11–7.19 (m, 7H), 7.62 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 21.36, 27.18, 55.81, 71.88, 79.13, 126.46, 126.98, 127.62, 128.24, 129.29, 137.08, 139.07, 143.14; IR (film) $\tilde{\nu}$=3299, 1598, 1162 cm^{-1}; EI-MS *m/z* (%): 299 ($(M)^+$, 0.99), 260 (50), 155 (35), 91 (100), 77 (10). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.10; H, 5.74; N, 4.58.

3.3.19. 4-Methyl -4-*N*-(*p*-toluenesulfonyl)aminononyne-1 (4i). ^{1}H NMR ($CDCl_3$/TMS) δ=0.83 (t, J=6.9 Hz, 3H), 1.11–1.28 (m, 6H), 1.20 (s, 3H), 1.47–1.64 (m, 2H), 2.01–2.04 (m, 1H), 2.40–2.42 (m, 2H), 2.41 (s, 3H), 5.09 (s, 1H), 7.27 (d, J=7.8 Hz, 2H), 7.79 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.91, 21.40, 22.41, 23.07, 23.65, 31.03, 31.76, 39.60, 58.31, 71.50, 80.05, 126.95, 129.36, 140.06, 142.91; IR (film) $\tilde{\nu}$=3280, 2121, 1600, 1159 cm^{-1}; EI-MS *m/z* (%): 307 (M^+, 0.09), 268 (84), 236 (25), 155 (65), 91 (100). Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.02; H, 7.99; N, 4.27.

3.3.20. 4-*N*-(*p*-Toluenesulfonyl)aminoicosyne-1 (4m). ^{1}H NMR ($CDCl_3$/TMS) δ=0.88 (t, J=6.3 Hz, 3H), 1.13–1.30 (m, 28H), 1.45–1.54 (m, 2H), 1.96 (t, J=2.7 Hz, 1H), 2.27–2.29 (m, 2H), 2.42 (s, 3H), 3.29–3.36 (m, 1H), 4.85 (d, J= 9.0 Hz, 1H), 7.29 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H); IR (film) $\tilde{\nu}$=3275, 1599, 1171 cm^{-1}; EI-MS *m/z* (%): 408 ($(M-39)^+$, 39), 155 (55), 91 (100). Anal. Calcd for $C_{27}H_{45}NO_2S$: C, 72.43; H, 10.13; N, 3.13. Found: C, 72.34; H, 10.06; N, 2.95.

3.3.21. Reaction of aziridine 1e with hexyne 2d in the presence of ^{t}BuOK. To a stirred solution of ^{t}BuOK (0.375 mmol) in DMSO (2.0 mL) was added 1-hexyne **2d** (0.375 mmol) and aziridine **1e** (0.25 mmol) successively under argon. The reaction mixture was stirred at room temperature till complete consumption of substrate (monitored by TLC). After work-up as described above, the product **5**[11] was obtained as white solid. Yield: 54%; mp 44–46 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.85 (t, J=6.6 Hz, 3H), 1.05 (s, 9H), 1.09–1.26 (m, 8H), 1.42–1.47 (m, 2H), 2.42 (s, 3H), 3.08–3.26 (m, 3H), 4.88 (d, J=8.4 Hz, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.76 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.02, 21.41, 22.47, 25.52, 27.25, 28.95, 31.63, 32.49, 53.84, 62.52, 72.81, 127.05, 129.42, 138.22, 142.98; IR (film) $\tilde{\nu}$=3272, 1599, 1331, 1164 cm^{-1}; EI-MS *m/z* (%): 268 ($(M-87)^+$, 100), 155 (38), 91 (38), 57 (12).

3.4. General procedure for the synthesis of dihydropyrroles 6 from homopropargylamines 3

The homopropargylic sulfonamide **3** (0.15 mmol) was stirred in dry acetonitrile (2 mL) with anhydrous potassium carbonate (0.45 mmol) and silver acetate (0.45 mmol) at 0 °C. Iodine (0.45 mmol) was added and the resulting mixture allowed to warm to room temperature. The reaction mixture was stirred at room temperature till complete consumption of substrate (monitored by TLC). The reaction was quenched with saturated aqueous sodium thiosulfate until the mixture was decolorized and the organic layer was separated. The aqueous layer was then extracted with dichloromethane (3×10 mL) and the organic solutions were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel.

3.4.1. *trans*-*N*-Tosyl-3-phenyl-4-iodo-2-azabicyclo[4.3.0] non-3-ene (6a). White solid; mp 152–154 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=1.06–1.29 (m, 3H), 1.77–1.93 (m, 4H), 2.31–2.41 (m, 1H), 2.42 (s, 3H), 2.73–2.79 (m, 1H), 3.04–3.13 (m, 1H), 7.21–7.37 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.59, 25.42, 25.76, 31.32, 31.77, 54.18, 71.04, 87.14, 127.34, 128.13, 128.72, 129.29, 130.11, 132.93, 133.86, 143.93, 146.18; IR (film) $\tilde{\nu}$=1596, 1358, 1174 cm^{-1}; EI-MS *m/z* (%): 479 (M^+, 28), 197 (95), 169 (63), 91 (100). Anal. Calcd for $C_{21}H_{22}INO_2S$: C, 52.62; H, 4.63; N, 2.92. Found: C, 52.70; H, 4.64; N, 2.78.

3.4.2. 2-Phenyl-3-iodo-5-hexyl-1-(4-tolylsulfonyl)-2,3-dihydropyrrole (6e). White solid; mp 91–92 °C; ^{1}H NMR

($CDCl_3$/TMS) δ=0.91 (t, J=6.6 Hz, 3H), 1.25–1.48 (m, 6H), 1.52–1.62 (m, 3H), 1.74–1.81 (m, 1H), 2.15 (dd, J=1.5, 16.2 Hz, 1H), 2.42 (s, 3H), 2.47 (dd, J=8.7, 16.5 Hz, 1H), 4.18–4.26 (m, 1H), 7.26–7.29 (m, 2H), 7.38–7.43 (m, 3H), 7.53–7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.11, 21.66, 22.61, 24.75, 29.16, 31.74, 36.26, 46.18, 62.66, 79.83, 127.63, 127.66, 128.99, 129.49, 129.52, 132.77, 134.29, 143.00, 143.95; IR (film) $\tilde{\nu}$=1596, 1353, 1166 cm^{-1}; EI-MS m/z (%): 509 (M^+, 59), 354 (65), 298 (32), 156 (71), 91 (100). Anal. Calcd for $C_{23}H_{28}INO2S$: C, 54.22; H, 5.54; N, 2.75. Found: C, 54.34; H, 5.70; N, 2.81.

3.4.3. 2,5-Diphenyl-3-iodo-1-(4-tolylsulfonyl)-2,3-dihydropyrrole (6h). White solid; mp 124–125 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=2.46 (s, 3H), 2.66 (dd, J=2.4, 16.8 Hz, 1H), 3.01 (dd, J=9.6, 16.8 Hz, 1H), 5.34 (dd, J=2.4, 9.3 Hz, 1H), 7.26–7.44 (m, 8H), 7.51–7.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.63, 48.32, 64.34, 77.99, 125.82, 127.64, 127.68, 127.88, 128.84, 129.13, 129.53, 129.67, 132.19, 134.42, 142.26, 143.62, 144.09; IR (film) $\tilde{\nu}$=1597, 1356, 1168 cm^{-1}; EI-MS m/z (%): 502 ((M+1)$^+$, 88), 346 (78), 219 (100), 218 (96), 116 (93), 91 (62). Anal. Calcd for $C_{23}H_{20}INO_2SNa$ (M+Na): 524.0152. Found: 524.0157.

3.4.4. 2-Phenyl-3-iodo-5-butyl-1-(4-tolylsulfonyl)-2,3-dihydropyrrole (6n). White solid; mp 116–117 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=0.95 (t, J=6.6 Hz, 3H), 1.36–1.62 (m, 5H), 1.73–1.82 (m, 1H), 2.13 (dd, J=1.2, 16.2 Hz, 1H), 2.43 (s, 3H), 2.48 (t, J=8.4 Hz, 1H), 4.19–4.26 (m, 1H), 7.26 (d, J=8.4 Hz, 2H), 7.38–7.41 (m, 3H), 7.53–7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.05, 21.60, 22.54, 26.90, 35.89, 46.17, 62.58, 79.82, 121.58, 127.62, 128.95, 129.45, 129.49, 132.74, 134.25, 142.95, 143.92; IR (film) $\tilde{\nu}$=1597, 1355, 1168 cm^{-1}; EI-MS m/z (%): 482 ((M+1)$^+$, 31.7), 326 (68), 156 (58), 115 (67), 91 (100). Anal. Calcd for $C_{21}H_{24}INO_2S$: C, 52.39; H, 5.03; N, 2.91. Found: C, 52.45; H, 5.16; N, 2.69.

3.4.5. 2-Butyl-3-iodo-5-hexyl-1-(4-tolylsulfonyl)-2,3-dihydropyrrole (6o). Liquid; ^{1}H NMR ($CDCl_3$/TMS) δ=0.87 (t, J=6.9 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H), 1.28–1.75 (m, 14H), 1.89–1.94 (m, 1H), 2.18–2.27 (m, 1H), 2.43 (s, 3H), 2.46–2.56 (m, 1H), 2.77–2.87 (m, 1H), 3.97–4.03 (m, 1H), 7.28 (d, J=7.8 Hz, 2H), 7.60 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.91, 14.06, 21.58, 22.07, 22.54, 24.62, 29.06, 29.38, 29.97, 31.66, 36.13, 44.05, 62.56, 79.16, 127.19, 129.56, 134.46, 143.75, 144.86; IR (film) $\tilde{\nu}$=1598, 1353, 1167 cm^{-1}; EI-MS m/z (%): 489 (M^+, 33), 362 (69), 334 (41), 256 (44), 91 (100). Anal. Calcd for $C_{20}H_{20}INO_2S$: C, 51.53; H, 6.59; N, 2.86. Found: C, 51.34; H, 6.55; N, 2.75.

3.4.6. 2-Phenyl-3-iodo-5-benzyl-1-(4-tolylsulfonyl)-2,3-dihydropyrrole (6p). White solid; mp 93–94 °C; ^{1}H NMR ($CDCl_3$/TMS) δ=2.33 (dd, J=2.4, 16.8 Hz, 1H), 2.42 (s, 3H), 2.45 (dd, J=8.7, 16.5 Hz, 1H), 2.92 (dd, J=9.3, 13.5 Hz, 1H), 3.23 (dd, J=5.4, 13.5 Hz, 1H), 4.52–4.55 (m, 1H), 7.21–7.39 (m, 10H), 7.43–7.47 (m, 2H), 7.51–7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.56, 42.01, 44.78, 63.28, 78.64, 126.75, 127.52, 127.56, 128.49, 128.99, 129.44, 129.64, 132.31, 134.36, 136.55, 142.96, 143.91; IR (film) $\tilde{\nu}$=1595, 1491, 1352 cm^{-1}; EI-MS m/z (%): 515 (M^+, 11), 424 (47), 297 (54), 91 (100). Anal. Calcd for $C_{24}H_{22}INO_2S$: C, 55.93; H, 4.30; N, 2.72. Found: C, 55.75; H, 4.36; N, 2.80.

3.5. One-pot preparation of dihydropyrrole 6a from reaction of aziridine 1a with phenylacetylene 2a and iodo-cyclization

To a stirred solution of NaH (0.50 mmol) and 4 Å molecular sieves in DMSO (2.0 mL) was added phenylacetylene **2a** (0.375 mmol) and aziridine **1a** (0.25 mmol) successively under argon. The reaction mixture was stirred at room temperature for 2 h. Then silver acetate (0.30 mmol) and Iodine (0.75 mmol) was added. The reaction mixture was warmed to 40 °C and stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous sodium thiosulfate until the mixture was decolorized and the organic layer was separated. The aqueous layer was then extracted with dichloromethane (3×10 mL) and the organic solutions were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel to provide product **6a**.

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A mild and efficient aza-Diels–Alder reaction of *N*-benzhydryl imines with *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene catalyzed by $Yb(OTf)_3$

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Abstract—The aza-Diels–Alder reaction of *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene with *N*-benzhydryl imines in the presence of $Yb(OTf)_3$ in toluene at room temperature gave the corresponding 2,5-disubstituted 2,3-dihydro-4-pyridones in high yields. This reaction can also be carried out with diene, aldehydes, and amine in a three-component one-pot reaction manner in moderate to high yields under solvent-free conditions. The relationship between Lewis acids and activity, solvents and catalyst loading were studied. Some investigation towards the reaction mechanism was discussed.

1. Introduction

Six-membered nitrogen heterocycles such as piperidines and tetrahydroquinolines[1] are important units in medicinal chemistry and useful intermediates in organic synthesis.[2] Aza-Diels–Alder (ADA) reaction as one of the most powerful methodologies for the construction of these types of structures has attracted more and more attention. Recent advances have been made in a number of Lewis acid-catalyzed aza-Diels–Alder reactions in organic solvents[3–6] and aqueous media.[7] Kobayashi and co-workers carried out the reaction using Danishefsky's diene with imines catalyzed by AgOTf[7a] or alkaline salt[7b] in water with high yields. Ding et al. reported a highly efficient aza-Diels–Alder reaction in methanol under Lewis acid-free conditions.[6] Meanwhile, they found that the reaction proceeded through a Mannich-type condensation mechanism. Whiting and co-workers reported *N*-phosphoryl functions were suitable imine substituents for $Cu(OTf)_2$ catalyzed aza-Diels–Alder reaction with oxygenated dienes.[3f] Since Yamamoto firstly developed an enantioselective aza-Diels–Alder reaction of aldimines with Danishefsky's diene using a stoichiometric amount of a chiral boron complex,[8] asymmetric version of this transformation have also been reported. The first catalytic enantioselective aza-Diels–Alder reaction with chiral zirconium–binaphthol complexes as the catalysts was elegantly achieved by Kobayashi et al.[9] Jørgensen's group performed this reaction successfully using copper complexes of Binap and phosphino–oxaolines.[10] Snapper and Hoveyda disclosed an efficient Ag-catalyzed asymmetric addition of Danishefsky's diene to aryl imines to afford cycloadducts using low catalyst loading in excellent yields and enantioselectivities.[11] Carretero's group applied novel copper(I) Lewis acid catalysts to carry out this reaction between *N*-sulfonyl aldimines and Danishefsky's type dienes.[12] Recently, Whiting et al. had shown that Binol–zinc complex could efficiently catalyze the reaction of an electron-deficient imine with an electron-rich oxygenated diene in good enantioselectivities.[13] To the best of our knowledge, most of these works were performed using electron-deficient imines as dienophiles, but no report on *N*-benzhydryl imines has been reported.

Recently, we have reported our preliminary studies on a highly efficient aza-Diels–Alder reaction of *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene with *N*-benzhydryl imines catalyzed by $Yb(OTf)_3$.[14] Herein, we described the results of our studies of relationships between Lewis acids and activity, substrate generality.

2. Results and discussion

2.1. Optimization of the catalyst

In preliminary trials, various Lewis acids such as $ZnCl_2$,

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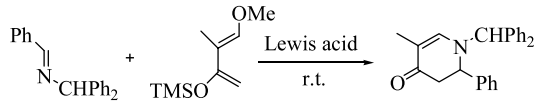
Table 1. Aza-Diels–Alder reaction of diene **2** with imine **1a** catalyzed by Lewis acids



1a **2** (2.0 equiv) **3a**

Entry[a]	Lewis acid	Catalyst loading (mol%)	Time (h)	Solvent	Yield (%)[b]
1	$TiCl_4$	50	48	CH_2Cl_2	18
2	$ZnCl_2$	20	48	CH_2Cl_2	16
3	NaI	40	48	THF	31
4	Me_4NI	20	48	THF	24
5	$NaBPh_4$	20	48	THF	27
6	$AgNO_3$	20	48	THF	24
7	AgOAc	20	48	THF	19
8	$AgBF_4$	20	48	THF	22
9	LiOTf	20	24	THF	36
10	$Cu(OTf)_2$	20	24	THF	45
11	$Sc(OTf)_3$	20	24	THF	60
12	$Zn(OTf)_2$	20	24	THF	62
13	$Yb(OTf)_3$	20	24	THF	70
14	—	—	24	Methanol	NR

[a] All reactions were performed with concentration of imine 0.125 M.
[b] Isolated yield.

$TiCl_4$ or metal triflates, and alkaline salts were tested as catalysts for the ADA reaction of diene **2** and *N*-benzhydryl imine **1a**. The initial attempts revealed that $Yb(OTf)_3$ exhibited a more promising catalytic capability than the others (Table 1, entry 13). The reaction with $TiCl_4$ or $ZnCl_2$ was sluggish and gave the desired product **3a** in poor yields (Table 1, entries 1–2).

Silver catalysts and alkaline salts had little catalytic activities in the reaction (Table 1, entries 3–8). Under Lewis acid-free conditions, the ADA reaction did not happen at all (Table 1, entry 14). Initiated by the results, the performances of $Yb(OTf)_3$ under varying conditions of different solvent, catalyst loading, and the concentration of imine were investigated. The reaction in THF, CH_2Cl_2, and Et_2O gave the product in good yields with 70, 71, and 81%, respectively (Table 2, entries 1–3), whilst toluene showed a strong solvent effect in which an excellent yield was obtained (Table 2, entry 4). Attempt to carry out the reaction in H_2O gave no product at all (Table 4, entry 5). The amount of catalyst loading also has a dramatic impact on the yield of this reaction. With the catalyst loading decreased from 20 to 2 mol%, the yield dropped sharply from 92 to 44% (Table 2, entries 4, 6–8). Further studies indicated that the concentration of imine had a strong impact on the rate of the ADA reaction. When the concentration of imine was 0.125 M, the reaction gave the desired product in 92% yield in 24 h. Further increasing the concentration to 0.625 M led to a little higher yield and the reaction time shortened greatly from 24 to 6 h (Table 2, entry 10). In summary, the extensive screening showed the optimal conditions of the ADA reaction was 20% $Yb(OTf)_3$ in 0.2 mL toluene at room temperature for 6 h.

2.2. Substrate generality

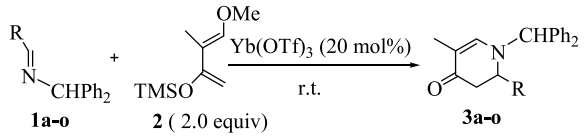
Encouraged by the results obtained from *N*-benzhydryl imine **1a**, a range of imines was investigated to probe their behavior under the optimized conditions (Table 3). It should be noted that the aldimines with electron-withdrawing groups gave lower yields compared those with the electron-donating ones generally. When the substituted groups of aromatic rings change from F, Cl, CH_3 to OCH_3, the reactivity was increased (Table 3, entries 11, 10, 4, and 7). However, 3,4-methylenedioxy-substituted imine **1l** only gave moderate yield (Table 3, entry 12). Interestingly, unsubstituted aldimine **1a** gave the best result with 94% yield in contrast with substituted ones (Table 3, entry 1). These could be attributed to the steric effect. Moreover, the results from Table 3 suggested that there was a negative

Table 2. Effects of solvents, catalyst loading, and concentration for imine on the ADA reaction

Entry[a]	Catalyst loading [mol%]	Time (h)	Solvent	Concn of imine (M)	Yield (%)[b]
1	20	24	THF	0.125	70
2	20	24	CH_2Cl_2	0.125	71
3	20	24	Et_2O	0.125	81
4	20	24	Toluene	0.125	92
5	20	24	H_2O	—	NR
6	10	24	Toluene	0.125	60
7	5	24	Toluene	0.125	49
8	2	24	Toluene	0.125	44
9	20	6	Toluene	0.25	83
10	20	6	Toluene	0.625	94

[a] All reactions were performed at room temperature.
[b] Isolated yield.

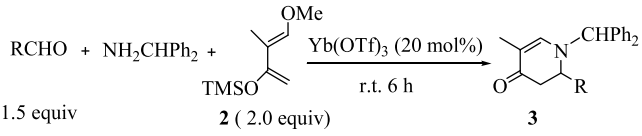
Table 3. $Yb(OTf)_3$-catalyzed ADA reaction of diene **2** with imine **1**



Entry[a]	R	Product	Yield (%)[b]
1	C_6H_5	**3a**	94
2	2-MeC_6H_4	**3b**	78
3	3-MeC_6H_4	**3c**	81
4	4-MeC_6H_4	**3d**	80
5	2-$MeOC_6H_4$	**3e**	84
6	3-$MeOC_6H_4$	**3f**	79
7	4-$MeOC_6H_4$	**3g**	90
8	2-ClC_6H_4	**3h**	76
9	3-ClC_6H_4	**3i**	69
10	4-ClC_6H_4	**3j**	76
11	4-FC_6H_4	**3k**	70
12	Piperonyl	**3l**	53
13	2-Furyl	**3m**	84
14	2-Pyridyl	**3n**	99
15	PhCH=CH	**3o**	62

[a] All reactions were performed in toluene for 6 h with concentration of imines 0.125 M.
[b] Isolated yield.

Table 4. Three-component ADA reaction under solvent-free conditions



Entry	R	Product	Yield (%)[a]
1	C_6H_5	**3a**	77
2	C_6H_5	**3a**	67[b]
3	2-MeC_6H_4	**3b**	83
4	3-MeC_6H_4	**3c**	79
5	4-MeC_6H_4	**3d**	72
6	2-$MeOC_6H_4$	**3e**	78
7	3-$MeOC_6H_4$	**3f**	78
8	4-$MeOC_6H_4$	**3g**	74
9	2-ClC_6H_4	**3h**	76
10	3-ClC_6H_4	**3i**	68
11	4-FC_6H_4	**3k**	52
12	2-Furyl	**3m**	78
13	2-Pyridyl	**3n**	75
14	PhCH=CH	**3o**	62
15	*c*-C_6H_{11}	**3p**	86
16	$(CH_3)_2CH$	**3q**	54
17	$CH_3CH_2CH_2$	**3r**	51

[a] Isolated yield.
[b] Carried out in toluene.

meta-substitution effect on reaction activity. Heteroaromatic aldimines **1m** and **1n** with no substitution, afforded the desired products **3m**, **3n** in high yields, 84 and 99%, respectively (Table 3, entries 13 and 14). This could be interesting in the synthesis of some biologically important compounds. The α,β-unsaturated aldimine also worked well, giving cycloadduct in good yield (Table 3, entry 15).

To the best of our knowledge, imines particularly those derived from aliphatic aldehydes are not always stable. So it is synthetically interesting to construct ADA products in a three-component one-pot reaction manner especially for aliphatic aldimines, in which the aldimines were prepared in situ and reacted with diene. Accordingly, the aldehyde was first allowed to react with amine, and diene **2** was introduced successively. Primary experimental results proved that the ADA reactions gave higher yield under solvent-free conditions than that in toluene (Table 4, entry 1 vs 2). The three components condensation reactions were carried out to afford the corresponding 2,5-disubstituted 2,3-dihydro-4-pyridones in moderate to high yields under solvent-free conditions as shown in Table 4. It was obvious that the yields of three-component ADA reaction were slightly lower than those obtained by the reaction of isolated aldimine. This efficient catalyst system is suitable for a wide range of aromatic, aliphatic, heteroaromatic, and olefininc aldehydes. Furthermore, aliphatic aldehydes successfully react with amines and diene **2** to afford corresponding pyridones (Table 4, entries 15–17), which could not be obtained in the stepwise system above. Particularly, sterically bulky cyclohexanal gave the desired product **3p** in 86% yield (Table 4, entry 15), which indicated a steric acceleration may be existed compared with normal aliphatic aldehydes.

2.3. Mechanism studies

Two mechanistic pathways, which have generally considered for Lewis acid-catalyzed ADA reaction were formulated as Mukaiyama aldol reaction pathway (stepwise mechanism) and Diels–Alder [4+2] cycloaddition pathway (concerted mechanism).[15] To clarify whether the reaction process through stepwise mechanism or concerted one, we carried out two parallel reactions of imine **1a** with the same optimal conditions above. These two reactions were monitored with Et_3N-treated TLC during the reaction process and only one product with the same R_f was found from the two reaction. After 6 h, one reaction was quenched with 1 M HCl and extracted with CH_2Cl_2. The product was isolated by silica gel column chromatography. The crude material of another reaction was purified directly by Et_3N-treated silica gel column chromatography at the end of reaction without the treatment with 1 M HCl. Interestingly, the cycloadduct product from these two reaction was identical (**3a**), as identified by ^1H NMR and ^{13}C NMR. At the same time, no Mannich-type condensation adduct was detected according to the ^1H NMR spectrum of the crude product. Even though, it was difficult to determine the reaction mechanism by these simple results obtained. Further mechanistic studies were underway in our laboratory.

3. Conclusion

In summary, the aza-Diels–Alder reactions of *trans*-methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene with *N*-benzhydryl imines in the presence of a catalytic amount of $Yb(OTf)_3$ proceed efficiently in toluene at room temperature to give the corresponding dihydro-4-pyridones in 53–99% yields. Three-component reactions of aldehydes, amines, and the diene were also conducted under solvent-free conditions in 51–88% yields. The mild experimental conditions, short reaction time, and the wide substrate generality represented the notable features of this procedure.

4. Experimental

4.1. General remarks

^{1}H NMR spectra were recorded on a Bruker (600 MHz) spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26). Data were reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants (Hz), integration. ^{13}C NMR spectroscopic data were collected on a Bruker (150 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm relative to tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ 77.0 ppm). HRMS was recorded on a BRUKER-APEX-2. Solvents were purified by the usual methods. CH_2Cl_2 was distilled over CaH_2. Other solvents were dried over Na. Diene **2** and imines were prepared according to literature procedures. All aldehydes and benzhydrylamine were purchased from Acros, Aldrich or Fluka. Liquid aldehydes were distilled in vacuo prior to use, and solid aldehydes were used directly without further purification. $Yb(OTf)_3$ and other Lewis acids were also purchased from Acros, Aldrich or Fluka.

4.2. Procedure for the aza-Diels–Alder reaction of diene 2 with imines

All reactions were carried out using anhydrous toluene and under nitrogen in over-dried tubes. Ytterbium triflate (15.5 mg, 0.025 mmol) and *N*-benzhydryl imine **1a** (33.9 mg, 0.125 mmol) were placed in tube. Toluene (0.2 mL) and diene **2** (56 μL, 0.25 mmol) were then added successively. After stirring for 6 h at room temperature, the reaction was quenched with 0.5 mL of 1.0 M HCl. The mixture was extracted with dichloromethane and concentrated. The crude material was purified by flash chromatography to give the cycloadduct **3a** as white crystal.

4.3. One-pot procedure for the three-component aza-Diels–Alder reaction without solvent

$Yb(OTf)_3$ (15.5 mg, 0.025 mmol) was placed in tube. Benzaldehyde (19 μL, 0.1875 mmol) and benzhydrylamine (22 μL, 0.125 mmol) were sequentially introduced, then diene **2** (56 μL, 0.25 mmol) was added. After stirring for 6 h, the reaction was quenched with 0.5 mL of 1.0 M HCl. The mixture was extracted with dichloromethane and concentrated. The crude material was purified by flash chromatography to give the cycloadduct **3a**.

4.3.1. 1-Benzhydryl-5-methyl-2-phenyl-2,3-dihydro-4-1*H*-pyridone (3a). The title compound was obtained as white crystal (mp = 120–121 °C) in 94% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33–6.98 (m, 15H, Ph-H), 6.91 (s, 1H, =CH), 5.29 (s, 1H, –$CHPh_2$), 4.41 (m, 1H, N–CHPh), 2.73 (m, 2H, –CH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.5, 149.6, 139.4, 138.9, 138.4, 129.5, 129.1, 129.0, 128.8, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 127.3, 106.4, 67.5, 66.0, 62.8, 44.1, 13.1; HRMS (ESI): calcd for $C_{25}H_{23}NO$ $[M+Na]^+$ 376.1672, found 376.1671.

4.3.2. 1-Benzhydryl-5-methyl-2-(2-methylphenyl)-2,3-dihydro-4-1*H*-pyridone (3b). The title compound was obtained as white solid (mp = 120–122 °C) in 78% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66–7.04 (m, 14H, Ph-H), 7.08 (s, 1H, =CH), 5.40 (s, 1H, –$CHPh_2$), 4.74 (m, 1H, N–CHPh), 2.80 (dd, J = 12.96, 16.56 Hz, 1H, CH_AH_B), 2.67 (dd, J = 6.06, 16.56 Hz, 1H, CH_AH_B), 1.85 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.7, 150.5, 138.9, 138.0, 137.2, 135.9, 131.2, 129.5, 129.0, 128.8, 128.1, 128.1, 128.0, 128.0, 126.9, 126.7, 106.6, 67.1, 58.8, 43.5, 18.7, 13.2; HRMS (ESI): calcd for $C_{26}H_{25}NO$ $[M+Na]^+$ 390.1828, found 390.1838.

4.3.3. 1-Benzhydryl-5-methyl-2-(3-methylphenyl)-2,3-dihydro-4-1*H*-pyridone (3c). The title compound was obtained as yellow solid (mp = 74–76 °C) in 81% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33–6.99 (m, 14H, Ph-H), 6.90 (s, 1H, =CH), 5.29 (s, 1H, –$CHPh_2$), 4.38 (m, 1H, N–CHPh), 2.72 (m, 2H, –CH_2), 2.28 (s, 3H, CH_3), 1.59 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.6, 149.6, 139.2, 138.9, 138.8, 138.5, 129.5, 129.1, 129.0, 128.9, 128.8, 128.2, 128.1, 128.1, 127.9, 124.4, 106.3, 67.4, 62.9, 44.1, 21.5, 13.1; HRMS (ESI): calcd for $C_{25}H_{23}NO$ $[M+Na]^+$ 390.1828, found 390.1849.

4.3.4. 1-Benzhydryl-5-methyl-2-(4-methylphenyl)-2,3-dihydro-4-1*H*-pyridone (3d). The title compound was obtained as white solid (mp = 130–132 °C) in 80% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7.08 (m, 14H, Ph-H), 7.00 (s, 1H, =CH), 5.39 (s, 1H, –$CHPh_2$), 4.47 (m, 1H, N–CHPh), 2.84 (dd, J = 11.40, 16.62 Hz, 1H, CH_AH_B), 2.77 (dd, J = 6.42, 16.44 Hz, 1H, CH_AH_B), 2.40 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.7, 149.7, 139.0, 138.4, 138.2, 136.3, 129.8, 129.5, 128.9, 128.8, 128.1, 128.0, 127.9, 127.3, 106.3, 67.2, 62.6, 44.2, 21.2, 13.1; HRMS (ESI): calcd for $C_{26}H_{25}NO$ $[M+H]^+$ 368.2009, found 369.2040.

4.3.5. 1-Benzhydryl-5-methyl-2-(2-methoxyphenyl)-2,3-dihydro-4-1*H*-pyridone (3e). The title compound was obtained as yellow solid (mp = 136–138 °C) in 84% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–6.90 (m, 14H, Ph-H), 6.96 (s, 1H, =CH), 5.36 (s, 1H, –$CHPh_2$), 4.43 (m, 1H, N–CHPh), 3.83 (s, 1H, OCH_3), 2.81 (dd, J = 11.52, 16.50 Hz, 1H, CH_AH_B), 2.73 (dd, J = 6.24, 16.50 Hz, 1H, CH_AH_B), 1.66 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.8, 159.6, 149.7, 139.1, 138.4, 131.2, 129.4, 128.9, 128.8, 128.7, 128.1, 128.0, 127.9, 114.4, 106.3, 67.1, 62.3, 55.3, 44.3, 13.1; HRMS (ESI): calcd for $C_{26}H_{25}NO_2$ $[M+H]^+$ 384.1958, found 384.1950.

4.3.6. 1-Benzhydryl-5-methyl-2-(3-methoxyphenyl)-2,3-dihydro-4-1*H*-pyridone (3f). The title compound was obtained as orange solid (mp = 96 °C) in 79% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–6.74 (m, 14H, Ph-H), 6.90 (s, 1H, =CH), 5.32 (s, 1H, –$CHPh_2$), 4.39 (m, 1H, N–CHPh), 3.70 (s, 1H, OCH_3), 2.73 (m, 2H, –CH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.5, 160.0, 149.6, 140.9, 138.9, 138.5, 130.2, 129.5, 128.9, 128.8, 128.1, 128.1, 127.9, 127.3, 119.6, 113.7, 113.0, 106.5, 67.5, 62.9, 55.2, 44.1, 13.1; HRMS (ESI): calcd for $C_{26}H_{25}NO_2$ $[M+H]^+$ 384.1958, found 384.1950.

4.3.7. 1-Benzhydryl-5-methyl-2-(4-methoxyphenyl)-2,3-dihydro-4-1*H*-pyridone (3g). The title compound was obtained as white solid (mp = 136–138 °C) in 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–6.90 (m, 14H, Ph-H), 6.96 (s, 1H, =CH), 5.36 (s, 1H, –$CHPh_2$), 4.43 (m, 1H, N–CHPh), 3.83 (s, 1H, OCH_3), 2.81 (dd, J = 11.40, 16.50 Hz, 1H, CH_AH$_B$), 2.73 (dd, J = 6.24, 16.50 Hz, 1H, CH$_A$$H_B$), 1.66 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.8, 159.6, 149.7, 139.1, 138.4, 131.2, 129.4, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 127.9, 127.4, 127.3, 114.4, 106.3, 67.1, 62.3, 55.3, 44.3, 13.1; HRMS (ESI): calcd for $C_{26}H_{25}NO_2$ $[M+H]^+$ 384.1958, found 384.1956.

4.3.8. 1-Benzhydryl-5-methyl-2-(2-chlorophenyl)-2,3-dihydro-4-1*H*-pyridone (3h). The title compound was obtained as yellow solid (mp = 126–128 °C) in 76% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7.01 (m, 14H, Ph-H), 6.95 (s, 1H, =CH), 5.31 (s, 1H, –$CHPh_2$), 4.95 (m, 1H, N–CHPh), 2.85 (dd, J = 7.56, 16.80 Hz, 1H, CH_AH$_B$), 2.68 (dd, J = 7.56, 16.80 Hz, 1H, CH$_A$$H_B$), 1.59 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.8, 149.4, 138.5, 138.5, 136.4, 133.1, 130.4, 129.5, 129.4, 129.0, 128.9, 128.3, 128.2, 127.8, 127.4, 106.0, 68.7, 58.8, 41.6, 13.1; HRMS (ESI): calcd for $C_{25}H_{22}ClNO$ $[M+H]^+$ 388.1463, found 388.1459.

4.3.9. 1-Benzhydryl-5-methyl-2-(3-chlorophenyl)-2,3-dihydro-4-1*H*-pyridone (3i). The title compound was obtained as yellow solid (mp = 98–100 °C) in 69% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.07 (m, 14H, Ph-H), 6.97 (s, 1H, =CH), 5.35 (s, 1H, –$CHPh_2$), 4.47 (m, 1H, N–CHPh), 2.84 (dd, J = 6.66, 16.44 Hz, 1H, CH_AH$_B$), 2.75 (dd, J = 9.78, 16.62 Hz, 1H, CH$_A$$H_B$), 1.66 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.8, 149.2, 141.5, 138.5, 138.3, 134.9, 130.4, 129.5, 129.0, 128.9, 128.6, 128.3, 128.3, 127.8, 127.5, 125.4, 106.6, 68.1, 62.1, 43.7, 13.1; HRMS (ESI): calcd for $C_{25}H_{22}ClNO$ $[M+H]^+$ 388.1463, found 388.1456.

4.3.10. 1-Benzhydryl-5-methyl-2-(4-chlorophenyl)-2,3-dihydro-4-1*H*-pyridone (3j). The title compound was obtained as yellow solid (mp = 146–148 °C) in 76% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.07 (m, 14H, Ph-H), 6.99 (s, 1H, =CH), 5.35 (s, 1H, –$CHPh_2$), 4.49 (m, 1H, N–CHPh), 2.79 (m, 2H, CH_2), 1.68 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.1, 149.3, 138.6, 138.2, 137.9, 134.2, 129.4, 129.3, 129.0, 128.9, 128.7, 128.3, 128.2, 127.8 106.7, 67.8, 62.1, 44.0, 13.1; HRMS (ESI): calcd for $C_{25}H_{22}ClNO$ $[M+H]^+$ 388.1463, found 388.1456.

4.3.11. 1-Benzhydryl-5-methyl-2-(4-fluorophenyl)-2,3-dihydro-4-1*H*-pyridone (3k). The title compound was obtained as yellow solid (mp = 126 °C) in 70% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.04 (m, 14H, Ph-H), 6.97 (s, 1H, =CH), 5.33 (s, 1H, –$CHPh_2$), 4.48 (m, 1H, N–CHPh), 2.77 (m, 2H, CH_2), 1.66 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.2, 163.4, 161.7, 149.4, 138.7, 138.3, 135.1, 129.4, 129.0, 128.9, 128.9, 128.2, 128.2, 127.8, 116.1, 116.0, 106.5, 67.6, 62.1, 44.1, 13.1; HRMS (ESI): calcd for $C_{25}H_{22}FNO$ $[M+H]^+$ 372.1758, found 372.1756.

4.3.12. 1-Benzhydryl-5-methyl-2-(3,4-methylenedioxyphenyl)-2,3-dihydro-4-1*H*-pyridone (3l). The title compound was obtained as yellow solid (mp = 104–106 °C) in 53% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.05 (m, 10H, Ph-H), 6.96 (s, 1H, =CH), 6.87 (s, 1H, =CH), 6.77 (d, J = 7.92 Hz, 1H, =CH), 6.64 (d, J = 7.68 Hz, 1H, =CH), 6.00 (d, J = 4.62 Hz, 2H, OCH_2O), 5.40 (s, 1H, –$CHPh_2$), 4.39 (m, 1H, N–CHPh), 2.75 (m, 2H, CH_2), 1.66 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.6, 149.6, 148.3, 147.7, 138.9, 138.4, 133.2, 129.4, 128.9, 128.8, 128.1, 128.1, 127.9, 121.2, 108.6, 107.2, 106.4, 101.3, 67.2, 62.6, 44.3, 13.1; HRMS (ESI): calcd for $C_{26}H_{23}NO_3$ $[M+H]^+$ 398.1751, found 398.1744.

4.3.13. 1-Benzhydryl-5-methyl-2-(2-furyl)-2,3-dihydro-4-1*H*-pyridone (3m). The title compound was obtained as brown solid (mp = 74–76 °C) in 84% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (d, J = 1.02 Hz, 1H, =CH–O), 7.46–7.08 (m, 10H, Ph-H), 6.76 (s, 1H, =CH), 6.38 (m, 1H, =CH), 6.23 (d, J = 3.24 Hz, 1H, =CH), 5.65 (s, 1H, –$CHPh_2$), 4.66 (t, 1H, N–CH), 2.86 (m, 2H, CH_2), 1.64 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.2, 151.7, 148.0, 142.7, 139.2, 138.7, 129.5, 129.0, 128.8, 128.2, 128.1, 127.6, 110.4, 109.0, 105.3, 68.8, 55.6, 40.0, 13.1; HRMS (ESI): calcd for $C_{23}H_{21}NO_2$ $[M+H]^+$ 344.1645, found 344.1638.

4.3.14. 1-Benzhydryl-5-methyl-2-(2-pyridyl)-2,3-dihydro-4-1*H*-pyridone (3n). The title compound was obtained as yellow solid (mp = 160–162 °C) in 99% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.65 (m, 1H, =NCH=), 7.67 (t, 1H, =CH), 7.39 (t, 2H, =CH), 7.36–7.12 (m, 10H, Ph-H), 6.91 (s, 1H, =CH), 5.60 (s, 1H, –$CHPh_2$), 4.72 (t, 1H, N–CH), 2.94 (m, 2H, CH_2), 1.63 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.8, 158.7, 150.0, 148.8, 139.1, 138.5, 136.9, 129.6, 129.0, 128.9, 128.3, 128.1, 127.7, 122.9, 121.6, 105.5, 69.2, 63.0, 41.4, 13.1; HRMS (ESI): calcd for $C_{24}H_{24}N_2O$ $[M+H]^+$ 355.1805, found 355.1802.

4.3.15. 1-Benzhydryl-5-methyl-2-styryl-2,3-dihydro-4-1*H*-pyridone (3o). The title compound was obtained as yellow solid (mp = 136 °C) in 62% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.05 (m, 15H, Ph-H), 6.72 (s, 1H, =CHN), 6.33 (d, J = 15.60 Hz, 1H, =CHPh), 6.26 (dd, J = 8.34, 15.84 Hz, 1H, =CH), 5.63 (s, 1H, –$CHPh_2$), 4.05 (m, 1H, N–CH), 2.75 (dd, J = 6.42, 16.44 Hz, 1H, CH_AH$_B$), 2.49 (dd, J = 7.50, 16.44 Hz, 1H, CH$_A$$H_B$), 1.56 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.3, 148.7, 139.2, 138.9, 136.0, 134.0, 129.5, 129.0, 128.9, 128.7, 128.3, 128.2, 128.1, 127.8, 126.7, 125.4, 105.5, 68.4, 61.3, 41.8, 13.2; HRMS (ESI): calcd for $C_{27}H_{25}NO$ $[M+H]^+$ 380.2009, found 380.2002.

4.3.16. 1-Benzhydryl-5-methyl-2-cyclohexyl-2,3-dihydro-4-1*H*-pyridone (3p). The title compound was obtained as yellow solid (mp = 180–182 °C) in 86% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46–7.13 (m, 10H, Ph-H), 6.77 (s, 1H, =CH), 5.68 (s, 1H, –$CHPh_2$), 3.29 (m, 1H, N–CH), 2.72 (dd, J = 7.98, 16.80 Hz, 1H, CH_AH$_B$), 2.44 (dd, J = 2.46, 16.80 Hz, 1H, CH$_A$$H_B$), 1.96–1.08 (m, 11H, CH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.7, 148.6, 148.6, 141.9, 140.2, 138.5, 129.6, 129.0, 128.9, 128.8, 128.3, 128.1, 127.5, 127.3, 103.9, 69.9, 62.3,

40.6, 36.5, 29.9, 28.5, 26.5, 26.4, 26.2, 12.9; HRMS (ESI): calcd for $C_{25}H_{29}NO$ $[M+H]^+$ 360.2322, found 360.2316.

4.3.17. 1-Benzhydryl-5-methyl-2-isopropyl-2,3-dihydro-4-1*H*-pyridone (3q). The title compound was obtained as white solid (mp = 98–100 °C) in 54% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46–7.14 (m, 10H, Ph-H), 6.79 (s, 1H, =CH), 5.70 (s, 1H, –$CHPh_2$), 3.29 (m, 1H, N–CH), 2.68 (dd, J = 7.68, 16.74 Hz, 1H, CH_AH_B), 2.44 (dd, J = 4.14, 16.74 Hz, 1H, CH_AH_B), 2.36 (m, 1H, –CH), 1.60 (s, 3H, CH_3), 1.04 (t, 6H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.9, 148.6, 140.0, 138.5, 129.6, 129.0, 128.9, 128.3, 128.1, 127.5, 104.1, 69.4, 62.7, 35.7, 29.8, 19.8, 17.8, 12.9; HRMS (ESI): calcd for $C_{22}H_{25}NO$ $[M+H]^+$ 320.2009, found 320.2003.

4.3.18. 1-Benzhydryl-5-methyl-2-propyl-2,3-dihydro-4-1*H*-pyridone (3r). The title compound was obtained as yellow solid (mp = 100–102 °C) in 51% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45–7.13 (m, 10H, Ph-H), 6.66 (s, 1H, =CH), 5.63 (s, 1H, –$CHPh_2$), 3.48 (m, 1H, N–CH), 2.78 (dd, J = 6.84, 16.56 Hz, 1H, CH_AH_B), 2.38 (dd, J = 3.06, 16.56 Hz, 1H, CH_AH_B), 1.88 (m, 1H, –CH_2), 1.65 (m, 1H, –CH_2), 1.61 (s, 3H, CH_3), 1.47 (m, 1H, –CH_2), 1.28 (m, 1H, –CH_2), 0.94 (t, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.3, 147.8, 140.1, 138.4, 129.5, 129.0, 128.9, 128.8, 128.4, 128.1, 127.5, 127.3, 103.7, 69.5, 57.5, 40.0, 31.4, 30.9, 18.8, 14.1, 13.0; HRMS (ESI): calcd for $C_{22}H_{25}NO$ $[M+H]^+$ 320.2009, found 320.2003.

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Self-assembly of a new series of quadruply hydrogen bonded heterotrimers driven by the donor–acceptor interaction

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Abstract—This paper describes the self-assembly of a new series of heterotrimers in chloroform-*d* by utilizing the cooperative interaction of hydrogen bonding and donor–acceptor interaction. Compounds **1** and **11**, in which an 2-ureido-4[1*H*]-pyrimidinone unit is connected to 34-crown-10 or 36-crown-10, were used as donor monomer, and **2** and **19**, in which an 2-ureido-4[1*H*]-pyrimidinone unit is connected to NDI, were used as acceptor monomer, while linear compound **4**, which contains two diamido-1,8-naphthyridines, was used as template. A large tri-*p*-(*t*-butyl)phenylmethoxyl group was introduced to **19** in order to compare its assembling behavior with that of **2**. Mixing **4** with dimer **1**·**2** caused **1**·**2** to fully decompose and to afford 55% of 'in–in'-oriented heterotrimer **1**·**4**·**2**. Adding **4** to the solution of **2**·**11** or **11**·**19** in chloroform-*d* also led to full dissociation of the dimers. However, in these systems the 'in–in'-arranged heterotrimer **2**·**4**·**11** or **11**·**4**·**19** could be produced exclusively.

1. Introduction

Cooperative interaction of different non-covalent forces play a critical role in the formation of biological structures and functions.[1] For example, the DNA double helixes are stabilized mainly by intermolecular hydrogen bonds between the complementary bases and stacking interactions between adjacent base pairs, whereas the secondary and tertiary structures of proteins are generated as a result of the cooperative behavior of specifically located hydrogen bonds, hydrophobic interaction, and Van der Waals force. One of the challenges in supramoleulcar chemistry is the construction of new molecular assemblies with defined structures or functions in a strong, selective, and directional way.[2] In the past decade, a large number of artificial supramolecular architecture have been constructed based on single non-covalent force including transition metal–ligand interaction,[3] hydrophobic interaction,[4] hydrogen bonding,[5] and electrostatic interaction.[6] In principle, the combination of two or more different non-covalent interactions may also function well or even more efficiently in constructing new supramolecular species. Nevertheless, only recently have examples of supramolecular assemblies of this kind been reported.[7]

Due to their remarkable stability and directionality, the self-complimentary 2-ureido-4[1*H*]-pyrimidinone-based quadruply hydrogen bonded AADD (A, hydrogen bonding acceptor; D, hydrogen bonding donor) homodimers have recently found extensive applications in self-assembly of discrete supramolecular systems.[8–10] Previously, we had reported that AADD-featured homodimers of **1** and **2** could dissociate to generate more stable quadruply hydrogen bonded heterodimer **1**·**2**,[11,12] as a result of the additional intermolecular donor–acceptor interaction between the electron-rich bis(*p*-phenylene)-34-crown-10 moiety of **1** and the electron-deficient naphthalene diimide (NDI) of **2**.[13] Moreover, the addition of **3** to the solution of **1**·**2** in chloroform-*d* led to the formation of heterodimers **1**·**3** and **2**·**3**, both of which possess a new ADDA–DAAD binding motif.[11a] The formation of the hydrogen bonded heterodimers from hydrogen bonded homodimers driven by additional donor–acceptor interaction represents a new and useful assembling strategy. In this paper we report that linear compounds incorporating two diamido-1,8-naphthyridine moieties have been successfully utilized to

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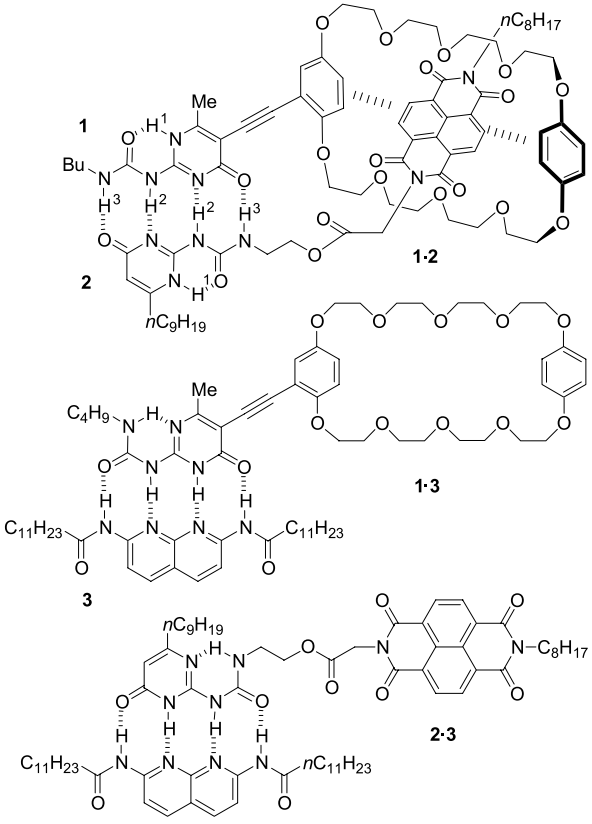
template the selective self-assembly of a new series of hydrogen bonded heterotrimers whose structures are regulated by additional donor–acceptor interaction.[14]



2. Results and discussion

Previous investigation has revealed that ADDA–DAAD-typed heterodimers such as **1**·**3** and **2**·**3** are remarkably more stable than the corresponding AADD–DDAA homodimers.[11a] In principle, linear molecules (A, Fig. 1) incorporating two 2,7-diamido-1,8-naphthyridine moieties connected by a flexible linker of proper length might also induce the dissociation of heterodimers of monomers B and C to generate a new generation of heterotrimers (Fig. 1). To explore this possibility, compound **4** was prepared. The four *n*-octyl groups were expected to provide solubility in common organic solvents. Molecular modeling for a system of **1**, **2**, and **4** revealed that the length of the linker between the two binding moieties of **4** is suitable for the formation of a potential heterotrimer **1**·**4**·**2**.

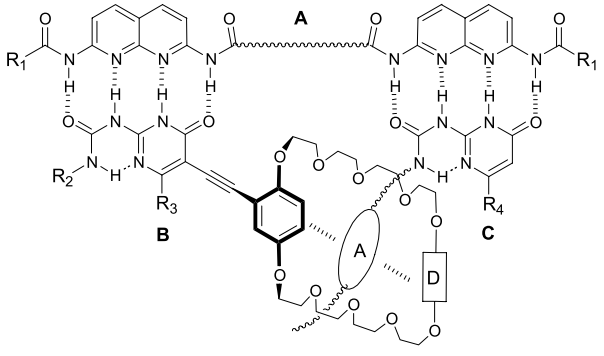
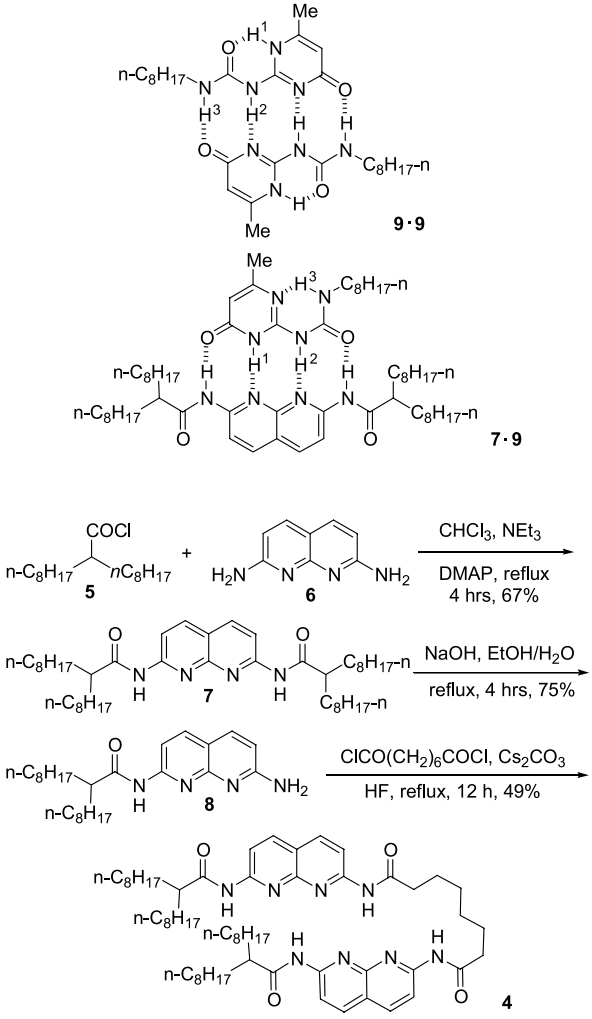


Figure 1. The underlying assembling strategy for the new generation of heterotrimers driven by cooperative hydrogen bonding and donor–acceptor interactions.

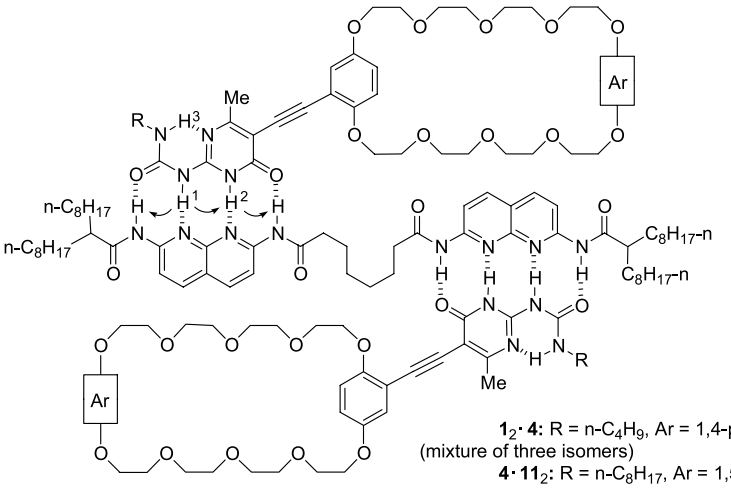
The synthetic route for **4** is shown in Scheme 1. Thus, diamide **7** was first produced from the reaction of **5** and **6** and then hydrolyzed with sodium hydroxide to yield **8**.[15] Subsequent treatment of **8** with suberoyl chloride in refluxed THF produced **4**, which is of good solubility in organic solvents such as chloroform and dichloromethane.



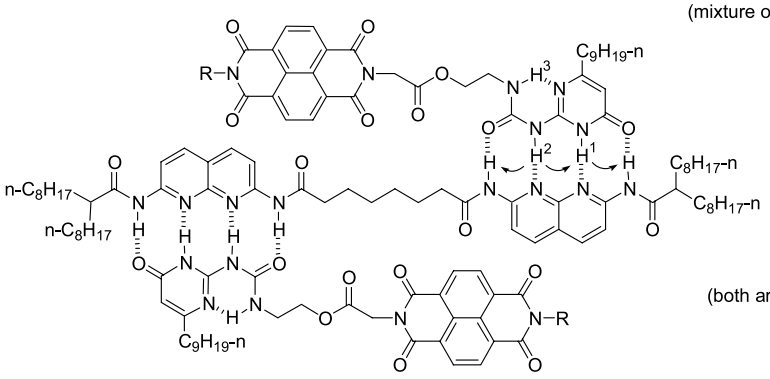
Scheme 1.

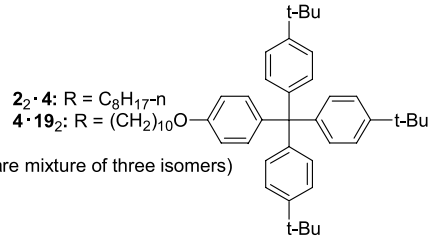
Prior to binding studies with **4**, the ability of **7** to induce the dissociation of homodimer **9**·**9** in chloroform-*d* were investigated by ^{1}H NMR spectroscopy.[16,17] Adding 1 equiv of **7** to the solution of **9** in chloroform-*d* induced the homodimer of the latter to fully dissociate and to afford heterodimer **7**·**9** exclusively (Fig. 2). The structure of **7**·**9** has been characterized by using the methods for the characterization of other similar heterodimers.[11a]

The binding behaviors of **4** with homodimers **1**·**1** and **2**·**2** were then investigated. As revealed by Figure 3b and d, adding 1 equiv of **4** to the solution of **1** or **2** in $CDCl_3$ also led to complete dissociation of the latter's homodimer due to the formation of new heterotrimers $\mathbf{1}_2$·**4** and $\mathbf{2}_2$·**4**, respectively. In principle, the two molecules of **1** or **2** in the

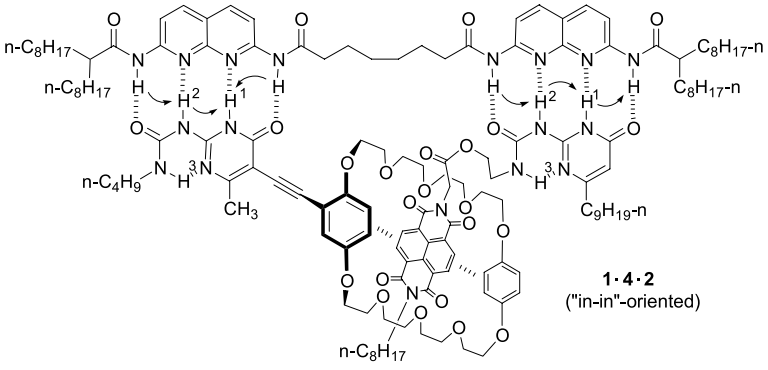


$1_2 \cdot 4$: R = n-C_4H_9, Ar = 1,4-phenylene
(mixture of three isomers)
$4 \cdot 11_2$: R = n-C_8H_{17}, Ar = 1,5-naphthylene
(mixture of three isomers)

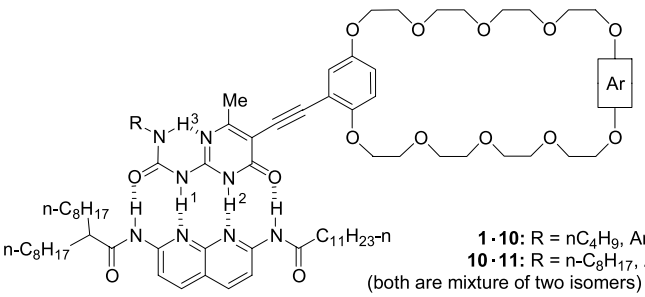




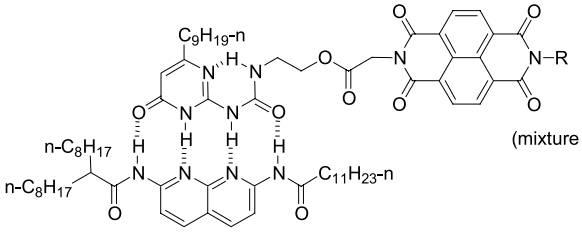
$2_2 \cdot 4$: R = C_8H_{17}-n
$4 \cdot 19_2$: R = $(CH_2)_{10}O$
(both are mixture of three isomers)



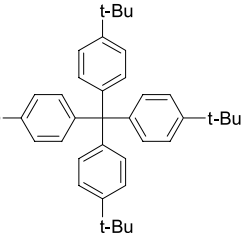
1·4·2
("in-in"-oriented)



1·10: R = nC_4H_9, Ar = 1,4-phenylene
10·11: R = n-C_8H_{17}, Ar = 1,5-naphthylene
(both are mixture of two isomers)



2·10: R = n-C_8H_{17}
10·19: R = $(CH_2)_{10}O$
(mixture of two isomers)



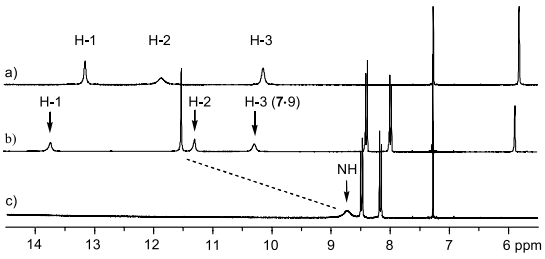


Figure 2. Partial ^{1}H NMR spectra (400 MHz, 5.0 mM) in $CDCl_3$ at 25 °C: (a) **9**; (b) **7**+**9** (1:1); (c) **7**. For signal numbering, see the structures in the text.

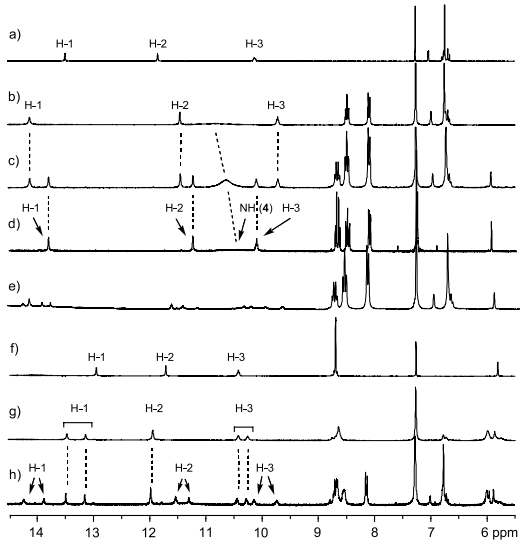
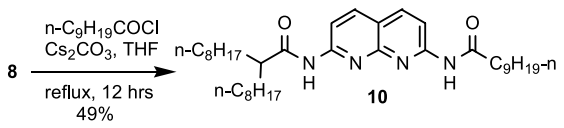


Figure 3. Partial ^{1}H NMR (400 MHz) spectra in $CDCl_3$ at 25 °C: (a) **1** (6.0 mM); (b) $\mathbf{1}_2\cdot\mathbf{4}$ ([**4**]=3.0 mM); (c) **1**·**2**·**4** ([**4**]=6.0 mM); (d) $\mathbf{2}_2\cdot\mathbf{4}$ ([**4**]=3.0 mM); (e) **1**·**2**·**4** ([**4**]=6.0 mM) at −20 °C; (f) **2**; (g) **1**·**2**; (h) **1**+**2**+**10** (12 mM) ([**1**]=[**2**]=6.0 mM).

trimers should have three possible arranging patterns, that is, the 'in–in', 'in–out', and 'out–out'-orientations for the cyclophane unit of **1** or the NDI unit of **2** relative to **4**. The fact that only one set of new signals were displayed in both systems implies that the exchange of the monomers among the possible trimeric isomers was fast on the NMR time scale. Intermolecular NOE effect was observed for both trimers. The facts that **1**·**1** and **2**·**2** were not formed in the mixture solution also implied that trimers $\mathbf{1}_2\cdot\mathbf{4}$ and $\mathbf{2}_2\cdot\mathbf{4}$ were formed quantitatively.

When 1 equiv of **4** was added to 1 equiv of the 1:1 solution of **1** and **2** in chloroform-*d*, the highly stable heterodimer **1**·**2** was also fully decomposed (Fig. 3c and g). The ^{1}H NMR spectrum revealed two sets of NH signals at 14.11, 11.44, 9.71 ppm and 13.78, 11.21, 10.09 ppm, respectively, which could be easily assigned to those of the binding moiety that exists in $\mathbf{1}_2\cdot\mathbf{4}$ or $\mathbf{2}_2\cdot\mathbf{4}$ by comparing Figure 3c with Figure 3b and d and also by adding $\mathbf{1}_2\cdot\mathbf{4}$ or $\mathbf{2}_2\cdot\mathbf{4}$ to the solution, which caused the corresponding signals to increase. NOESY experiment revealed intermolecular connections (see the structures of the trimers), which is also consistent with the DAAD–ADDA motif of the trimers. The identical result was obtained when 1 equiv of the 2:1 solution of **1** and **4** to 1 equiv of the 2:1 solution of **2** and **4** in chloroform-*d*. UV–vis experiment afforded an apparent ε value of 320 $cm^{-1}\,M^{-1}$ (λ_{max}=470 nm) for the charge-transfer absorbance band of the new mixture solution. Because the ^{1}H NMR spectrum had revealed that there was no important amount of **1**·**2** in the solution, this charge-transfer absorbance band was obviously produced by the 'in–in'-oriented heterotrimer **1**·**4**·**2**, which, together with other isomeric trimers, contributed to the two sets of signals in Figure 3c. Similar to the above structurally similar heterotrimers, trimer **1**·**4**·**2** should also be mixtures of four possible isomers, depending on the orientation of **1** and **2** relative to **4**. Reducing the solution temperature to −20 °C led to the NH signals to split (Fig. 3e). Although these signals could not be definitely assigned to either of the heterotrimers, this observation revealed that, besides the 'in–in'-oriented **1**·**4**·**2**, other isomeric heterotrimers might also exist in the solution and at the lowered temperature, the exchange of the monomers among the different trimers became slow on the ^{1}H NMR time scale.

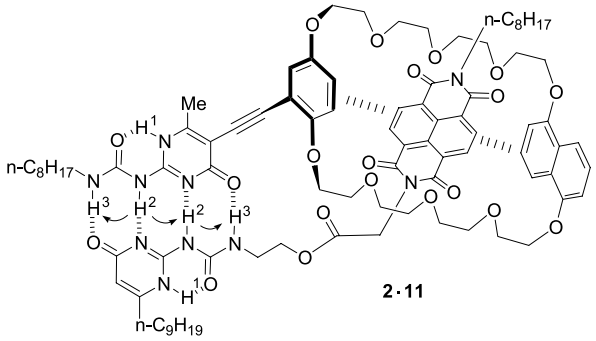
Because the above ^{1}H NMR and UV–vis results could not be utilized to determine the percentage of the 'in–in'-oriented heterotrimer **1**·**4**·**2**, compound **10** was prepared from **8** and docanoyl chloride in refluxed THF (Scheme 2). Adding 2 equiv of **10** to the solution of **1**·**2** in chloroform-*d* induced the heterodimer to partially dissociate as a result of the formation of heterodimers **1**·**10** and **2**·**10**, which gave rise to two sets of new signals at 14.21, 11.51, 9.72 and 13.85, 11.28, 10.12 ppm, respectively, in the ^{1}H NMR spectrum. Although only one set of signals was displayed for each of them, in principle both **1**·**10** and **2**·**10** should also be mixtures of two isomeric dimers. Figure 3h shows the partial ^{1}H NMR spectrum of the 1:1:2 solution of **1**, **2**, and **10** in chloroform-*d*. Based on the relative integrated intensity of the H-1 signals of **1**·**10** and **2**·**10**, we determined the yields of both **1**·**10** and **2**·**10** to be approximately 44%, which implied approximately 44% dissociation of **1**·**2** in the tri-component solution. Because the linker between the two heterocyclic moieties of **4** is not short, it should be acceptable to assume that the DAAD–ADDA motifs of dimers **1**·**10** and **2**·**10** and all possible trimers $\mathbf{1}_2\cdot\mathbf{4}$, $\mathbf{2}_2\cdot\mathbf{4}$, and **1**·**4**·**2** should possess comparable stability when the donor–acceptor interaction in the 'in–in'-oriented **1**·**4**·**2** was not considered. Quantitative dissociation of **1**·**2** in the 1:1:1 solution of **1**, **2**, and **4** in chloroform-*d* suggested that at least 56% of 'in–in'-oriented **1**·**4**·**2** was formed as a result of the additional donor–acceptor interaction between the electron-rich cyclophane unit of **1** and the electron-deficient NDI unit of **2**.[18]



Scheme 2.

It is well-established that 1,5-dialkoxynaphthalene (DAON) is a stronger electron donor than 1,4-dialkoxybenzene for supramolecular self-assembly.[13,19] Therefore, it was envisioned that replacement of the 1,4-dialkoxybenzene unit of **1** with the DAON unit would produce a compound

with a stronger electron-donating ability than **1**. Such a compound might lead to more selective formation of more stable heterotrimers similar to **1**·**4**·**2**. Therefore, compound **11** was synthesized as outline in Scheme 3. In brief, **12** was first reacted with **13** in refluxed acetonitrile to produce cyclophane **14**. The Heck reaction of **14** with **15** in hot pyrrolidine yielded **16**, which was then de-protected with sodium hydroxide to afford **17**. Finally, a palladium(II)-catalyzed reaction of **17** with **18** in THF yielded **11** in 31% yield.

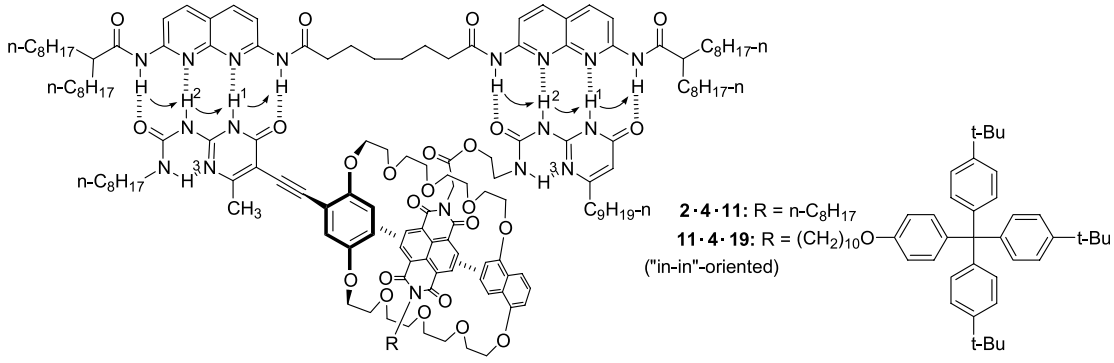


As expected, mixing 1 equiv of **11** with 1 equiv of **2** in chloroform-*d* caused complete dissociation of homodimers **11**·**11** and **2**·**2** and led to the formation of heterodimer **2**·**11** exclusively (Fig. 4d–f). The structure of heterodimer **2**·**11** had been determined by using the methods reported previously for dimer **1**·**2**.[11a] The solution turned to dark orange as a result of the strong intermolecular donor–acceptor interaction between the cyclophane unit of **11** and the NDI unit of **2**. UV–vis experiment afforded a ε value of 1020 M^{-1} cm^{-1} (λ_{max}=488 nm) for the charge-transfer absorbance band of dimer **2**·**11**. This value is substantially larger than that of dimer **1**·**2** (429 M^{-1} cm^{-1}, λ_{max}=475 nm),[11a] indicative of the higher stability of **2**·**11** compared to **1**·**2**. ^{1}H NMR dilution experiments in $CDCl_3$–DMSO-d_6 (4%) derived a binding constant of ca. 2.1×10^5 M^{-1} for dimer **2**·**11**.[11a] The value is significantly larger than that of dimer **1**·**2** (3.7×10^4 M^{-1}),[11a] which is consistent with the above UV–vis result.

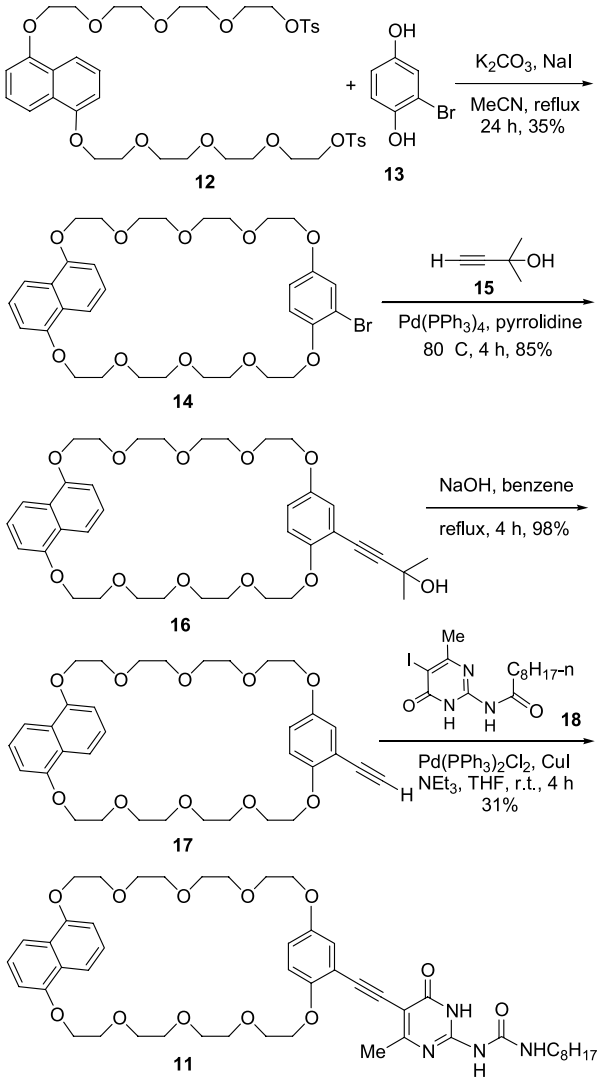
The addition of 1 equiv of **4** to the solution of heterodimer **2**·**11** in chloroform-*d* led to the signals of the heterodimer to disappear in the ^{1}H NMR spectrum (Fig. 4c). Similar to the system of **1**, **2**, and **4** (Fig. 3), two new sets of NH signals were also displayed at 14.13, 11.46, 9.70 ppm and 13.82, 11.26, 10.10 ppm, respectively. These signals were assigned to those of the two binding moieties in heterotrimers **2**·**4**·**11**, $\mathbf{2}_2$·**4**, and $\mathbf{11}_2$·**4** by using the methods described above for other tri-component systems. The orange color of the solution did not change substantially after **11** was added, and UV–vis experiment gave an apparent ε value of 850 M^{-1} cm^{-1} (λ_{max}=487 nm) for the charge-transfer absorbance band. Since the ^{1}H NMR study revealed that there was no detectable amount of dimer **2**·**11** in the tri-component solution, this absorbance band should be produced exclusively by the 'in–in'-arranged heterotrimer **2**·**4**·**11**.

Adding 2 equiv of **10** to 1 equiv of the solution of heterodimer **2**·**11** in chloroform-*d* induced the dimer to partially decompose as a result of the formation of heterodimers **2**·**10** and **10**·**11** (vide supra) (Fig. 4a and d). Based on the integrated intensity of the H-1 signals of the dimers, we determined the yields of dimers **2**·**10** and **10**·**11** to be approximately 12%. If the additional donor–acceptor interaction in the 'in–in'-arranged trimer **2**·**4**·**11** were not considered, it should be reasonable to assume that the ADDA–DAAD binding motif in dimers **2**·**10** and **10**·**11** and all possible trimers **2**·**4**·**11**, $\mathbf{2}_2$·**4**, and $\mathbf{11}_2$·**4** should be comparable. The above ^{1}H NMR result suggested that at least 88% of 'in–in'-oriented trimer **2**·**4**·**11** was formed in the 1:1:1 solution of **2**, **4**, and **11** in $CDCl_3$ due to the additional intermolecular donor–acceptor interaction between **2** and **11**.

Different from the observation that the NH protons split at lowered temperature (−20 °C) (Fig. 3e), reducing the temperature to −25 °C did not lead to the ^{1}H NMR signals of the 1:1:1 mixture solution of compounds **2**, **4**, and **11** to split in chloroform-*d*. Because compounds **1** and **11** possess the same binding unit, heterotrimers of the same skeleton generated from them with **2** and **4** should have very close stability except the 'in–in'-oriented heterotrimers **1**·**4**·**2** and **2**·**4**·**11**, in which the additional donor–acceptor interaction existed. Therefore, the above observation suggested that the 'in–in'-oriented heterotrimer **2**·**4**·**11** was actually formed exclusively at least at the low temperature of −20 °C (≥97% considering the sensitivity of the ^{1}H NMR method).



Further evidence to support the selective formation of the 'in–in'-oriented heterotrimer **2**·**4**·**11** came from the ^{1}H NMR and UV–vis studies of the system of **4**, **11**, and **19**. A large tri-*p*-(*t*-butyl)phenylmethoxyl group was introduced in **19** in order to reduce the exchanging rate between the threaded pseudorotaxane-styled trimeric isomer and all other possible isomers, because such a large group could not



Scheme 3.

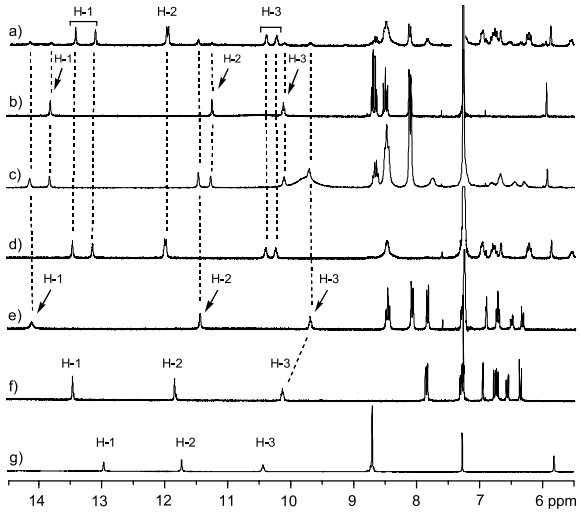
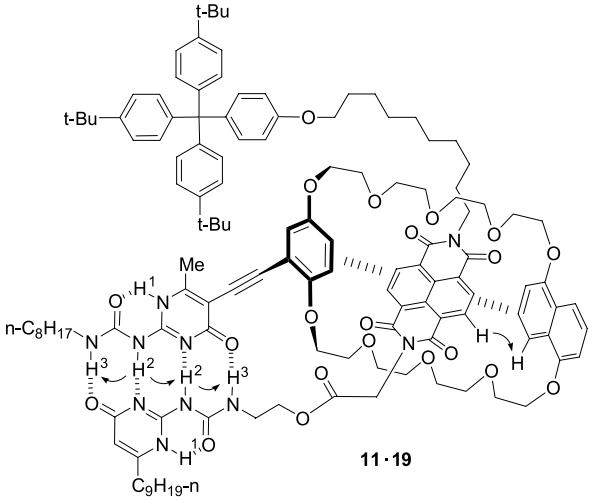


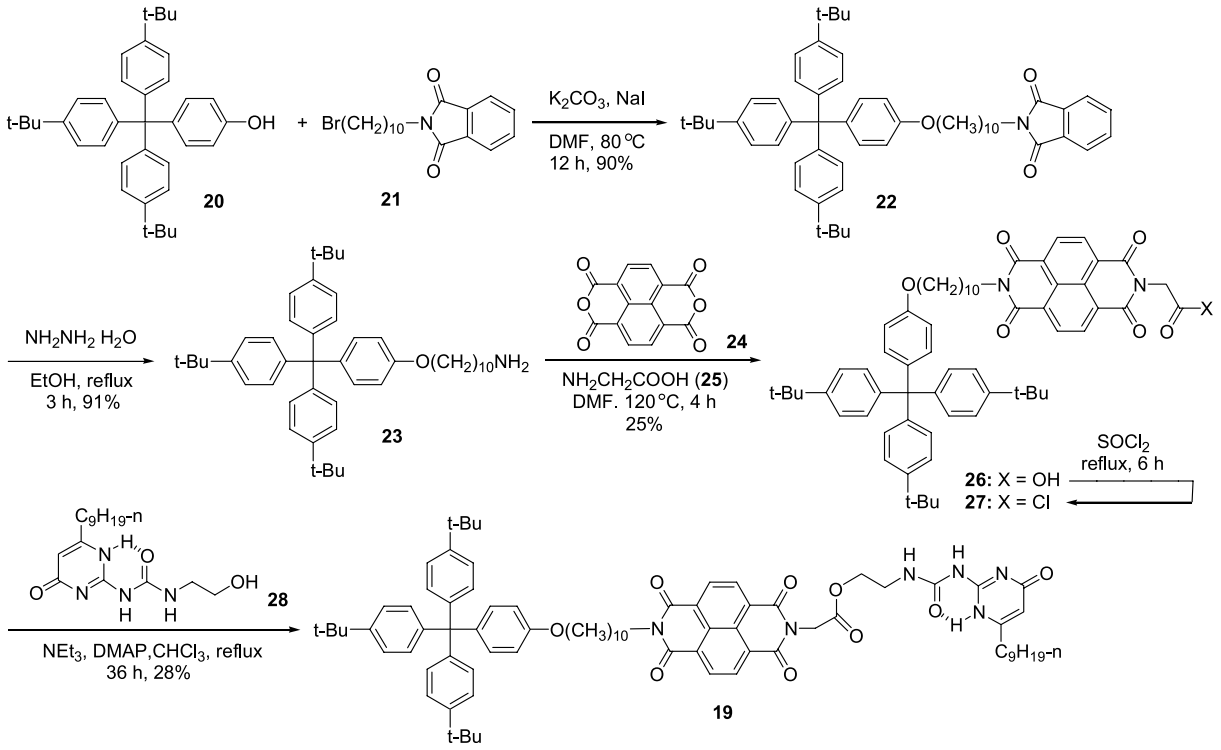
Figure 4. Partial ^{1}H NMR (400 MHz, 4.0 mM) spectra in $CDCl_3$ at 25 °C: (a) **2**+**11**+**10** (1:1:2); (b) **2**+**4** (2:1, [**4**]=2.0 mM); (c) **2**+**4**+**11** (1:1:1); (d) **2**+**11** (1:1); (e) **4**+**11** (1:2, [**4**]=2.0 mM); (f) **11**; (g) **2**.

be de-threaded from the cavity of the cyclophane of **11**.[20] The synthesis of **19** is shown in Scheme 4. In brief, **22** was first prepared from the reaction of **20** and **21** in hot DMF and then hydrolyzed with hydrazine to produce **23**. Treatment of **23** with **24** and **25** in hot DMF yielded **26**, which was then converted into **27** in refluxed thionyl chloride. Finally, compound **27** was reacted with **28** in hot chloroform to afford **19** in 28% yield.

As expected, heterotrimer $\mathbf{4}\cdot\mathbf{19}_2$ (vide supra) was generated exclusively when adding 1 equiv of **14** to 2 equiv of **19** in chloroform-*d* (Fig. 5a and b), and heterodimer **11**·**19** was also formed quantitatively in the 1:1 mixture solution of **11** and **19** in chloroform-*d*. The structure of dimmer **11**·**19** was supported by the NOESY spectrum, which revealed intermolecular NOEs between the NH signals as shown in the structure. Different from that of dimer **2**·**11**, which revealed a single signals at 8.40 ppm for the four protons of the NDI unit (Fig. 4d), the ^{1}H NMR spectrum of **11**·**19** revealed two sets of doublets (8.56, 8.50, 8.43, and 8.34 ppm) for the NDI protons as a result of the increased shielding effect of the cyclophane unit of **11** (Fig. 5d). Moreover, lowering the solution temperature to −35 °C did not cause the NH signals of the dimer to split. By using the ^{1}H NMR dilution method, we determined the K_a of **11**·**19** in chloroform-*d* and DMSO-d_6 (4%) to be ca. 2.2×10^5 M^{-1}, which is very close to that of dimer **2**·**11** in the same solvent. The solution of dimer **11**·**19** in chloroform-*d* displayed a dark orange color as a result of the strong intermolecular donor–acceptor interaction and UV–vis study afforded an apparent ε value of 880 M^{-1} cm^{-1}. This value was independent of concentration (0.5–50 mM) and also comparable to that of dimer **2**·**11**. All these observations indicated that the NDI moiety of **19** was completely threaded through the cavity of the cyclophane of **11** and **11**·**19** existed as a stable pseudo[2]rotaxane.



Adding 2 equiv of **10** to the solution of dimer **11**·**19** in chloroform-*d* caused approximately 15% of the dimer to dissociate and to afford new heterodimers **10**·**11** and **10**·**19** (vide supra) as indicated by the ^{1}H NMR spectrum (Fig. 5f). In contrast, addition of a small excess of **4** to a solution of dimer **11**·**19** in chloroform-*d* caused the NH signals of the dimer to disappear, and two sets of NH signals at 14.15, 11.46, 9.70 ppm and 13.82, 11.25, 10.11 ppm, respectively,



Scheme 4.

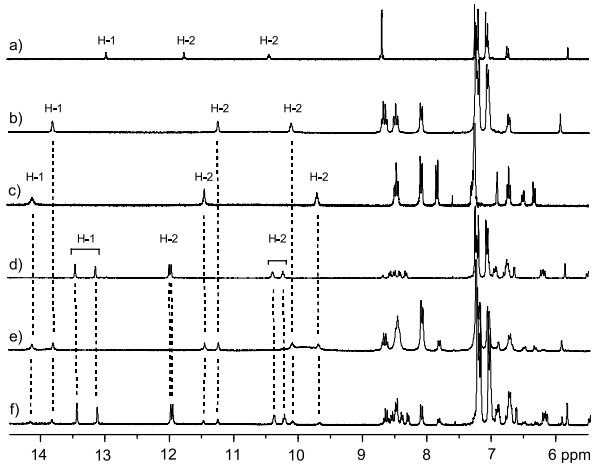


Figure 5. Partial ^{1}H NMR (400 MHz) spectra in $CDCl_3$ at 25 °C: (a) **19** (4.0 mM); (b) **4**+**19** (1:2, [**4**]=2.0 mM); (c) **4**+**11** (1:2 [**11**]=4.0 mM); (d) **11**+**19** (1:1, 4.0 mM); (e) **4**+**11**+**19** (1:1:1, 4.0 mM); (f) **10**+**11**+**19** (1:1:2, [**10**]=4.0 mM).

were displayed. The result is very similar to that observed for the system of **2**, **4**, and **11**, indicating the formation of new heterotrimers **11**·**4**·**19** (vide supra). The ^{1}H NMR spectrum did not exhibit new signals at the low temperature of −25 °C. In principle, the existence of the large tri-*p*-(*t*-butyl)phenylmethoxyl group in **19** would greatly slow down the exchanging processes between the 'in–in'-oriented heterotrimer **11**·**4**·**19** and any other possible trimers.[20] The above results clearly showed that there were no important amount of other kinds of heterotrimers in the tri-component solution, because such possible exchange processes, if existing, would be revealed by the NH signal splitting at the temperature of ≥ −20 °C, as observed above for the solution of compounds **1**, **2**, and **4** in chloroform-*d*.

Different from those of dimers **2**·**11** and **11**·**19**, the NOESY spectrum of the 1:1:1 solution of **2**, **4**, and **11** or **4**, **11**, and **19** in chloroform-*d* did not reveal any intermolecular NOEs between the NH signals of the 2-ureido-4-pyrimidinone units. This observation is also consistent with the formation of heterotrimers **2**·**4**·**11** and **11**·**4**·**19** in the solution. In addition, vapor pressure osmometry (VPO) in chloroform–toluene (85:15 v:v) at 30 °C gave average molecular masses of 2400 (±300 u) and 2800 (±400 u) for the two systems, which was also in agreement with the formation of the two heterotrimers, whose calculated masses are 2620 and 3150, respectively. A energy-minimized structure of heterotrimer **2**·**4**·**11** has been obtained and is shown in Figure 6, which reveals a triangle skeleton for the trimer due to the intermolecular hydrogen bonding and donor–acceptor interactions.

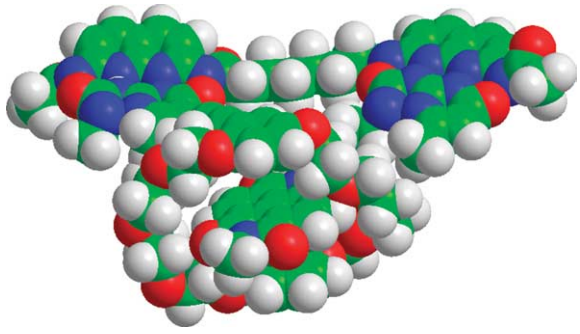


Figure 6. Energy-minimized structures of dimers **2**·**4**·**11**. All the side chains of the monomers are replaced with methyl groups for clarity.

3. Conclusion

We have reported the self-assembly of a new class of heterotrimers in chloroform by making use of both the quadruply hydrogen bonding and the donor–acceptor interaction as the driving forces. The effect of the structure of the monomers on the self-assembling selectivity of the new series of heterotrimers has been investigated. Strong ADDA–DAAD quadruply hydrogen bonding has been used to 'glue' three discrete components together, whereas additional intermolecular donor–acceptor interaction makes the components arrange in order. As a result, among other nine possible heterotrimers, one special heterotrimer has been selectively assembled from elaborately designed monomer molecules. The results demonstrate the great potential of the cooperative interaction between different co-valent forces for assembling new kind of supramolecular architectures.

4. Experimental

4.1. General procedure. See Ref. 11a

4.1.1. Compound 7. To a suspension of **6** (0.72 g, 4.50 mmol), NEt_3 (2.00 mL) and DMAP (50 mg) in chloroform (300 mL) was added a solution of **5**[21] (2.95 g, 9.90 mmol) in chloroform (25 mL). The mixture was stirred under reflux for 4 h and then cooled. The insoluble materials were filtered off and the filtrate was washed with dilute hydrochloric acid, saturated $NaHCO_3$ solution, water, brine, and dried over sodium sulfate. After the solvent was removed, the crude product was purified by column chromatography (hexane/dichloromethane 5:1–1:2) to afford compound **7** as a yellowish oil (2.10 g, 67%). ^{1}H NMR ($CDCl_3$): δ 0.82–0.86 (m, 12H), 1.23–1.28 (m, 48H), 1.46–1.55 (m, 4H), 1.64–1.74 (m, 4H), 2.29–2.35 (m, 2H), 8.13 (d, J=9.0 Hz, 2H), 8.48 (d, J=8.7 Hz, 2H), 8.70 (s, 4H). MALDI-HRMS: m/z: 693.6020 [M^++H]. Calcd for $C_{44}H_{76}N_4O_2$: 693.6041.

4.1.2. Compound 8. A solution of **7** (1.25 g, 1.80 mmol) and NaOH (0.30 g) in ethanol (20 mL) and water (4 mL) was heated under reflux for 4 h and then concentrated in vacuo. The residue was triturated with dichloromethane (250 mL). The organic phase was washed with water, brine, and dried over magnesium sulfate. After the solvent was removed, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 20:1) to obtain **8** as a white solid (0.57 g, 75%). Mp 197–198 °C. ^{1}H NMR ($CDCl_3$): δ 0.82–0.89 (m, 6H), 1.28–1.39 (m, 24H), 1.43–1.56 (m, 2H), 1.64–1.73 (m, 2H), 2.26–2.32 (m, 1H), 5.45 (s, 2H), 6.66 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.7 Hz, 1H), 7.94 (d, J=9.0 Hz, 1H), 8.27 (d, J=9.0 Hz, 1H), 8.57 (s, 1H). MALDI-MS: m/z: 427 [M+H]$^+$. Elemental Anal. Calcd (%) for $C_{26}H_{42}N_4O$ (426.64): C, 73.20; H, 9.92; N, 13.13. Found: C, 73.30; H, 9.97; N, 13.04.

4.1.3. Compound 4. To a stirred suspension of **8** (0.43 g, 1.00 mmol) and Cs_2CO_3 (0.50 g, 1.56 mmol) in THF (40 mL) was added a solution of suberoyl chloride (91 mg, 0.45 mmol) in THF (5 mL). The mixture was refluxed for 12 h and then concentrated. Chloroform (300 mL) was added and the insoluble solid was filtered off. The filtrate was washed with water, brine, and dried. After the solvent was removed in vacuo, the crude product was chromatographed (CH_2Cl_2/MeOH 50:1) to give **4** as a yellow solid (0.22 g, 49%). Mp 156–158 °C. ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J=6.9 Hz, 12H), 1.22–1.54 (m, 52H), 1.63–1.75 (m, 12H), 2.27–2.30 (m, 2H), 2.46 (t, J=7.2 Hz, 4H), 8.11 (d, J=9.0 Hz, 4H), 8.44 (t, J=8.4 Hz, 4H), 8.65 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 24.7, 27.6, 28.6, 29.3, 29.5, 29.7, 31.8, 33.0, 37.6, 49.3, 113.7, 118.3, 139.0, 139.1, 154.0, 154.0, 172.8, 175.8. IR (cm^{-1}): ν 3421, 3307, 2926, 2855, 1708, 1689, 1610, 1388, 1286, 1136, 855, 803. MALDI-HRMS: m/z: 991.7435, [M+H]$^+$. Calcd for $C_{60}H_{94}N_8O_4$: 991.7471.

4.1.4. Compound 9. This compound was prepared from 2-amino-4-hydroxy-6-methylpyrimidine and *n*-octyl isocyanate (97%) as a white solid following the reported procedure for preparation of a similar compound.[8] Mp 171–173 °C. ^{1}H NMR: δ 0.86 (t, J=6.6 Hz, 3H), 1.25–1.30 (m, 10H), 1.54–1.61 (m, 2H), 2.22 (s, 3H), 3.20–3.26 (m, 2H), 5.81 (s, 1H), 10.13 (s, 1H, NH), 11.85 (s, 1H, NH), 13.14 (s, 1H, NH). MS (EI): m/z: 280 [M^+]. Elemental Anal. Calcd (%) for $C_{14}H_{24}N_4O_2$ (280.37): C, 59.98; H, 8.63; N, 19.98. Found: C, 59.84; H, 8.60; N, 19.97.

4.1.5. Compound 10. To a stirred solution of **8** (0.30 g, 0.70 mmol), NEt_3 (1 mL), and DMAP (50 mg) in $CHCl_3$ (20 mL) was added a solution of docanoyl chloride (0.22 g, 1.0 mmol) in $CHCl_3$ (5 mL). The solution was then stirred under reflux for 14 h. After work-up, the crude product was subjected to flash chromatography (CH_2Cl_2) to give **10** as a white solid (0.30 g, 73.5%). Mp 133–134 °C. ^{1}H NMR ($CDCl_3$): δ 0.83–0.89 (m, 9H), 1.23–1.26 (m, 36H), 1.47–1.56 (m, 2H), 1.64–1.80 (m, 4H), 2.25–2.29 (m, 1H), 2.46 (t, J=7.5 Hz, 2H), 8.12–8.15 (m, 4H), 8.45 (t, J=6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.3, 27.6, 29.2, 29.3, 29.3, 29.4, 29.7, 31.9, 31.8, 33.1, 38.0, 49.4, 113.5, 113.6, 118.4, 139.0, 153.9, 154.0, 172.5, 175.6. IR (cm^{-1}): ν 3310, 2925, 2854, 1689, 1610, 1506, 1288, 1136, 854, 802. MALDI-MS: m/z: 581 [M+H]$^+$. Elemental Anal. Calcd (%) for $C_{36}H_{60}N_4O_2$ (580.89): C, 74.44; H, 10.41; N, 9.64. Found: C, 74.66; H, 10.51; N, 9.62.

4.1.6. Compound 14. To a stirred suspension of **12**[13a] (7.30 g, 11.4 mmol), K_2CO_3 (13.0 g, 94.2 mmol) and NaI (2.00 g, 13.3 mmol) in MeCN (200 mL) was added a solution of **13**[22] (2.15 g, 11.4 mmol) in MeCN (20 mL). The reaction mixture was then heated at 80 °C for 24 h and cooled. The solid was filtered off and washed with AcOEt. The combined filtrate was concentrated in vacuo and the resulting residue triturated with AcOEt (200 mL). The organic phase was washed with water, brine, and dried. Upon removal of the solvent, the oily residue was purified by column chromatography (EtOAc/CH_3OH 50:1) to afford **14** as a yellow solid (2.66 g, 35%). Mp 98–100 °C. ^{1}H NMR ($CDCl_3$): δ 3.65–3.86 (m, 24H), 3.98–4.01 (m, 4H), 4.20–4.24 (m, 4H), 6.48 (d, J=1.5 Hz, 2H), 6.74 (d, d, J_1=3.0 Hz, J_2=7.2 Hz, 2H), 6.94 (d, J=0.9 Hz, 1H), 7.26–7.29 (m, 2H), 7.85 (d, d, J_1=2.7 Hz, J_2=8.4 Hz, 2H). EI-MS: m/z: 664 [M^+]. Elemental Anal. Calcd (%) for $C_{32}H_{41}BrO_{10}$ (665.57): C, 57.75; H, 6.21. Found: C, 57.77; H, 6.27.

4.1.7. Compound 16. To a solution of **14** (0.33 g, 0.50 mmol) in pyrrolidine (4 mL) were added $Pd(PPh_3)_4$ (30.0 mg, 0.040 mmol, 8%) and **15** (65.0 mg, 0.75 mmol). The mixture was stirred at 80 °C for 4 h and then concentrated in vacuo. The resulting residue was triturated with CH_2Cl_2 (50 mL). The organic phase was washed with hydrochloric acid, water, brine, and dried. After the solvent was removed, the crude product was purified by column chromatography (EtOAc/CH_3OH 50:1) to obtain **16** as a yellow solid (0.29 g, 85%). Mp 95–96 °C. ^1H NMR ($CDCl_3$): δ 1.57 (s, 6H), 3.69–3.89 (m, 24H), 3.98–4.01 (m, 4H), 4.17–4.25 (m, 4H), 4.48 (d, $J=9.0$ Hz, 1H), 6.61 (d, d, $J_1=3.0$ Hz, $J_2=9.0$ Hz, 1H), 6.67 (d, $J=8.1$ Hz, 1H), 6.73–6.75 (m, 2H), 724–7.28 (m, 2H), 7.83 (d, d, $J_1=3.0$ Hz, $J_2=8.1$ Hz, 2H). EI-MS: *m/z*: 668 $[M]^+$. Elemental Anal. Calcd (%) for $C_{37}H_{48}O_{11}$ (668.77): C, 66.45; H, 7.23. Found: C, 66.59; H, 7.08.

4.1.8. Compound 17. To a solution of **16** (0.29 g, 0.43 mmol) in benzene (10 mL) was added NaOH (52.0 mg, 1.30 mmol). The mixture was refluxed for 4 h, cooled and washed with water, brine, and dried. After the solvent was removed in vacuo, the residue was chromatographed (EtOAc/CH_3OH 50:1) to afford **17** as a white solid (0.26 g, 98%). Mp 92–93 °C. ^1H NMR ($CDCl_3$): δ 3.21 (s, 1H), 3.67–3.92 (m, 24H), 3.97–4.01 (m, 4H), 4.21–4.25 (m, 4H), 4.48 (d, $J=9.0$ Hz, 1H), 6.56 (d, d, $J_1=3.0$ Hz, $J_2=9.0$ Hz, 1H), 6.75 (d, d, $J_1=3.3$ Hz, $J_2=7.8$ Hz, 2H), 6.82 (d, $J=2.7$ Hz, 1H), 728–7.29 (m, 2H), 7.85 (d, d, $J_1=2.4$ Hz, $J_2=8.1$ Hz, 2H). EI-MS: *m/z*: 610 $[M]^+$. Elemental Anal. Calcd (%) for $C_{34}H_{42}O_{10}$ (610.69): C, 66.87; H, 6.93. Found: C, 66.90; H, 6.89.

4.1.9. Compound 18. A solution of 2-amino-5-iodo-6-methyl-3*H*-pyrimidin-4-one[23] (3.00 g, 12.0 mmol) and *n*-*n*-octyl isocyanate (2 mL) in THF (200 mL) was heated under reflux for 24 h. After work-up,[11a] the crude product was purified by column chromatography (CH_2Cl_2/MeOH 30:1) to afford **18** (3.50 g, 73%) as a white solid. Mp 150–152 °C. ^1H NMR ($CDCl_3$): δ 0.85–0.88 (m, 3H), 1.27–1.32 (m, 10H), 1.58–1.62 (m, 2H), 2.45 (s, 3H), 3.26 (m, 2H), 9.83 (s, 1H), 11.66 (s, 1H), 13.44 (s, 1H). EI-MS: *m/z*: 406 $[M^+]$. Elemental Anal. Calcd (%) for $C_{14}H_{23}IN_4O_2$ (406.27): C, 41.39; H, 5.71; N, 13.79. Found: C, 41.30; H, 5.71; N, 13.52.

4.1.10. Compound 11. A suspension of **17** (0.31 g, 0.50 mmol), **18** (0.31 g, 0.77 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 6%), and CuI (10 mg, 10%) in THF (10 mL) and NEt_3 (1.5 mL) was stirred at rt for 5 h and then concentrated under reduced pressure. The residue was triturated with CH_2Cl_2 (50 mL). After work-up, the resulting residue was purified by column chromatography (CH_2Cl_2/CH_3OH 20:1) to produce **11** (0.14 g, 31%) as a yellow solid. Mp 150–152 °C. ^1H NMR $CDCl_3$): δ 0.84 (t, $J=6.6$ Hz, 3H), 1.23–1.28 (m, 12H), 2.49 (s, 3H), 3.22–3.29 (m, 2H), 3.65–3.84 (m, 24H), 3.96–4.02 (m, 4H), 4.21–4.23 (m, 4H), 6.35 (d, $J=9.0$ Hz, 1H), 6.56 (d, d, $J_1=3.3$ Hz, $J_2=9.0$ Hz, 1H), 6.71–6.78 (m, 2H), 6.95 (d, $J=3.3$ Hz, 1H), 7.26–7.29 (m, 2H), 7.84 (d, d, $J_1=2.1$ Hz, $J_2=8.7$ Hz, 2H), 10.13 (t, $J=5.1$ Hz, 1H), 11.83 (s, 1H), 13.45 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 18.7, 22.7, 27.0, 29.3, 29.4, 29.6, 29.7, 31.9, 40.2, 53.2, 68.0, 68.5, 69.7, 69.7, 69.8, 70.6, 70.8, 70.9, 71.0, 71.1, 93.7, 104.3, 105.6, 105.7, 113.1, 113.4, 114.6, 116.7, 118.2, 125.2, 125.2, 126.7, 151.5, 152.4, 152.8, 153.8, 154.3, 156.5, 170.4. IR (cm^{-1}): ν 3211, 2926, 2855, 1697, 1594, 1264, 1080, 768. MALDI-HRMS: *m/z*: 911.4406 $[M+Na]^+$. Calcd for $C_{48}H_{64}N_4O_{12}$: 911.4413.

4.1.11. Compound 22. A solution of **20**[24] (1.04 g, 2.00 mmol), **21**[25] (0.74 g, 2.00 mmol), K_2CO_3 (1.10 g, 8.00 mmol), and KI (0.10 g) in DMF (20 mL) was stirred at 80 °C for 12 h and then cooled. The insoluble materials were filtered off and the solvent was removed under reduced pressure. The residue was triturated with AcOEt (150 mL). The organic phase was washed with aqueous HCl solution, $NaHCO_3$ solution, water, brine, and dried (Na_2SO_4). After the solvent was removed in vacuo, the crude product was recrystallized from AcOEt to obtain **22** (1.44 g, 90%) as a white solid. Mp 154–156 °C. ^1H NMR ($CDCl_3$): δ 1.26–1.36 (m, 39H), 1.65–1.77 (m, 4H), 3.67 (t, $J=7.2$ Hz, 2H), 3.91 (t, $J=6.9$ Hz, 2H), 6.75 (d, $J=7.8$ Hz, 2H), 7.05–7.09 (m, 8H), 7.21–7.26 (m, 6H), 7.70–7.71 (m, 2H), 7.82–7.84 (m, 2H). MALDI-MS: *m/z*: 812 $[M+Na]^+$. Elemental Anal. Calcd (%) for $C_{55}H_{67}NO_3\cdot 0.25H_2O$ (794.64): C, 83.13; H, 8.58; N, 1.76. Found: C, 83.31; H, 8.54; N, 1.33.

4.1.12. Compound 23. Hydrazine hydrate (2.0 mL, 85%) was added to a solution of **22** (1.10 g, 1.40 mmol) in ethanol (30 mL). The solution was refluxed for 3 h and then concentrated in vacuo to give a residue, which was triturated with chloroform (100 mL). The organic phase was washed with water, brine, and dried ($NaSO_4$). After removal of the solvent under reduced pressure, the crude product was recrystallized from AcOEt to afford compound **23** as a white solid (0.90 g, 91%). Mp 94–96 °C. ^1H NMR ($CDCl_3$): δ 1.26–1.43 (m, 39H), 1.73–1.78 (m, 4H), 2.68 (t, $J=7.2$ Hz, 2H), 3.92 (t, $J=6.6$ Hz, 2H), 6.75 (d, $J=9.0$ Hz, 2H), 7.06–7.10 (m, 8H), 7.21–7.26 (m, 6H). ESI-MS: *m/z*: 610 $[M+H]^+$. Elemental Anal. Calcd (%) for $C_{47}H_{65}NO\cdot 0.25H_2O$ (664.54): C, 84.94; H, 9.96; N, 2.11. Found: C, 84.99; H, 9.98; N, 1.55.

4.1.13. Compound 26. A solution of compounds **23** (0.45 g, 0.68 mmol), **24** (0.18 g, 0.68 mmol), and **25** (0.05 g, 0.68 mmol) in DMF (10 mL) was stirred at 120 °C for 4 h. Upon cooling, the insoluble materials were filtered off and the solvent was removed in vacuo. The resulting residue was triturated in chloroform (50 mL) and the solution was washed with water, brine, and dried ($MgSO_4$). The solvent was then removed and the crude product purified by column chromatography (CH_2Cl_2/MeOH 50:1) to give **26** as a pink solid (0.17 g, 25%). Mp 242–243 °C. ^1H NMR ($CDCl_3$): δ 1.25–1.39 (m, 39H), 1.71–1.75 (m, 4H), 3.91 (t, $J=6.6$ Hz, 2H), 4.19 (t, $J=7.2$ Hz, 2H), 5.00 (s, 2H), 6.75 (d, $J=8.4$ Hz, 2H), 7.05–7.09 (m, 8H), 7.22 (d, $J=8.7$ Hz, 6H), 8.78 (s, 4H). MALDI-MS: *m/z*: 989 $[M+Na]^+$. Elemental Anal. Calcd (%) for $C_{63}H_{70}N_2O_7$ (967.24): C, 78.23; H, 7.29; N, 2.90. Found: C, 78.45; H, 7.01; N, 2.76.

4.1.14. Compound 19. A suspension of **26** (0.28 g, 0.29 mmol) in thionyl chloride (5 mL) was refluxed for 6 h and then concentrated in vacuo to afford compound **27** as an oil, which was used directly for next step. To a stirred solution of **28**[11a] (94 mg, 0.29 mmol), triethylamine (0.8 mL) and DMAP (10 mg) in $CHCl_3$ (15 mL) was added a solution of the above **27** in chlroform (5 mL). The

mixture was heated under reflux for 36 h, cooled, washed with water, brine, and dried ($MgSO_4$). The solvent was removed and the residue was subjected to flash chromatography (CH_2Cl_2/MeOH 50:1) to afford **19** as a pink solid (104 mg, 28%). Mp 212–214 °C. ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J=6.9 Hz, 3H), 1.24–1.67 (m, 57H), 2.49 (t, J=8.1 Hz, 2H), 3.57–3.59 (m, 2H), 3.98 (t, J=7.2 Hz, 2H), 4.16 (t, J=8.4 Hz, 2H), 4.40 (t, J=5.4 Hz, 2H), 5.02 (s, 2H), 5.82 (s, 1H), 6.73–6.76 (m, 2H), 7.04–7.09 (m, 8H), 7.20–7.25 (m, 6H), 8.70 (s, 4H), 10.44 (t, J=3.6 Hz, 1H), 11.76 (s, 1H), 12.97 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 26.2, 27.0, 27.1, 28.1, 29.0, 29.2, 29.3, 29.4 (d), 29.5 (d), 29.6, 31.4, 31.8, 32.7, 34.3, 34.3, 38.7, 41.1, 41.8, 63.0, 63.9, 67.8, 106.0, 112.9, 124.0, 124.2, 126.1, 126.7, 126.8, 126.9, 130.6, 130.7, 130.8, 131.2, 132.2, 139.3, 143.6, 144.2, 148.3, 148.5, 152.5, 154.3, 156.8, 156.9, 162.4, 162.6, 167.6, 172.9. IR (cm^{-1}): ν 3040, 2959, 2928, 2856, 1757, 1709, 1672, 1584, 1246, 823, 771. MALDI-MS: *m/z*: 1273 [M^++H]. Elemental Anal. Calcd (%) for $C_{79}H_{96}N_6O_9\cdot 0.25H_2O$ (1278.15): C, 74.23; H, 7.63; N, 6.58. Found: C, 74.09; H, 7.70; N, 6.34.

4.2. Vapor pressure osmometry (VPO)

The VPO experiments were performed in chloroform–toluene (85:15 v:v) at 30 °C with a Knauer-K-700 osmometer, with a synthetic amide (M_W: 1772) used for calibration. Reported results represent single experimental runs.

4.3. Binding constants

Measurement of binding constants has been described in the previous paper.[11a]

4.4. Computational method

The binding pattern was constructed by using the Builder program within the package HyperChem. Then they were optimized by the conjugate gradient with the AMBER force field and the RMS derivative criteria of 0.00001 kcal mol^{-1}. In order to explore lower-energy conformation on the potential energy surface, molecular dynamics calculations were performed with constraint of hydrogen bonds at ca. 2.15 Å. After 100 ps molecular dynamics simulation, an additional round of energy minimization was again completed.

Acknowledgements

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16. The K_{dim} values for the self-association of **7** were determined to be approximately $<11\ M^{-1}$ by ^1H NMR dilution studies (60–0.1 mM) in $CDCl_3$. Therefore, its self-association could be reasonably ignored.
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18. Because all the possible heterotrimers exchange to each other in the solution, the 'in–in' arranged heterotrimer **1**·**4**·**2** should be of higher yield, since only in this trimer that the additional donor–acceptor interaction could occur.
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The conversion of pentoses to 3,4-dihydroxyprolines

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Abstract—The synthesis of two naturally-occurring isomers of 3,4-dihydroxyproline is reported. L-2,3-*cis*-3,4-*trans*-3,4-Dihydroxyproline was synthesized from L-arabinose in 10 steps and 31% overall yield. The same series of reactions was employed to convert L-xylose to L-2,3-*trans*-3,4-*trans*-3,4-dihydroxyproline. Orthogonally protected versions of these amino acids were produced on gram scale, en route to the free amino acids, and these will serve as versatile intermediates in peptide synthesis. This synthetic strategy involved *N*α-Fmoc protection and protection of the C3 and C4 secondary alcohols as methoxyethoxymethyl (MEM) ethers.

1. Introduction

3,4-Dihydroxyproline (DHP)[1] contains three stereogenic centers: C2, C3 and C4 and so there are eight possible stereoisomers. Three members of the L-series have been isolated from natural sources (Fig. 1). The L-2,3-cis-3,4-trans isomer (**1**) was isolated from the cell wall of the diatom *Navicula pelliculosa* more than 30 years ago.[2] In 1980, the L-2,3-trans-3,4-trans isomer (**2**) was isolated from the acid hydrolysates of the toxic mushroom *Amanita virosa*[3] and identified in the virotoxin cyclic heptapeptides.[4] In 1994, the L-2,3-trans-3,4-cis isomer **3** was identified as the sixth residue in the repeating decapeptide sequence of Mepf1, an adhesive protein produced by the marine mussel *Mytilus edulis*.[5]

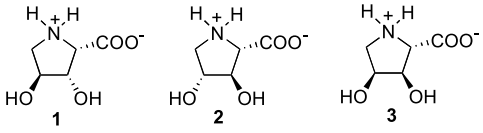

Figure 1. Naturally occurring 3,4-dihydroxyprolines.

There are many syntheses of dihydroxyprolines in the literature.[6] When we began our bid to synthesize the Mefp1 decapeptide,[7] we utilized the approach of Fleet and co-workers[8] to prepare a suitably protected derivative of **3** from D-gulonolactone. Our long term goal, however, was to investigate the role of 3,4-dihydroxyprolines in nature and as such we required a synthesis, which was capable of delivering any of the eight stereoisomers. Most other approaches are limited in this regard to the preparation of only a subset of these target molecules. For example, *syn*-dihydroxylation of a 3,4-dehydroproline can lead only to DHPs with 3,4-cis relative stereochemistry.[9,10] Conversely, the opening of an epoxide has been a useful tool in the synthesis of DHPs with a 3,4-trans relative stereochemistry.[11,12]

Our goal over the past several years has been to develop a synthesis of 3,4-dihydroxyprolines, which should be amenable to producing useful quantities of any stereoisomer, in an efficient and stereochemically predictable manner. We reasoned that the eight stereoisomers of 3,4-dihydroxyproline ought to be accessible from the eight pentose sugars, utilizing Fleet's double displacement chemistry, which we had adopted previously to good effect.[13] The configuration at C3 and C4 would be derived directly from the sugar and that at C2 inverted during the sequence. The overall retrosynthetic analysis is embodied in Table 1.

2. Results and discussion

In our previous endeavors, we utilized *tert*-butyldimethylsilyl (TBDMS) ethers for protection of the secondary alcohols at C3 and C4 (DHP numbering).[14] Thus, we demonstrated the proof of concept by converting D-ribonolactone (**4**) to amino acid building block **7**.[14a] We later reported full experimental details for the application of this chemistry to the synthesis of two other stereoisomers of compound **7**.[14b] We felt compelled to publish this work, given the amount of effort that had been expended.

Keywords: Dihydroxyprolines; Pentose sugars.
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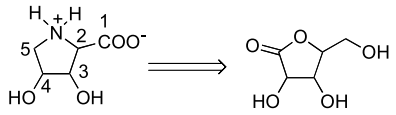
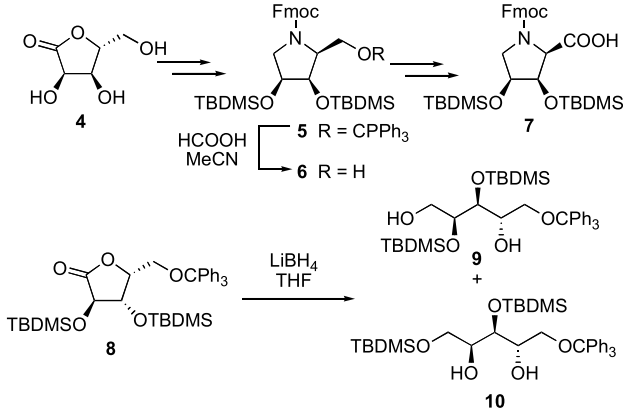
Table 1. Retrosynthetic scheme of 3,4-dihydroxyprolines



DHP isomer	Pentose precursor
L-2,3-cis-3,4-cis-	L-ribose
L-2,3-cis-3,4-trans-	L-arabinose
L-2,3-trans-3,4-cis-	L-lyxose
L-2,3-trans-3,4-trans-	L-xylose
D-2,3-cis-3,4-cis-	D-ribose
D-2,3-cis-3,4-trans-	D-arabinose
D-2,3-trans-3,4-cis-	D-lyxose
D-2,3-trans-3,4-trans-	D-xylose

Unfortunately, the overall efficiency of the synthesis was disappointing and our goal of producing useful quantities of DHP building blocks for peptide synthesis was not realized.

An objective assessment of our previous work (Scheme 1) led us to the conclusion that the problems encountered in the syntheses were directly, or indirectly, associated with the TBDMS protecting group. For example, the reductive opening of the lactone ring in compound **8** was anticipated to give **9** (by analogy to the reduction of two diastereoisomers of **8**). Unfortunately, the major product **10** arose from migration of the silyl group to the primary alcohol.[14b] Another problem in the synthesis involved the chemoselective hydrolysis of the trityl ether from compound **5**; partial removal of one TBDMS group was also observed. The extent of this problem varied from one stereoisomer to another, requiring close monitoring of the reaction progress and fine-tuning of reaction times to optimize the yield of desired products.



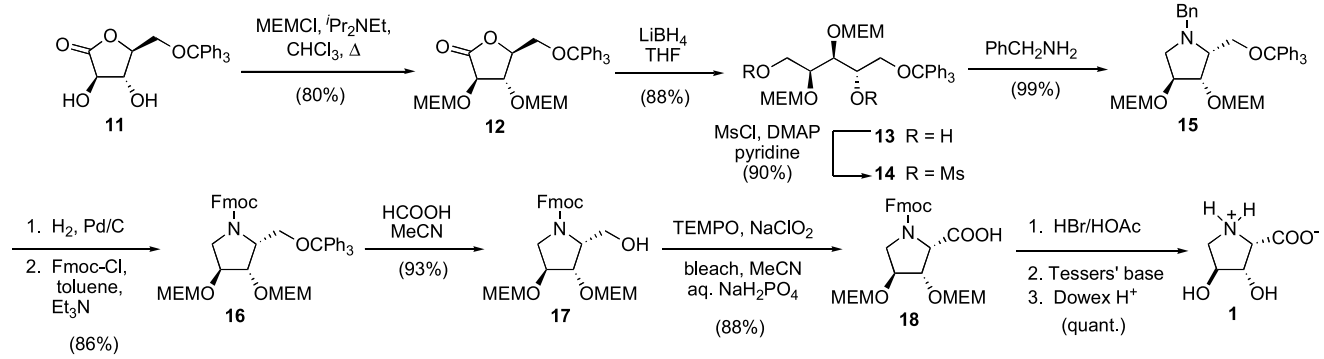
Scheme 1. Important issues from previous work.

We proposed that substitution of the MEM (methoxyethoxymethyl) group for the TBDMS group might improve the viability of the synthesis. Indeed, the use of the MEM protecting group has been described previously for trans-4-hydroxyproline building blocks during the synthesis of collagen mimetics.[15]

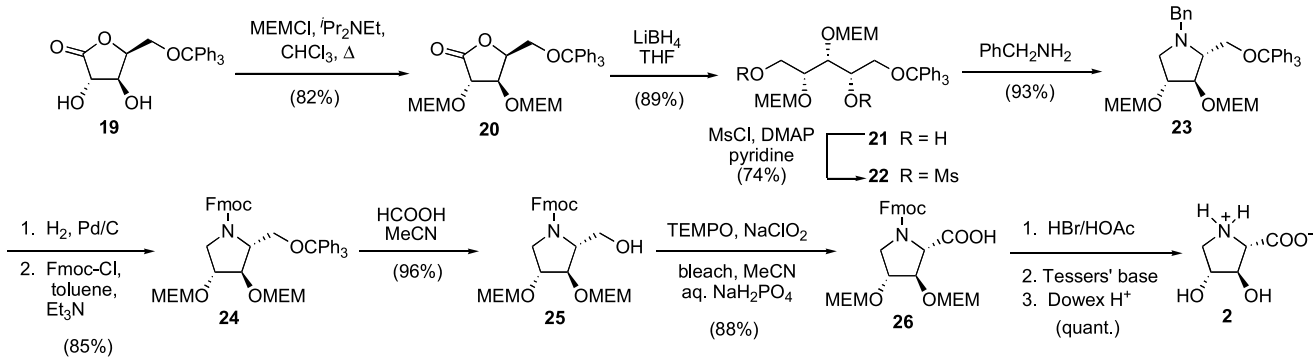
Herein, we report the synthesis of two isomers of 3,4-dihydroxyproline in this manner, on reasonable scale and with greatly improved overall yields. While our original aim was to produce building blocks for peptide synthesis, we are becoming increasingly aware of the need for the free amino acids as authentic samples for comparison in amino acid analyses where the occurrence of 3,4-dihydroxyprolines is suspected in peptides and proteins.[16] Thus, we also describe conditions for producing the free amino acids.

The conversion of compound **11** (derived from L-arabinose) to 2,3-*cis*-3,4-*trans*-3,4-dihydroxy-L-proline (**1**) is summarized in Scheme 2. In our 2002 paper,[14b] we described some of the trials and tribulations associated with producing the 5-*O*-triphenylmethyl ethers typified by **11**. Some further observations and recommendations are given in the Section 4. Standard conditions for the protection of alcohols as MEM ethers (MEMCl, $^{i}Pr_2NEt$, CH_2Cl_2, rt)[17] were ineffective for the conversion of **11** to **12**. Optimized conditions involved heating at reflux in chloroform with 5 equiv of alkylating agent. A drawback of the MEM protecting group, which is perhaps not widely appreciated, is the complexity that it introduces into ^{1}H NMR spectra. Each MEM group introduces a singlet at ~3 ppm; in addition there are three $-CH_2-$ groups, which give rise to six signals, since the two protons of each $-CH_2-$ unit are diastereotopic. ^{1}H NMR spectra of intermediates in Schemes 2 and 3 were thus difficult to fully assign. However, ^{13}C NMR spectra were less complex and provided evidence for the identity and purity of compounds.

Reduction of the fully protected lactone **12** gave diol **13**, which was readily converted to the bis-mesylate **14**. Cyclization to form the pyrrolidine **15** gave an essentially quantitative yield if the benzylamine was distilled immediately prior to the reaction. Benzylamine, which had been distilled in recent weeks and stored over KOH



Scheme 2. Synthesis of L-2,3-*cis*-3,4-*trans*-3,4-dihydroxyproline.



Scheme 3. Synthesis of L-2,3-*trans*-3,4-*trans*-3,4-dihydroxyproline.

gave yields in the order of 60–70%. Due to the MEM ethers, pyrrolidine **15** is much more polar than analogous compounds with other protecting groups at C3 and C4 (acetonide,[13] TBDMS[14]). This facilitated separation of the pyrrolidine from benzylamine-derived byproducts, including benzaldehyde. The benzyl group was removed hydrogenolytically from pyrrolidine **15** and the amine protected as its Fmoc derivative. The trityl ether was removed cleanly in 2 h. The differential in acid lability of the two ethers (trityl vs. MEM) removed all problems associated with the chemoselectivity in this step (vide supra, conversion of **5**→**6**, Scheme 1).

As in our previous work, we intially utilized a two step oxidation of **17**: Swern oxidation to the aldehyde, followed by sodium chlorite oxidation to acid **18**.[14b] The NMR spectra of compound **18** featured very broad peaks, which were doubled up in the ^{13}C NMR. We attributed this to restricted rotation about the carbamate C–N bond. Unfortunately, removal of the protecting groups gave a 3:1 mixture (determined by integration of ^{1}H NMR signals) of two dihydroxyprolines, which appeared to be diastereoisomers. HPLC analysis of compound **18** (from Swern/$NaClO_2$ oxidation of **17**) revealed the same ratio of two similar compounds. Our suspicion was that the α-amino aldehyde derived via Swern oxidation of **17** was undergoing epimerization. This was not observed for the analogous compound bearing TBDMS ethers.[14b] Moreover, others have reported the successful Swern oxidation of similar prolinol compounds.[18]

Ruthenium (III) oxidation of **17** under Sharpless conditions[19] gave acid **18** directly; deprotection yielded a stereoisomerically pure sample of **1**. Our hunch was confirmed, but as we had found earlier,[14a] the yield of this oxidation (36%) was unsatisfactory. A number of recent reports suggested that TEMPO may be the best reagent for this oxidation.[20] Indeed, oxidation of **17** to **18** was achieved in good yield, with no loss of stereochemical integrity.

The deprotection of the amino acid was attempted in a number of ways. Reactions employing TFA/dichloromethane, 95% TFA/H_2O or 1 N HCl in TFA were slow and not clean. The best results were obtained using a solution of HBr in acetic acid. This acid treatment removed the MEM protecting groups. The Fmoc group was removed using Tesser's base[21] and the free amino acid was purified by ion exchange chromatography.

For clarity, the reaction sequence, as applied to the conversion of L-xylose to amino acid building block **26**, is depicted in Scheme 2. The intermediates behaved similarly and yields were comparable.

3. Conclusion

In summary, two isomers of 3,4-dihydroxyproline have been synthesized, via orthogonally protected derivatives. Building blocks **18** and **26** ought to prove useful in peptide synthesis. We believe that the synthetic route should be applicable to the conversion of the appropriate pentose sugar to any of the eight stereoisomers of 3,4-dihydroxyproline. This route has been arrived at via the exploration of several protecting groups and reaction conditions for each step. While the bromine oxidation of the pentose sugars, followed by 5-*O*-trityl ether formation remains a somewhat capricious undertaking, the subsequent steps are highly reproducible. The overall yield for the production of **1** from **11** is 44% (eight steps); this reduces to 31% starting from L-arabinose (10 steps). Likewise, isomer **2** was produced from lactone **19** in 36% yield (eight steps); or 22% yield (ten steps) from L-xylose.

4. Experimental

4.1. General details

All reactions were conducted under a dry nitrogen atmosphere unless otherwise noted. Reagents were obtained from commercial suppliers and used directly with the following exceptions. Tetrahydrofuran was dried over sodium/benzophenone and distilled prior to use. Diisopropylethylamine, triethylamine and pyridine were dried and distilled from CaH_2 and stored over KOH pellets. Acetonitrile and benzylamine were freshly distilled from CaH_2. Methanesulfonyl chloride was best distilled from P_2O_5 immediately prior to use. Flash chromatography was performed using Scharlau 60 silica gel (230–400 mesh) with the indicated solvents. Thin-layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence or by staining with anisaldehyde or ninhydrin. ^{1}H and ^{13}C NMR spectra were obtained using either a JEOL JNM-GX270W or a Bruker Avance 400 spectrometer. Chemical shifts for spectra in $CDCl_3$ are given in parts per million

(ppm) downfield from tetramethylsilane as internal standard (^{1}H) or relative to residual solvent (^{13}C). Spectra of the free amino acids in D_2O were referenced to DSS as an external standard. High resolution mass spectra were recorded using a VG7070 mass spectrometer operating at nominal accelerating voltage of 70 eV.

4.1.1. 5-*O*-Trityl-L-arabinono-γ-lactone (11). Potassium carbonate (2.26 g, 16.3 mmol, 1.22 equiv) was added in portions, over 2 h, to a solution of L-arabinose (2.00 g, 13.3 mmol, 1.00 equiv) in Milli-Q water (6 mL) at 0 °C. Bromine (0.8 mL, 2.48 g, 15.5 mmol, 1.16 equiv) was then added dropwise, from a dropping funnel (constructed of glass and teflon only) over 2 h. The solution was warmed to rt and left to stir overnight. The solution was still yellow/orange (if it was a not, a couple more drops of bromine were added and the mixture left to stir another 12 h) and the excess bromine was quenched by the addition of neat formic acid (two drops from a Pasteur pipette). Decolorization was not immediate, but was complete within 10 min. The mixture was concentrated on a rotary evaporator, with the water bath at 60 °C. When the volume of the mixture reached ~10 mL, glacial acetic acid (1 mL) was added. Rotary evaporation at 60 °C was continued for at least 2 h and then under high vacuum. The dry residue was suspended in pyridine (25 mL) under N_2. DMAP (325 mg, 2.7 mmol, 0.2 equiv) was added, followed by trityl chloride (4.45 g, 16.0 mmol, 1.2 equiv) and the mixture heated at reflux for 12 h. The brown solution was cooled, diluted with CH_2Cl_2 (300 mL) and washed successively with water (250 mL), 1 M HCl (250 mL), satd aq $NaHCO_3$ (250 mL) and brine (250 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 1:1 EtOAc/hexane to give **11** as a colorless foam (3.71 g, 71%). Data reported elsewhere.[14b]

4.1.2. 5-*O*-Trityl-L-xylono-γ-lactone (19)[22]. By analogy to the procedure in Section 4.1.1, on a scale of 13.3 mmol, affording 5-*O*-trityl-L-xylono-γ-lactone (**19**) as a colorless oil (3.25 g, 63%). R_f 0.19 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.34 (dd, J=11.1, 2.8 Hz, 1H), 3.38 (d, J=6.7 Hz, 1H), 3.64 (dd, J=11.1, 2.8 Hz, 1H), 4.29 (br s, 1H), 4.50 (q, J=7.5 Hz, 1H), 4.57 (dt, J=7.5, 2.8 Hz, 1H), 4.82 (d, J=7.5 Hz, 1H), 7.18–7.36 (m, 9H), 7.50–7.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 60.9, 73.5, 74.2, 78.3, 88.0, 127.3, 128.0, 128.4, 142.8, 175.3; HRMS (FAB^+, NBA, CH_2Cl_2) calcd for $C_{24}H_{22}O_5$ (M^+): 390.146088; obsd: 390.1461.

4.1.3. 2,3-Di-*O*-(methoxyethoxymethyl)-5-*O*-trityl-L-arabinono-γ-lactone (12). MEMCl (4.12 mL, 4.50 g, 36.1 mmol, 5.0 equiv) was added dropwise to a solution of 5-*O*-trityl-L-arabinono-γ-lactone (**11**) (2.82 g, 7.2 mmol, 1.0 equiv) and diisopropylethylamine (6.29 mL, 4.67 g, 36.1 mmol, 5.0 equiv) in AR-grade chloroform (45 mL) at rt under N_2. The mixture was heated at reflux for 11 h, cooled, diluted with chloroform (200 mL), washed with 10% aq citric acid (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The orange residue was purified by flash chromatography, eluting with 2:1 hexanes/EtOAc to give **12** as a colorless oil (3.89 g, 95%). R_f 0.31 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.26 (dd, J=10.9, 4.6 Hz, 1H), 3.29 (s, 3H), 3.34 (t, J=4.6 Hz, 2H), 3.38 (s, 3H), 3.39–3.61 (m, 5H), 3.71–3.87 (m, 2H), 4.35–4.38 (m, 1H), 4.47 (t, J=7.1 Hz, 1H), 4.58 (d, J=7.3 Hz, 1H), 4.64 (d, J=6.9 Hz, 1H), 4.73 (d, J=5.9 Hz, 1H), 4.89 (d, J=6.9 Hz, 1H), 5.12 (d, J=6.9 Hz, 1H), 7.22–7.32 (m, 9H), 7.43–7.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.9, 59.0, 62.0, 67.4, 67.7, 71.4, 71.6, 76.4, 77.6, 79.8, 86.8, 95.0, 95.2, 127.1, 127.9, 128.6, 143.3, 172.1; HRMS (EI^+) calcd for $C_{32}H_{38}O_9$ (M^+): 566.25158; obsd: 566.25163.

4.1.4. 2,3-Di-*O*-(methoxyethoxymethyl)-5-*O*-trityl-L-xylono-γ-lactone (20). By analogy to the procedure in Section 4.1.3, on a scale of 10.1 mmol of lactone **19**, affording **20** as a colorless oil (4.70 g, 82%). R_f 0.46 (2:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29 (s, 3H), 3.35 (s, 3H), 3.26–3.44 (m, 8H), 3.45–3.82 (m, 2H), 4.44 (app. t, J=7.1 Hz, 1H), 4.59–4.70 (m, 3H), 4.87 (d, J=6.6 Hz, 1H), 4.90 (d, J=7.3 Hz, 1H), 5.04 (d, J=6.8 Hz, 1H), 7.20–7.32 (m, 9H), 7.42–7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 58.9 (2C), 61.0, 67.5, 67.6, 71.4, 71.5, 74.6, 77.9, 78.5, 87.5, 95.0, 95.9, 127.0, 127.7, 128.6, 143.1, 172.5; HRMS (FAB^+, NBA, CH_2Cl_2) calcd for $C_{32}H_{39}O_9$ (MH^+): 567.259408; obsd: 567.259347.

4.1.5. 2,3-Di-*O*-(methoxyethoxymethyl)-5-*O*-trityl-L-arabinitol (13). A solution of $LiBH_4$ (2 M in THF, 6.87 mL, 13.7 mmol, 2.0 equiv) was added dropwise over 1 h to a solution of lactone **12** (3.89 g, 2.20 mmol, 1.0 equiv) in THF (40 mL) at rt under N_2. The mixture was stirred for 1.5 h after the addition was complete, then quenched by the cautious, dropwise addition of satd aq NH_4Cl (5 mL). The mixture was stirred 10 min then partitioned between EtOAc (300 mL) and brine (300 mL). The brine was extracted with a further portion of EtOAc (300 mL). The organic layers were filtered through $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 95:5 CH_2Cl_2/MeOH, to give **13** as a colorless oil (3.46 g, 88%). R_f 0.15 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.16 (dd, J=9.7, 5.1 Hz, 1H), 3.33–3.58 (m, 7H), 3.35 (s, 3H), 3.38 (s, 3H), 3.65–3.77 (m, 4H), 3.86 (dd, J=7.6, 2.7 Hz, 1H), 3.92–4.00 (m, 2H), 4.43 (d, J=6.8 Hz, 1H), 4.58 (d, J=6.8 Hz, 1H), 4.70–4.83 (m, 2H), 7.20–7.32 (m, 9H), 7.42–7.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 59.0 (2C), 61.5, 64.4, 67.6, 67.7, 69.8, 71.4, 71.6, 78.5, 80.0, 86.6, 96.2, 96.7, 126.9, 127.7, 128.6, 143.6; HRMS (FAB^+, NBA) calcd for $C_{32}H_{43}O_9$ (MH^+): 571.29163; obsd: 571.29163.

4.1.6. 2,3-Di-*O*-(methoxyethoxymethyl)-5-*O*-trityl-L-xylitol (21). By analogy to the procedure in Section 4.1.5, on a scale of 8.29 mmol of lactone **20**, affording **21** as a colorless oil (4.20 g, 89%). R_f 0.22 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.80 (br s, 2H), 3.14 (dd, J=9.2, 6.2 Hz, 1H), 3.25 (dd, J=9.2, 6.0 Hz, 1H), 3.32 (s, 3H), 3.35 (s, 3H), 3.42–3.89 (m, 13H), 4.05 (td, J=5.9, 2.6 Hz, 1H), 4.61–4.67 (m, 2H), 4.77 (d, J=7.3 Hz, 1H), 7.17–7.30 (m, 9H), 7.40–7.43 (m, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 58.9, 59.0, 61.0, 64.4, 67.6, 68.9, 71.5, 77.9, 80.9, 86.6, 96.0, 96.9, 126.9, 127.7, 127.9, 143.6; HRMS (FAB^+, NBA, CH_2Cl_2) calcd for $C_{32}H_{43}O_9$ (MH^+): 571.2907; obsd: 571.2898.

4.1.7. 1,4-Bis-*O*-(methanesulfonyl)-2,3-di-*O*-(methoxyethoxymethyl)-5-*O*-trityl-L-arabinitol (14). *N*,*N*-Dimethylaminopyridine (75 mg, 0.62 mmol, 0.2 equiv) was added to neat methanesulfonyl chloride (0.95 mL, 1.41 g, 12.3 mmol, 4.0 equiv) at 0 °C under N_2. A solution of diol **13** (1.76 g, 3.08 mmol, 1.0 equiv) in pyridine (8, 2 mL rinse) was added dropwise over 40 min. The mixture was gradually warmed to rt and stirred 5 h. The mixture was concentrated and the residue partitioned between chloroform (150 mL) and water (150 mL). The aqueous layer was extracted further with chloroform (2×80 mL). The organic extracts were filtered through $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 2:1 EtOAc/hexanes, to give **14** as a slightly yellow oil (2.01 g, 90%). R_f 0.26 (2:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.02 (s, 3H), 3.11 (s, 2H), 3.34 (s, 3H), 3.36 (s, 3H), 3.36–3.74 (m, 10H), 3.98 (app. q, J=5.0 Hz, 1H), 4.05 (t, J=4.3 Hz, 1H), 4.28 (dd, J=10.5, 5.8 Hz, 1H), 4.34 (dd, J=10.5, 5.2 Hz, 1H), 4.61 (d, J=7.0 Hz, 1H), 4.67–4.75 (m, 3H), 5.00–5.03 (m, 1H), 7.23–7.27 (m, 3H), 7.29–7.34 (m, 6H), 7.41–7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.2, 28.8, 58.9, 62.6, 67.6, 68.0 (2C), 71.5 (2C), 75.4, 76.0, 80.9, 87.4, 96.4, 96.7, 127.3, 128.0, 128.6, 143.1; HRMS (FAB$^+$, NBA) calcd for $C_{35}H_{47}O_{13}S_2$ (MH^+): 727.24581; obsd: 727.24494.

4.1.8. 1,4-Bis-*O*-(methanesulfonyl)-2,3-di-*O*-(methoxyethoxymethyl)-5-*O*-trityl-L-xylitol (22). By analogy to the procedure in Section 4.1.7, on a scale of 5.14 mmol of diol **21**, affording **22** (2.776 g, 74%). R_f 0.19 (2:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.99 (s, 3H), 3.06 (s, 3H), 3.32 (s, 3H), 3.34 (s, 3H), 3.42–3.75 (m, 7H), 3.65 (dd, J=10.0, 4.7 Hz, 1H), 3.68 (app. t, J=4.7 Hz, 1H), 4.37–4.42 (m, 3H), 4.54–4.60 (m, 3H), 4.54–4.60 (m, 3H), 4.75–4.81 (m, 3H), 5.02–5.03 (m, 1H), 7.22–7.35 (m, 9H), 7.41–7.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.1, 38.8, 58.8, 58.9, 62.8, 67.7, 68.2, 68.4, 71.4, 71.5, 75.3, 75.9, 80.7, 87.3, 96.3, 97.5, 127.3, 128.0, 128.5, 143.0; HRMS (FAB$^+$, NBA) calcd for $C_{35}H_{47}O_{13}S_2$ (MH^+): 727.24581; obsd: 727.243268.

4.1.9. (2*R*,3*S*,4*S*)-1-Benzyl-3,4-di-*O*-(methoxyethoxymethyl)-2-triphenylmethoxymethyl-pyrrolidine (15). A solution of bis-mesylate **14** (1.80 g, 2.48 mmol) in freshly distilled benzylamine (10 mL) was stirred at 90 °C under N_2 for 4 days. The mixture was cooled and partitioned between chloroform (50 mL) and brine (50 mL). The aqueous layer was extracted further with chloroform (2×50 mL). The combined organic extracts were washed with water (100 mL), filtered through $MgSO_4$ and concentrated. The residue was applied directly to a flash column, eluting with 5:1 hexanes/EtOAc until the benzaldehyde had eluted (R_f 0.63, 1:1 EtOAc/hexanes). The eluant was changed to 1.5:1.0 EtOAc/hexanes to elute pyrrolidine **15** as a yellow oil (1.590 g, 99%). R_f 0.28 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.31 (dd, J=10.8, 4.4 Hz, 1H), 3.10–3.68 (m, 13H), 3.34 (s, 3H), 3.32 (s, 3H), 3.98 (d, J=13.4 Hz, 1H), 4.06–4.10 (m, 1H), 4.26 (dd, J=5.0, 1.9 Hz, 1H), 4.59 (d, J=7.2 Hz, 1H), 4.68–4.71 (m, 2H), 4.77 (d, J=7.2 Hz, 1H), 7.15–7.30 (m, 14H), 7.41–7.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 57.7, 58.9 (2C), 59.5, 62.2, 65.5, 66.9, 67.0, 71.5, 71.6, 79.7, 81.5, 86.9, 94.4, 95.1, 126.6, 126.8, 127.6, 127.9, 128.5, 128.7, 138.6, 143.9; HRMS (FAB$^+$, NBA) calcd for $C_{39}H_{48}NO_7$ (MH^+): 642.34294; obsd: 642.34294.

4.1.10. (2*R*,3*R*,4*R*)-1-Benzyl-3,4-di-*O*-(methoxyethoxymethyl)-2-triphenylmethoxymethyl-pyrrolidine (23). By analogy to the procedure in 4.1.9, on a scale of 5.47 mmol of bis-mesylate **22**, to give pyrrolidine **23** as a yellow oil (3.23 g, 93%). R_f 0.32 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (dd, J=10.8, 4.8 Hz, 1H), 2.80 (dd, J=10.0, 5.7 Hz, 1H), 2.94 (d, J=10.8 Hz, 1H), 3.23 (ddd, J=16.0, 10.0, 5.7 Hz, 2H), 3.31 (s, 3H), 3.32 (s, 3H), 3.36–3.46 (m, 2H), 3.54–3.61 (m, 2H), 4.03 (m, 1H), 4.11 (d, J=9.4 Hz, 1H), 4.58 (d, J=7.2 Hz, 1H), 4.65 (d, J=7.2 Hz, 1H), 4.76 (d, J=2.8 Hz, 2H), 7.12–7.28 (m, 14H), 7.43–7.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 57.7, 58.8, 58.9, 59.5, 64.8, 66.8, 67.0, 69.5, 71.5, 71.6, 79.4, 83.4, 86.7, 94.0, 94.3, 126.8, 127.0, 127.7, 128.1, 128.7, 128.8, 138.8, 144.0; HRMS (FAB$^+$, NBA) calcd for $C_{39}H_{48}NO_7$ (MH^+): 642.34294; obsd: 642.34294.

4.1.11. (2*R*,3*S*,4*S*)-1-Fluorenylmethoxycarbonyl-3,4-di-*O*-(methoxyethoxymethyl)-2-triphenylmethoxy-methyl-pyrrolidine (16). Pd/C (10%, 600 mg) was added to a solution of the pyrrolidine **15** (2.43 g, 3.79 mmol) in absolute ethanol (30 mL). The flask was evacuated and then opened up to an atmosphere of H_2 and stirred for 16 h. The mixture was filtered through a pad of Celite, washing well with ethanol. The filtrate was concentrated and evaporated down from toluene. A solution of the pyrrolidine in toluene (15, 4 mL rinse) was added dropwise to a solution of fluorenylmethyl chloroformate (1.08 g, 4.17 mmol, 1.1 equiv) in toluene (8 mL) at 0 °C. Triethylamine (380 μL, 276 mg, 2.73 mmol, 1.1 equiv) was added over 10 min, the mixture warmed to rt and stirred for 2 h. The suspension was filtered through a sintered glass funnel, washing well with toluene. The filtrate was concentrated and the residue purified by flash chromatography, eluting with 1:1 EtOAc/hexanes to give **16** (2.56 g, 87%). R_f 0.27 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.22–3.55 (m, 1H), 3.37–3.48 (m, 4H), 3.52–3.62 (m, 4H), 3.71–3.82 (m, 3H), 3.95–4.38 (m, 5H), 4.53–4.86 (m, 5H), 7.17–7.30 (m, 11H), 7.35–7.48 (m, 9H), 7.59 (t, J=7.6 Hz, 1H), 7.71–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.0 and 47.1, 49.8 and 49.9, 57.9 and 58.2, 59.0 (2C), 60.0 and 60.3, 67.3, 71.5, 71.6, 77.2, 78.5 and 79.0, 80.1 and 80.7, 87.1 and 87.2, 95.3 and 95.5, 96.1, 119.9, 124.8, 124.9, 125.0, 126.9, 127.0, 127.5, 127.6, 127.7, 128.6, 128.7, 141.2, 143.8, 143.9, 154.8 and 154.9; HRMS (FAB$^+$, NBA) calcd for $C_{47}H_{52}NO_9$ (MH^+): 774.364208; obsd: 774.362996.

4.1.12. (2*R*,3*R*,4*R*-1-Fluorenylmethoxycarbonyl-3,4-di-*O*-(methoxyethoxymethyl)-2-triphenyl-methoxymethyl)-pyrrolidine (24). By analogy to the procedure in Section 4.1.11, on a scale of 3.41 mmol of pyrrolidine **23**, to give compound **24** (2.247 g, 85%). R_f 0.28 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (t, J=8.7 Hz, 1H), 3.27 (t, J=8.7 Hz, 1H), 3.36 (s, 3H), 3.37 and 3.38 (2s, 3H), 3.42–3.62 (m, 7H), 3.70–3.75 (m, 2H), 3.84 (ddd, J=23.0, 11.8, 5.5 Hz, 1H), 4.02–4.33 (m, 5H), 4.45–4.65 (m, 3H), 4.79–4.85 (m, 2H), 7.14–7.29 (m, 11H), 7.36–7.45 (m, 8H), 7.47 (d, J=7.6 Hz, 1H), 7.57 (d, J=7.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.1 and

47.2, 51.1 and 51.3, 59.0 (2C), 61.3 and 61.8, 62.8 and 63.1, 67.1, 67.2, 67.5, 71.5, 71.6, 77.2, 78.2 and 79.1, 79.6 and 80.8, 86.6 and 86.7, 94.4, 94.5, 119.9, 124.9, 125.0, 125.2, 127.0, 127.7, 128.6, 141.2, 143.6, 143.8, 144.0, 144.2, 154.8; HRMS (FAB^+, NBA) calcd for $C_{47}H_{52}NO_9$ (MH^+): 774.364208; obsd: 774.362996.

4.1.13. (2*R*,3*S*,4*S*)-1-Fluorenylmethoxycarbonyl-3,4-di-*O*-(methoxyethoxymethyl)-2-hydroxymethyl-pyrrolidine (17). A mixture of formic acid (6.5 mL) and acetonitrile (45 mL) was added to the pyrrolidine **16** (1.637 g, 1.90 mmol) and stirred at rt under N_2 for 2.5 h. The mixture was partitioned between EtOAc (200 mL) and satd aq $NaHCO_3$ (200 mL). The organic layer was washed further with brine (200 mL), filtered through $MgSO_4$, and concentrated. The residue was purified by flash chromatography, eluting with 2% MeOH in EtOAc to give compound **17** (1.049 g, 93%). R_f 0.18 (100% EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.38 (s, 3H), 3.40 (s, 3H), 3.54–3.57 (m, 5H), 3.64–3.91 (m, 7H), 4.07–4.10 (m, 1H), 4.19–4.29 (m, 3H), 4.38–4.56 (m, 2H), 4.73–4.85 (m, 4H), 7.32 (t, J=7.5 Hz, 2H), 7.41 (t, J=7.5 Hz, 2H), 7.59 (d, J=7.4 Hz, 2H), 7.77 (d, J=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 47.2, 50.7, 59.0, 62.1 and 62.3, 67.3, 67.5, 67.7, 71.6, 77.3, 80.6, 94.6, 95.3, 119.9, 124.9, 126.9, 127.6, 141.2, 143.7, 156.3; HRMS (FAB^+, NBA) calcd for $C_{28}H_{38}NO_9$ (MH^+): 532.25466; obsd: 532.25662.

4.1.14. (2*R*,3*R*,4*R*)-1-Fluorenylmethoxycarbonyl-3,4-di-*O*-(methoxyethoxymethyl)-2-hydroxymethyl-pyrrolidine (25). By analogy to the procedure in Section 4.1.13, on a scale of 3.26 mmol of pyrrolidine **24**, to give compound **25** (1.66 g, 96%). R_f 0.19 (100% EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.38 (s, 6H), 3.49–3.56 (m, 5H), 3.65–3.89 (m, 7H), 3.97 (d, J=5.8 Hz, 1H), 4.17 (br s, 2H), 4.23 (t, J=7.0 Hz, 1H), 4.32–4.50 (m, 2H), 4.75–4.87 (m, 4H), 7.31 (td, J=7.4, 0.9 Hz, 2H), 7.39 (t, J=7.4 Hz, 2H), 7.59 (dd, J=6.9, 4.2 Hz, 2H), 7.75 (d, J=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.1, 51.0 and 51.4, 58.9, 61.2 and 63.2, 64.6 and 65.6, 66.9 and 67.1, 67.3, 67.5, 71.5, 78.9, 80.4 and 81.1, 94.4, 94.9 and 95.0, 119.8, 124.9, 125.0, 126.9, 127.6, 141.2, 143.7, 143.8, 154.9 and 156.2; HRMS (FAB^+, NBA) calcd for $C_{28}H_{38}NO_9$ (MH^+): 532.25466; obsd: 532.25514.

4.1.15. (2*R*,3*S*,4*S*)-1-Fluorenylmethoxycarbonyl-3,4-di-*O*-(methoxyethoxymethoxy)-L-proline (18). Sodium chlorite (78 mg, 0.87 mmol, 2.0 equiv) and TEMPO (4 mg, cat.) were added to a solution of alcohol **17** (229 mg, 0.43 mmol, 1.0 equiv) in a mixture of acetonitrile (0.85 mL) and 0.67 M aq NaH_2PO_4 (0.75 mL). This mixture was heated to 40 °C and bleach (12 μL) added, resulting in a deep rose color. The reaction mixture was checked by TLC and bleach added periodically to maintain the deep rose color, and until the conversion to the acid was complete. The mixture was poured onto ice-water (20 mL) containing Na_2SO_3 (100 mg). This led to immediate decolorizaton; the pH was 5–6 and 2 M HCl (~0.5 mL) was added to give a pH of 2 and considerable precipitation. The mixture was extracted with EtOAc (3×20 mL). The combined extracts were filtered through $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 10–20% MeOH in CH_2Cl_2 to isolate **18** (207 mg, 88%). R_f 0.36 (9:1 CH_2Cl_2/MeOH); $[\alpha]_D^{20}$ −23.9 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3500–2384 (O–H), 1708 (C=O), 1122 (C–O–C); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.34–3.37 (m, 6H), 3.50–3.81 (m, 10H), 4.14–4.82 (m, 10H), 7.24–7.38 (m, 4H), 7.52–7.57 (m, 2H), 7.67–7.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.0, 50.0 and 50.8, 58.8, 59.0, 67.2, 67.6 and 67.8, 71.4 and 71.5, 77.2 and 77.8, 79.4 and 80.4, 94.7, 95.3, 119.8, 125.0, 125.1, 126.9, 127.5, 141.1, 143.5, 143.7, 143.9, 154.7 and 155.3, 172.9; HRMS (EI+) calcd for $C_{28}H_{36}NO_{10}$ (MH^+): 546.23392; obsd: 546.23345.

4.1.16. (2*R*,3*R*,4*R*)-1-Fluorenylmethoxycarbonyl-3,4-di-*O*-(methoxyethoxymethoxy)-L-proline (26). By analogy to the procedure in Section 4.1.15 on a scale of 0.63 mmol of alcohol **25**, to afford acid **26** (302 mg, 88%). R_f 0.22 (9:1 CH_2Cl_2/MeOH); $[\alpha]_D^{20}$ −13.6 (*c* 1.04, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$), 3502–2600 (O–H), 1703 (C=O), 1160 (O–C–O); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.31 (s, 6H), 3.30–3.80 (m, 10H), 4.12–4.18 (m, 10H), 7.19–7.66 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.9 and 47.0, 50.8, 58.8, 64.3 and 64.9, 67.2, 67.8 and 68.0, 71.4, 71.5, 77.3 and 78.1, 71.5 and 83.0, 94.4, 94.7, 119.8, 125.1, 127.0, 127.6, 141.1, 143.6, 143.7, 144.0, 154.8 and 156.0, 172.9; HRMS (EI^+) calcd for $C_{28}H_{36}NO_{10}$ (MH^+): 546.23392; obsd: 546.23412.

4.1.17. 2,3-*cis*-3,4-*trans*-3,4-Dihydroxy-L-proline (1). A solution of acid **18** (96 mg, 0.18 mmol) in a solution of HBr in glacial acetic acid (33 wt%; 3 mL) was stirred for 18 h at rt. The mixture was concentrated and then dissolved in Tesser's base.[21] The pH was adjusted to about 10 by the addition of a few drops of 2 M aq NaOH. The mixture was stirred for 3 h and then concentrated. The residue was partitioned between water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted further with EtOAc (4×5 mL). The aqueous layer was added to the top of a short column of Dowex H^+ resin and eluted with two column volumes of water. The eluant was changed to 0.5 M NH_4OH and the fractions checked by TLC, staining with ninhydrin. Relevant fractions were lyophilized to give a colorless solid, which was dissolved in water, filtered through a 0.2 μ nylon filter and lyophilized again to give compound **1** (25 mg, quant.). R_f 0.26 (3:3:3:1 ^{n}BuOH, EtOH, NH_3, H_2O); $[\alpha]_D^{20}$ −48.1 (*c* 1.00, H_2O) lit.[2a] $[\alpha]_D^{20}$ −61.2 (*c* 0.5, H_2O) lit.[11] $[\alpha]_D^{27}$ −56 (*c* 0.62, H_2O) lit.[23] $[\alpha]_D^{27}$ −63.2 (*c* 0.5, H_2O) lit.[24] $[\alpha]_D^{27}$ −63.0 (*c* 0.8, H_2O); ^1H NMR (D_2O, 400 MHz) δ 3.16 (d, J=12.8 Hz, 1H), 4.56 (dd, J=12.8, 3.7 Hz, 1H), 4.21 (d, J=4.0 Hz, 1H), 4.27 (d, J=3.7 Hz, 1H), 4.32 (d, J=4.0 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 50.9, 65.2, 75.0, 75.4, 171.0; HRMS (FAB^+, glycerol) calcd for $C_5H_{10}NO_4$ (MH^+): 148.06098; obsd: 148.06063.

4.1.18. 2,3-*trans*-3,4-*trans*-3,4-Dihydroxy-L-proline (2). By analogy to the procedure in Section 4.1.17, starting with acid **26** (80 mg) and giving rise to **2** (21 mg, quant.). R_f 0.39 (3:3:3:1 ^{n}BuOH, EtOH, NH_3, H_2O); $[\alpha]_D^{20}$ −21.4 (*c* 0.28, H_2O) lit.[11] $[\alpha]_D^{25}$ −19 (*c* 0.4, H_2O) lit.[24] $[\alpha]_D^{22}$ −12.6 (*c* 0.53, H_2O);[22] ^1H NMR (D_2O, 400 MHz) δ 3.36 (d, J=12.4 Hz, 1H), 3.33 (dd, J=12.7, 3.7 Hz, 1H), 3.89 (m, 1H), 4.16 (m, 1H), 4.37 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 50.9, 67.6, 74.1, 78.5, 171.6; HRMS (FAB^+, glycerol) calcd for $C_5H_{10}NO_4$ (MH^+): 148.06098; obsd: 148.06062.

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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.2005.07.072.^{13}C NMR spectra for compounds **1**, **2** and **12–26**.

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Synthesis of furo[2,3-*c*]-2,7-naphthyridine derivatives via domino heterocyclization reaction

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Abstract—2-Amino-4-cyanomethyl-6-dialkylamino-3,5-pyridinedicarbonitriles were found to react with substituted oxiranes yielding 5,6-diamino-8-dialkylamino-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitriles. The oxirane ring was shown to be opened selectively from the unsubstituted side and further cyclization occurred with participation of 3-CN, but not 5-CN of the starting pyridines. The furonaphthyridines obtained were converted into 2-dialkylamino-5-methyl-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitriles and 2-dialkylamino-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitriles by treatment with acetic anhydride and cyclohexanone, respectively. The structure of prepared compounds was confirmed unambiguously by X-ray crystallographic study.

1. Introduction

Furo[2,3-*c*]-2,7-naphthyridine is a rare and uninvestigated heterocyclic system. To date only four derivatives of this framework have been reported.[1,2] All were prepared through the same three-step approach including the classic Hantzsch pyridine synthesis using 2-nitrofuran-3-carbaldehyde, methyl acetoacetate and ammonia, further aromatization of the dihydropyridine obtained and, finally, reduction of the nitro group accompanied by intramolecular interaction of the amino group formed with the suitably situated ester. The method is limited, first of all, by the single applicable furancarbaldehyde and secondly, by the Hantzsch synthesis restrictions.

Over recent years so-called domino reactions have got an increasing importance in condensed heterocyclic chemistry,[3–7] since they allow creation of two or more rings at once at the expense of sequential chemical transformations, induced one by another. Recently the domino principle based approaches were applied by us and other researchers to preparation of pyrrolo- and thieno[2,3-*c*]-2,7-naphthyridines, respectively.[8,9] Continuing the investigations in the field it would be interesting to elaborate a domino synthesis of the corresponding furo analogues as an alternative to the known stepwise procedure.[1,2]

2. Results and discussion

Malonodinitrile and ethyl cyanoacetate were reported to react with epoxides yielding aminofurans **1**[10–15] (Fig. 1). When propenetricarbonitrile **2** (malonodinitrile dimer) was used as starting material the intermediate furans of type **1** (X is $C(NH_2)=C(CN)_2$) underwent further intramolecular addition of the amino group to the nitrile resulting in furopyridines **3**.[16] Thus, compounds **3** were obtained by formation of the two rings at once via the domino sequence including methylene alkylation and consecutive intramolecular additions of hydroxy and amino groups to nitriles. Previously the readily available pyridines **4–6**

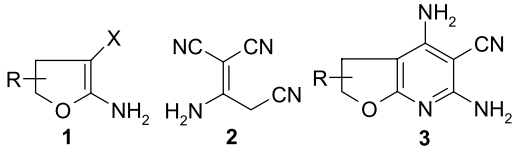

Figure 1. X=CN, CO_2Et.

Keywords: Domino reactions; Furo[2,3-*c*]-2,7-naphthyridines; Nitriles; Oxiranes; Spiro compounds.
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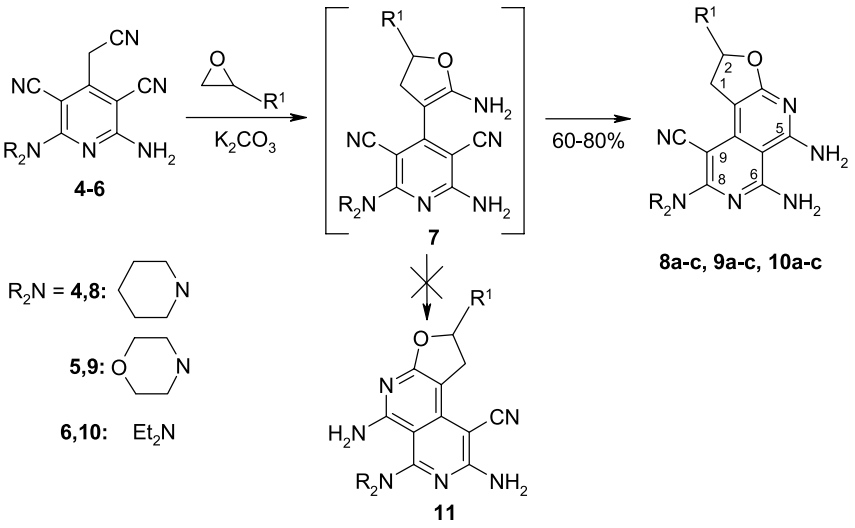


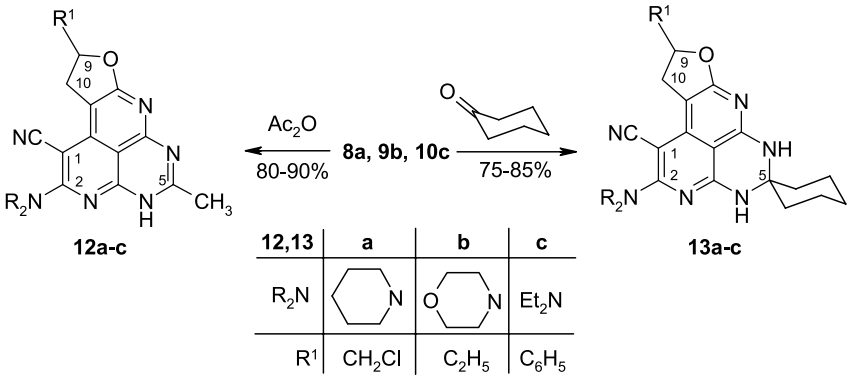
Scheme 1. R^1 = a: CH_2Cl, b: C_2H_5, c: C_6H_5.

were shown to be suitable precursors of various 2,7-naphthyridines.[8,17] Like compound **2** derivatives **4–6** contain the same vicinal CH_2CN groups moiety and CN and therefore, their reaction with epoxides should occur similarly and should afford the target furonaphthyridines. However, contrary to compound **2** there are two possibilities of a ring closure in the intermediates **7** (Scheme 1) with participation of 3-CN or 5-CN leading to the isomers **8–10** and **11**, respectively. Moreover different directions of the epoxide ring opening could not be excluded. Although in most cases oxiranes were reported to react with active methylenes from the less substituted side[10–16,18–23] a few examples of nucleophilic attack at the more substituted side[13,16,24–26] have also been noted. Hence the possible furan moiety isomerism in the products should be taken into consideration as well.

Nevertheless, treatment of the pyridines **4–6** with substituted oxiranes in ethanol in the presence of K_2CO_3 was found to give individual compounds isolated in 60–80% yields. ^1H and ^{13}C NMR spectra of isomeric 4- and 5-substituted furans **1** were well documented.[11–13] Comparison of the published data with the spectra of compounds obtained in the aliphatic region revealed their close resemblance with those of 5-substituted derivatives **1**. Hence the prepared compounds were assumed to be 2-substituted furonaphthyridines **8–10** or **11**, but not the 1-substituted isomers. Additional chemical transformations were used to distinguish the structures **8–10** and **11**. Thus, the selected derivatives **8a**, **9b**, **10c** were treated with acetic anhydride and cyclohexanone (Scheme 2). Both reactions resulted in a ring annulation and afforded fused heterocycles **12** and spirocyclic compound **13**. The similar transformations are well known for 1,8-naphthalenediamines[27–31] and have also been reported for certain 2,7-naphthyridine-1,8-diamines.[8,32] So the synthesis of derivatives **12**,**13** establishes the neighboring arrangement of the amino groups in the prepared furonaphthyridines thus excluding the structure **11**. Therefore the structures **8–10** should be assigned to the obtained compounds.

Of course, an X-ray crystallographic study would be desirable to determine the structures **8–10** undoubtedly. Unfortunately, we failed to grow a suitable crystal from the diamines **8–10**, but it was obtained from the cyclohexylidene derivative **13b**. An X-ray study confirmed its structure (Fig. 2) and therefore, proved the structure of the diamine precursors **8–10** unambiguously.

It should be emphasized that there were no detectable amounts of isomers in the reaction mixtures during synthesis of **8–10**. Hence the reaction occurs selectively both on the steps of epoxide ring cleavage and the amino group addition to nitrile. Considering the literature



Scheme 2.

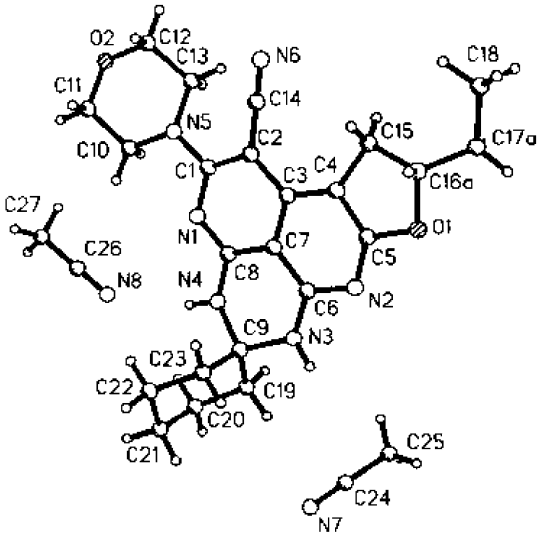


Figure 2. X-ray molecular structure of compound **13b** (a solvate with two molecules of acetonitrile) with the atom numbering used in the crystallographic analysis. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 270785. 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].

data[10–16,18–23] the selectivity of the oxiranes opening is expected. Additional steric hindrances at the active methylene of the pyridines **4–6** produced by neighboring nitriles seem only to uphold the selectivity. Predominant reactivity of 3-CN versus 5-CN in the pyridines **4–6** and related compounds was described earlier.[8,17,32] Its reasons were discussed in detail in our previous work[8] and are believed to be the same in the present case. Also it is interesting to note that the epichlorohydrine reacted clearly as epoxide saving the chloromethyl group and yielding furonaphthyridines **8a**,**9a**,**10a**. According to the literature both its reactions with active methylenes with and without participation of the chlorine are known.[16,33] Furthermore, it should be stated that derivatives **12**,**13** are the representatives of hitherto unknown heterocyclic systems, namely furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine and spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}.

To resume, present investigations has resulted in a simple and convenient synthesis of furo[2,3-*c*]-2,7-naphthyridine derivatives **8–10** based on the domino principle. Moreover, the derivatives of two novel heterocyclic frameworks **12**,**13** have been obtained by further ring annulations to the compounds **8–10**. The starting pyridines **4–6** are available in quantitative yields by reaction of 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile with appropriate secondary amines.[17] The chloropyridine precursor, in turn, was prepared from malonodinitrile and inorganic reagents in two steps.[32] Hence, the furonaphthyridines **8–10** and their condensed derivatives **12**,**13** have been synthesized from malonodinitrile in four and five steps, respectively. Other reagents used, for example, epoxides, acetic anhydride and cyclohexanone are also of general access. So the new heterocycles **8–10**,**12**,**13** of high complexity degree have been obtained, in fact, from simplest and cheapest sources through the sequence of moderate length. This exhibits a power and effectiveness of the domino strategy in heterocyclic synthesis. Apparently, the present method extends considerably the scope of furonaphthyridines chemistry and has significant advantages in comparison with the stepwise approach described.[1,2]

3. Experimental

The pyridines **4–6** were prepared as reported.[17] Other reagents were commercially available and were used without additional purification. Ethanol was dried with CaO. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. J values are in Hz. The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

3.1. Furo[2,3-*c*]-2,7-naphthyridines 8–10. General procedure

Powdered K_2CO_3 (0.41 g, 3 mmol) was added to a solution of pyridine **4–6** (3 mmol) and corresponding epoxide (3 mmol) in ethanol (5 mL). The resulting mixture was refluxed for 1 h. After cooling the precipitate formed was filtered and thoroughly washed with water to remove inorganic materials. Recrystallization from an appropriate solvent afforded compounds **8–10**.

3.1.1. 5,6-Diamino-2-chloromethyl-8-(1-piperidinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (8a). Yield 71%. Mp 294–296 °C (from dioxane); δ_H 1.56–1.61 (6H, m, NR_2), 3.19 (1H, dd, $J^3=6.8$ Hz, $J^2=15.6$ Hz, 1-H), 3.54 (1H, dd, $J^3=9.6$ Hz, $J^2=15.6$ Hz, 1-H), 3.65 (4H, m, NR_2), 3.87 (1H, dd, $J^3=4.8$ Hz, $J^2=11.6$ Hz, CH_2Cl), 3.96 (1H, dd, $J^3=4.0$ Hz, $J^2=11.6$ Hz, CH_2Cl), 5.03 (1H, m, 2H), 6.46 (2H, s, NH_2), 7.10 (2H, s, NH_2). δ_C 24.5 (4-C_{NR2}), 26.2 (3,5-C_{NR2}), 31.3 (1-C), 47.8 (CH_2Cl), 48.8 (2,6-C_{NR2}), 68.1 (9-C), 79.7 (2-C), 92.5 (5a-C), 94.1 (9b-C), 121.2 (CN), 145.9 (9a-C), 159.4 (5-C), 159.8 (6-C), 162.3 (8-C), 167.4 (3a-C). Found: 56.78% C, 5.42% H, 9.80% Cl, 23.34% N; $C_{17}H_{19}ClN_6O$ requires 56.90% C, 5.34% H, 9.88% Cl, 23.42% N.

3.1.2. 5,6-Diamino-2-ethyl-8-(1-piperidinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (8b). Yield 81%. Mp 191–192 °C (from EtOH); δ_H 1.03 (3H, t, $J=7.2$, CH_3), 1.66 (6H, m, NR_2), 1.74 (2H, m, CH_2CH_3), 3.02 (1H, dd, $J^3=6.4$ Hz, $J^2=15.2$ Hz, 1-H), 3.54 (1H, dd, $J^3=10.0$ Hz, $J^2=15.2$ Hz, 1-H), 3.66 (4H, m, NR_2), 4.68 (1H, m, 2-H), 6.12 (2H, s, NH_2), 6.69 (2H, s, NH_2). δ_C 9.0 (CH_3), 24.1 (3,5-C_{NR2}), 25.2 (4-C_{NR2}), 27.3 (CH_2CH_3), 34.9 (1-C), 47.1 (2,6-C_{NR2}), 66.4 (9-C), 82.3 (2-C), 89.5 (5a-C), 92.1 (9b-C), 121.8 (CN), 146.0 (9a-C), 157.3 (6-C), 160.7 (5-C), 164.2 (8-C), 168.5 (3a-C). Found: 63.97% C, 6.53% H, 24.82% N; $C_{18}H_{22}N_6O$ requires 63.89% C, 6.55% H, 24.83% N.

3.1.3. 5,6-Diamino-2-phenyl-8-(1-piperidinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (8c). Yield 62%. Mp 206–207 °C (from acetonitrile); δ_H 1.42

(2H, m, NR_2), 1.54 (4H, m, NR_2), 3.48 (4H, m, NR_2), 4.30 (1H, dd, $J^3=1.4$ Hz, $J^2=8.8$ Hz, 1-H), 4.79 (1H, dd, $J^3=8.4$ Hz, $J^2=8.8$ Hz, 1-H), 5.00 (1H, dd, $J^3=1.4$ Hz, $J^3=8.4$ Hz, 2-H), 6.63 (2H, s, NH_2), 7.02 (2H, d, $J=7.6$ Hz, 2,6-H_{Ph}), 7.14 (2H, s, NH_2), 7.17 (1H, t, $J=7.6$ Hz, 4-H_{Ph}), 7.25 (2H, t, $J=7.6$ Hz, 3,5-H_{Ph}). δ_C 24.1 (4-C_{NR2}), 25.7 (3,5-C_{NR2}), 44.3 (1-C), 48.3 (2,6-C_{NR2}), 67.8 (9-C), 77.4 (2-C), 92.2 (5a-C), 97.5 (9b-C), 120.2 (CN), 126.4 (4-C_{Ph}), 126.9 (3,5-C_{Ph}), 128.4 (2,6-C_{Ph}), 144.4 (1-C_{Ph}), 145.9 (9a-C), 159.2 (5-C), 160.0 (6-C), 161.9 (8-C), 168.4 (3a-C). Found: 68.50% C, 5.60% H, 21.80% N; $C_{22}H_{22}N_6O$ requires 68.38% C, 5.74% H, 21.75% N.

3.1.4. 5,6-Diamino-2-chloromethyl-8-(4-morpholinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (9a). Yield 73%. Mp >300 °C (from DMF); δ_H 3.19 (1H, dd $J^3=6.8$ Hz, $J^2=16.0$ Hz, 1-H), 3.54 (1H, dd $J^3=9.6$ Hz, $J^2=16.0$ Hz, 1-H), 3.65 (8H, m, NR_2), 3.87 (1H, dd $J^3=4.4$ Hz, $J^2=11.2$ Hz, CH_2Cl), 3.95 (1H, dd $J^3=3.6$ Hz, $J^2=11.2$ Hz, CH_2Cl), 5.04 (1H, m, 2-H), 6.52 (2H, s, NH_2), 7.21 (2H, s, NH_2). δ_C 31.1 (1-C), 45.4 (CH_2Cl), 46.1 (NCH_2), 65.6 (OCH_2), 69.7 (9-C), 79.0 (2-C), 93.0 (5a-C), 94.1 (9b-C), 119.1 (CN), 145.4 (9a-C), 158.6 (6-C), 159.0 (5-C), 162.9 (8-C), 165.4 (3a-C). Found: 53.48% C, 4.67% H, 9.80% Cl, 23.34% N; $C_{16}H_{17}ClN_6O_2$ requires 53.26% C, 4.75% H, 9.83% Cl, 23.29% N.

3.1.5. 5,6-Diamino-2-ethyl-8-(4-morpholinyl)-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (9b). Yield 77%. Mp 263–264 °C (from EtOH); δ_H 0.94 (3H, t, $J=7.4$ Hz, CH_3), 1.69 (2H, m, CH_2CH_3), 2.97 (1H, dd, $J^3=7.2$ Hz, $J^2=15.2$ Hz, 1-H), 3.51 (1H, dd, $J^3=9.6$ Hz, $J^2=15.2$ Hz, 1-H), 3.65 (8H, m, NR_2), 4.71 (1H, m, 2-H), 6.46 (2H, s, NH_2), 7.18 (2H, s, NH_2). δ_C 9.2 (CH_3), 28.7 (CH_2CH_3), 32.6 (1-C), 48.0 (NCH_2), 66.2 (OCH_2), 68.6 (9-C), 82.3 (2-C), 92.1 (5a-C), 94.4 (9b-C), 120.7 (CN), 145.3 (9a-C), 159.2 (5-C), 159.6 (6-C), 162.3 (8-C), 167.5 (3a-C). Found: 59.95% C, 5.96% H, 24.92% N; $C_{17}H_{20}N_6O_2$ requires 59.99% C, 5.92% H, 24.69% N.

3.1.6. 5,6-Diamino-8-(4-morpholinyl)-2-phenyl-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (9c). Yield 65%. Mp 242–243 °C (from dioxane); δ_H 3.57 (8H, m, NR_2), 4.28 (1H, dd, $J^3=1.6$ Hz, $J^2=10.4$ Hz, 1-H), 4.79 (1H, dd, $J^3=8.8$ Hz, $J^2=10.4$ Hz, 1-H), 5.00 (1H, dd, $J^3=8.8$,1.6 Hz, 2-H), 7.02 (2H, d, $J=7.6$ Hz, 2,6-H_{Ph}), 7.13 (2H, s, NH_2), 7.17 (3H, m, NH_2, 4-H_{Ph}), 7.25 (2H, dd, $J=7.6$, 7.6 Hz, 3,5-H_{Ph}). δ_C 43.7 (1-C), 49.0 (NCH_2), 64.9 (OCH_2), 65.0 (9-C), 78.2 (2-C), 92.4 (5a-C), 97.0 (9b-C), 120.7 (CN), 124.3 (3,5-C_{Ph}), 125.6 (4-C_{Ph}), 128.0 (2,6-C_{Ph}), 144.7 (1-C_{Ph}), 147.6 (9a-C), 160.6 (5-C), 161.0 (6-C), 162.3 (8-C), 169.9 (3a-C). Found: 64.65% C, 5.14% H, 21.66% N; $C_{21}H_{20}N_6O_2$ requires 64.94% C, 5.19% H, 21.64% N.

3.1.7. 5,6-Diamino-2-chloromethyl-8-diethylamino-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (10a). Yield 76%. Mp 300–301 °C (from dioxane); δ_H 1.23 (6H, t, $J=6.0$ Hz, $2CH_3$), 3.29 (1H, dd, $J^3=6.4$ Hz, $J^2=15.6$ Hz, 1-H), 3.63 (5H, m, NCH_2, 1-H), 3.77 (1H, dd $J^3=4.4$ Hz, $J^2=10.8$ Hz, CH_2Cl), 3.83 (1H, dd $J^3=3.2$ Hz, $J^2=10.8$ Hz, CH_2Cl), 4.97 (1H, m, 2-H), 6.17 (2H, s, NH_2), 6.64 (2H, s, NH_2). δ_C 13.6 (CH_3), 31.2 (1-C), 43.2 (NCH_2), 47.5 (CH_2Cl), 65.8 (9-C), 79.1 (2-C), 91.8 (5a-C), 93.7 (9b-C), 121.2 (CN), 145.9 (9a-C), 158.8 (5-C), 159.3 (6-C), 160.1 (8-C), 167.1 (3a-C). Found: 55.34% C, 5.60% H, 10.43% Cl, 24.17 N; $C_{16}H_{19}ClN_6O$ requires 55.41% C, 5.52% H, 10.22% Cl, 24.23 N.

3.1.8. 5,6-Diamino-8-diethylamino-2-ethyl-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (10b). Yield 83%. Mp 212–213 °C (from *i*-PrOH); δ_H 1.03 (3H, t, $J=7.4$ Hz, CH_3), 1.23 (6H, t, $J=6.8$ Hz, $2CH_3$), 1.74 (2H, m, CH_2CH_3), 3.05 (1H, dd, $J^3=6.8$ Hz, $J^2=15.2$ Hz, 1-H), 3.57 (1H, dd, $J^3=9.6$ Hz, $J=15.2$, 1-H), 3.63 (4H, q, $J=6.8$ Hz, NCH_2), 4.66 (1H, m, 2-H), 6.07 (2H, s, NH_2), 6.59 (2H, s, NH_2). δ_C 9.5 (CH_2CH_3), 13.8 (CH_3), 27.3 (CH_2CH_3), 33.0 (1-C), 44.0 (NCH_2), 65.9 (9-C), 82.6 (2-C), 93.7 (9b-C), 94.6 (5a-C), 120.1 (CN), 142.9 (9a-C), 158.4 (5-C), 162.2 (6-C), 162.4 (8-C), 167.0 (3a-C). Found: 62.40% C, 6.76% H, 25.83% N; $C_{17}H_{22}N_6O$ requires 62.56% C, 6.79% H, 25.75% N.

3.1.9. 5,6-Diamino-8-diethylamino-2-phenyl-1,2-dihydrofuro[2,3-*c*]-2,7-naphthyridine-9-carbonitrile (10c). Yield 79%. Mp 170–171 °C (from dioxane); δ_H 1.11 (6H, t, $J=7.0$ Hz, $2CH_3$), 3.48 (4H, m, NCH_2), 4.33 (1H, dd, $J^3=2.0$ Hz, $J^2=8.4$ Hz, 1-H), 4.78 (1H, dd, $J^3=8.8$ Hz, $J^2=8.4$ Hz, 1-H), 5.09 (1H, dd, $J^3=8.8$, 2.0 Hz, 2-H), 6.34 (2H, s, NH_2), 6.61 (2H, s, NH_2), 7.08–7.14 (3H, m, 2,6,4-H_{Ph}), 7.22 (2H, dd, $J=7.6$, 7.6 Hz, 3,5-H_{Ph}). δ_C 16.7 (CH_3), 43.4 (NCH_2), 44.9 (1-C), 67.1 (9-C), 78.6 (2-C), 93.0 (5a-C), 98.3 (9b-C), 119.7 (CN), 126.9 (2,6-C_{Ph}), 127.1 (4-C_{Ph}), 127.2 (3,5-C_{Ph}), 146.5 (9a-C), 146.8 (1-C_{Ph}), 158.1 (5-C), 161.4 (6-C), 164.4 (8-C), 168.3 (3a-C). Found: 67.57% C, 5.81% H, 22.48% N; $C_{21}H_{22}N_6O$ requires 67.36% C, 5.92% H, 22.44% N.

3.2. Furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridines 12a–c. General procedure

A solution of the diamine **8a**,**9b**,**10c** (2.5 mmol) in acetic anhydride (3 mL) was heated at 100–110 °C for 1 h. After cooling the precipitated solid was filtered, washed with water and recrystallized from DMF to give derivatives **12a**–**c**.

3.2.1. 9-Chloromethyl-5-methyl-2-(1-piperidinyl)-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitrile (12a). Yield 92%. Mp >300 °C (from DMF); δ_H 1.63 (6H, m, NR_2), 2.36 (3H, s, 5-CH_3), 3.22 (1H, dd $J^3=7.2$ Hz, $J^2=16.0$ Hz, 10-H), 3.57 (1H, dd $J^3=9.6$ Hz, $J^2=16.0$ Hz, 10-H), 3.70 (4H, m, NR_2), 3.95 (1H, dd $J^3=4.8$ Hz, $J^2=11.6$ Hz, CH_2Cl), 4.03 (1H, dd $J^3=4.0$ Hz, $J^2=11.6$ Hz, CH_2Cl), 5.15 (1H, m, 9-H), 12.84 (1H, br s, NH). δ_C 24.6 (5-CH_3), 24.7 (4-C_{NR2}), 27.8 (3,5-C_{NR2}), 32.6 (10-C), 46.3 (CH_2Cl), 47.8 (2,6-C_{NR2}), 74.6 (1-C), 86.1 (9-C), 103.0 (10a-C), 110.0 (10c-C), 121.1 (CN), 149.6 (10b-C), 151.7 (6a-C), 156.1 (3a-C), 162.8 (2-C), 168.0 (5-C), 168.7 (7a-C). Found: 59.81% C, 5.10% H, 9.39% Cl, 21.92% N; $C_{19}H_{19}ClN_6O$ requires 59.61% C, 5.00% H, 9.26% Cl, 21.95% N.

3.2.2. 9-Ethyl-5-methyl-2-(4-morpholinyl)-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitrile (12b). Yield 81%. Mp >300 °C (from DMF); δ_H 0.97 (3H, t, $J=7.2$ Hz, CH_2CH_3), 1.75 (2H, m,

CH_2CH_3), 2.36 (3H, s, 5-CH_3), 2.97 (1H, dd, $J^3=8.0$ Hz, $J^2=16.4$ Hz, 10-H), 3.49 (1H, dd, $J^3=9.2$ Hz, $J^2=16.4$ Hz, 10-H), 3.69 (8H, m, NR_2), 4.80 (1H, m, 9-H), 13.11 (1H, br s, NH). δ_C 9.9 (CH_2CH_3), 22.9 (5-CH_3), 31.1 (CH_2CH_3), 33.9 (10-C), 51.7 (NCH_2), 69.0 (OCH_2), 76.4 (1-C), 94.1 (9-C), 104.2 (10a-C), 108.7 (10c-C), 118.2 (CN), 147.1 (10b-C), 153.8 (6a-C), 156.3 (3a-C), 163.0 (2-C), 168.2 (5-C), 168.7 (7a-C). Found: 62.74% C, 5.40% H, 22.94% N; $C_{19}H_{20}N_6O_2$ requires 62.62% C, 5.53% H, 23.06% N.

3.2.3. 2-Diethylamino-5-methyl-9-phenyl-9,10-dihydro-4*H*-furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-1-carbonitrile (12c). Yield 93%. Mp >300 °C (from DMF); δ_H 1.12 (6H, t, $J=6.8$ Hz, $2CH_3$), 2.41 (3H, s, 5-CH_3), 3.56 (4H, m, NCH_2), 4.39 (1H, dd, $J^3=1.2$ Hz, $J^2=8.8$ Hz, 10-H), 4.93 (1H, dd, $J^3=8.4$ Hz, $J^2=8.8$ Hz, 10-H), 5.10 (1H, dd, $J^3=8.4$ Hz, 1.2,-H), 7.08 (2H, d, $J=8.0$ Hz, 2,6-H_{Ph}), 7.21 (1H, t, $J=8.0$ Hz, 4-H_{Ph}), 7.29 (2H, dd, $J=8.0$, 8.0 Hz, 3,5-H_{Ph}), 12.51 (1H, s, NH). δ_C 13.8 (CH_3), 24.4 (5-CH_3), 44.9 (10-C), 45.3 (NCH_2), 77.0 (1-C), 89.1 (9-C), 104.8 (10a-C), 108.9 (10c-C), 116.7 (CN), 127.1 (3,5-C_{Ph}), 128.0 (2,6-C_{Ph}), 128.9 (4-C_{Ph}), 142.9 (1-C_{Ph}), 145.3 (10b-C), 152.6 (6a-C), 156.0 (3a-C), 164.3 (2-C), 166.7 (5-C), 168.0 (7a-C). Found: 69.37% C, 5.35% H, 21.19% N; $C_{23}H_{22}N_6O$ requires 69.33% C, 5.57% H, 21.09% N.

3.3. Spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexanes} 13a–c. General procedure

A solution of the diamine **8a**,**9b**,**10c** (2.5 mmol) in cyclohexanone (3 mL) was heated at 100 °C for 2 h. After cooling it was diluted with water resulting in a brown oil separation. The liquid was decanted and the oil was dissolved in ethanol (10 mL). Water (10 mL) was added to ethanolic solution and a pale solid precipitated. It was filtered and recrystallized from DMF–H_2O (1:1 v/v) mixture yielding compounds **13a–c**. During the recrystallization, a long heating time should be avoided.

3.3.1. 9-Chloromethyl-2-(1-piperidinyl)-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (13a). Yield 82%. Mp 186–187 °C (from aqueous DMF); δ_H 1.36 (1H, m, 4′-H), 1.46 (1H, m, 4′-H), 1.68 (12H, m, NR_2, 2′,3′,5′,6′-H), 1.82 (2H, m, 2′,6′-H), 3.20 (1H, dd, $J^3=6.8$ Hz, $J^2=16.0$ Hz 10-H), 3.52 (1H, dd, $J^3=9.6$ Hz, $J^2=16.0$ Hz 10-H), 3.66 (4H, m, NR_2), 3.78 (1H, dd, $J^3=5.2$ Hz, $J^2=11.2$ Hz, CH_2Cl), 3.84 (1H, dd, $J^3=5.2$ Hz, $J^2=11.2$ Hz, CH_2Cl), 4.98 (1H, m, 9-H), 7.58 (1H, s, NH), 7.60 (1H, s, NH). δ_C 20.9 (3′,5′-C), 24.6 (4′-C), 25.1 (4-C_{NR2}), 26.3 (3,5-C_{NR2}), 30.6 (10-C), 37.3 (2′,6′-C), 47.7 (CH_2Cl), 49.4 (2,6-C_{NR2}), 68.5 (1-C), 68.7 (5-C), 79.9 (9-C), 89.8 (10c-C), 93.3 (10a-C), 121.0 (CN), 143.7 (10b-C), 156.0 (6a-C), 156.2 (3a-C), 164.5 (2-C), 169.5 (7a-C). Found: 62.76% C, 6.13% H, 8.10% Cl, 19.30% N; $C_{23}H_{27}ClN_6O$ requires 62.93% C, 6.20% H, 8.08% Cl, 19.15% N.

3.3.2. 9-Ethyl-2-(4-morpholinyl)-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (13b). Yield 76%. Mp 237 °C (from aqueous DMF); δ_H 1.04 (1H, t, $J=7.2$ Hz, CH_3), 1.36 (1H, m, 4′-H), 1.47 (1H, m, 4′-H), 1.61–1.82 (10H, m, CH_2CH_3, 2′,3′,5′,6′-H), 2.96 (1H, dd, $J^3=8.0$ Hz, $J^2=14.8$ Hz, 10-H), 3.48 (1H, dd, $J^3=9.6$ Hz, $J^2=14.8$ Hz, 10-H), 3.65 (4H, m, NR_2), 3.71 (4H, m, NR_2), 4.68 (1H, m, 9-H), 7.57 (1H, s, NH), 7.61 (1H, s, NH). δ_C 9.4 (CH_2CH_3), 22.7 (3′,5′-C), 22.8 (4′-C), 31.3 (10-C), 33.2 (CH_2CH_3), 36.2 (2′,6′-C), 46.5 (NCH_2), 67.6 (1-C), 68.0 (5-C), 68.6 (OCH_2), 82.8 (9-C), 88.5 (10c-C), 92.3 (10a-C), 118.9 (CN), 142.7 (10b-C), 154.1 (6a-C), 155.5 (3a-C), 163.7 (2-C), 167.8 (7a-C). Found: 65.60% C, 6.63% H, 19.83% N; $C_{23}H_{28}N_6O_2$ requires 65.69% C, 6.71% H, 19.98% N.

3.3.3. 2-Diethylamino-9-phenyl-5,6,9,10-tetrahydro-4*H*-spiro{furo[2,3-*c*]pyrimido[4,5,6-*ij*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (13c). Yield 87%. Mp 198–199 °C (from aqueous DMF); δ_H 1.06 (6H, t, $J=7.0$ Hz, $2CH_3$), 1.28 (1H, m, 4′-H), 1.40 (1H, m, 4′-H), 1.63–1.80 (8H, m, 2′,3′,5′,6′-H), 3.49 (4H, q, $J=7.0$ Hz, NCH_2), 4.28 (1H, dd, $J^3=2.0$ Hz, $J^2=8.8$ Hz, 10-H), 4.80 (1H, dd, $J^3=9.2$ Hz, $J^2=8.8$ Hz, 10-H), 4.97 (1H, dd, $J^3=2.0$, 9.2 Hz, 9-H), 7.04 (2H, d, $J=7.2$ Hz, 2,6-H_{Ph}), 7.17 (1H, t, $J=7.2$ Hz, 4-H_{Ph}), 7.26 (2H, t, $J=7.2$ Hz, 3,5-H_{Ph}), 7.88 (2H, s, 2NH). δ_C 13.6 (CH_3), 18.7 (3′,5′-C), 23.5 (4′-C), 37.8 (2′,6′-C), 43.7 (10-C), 43.9 (NCH_2), 68.0 (1-C), 68.5 (5-C), 88.5 (10c-C), 89.1 (9-C), 91.5 (10a-C), 119.7 (CN), 125.2 (4-C_{Ph}), 127.2 (3,5-C_{Ph}), 130.8 (2,6-C_{Ph}), 141.2 (10b-C), 144.6 (1-C_{Ph}), 155.1 (6a-C), 159.5 (3a-C), 163.9 (2-C), 167.7 (7a-C). Found: 71.20% C, 6.51% H, 18.27% N; $C_{27}H_{30}N_6O$ requires 71.34% C, 6.65% H, 18.49% N.

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An approach to the synthesis of chemically modified bisazocalix[4]arenes and their extraction properties

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Abstract—Bisazocalix[4]arenes [*N*,*N*′-bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)benzene (**1**), *N*,*N*′-bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)biphenyl (**2**) and *N*,*N*′-bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)-2,2′-dinitro biphenyl (**3**)] have been synthesized from 25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene by diazocoupling with the corresponding aromatic diamines (*p*-phenylenediamine, 4,4′-diamino biphenyl and 4,4′-diamino-2,2′-dinitrobiphenyl). Extraction studies of bisazocalix[4]arenes **1**, **2**, and **3** show no difference in their extraction behavior and selectivity, whereas azocalix[4]arenes are a poor extractant for heavy metal cations. The absorption spectra of the prepared bisazocalix[4]arenes are discussed, both the effect of varying pH and solvent upon the absorption ability of bisazocalix[4]arenes.

1. Introduction

Recent developments in calixarene chemistry[1] have led to remarkable advances in which these developments have been used as building blocks for host molecules with various applications in supramolecular chemistry.[2] Functionalized calixarenes are fascinating objects for the study of various aspects of their supramolecular chemistry, from simple host–guest interactions[3] to applications as artificial sensors,[4] as synthetic receptors for biological agents,[5] as antibody mimetics[6] or as building blocks for molecular boxes.[7] The synthesis, structures and cation-binding properties of calixarene derivatives as a new class of macrocyclic molecular receptors have been reviewed.[8] Calixarene esters have shown unusual ionophoric properties toward alkali metal ions such as sodium and cesium ions.[9]

In our recent work, we have reported the synthesis of azocalix[*n*]arene in which a *p*-position is substituted by a nitrogen atom[10,11] and discussed their selective extraction of transition metal cations.[12] Chromogenic calix[*n*]arenes ($n=4, 6$) substituted by phenylazo and hetarylazo groups have been previously characterized and their absorption spectra have been investigated with a variation in pH and different solvents. The presence of azo-chromophores in these compounds allow detection of changes of optical absorption in the visible range, which is resulting from the interaction of the heterocyclic ring with the π-electrons of the azo-chromophores.[13–16]

The functionalization of the lower rim, including with phenyl groups such as benzoyl esters,[17] has frequently been used to create calixarenes with solubility in various solvents; but mainly with the focus on increasing solubility in basic solvents. We set out to introduce benzoyl substituents of the lower rim (–OH) selectively for the cone conformation[18] with the aim of obtaining a transition metal complex at the bottom of a molecular cavity. We examined the introduction of diazo substituents by diazocoupling reaction: 25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene was treated with an excess of *p*-phenylenediamine, 4,4′-diamino biphenyl and 4,4′-diamino-2,2′-dinitrobiphenyl in the presence of an excess of sodium nitrite and concd HCl under neat conditions at lower temperatures. As part of our work on this bisazocalix[4]arenes, we report herein the synthesis and solid-state structures of *N*,*N*′-bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene) benzene (**1**), *N*,*N*′-bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)biphenyl (**2**) and *N*,*N*′-bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)-2,2′-dinitrobiphenyl (**3**) having two symmetric ligating sites on the calixarene framework.

Keywords: Calix[*n*]arenes; Bisazocalix[4]arenes; Diazocoupling reaction; Solvent extraction; Absorption properties.
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2. Results and discussion

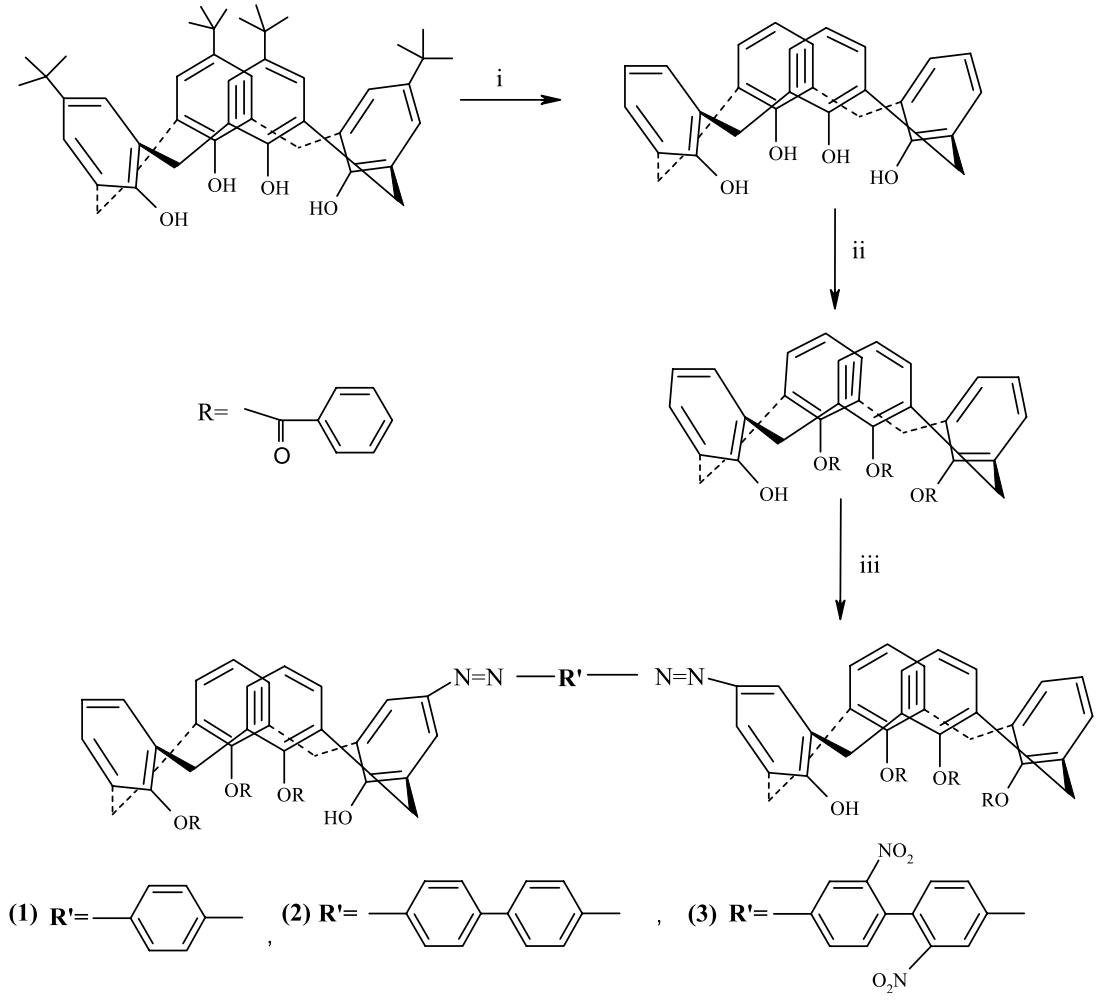
In recent years, various attempts have been undertaken to incorporate calixarenes into different polymers, including self-assembled systems.[19] There are two general strategies to prepare covalently linked calixarene-based polymers: the first is the attachment of the calixarene by reaction with a suitably functionalized polymer or oligomer and the second is the preparation of calixarene monomer and its polymerization or copolymerization with typical monomers.[20,21] The former approach gives better defined products since there is no risk of incomplete substitution of the functionalized polymer. Thus, calixarene monomers have been incorporated into dimer backbones by utilizing functional groups at the wide as well as at the narrow rim.

Previously, we reported the synthesis of azocalix[*n*]arene derivatives in which a hydrogen atom is replaced by a nitrogen atom[10] and their selective metal extraction[12] or dye absorption properties.[13–16] As part of our work, some bisazocalix[4]arenes include two ligating sites (benzoyl ester and diazo moieties) on the calix[4]arene framework.

The synthesis of some bisazocalix[4]arene derivatives is now reported. No details of the synthesis and physical properties of such compounds have been published hitherto.

The target bisazocalix[4]arenes were prepared according to the synthetic route shown in Scheme 1. The effects of the bis-structure on the color and the selectivity of the bisazocalix[4]arenes are discussed. Their dyeing behavior and performance on solvent and framework effects are assessed.

In this study, the synthesis of three new bisazocalix[4]arene derivatives is reported. Firstly, *p-tert*-butylcalix[4]arene was prepared by reaction of *p-tert*-butylphenol with formaldehyde according to the method of Gutsche.[19] Treatment of *p-tert*-butylcalix[4]arene with anhydrous aluminium chloride gave calix[4]arene according to the method described by Gutsche.[23] Then the reaction of 25,26,27-tribenzoyloxy lower-rim substituted calix[4]arene with 9 equiv of the appropriate benzoyl chloride in the presence of pyridine gave the calix[4]arene ester in yield of 78%.[23] The diazonium salts were excellent electrophiles and would attack any available position on the calixarenes to yield complex mixtures. The diazonium salt derivatives were synthesized from aromatic diamines in sodium nitrite and concd HCl, finally we employed 1 equiv of these salts



Scheme 1. The synthetic route for three novel bisazocalix[4]arene derivatives (i = $AlCl_3$/toluene, ii = PhCOCl, pyridine, iii = $NaNO_2$/concd HCl, NH_2-**R′**-NH_2).

Table 1. Extraction of metal picrates with ligands[a]

	Picrate salt extracted (%)							
Ligand	Ag^+	Hg^+	Hg^{2+}	Cd^{2+}	Pb^{2+}	Al^{3+}	Cr^{3+}	La^{3+}
1	6.3	29.9	28.0	3.2	5.7	3.5	4.7	2.0
2	10.1	30.9	29.1	9.2	12.0	14.7	16.0	15.2
3	15.0	35.2	27.8	$\leq$1.0	2.6	10.3	$\leq$1.0	$\leq$1.0
4[25]	54.0	37.0	77.0	20.0	—	28.0	41.0	16.0

[a] Aqueous phase ($H_2O/CHCl_3$=10 mL v/v), [metal picrate]=2.0×10^{-5} M; organic phase, chloroform, [ligand]=1.0×10^{-3} M, at 25 °C, for 1 h contact time. Experimental error was ±2%.

in DMF with 2 equiv of calix[4]arene to obtain the corresponding bisazocalix[4]arenes (**1–3**). Work up of the reaction mixture afforded the corresponding three new bisazocalix[4]arenes **1**, **2**, and **3** in yields of 66, 77 and 73%, respectively.

All newly synthesized bisazocalix[4]arenes (**1**, **2**, and **3**) were identified by a combination of ^{1}H NMR spectral data, FT-IR, UV–vis and elemental analysis. Completion of the reaction was followed by IR spectroscopy, which shows the disappearence of the band due to the amino groups at 3383 cm^{-1}, and the appearance of a new band at 1465–1462 cm^{-1} for the diazo groups. The dimerization reaction of the prepared compounds have been performed sequentially with diazonium chloride salts of diamines in the presence of DMF to give bisazocalix[4]arenes **1–3** in quantitative yields after purification by reprecipitation from DMF/H_2O system.

The ^{1}H NMR spectra of bisazocalix[4]arene **1–3** have revealed singlet peaks at 3.01–3.86 ppm for methylene protons (–CH_2–), multiplets between 6.80–8.20 ppm for aromatic protons (Ar–H) and broad peaks at 5.21–5.62 ppm for hydroxyl groups (OH). A conformational study has been perfected by ^{1}H NMR spectra, which is a versatile tool for the identification of calixarene conformation.[24] The ^{1}H NMR spectra of bisazocalix[4]arenes **1–3** exhibited an AB system formed by the equatorial protons at 3.01–3.86 ppm (J=13 Hz) for the ArCH_2–Ar bridges at room temperature. For compounds **1**, **2**, and **3**, ^{1}H NMR data have revealed that each calix[4]arene moiety of the biscalix[4]arene derivatives exists in several conformational forms at room temperature.

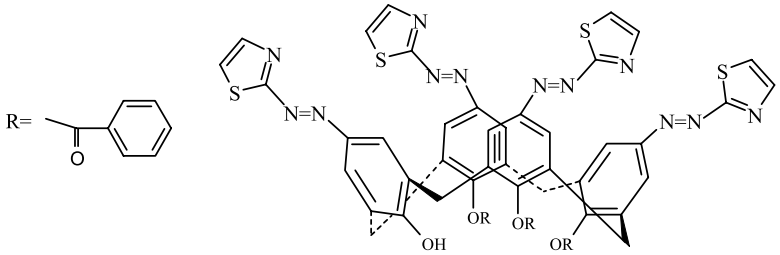
2.1. Extraction studies

The evaluation of the extraction efficiencies of the compounds have been carried out by the two-phase solvent extraction of heavy metal picrates (Ag^+, Hg^+, Hg^{2+}, Cd^{2+}, Pb^{2+}, Al^{3+}, Cr^{3+} and La^{3+}) into chloroform under neutral conditions. The results obtained from bisazocalix[4]arenes are summarized in Table 1 for comparison purposes. These data have been obtained by using chloroform solutions of these compounds **1–3** to extract metal picrates from an aqueous phase. Then, the equilibrium concentrations of picrates in the aqueous phase were determined spectrophotometrically.

From the data in Table 1 it can be seen that bisazocalix[4]-arene **1**, **2**, and **3** are not effective in transferring heavy metal ions into organic phase, whereas azocalix[4]arene derivative **4** is effective for all these heavy metal ions. Here we should note that tetra substituted azocalix[4]arenes in cone conformations show high extraction ability toward heavy metal cations (Scheme 2).

We first checked the transferring ability of azocalix[4]arenes **4** and compared the results with the data obtained for three dimeric bisazocalix[4]arenes **1–3**. As shown in Table 1, neither soft (Ag^+, Hg^+, Hg^{2+}) nor hard (Cd^{2+}, Pb^{2+}, Al^{3+}, Cr^{3+}, La^{3+}) metal cations were significantly extracted by bisazocalix[4]arene **1–3** from the aqueous to the organic phase. However, with the introduction of tribenzoyl ester groups to the cone conformation on the lower rim of azocalix[4]arene **4**, the characteristic soft metals were transferred more effectively than bisazocalix[4]arene **1–3**, but the hard metal cations were extracted very poorly.[25]

By comparing the solvent extraction results of bisazocalix[4]arenes **1–3** and azocalix[4]arene **4**, we observed that compounds **1–3** almost did not extract any of the metal ions used in the extraction studies, whereas compound **4** was particularly selective for Ag^+, Hg^+ and Hg^{2+}. From these observations, it was concluded that the size of the macrocycle does not play a major role in the complexation phenomenon alone, but the nature and the ionic diameter of the metal ions, the calixarene conformation, and the effectiveness and aggregation of functional groups are important factors in complexation.[26] In the case of extractants **1–3**, the decreased affinity in complexation compared with the azocalix[4]arene **4** can be explained by



Scheme 2. The structure of 25,26,27-tribenzoyloxy-*p*-(2-thiazolylazo)calix[4]arene.

Table 2. Absorption maxima (nm) of bisazocalix[4]arenes **1–3**

Ligand	Chloroform	Chloroform + piperidine	Methanol	Methanol + KOH	Methanol + HCl	Acetic acid
1	307	315, 440s	311	399, 450s	310, 353s	308
2	309	315	311	309, 354s	436, 384s	307
3	306, 386s, 434s	320s, 435s	310	393, 460s	308, 356s	308

s: Shoulder.

the fact that the bridge provides greater size between the calixarene moieties due to the aromatic structure. On the other hand, the hard soft acid and base principle[27] seems not to be an important factor in selectivity. As the molecule triester functionalities are deeply hidden in the molecular framework, the molecules are restricted from having a pertinent conformation and do not participate in binding metal ions. Moreover, in the two phase extraction system, azocalix[4]arene **4** showed a strong affinity toward Hg^{2+}.

In this study, another purpose was to synthesize a conformationally stable form of the azocalix[4]arene, which has led to the enhancement of Ag^{+} and Hg^{+} ion selectivity by minimizing the side arm effect. However, extraction results of bisazocalix[4]arenes **1–3** showed no selectivity toward heavy metal ions. The increased affinity of bisazocalix[4]arenes in the complexation can be explained by the fact that there may be an important role played by the azo bridges of the dimeric skeleton at the water–chloroform interface, which is also in agreement with our previous result.[12]

2.2. Absorption properties

UV–vis absorption spectra were recorded on the bisazocalix[4]arenes **1–3** in various solvents. The spectral changes clearly reflect the fact that the absorption spectra of compounds in solvents generally change with respect to the absorption spectra in chloroform: λ_{max} of the bisazocalix[4]arenes **1–3** shifted considerably in chloroform (e.g., for compounds **1**, **2**, and **3**, λ_{max} is 307, 309 and 306 nm, respectively).

It appears that the equilibrium depends on the basicity of the solvents used in this study, and changes significantly upon varying the solvent. For compound **2**, however, a red or a blue of shift increases in solvents with hydrogen bond donor properties, for example, methanol and acetic acid. Shifts were observed in both proton accepting solvents such as methanol in which the λ_{max} of the compounds displayed slightly a red shift of the λ_{max}, and in proton donating solvents such as acetic acid in which the λ_{max} of the compounds displayed blue shift of λ_{max} (Table 2).

The λ_{max} values of the compounds showed bathochromic effects when a small amount of piperidine was added to each of the compounds in chloroform (Table 2). The λ_{max} of the compounds in methanol also showed bathochromic effects when 0.1 M KOH was added. The λ_{max} of the compounds in methanol also showed slightly hypsochromic effects when 0.1 M HCl was added.

It was shown that the mechanism of absorption shifting is based on the interaction between additional protons or hydroxyl and azo groups.

3. Conclusion

Three new calixarene-based receptors with three benzoyl ester groups immersed in a large cavity have been synthesized. The synthesis of all the diazo-coupled compounds was been achieved using the method of Morita.[28] We have shown that bisazocalix[4]arene derivatives as a starting point in the synthesis of double calixarenes can be connected together with 'classical' calixarenes and polymeric calixarene building blocks. The application of ionic interactions for the self-assembly of supramolecular structures is a very interesting approach for two reasons: these compounds represent a first step toward calixarene-based diazo dye structures and exhibit interesting dynamic behavior because of selective metal extraction.

In conclusion, the dimeric cups combine a chemical coupling control of assembly with desirable properties such as a cone conformation. Finally, because the assembly depends on encapsulation of a suitable guest, reversible polymerization can be triggered by molecular recognition, providing macroscopic structural changes in response to chemical signals.

4. Experimental section

General Remarks: All solvents and compounds were commercial grade reagents that were used without further purifications. Melting points (°C, uncorrected values) were determined with a gallenkamp in a sealed capillary tubes. The elemental analyses were performed in the TUBITAK laboratory (Center of Science and Technology Research of Turkey). IR spectra was recorded on a Mattson 1000 FT-IR spectrometer as KBr pellets (ν in cm^{-1}). UV–vis spectra were obtained on a Schimadzu 160A UV–vis recording spectrophotometer (λ_{max} in nm). ^{1}H NMR spectra were referenced to tetramethylsilane (TMS) at 0.00 ppm as internal standard and were recorded on a Bruker 400 MHz spectrometer at room temperature (25 °C ±1).

The *p-tert*-butylcalix[4]arene, calix[4]arene and 25,26,27-tribenzoyloxy-28-hydroxy calix[4]arene were synthesized according to the literature procedures.[19,22,23] The other bisazocalix[4]arenes employed in this work as illustrated in Scheme 1 have been synthesized follows.

4.1. General procedure

4.1.1. *N,N′*-Bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)benzene (1). A solution of *p*-phenylenebisdiazonium chloride, prepared from *p*-phenylenediamine (0.04 g, 0.37 mmol), sodium nitrite (0.05 g, 0.74 mmol) and concd HCl (1 mL) in water (10 mL), was added slowly to a

cold (5 °C) solution of calix[4]arene (0.54 g, 0.74 mmol) and sodium acetate trihydrate (1.10 g, 8 mmol) in DMF (15 mL) to give a yellow suspension. After standing for 2 h at room temperature, the suspension was acidified with aqueous HCl (150 mL, 0.1 M) and the mixture was then warmed to 60 °C for 30 min to give **1** (yield, 0.40 g, 67%) as a yellow solid, which was filtered and washed with water and methanol. A representative analysis was obtained as follows: **1** was dissolved in 100 mL of hot aqueous $NaHCO_3$ (4.20 g) solution; activated charcoal was added to this solution (1 g). After the charcoal was filtered, the filtrate was cooled to room temperature and acidified with concd HCl (1 or 2 mL). The solution was heated to 60 °C for 30 min and then cooled. The resulting solid was filtered, washed with water, and dried. Recrystallization from DMF/H_2O mixture gave a light yellow product.

Yield: 0.40 g (66%); mp 265 °C. UV–vis ($CHCl_3$): $\lambda_{max}=307$ nm. IR (KBr): $\nu_{max}=3536\ cm^{-1}$ (OH), $3060\ cm^{-1}$ (arom. C–H), $2970\ cm^{-1}$ (aliph. C–H), $1785\ cm^{-1}$(C=O), $1572\ cm^{-1}$ (C=C), $1464\ cm^{-1}$(N=N) and $1178\ cm^{-1}$(C–O). ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.62$ (s, 2H, OH), 6.80–8.20 (m, 56H, ArH), 3.82–3.58 (m, 16H, $ArCH_2Ar$). Elemental Anal. Calcd for $C_{104}H_{74}N_4O_{14}$ (1602): C 77.9%, H 4.6%, N 3.49%. Found C 77.6%, H 4.5%, N 3.50%.

4.1.2. *N,N′*-Bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)biphenyl (2). Compound **2** was prepared as described above, using 4,4′-diaminobiphenyl and obtained as pink solid, which was filtered and washed with water and methanol, as a pale pink solid.

Yield: (77%); mp 272 °C. UV–vis ($CHCl_3$): $\lambda_{max}=309$ nm. IR (KBr): $\nu_{max}=3517\ cm^{-1}$ (OH), $3055\ cm^{-1}$(arom. C–H), $2892\ cm^{-1}$(aliph. C–H), $1767\ cm^{-1}$(C=O), $1607\ cm^{-1}$ (C=C), $1462\ cm^{-1}$ (N=N) and $1125\ cm^{-1}$(C–O). ^1H NMR (400 MHz, DMSO-d_6): $\delta=5.34$ (s, 2H, OH), 6.55–8.10 (m, 60H, ArH), 3.21–3.86 (m, 16H, $ArCH_2Ar$). Elemental Anal. Calcd for $C_{110}H_{78}N_4O_{14}$ (1678): C 78.66%, H 4.64%, N 3.37%. Found C 78.69%, H 4.62%, N 3.35%.

4.1.3. *N,N′*-Bis(5-azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene)-2,2′-dinitrobiphenyl (3). Compound **3** was prepared as described above, using 4,4′-diamino-2,2′-dinitrobiphenyl and obtained as a yellow solid, which was filtered and washed with water and methanol, as a dark yellow solid.

Yield: (74%); mp 270 °C. UV–vis ($CHCl_3$): $\lambda_{max}=306$ nm. IR (KBr): $\nu_{max}=3518\ cm^{-1}$(OH), $3032\ cm^{-1}$(arom. C–H), $2960\ cm^{-1}$ (aliph. C–H), $1686\ cm^{-1}$ (C=O), $1554\ cm^{-1}$ (C=C), $1550\ cm^{-1}$(NO_2), $1465\ cm^{-1}$(N=N) and $1107\ cm^{-1}$(C–O). ^1H NMR (400 MHz, DMSO-d_6): $\delta=$ 6.55–7.90 (m, 54H, ArH), 5.21 (s, 2H, OH), 3.28–3.76 (m, 16H, $ArCH_2Ar$). Elemental Anal. Calcd for $C_{110}H_{76}N_6O_{18}$ (1768): C 74.66%, H 4.3%, N 4.75%. Found C 74.68%, H 4.50%, N 4.72%.

4.2. Solvent extraction

Picrate extraction experiments were performed as described our in earlier procedure:[29] A 10 mL aliquot of 2.0×10^{-5} M picric acid and 1.0×10^{-2} M metal nitrate and either 10 mL of 1.0×10^{-3} M solution of bisazocalix[4]arene (**1**, **2**, and **3**) in $CHCl_3$ were vigorously agitated in a stoppered glass tube with a mechanical shaker for 2 min. The two phase systems were then magnetically stirred in a thermostated water-bath at 25 °C for 1 h, and finally left standing for an additional 30 min. The concentration of picrate ion remaining in the aqueous phase was then determined spectrophotometrically. Blank experiments showed that no picrate extraction occurred in the absence of calixarene. The percent extraction (E%) has been calculated as:

$$(E\%)=(A_o-A/A_o)\times100,$$

where A_o and A are the initial and final concentrations of the metal picrate before and after the extraction, respectively.

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Efficient synthesis of analogs of safflower yellow B, carthamin, and its precursor: two yellow and one red dimeric pigments in safflower petals

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Abstract—The synthesis of analogs (**8**, **12**, **14**) of two yellow pigments, safflower yellow B and the precursor of carthamin, and carthamin itself, a red pigment, which are produced in safflower (*Carthamus tinctrious* L.) petals and, which have a common dimeric quinochalcone structure, is reported. The key compound for the synthesis of these analogs, (*p*-hydroxycinnamoyl)filicinic acid (**7**) was synthesized in six steps from phloroglucinol in a total yield of 39%, which was reacted with 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-glucose, glyoxylic acid, and ethyl orthoformate in the presence of base to afford the corresponding analog, **8**, **12**, **14**, in good yields, respectively. Precursor analog **12** was then converted to carthamin analog **14** by oxidative decarboxylation by treatment with potassium permanganate as well as the natural specimen.

1. Introduction

Carthamin (**5**),[1] a brilliant-red component of the flower petals of the safflower has long been used as a dye, rouge, and Chinese medicine. Currently, **5** and the water-soluble yellow components of safflower petals are used as a natural food colorant. The major yellow components of safflower petals, safflomin-A (**2**),[1b,2] safflower yellow B (**1**),[3] safflomin-C (**3**),[4] and carthamin precursor (**4**)[5] were isolated and their structures were elucidated. In addition, recently the *N*-containing yellow pigments, tinctromin[6] and cartormin[7] have also been isolated from safflower petals and their structures were elucidated. The above pigments share a unique *C*-glycosylquinochalcone, which has not been found in any other naturally occurring products to date.

The recently proposed[8] biosynthetic pathway of the main pigments, starting from **1**, is shown in Figure 1; the hydrolysis of **1** forms **2** and an unstable *C*-glycosylquinochalcone (**6**),[8] which rapidly reacts with glyoxylic acid or *p*-hydroxycinnamic acid to form the yellow pigments, **4** or **3**. Because **4** is unstable, it readily undergoes oxidative decarboxylation to the red pigment **5**. The biosynthesis of **1** has not been reported, but it is assumed that **1** is formed by the condensation of 2 equiv of reactive **6** and 1 equiv of D-glucose. The unstable **6** can be formed by the oxidation of *C*-glucosylchalcone or the glycosylation of pentahydroxychalcone.[8b]

In the total synthesis of these pigments, asymmetric synthesis of **5** (as the acetate) has been achieved,[9] and the stereochemistry of its chiral carbon was determined to be *S*.[10] The total synthesis of the other yellow pigments have not yet been carried out, but the synthesis of analogs (**9**, **10**, **11**, **12**, **13**, and **14**) in which the glucosyl group, or the glucosyl and hydroxyl groups on the chiral carbon were replaced by one or two methyl groups has been achieved for **2**,[11a] **3**,[11b] **4**,[11e], and **5**.[11c,d] Since the *C*-glucopyranosylquinochalcone structure is unique and is present as a complex mixture of keto–enol tautomers, we have synthesized analogs of these pigments as model compounds, and explored the characteristics and behavior of these unique quinochalcone pigments, and further proved the proposed structure. However, the yield was unsatisfactory, and the synthesis of an analog (**8**) of safflower yellow B (**1**), which has the characteristic dimeric structure cross-linked with a 1-deoxyglucitol, has not yet been reported.

Keywords: Safflower petals; Yellow and red pigments; Safflower yellow B; Carthamin; Carthamin precursor; Analog; (*p*-Hydroxycinnamoyl)filicinic acid.
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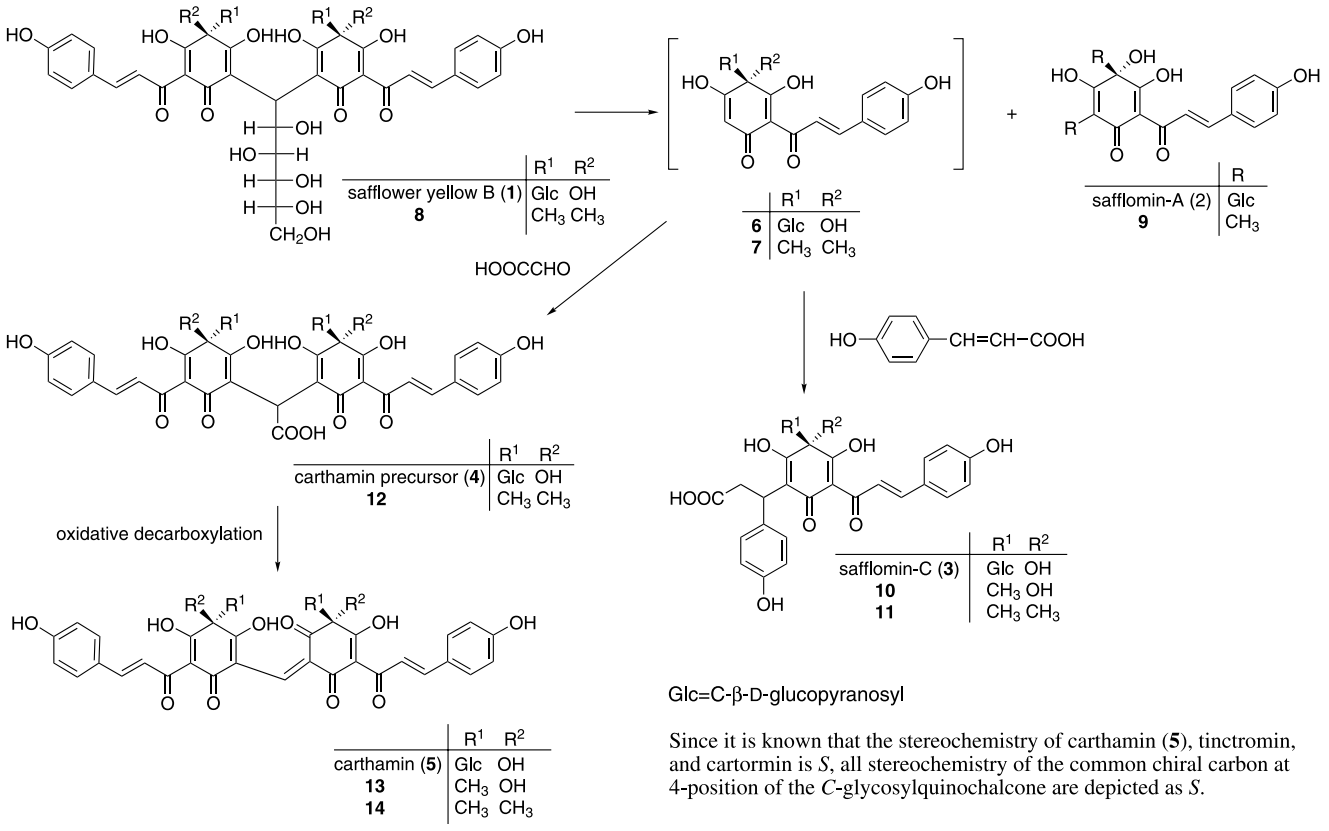


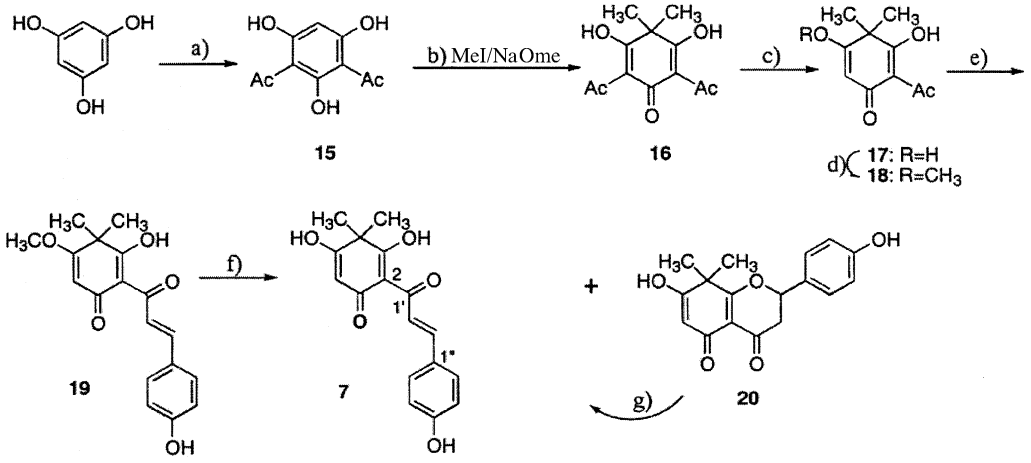
Since it is known that the stereochemistry of carthamin (**5**), tinctromin, and cartormin is *S*, all stereochemistry of the common chiral carbon at 4-position of the *C*-glycosylquinochalcone are depicted as *S*.

Figure 1. Proposed biosynthetic pathway for the yellow and red pigments from safflower yellow B in safflower petals and their analogs.

Herein, we wish to report on the efficient synthesis of analogs (**8**, **12**, and **14**) of the above three dimeric pigments (**1**, **4**, and **5**), in which both the *C*-glucosyl and hydroxyl group on the chiral carbon are replaced by methyl groups. The key compound in the synthesis of the analog of these dimeric pigments, (*p*-hydroxycinnamoyl)filicinic acid (**7**), which is also a stable analog of the reactive and unstable *C*-glucopyranosylquinochalcone (**6**), was able to be synthesized in six steps from phloroglucinol in a total yield of 39%, via the improvement of the yield.

2. Results and discussion

The synthesis of **7**, a key-compound in the synthesis of the three dimeric analogs **8**, **12**, and **14**, was carried out by modifying the previous method[11c,e,12] as follows (see Scheme 1); phloroglucinol was diacetylated by heating at 100 °C in the presence of boron trifluoride acetic acid complex ($BF_3 \cdot 2AcOH$) to give diacetylphloroglucinol (**15**) in 84% yield. Diacetylphloroglucinol (**15**) was then methylated by reaction with iodomethane in the presence

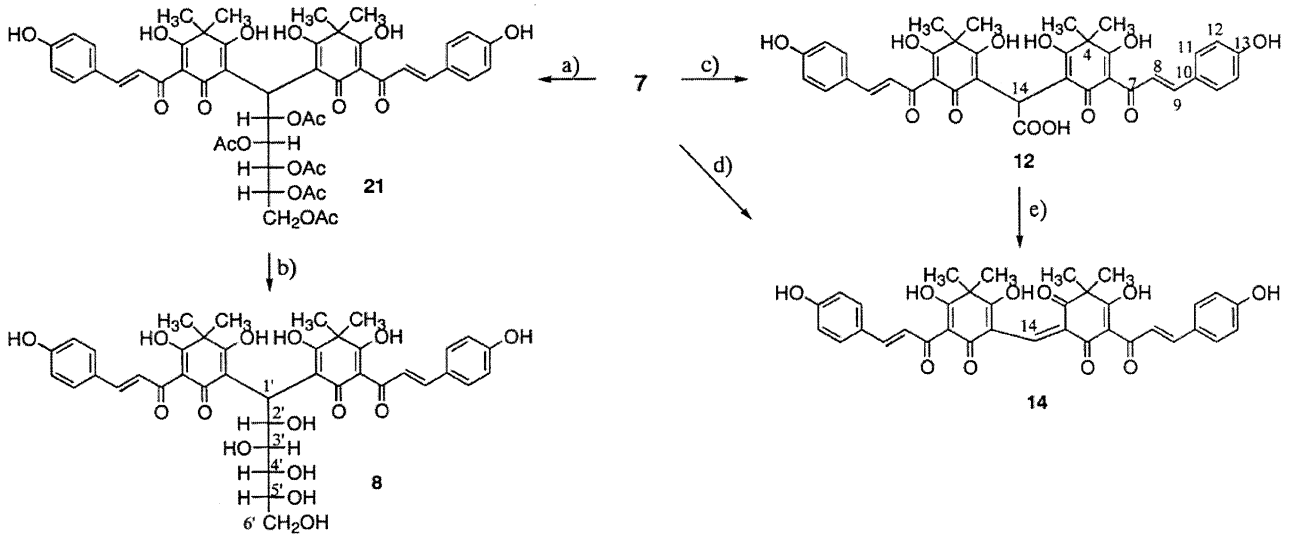


Scheme 1. Efficient synthesis of the key-compound (**7**) in the synthesis of analogs of pigments in safflower petals. Reagents and conditions: (a) $BF_3 \cdot 2AcOH$, 100 °C, 2 h, Y: 84%; (b) MeI/NaOme, Y: 78%; (c) 80% H_2SO_4 aqueous solution, 80 °C, 50 min, Y: 89%; (d) CH_2N_2, Y: 99%; (e) *p*-hydroxybenzaldehyde (4 equiv)/piperidine, 80 °C, 1 h, Y: 79%; (f) 28% HBr–AcOH, 70 °C, 0.5 h, Y: 68% for **7**, 15% for **20**; (g) NaOMe, Y: 60%.

of sodium methoxide (NaOMe) to give 2,4-diacetyl-6,6-dimethylcyclohexa-1,3,5-trione (**16**) in 78% yield, which was then mono-deacetylated by heating at 80 °C for 50 min in an 80% H_2SO_4 aqueous solution to give acetylfilicinic acid (**17**) in 89% yield. In the previous paper,[11c] after benzoylphloroglucinol was acetylated, **7** was synthesized by aldol reaction followed by debenzoylation. However, the yield of final debenzoylation was low. Furthermore, **7** has been synthesized by mono-aldol condensation of diacetylfilicininc acid followed by selective deacetylation, however, the yield by this method was also low due to the poor selectivity.[11e] To prevent side-reactions at the 6-position of **17** in the next aldol reaction, the enol-hydroxyl group of **17** was selectively methylated by treatment with diazomethane to give 2-acetyl-3-hydroxy-5-methoxy-4,4-dimethylcyclohexa-2,5-dienone (**18**) as colorless prisms in quantitative yield. Aldol condensation of cyclohexadienone **18** with *p*-hydroxybenzaldehyde (4 equiv) in piperidine at 80 °C for 1 h afforded the desired 2-cinnamoyl-5-*O*-methylfilicinic acid (**19**) in 79% yield. Since the yield of de-*O*-methylation reaction of **19** by refluxing in concd HCl–methanol was poor due to its low solubility,[12] de-*O*-methylation by heating at 70 °C for 0.5 h in a 28% HBr acetic acid solution was carried out to give the desired cinnamoylfilicinic acid **7** and its ring-closed flavanone **20** in 68 and 15% yield, respectively. Flavanone **20** was then partially ring-opened by treatment with NaOMe to give **7** in 60% yield.

With the key-compound **7** in hand, we initially examined the first synthesis of **9** the condensation of 2 equiv of **7** with an aldehydo-glucose in the presence of NaOMe. Three aldehydo-glucose derivatives were prepared by the acetonide-, benzyl-, or acetyl-protection of the 2,3,4,5,6-hydroxyl groups. The results for each of the condensation reactions of **7** and these aldehydo-glucose derivatives was satisfactory, but the subsequent deprotection of the glucitol moiety of the resulting dimer was difficult. Deprotection of the acetonide by treatment with a weak acid or even hydrogenolysis of the benzyl protecting group gave a mixture of xanthene-type products, which were produced by dehydration and ring-closure between two enol-hydroxyl groups. However, removal of the acetate groups under alkaline conditions gave the desired compound **8**, as follows; 2 equiv of **7** were condensed with 1 equiv of 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-glucose[17,18] prepared from D-glucose via three steps in a 78% yield in the presence of catalytic amount of NaOMe in dry methanol at room temperature for 5 h, followed by de-*O*-acetylation with a 28% NaOMe methanol solution. Although the de-*O*-acetylation partially proceeded under these condensation reaction conditions, the desired dimer **21** and its partial de-*O*-acetates were obtained in a total yield of 75–85%. Purification of their de-*O*-acetylation products by silica gel and Sephadex column chromatography gave an analog **8** of safflower yellow B (**1**) as a yellow powder in a yield of 71% from **7** (Scheme 2).

The synthesis of an analog **12** of carthamin precursor (**4**) was achieved by a coupling reaction of 2 equiv of **7** with 1 equiv of glyoxylic acid employing the same alkaline conditions as for the synthesis of **21**. The reaction proceeded smoothly to afford **12** as the sole product, in an excellent 99% yield.[11d] In the ^{1}H NMR spectrum of **12** in pyridine-d_5, the methine proton of the central acetic acid moiety appeared at a low field of δ 7.15 ppm, which was confirmed by C–H COSY between the methine carbon (δ_C 34.8 ppm). In the synthesis of carthamin analog **14**, the coupling of **7** with triethyl orthoformate did not proceed under alkaline conditions using NaOMe as well as the synthesis of **21**, and **12**. However, in the presence of 12.5 equiv of sodium hydride (NaH),[11c] the reaction proceeded smoothly, affording **14** as the sole product. After recrystallization the overall yield was 90%. The precursor analog **12** was then subjected to oxidative decarboxylation by treatment with an aqueous solution of permanganate at room temperature to give **14** in 52% yield as well as the natural specimen.[5b] Both the ^{1}H and ^{13}C NMR spectra of **8**, **12**, and **14** in DMSO-d_6 gave unsymmetrical and complicated spectra due to the complex mixture of keto–enol tautomers. However, the use of pyridine-d_5 as a solvent gave symmetrical and simple



Scheme 2. Synthesis of analogs (**8**, **12**, and **14**) of the three dimeric yellow and red pigments in safflower petals via quinocalcone **7**. Reagents and conditions: (a) 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-glucose/NaOMe; (b) NaOMe or 10% NaOH aqueous solution-MeOH, Y: 71% (from **7**); (c) HO_2CCHO/NaOMe, Y: 99%; (d) $HC(OEt)_3$/NaH, Y: 90%; (e) 0.23% $KMnO_4$ aqueous solution in acetone, Y: 52%.

spectra. ^{1}H and ^{13}C NMR spectra of the 1-deoxyglucitol moiety of **8** were very analogous to those of **1**, except for the coupling constants between H3 and H4 (**8**: $J_{3,4}=\sim 0$ Hz.; **1**[8b]: $J_{3,4}=7.0$ Hz). The UV–vis spectra of **8**, **12**, and **14** were also very analogous to the natural specimen and they were liable to including a solvent such as water, alcohol, or ethyl acetate. Yellow-colored **12** was converted to red-colored **14** by treatment of peroxidase–H_2O_2 solution as well as the natural specimen. Carthamin analog **14** also dyed silk and cotton pink-red in a similar way to the natural specimen.

3. Conclusion

We established an efficient method for the synthesis of an analog of the main dimeric pigments in safflower petals, by using the key compound, (*p*-hydroxycinnamoyl)filicinic acid (**7**). Since spectral data for each synthesized analog was quite analogous to its natural specimen, it was supported that the proposed structure of three dimeric pigments was appropriate. We are currently attempting the total synthesis of the main yellow pigments in safflower petals on the basis of this result.

4. Experimental

4.1. General

The solvents used in this reaction were prepared by distillation. The synthesized compounds were separated and purified by flash column chromatography using silica gel (Fuji-Silysia Co., Ltd, BW-300) and by column chromatography using Sephadex LH-20 gel (Amersham Pharmacia Biotech AB). Melting points were determined on a Shibayama micro-melting point apparatus and are uncorrected. UV–vis spectra were recorded on a Hitachi U-2010 spectrophotometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Mass spectral data were obtained by electron ionization (EI) or fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA), glycerol, or thioglycerol as the matrix on a JEOL JMS-AX505HA instrument. IR spectra were recorded on a Horiba FT-720 IR spectrometer. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as an internal standard.

4.2. Synthesis of the key-compound, (*p*-hydroxycinnamoyl) filicinic acid; 2-[3′-(*p*-hydroxyphenyl)-2′-propenoyl]-3,5-dihydroxy-6,6-dimethyl-2,4-cyclohexadien-1-one (7)

4.2.1. Diacetylphloroglucinol (15). A solution of phlroglucinol (20.0 g, 158 mmol) in $BF_3\cdot 2AcOH$ (95 mL) was stirred on an oil bath at 100 °C for 3 h. The reaction mixture was cooled to room temperature and then poured into 1 L of an aqueous KOAc (50.1 g/L) solution and the mixture was stirred for 3 h. The precipitated orange prisms were collected by filtration. The crude product was recrystallized from hot water–methanol to give **15** (23.6 g, 71%) as pale-yellow prisms. Colorless prisms. Mp 173–174 °C (lit.[13] 168 °C). ^{1}H NMR (DMSO-d_6) δ 2.60 (6H, s, $COCH_3\times 2$), 5.87 (1H, s, ArH), 13.23 (2H, s, OH), 16.30 (1H,s,OH).

4.2.2. 2,6-Diacety1-4,4-dimethylcyclohexan-1,3,5-trione (16).[12] Colorless prisms. Mp 65–66 °C (lit.[14] mp 65–66 °C). ^{1}H NMR ($CDCl_3$) δ 1.45 (6H, s, $CH_3\times 2$), 2.62 and 2.75 (each 3H, s, $COCH_3\times 2$), 18.87 and 19.20 (each 1H, s, OH).

4.2.3. Acetylfilicinic acid; 2-acetyl-4,4-dimethylcyclohexan-1,3,5-trione (17).[12] Colorless prisms. Mp 172–174 °C (lit.[15] 174–176 °C). ^{1}H NMR (DMSO-d_6) δ 1.28 (6H, s, $CH_3\times 2$), 2.47 (3H, s, $COCH_3$), 5.43 (1H, s, olefinic H), 18.41 (1H, s, OM. ^{13}C NMR (DMSO-d_6) δ 24.6 (CH_3), 28.3 ($CO\mathit{CH}_3$), 48.7 (C4), 94.9 (C6), 105.2 (C2), 182.5 (C=O), 188.7, 196.7, and 200.5 (C1, 3, 5).

4.2.4. 2-Acetyl-2-hydroxy-5-methoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (18).[12] Colorless prisms. Mp 108–109 °C (lit.[12,16] 107–109 °C). IR (KBr) ν 2989, 2945, 1651, 1614, 1508 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.36 (6H, s, $CH_3\times 2$), 2.60 (3H, s, $COCH_3$), 3.82 (3H, s, OCH3), 5.42 (1H, s, olefinic H), 18.44 (1H, s, OH). EI-MS (*m*/*z*) 210 (M^+).

4.2.5. 2-[3-(*p*-Hydroxyphenyl)-2-propenoyl]-3-hydroxy-5-methoxy-6,6-dimethyl-2,4-cyclohexadien-1-one (19).[12] Yellow prisms. Mp 137–138 °C (lit.[16] 138–140 °C). IR (KBr) ν 3159, 3020, 2993, 2947, 1599, 1440 cm^{-1}. ^{1}H NMR ($CDCl_3$ including a small amount of DMSO-d_6) δ 1.39 (6H, s, $CH_3\times 2$), 3.83 (3H, s, OMe), 5.49 (1H, s, olefinic H), 6.87 and 7.56 (each 2H, d, $J=8.3$ Hz, *p*-substituted ArH), 7.90 and 8.12 (each 1H, d, $J=15.9$ Hz, *trans*-vinyl H), 9.37 (1H, s, ArOH), 19.00 (1H, s, OH). ^{13}C NMR (DMSO-d_6) δ 24.4 (CH_3), 57.1 (OCH_3), 48.6 (C6), 95.4 (C4), 104.6 (C2), 116.1 (C3″), 119.0 (C2′), 130.9 (C2″), 144.9 (C3′), 160.6 (C4″), 179.9 (C1′), 186.8 (C5), 190.5 (C3), 196.4 (C1). EI-MS (*m*/*z*) 314 (M^+).

4.3. De-*O*-methylation of 19

Methyl enol–ether **15** (1.187 g, 3.780 mmol) was added to 24 mL of a 33% HBr–acetic acid solution, and the mixture was stirred at 80 °C for 0.5 h. The reaction mixture was poured into ice-cold water (100 mL). The precipitated yellow powder was filtered and washed with water. The filtrate was extracted twice with EtOAc. The EtOAc extract was washed with water and brine, and then dried over anhydrous Na_2SO_4. After removing the organic solvents, the residual yellow solid and the above yellow powder were crystallized from EtOAc to give **7** (604 mg, 53%) as a yellow powder. The filtrate was separated by flash column chromatography on silica gel (6:1:0.1 toluene–EtOAc–AcOH) to give **7** (170 mg, 15%) as a yellow powder and **20** (178 mg, 15%) as a pale-yellow, solid.

4.3.1. *p*-Hydroxycinnamoylfilicinic acid; 2-[3′-(*p*-hydroxyphenyl)-2′-propenoyl]-3,5-dihydroxy-6,6-dimethyl-2,4-cyclohexndien-1-one (7). Yellow powder. Mp 205–206 °C (lit.[11c] 204–206 °C).UV–vis (EtOH) λ_{max} (log ε) 393 (4.39) nm (lit.[11c] 405 (4.5)). IR (KBT) ν 3159, 1593, 1416, 1234, 1165 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.32 (6H, s, $CH_3\times 2$), 5.51 (1H, s, olefinic H), 6.87 (2H, d, $J=8.5$ Hz, *p*-substituted ArH$\times 2$), 7.56 (2H, d, $J=8.5$ Hz, *p*-substituted ArH$\times 2$), 7.79 (1H, d, $J=15.9$ Hz, *trans*-vinyl H), 8.10 (1H, d, $J=15.9$ Hz, *trans*-vinyl H), 10.17 (1H, s, OH), 12.45 (1H, br. s, enol OH), 19.12 (1H, s, OH). ^{13}C NMR (DMSO-d_6) δ 24.4 ($CH_3\times 2$), 48.6 (C6), 96.5 (C4), 104.3 (C2), 116.1 (C3″ 5″), 119.5 (C-2′), 125.9 (C1″), 130.7 (C2″, 6″), 144.0 (C3′), 160.4 (C4″), 181.4 (C1′), 186.5 (C5), 190.4

(C3), 197.0 (C1). ^{1}H NMR (C_5D_5N) δ 1.63 (6H, s, $CH_3\times2$), 5.87 (1H, s, olefinic H), 7.16 (2H, d, $J=8.6$ Hz, *p*-substituted ArH×2), 7.73 (2H, d, $J=8.6$ Hz, *p*-substituted ArH×2), 8.29 (2H, d, $J=15.6$ Hz, *trans*-vinyl H), 8.86 (2H, d, $J=15.6$ Hz, *trans*-vinyl H). ^{13}C NMR (D_5D_5N) δ 25.2 ($CH_3\times2$), 50.1 (br. s, quaternary C), 97.2, 105.6, 117.0, 121.0, 127.2, 131.4, 144.6, 161.9, 183.7, 187.8, 192.7, 198.2. FAB-MS (NBA, *m/z*) 301 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.10; H, 5.39.

4.3.2. 7-Hydroxy-2-(4-hydroxyphenyl)-8,8-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4,5(8*H*)-dione (20). Yellow powder. Mp 188.5 °C (dec). UV–vis (EtOH) λ_{max} (log ε) 229 (4.29), 283 (4.08), 357 (3.73) nm. IR (KBr) ν 3300, 2981, 1670, 1627, 1616, 1533, 1520, 1456, 1414, 12591, 1223, 1144 cm^{-1}. ^{1}H NMR ($CDC1_3$+DMSO-d_6) δ 1.40 and 1.43 (each 3H, s, $CH_3\times2$), 2.85 (1H, dd, $J=3.0$, 18.5 Hz, $>CH_2$), 3.11 (1H, dd, $J=18.5$, 11.5 Hz, $>CH_2$), 5.24 (1H, dd, $J=3.0$, 11.5 Hz, >CH–), 5.47 (1H, s, olefinic H), 6.91 (2H, d, $J=8.5$ Hz, *p*-substituted ArH×2), 7.24 (2H, d, $J=8.5$ Hz, *p*-substituted ArH×2), 9.03 (1H, s, OH), 16.0 (1H, s, OH). FAB-MS (NBA, *m/z*) 301 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.15; H, 5.50.

4.4. The conversion of 20 to 7

To a stirred solution of **20** (178 mg, 0.593 mmol) in dry MeOH (1.5 mL), 28% NaOMe (60 mg) was added dropwise at room temperature and the mixture was stirred for 1 h. The reaction mixture was neutralized by the addition of Dowex 50W (H^+) resins, and then filtered and washed with MeOH. The filtrate was evaporated in vacuo to give a brown solid, which was separated by column chromatography on silica gel (6:1:0.1 toluene–EtOAc–AcOH) to give **7** (107 mg, 60%) as a yellow powder and **20** (26.5 mg, 15%) as a pale-yellow solid.

4.5. Synthesis of the analogs (14, and 12) of carthamin and its precursor

4.5.1. 2,2-Bis[3-(*p*-hydroxycinnamoyl)filicinic acid-5-yl] acetic acid (12). To a stirred suspension of **7** (52.4 mg, 0.175 mmol) in dry methanol (1 mL), a 25% solution of NaOMe in methanol was added dropwise until **7** dissolved completely. To the stirred mixture, glyoxylic acid monohydrate (8.5 mg, 0.092 mmol) was added and the reaction mixture was further stirred at room temperature for 4 h until **7** disappeared by TLC monitoring (6:1:0.2 or 5:2:0.5 toluene–EtOAc–AcOH). The reaction mixture was poured into 15 mL of ice-cold 2 M HCI and extracted three times with EtOAc, The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was separated by flash column chromatography on silica gel (6:1:0.1 toluene–EtOAc–AcOH) to give **12** (56.6 mg, 99%) as a yellow powder.

Mp 195–198 °C (lit.[11e] 195 °C (dec)). Silica gel TLC: R_f 0.43 (5:2:0.5 toluene–EtOAc–AcOH). HPLC: t_R 7.28 min (80:20 MeOH–25% AcOH aqueous solution). UV–vis (EtOH) λ_{max} (log ε) 221 (4.55), 397 (4.74) nm; carthamin precursor (**4**): lit.[5b] MeOH λ_{max} (log ε) 238 (4.37), 406 (4.67) nm; lit.[5a] EtOH λ_{max} (log ε) 343 (4.25), 423 (4.56) nm. IR (KBr) ν 3406, 2983, 1618, 1601, 1516, 1414 cm^{-1}. ^{1}H NMR (C_5D_5N) δ 1.74 and 1.89 (each 6H, s, $CH_3\times6$), 7.09 (4H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 7.15 (1H, s, >CH–), 7.63 (4H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 8.17 (2H, d, $J=15.8$ Hz, *trans*-vinyl H), 8.90 (2H, d, $J=15.8$ Hz, *trans*-vinyl H). ^{13}C NMR (C_5D_5N) δ 24.6, 26.9 (CH_3), 34.8 (>CH–), 52.1 (quaternary C), 105.5, 107.7, 116.8, 123.4, 127.8, 130.8, 136.0, 161.0, 175.9, 186.0, 188.4, 189.1, 199.7. FAB-MS (NBA, *m/z*) 657 $(M+H)^+$. Anal. Calcd for $C_{36}H_{32}O_{12}$ $0.1H_2O$: C, 65.67; H, 4.93. Found: C, 65.44; H, 5.31.

4.5.2. Dehydro-3,3′-bis(*p*-hydroxycinnamoyl)-5,5′-methylenedifilicinic acid (14). To a stirred suspension of **7** (60 mg, 0.2 mmol) in ethyl orthoformate (8.5 mL), NaH (50∼60% in oil, 60 mg (12.5 mmol) with a content of 55%) was added at room temperature. The reaction mixture gradually dissolved and its color changed from yellow to red. The stirring was continued at room temperature for 4 h. After confirming that the reaction was complete by the disappearance of **7** by silica gel TLC (5:2:0.5 toluene–EtOAc–AcOH), the red-colored reaction mixture was poured into 15 mL of ice-cold 2 M HCI solution, and extracted twice with EtOAc. The combined extract was washed with brine and then dried over anhydrous Na_2SO_4. After removing the organic solvents in vacuo, the residual solid was recrystallized from MeOH to give **14** (55.2 mg, 91%) as a reddish orange powder.

Mp 230–240 °C (dec) (lit.[11C] 230 °C (dec)). Silica gel TLC: R_f 0.56 (5:2:0.5 toluene–EtOAc–AcOH). HPLC: t_R 8.82 min (8:2 MeOH–25% AcOH aqueous solution). UV–vis (EtOH) λ_{max} (log ε) 241 (4.37), 373 (4.57), 535 (4.95) nm; carthamin (**5**): lit.[8b] EtOH λ_{max} (log ε) 244 (4.13), 377 (4.28), 515 (4.69) nm. IR (KBr) ν 3288, 2985, 1622, 1599, 1581, 1513, 1412 cm^{-1}. ^{1}H NMR (C_5D_5N) δ 1.73 (1H, s, $CH_3\times4$), 7.71 (4H, d, $J=8.7$ Hz, *p*-substituted ArH×4), 7.81 (4H, d, $J=8.7$ Hz, *p*-substituted ArH×4), 8.23 (2H, d, $J=15.4$ Hz, *trans*-vinyl H×2), 8.72 (2H, d, $J=15.4$ Hz, *trans*-vinyl H×2), 8.94 (1H, s, =CH–). ^{13}C NMR (C_5D_5N, at 60 °C) δ 22.8 and 23.0 (CH_3,×4), 52.5 (C4), 107.5 and 115.1 (C2, 6), 117.1 (C12), 120.4 and 120.6 (C8), 127.2 (C10), 131.5 and 131.8 (C11), 145.9 (C9), 147.1 (C14), 162.3 (C13), 185.2 (C7), 187.3, 188.1, 198.7 (C1, 3, 5). FAB-MS (thioglycerol, negative ion, *m/z*) 609 $(M-H)^-$. Anal. Calcd for $C_{35}H_{30}O_{10}$ $0.1H_2O$: C, 68.64; H, 4.97. Found: C, 68.43; H, 4.90.

4.6. Conversion reaction of 12 to 14 via oxidative decarboxylation using an aqueous permanganate solution.[5b]

To a stirred solution of **12** (45 mg, 0.0686 mmol) in acetone (1.5 mL), a 0.23% aqueous solution of potassium permanganate (1.8 mL) was added in small portions over a period of 1.5 h at room temperature, and the stirring was continued for an additional 0.5 h. After confirming the disappearance of **12**, the reaction mixture was added to a 1 M HCI solution (10 mL) and then extracted twice with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and then evaporated in vacuo. The residue was purified by flash column chromatography on silica

gel (6:1:0.1 toluene–EtOAc–AcOH) to give **14** (21.8 mg, 52%) as a reddish orange powder.

4.7. Synthesis of the analog (8) of safflower yellow B (1)

4.7.1. 1-Deoxy-1,1-bis[3′-(*p*-hydroxycinnamoyl)filicinic acid-5′-yl]-2,3,4,5,6-penta-*O*-acetyl-D-glucitol (21). To a stirred suspension of **7** (107 mg, 0.356 mmol) in dry methanol (1.5 mL), a 28% NaOMe methanol solution was added dropwise until **7** dissolved. To the stirred mixture, 2,3,4,5,6-penta-*O*-acetyl-D-aldehydo-glucose (161 mg, 0.356 mmol) was added in small portions over a period of 3 h and then stirred at room temperature for 8 h. The progress of the reaction was monitored by silica gel TLC (5:2:0.5 toluene–EtOAc–AcOH). The reaction mixture was poured into 20 mL of ice-cold 2 M HCl and extracted three times with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solution evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (6:1:0.1 and 5:2:0.2 toluene–EtOAc–AcOH) to give **7** (14.5 mg, 14%), **21** (67 mg, 39%), and its mono- and di-de-*O*-acetates (71 mg, 42–45%) as a yellow powder, respectively.

Data for **21**. Mp 140–143 °C. Silica gel TLC: R_f 0.47 (5:2:0.5 toluene–EtOAc–AcOH). HPLC: t_R 16.92 min (90:10 MeOH–25% AcOH aqueous solution). IR (KBr) ν 3417, 2995, 2937, 2885, 1751, 1620, 1601, 1516, 1416, 1217 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.16, 1.17, 1.20, 1.32 (each 3H, s, $CH_3\times4$), 1.85, 1.94, 1.96, 1.96, 2.05 (each 3H, s, OAc×5), 4.19 (2H, d, $J=4.9$ Hz, H-6′a,b), 4.98 (1H, dd, $J=4.4$, 4.9 Hz, H-5′), 4.98 (1H, br. d, $J=8.5$ Hz, H-3′), 5.19 (IH, dd, $J=8.5$, 4.4 Hz, H-4′), 5.31 (1H, d, $J=10.7$ Hz, H-2′), 6.28 (1H, br. d, $J=10.7$ Hz,H-2′), 6.82 (2H, d, $J=$ 8.8 Hz, *p*-substituted ArH×2), 6.83 (2H, d, $J=8.3$ Hz, *p*-substituted ArH×2), 7.50 (2H, d, $J=8.8$ Hz, *p*-substituted ArH×2), 7.53 (2H, d, $J=8.3$ Hz, *p*-substituted ArH×2), 7.61 (1H, d, $J=15.6$ Hz, *trans*-vinyl H), 7.71 (1H, d, $J=$ 15.6 Hz, *trans*-vinyl H), 8.06 (2H, $J=15.6$ Hz, *trans*-vinyl H), 10.5 (2H, br. s, OH×2), 19.4, 19.6 (each 1H, s, OH×2). ^1H NMR (C_5D_5N) δ 1.62, 1.75, 1.82, 1.92 (each 3H, s, $CH_3\times4$), 2.02, 2.08, 2.13, 2.16, 2.23 (each 3H, s, OAc×5), 4.83 (1H, dd, $J=8.1$, 11.9 Hz, H-6a) 4.94 (1H, dd, $J=2.6$, 11.9 Hz, H-6b), 5.85 (1H, ddd $J=2.6$, 4.3, 8.1 Hz, H-5), 5.93 (1H, dd, $J=1.3$, 8.5 Hz, H-3), 6.10 (1H, dd, $J=4.3$, 8.5 Hz, H-4), 6.49 (1H, d, $J=11.1$ Hz, H-1), 7.06, 7.09 (each 1H, d, $J=9.0$ Hz, *p*-substituted ArH×2), 7.32 (1H, dd, $J=1.2$, 11.1 Hz, H-2), 7.58, 7.65 (each 2H, d, $J=9.0$ Hz, *p*-substituted ArH×4), 8.09, 8.21 (each 1H, d, $J=15.8$ Hz, *trans*-vinyl H×2), 8.87, 8.88 (each 1H, *trans*-vinyl H×2), 17.56 (1H, br. s, chelated OH). ^{13}C NMR (C_5D_5N) δ 20.5, 20.7, 20.9, 21.1, 21.4 ($COCH_3\times5$), 29.4 (C1′) 51.3 and 52.6 (C4), 61.7 (C6′), 70.7, 71.0, 71.2, 71.5 (C2′ 3′, 4′, 5′) 105.3 and 105.8 (C2), 106.0 and 106.8 (C6), 116.7 and 116.8 (C12), 122.6 and 125.6 (C8), 128.7 and 129.4 (C10), 130.7 and 130.9 (C11), 141.4 and 142.6 (C9), 160.9 and 161.2 (C13) 170.1, 170.2 170.4, 170.7, and 170.9 ($COCH_3\times5$), 173.4 (C7), 186.1 and 186.8, 189.0 and 190.1, 199.2 and 200.1 (C1, 3, 5). FAB-MS (NBA, *m/z*) 973 $(M+H)^+$. Anal. Calcd for $C_{50}H_{52}O_{20}$: C, 61.72; H, 5.39. Found: C, 61.79; H, 5.53.

4.7.2. Deoxy-1,1-bis[3′-(*p*-hydroxycinnamoyl)filicinic acid-5′-yl]-D-glucitol (8). To a solution of acetate **21** (67 mg), and its mono- and di-de-*O*-acetates (71 mg) in dry MeOH (2 mL) was added dropwise 0.44 mL of a 28% NaOMe methanol solution followed by stirring at room temperature for 1 h. After confirming the completion of the de-*O*-acetylation by silica get TLC (5:4:1 toluene–ethyl formate–formic acid), the reaction mixture was neutralized by the addition of Dowex 50 W (H^+) resin, and then filtered and washed with methanol. The filtrate was evaporated in vacuo and then purified by column chromatography on silica get (5:4:1 toluene–ethyl formate–formic acid) and then Sephadex LH-20 gel (MeOH) to give **9** (193 mg, 71% from **7**) as an orange powder.

Mp 173–176 °C. $[\alpha]_D^{22}$ +101 (*c* 0.55, MeOH). HPLC: t_R 5.03 min (80:20 MeOH–25% AcOH aqueous solution). UV–vis (EtOH) λ_{max} (log ε) 218 (4.53), 403 (4.67) nm; safflower yellow B (**1**): lit.[8b] MeOH A_{max} (log ε) 239 (4.43), 410 (4.77) nm. IR (KBr) ν 3392, 2981, 2939, 1622, 1601, 1516, 1471, 1437, 1277, 1244, 1167 cm^{-1}. ^1H NMR (C_5D_5N-CD_3OD 98:2, 60 °C) δ 1.47, 1.62, 1.68, 1.72 (each 3H, s, $CH_3\times4$), 4.31 (1H, dd, $J=4.6$, 11.5 Hz, H-6a), 4.36 (2H, dd, $J=4.1$, 5 Hz, H-6b), 4.36 (1H, m, H-5), 4.54 (1H, d, $J=8.5$ Hz, H-4), 4.73 (1H, d, $J=7.0$ Hz, H-3), 5.61 (1H, d, $J=7.0$ Hz, H-1), 5.73 (1H, t, $J=7.0$ Hz, H-2), 7.59 and 7.61 (each 2H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 7.03, 7.04 (each 2H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 8.03, 8.04 (each 1H, d, $J=15.6$ Hz, *trans*-vinyl H×2), 8.55, 8.83 (each 2H, d, $J=15.6$ Hz, *trans*-vinyl H×2). ^{13}C NMR (C_5D_5N-CD_3OD 98:2, 80 °C) δ 23.6, 23.9, 24.4, and 25.2 ($CH_3\times4$), 38.2 and 38.4 (C1′), 46.2 and 53.3 (C4), 64.3 (C6′), 70.8, 72.6 and 72.8 (two peaks), 73.0 and 73.1 (two peaks), 93.8 (C2′, 3′, 4′, 5′) 104.7, 105.2, 106.7, and 111.5 (C2, 6), 116.5 and 116.6 (C12), 120.6 and 121.2 (C8), 127.6 and 128.6 (C10), 130.3 and 131.0 (C11), 139.9 and 143.8 (C9), 160.0 and 161.01 (C13), 179.3 (C7), 184.0 and 185.3, 185.8 and 187.6, 199.5 and 200.3 (C1, 3, 5). FAB-MS (glycerol, negative ion, *m/z*) 761 $(M-H)^-$. Anal. Calcd for $C_{40}H_{42}O_{15}$ C.62.25; 5; H, 5.62. Found: C, 62.08; H, 5.65.

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Metallation of pyridin-2-yldiazines. Use of pyridine ring as *ortho*-directing group. Diazines. Part 45

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Abstract—Starting from commercial chlorodiazines, we report the synthesis of pyridin-2-yldiazines. The first lithiation and functionalization of these compounds are reported and the regioselectivity of the metallation is discussed. The functionalization via the metallation reaction, provides a new access to substituted pyridin-2-yldiazines, which could be used as building blocks in supramolecules.

1. Introduction

Various polydentate nitrogen ligands based on pyridine, pyrazine, pyrimidine and pyridazine units have been described in the literature and have become the scaffold of choice for designing and assembling novel ligand architectures.[1] Several types of oligoheterocyclic pyridine–pyrimidine and pyridine–pyridazine are able to induce helical self-organisation leading to extended supramolecular fibers.[2] Functionalization of pyridin-2-yldiazines via the metallation reaction could provide an original access to new building blocks for elaboration of supramolecules.

The regiospecific introduction of lithium onto aromatic rings requires generally the presence of substituents with heteroatoms. This transformation (known as '*ortho*-directed lithiation') has great synthetic potential and has been extensively studied in pyridine and diazine series.[3] During the metallation reaction, the assistance of the directing metallation group (DMG) can be described as follows: (1) The inductive electron-withdrawing effect of the DMG activates *ortho* hydrogens toward strong bases.[4] (2) Coordination of heteroatom-containing DMG to lithium atom leads to various effects, more especially the complex-induced proximity effect of the base (CIPE), which favors the deprotonation and the stabilization of the lithio derivative.[5] According to their π-deficient character, heteroaromatic system such as a pyridine or a diazine ring have electron-withdrawing effect and could play the role of DMG with the intramolecular ring nitrogen atom complexation. Few studies dealing with the efficient lithiation of aromatic and heteroaromatic groups assisted by the pyridyl group have been previously reported.[6]

Starting from commercial materials and using the Stille cross-coupling reaction, we report here the synthesis of three pyridin-2-yldiazines **1**–**3** (Scheme 1).

Following our studies on the metalation of diazines, we studied the lithiation and the functionalization of the pyridin-2-yldiazines **1**–**3**.

For these compounds, the assistance of the cyclic nitrogen atom to induce the complexation giving a CIPE effect could come either from the pyridine nitrogen, a diazine nitrogen or both. For compound **2**, only the pyridine nitrogen could give this effect, whereas for **1** and **3**, both effects must be taken into account besides the cisoid or transoid conformers. An evaluation of the relative energy difference between these conformers has been calculated for 2,2′-bipyridine, 2-pyridin-2-yl-pyrazine 3-pyridin-2-yl-pyridazine and 4-pyridin-2-yl-pyrimidine by B3LYP.[2] In all cases, the transoid conformer was 6–7 kcal mol^{-1} lower in energy than the lowest energy cisoid conformer. Taken into account these results and considering the compounds **1**–**3** under planar transoid conformer, we could anticipate the site of pyridine ring influenced by the diazine nitrogen and vice versa (Scheme 2). Comparison with the experimental regioselectivity for the metallation allows to appreciate the relative influence of the pyridine or the diazine nitrogens.

Keywords: Pyridin-2-yldiazines; Metallation; Functionalization; *ortho*-directing group.
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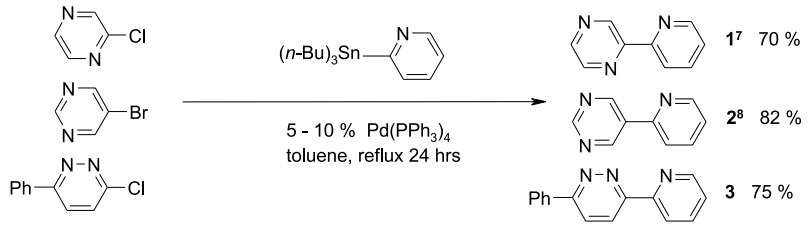
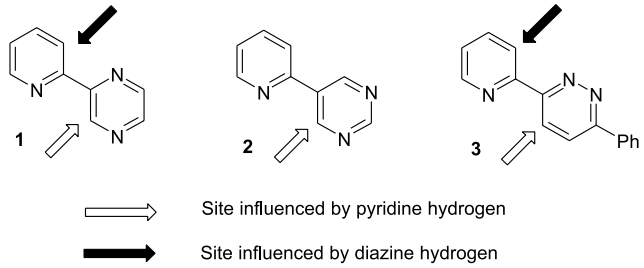


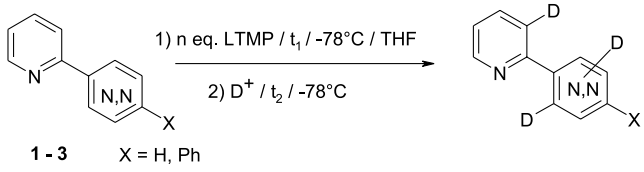
Scheme 1.



Scheme 2.

2. Results

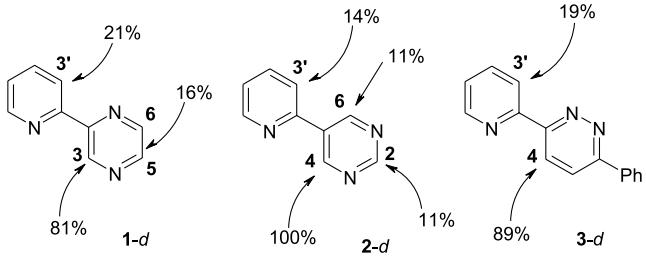
In a prelimary study, we examined the lithiation of **1**–**3** with an excess of LTMP in THF at −78 °C. The lithiated intermediates were quenched at −78 °C by DCl or EtOD leading to the deuteriated pyridin-2-yldiazines (Scheme 3). Several experimental conditions have been tested, the best results are obtained with 3 or 4 equiv of LTMP, a reaction time t_1 of 15 min followed by an immediate quenching with the deuteriated reagent ($t_2=0$).



Scheme 3.

Examination of the ^{1}H NMR spectra of the crude reaction mixtures allowed us to appreciate the percentage of the incorporated deuterium and to determine the regioselectivity of the metallation. So, we compared the intensity of the signal of an unaffected proton (for example, H_4 or H_5 of pyridine ring) with a decreased signal of a deuteriated position. The results are given in Table 1, (Scheme 4).

A high regioselectivity of deuteriation was observed on the diazine ring at the *ortho* position of the pyridine–diazine linkage (81–100%), whereas a low percentage of deuteriation was obtained at C-3′ position of the pyridine ring (14–21%). It must be noted that for compounds **1** and **2**, a low percentage of deuteriation (11–16%) was also observed at the other positions of the diazine moiety.



Scheme 4.

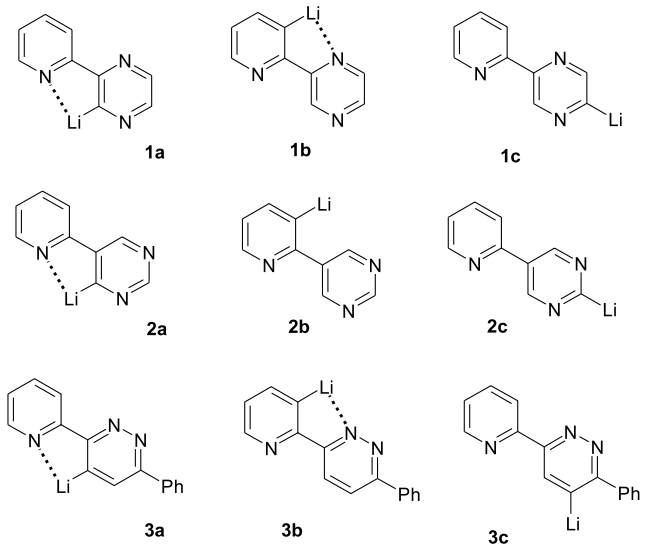
Metallation at the *ortho* positions of the pyridine–diazine linkage could be explained by assistance of the ring nitrogen atom as DMG, which stabilizes by complexation the lithio derivative. In such a hypothesis, the results highlight a greater deprotonation of the diazine ring, which indicates that the 2-pyridyl group could be considered as a far better DMG than the diazinyl group. This can be rationalized in terms of pK_a values: the stronger basicity of the pyridine nitrogen (p$K_a=5.2$) in comparison with the diazine nitrogens (p$K_a=0.5$–2.1). This effect ensures a better stabilisation of the lithiated intermediates on the pyridine ring. To bear out this proposition, heats of formation of various monolithio pyridine-2-yldiazines have been determined by semi-empirical Li/PM3 method (Table 2, Scheme 5).

Table 2. Heats of formation of 2-pyridyl diazines monolithiated (kcal mol^{-1})

Compounds isomers	a	b	c
1	83.13	87.44	87.84
2	81.43	98.52	83.80
3	125.03	129.18	140.71

Table 1. Metallation and deuteriation of compounds **1**–**3**

	Lithiation conditions			Incorporated deuterium (%) δ (ppm) and (multiplicity)					
				Diazine ring					Pyridine ring
	n (equiv LTMP)	t_1 (min)	D^+	H-2	H-3	H-4	H-5	H-6	H-3′
1-*d*	3	20	DCl or DCl/ETOD	—	81, 9.61 (s)	—	16, 8.58–8.56 (m)		21, 8.33 (d)
2-*d*	4	15	DCl/EtOD	11 9.22 (s)	—	100, 9.30 (s)	—	11 9.30 (s)	14, 7.73 (d)
3-*d*	3	20	EtOD	—	—	89, 8.61 (d)	0	—	19, 8.75 (d)



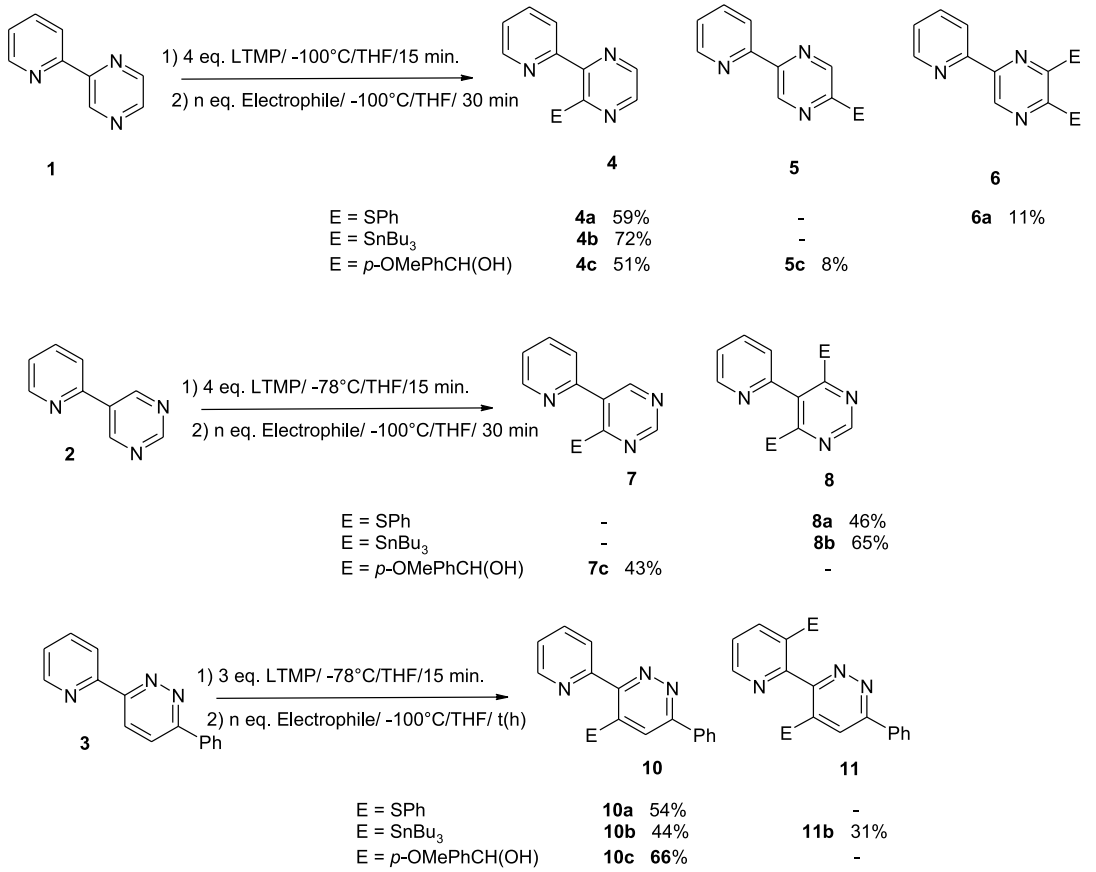
Scheme 5.

The lowest heat of formation of pyridin-2-yldiazines was observed for the lithio derivatives complexed by the nitrogen atom of the pyridine moiety (isomers **a**). In comparison, the complexation with a nitrogen atom of the diazine ring (**1b**, **3b**) causes an increase of the heat of formation of more than 4 kcal mol^{-1}. This is well correlated with the deuteriation percentages given in Table 1. In the case of compounds **1** and **2**, some deuteriation occurred at C2 and C5 positions. This can be explained by metallation without metalling-directed-group as reported previously in the diazines series.[9] The heat of formation of lithio derivative **2b** is much lower than the other uncomplexed of isomers **1c**–**3c** and could explain the deuteriation observed at C3′ position of the compound **2**.

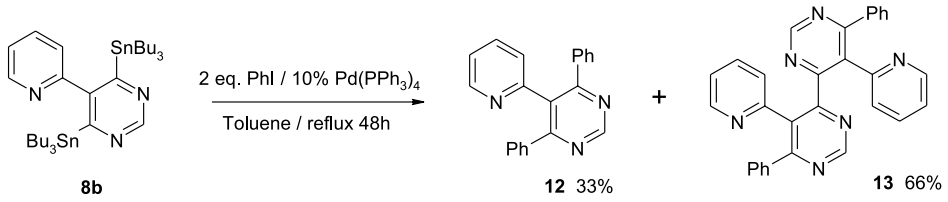
This preliminary study of metallation of compounds **1**–**3** with deuteriated reagents as the electrophile highlights ability to functionalize the diazine ring, more particulary at the *ortho* position of the pyridine–diazine linkage. Thus, we have then extended our study to other electrophiles. Metallations were carried out with an excess of LTMP (3 or 4 equiv) at −100 °C or −78 °C in THF, with short reaction time (15 min). The results are consigned in Scheme 6.

With *p*-methoxybenzaldehyde as the electrophile, compounds monofunctionalized on the diazine ring were obtained in moderate yields. Nevertheless, in case of the pyridin-2-ylpyrazine **1**, a small amount (8%) of a position isomer **5c** was observed besides the major product **4c**. For the 3-(pyridin-2-yl)pyrimidine **2**, use of diphenyl sulfide or tributyltin chloride as electrophile led to the compounds **8a** and **8b** disubstituted at the *ortho* position of the pyridine–pyrimidine linkage. It must be noted that for compound **3**, reaction of 1 equiv of $SnBu_3Cl$ afforded the monosubstituted compound **10b** as the major product besides the disubstituted compound **11b**.

A Stille cross-coupling reaction has been tested with



Scheme 6.



8b **12** 33% **13** 66%

Scheme 7.

compound **8b** and iodobenzene. Reaction with 2 equiv of iodobenzene in toluene under reflux for 48 h with $Pd(PPh_3)_4$ as catalyst gave a mixture of the expected 4,6-diphenyl-5-(2-pyridyl)-pyrimidine **12** as minor product and a dimer the bis-(4-phenyl-5-(2-pyridyl)-pyrimidine) **13** (Scheme 7).

3. Conclusion

Starting from commercial chlorodiazines, we synthesized three pyridine-2-yldiazines. The first lithiation and functionalization of these compounds are reported allowing to access to pyridine-2-yldiazines substituted on the diazines moiety. Synthesis of supramolecules using these compounds as building blocks are in progress.

4. Experimental

Melting points were determined on a Electrothermal 1100 instrument. The ^1H and ^{13}C spectra were recorded on a Bruker AC 300 (300 MHz ^1H, 75 MHz ^{13}C) instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin-Elmer 16 PC FT-IR spectrometer. Mass spectra were recorded on an ATI-Unicam Automass® apparatus.

4.1. General procedure A for synthesis of pyridine-2-yldiazines by cross-coupling reaction

A solution of 2-tributylstannylpyridine (2.531 g, 80%, 5.5 mmol) halogenodiazine (5.5 mmol) and $Pd(PPh_3)_4$ (0.433 g, 0.375 mmol) in degassed toluene (50 mL) was heated under reflux under nitrogen atmosphere for 24 h. After cooling at room temperature, dichloromethane (50 mL) was added. The organic phase was washed with aqueous ammonia (15%, 100 mL), then with water to neutrality, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel.

4.2. General procedure B for deuteriation via metallation of pyridine-2-yldiazines

A solution of *n*-butyllithium (0.790 mL, 1.6 M, 1.26 mmol in hexane) was added to cold (−10 °C), stirred and anhydrous mixture of THF (30 mL) and 2,2,6,6-tetramethylpiperidine (0.216 mL, 0.178 g, 1.26 mmol) under an atmosphere of dry nitrogen. After 30 min at this temperature, the mixture temperature was carried to θ °C and added to cold (θ °C) solution of the pyridine-2-yldiazine (*n* equiv) in THF (10 mL). Then, the mixture was stirred for t_1 at θ °C, then the reaction mixture was quenched at −78 °C with an appropriate deuteriate electrophile (6 equiv). Temperature was increased to room temperature, then dichloromethane (20 mL) and water (20 mL) were added to the mixture. The aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic extracts were washed with water (2×20 mL) then dried over magnesium sulfate and evaporated. The crude product, as a brownish solid was analyzed by ^1H NMR.

4.3. General procedure C for metallation of pyridine-2-yldiazines by lithium 2,2,6,6-tetramethylpiperidide

A solution of *n*-butyllithium (1.6 M in hexane) was added to cold (−78 °C), stirred and anhydrous mixture of THF (15 mL) and 2,2,6,6-tetramethylpiperidine (TMPH) under an atmosphere of dry nitrogen. The mixture was warmed to 0 °C. After 30 min, the mixture temperature was carried to *T* °C and added to cold (*T* °C) solution of the 2-pyridyldiazine dissolved in THF (10 mL). Then, the mixture was stirred for t_1 at *T* °C, then the electrophile introduced and stirring was continued for t_2 hour(s) at this temperature. Hydrolysis was then carried out at θ °C using a solution of THF/EtOH/water (5:4:1). Temperature was increased to room temperature, then dichloromethane (10 mL) and water were added to the mixture. After decantation, the organic layer was washed with water to neutrality and the aqueous phase was twice extracted with dichloromethane. The combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

4.4. Procedure D for cross-coupling of iodobenzene with 4,6-bistributylstannyl-5-(2-pyridyl)-pyrimidine under Stille conditions

A solution of 4,6-bistributylstanny-5-(2-pyridyl)-pyrimidine **8b** (120 mg, 0.16 mmol), iodobenzene (0.04 mL, 65.3 mg, 0.32 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.016 mmol) in degassed toluene (15 mL) was heated under reflux and under nitrogen atmosphere for 48 h. After cooling, the reaction mixture was evaporated under vacuum to dryness, then aqueous ammonia (5%, 10 mL) and ethyl acetate (50 mL) were added with stirring. The organic phase was washed with water to neutrality, dried over magnesium sulfate, filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (eluent ethyl acetate) and giving a mixture of equimolecular compounds **12** and **13**.

4.4.1. 2-(2′-Pyridyl)-pyrazine (1).[7] Reaction of chloropyrazine (572 mg, 0.456 mL, 5 mmol) according the general procedure A gave after purification by column chromatography (silica, eluent petroleum ether/ethyl acetate

(2:1)) and sublimation 550 mg of **1** (70%) as a colorless solid, mp 57–58 °C; ^{1}H NMR ($CDCl_3$): δ 9.61 (1H, d, J= 1.5 Hz, H-3), 8.69 (1H, d, J=4.5 Hz, H-6′), 8.60–8.57 (2H, m, H-5, H-6), 8.33 (1H, d, J=7.9 Hz, H-3′), 7.82 (1H, ddd, J=7.9, 7.5, 1.8 Hz, H-4′), 7.34 (1H, ddd, J=7.5, 4.5, 1.1 Hz, H-5′); ^{13}C NMR ($CDCl_3$): δ 154.6 (1C, C-2′), 151.5 (1C, C-2), 149.9 (1C, C-6′), 144.8 (1C, C-5), 143.9 (1C, C-6), 143.7 (1C, C-3), 137.5 (1C, C-4′), 124.8 (1C, C-5′), 121.8 (1C, C-3′); MS (CI); *m/z* (rel int. %) 157 [M^+] (100), 129 (5), 105 (38), 79 (32), 52 (18). Anal. Calcd for $C_9H_7N_3$ (M_w=157.18) C, 68.78; H, 4.49; N, 26.73. Found: C, 68.67; H, 4.56; N, 26.66.

4.4.2. 5-(2′-Pyridyl)-pyrimidine (2).[8] Reaction of 5-bromopyrimidine (832 mg, 5 mmol) according to the general procedure A gave after purification by column chromatography (silica, eluent petroleum ether/ethyl acetate (4:1)) and sublimation 644 mg of **2** (82%) as a colorless solid, mp 130–132 °C; ^{1}H NMR ($CDCl_3$): δ 9.31 (2H, s, H-4, H-6), 9.24 (1H, s, H-2), 8.74 (1H, d, J=4.7 Hz, H-6′), 7.82 (1H, ddd, J=7.9, 7.5, 1.6 Hz, H-4′), 7.74 (1H, dd, J=7.9, 1.1 Hz, H-3′), 7.34 (1H, ddd, J=7.5, 4.7, 1.1 Hz, H-5′); ^{13}C NMR ($CDCl_3$): δ 159.0 (1C, C-2), 155.5 (2C, C-4, C-6), 152.4 (1C, C-2′), 150.8 (1C, C-6′), 137.6 (1C, C-4′), 132.8 (1C, C-5), 124.0 (1C, C-5′), 120.9 (1C, C-3′); MS (CI); *m/z* (rel int. %) 157 [M^+] (100), 130 (68), 79 (93), 51 (47). Anal. Calcd for $C_9H_7N_3$ (M_w=157.18) C, 68.78; H, 4.49; N, 26.73. Found: C, 68.85; H, 4.28; N, 26.90.

4.4.3. 6-Phenyl-3-(2′-pyridyl)-pyridazine (3). Reaction of 6-chloro-3-phenylpyridazine (970 mg, 5 mmol) according the general procedure A gave after purification by column chromatography (silica, eluent petroleum ether/ethyl acetate (2:1)) 875 mg of **3** (75%) as a yellow solid, mp 155–157 °C; ^{1}H NMR ($CDCl_3$): δ 8.73 (1H, d, J=7.9 Hz, H-3′), 8.69 (1H, dd, J=4.7, 1.8 Hz, H-6′), 8.58 (1H, d, J=8.9 Hz, H-4), 8.17–8.13 (2H, m, H_{Ph}), 7.96 (1H, d, J=8.9 Hz, H-5), 7.86 (1H, ddd, J=7.9, 7.5, 1.8 Hz, H-4′), 7.55–7.45 (3H, m, H_{Ph}), 7.35 (1H, ddd, J=7.5, 4.9, 1.1 Hz, H-5′); ^{13}C NMR ($CDCl_3$): δ 159.1 (1C, C-3), 157.4 (1C, C-6), 153.8 (1C, C-2′), 149.8 (1C, C-6′), 137.5 (1C, C-4′), 136.5 (1C, C_{Ph}), 130.6 (1C, C_{Ph}), 129.4 (2C, C_{Ph}), 127.5 (2C, C_{Ph}), 125.3, 125.0 (2C, C-4, -5), 124.8 (1C, C-5′), 121.8 (1C, C-3′); MS (CI); *m/z* (rel int. %) 233 [M^+] (74), 204 (100), 176 (5), 128 (3), 102 (44), 76 (16). Anal. Calcd for $C_{15}H_{11}N_3$ (M_w= 233.28) C, 77.23; H, 4.75; N, 18.01. Found: C, 77.13; H, 4.88; N, 17.90.

4.4.4. [^{2}H]-2-(2′-Pyridyl)-pyrazine (1-*d*). ^{1}H NMR ($CDCl_3$): δ 9.62 (0.18H, s, H-3), 8.70 (1.17H, d, J= 4.4 Hz, H-6′), 8.60–8.57 (1.53H, m, H-5, H-6), 8.34 (0.79H, d, J=7.9 Hz, H-3′), 7.83 (1.00H, ddd, J=7.9, 7.5, 1.8 Hz, H-4′), 7.34 (1.00H, dd, J=7.5, 4.4 Hz, H-5′).

4.4.5. [^{2}H]-5-(2′-Pyridyl)-pyrimidine (2-*d*). ^{1}H NMR ($CDCl_3$): δ 0.98 (H, s, H-4(6), 9.22 (0.98H, s, H-2), 8.72 (1.18H, d, J=4.9 Hz, H-6′), 7.81 (1.24H, ddd, J=7.9, 7.5, 1.6 Hz, H-4′), 7.73 (1.07H, d, J=7.9 Hz, H-3′), 7.33 (1.24H, dd, J=7.5, 4.9 Hz, H-5′).

4.4.6. [^{2}H]-6-Phenyl-3-(2′-pyridyl)-pyridazine (3-*d*). ^{1}H NMR ($CDCl_3$) δ: 8.75 (0.89H, d, J=7.9 Hz, H-3′), 8.71 (1.00H, d, J=4.5 Hz, H-6′), 8.61 (0.11H, d, J=9.0 Hz, H-4), 8.19–8.15 (1.94H, m, H_{Ph}), 7.98 (1.00H, s, H-5), 7.87 (1.05H, ddd, J=7.9, 7.5, 1.6 Hz, H-4′), 7.57–7.49 (3.19H, m, H_{Ph}), 7.37 (1.18H, ddd, J=7.5, 4.5, 1.1 Hz, H-5′).

4.4.7. 2-(2′-Pyridyl)-3-phenylthiopyrazine 4a. Metallation of **1** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, T=−100 °C), followed by reaction with diphenylsulfide (4 equiv, 574 mg) in solution with anhydrous THF (10 mL), t_1=15 min, t_2=30 min, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (4:1)) 99 mg (59%) of **4a** as a yellow solid, mp 99–100 °C; ^{1}H NMR ($CDCl_3$): δ 8.81 (1H, d, J=4.9 Hz, H-6′), 8.28 (1H, d, J=2.5 Hz, H-5), 8.23 (1H, d, J=2.5 Hz, H-6), 8.20 (1H, d, J=7.9 Hz, H-3′), 7.86 (1H, ddd, J=7.9, 7.5, 1.5 Hz, H-4′), 7.55–7.52 (2H, m, H-phenyl), 7.40–7.36 (4H, H-phenyl, H-5′); ^{13}C NMR ($CDCl_3$): δ 157.0 (1C, C-2), 155.8 (1C, C-2′), 148.9 (1C, C-3), 148.4 (1C, C-6′), 143.4 (1C, C-6), 139.1 (1C, C-5), 137.2 (1C, C-4′), 136.0 (2C, CH-phenyl), 131.8 (1C, Cq-phenyl), 129.5 (2C, CH-phenyl), 129.3 (1C, CH-phenyl), 124.3 (1C, C-5′), 123.9 (1C, C-3′); MS (CI, rel int. %) 266 [M^++1] (100). Anal. Calcd for $C_{15}H_{11}N_3S$ (M_w=265.34) C, 67.90; H, 4.10; N, 15.84. Found: C, 68.01; H, 4.05; N, 15.97.

4.4.8. 5,6-Bis(phenylthio)-2-(2′-pyridyl)-pyrazine 6a. Metallation of **1** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, T=−100 °C), followed by reaction with diphenylsulfide (4 equiv, 574 mg) in solution with anhydrous THF (10 mL), t_1=15 min, t_2=30 min, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (4:1)) 26 mg (11%) of **6a** as a yellow solid, mp 106–108 °C; ^{1}H NMR ($CDCl_3$): δ 9.06 (1H, H-3), 8.54 (1H, d, J=4.9 Hz, H-6′), 7.65–7.55 (6H, m, H-phenyl, H-3′, H-4′), 7.49–7.40 (6H, m, H-phenyl), 7.18 (1H, ddd, J=7.2, 4.9, 1.5 Hz, H-5′); ^{13}C NMR ($CDCl_3$): δ 154.4 (1C, C-2′), 153.3 (1C, C-2), 149.6 (1C, C-6′), 147.0 (2C, C-5, C-6), 138.4 (1C, C-3), 137.2 (1C, C-4′), 136.0 (2C, CH-phenyl), 134.9 (2C, CH-phenyl), 129.7 (2C, CH-phenyl), 129.6 (1C, CH-phenyl), 129.5 (1C, CH-phenyl), 129.48 (1C, CH-phenyl), 129.43 (2C, Cq-phenyl), 124.2 (1C, C-5′), 121.1 (1C, C-3′) ppm; MS (FAB$^+$, rel int. %) 374 [M^++1] (55), 154 (100), 136 (70). Anal. Calcd for $C_{21}H_{15}N_3S_2$ (M_w=373.50) C, 67.53; H, 4.05; N, 11.25. Found: C, 67.68; H, 4.21; N, 11.16.

4.4.9. 2-(2′-Pyridyl)-3-tributylstannylpyrazine 4b. Metallation of **1** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, T=−100 °C), followed by reaction with tributyltin chloride (4 equiv, 0.54 mL) in solution with anhydrous THF (10 mL), t_1=15 min, t_2=30 min, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (20:1)) 205 mg (72%) of **4b** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.74 (1H, dd, J= 2.6, 2.3 Hz, H-5), 8.57 (1H, d, J=4.5 Hz, H-6′), 8.42 (1H, d, J=8.3 Hz, H-3′), 8.39 (1H, d, J=2.6 Hz, H-6), 7.79 (1H, ddd, J=7.9, 7.5, 1.5 Hz, H-4′), 7.32 (1H, ddd, J= 7.5, 4.5, 1.1 Hz, H-5′), 1.58–1.37 (6H, m, CH_2), 1.30–1.18 (6H, m, CH_2), 1.08–0.94 (6H, m, CH_2), 0.89–0.77 (9H, m, CH_3); ^{13}C NMR ($CDCl_3$): δ 170.9 (1C, C-3), 156.2 (1C,

C-2′), 154.5 (1C, C-2), 147.8 (1C, C-6′), 145.9 (1C, C-5), 141.5 (1C, C-6), 137.1 (1C, C-4′), 124.3 (1C, C-5′), 122.0 (1C, C-3′), 29.7 (3C, CH_2), 27.9 (3C, CH_2), 14.2 (3C, CH_3), 13.2 (3C, CH_2); MS (FAB$^+$, rel int. %) 446 [$M^+ + 1$] (<1), 390 (100), 276 (32). Anal. Calcd for $C_{21}H_{33}N_3Sn$ (M_w= 446.21) C, 56.50; H, 7.40; N, 9.42. Found: C, 56.38; H, 7.34; N, 9.29.

4.4.10. 3-(Hydroxy-(*p*-methoxyphenyl)methyl)-2-(2′-pyridyl)-pyrazine 4c. Metallation of **1** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, $T=-100$ °C), followed by reaction with *p*-methoxybenzaldehyde (4 equiv, 0.348 mg) in solution with anhydrous THF (10 mL), $t_1=$ 15 min, $t_2=30$ min, gave after purification by column chromatography (silicagel, eluent dichloromethaneäcetone (10:1), 96 mg (51%) of **4c** as a reddish oil; ^{1}H NMR ($CDCl_3$): δ 8.61 (1H, d, $J=4.9$ Hz, H-6′), 8.58 (2H, s, H-5, -6), 7.97 (1H, d, $J=7.9$, H-3′), 7.78 (1H, ddd, $J=7.9$, 7.5, 1.8 Hz, H-4′), 7.32 (1H, ddd, $J=7.5$, 4.9, 1.1 Hz, H-5′), 7.09 (2H, d, $J=8.7$ Hz, H-phenyl), 7.05 (1H, d, $J=7.0$ Hz, C*H*OH), 6.69 (2H, d, $J=8.7$ Hz, H-phenyl), 6.29 (1H, d, $J=7.0$ Hz, CHO*H*), 3.69 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$): δ 158.8 (1C, Cq-phenyl), 157.5 (1C, C-3), 156.4 (1C, C-2′), 151.3 (1C, C-2), 148.0 (1C, C-6′), 143.0 and 142.7 (2C, C-5, C-6), 138.0 (1C, C-4′), 134.3 (1C, Cq-phenyl), 128.1 (2C, CH-phenyl), 125.1 (1C, C-3′), 124.4 (1C, C-5′), 113.6 (2C, CH-phenyl), 74.9 (1C, CHOH), 55.5 (1C, CH_3) ppm; MS (ESI, rel int. %) 316 [$M^+ + Na^+$] (5), 276 (13), 262 (6), 184 (9), 171 (79), 126 (100). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (M_w=293.33) C, 69.61; H, 5.15; N, 14.13. Found: C, 69.37; H, 5.21; N, 14.14.

4.4.11. 6-(Hydroxy-(*p*-methoxyphenyl)methyl)-2-(2′-pyridyl)-pyrazine 5c. Metallation of **1** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, $T=-100$ °C), followed by reaction with *p*-methoxybenzaldehyde (4 equiv, 0.348 mg) in solution with anhydrous THF (10 mL), $t_1=15$ min, $t_2=30$ min, gave after purification by column chromatography (silicagel, eluent dichloromethane/acetone (10:1), 15 mg (8%) of **5c** as a reddish oil; ^{1}H NMR ($CDCl_3$): δ 9.47 (1H, s, H-3), 8.67 (1H, d, $J=3.8$ Hz, H-6′), 8.53 (1H, s, H-5), 8.34 (1H, d, $J=$ 7.9 Hz, H-3′), 7.81 (1H, ddd, $J=7.9$, 7.5, 1.8 Hz, H-4′), 7.35–7.29 (1H, m, H-5′), 7.32 (2H, d, $J=8.7$ Hz, H-phenyl), 6.85 (2H, d, $J=8.7$ Hz, H-phenyl), 5.86 (1H, s, C*H*OH), 4.80 (1H, br s, CHO*H*), 3.75 (3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 159.9 (1C, Cq-phenyl), 156.1 (1C, C-6), 154.1 (1C, C-2′), 149.9 (1C, C-6′), 149.3 (1C, C-2), 143.3 (1C, C-5), 141.8 (1C, C-3), 137.5 (1C, C-4′), 134.5 (1C, Cq-phenyl), 128.7 (2C, CH-phenyl), 125.0 (1C, C-5′), 121.9 (1C, C-3′), 114.6 (2C, CH-phenyl), 74.1 (1C, CHOH), 55.7 (1C, CH_3); MS (ESI, rel int. %) 316 [$M^+ + Na^+$] 276 (3), 171 (100), 126 (72). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (M_w=293.33) C, 69.61; H, 5.15; N, 14.13. Found: C, 69.81; H, 5.07; N, 14.39.

4.4.12. 4,6-Bis(phenylthio)-5-(2′-pyridyl)-pyrimidine 8a. Metallation of **2** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with diphenylsulfide (4 equiv, 574 mg) in solution with anhydrous THF (10 mL), $t_1=15$ min, $t_2=30$ min, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (2:1)) 110 mg (46%) of **8a** as a yellow solid, mp 176–178 °C; ^{1}H NMR ($CDCl_3$): δ 8.88 (1H, d, $J=4.5$ Hz, H-6′), 8.48 (1H, s, H-2), 7.90 (1H, ddd, $J=7.9$, 7.5, 1.6 Hz, H-4′), 7.63 (1H, d, $J=7.9$ Hz, H-3′), 7.51–7.37 (11H, H-phenyl, H-5′); ^{13}C NMR ($CDCl_3$): δ 167.4 (2C, C-4, C-6), 157.2 (1C, C-2), 153.2 (1C, C-2′), 151.1 (1C, C-6′), 137.6 (1C, C-4′), 135.9 (4C, CH-phenyl), 129.8 (2C, CH-phenyl), 129.6 (4C, CH-phenyl), 128.8 (2C, Cq-phenyl), 128.1 (1C, C-5), 126.2 (1C, C-3′), 124.4 (1C, C-5′) ppm; MS (CI, rel int. %) 172 [M^+ − PhSPh–NH](100). Anal. Calcd for $C_{21}H_{15}N_3S_2$ (M_w= 373.50) C, 67.53; H, 4.05; N, 11.25. Found: C, 67.50; H, 4.19; N, 11.20.

4.4.13. 4,6-Bistributylstannyl-5-(2′-pyridyl)-pyrimidine 8b. Metallation of **2** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with diphenylsulfide (4 equiv, 574 mg) in solution with anhydrous THF (10 mL), $t_1=15$ min, $t_2=30$ min, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (5:1)) 306 mg (65%) of **8b** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 9.23 (1H, s, H-2), 8.67 (1H, d, $J=4.5$ Hz, H-6′), 7.75 (1H, ddd, $J=7.9$, 7.5, 1.6 Hz, H-4′), 7.32 (1H, dd, $J=7.9$, 7.5 Hz, H-5′), 7.31 (1H, d, $J=7.9$ Hz, H-3′), 1.37–1.27 (12H, m, CH_2), 1.23–1.11 (12H, CH_2), 0.90–0.67 (30H, m, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 180.7 (2C, C-4, C-6), 159.9 (1C, C-2′), 155.6 (1C, C-2), 151.2 (1C, C-5), 150.0 (1C, C-6′), 136.7 (1C, C-4′), 124.3 and 123.0 (2C, C-3′, -5′), 29.3 (6C, CH_2), 27.6 (6C, CH_2), 14.0 (6C, CH_3), 11.6 (6C, CH_2); MS (CI, rel int. %) 446 [$M^+ - Sn(n\text{-}Bu)_3$] (80), 332 (15), 219 (29), 184 (60), 170 (100). Anal. Calcd for $C_{33}H_{59}N_3Sn_2$ (M_w= 735.24) C, 53.91; H, 8.09; N, 5.72. Found: C, 53.79; H, 8.23; N, 5.78.

4.4.14. 4-(Hydroxy-(*p*-methoxyphenyl)methyl)-5-(2′-pyridyl)-pyrimidine 7c. Metallation of **2** (100 mg, 0.64 mmol) according to the general procedure C with *n*-BuLi (4 equiv, 1.58 mL), TMPH (4 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with *p*-methoxybenzaldehyde (4 equiv, 0.348 mg) in solution with anhydrous THF (10 mL), $t_1=15$ min, $t_2=30$ min, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (1:10)), 81 mg (43%) of **7c** as a reddish oil; ^{1}H NMR ($CDCl_3$): δ 9.24 (1H, s, H-2), 8.71 (1H, s, H-6), 8.66(1H, dd, $J=4.1$, 0.8 Hz, H-6′), 7.70 (1H, ddd, $J=7.9$, 7.5, 1.8 Hz, H-4′), 7.30 (1H, ddd, $J=7.5$, 4.6, 1.1 Hz, H-5′), 7.19 (1H, d, $J=7.9$ Hz, H-3′), 6.89 (2H, d, $J=8.7$ Hz, H-phenyl), 6.62 (2H, d, $J=8.7$ Hz, H-phenyl), 6.57 (1H, s, C*H*OH), 6.12 (1H, s, CHO*H*), 3.67 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$): δ 168.6 (1C, C-4), 159.2 (1C, Cq-phenyl), 157.8 (1C, C-2), 157.7 (1C, C-6), 154.1 (1C, C-2′), 149.6 (1C, C-6′), 137.9 (1C, C-4′), 133.6 (1C, Cq-phenyl), 132.5 (1C, C-5), 128.3 (2C, CH-phenyl), 124.3 (1C, C-3′), 123.8 (1C, C-5′), 113.8 (2C, CH-phenyl), 73.5 (1C, CHOH), 55.5 (1C, CH_3); MS (ESI, rel int. %) 293 [M^+] (25), 276 (40), 260 (30), 158 (100), 130 (45), 79 (55). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (M_w=293.33) C, 69.61; H, 5.15; N, 14.13. Found: C, 69.65; H, 5.20; N, 14.40.

4.4.15. 6-Phenyl-4-phenylthio-3-(2′-pyridyl)pyridazine 10a. Metallation of **3** (200 mg, 0.85 mmol) according to the general procedure C with *n*-BuLi (3 equiv, 1.58 mL), TMPH (3 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with diphenylsulfide (3 equiv, 556 mg) in solution with anhydrous THF (10 mL), $t_1=20$ min, $t_2=4$ h, gave after purification by column chromatography (silicagel, eluent petroleum ether/etoneac (3:1)) 156 mg (54%) of **10a** as a yellow solid, mp 141–142 °C; ^{1}H NMR ($CDCl_3$): δ 8.82 (1H, d, $J=4.9$ Hz, H-6′), 8.56 (1H, d, $J=7.9$ Hz, H-3′), 7.93 (1H, ddd, $J=7.9$, 7.5, 1.5 Hz, H-4′), 7.84–7.80 (2H, m, H-phenyl), 7.65–7.62 (2H, m, H-phenyl), 7.53–7.51 (3H, m, H-phenyl), 7.44–7.41 (4H, m, H-phenyl, H-5′), 7.20 (1H, s, H-5); ^{13}C NMR ($CDCl_3$): δ 157.3 (1C, C-3), 155.4 (1C, C-6), 153.6 (1C, C-2′), 148.0 (1C, C-6′), 145.5 (1C, C-4), 137.4 (1C, C-4′), 136.3 (2C, CH-phenyl), 131.0 (2C, Cq-phenyl), 130.8 (2C, CH-phenyl), 130.7 (1C, CH-phenyl), 130.4 (1C, CH-phenyl), 129.3 (2C, CH-phenyl), 127.4 (2C, CH-phenyl), 124.4 (1C, C-5′), 123.9 (1C, C-5), 121.3 (1C, C-3′) ppm; MS (ESI, rel int. %) 364 [M^++Na] (100). Anal. Calcd for $C_{21}H_{15}N_3S$ (M_w=341.44) C, 73.90; H, 4.40; N, 12.32. Found: C, 73.80; H, 4.36; N, 12.28.

4.4.16. 6-Phenyl-4-tributylstannyl-3-(2′-pyridyl)-pyridazine 10b. Metallation of **3** (200 mg, 0.85 mmol) according to the general procedure C with *n*-BuLi (3 equiv, 1.58 mL), TMPH (3 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with tributultin chloride (1.1 equiv, 0.79 mL) in solution with anhydrous THF (10 mL), $t_1=20$ min, $t_2=1$ h, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (4:1)) 195 mg (44%) of **10b** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.90 (1H, d, $J=7.9$ Hz, H-3′), 8.59 (1H, d, $J=4.9$ Hz, H-6′), 8.21 (1H, s, H-5), 8.20 (2H, d, $J=9.8$ Hz, CH-phenyl), 7.92 (1H, ddd, $J=7.9$, 7.5, 1.1 Hz, H-4′), 7.60–7.49 (3H, m, H-phenyl), 7.41 (1H, ddd, $J=7.5$, 4.9, 1.1 Hz, H-5′), 1.60–1.39 (6H, m, CH_2), 1.35–1.23 (6H, m, CH_2), 1.21–0.99 (6H, m, CH_2), 0.84 (9H, m, CH_3); ^{13}C NMR ($CDCl_3$): δ 160.5 (1C, C-3), 157.3 (1C, C-6), 155.0 (1C, C-2′), 147.5 (1C, C-6′), 143.9 (1C, C-4), 138.0 (1C, C-4′), 137.2 (1C, Cq-phenyl), 134.3 (1C, C-5), 130.2 (1C, CH-phenyl), 129.4 (2C, CH-phenyl), 127.6 (2C, CH-phenyl), 124.8 (1C, C-5′), 122.1 (1C, C-3′), 29.6 (3C, CH_2), 27.8 (3C, CH_2), 14.1 (3C, CH_3), 13.2 (3C, CH_2) ppm; MS (ESI, rel int. %) 546 [M^++Na] (100), 466 (30), 227 (47), 195 (82), 183 (100), 165 (68), 109 (46). Anal. Calcd for $C_{27}H_{37}N_3Sn$ (M_w=522.31) C, 62.07; H, 7.09; N, 8.05. Found: C, 61.98; H, 7.15; N, 8.12.

4.4.17. 4-Tributylstannyl-3-(3′-tributylstannylpyrid-2′-yl)-6-phenylpyridazine 11b. Metallation of **3** (200 mg, 0.85 mmol) according to the general procedure C with *n*-BuLi (3 equiv, 1.58 mL), TMPH (3 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with tributultin chloride (3 equiv, 2.15 mL) in solution with anhydrous THF (10 mL), $t_1=20$ min, $t_2=2$ h, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (25:1)) 317 mg (46%) of **11b** as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.52 (1H, dd, $J=-4.5$, 1.5 Hz, H-6′), 8.21 (1H, s, H-5), 8.19–8.16 (2H, m, H-phenyl), 8.13 (1H, dd, $J=7.2$, 1.5 Hz, H-4′), 7.61–7.49 (3H, m, H-phenyl), 7.36 (1H, dd, $J=7.2$, 4.5 Hz, H-5′), 1.55–1.42 (12H, m, CH_2), 1.35–1.08 (24H, m, CH_2), 0.91–0.80 (18H, m, CH_3); ^{13}C NMR ($CDCl_3$): δ 160.3 (1C, C-3), 158.3 (1C, C-6), 157.2 (1C, C-2′), 146.9 (1C, C-6′), 146.7 (1C, C-4′), 144.3 (1C, C-4), 138.8 (1C, C-3′), 137.5 (1C, Cq-phenyl), 134.7 (1C, C-5), 130.1 (1C, CH-phenyl), 129.4 (2C, CH-phenyl), 127.6 (2C, CH-phenyl), 124.4 (1C, C-5′), 29.6 and 29.5 (2C, CH_2), 27.9 and 27.8 (2C, CH_2), 14.2 and 14.1 (2C, CH_3), 13.3 and 13.0 (2C, CH_2); MS (FAB$^+$, rel int. %) 811 [M^+] (100). Anal. Calcd for $C_{39}H_{63}N_3Sn_2$ (M_w=811.34) C, 57.71; H, 7.77; N, 5.18. Found: C, 57.80; H, 7.90; N, 5.08.

4.4.18. 4-(Hydroxy-(*p*-methoxyphenyl)methyl)-6-phenyl-3-(2′-pyridyl)-pyridazine 10c. Metallation of **3** (200 mg, 0.85 mmol) according to the general procedure C with *n*-BuLi (3 equiv, 1.58 mL), TMPH (3 equiv, 0.44 mL, $T=-78$ °C), followed by reaction with *p*-methoxybenzaldehyde (3 equiv, 347 mg) in solution with anhydrous THF (10 mL), $t_1=20$ min, $t_2=3$ h, gave after purification by column chromatography (silicagel, eluent petroleum ether/ethyl acetate (1.5:1)) 207 mg (66%) of **10c** as a yellow solid, mp 152–153 °C; ^{1}H NMR ($CDCl_3$): δ 8.84 (1H, $J=4.9$ Hz, H-6′), 8.61 (1H, d, $J=7.9$ Hz, H-3′), 8.23–8.20 (2H, m, H-phenyl), 8.13 (1H, ddd, $J=7.9$, 7.5, 1.8 Hz, H-4′), 7.89 (1H, br s, CHO*H*), 7.77 (1H, s, H-5), 7.70–7.66 (3H, m, H-phenyl), 7.62 (1H, ddd, $J=7.5$, 4.9, 1.0 Hz, H-5′), 7.45 (2H, d, $J=8.7$ Hz, H-phenyl), 7.05 (2H, d, $J=8.7$ Hz, H-phenyl), 6.19 (1H, C*H*OH), 3.97 (3H, s, CH3); ^{13}C NMR ($CDCl_3$): δ 159.3 (1C, C-3), 159.2 (1C, Cq-phenyl), 157.3 (1C, C-6), 155.8 (1C, C-2′), 147.9 (1C, C-6′), 144.1 (1C, C-4), 138.4 (1C, C-4′), 136.2 (1C, Cq-phenyl), 132.3 (1C, Cq-phenyl), 130.7 (1C, CH-phenyl), 129.4 (2C, CH-phenyl), 128.3 (2C, CH-phenyl), 127.6 (2C, CH-phenyl), 125.7, 124.7 and 124.2 (3C, C-5, -5′, -3′), 114.1 (2C, CH-phenyl), 72.1 (1C, CHOH), 55.6 (1C, CH_3); MS (ESI, rel int. %) 392 [M^++Na] (100), 177 (38), 126 (47). Anal. Calcd for $C_{23}H_{19}N_3O_2$ (M_w=369.43) C, 74.80; H, 5.15; N, 11.38. Found: C, 74.70; H, 5.20; N, 14.42.

4.4.19. 4,6-Diphenyl-5-(2′-pyridyl)-pyrimidine 12. Reaction of **8b** according to procedure D gave 16.7 mg (0.054 mmol, 33%) of **12** as a colorless solid, mp 155–156 °C; ^{1}H NMR ($CDCl_3$): δ 9.32 (1H, s, H-2), 8.43 (1H, dd, $J=4.9$, 1.6 Hz, H-6′), 7.42 (1H, ddd, $J=7.9$, 7.5, 1.6 Hz, H-4′), 7.26–7.14 (10H, m, H-phenyl), 7.06 (1H, ddd, $J=7.9$, 4.9, 1.0 Hz, H-5′), 6.94 (1H, d, $J=7.5$ Hz, H-3′); ^{13}C NMR ($CDCl_3$): δ 165.9 (2C, C-4, C-6), 158.2 (1C, C-2), 156.3 (1C, C-2′), 150.0 (1C, C-6′), 138.4 (2C, Cq-phenyl), 136.5 (1C, C-4′), 131.3 (1C, C-5), 129.8 (4C, CH-phenyl),129.4 (2C, CH-phenyl), 128.4 (4C, CH-phenyl), 126.8 (1C, C-3′), 122.7 (1C, C-5′); MS (FAB$^+$, rel int. %) 310 [M^++1] (100), 154 (40). Anal. Calcd for $C_{21}H_{15}N_3$ (M_w=309.17) C, 81.55; H, 4.85; N, 13.59. Found: C, 81.60; H, 4.79; N, 13.74.

4.4.20. Bis-4,4-[6-phenyl-5-(2′-pyridyl)]pyrimidine 13. Reaction of **8b** according to procedure D gave 25 mg (0.054 mmol, 66%) of **13** as a yellow solid, mp 202–204 °C; ^{1}H NMR ($CDCl_3$): δ 8.90 (2H, s, H-2), 8.20 (2H, d, $J=4.9$ Hz, H-6′), 7.21–7.01 (12H, m, H-phenyl, H-4′), 6.86 (2H, m, H-5′), 6.82 (2H, d, $J=7.5$ Hz, H-3′); ^{13}C NMR ($CDCl_3$): δ 165.5 (2C, C-6), 164.2 (2C, C-4), 157.2 (2C, C-2), 154.8 (2C, C-2′), 149.8 (2C, C-6′), 137.8 (2C, Cq-phenyl), 136.1 (2C, C-4′), 131.5 (2C, C-5), 130.1 (4C, CH-phenyl), 129.8 (2C, CH-phenyl), 128.5 (4C, CH-phenyl), 126.6 (2C, C-3′), 122.6 (2C, C-5′) ppm; MS

(FAB$^+$, rel int. %) 465 [M$^+$+1] (89), 138 (100), 77 (58). Anal. Calcd for $C_{30}H_{20}N_{36}$ (M_w=464.53) C, 77.59; H, 4.31; N, 18.10. Found: C, 77.65; H, 4.40; N, 18.19.

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Corrigendum

Corrigendum to "Versatility of an intramolecularly hydrogen-bonded 4-(*N*,*N*-dimethylamino)benzoate group as a signaling subunit for anion recognition" [Tetrahedron 61 (2005) 5866]

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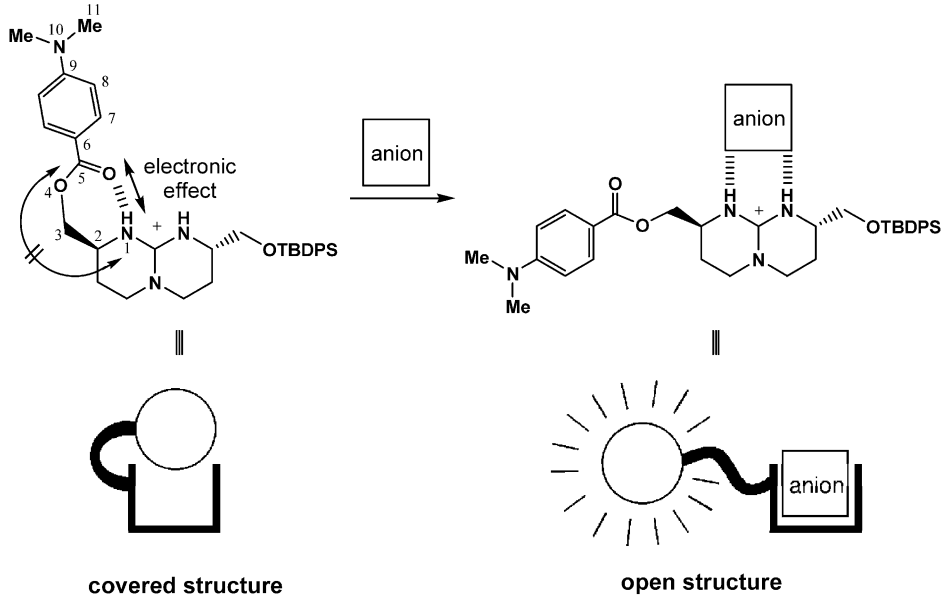
Scheme 1 should have appeared as follows:



Scheme 1.

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