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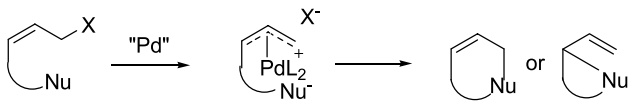
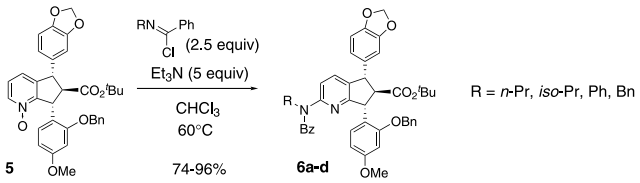
Contents

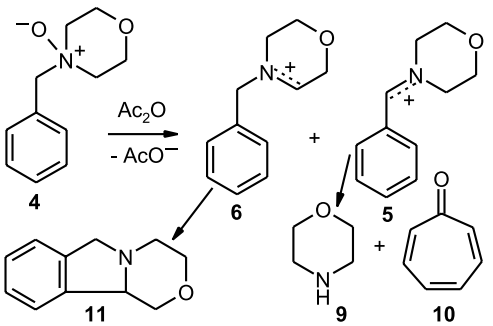
REPORT

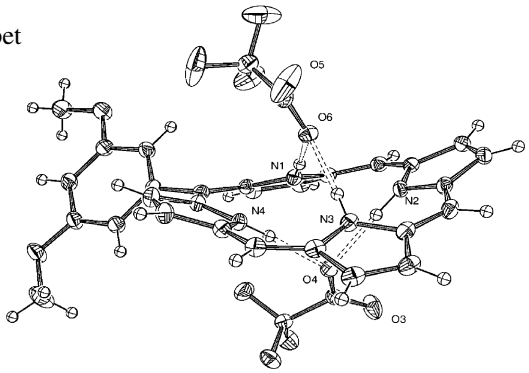


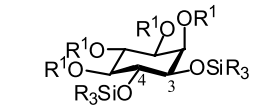
ARTICLES

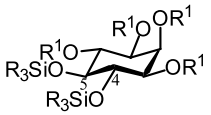


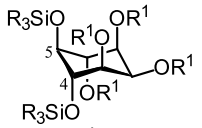
The Polonowski reaction of NBnMO surprisingly affords tropone (**10**) and isoindole **11** besides the expected products benzaldehyde and acetmorpholide. The reaction proceeds via two competing carbenium–imonium ion intermediates **5** and **6**.

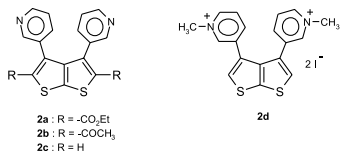




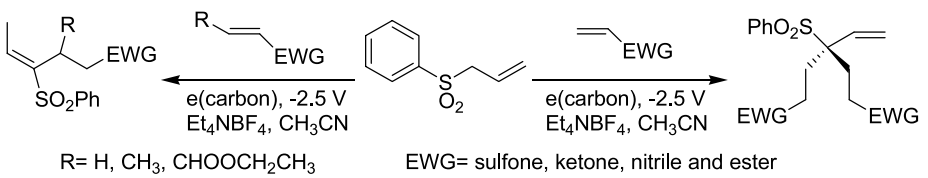


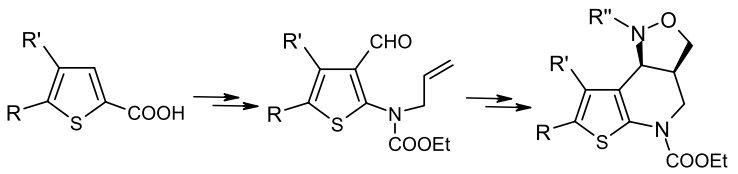


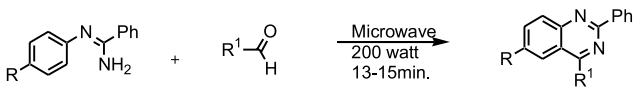




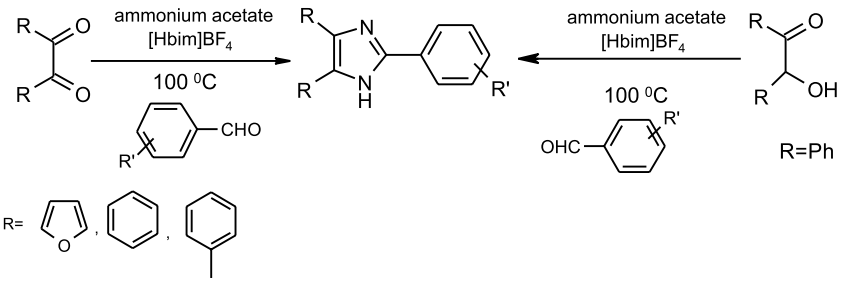
Dipyridylthieno[2,3-*b*]thiophenes **2a** and **2b** exhibit *syn*/*anti* atropisomerism with energy barrier to rotation $\Delta G^{\neq}$ in the range of 17–18 kcal/mol, whereas **2c** and **2d** exhibit free rotation at least up to -50 °C with $\Delta G^{\neq} \leq 10$ kcal/mol.

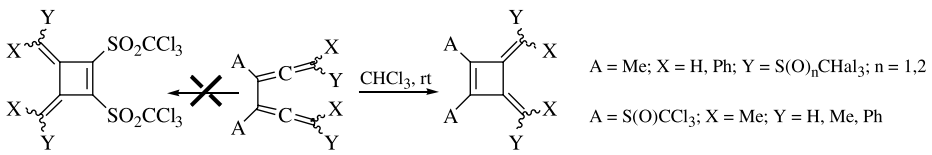


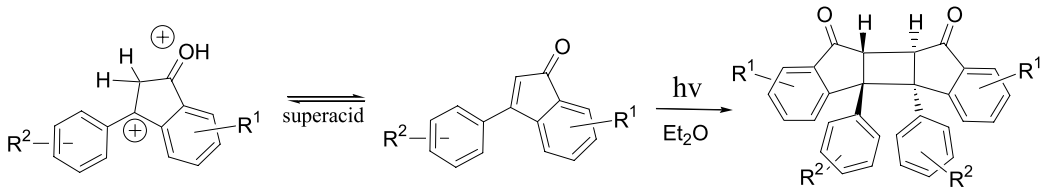




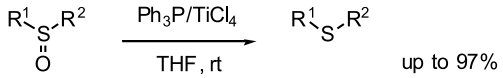
A solvent-free and catalyst-free approach towards the selective synthesis of quinazolines and benzo[*g*] quinazolines has been developed using conventional microwave oven with excellent yields and reproducibilty.

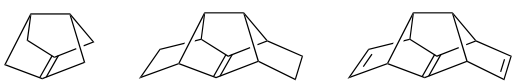




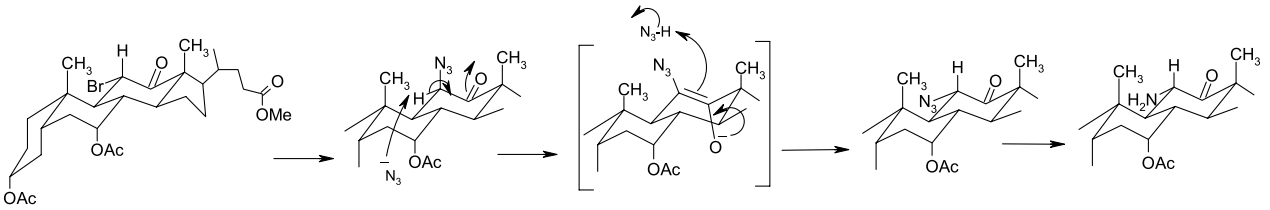


Dicationic form of 3-arylindenones generated in superacidic media as well as their [2+2] photodimerization have been studied.





1 **10** **26**



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Cyclisations of allylic substrates via palladium catalysis

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Contents

1. Introduction

Ring systems have proved to be an immense source of synthetic attention, in part due to their biological significance. New methods for ring construction are constantly being uncovered and there is a particular demand for those methods that can deliver the desired systems in a chemo-, regio-, diastereo- and enantioselective manner.

Palladium-catalysed allylic alkylations in the intramolecular mode have been particularly notable in this area due to their ability to elicit control in the aforementioned areas, often under very mild conditions. The allylic compounds **1**, required as the electrophilic component of palladium-allyl alkylations, are usually quite unreactive in the absence of a suitable palladium catalyst (Fig. 1). This allows easier handling of the substrates, which is particularly important for intramolecular cyclisations where the nucleophile is tethered to the electrophilic fragment. The catalytic cycle for intramolecular palladium-allyl alkylation is shown in Figure 1.

Another advantage of palladium-allyl cyclisations is the complementary stereochemical outcome compared to non-metal-catalysed cyclisations. That is, the substitution

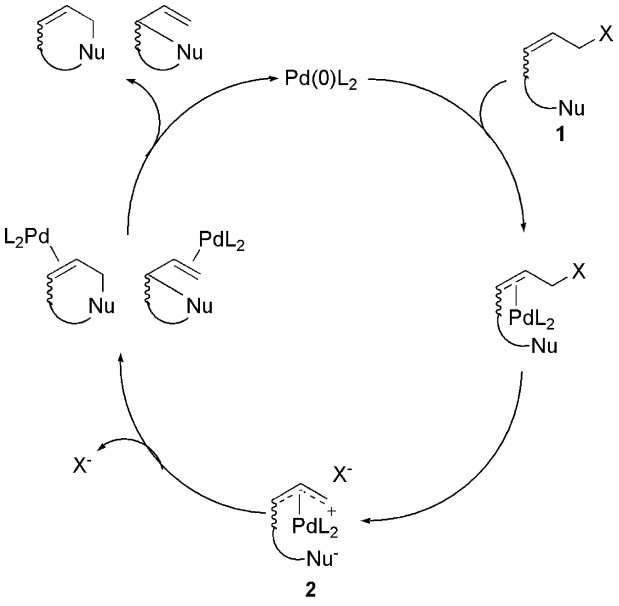

Figure 1.

Keywords: Cyclisation; Allylpalladium; Allylation; Palladium catalysis.
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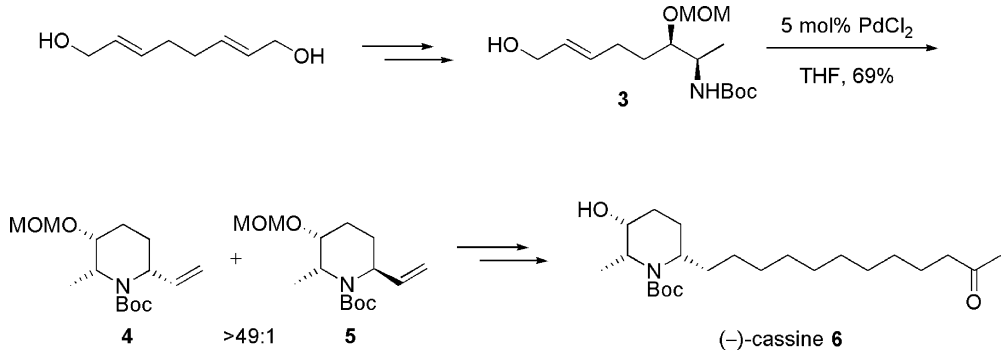


Scheme 1.

process proceeds via a double inversion by direct attack at carbon on the palladium-allyl complex, which is formed by inversion, giving overall retention of configuration with soft nucleophiles. However, for hard nucleophiles, initial attack on the metal is followed by reductive elimination resulting in overall inversion of configuration. In contrast to traditional methods, various ring sizes can be accessed with palladium-allyl chemistry. For example, with suitable substrates, even macrocyclisations can be carried out under normal concentrations. The regiochemistry of palladium-allyl cyclisations is governed by a number of factors, namely:[1]

1. Charge distribution in the π-allylpalladium complex **2**, favouring attack at the more-substituted terminus.
2. Steric hindrance to nucleophile attack, favouring attack at the less-substituted terminus.
3. Nature and length of the tether.

With all these factors controlling the regioselectivity of cyclisation, it is possible to govern the ring size by appropriate fine-tuning of the substrate. Further, diastereoselectivity is often high, arising from highly ordered transition states induced by the presence of the palladium template. These factors, combined with the growing use of chiral ligands for enantioselective cyclisations, make palladium-allyl cyclisations immensely powerful in the controlled synthesis of a variety of carbo- and heterocyclic ring systems.

The proceeding review intends to give an overview of palladium-allyl cyclisations, divided by class of nucleophile, reported from 1989 onwards and work prior to this is covered in a comprehensive review by Trost.[1] Additionally covered in the review are cyclisations of allylic substrates that do not necessarily proceed via Pd-allyl intermediates.

2. Heteroatom nucleophiles

2.1. Nitrogen nucleophiles

Amines are amongst the best nucleophiles for Pd-allyl alkylation and are, therefore, ideally suited to Pd-allyl cyclisations. There is a wealth of examples in the literature, most commonly dealing with the formation of 5- and 6-membered heterocycles containing one or more heteroatoms. The importance of these cyclisations is highlighted by the number of nitrogen-containing heterocycles found abundantly in nature, with many displaying pharmacological activity. Once such example in the family of 2,6-disubsitututed piperidin-3-ols is (−)-cassine **6**, which exhibits antimicrobial activity against *Staphylococcus aureus*.[2] The task of installing the 2,6-*cis* relationship has been elegantly solved by a palladium-catalysed cyclisation of **3** (Scheme 1).[3]

The highly selective formation of **4** over **5** can be explained by assuming that the cyclisation proceeds through the transition state **7** (Fig. 2). The alternative transition state **8** would not be favoured due to steric hindrance between the Boc group and the palladium complex. In highly selective reactions of this type, chelation between the palladium and oxygen atoms of the allyl alcohol and the Boc group are important in maintaining a highly ordered transition state.

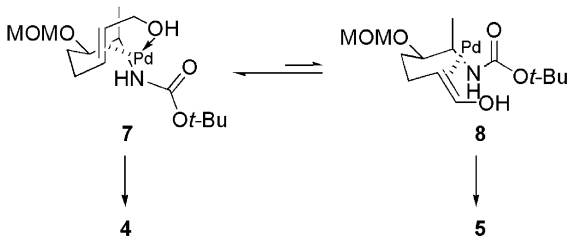
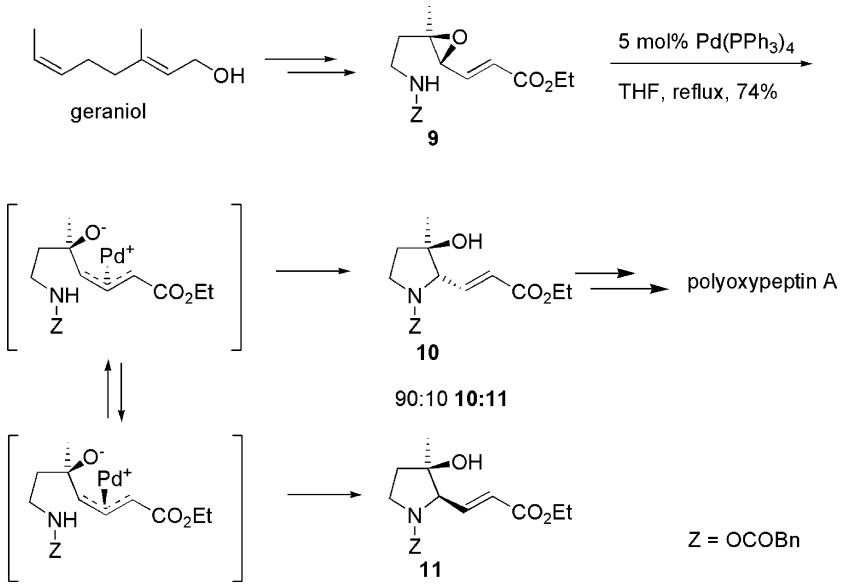


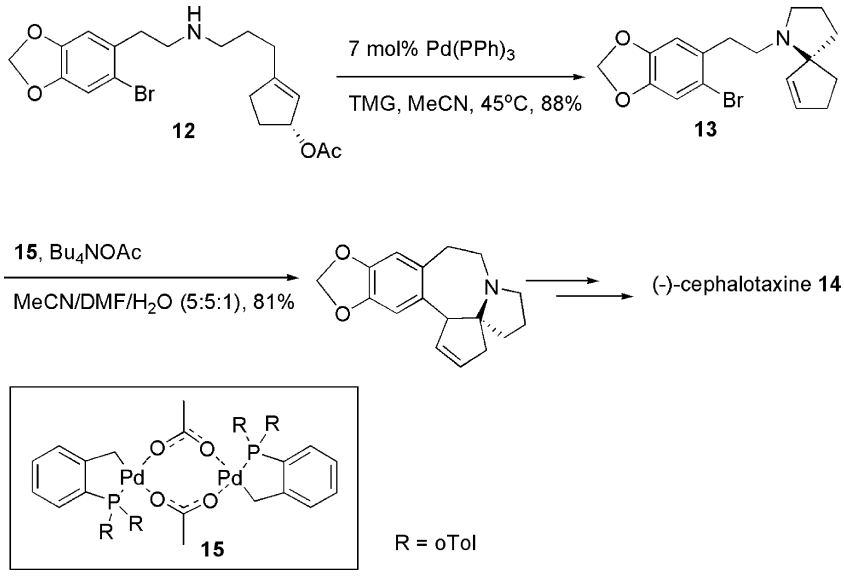
Figure 2.

Pyrrolidine rings are also found in many biologically important alkaloids and may be readily formed by the application of π-allylpalladium chemistry. Polyoxypeptin A,[4] contains a (2*S*,3*R*)-3-hydroxy-3-methylproline fragment **10**. Its facile and stereoselective synthesis has been carried out using an enantiomerically pure allylic epoxide **9** obtained from a Sharpless asymmetric epoxidation (Scheme 2).[5] The stereoselectivity of this cyclisation is derived from the clean inversion of oxidative addition to the allylic epoxide followed by attack of nitrogen on the opposite face to palladium. Some erosion of stereoselectivity is observed which the authors attribute to nucleophilic attack of Pd(0) upon the initially formed complex to give the alternative diastereoisomer **11**.

Similarly, the pyrrolidine-containing spiro-heterocyclic core of (−)-cephalotaxine **14** has been prepared by cyclisation of the enantiopure cyclic acetate **12** in the



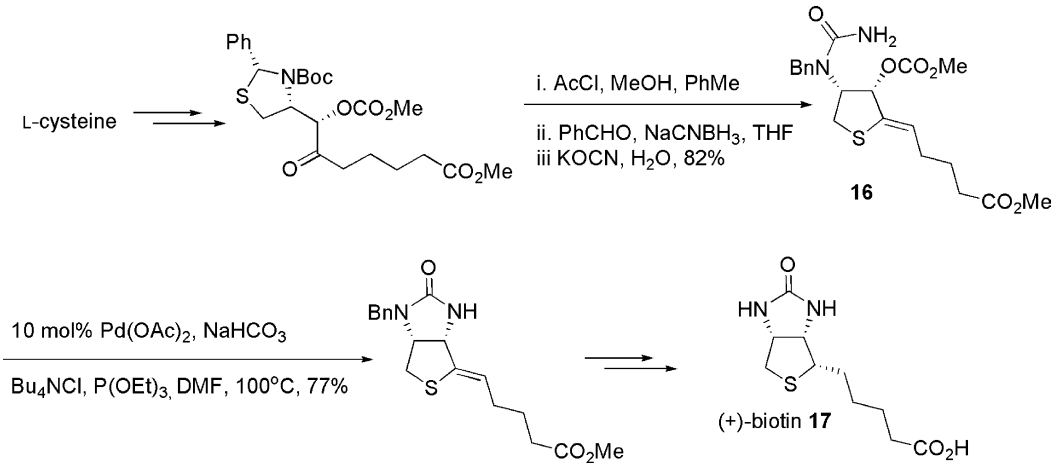
Scheme 2.



Scheme 3.

presence of catalyst **15** (Scheme 3).[6] The reaction, in contrast to that in the polyoxypeptin A synthesis, is completely stereoselective. Interestingly, when substrate **15** contains iodine in place of bromine, no reaction takes place. This is because Pd prefers to undergo oxidative addition to the comparatively more reactive Ar–I bond over the allylic acetate. Switching to the more reactive allylic carbonate would be an alternative strategy that could have been used if the aryl bromide **13** had not been sufficiently reactive in the subsequent Heck reaction. Tetramethylguanidine (TMG) is incorporated to prevent amine **12** acting competitively as a base. TMG is strong enough to prevent this competitive activity, but not so strong that it causes β-hydride elimination or nucleophilic enough to attack the π-allyl complex.[7]

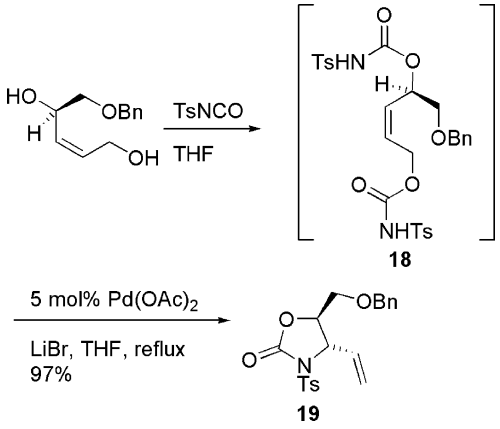
Palladium π-allyl chemistry has also been found to be highly effective for forming heterocycles containing more than one heteroatom. For example, the imidazolidinone ring of (+)-biotin **17** has been made by an intramolecular allylic amination of *cis*-allylic carbonate **16** (Scheme 4).[8] It is of note that the cyclisation only proceeds in poor yield when the nitrogen is not benzyl protected. This is an observation also noted by De Clercq and co-workers in their elegant thermal ring closure of an ene carbamozyl azide at the C-3 and C-3a positions of the (+)-biotin ring skeleton.[9] They considered that the presence of the *N*-benzyl group enforced a productive rotameric conformation for successful cyclisation; a similar effect may be operating here. It is also noteworthy that elevated temperatures in combination with a π-acceptor ligand and a polar aprotic solvent are required



Scheme 4.

for the cyclisation to take place. This is most likely to be due to the strain inherent in the formation of a fused 5,5 bicyclic system. The π-acceptor ligand results in a more electrophilic Pd-allyl complex that is in turn stabilised by DMF. This tuning of reactivity by variation of ligand and solvent properties highlights the strength and versatility of Pd-catalysed cyclisations.

Similarly, the highly regio- and diastereoselective synthesis of 4-vinyl-2-oxazolidinone **19** has been carried out by in situ formation of difunctional allylic *N*-tosylcarbamate **18** followed by palladium-allyl cyclisation (Scheme 5).[10] When starting with optically pure 1-substituted precursors, as shown, the 3,4-*trans* products are obtained exclusively. Additionally, none of the regiosiomer was observed, which is surprising considering both nitrogen atoms can attack the Pd(II)-activated alkene. No explanation is put forward, but this regioselectivity might be attributed to the extra substitution hindering elimination by palladium.



Scheme 5.

The authors propose that the mechanism proceeds though a Pd(II) activation of the double bond rather than formation of a Pd(0) π-allyl complex (Fig. 3). Although a Pd(0) mechanism is not completely discounted, the accelerating effect of LiBr and inactivity of $Pd_2(dba)_3 \cdot CHCl_3$ provide evidence for a Pd(II) mechanism. The 3,4-*trans* selectivity probably results from the favoured intermediate **20**, where the Pd(II)-activated alkene and associated *N*-tosylcarbamate are oriented to avoid interactions with the 1-substituent.

Oxazolidinones can be used as nucleophiles in intramolecular aminations leading to bicyclic systems. Having the nucleophile contained within the oxazolidinone rings is advantageous, as it inevitably results in a transition state where the Pd-alkene complex is oriented to avoid unfavourable interactions with the ring. An excellent example is illustrated *en route* to the synthesis of

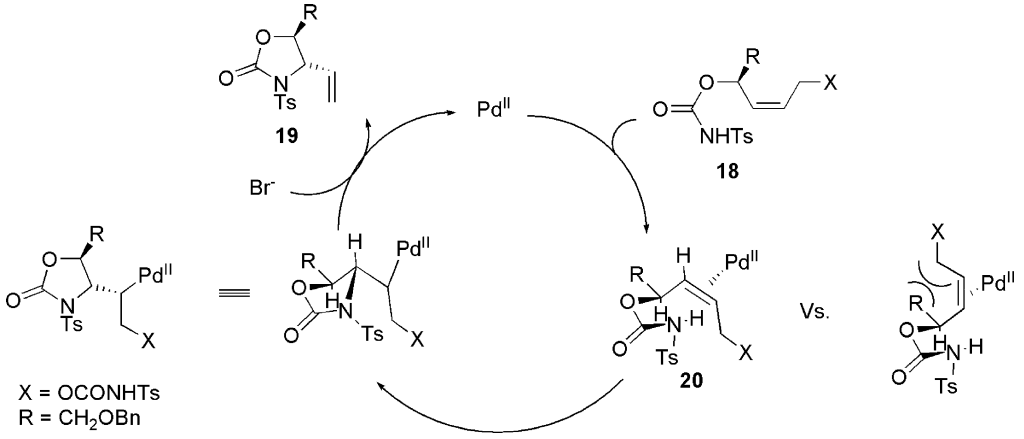
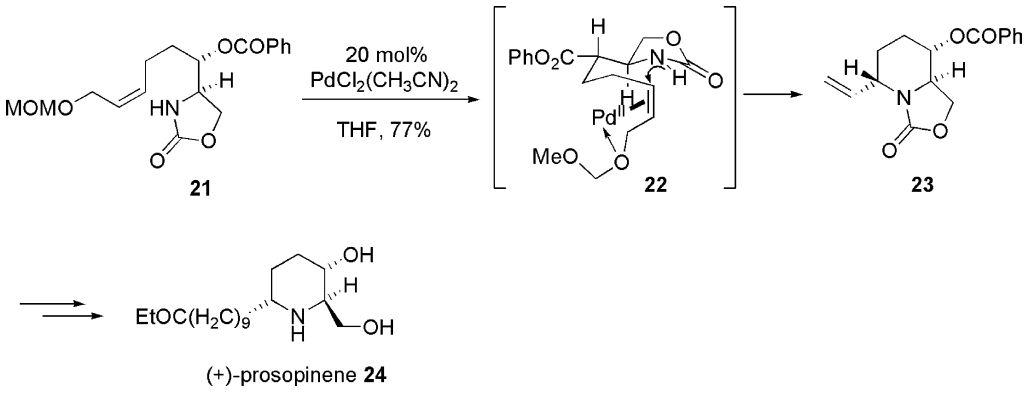
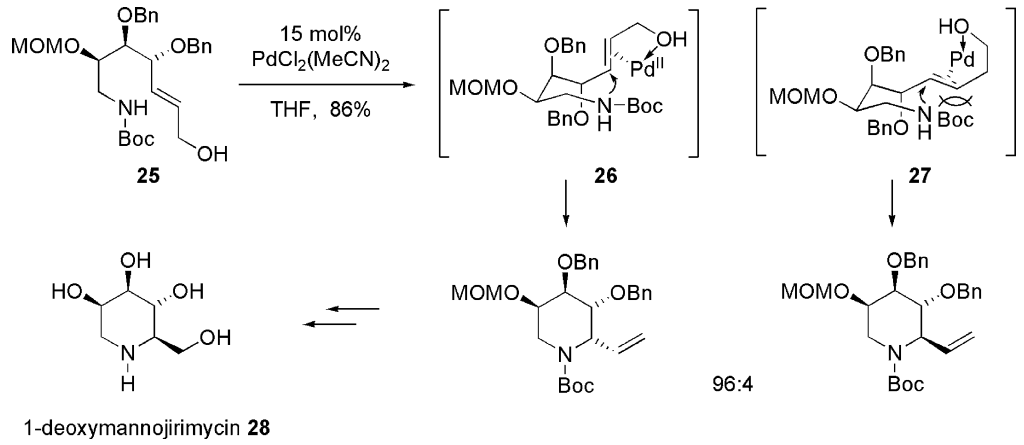


Figure 3.

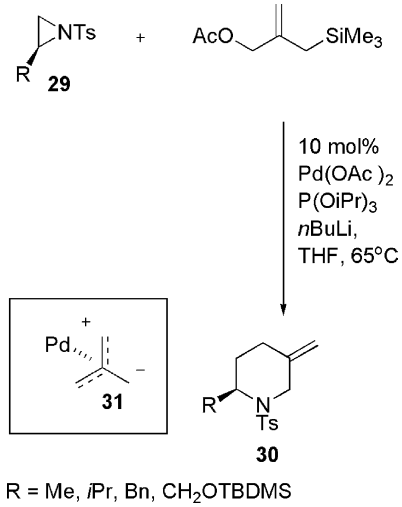


Scheme 6.



Scheme 7.

(+)-prosopinene **24** (Scheme 6).[11] Allylic MOM-ether **21** undergoes cyclisation, again via a Pd(II) mechanism, to yield exclusively **23**, the 2,6-*trans* piperidine skeleton of (+)-prosopinene. Transition state **22** is favoured due to minimisation of nonbonding interactions between the Pd(II)-bound alkene and the oxazolidinone ring. The oxazolidinone serves not only to aid the stereoselectivity of the cyclisation, but also as a useful appendage for further functionalisation.

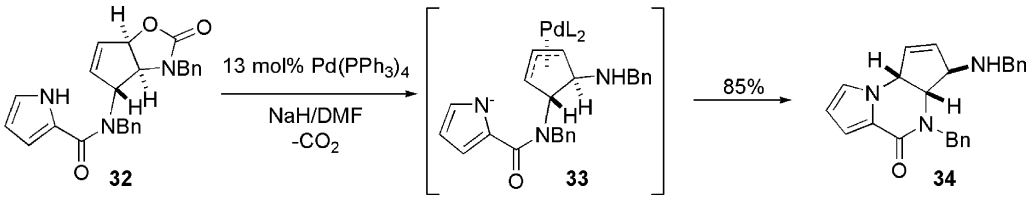


Scheme 8.

In relation to this work, the skeleton of the piperidine alkaloid, 1-deoxymannojirimycin **28** has been synthesised by palladium-catalysed cyclisation of **25** (Scheme 7).[12] Here, the *N*-Boc group is functioning in the same fashion as the oxazolidinone ring, favouring transition state **26** over **27**. The transformation is highly, but not completely, selective as was the case with the (+)-prosopinene synthesis. It is likely that this is a result of the oxazolidinone ring in **22** holding the palladium-bound intermediate in a more conformationally restricted state, compared to that of the *N*-Boc substrate.

Piperidines have also been elegantly constructed the by use of a formal [3+3] cycloaddition between the palladium-trimethylenemethane complex (Pd-TMM) **31** and enantiomerically pure aziridines **29** (Scheme 8).[13] Pd-TMM reacts at the least hindered end of the aziridine and attack of nitrogen on the complex then yields the piperidines **30** bearing an exocyclic alkene, which are amenable to further functionalisation.

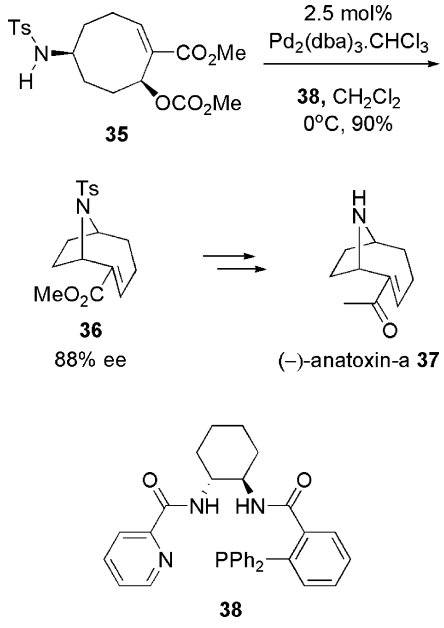
The first use of pyrrole in an allylic amination reaction has recently been reported during the attempted synthesis of the B-ring **34** of an anti-tumour marine sponge alkaloid agelastatin A (Scheme 9).[14] One particularly interesting facet of this cyclisation is the *syn* attack of the nitrogen nucleophile on the π-allylpalladium complex **33**, which is formed with inversion from the allylic carbamate **32**.



Scheme 9.

Although pyrrole is a soft nucleophile, the overriding stereoelectronic preference for formation of the *cis*-fused B/C-ring results in attack *syn* to palladium.

Most examples of palladium-catalysed allylic amination leading to ring formation have involved acyclic or 5/6-membered ring substrates. Medium-sized rings have generally proven to be poor substrates in metal-catalysed allylic alkylations due to conformational reasons. Despite this limitation, the asymmetric synthesis of (−)-anatoxin-a **37** has been realised by deploying an asymmetric palladium π-allyl cyclisation of cyclooctene **35** as the key step (Scheme 10).[15]

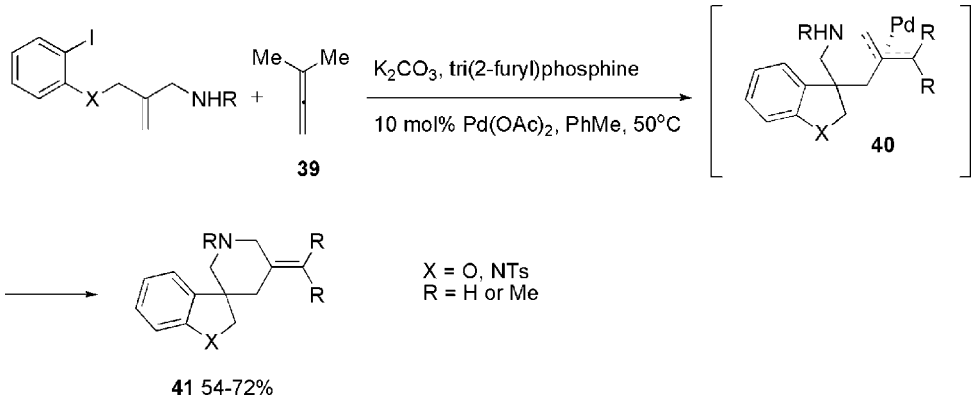


Scheme 10.

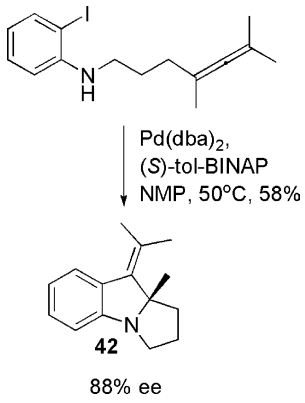
The initially deployed bis-phosphine resulted in a low ee with high temperatures necessary to drive the reaction to completion. It was postulated that the chiral pocket of the ligand was too small to accommodate sterically demanding medium-ring substrates Therefore, the P,N-bidentate ligand **38**, where one side of the chiral pocket is effectively removed to alleviate unfavourable steric interaction, was designed and synthesised. This modified ligand led to a considerable increase in the rate of cyclisation to **36** and a high ee was observed.

Previous work has shown that ionisation of cyclic allylic esters to *meso* π-allyl complexes can lead to intimate ion pairs with the leaving group.[16] This intermediate must undergo equilibration faster than it is intercepted by the nucleophile for the reaction to be highly enantioselective; having a tethered nucleophile, as in **35**, will speed up attack vs equilibration. The authors propose the formation of an intimate ion pair may be an additional reason for the low ee observed with the bis-phosphine ligand. However, the nitrogen in ligand **38** should decrease the electrophilicity of the π-allylpalladium species. Thus, nucleophilic attack would be slowed down, permitting the required equilibration to take place. Conversely, the better donor properties of nitrogen vs phosphorous would speed up formation of the π-allylpalladium, which is proposed to be the rate-determining step. Ligand **38**, therefore, has a 2-fold effect: facilitating ionisation to increase rate of reaction, but slowing nucleophilic attack, therefore enhancing ee.

Finally, a distinct group of cyclisations via palladium-catalysed allylic aminations utilising allenes has been the subject of a recent investigation (Scheme 11).[17] Allenes can form intermediate π-allyl complexes **40** via carbo-palladation, which are then intercepted by nucleophiles. Such cascade-type processes can lead to a rapid increase in molecular complexity from relatively simple starting



Scheme 11.



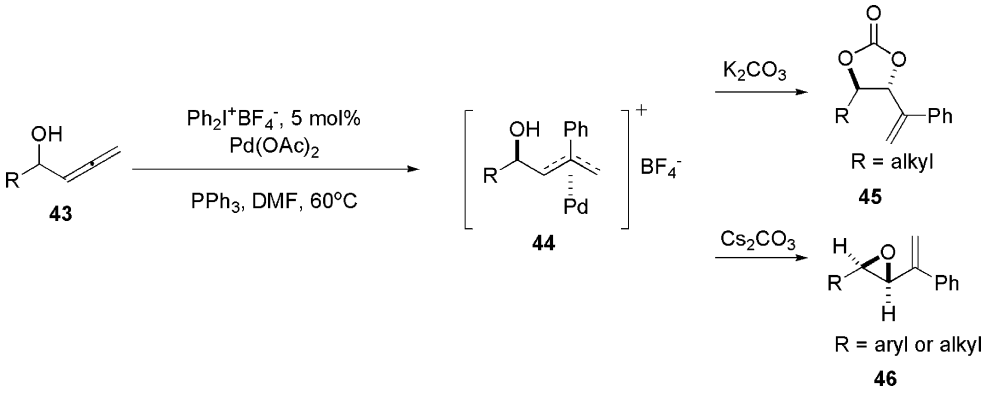
Scheme 12.

materials. A particularly interesting example of such a cascade is demonstrated in the synthesis of spiro-nitrogen heterocycles **41** by intermolecular hetero-annulation cascades of allene **39**.[18]

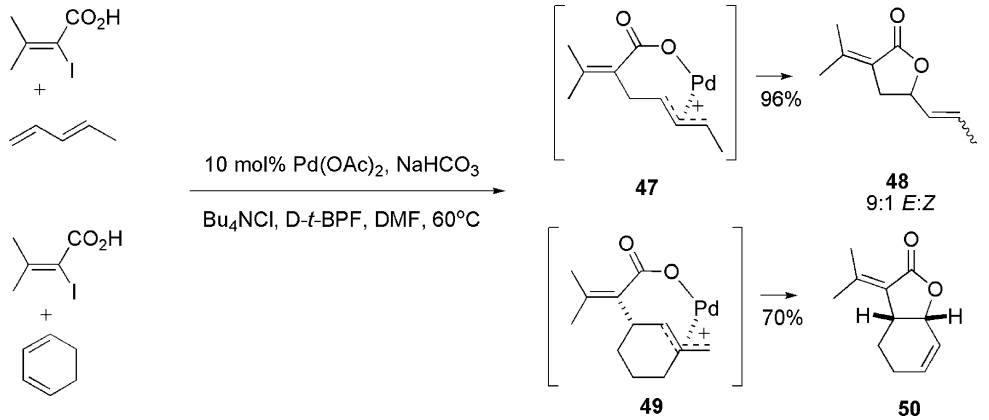
The cascade is initiated by oxidative insertion of Pd(0) into the Ar–I bond and *exo–trig* cyclisation is then followed by intermolecular allene insertion and nitrogen attack on the resultant π-allyl complex providing spiro-heterocycles **41**. These allene-involving cyclisations represent highly versatile heterocyclic syntheses that would find ideal application in analogue synthesis. Indeed, a similar procedure has been used for the asymmetric synthesis of cyclic indole derivatives **42** (Scheme 12).[19] The asymmetric induction is proposed to be due to avoidance of steric interference between the amine nucleophile and edge group of the ligand.

2.2. Oxygen nucleophiles

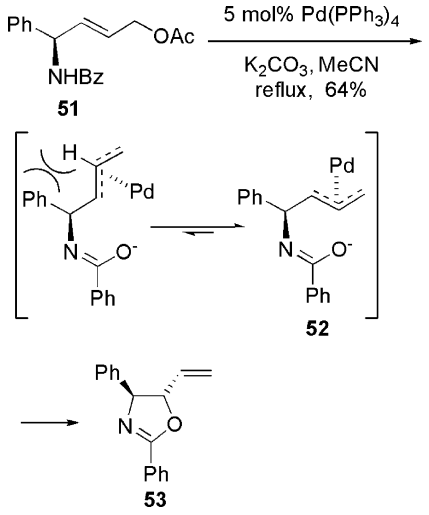
Whilst the majority of work on cyclisations of allylic substrates via palladium catalysis has focused on allylic alkylation and amination, there have also been some interesting examples employing oxygen nucleophiles. This trend is not surprising considering that π-allylpalladium complexes are 'soft' electrophiles and oxygen nucleophiles are relatively 'hard'. Therefore, stabilised oxygen nucleophiles such as carboxylate and phenol anions react more readily than alkoxides. However, in the case of carboxylates, the products are allyl carboxylates, which are themselves substrates for Pd π-allyl formation. Thus, these reactions are generally only viable if the substrate forms the π-allylpalladium complex more rapidly than the allyl carboxylate. For example, the recent Pd(0)-catalysed arylation of allenic alcohols **43** with hypervalent iodonium salts in the presence of K_2CO_3 provided *syn*-diol cyclic carbonates **45** (Scheme 13).[20] The mechanism is proposed to involve the formation of π-allyl complex **44**, followed by conversion into the carboxylate anion and interception of the allyl complex. Interestingly, epoxide **46** is formed when the stronger base Cs_2CO_3 is used or when R = aryl, suggesting in these cases that deprotonation occurs rapidly and the alkoxide intercepts the π-allylpalladium complex before the carbonate can be formed.



Scheme 13.



Scheme 14.



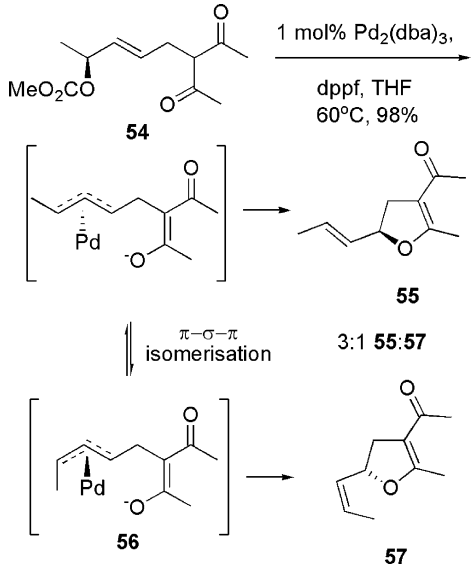
Scheme 15.

Another example of a carboxylate anion nucleophile is found in the synthesis of α-alkylidene-γ-butyrolactones **48** and **50** from α-iodoacrylic acids and 1,3-dienes (Scheme 14).[21] For the reaction to proceed in the presence of the coordinating carboxyl group, D-*t*-BPF [(di-*tert*-butylphosphino)ferrocene] had to be employed as the ligand. This sterically encumbered ligand is proposed to reduce any unwanted coordination of the vinyl palladium species and the neighbouring carboxylic acid. Additionally, being an alkylphosphine, it binds more strongly to palladium than an arylphosphine, so that the electron density at the metal centre is increased, thus accelerating the rate of reaction. When 1,3-cyclohexadiene is used, only the *cis*-fused product **50** is observed, suggesting the reaction proceeds through *syn* attack of the carboxylate anion on the π-allylpalladium complex **59**. The *E* selectivity observed for acyclic systems results from the π-allylpalladium intermediate conforming mainly to the more stable *syn*-η^3-allyl complex **47**.[22]

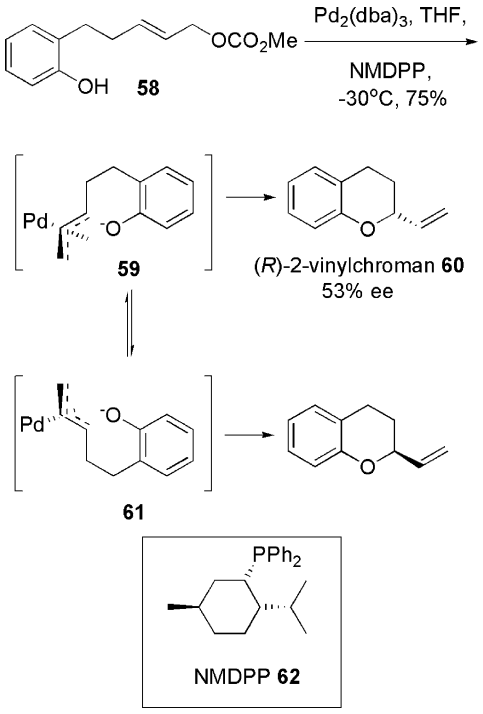
The *N*-benzoyl group has been found to undergo addition to palladium-allyl complexes at oxygen. These oxygen nucleophiles are highly stabilised and can, therefore, be considered 'soft'. Thus, under Pd(0) conditions, enantiomerically pure allylic benzamides such as **51** undergo facile cyclisation to yield exclusively *trans*-oxazoline **53** (Scheme 15).[23] Cyclisation proceeds though transition state **52**, avoiding unfavourable interactions between the Ph group and the hydrogen of the palladium-allyl complex. When less bulky groups are present in place of Ph, some of the *cis*-diastereoisomer is detected. Importantly, the vinyloxazoline products such as **53** can be employed in the synthesis of β-amino-α-hydroxy acids and γ-amino-β-hydroxy acids conveniently protected as the oxazoline. These structural motifs are found in a wide range of biologically important compounds such as the C-13 side chain of Taxol© and statin.[24]

Similarly, enantiomerically pure allylic carbonate **54** has been reported to undergo cyclisation to dihydrofuran **55** by the standard double inversion mechanism (Scheme 16).[25] Interestingly, **57** was also obtained as the minor component and is the result of π–σ–π isomerisation to **68**.

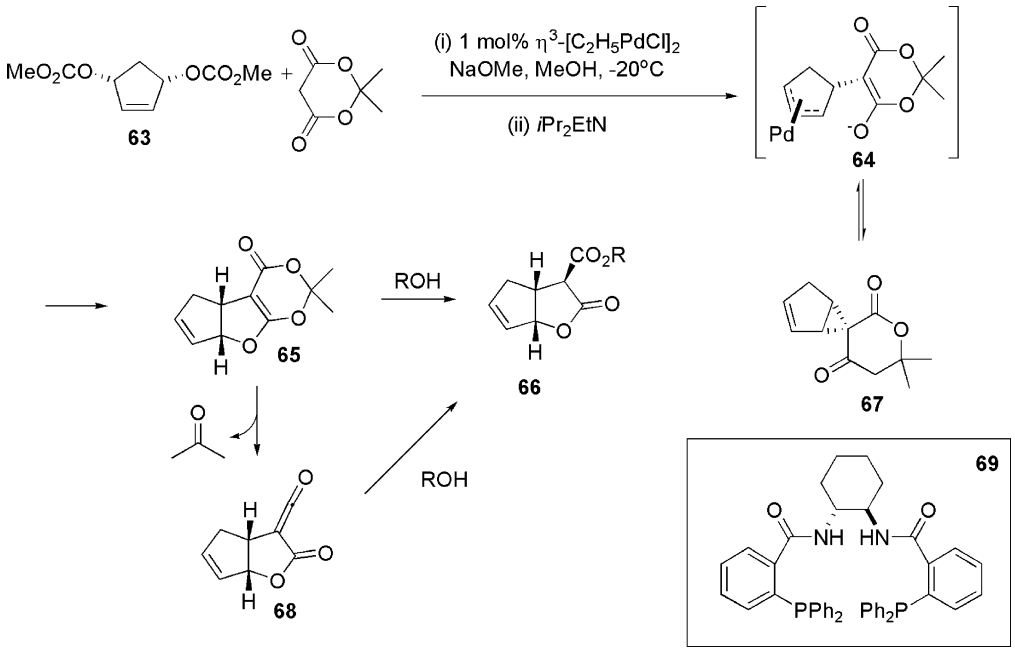
The use of chiral ligands to induce asymmetry in palladium-catalysed alkoxylation cyclisations has received limited treatment. However, one recent example has dealt with the asymmetric synthesis of 2-vinylchroman **60**, a useful intermediate for the synthesis of biologically active compounds such as vitamin E (Scheme 17).[26] Cyclisation of carbonate **58** with the chiral phosphine NMDPP **62** yields (*R*)-2-vinylchroman with a fair ee of 53%. Monodentate NMDPP **75** was found to be superior to bidentate chiral phosphines as its faster dissociation enables rapid equilibration between the two π-allyl intermediates **59** and **61**. Complex **59** is presumed to be the more stable intermediate, leading to the favoured formation of (*R*)-**60**.



Scheme 16.



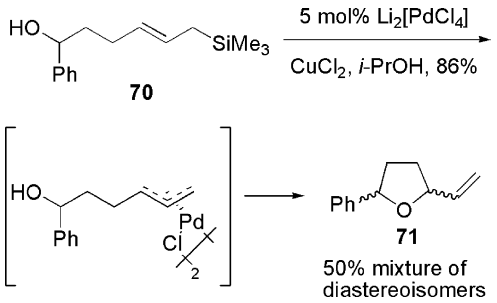
Scheme 17.



Scheme 18.

A more successful approach to the introduction of asymmetry has been shown by desymmetrisation of *meso* dicarbonates **63** with Meldrum's acid in conjunction with chiral racemic ligand **69**, yielding lactones **66** in excellent ee (Scheme 18).[27] Initial mono-alkylation by Meldrum's acid yields π-allyl complex **64**, which subsequently undergoes an unprecedented *O*-alkylation to give **65**. Lactone **66** can then be formed by either a retro-Diels–Alder reaction and alcohol interception of the resultant ketene **68**, or undergo direct attack by the alcohol. It is also speculated that an alternative mechanism for the formation of **66** could involve cyclopropane intermediate **67**. It should be noted that racemic ligand **69** is required for a swift reaction to take place as the enantiomer that is 'matched' for the first alkylation is 'mismatched' for the second. This one-pot asymmetric synthesis of bicyclic lactones should be regarded as particularly important, as such compounds are found widely in a variety of synthetic targets and their syntheses are usually multistep processes starting from enantiomerically pure building blocks.

Allylic acetates, carbonates, halides and epoxides are frequently exploited in allylic alkylations. However, allylsilanes have been shown to be unreactive to Pd(0) and in fact, many Pd(0)-catalysed processes have been employed for the synthesis of functionalised allylsilanes.[28] In contrast, Pd(II)-catalysed intramolecular cyclisation of allylsilane **70** has been demonstrated to be a facile process to form tetrahydrofuran derivatives **71** (Scheme 19).[29] The process is highly regioselective for the formation of the 5-membered ring. Mechanistic studies revealed that the copper(II) chloride, as well as regenerating the Pd(II), activates the π-allylpalladium complex. Moreover, copper(II) chloride acts as a source of chloride ion, which facilitates the formation of the π-allylpalladium complex from an η^2-intermediate by coordination to the silicon atom. The β-silicon effect is relatively weak with Pd(II)-complexed allylsilanes because there is no carbocation at C2, as is the case with normal electrophilic attack. Coordination of chloride, therefore, aids the cleavage of the C–Si bond. This methodology has also been extended to allylsilanes containing tosylamide groups, which lead to piperidine or pyrrolidine derivatives, depending on the chain length.



Scheme 19.

3. Carbon nucleophiles

Carbon nucleophiles have featured widely in the synthesis of both carbocyclic and hetereocyclic compounds. Soft nucleophiles generally give the best results and for carbon–carbon bond formation, stabilised enolates such as malonates are, therefore, often deployed. However, nucleophilic components stabilised by other electron-withdrawing groups such as sulfones and nitriles are also widely reported.

One area in which the use of carbon nucleophiles has found particular application is the regioselective synthesis of medium and large rings. The preference for the nucleophile to attack the less-substituted terminus of an allyl system is often the main driving force behind which ring system is formed (Fig. 4).

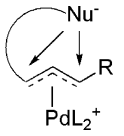
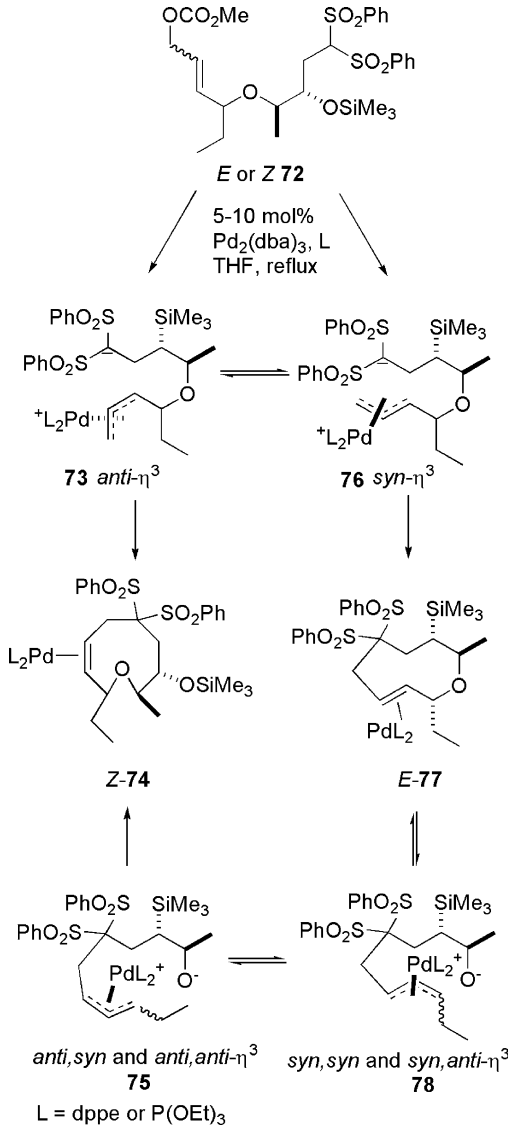


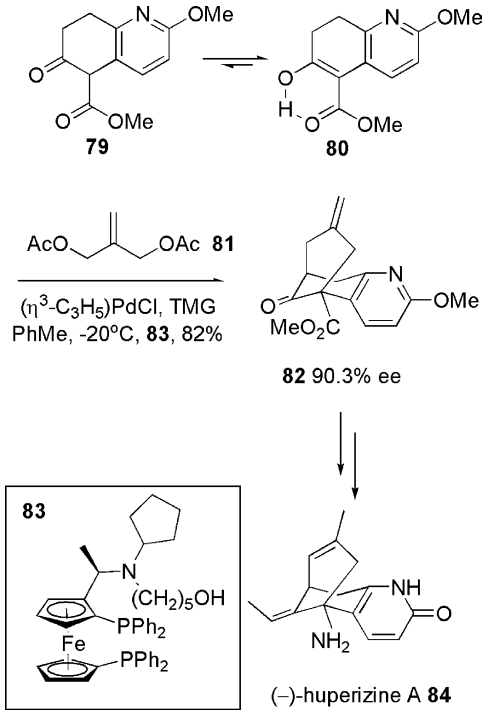
Figure 4.

The introduction of a heteroatom into the tether connecting the cyclisation termini can have a profound influence, due to conformation and coordinating effects. For example, *E*/*Z* ethers **72** undergo cyclisation exclusively to the *E*/*Z*-nine-membered ethers **77** and **74**, rather than the seven-membered alternative (Scheme 20).[30] This is a result of attack of a relatively hindered nucleophile on the less-hindered terminus of allyl complexes **73** or **76**. This example also provides an insight into the fascinating mechanistic details of palladium π-allyl chemistry. When *Z*-**72** is used with triethyl phosphite, a π-acceptor monodentate ligand, along with short reaction times, the kinetic product *E*-**77** is almost exclusively obtained. Conversely, when dppe is employed as the ligand, with either *E*- or *Z*-**72**, the major product obtained is the more stable *Z*-**74**. This effect is a result of palladium-mediated cleavage of the strained *E*-**77** and subsequent diastereoselective recyclisation to the more stable *Z*-**74** in favour of the 2,9-*trans* diastereomer over the 2,9-*cis* diastereomer. Electron-rich dppe facilitates the allylic ether cleavage and isomerisation of allyl intermediate **78** to **75**, thus allowing the reaction to operate under thermodynamic control. Allylic ether cleavage with electron-poor triethyl phosphite is, however, unlikely to be facile, and in any case, the resulting allyl complex **78** would be very electropositive and more readily undergo recombination prior to isomerisation; thus kinetic control is observed.



Scheme 20.

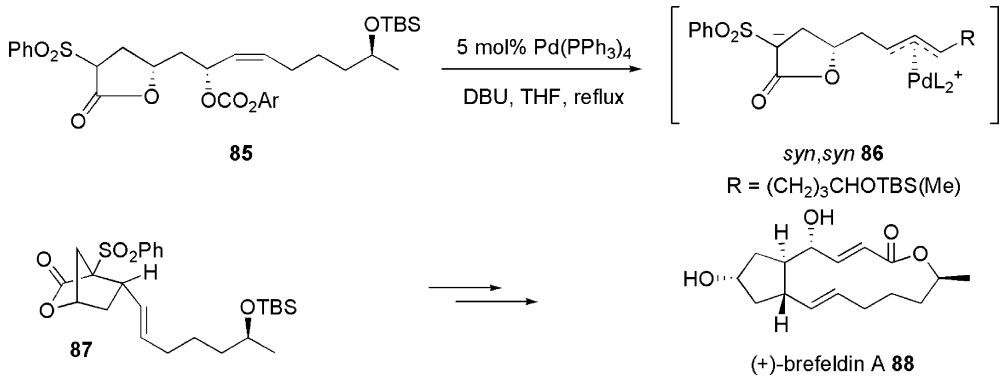
Bicyclic ring systems have also been assembled by intermolecular alkylation with bifunctional allylic agents such as **81** (Scheme 21).[31] With the use of the chiral ferrocenylphosphine ligand **83**, the enantioselective palladium-catalysed bicycloannulation of β-keto-ester **79**, which exists in the achiral form **80**, has been carried out in high yield and ee. The key intermediate **82** was then transformed by a short sequence to the *Lycopodium* alkaloid (−)-huperzine A **84**, a new drug for the treatment of Alzheimer's disease.



Scheme 21.

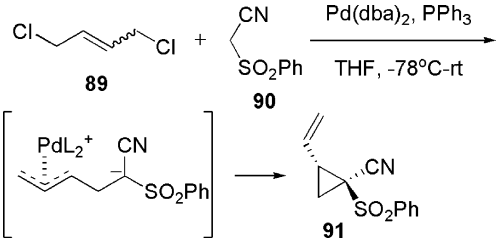
When the substitution pattern at the termini of the palladium allyl system is similar, the preference for attack at the least-substituted end no longer exists, and so other factors dictate which ring size is formed. One example of this effect is the cyclisation of **85** to bicyclic lactone **87** via the preferred *syn*,*syn* transition state **86** *en route* to the total synthesis of (+)-brefeldin A **88** (Scheme 22).[32] The product originating from attack on the other end of the palladium allyl system would have an internal *trans* olefin, so its formation is thermodynamically unfavourable.

A single nucleophilic site can attack a bifunctional allylic



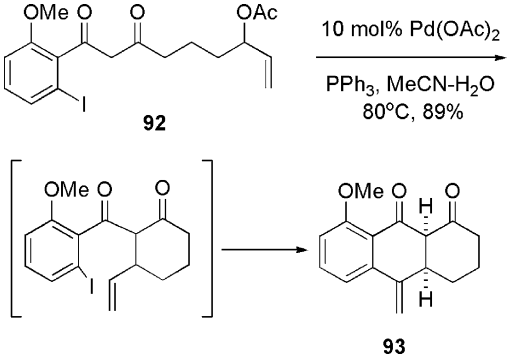
Scheme 22.

reagent twice to yield cyclic products. The double alkylation of bis-allyl chlorides **89** with α-cyanosulfone **90** to give cyclopropane **91** is one such example of this strategy (Scheme 23).[33] The stereochemistry at the nucleophilic carbon is often lost in palladium-catalysed alkylations. In this case, molecular mechanics calculations have rationalised the observed diastereoselectivity in terms of the smaller cyano group being placed on the more-hindered face of the cyclopropane.



Scheme 23.

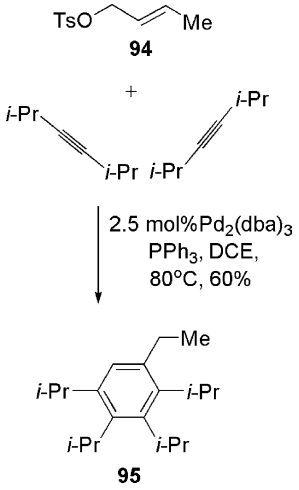
Bis-allylations are efficient processes for the rapid increase of molecular complexity from relatively simple starting materials. An alternative strategy that requires more complex cyclisation precursors, but often allows more control, is the use of cascade reactions. The recently reported Tsuji–Trost–Heck process for the synthesis of tetrahydroanthracenes such as **93** is an elegant example of such an approach (Scheme 24).[34] Cascade processes involving two or more palladium-catalysed reactions require differentiation between the reacting groups. In this case, the allylic acetate **92** is sufficiently more reactive than the aryl iodide to allow the allylic alkylation to take



Scheme 24.

place prior to the Heck reaction. This differentiation is aided by the electron-rich nature of the aromatic ring, which slows down oxidative insertion of palladium.

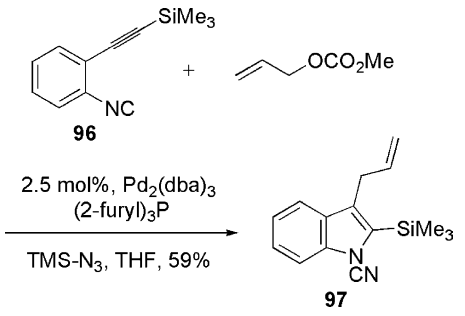
A novel approach to penta-substituted benzene derivatives such as **95** involves palladium-catalysed benzannulation of allyl tosylate **94** with 2,5-dimethylhex-3-yne (Scheme 25).[35] NMR experiments indicated that the mechanism proceeds via π-allyl intermediates, rather than by a palladium-mediated [2+2+2] cycloaddition. Although interesting, the method is so far limited to the use of a single alkyne component.



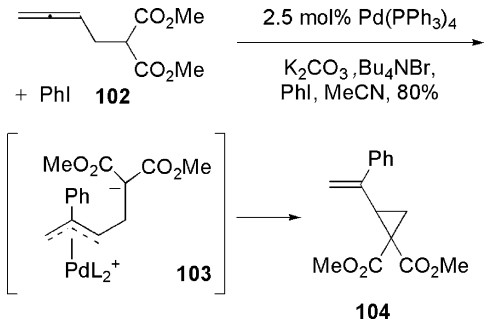
Scheme 25.

A synthetically versatile class of aromatic compounds, *N*-cyanoindoles,[36] for example, **97** have been made by the palladium-catalysed 3-component coupling reaction of *ortho*-alkynylisocyanobenzenes such as **96**, allyl methyl carbonate and trimethylsilyl azide (Scheme 26).[37]

The reaction is purported to go via insertion of the isocyanide **96** into the Pd–N_3 bond of palladium π-allyl azide **98** (Fig. 5). Elimination of N_2 followed by 1,2-migration of the π-allyl moiety from carbon to the α-nitrogen in **99** gives **100**. This transformation can be considered to be a π-allylpalladium mimic of the Curtius rearrangement.[38] The palladium-carbodiimide complex **100** is in equilibrium with palladium-cyanamide complex **101**. At 100 °C, the product *N*-cyanoindoles such as **97** are then



Scheme 26.



Scheme 27.

formed via insertion of the alkyne moiety into the Pd–N bond of **100** followed by reductive elimination of Pd(0). This intriguing reaction is tolerant of a wide variety of functionality, notably the $SiMe_3$ group (as illustrated), which is amenable to synthetic manipulation.

Most of the examples discussed so far have involved allylic acetates, carbonates and similar derivatives for the generation of a π-allylpalladium intermediate. However, a Pd–C bond can add to other groups, such as cyclopropanes, dienes and allenes to generate the same intermediate. For example, addition of I–Pd–Ph to allene **102** has led to the formation of cyclopropane **104** via the more stable *syn*-complex **103** (Scheme 27).[39] If the cyclisation proceeds via the *anti*-complex, then a 5-*endo–trig* closure results in formation of cyclopentene derivatives; this is usually only the case with groups that are more sterically bulky than Ph.[40]

Carbon nucleophiles originating from acidic methine and methylene are widespread, but not exclusive. One alternative is exemplified by the intramolecular palladium-catalysed coupling of allylstannanes with allyl acetates (Scheme 28).[41] The intramolecular coupling leads selectively to *trans* five-membered carbocycles **108** and *cis* six-membered carbocycles **106**, regardless of the geometry of the alkenes in the starting material. The *cis* selectivity has been elegantly applied in the stereoselective synthesis of 10-*epi*-elemol. Density functional theory has indicated η^1-complexes **105** and **107** as the most likely intermediates, although, no rationale for the observed *cis* and *trans* selectivities has been put forward.

A cyclisation does not have to be limited to one type of nucleophile. This is shown effectively in the two-component cycloaddition of activated olefins **109** and allylic carbonates **110** to form 5- or 6-membered cyclic ethers **111** or **112** (Scheme 29).[42] Here, *O*-alkylation of the activated olefin results in anion **113**, which undergoes subsequent cyclisation (Fig. 6). Interestingly, the tetrahydrofurans are formed with a degree of *trans* selectivity of up to 73:23 depending on the R group. On the other hand, the tetrahydropyrans are formed with a degree of *cis* selectivity, again depending upon the R group. This selectivity has been rationalised through the favoured transition states **114** and **116**, both of which minimise steric interactions.

The biologically important γ-lactam skeleton has been constructed in a related single-component cyclisation using the pre-constructed palladium π-allyl substrate **118** (Scheme 30).[43] The *trans* diastereoselectivity resulting in **119** is believed to be attained during the C–C bond-forming step, rather than by equilibration of the cyclised material. It is interesting to note that this substrate does not undergo a

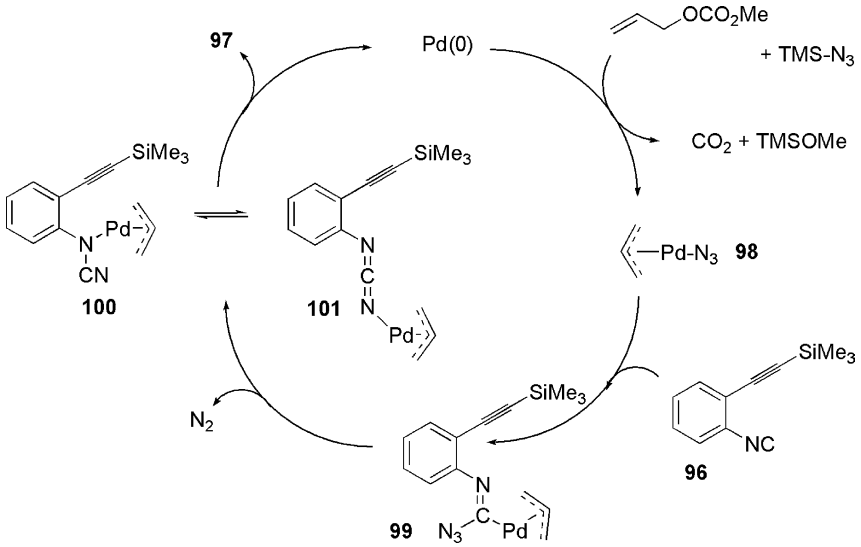
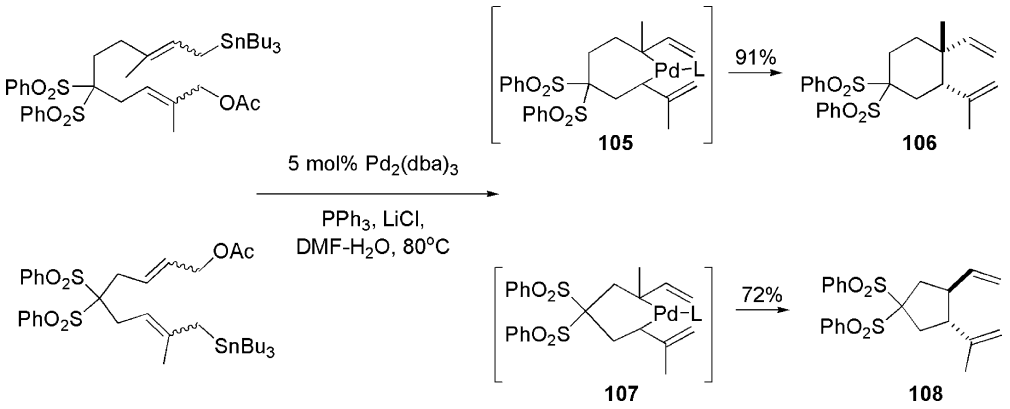
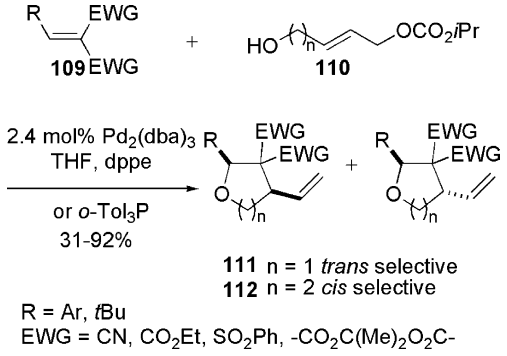


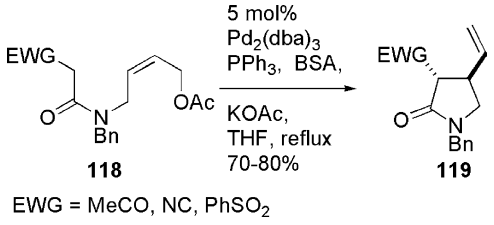
Figure 5.



Scheme 28.



Scheme 29.



Scheme 30.

7-*endo–trig* cyclisation, as has been observed with the keto analogue.[44] This difference may be due to the incorporation of the amide functionality, which shortens the chain to some extent.

4. Conclusions

The preceding examples have shown that palladium-allyl cyclisations enable the synthesis of a wide range of carbo- and heterocyclic systems, often in a region- and diastereoselective manner. The intimate effects of the metal and its associated ligands on the stereochemical outcome of the reaction are particularly fascinating. The number of control elements present in cyclisations of this nature allows fine-tuning of reactivity; however, they can also make prediction of the stereoselectivity of a reaction challenging. Whilst the use of chiral ligands for asymmetric induction in cyclisations has met with some notable successes, this remains an area for further development. Finally, another area of immense potential is that of multi-component cyclisation, which allow a rapid increase in molecular complexity from relatively simple starting materials.

Acknowledgements

The author would like to thank Professor Donald Craig for

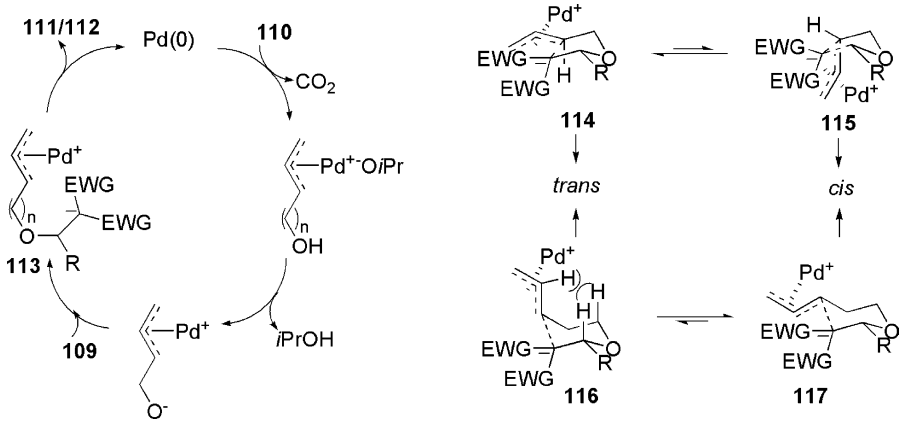


Figure 6.

encouragement and Professor William Motherwell for help with corrections.

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Biographical sketch

Christopher J.T. Hyland was born in Jersey, UK in 1978. He received his M.Sci. degree in 2000 from Imperial College, London, where he earned the SmithKline Beecham award for excellence in organic chemistry. He then remained at Imperial College to complete his doctoral studies under the supervision of Professor Donald Craig in the area of stereoselective γ-lactam synthesis. In 2004, he joined the group of Professor Louis Hegedus at Colorado State University as a postdoctoral researcher where he is currently working on the stereoselective synthesis of novel chiral allenamides.

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Convenient synthesis of 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines via direct acylamination with imidoyl chlorides

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Abstract—A robust synthetic method for 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines via acylamination at the alpha position of the functionalized pyridine system has been developed. The key step in this method was achieved by treatment of the corresponding pyridine *N*-oxides with 2.5 equiv of imidoyl chlorides in the presence of triethylamine, thus producing the desired 2-acylaminopyridines in good yields (74–96%).

1. Introduction

Endothelin-1 (ET-1)[1] and its closely related isopeptides (ET-2, ET-3) have been identified as potent vasoconstrictor peptides. The endothelins exert diverse biological actions through distinct cell surface G-protein coupled receptors (GPCR) termed ET_A and ET_B.[2] Elevated levels of endothelins have been observed in numerous disease states including hypertension, congestive heart failure and renal diseases.[3] Therefore, non-peptide endothelin receptor antagonists are currently being evaluated by a number of pharmaceutical companies as potential therapeutic agents for the treatment of these disease states.

Previously, we reported that potent and selective ET_A antagonists (**1** and **2**) were identified in a series of 6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines.[4,5] It is of significant interest to further clarify the structure–activity relationships (SARs) of the alkylamino group (Fig. 1, R^1) at the 2-position of the pyridine ring and the substituent (Fig. 1, R^2) at the 2′-position of the 7-(4-methoxyphenyl) ring. However, incorporation of the alkylamino group by the previous synthetic method is tedious and the subsequent functionalization on the 7-aryl ring was limited (Route A in Scheme 1). Therefore, the development of a efficient and convenient alternative method for this highly functionalized 2-alkylaminocyclopentenopyridine system is necessary.

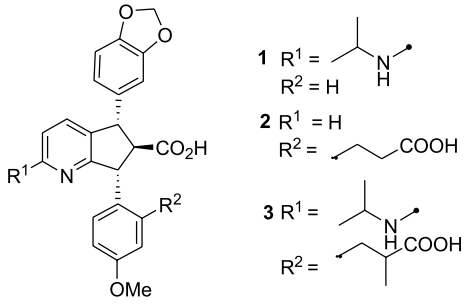

Figure 1.

A number of substituents (Fig. 1, R^2) are easily incorporated in the 7-aryl ring at an early stage in the synthesis,[4] therefore, route B is more available than route A in terms of the synthesis of 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine derivatives. However, the incorporation of the alkylamino group (Fig. 1, R^1) is a crucial step in this route. A previous work introduced an alkylamino group at the 2-position of a pyridine ring by reacting a readily available pyridine *N*-oxide with an imidoyl chloride.[6] This reaction is thought to be applicable to our highly functionalized pyridine system. Unfortunately, the reaction

Keywords: Acylamination; Imidoyl chloride; Cyclopenteno[1,2-b]pyridines; ETA antagonist.
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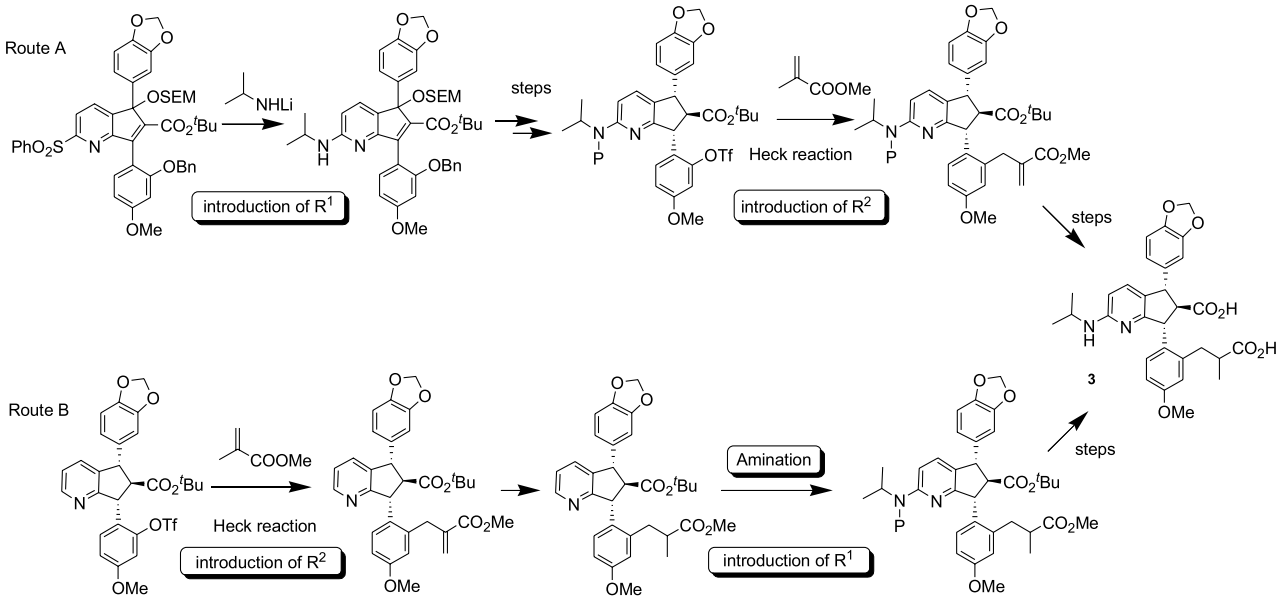


Scheme 1. Possible synthetic route for compound **3**.

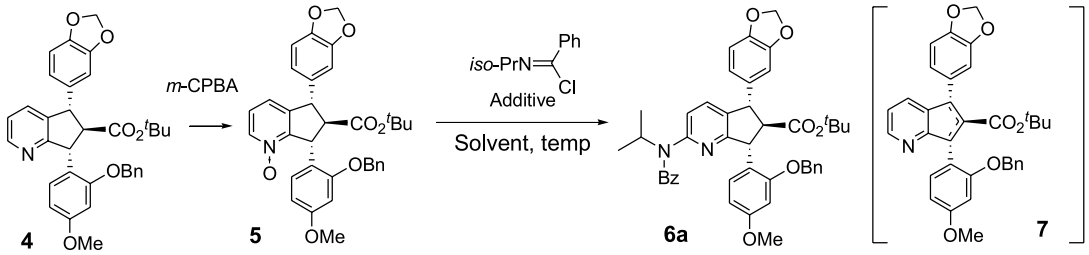
of the pyridine *N*-oxide **5** with one equivalent of *N*-isopropylbenzimidoyl chloride afforded the desired compound **6a** in a very low yield (4.5%). Optimization of the detailed reaction conditions is necessary in order to apply this reaction to the current system.

Herein, we describe the results of the optimization of the direct acylamination at the 2-position of functionalized pyridine derivatives with an imidoyl chloride, as well as a flexible and convenient synthesis of 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine derivatives.

2. Results and discussion

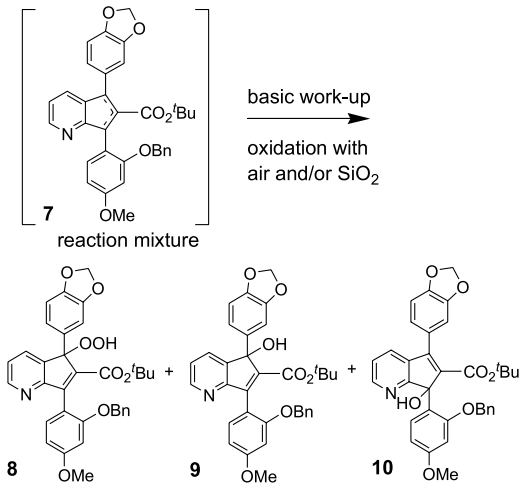
The optimized acylamination reaction conditions utilizing pyridine *N*-oxide **5** and *N*-isopropylbenzimidoyl chloride are shown in Table 1. Pyridine *N*-oxide **5** was readily prepared from **4** by treatment with *m*-CPBA at 0 °C under a nitrogen atmosphere. The initial conditions (entry 1) afforded the desired amide **6a** in a 4.5% yield.[6] Under these conditions, half of the starting material *N*-oxide **5** was recovered together with by-products. The structure of the major by-product was estimated by Mass spectral analysis

Table 1. Acylamination of *N*-oxide **5** with *N*-isopropylbenzimidoyl chloride



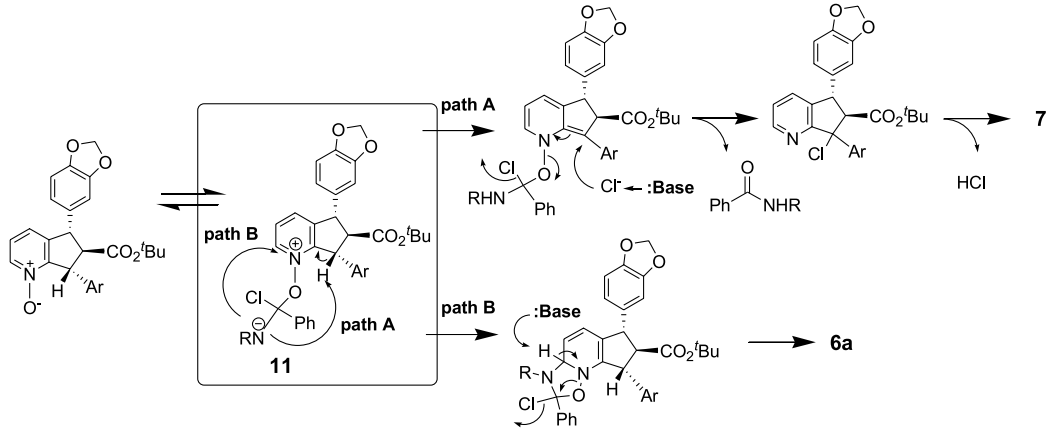
Entry	Imidoyl chloride (equiv)	Solvent	Additive	Temp. (°C)	Results		
					6a	**7**[a]	**5**
1	1	$ClCH_2CH_2Cl$	None	100	4.5%	22%	42%
2	1	$CHCl_3$	None	60	10%	15%	63%
3	10	$CHCl_3$	None	60	13%	21%	40%
4	5	$CHCl_3$	K_2CO_3 (10 equiv)	60	17%	13%	44%
5	5	$CHCl_3$	Cs_2CO_3 (10 equiv)	60	26%	27%	24%
6	5	$CHCl_3$	CsF (10 equiv)	60	69%	6.1%	14%
7	5	$CHCl_3$	Ag_2O (10 equiv)	60	10%	—[b]	19%
8	5	$CHCl_3$	DBU (10 equiv)	60	—	—[b]	79%
9	5	$CHCl_3$	Et_3N (10 equiv)	60	96%	—	—
10	5	Toluene	Et_3N (10 equiv)	60	1.4%	1.2%[b]	75%
11	5	THF	Et_3N (10 equiv)	60	16%	—[b]	39%
12	2.5	$CHCl_3$	Et_3N (5 equiv)	60	94%	—	—

[a] Total yield of **7**, **8**, **9** and **10**.[7]
[b] **4** was isolated as a byproduct



Scheme 2. Identification of side products.

Among the inorganic bases tested, cesium fluoride (CsF) was found to dramatically enhance the desired reaction pathway resulting in a 69% yield of the 2-acylaminated pyridine (**6a**), however the starting material was still recovered (14%). In evaluating the organic bases, unfortunately, DBU was reacted with the imidoyl chloride to produce an ammonium salt rapidly; resulting in a 79% recovery of the starting material (entry 8). In contrast, Et_3N worked very well affording **6a** in an excellent yield (96%, entry 9). With regard to a solvent, chloroform is the best choice for this reaction. Using toluene or tetrahydrofuran instead of chloroform, Et_3N did not work well and a considerable amount of the starting material was recovered (entries 10 and 11). Further experiments around these conditions revealed that 2.5 equiv of imidoyl chlorides in the presence of 5 equiv of Et_3N (entry 12) afforded the product **6a** in 94% yield. These conditions were determined to be the optimal conditions.



Scheme 3. Proposed reaction mechanism.

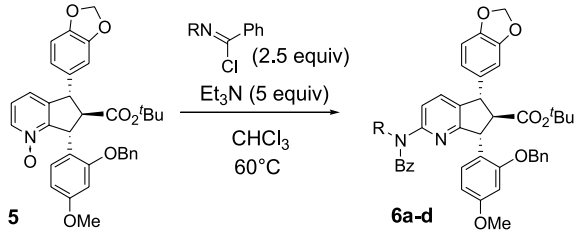
to be **7** in the reaction mixture. However, compound **7** was labile and easily changed by usual work-up and following isolation using silica-gel column chromatography to a mixture of **7**, **8**, **9** and **10** (Scheme 2).[7] Lower reaction temperature with one equivalent of imidoyl chloride (entry 2) or with an excess of imidoyl chloride (entry 3) resulted in an improved yield of **6a**, however, a considerable amount of the starting material and by-products still recovered.

Based on these results, we speculated that the formation of intermediate **11** may be a critical step in this reaction. Further, two reaction pathways were expected to exist for this reaction (Scheme 3). In this reaction, additive(s) are thought to facilitate the formation of the intermediate and the subsequent desired reaction steps, while formation of the by-product **7** can be controlled to trap chloride ions. Moreover, it was reported that addition of a base, such as DBU or triethylamine (Et_3N), increased the yields of 2-acylaminated pyridines in this type of reaction.[6f] However, simple pyridine substrates were used in the optimization of this reaction. Thus, we reexamined the effect of several additional bases in order to accelerate the desired reaction pathway in this highly functionalized pyridine system.

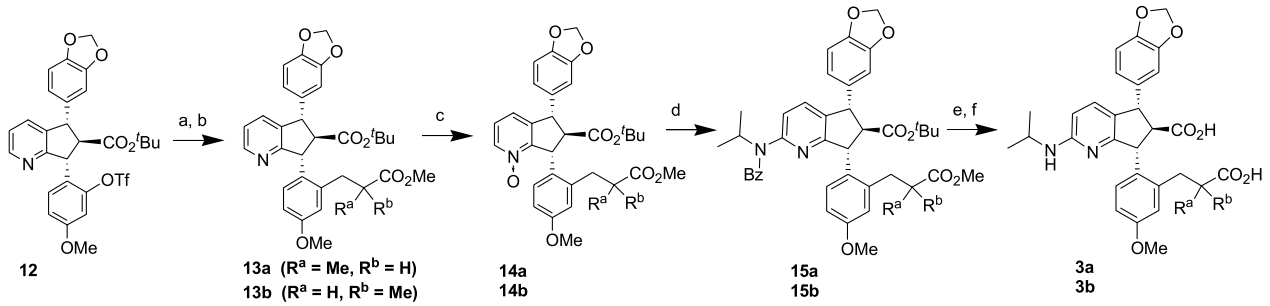
In an effort to examine the applicability of these reaction conditions, pyridine *N*-oxide **5** was reacted with other imidoyl chlorides (Table 2). As expected, the reaction conditions were well tolerated, and the corresponding 2-benzoylaminopyridines (**6a–6d**) were obtained in good to excellent yields.

The previously described encouraging results prompted the

Table 2. Acylamination with various imidoyl chlorides



Entry	Imidoyl chloride	Product	Yield (%)
1	R=*iso*-Pr	**6a**	94
2	R=*n*-Pr	**6b**	93
3	R=Benzyl	**6c**	96
4	R=Phenyl	**6d**	74



Scheme 4. Synthetic route for **3**. Reaction conditions: (a) Methyl Methacrylate, $PdCl_2(PPh_3)_2$, $NaHCO_3$, DMF, 130 °C; (b) 10% Pd-C, $HCOONH_4$, EtOH, 80 °C (**13a**, 37%; **13b**, 28% 2 steps); (c) *m*-CPBA, $CHCl_3$, 6 °C (**14a**, 96%; **14b**, 83%); (d) *N*-isopropylbenzimidoyl chloride, Et_3N, $CHCl_3$, 60 °C (**15a**, 72%; **15b**, 74%); (e) TFA, r.t. (f) NaOH, aq-MeOH, 100 °C (**3a**, 74%; **3b**, 67% 2 steps).

synthesis of **3** by route B (Scheme 4). The Heck reaction of triflate **12** with methyl methacrylate [$PdCl_2(PPh_3)_2$, $NaHCO_3$, DMF, 130 °C] followed by subsequent hydrogenation of the resultant olefin afforded a mixture of diastereomers (**13a** and **13b**) in a moderate yield.[5] The diastereomers were easily separated by silica gel column chromatography. Pyridine *N*-oxide **14a** was treated with *N*-isopropylbenzimidoyl chloride (2.5 equiv) in the presence of Et_3N (5.0 equiv) at 60 °C and afforded 2-acylaminated pyridine **15a** in a 72% yield. The stepwise deprotection of the protecting groups (*tert*-butyl ester, methyl ester, benzamide) on **15a** was achieved by treatment with trifluoroacetic acid (TFA), followed by basic hydrolysis (NaOH) to afford the target compound **3a**. The transformation of **13b** to **3b** was successfully achieved in a manner similar to that described above.

3. Conclusions

A novel synthetic method for 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines via a key acylamination of the corresponding *N*-oxides with imidoyl chlorides has been developed. This mild acylamination is thought to be applicable to the other highly functionalized pyridine derivatives.[8]

4. Experimental

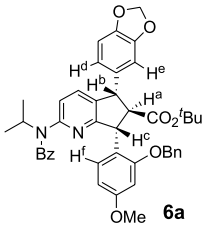
4.1. General

All reagents and solvents were of commercial quality and used without further purification unless otherwise noted. Melting points were determined using a Yanaco MP micromelting point apparatus (Yanaco New Science Inc. Kyoto, Japan) and were not corrected. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian MERCURYvx 400 (Varian, Inc. CA, USA) or JEOL JNM-AL 400 (JEOL Ltd. Tokyo, Japan) instrument at 400 MHz. Chemical shifts were reported in parts per million as δ units relative to tetramethylsilane as an internal standard. Mass spectrometry was performed using micromass Q-Tof 2 (Waters Co. MA, USA) (ESI positive). Analytical and Preparative TLC were preformed using E-Merck Kieselgel F_{254} precoated plates (Merck KGaA. Darmstadt, Germany). Silica gel column chromatography was carried out on Wako gel C-300 (Wako Pure Chemical Industries Ltd, Osaka, Japan.

4.1.1. (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-cyclopenteno[1,2-*b*]pyridine *N*-oxide (5). To a solution of (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine **4** (5.29 g, 9.59 mmol) in $CHCl_3$ (50 ml) was added *m*-CPBA (3.33 g, 19.2 mmol) at 0 °C and the mixture was stirred for 15 h at cold-room temperature (6 °C) under N_2. The reaction was quenched with 1 M $Na_2S_2O_3$ solution while stirring at 6 °C for 30 min and subsequently extracted using EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100:0 to 30:1) to give **5** as a pale brown amorphous solid (2.89 g, 53%). ^1H NMR ($CDCl_3$) δ 7.99 (d, J = 6.6 Hz, 1H), 7.25–7.19 (m, 4H), 7.15–6.96 (m, 3H), 6.62 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.50–6.43 (m, 2H), 6.38–6.24 (m, 2H), 5.90 (q, J = 1.7 Hz, 2H), 4.98–4.68 (m, 3H), 4.38 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.27 (t, J = 9.5 Hz, 1H), 1.33 (s, 9H). HRMS calcd for $C_{34}H_{34}NO_7$ (M + 1) 568.2335, found 568.2331.

4.1.2. Preparation of *N*-isopropylbenzimidoyl chloride. A solution of isopropylamine (35.0 ml, 410 mmol) and Et_3N (69.0 ml, 490 mmol) in THF (200 ml) was cooled in an ice bath and benzoyl chloride was added to the solution. After the mixture was stirred at the same temperature for 3 h, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 2 N HCl, water, saturated $NaHCO_3$ solution and brine, and subsequently dried over Na_2SO_4 and concentrated to give benzisopropylamide as a white solid (51.9 g, 78%). A mixture of benzisopropylamide (6.09 g, 36.8 mmol) and thionyl chloride (4.50 ml, 61.7 mmol) was stirred at 90 °C under a N_2 atmosphere. After 2.5 h, thionyl chloride was removed in vacuo and distilled under reduced pressure to give *N*-isopropylbenzimidoyl chloride as a colorless liquid (6.08 g, 91% yield). Bp 82–83 °C/5 mmHg. (lit.,[9] 52–54 °C/1 mmHg). d = 1.15 (1.15 g/1.0 ml). ^1H NMR ($CDCl_3$) δ 7.97–7.94 (m, 2H), 7.47–7.34 (m, 3H), 4.14 (sept, J = 6.2 Hz, 1H), 1.27 (d, J = 6.2 Hz, 6H).

4.1.3. Reaction of (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine *N*-oxide (5) with *N*-isopropylbenzimidoyl chloride (Table 1). In cases in which inorganic bases were employed as additives, the bases were used before being dried under heat. In cases in which organic bases were used as additives, bases were dried over NaOH. Imidoyl chloride (1, 2.5, 5 or 10 equiv) was added to a mixture of **5** (170 mg, 0.30 mmol) and additive (none, 5 or 10 equiv) in either $ClCH_2CH_2Cl$ or $CHCl_3$ (1.0 ml) and stirred in oil bath at a prescribed temperature under an Ar atmosphere overnight. After cooling the reaction mixture, saturated $NaHCO_3$ solution was added to the mixture and extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (Hexane–EtOAc–MeOH as eluent) and if needed, further isolation was performed by preparative TLC ($CHCl_3$–MeOH as eluent). **6a**. ^{1}H NMR ($CDCl_3$) δ 7.27–7.19 (m, 6H), 7.17–7.11 (m, 2H), 7.08–7.04 (m, 2H), 6.97 (d, J=8.2 Hz, 1H), 6.94 (dd, J=7.8, 1.2 Hz, 1H), 6.57–6.53 (m, 2H), 6.53 (d, J=2.3 Hz, 1H), 6.49 (dd, J=8.4, 2.3 Hz, 1H), 6.39–6.35 (m, 2H), 5.89 (br s, 2H), 5.01–4.91 (m, 1H), 4.94 (d, J=11.3 Hz, 1H), 4.90 (d, J=11.3 Hz, 1H), 4.82 (d, J=10.0 Hz, 1H), 4.40 (d, J=10.0 Hz, 1H), 3.82 (s, 3H), 3.40 (t, J=10.0 Hz, 1H), 1.28 (s, 9H), 1.25 (d, J=6.8 Hz, 3H), 1.15 (d, J=6.8 Hz, 3H). The configuration of **6a** were determined by NOE experiments.[7] NOEs were observed between δ 3.40 (H^a) and δ 6.36 (H^d), δ 3.40 (H^a) and δ 6.37 (H^e), δ 4.40 (H^b) and δ 4.82 (H^c), δ 4.40 (H^b) and δ 6.36 (H^d), δ 4.40 (H^b) and δ 6.37 (H^e), δ 4.82(H^c) and δ 6.97 (H^f).

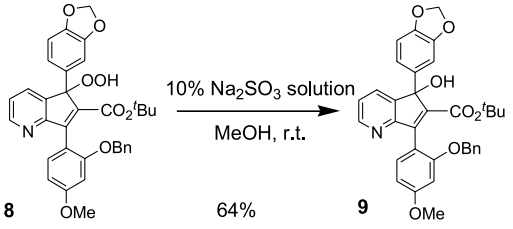


6a

^{13}C NMR ($CDCl_3$) δ 20.6, 21.5, 28.1, 48.9, 51.1, 51.2, 55.4, 61.29, 70.0, 80.7, 99.8, 100.8, 104.5, 108.1, 108.4, 121.3, 121.5, 122.6, 127.1, 127.5, 127.7, 128.2, 128.3, 129.1, 131.4, 133.0, 135.4, 135.9, 136.3, 137.2, 146.3, 147.5, 153.8, 157.3, 159.7, 164.1, 170.0, 172.4. HRMS calcd for $C_{44}H_{45}N_2O_7$ (M+1) 713.3227, found 713.3232. Anal. Calcd for $C_{44}H_{44}N_2O_7$: C, 74.14; H, 6.22; N, 3.93. Found C, 73.93; H, 6.23; N, 3.83.

Compound **7** (mixture of 2 isomers). ^{1}H NMR ($CDCl_3$) δ 8.51 and 8.43 (dd, J=4.9, 1.5 Hz, 1H), 7.06–7.48 (m, 8H), 6.82–6.44 (m, 5H), 5.98 and 5.87 (br s, 2H), 5.18–4.68 (m, 4H), 3.83 and 3.76 (s, 3H), 1.21 and 1.17 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_6$ (M+1) 550.2230, found 550.2229. **8**. ^{1}H NMR ($CDCl_3$) δ 9.44 (s, 1H), 8.47 (dd, J=4.9, 1.6 Hz, 1H), 7.61 (dd, J=7.5, 1.6 Hz, 1H), 7.37 (d, J=9.0 Hz, 1H), 7.23 7.17 (m, 5H), 7.11 (dd, J=7.5, 4.9 Hz, 1H), 6.98 (d, J=1.8 Hz, 1H), 6.85 (dd, J=8.2, 1.8 Hz, 1H), 6.64 (dd, J=7.0, 2.4 Hz, 1H), 6.63 (br s, 1H), 6.56 (d, J=8.2 Hz, 1H), 5.90 (br s, 2H), 5.00 (d, J=11.2 Hz, 1H), 4.95 (d, J=11.2 Hz, 1H), 3.85 (s, 3H), 1.21 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_8$ (M+1) 582.2128, found 582.2134. **9**. ^{1}H NMR ($CDCl_3$) δ 8.46 (dd, J=5.1, 1.5 Hz, 1H), 7.50 (dd, J=7.3, 1.5 Hz, 1H), 7.34 (br s, 1H), 7.24–7.19 (m, 5H), 7.11–7.05 (m, 1H), 7.07 (dd, J=7.3, 5.1 Hz, 1H), 6.94–6.82 (m, 1H), 6.67–6.63 (m, 2H), 5.88 (s, 2H), 5.05 (s, 2H), 4.39 (br s, 1H), 3.84 (s, 3H), 1.17 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_7$ (M+1) 566.2179, found 566.2176. **10**. ^{1}H NMR ($CDCl_3$) δ 8.39 (dd, J=5.1, 1.5 Hz, 1H), 8.01 (d, J=8.8 Hz, 1H), 7.22 (d, J=7.3 Hz, 1H), 7.19–7.12 (m, 3H), 7.07 (dd, J=7.3, 5.1 Hz, 1H), 6.85–6.81 (m, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.65 (dd, J=8.8, 2.2 Hz, 1H), 6.43 (dd, J=8.1, 1.5 Hz, 1H), 6.39 (d, J=1.5 Hz, 1H), 6.36 (d, J=2.2 Hz, 1H), 5.98 (br s, 2H), 4.66 (d, J=11.0 Hz, 1H), 4.57 (d, J=11.0 Hz, 1H), 4.20 (s, 1H), 3.78 (s, 3H), 1.24 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_7$ (M+1) 566.2179, found 566.2182.

4.1.4. Determination of 8 (Scheme 5). To a solution of **8** (32.0 mg, 0.0552 mmol) in MeOH (0.50 ml) was added 10% Na_2SO_3 solution (0.50 ml). After stirring at room temperature for 0.5 h, the mixture was diluted using water and extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane–EtOAc=10:0 to 3:1) to yield **9** as a white amorphous solid (14.0 mg, 64%).



8 64% **9**

Scheme 5. Conversion of **8** to **9**.

4.1.5. Preparations of imidoyl chlorides (Table 2). All imidoyl chlorides were prepared from the corresponding amines by a procedure similar to that described for the preparation of *N*-isopropylbenzimidoyl chloride. *N*-*n*-propylbenzimidoyl chloride. Colorless liquid. Bp 72–73 °C/1.1 mmHg. ^{1}H NMR ($CDCl_3$) δ 8.03–8.00 (m, 2H), 7.49–7.39 (m, 3H), 3.69 (t, J=7.0 Hz, 2H), 1.78 (qt, J=7.4, 7.0 Hz, 2H), 1.04 (t, J=7.4 Hz, 3H). *N*-benzylbenzimidoyl chloride. Colorless liquid. Bp 139–141 °C/1.1 mmHg. ^{1}H NMR ($CDCl_3$) δ 8.10–8.07 (m, 2H), 7.51–7.27 (m, 8H), 4.95 (s, 2H). *N*-phenylbenzimidoyl chloride. White solid. Bp 120–129 °C/1.1 mmHg. (lit.[6c] 100 °C/0.05 mmHg). Mp 35–37 °C (lit.[6c] 34–35 °C). ^{1}H NMR ($CDCl_3$) δ 8.20–8.17 (m, 2H), 7.59–7.40 (m, 5H), 7.25–7.20 (m, 1H), 7.04–7.01 (m, 2H).

4.1.6. Reaction of (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine *N*-oxide (5) with various imidoyl chlorides (Table 2). Imidoyl chloride (0.75 mmol) was added to a mixture of **5** (170 mg, 0.30 mmol) and Et_3N (0.21 ml, 1.50 mmol) in $CHCl_3$ (1.0 ml) and stirred in oil bath (60 °C) under an Ar atmosphere overnight. After cooling the reaction mixture, saturated $NaHCO_3$ solution was added to the mixture and

extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (Hexane–EtOAc as eluent) to give **6b–6d**. **6b**. white amorphous solid (201 mg, 93% yield). ^{1}H NMR ($CDCl_3$) δ 7.32–7.15 (m, 8H), 7.07 (d, J=8.2 Hz, 1H), 6.99–6.95 (m, 2H), 6.90 (dd, J=8.0, 1.2 Hz, 1H), 6.56–6.48 (m, 4H), 6.35 (d, J=1.7 Hz, 1H), 6.31 (dd, J=7.9, 1.7 Hz, 1H), 5.89 (br s, 2H), 4.92 (d, J=11.4 Hz, 1H), 4.85 (d, J=11.4 Hz, 1H), 4.75 (d, J=10.1 Hz, 1H), 4.39 (d, J=10.1 Hz, 1H), 3.98–3.84 (m, 1H), 3.82 (s, 3H), 3.42 (t, J=10.1 Hz, 1H), 1.71–1.45 (m, 2H), 1.29 (s, 9H), 0.79 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 11.4, 21.2, 28.1, 50.4, 51.3, 51.9, 55.4, 61.2, 70.0, 80.8, 100.0, 100.9, 104.5, 108.2, 108.6, 120.7, 121.1, 121.7, 127.3, 127.9, 128.0, 128.5, 128.6, 129.8, 132.1, 133.4, 135.4, 135.7, 136.4, 136.7, 146.5, 147.7, 155.6, 157.6, 160.2, 164.5, 170.5, 172.8. HRMS calcd for $C_{44}H_{45}N_2O_7$ (M+1) 713.3227, found 713.3226. Anal. Calcd for $C_{44}H_{44}N_2O_7$: C, 74.14; H, 6.22; N, 3.93. Found C, 74.05; H, 6.38; N, 3.75. **6c**. White amorphous solid (219 mg, 96% yield). ^{1}H NMR ($CDCl_3$) δ 7.37–7.05 (m, 14H), 6.76 (d, J=8.0 Hz, 1H), 6.74–6.68 (m, 2H), 6.57–6.52 (m, 2H), 6.48–6.41 (m, 2H), 6.25 (d, J=1.4 Hz, 1H), 6.15 (dd, J=7.9, 1.4 Hz, 1H), 5.86 (s, 2H), 5.23 (s, 2H), 4.77 (d, J=11.0 Hz, 1H), 4.71 (d, J=10.2 Hz, 1H), 4.67 (d, J=11.0 Hz, 1H), 4.34 (d, J=10.2 Hz, 1H), 3.85 (s, 3H), 3.41 (t, J=10.2 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 28.1, 51.3, 51.7, 52.1, 55.5, 60.9, 70.0, 80.8, 100.0, 100.9, 104.4, 108.3, 108.7, 120.5, 121.1, 121.6, 127.1, 127.6, 127.9, 128.0, 128.3, 128.7, 130.2, 132.2, 133.1 135.1, 135.6, 136.2, 136.2, 138.0, 146.4, 147.6, 155.2, 157.7, 160.3, 164.4, 171.0, 172.9. HRMS calcd for $C_{48}H_{45}N_2O_7$ (M+1) 761.3227, found 761.3214. Anal. Calcd for $C_{48}H_{44}N_2O_7$: C, 75.77; H, 5.83; N, 3.68. Found C, 75.75; H, 5.96; N, 3.55. **6d**. White amorphous solid (167 mg, 74% yield). ^{1}H NMR ($CDCl_3$) δ 7.45–7.41 (m, 2H), 7.31–7.09 (m, 12H), 7.00 (dd, J=8.0, 0.8 Hz, 1H), 6.90–6.85 (m, 3H), 6.52 (d, J=8.0 Hz, 1H), 6.44 (d, J=2.4 Hz, 1H), 6.40 (dd, J=8.2, 2.4 Hz, 1H), 6.33 (d, J=1.7 Hz, 1H), 6.26 (dd, J=8.0, 1.7 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 4.75 (d, J=11.2 Hz, 1H), 4.64 (d, J=10.0 Hz, 1H), 4.63 (d, J=11.2 Hz, 1H), 4.38 (d, J=10.0 Hz, 1H), 3.80 (s, 3H), 3.33 (t, J=10.0 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 28.1, 51.3, 51.8, 55.4, 61.3, 70.0, 80.7, 99.9, 100.9, 104.5, 108.3, 108.7, 120.1, 121.1, 121.7, 126.7, 127.7, 127.8, 127.9, 128.4, 129.0, 129.0, 130.1, 131.8, 134.2, 135.8, 136.1, 136.4, 136.5, 142.9, 146.5, 147.7, 155.9, 157.6, 160.0, 164.6, 170.9, 172.7. HRMS calcd for $C_{47}H_{43}N_2O_7$ (M+1) 747.3070, found 747.3078. Anal. Calcd for $C_{47}H_{42}N_2O_7$: C, 75.58; H, 5.67; N, 3.75. Found C, 75.26; H, 5.71; N, 3.61.

4.1.7. (5*RS*,6*SR*,7*SR*)-6-*tert*-Butoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (13a, 13b). A mixture of $PdCl_2(PPh_3)_2$ (2.37 g, 3.37 mmol), $NaHCO_3$ (5.66 g, 67.4 mmol), methyl methacrylate (90 ml, 841 mmol) and **12**[5] (9.99 g, 16.9 mmol) in DMF (240 ml) was heated with stirring at 130 °C for 15 h under a N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with EtOAc (200 ml). Insoluble materials were filtered off using Celite pad and the Celite pad was washed with EtOAc. The combined filtrate was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=4:1 to 3:2) to give mixture of *endo* and *exo* olefins (1:5 by ^{1}H NMR) as a pale brown amorphous solid (9.48 g, quant). This solid was used in the subsequent reaction without further separation. Pure samples of each *exo* and *endo* olefins were isolated by further separation with silica gel column chromatography (hexane–EtOAc=3:1 to 2:1). The *exo* olefin. white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J=4.9 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.08 (dd, J=7.6, 4.9 Hz, 1H), 7.04–6.63 (m, 6H), 6.26 (d, J=1.1 Hz, 1H), 5.95 (br s, 2H), 5.46 (br s, 1H), 4.79 (d, J=10.2 Hz, 1H), 4.51 (d, J=10.2 Hz, 1H), 4.00–3.40 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.21 (t, J=10.2 Hz, 1H), 1.35 (s, 9H). HRMS calcd for $C_{32}H_{34}NO_7$ (M+1) 544.2335, found 544.2327. The *endo* olefin. Pale brown amorphous solid. ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J=4.9 Hz, 1H), 7.49 (s, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.16–6.67 (m, 6H), 7.10 (dd, J=7.6, 4.9 Hz, 1H), 5.97 (br s, 2H), 4.75 (d, J=10.4 Hz, 1H), 4.53 (d, J=10.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.19 (t, J=10.4 Hz, 1H), 1.92 (d, J=1.3 Hz, 3H), 1.32 (s, 9H). HRMS calcd for $C_{32}H_{34}NO_7$ (M+1) 544.2335, found 544.2330.

A quantity of 6.5 g of 10% Pd–C and 20.2 g $HCOONH_4$ was added to a suspension of the olefin (9.48 g, 16.9 mmol) in EtOH (160 ml). After the mixture was heated with stirring at 80 °C for 24 h, insoluble materials were filtered off using a Celite pad and the Celite pad was washed with EtOAc and MeOH. After the combined filtrate was concentrated, the residue was diluted with EtOAc and water and the organic layer was separated. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=9:1 to 2:1) to give the more polar diastereomer **13a** as a colorless oil (3.44 g, 37%) and the less polar diastereomer **13b** as a white amorphous solid (2.54 g, 28%).

4.1.8. More polar diastereomer 13a. ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J=5.0 Hz, 1H), 7.29 (d, J=7.6 Hz, 1H), 7.09 (dd, J=7.6, 5.0 Hz, 1H), 6.92–6.65 (m, 6H), 6.37 (s, 1H), 5.97 (br s, 2H), 4.91 (d, J=10.1 Hz, 1H), 4.53 (d, J=10.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.20 (t, J=10.1 Hz, 1H), 3.19–2.79 (m, 3H), 1.34 (s, 9H), 1.22 (d, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 17.1, 27.9, 36.5, 41.2, 49.5, 51.5, 51.9, 55.0, 64.4, 81.0, 100.8, 108.1, 108.1, 112.6, 115.0, 121.6, 121.7, 129.4, 132.0, 132.3, 135.5, 137.6, 139.6, 146.4, 147.7, 149.2, 157.7, 164.6, 172.1, 176.3. HRMS calcd for $C_{32}H_{36}NO_7$ (M+1) 546.24292, found 546.2488.

4.1.9. Less polar diastereomer 13b. ^{1}H NMR ($CDCl_3$) δ 8.41 (d, J=4.9 Hz, 1H), 7.29 (d, J=7.6 Hz, 1H), 7.08 (dd, J=7.6, 4.9 Hz, 1H), 6.94–6.86 (m, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.79–6.67 (m, 4H), 5.97 (br s, 2H), 4.94 (d, J=9.7 Hz, 1H), 4.55 (d, J=9.7 Hz, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 3.48–3.24 (m, 1H), 3.24 (t, J=9.7 Hz, 1H), 2.95–2.50 (m, 2H), 1.34 (s, 9H), 1.28–1.15 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 17.1, 28.1, 37.3, 41.0, 49.1, 51.7, 52.0, 55.2, 64.6, 81.1, 101.0, 108.2, 108.3, 112.7, 115.6, 121.8, 129.6, 132.2, 132.4, 135.8, 137.7, 139.6, 146.6, 147.9, 149.4, 157.7, 164.9, 172.2, 176.5. HRMS calcd for $C_{32}H_{36}NO_7$ (M+1) 546.2492, found 546.2485.

4.1.10. (5*RS*,6*SR*,7*SR*)-6-*tert*-Butoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine *N*-oxide (14a). To a solution of **13a** (3.63 g, 6.65 mmol) in $CHCl_3$ (50 ml) was added *m*-CPBA (2.47 g, 14.3 mmol) at 0 °C and the mixture was stirred for 15 h at cold room temperature (6 °C) under a N_2 atmosphere. The reaction was quenched with 1 M $Na_2S_2O_3$ solution, stirred at 6 °C for 30 min and then extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH=30:1) to give **14a** as a pale brown amorphous solid (3.58 g, 96%). ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J=6.2 Hz, 1H), 7.14 (dd, J=7.7, 7.0 Hz, 1H), 6.92 (d, J=7.7 Hz, 1H), 6.82–6.60 (m, 6H), 5.96 (br s, 2H), 5.05 (d, J=7.0 Hz, 1H), 4.56 (d, J=7.7 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.40–2.98 (m, 4H), 1.42 (s, 9H), 1.31 (d, J=7.0 Hz, 3H). HRMS calcd for $C_{32}H_{36}NO_8$ (M+1) 562.2441, found 562.2444.

4.1.11. A diastereomer of 14a (14b). *Compound* **14b** was prepared from **13b** (starting material) in a similar procedure to that described for the preparation of **14a**. White amorphous solid (83% yield); ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J=6.4 Hz, 1H), 7.15 (t, J=7.1 Hz, 1H), 6.94 (d, J=7.9 Hz, 1H), 6.80–6.66 (m, 6H), 5.96 (s, 2H), 5.09 (d, J=7.3 Hz, 1H), 4.61 (d, J=8.2 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.52 (dd, J=13.9, 4.6 Hz, 1H), 3.40–3.29 (m, 1H), 3.15 (dd, J=8.2, 7.3 Hz, 1H), 2.64 (dd, J=13.9, 10.4 Hz, 1H), 1.42 (s, 9H), 1.20 (d, J=6.8 Hz, 3H). HRMS calcd for $C_{32}H_{36}NO_8$ (M+1) 562.2441, found 562.2441.

4.1.12. (5*RS*,6*SR*,7*SR*)-2-(1-Benzoyl-1-*iso*-propylamino)-6-*tert*-butoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (15a). To a solution of **14a** (3.40 g, 6.05 mmol) and Et_3N (2.7 ml, 19.4 mmol) in $CHCl_3$ (30 ml) was added *N*-isopropylbenzoylimidoyl chloride (2.97 ml, 18.9 mmol) at room temperature. After stirring overnight at 60 °C under N_2, the mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=10:0 to 4:1) to give **15a** as a pale brown amorphous solid (3.20 g, 72% yield). ^{1}H NMR ($CDCl_3$) δ 7.27–7.12 (m, 5H), 7.02–6.97 (m, 1H), 6.79–6.48 (m, 7H), 5.94 (br s, 2H), 4.98 (sept, J=6.8 Hz, 1H), 4.89 (d, J=9.8 Hz, 1H), 4.46 (d, J=9.8 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.14 (t, J=9.8 Hz, 1H), 3.07–2.96 (m, 2H), 2.92–2.82 (m, 1H), 1.34 (s, 9H), 1.25 (d, J=7.0 Hz, 3H), 1.13 (d, J=7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 17.0, 20.8, 21.1, 28.0, 36.6, 41.8, 48.2, 49.0, 51.3, 51.7, 55.2, 64.7, 81.3, 101.1, 108.1, 108.3, 113.0, 114.4, 121.8, 123.5, 127.6, 128.4, 129.2, 129.4, 133.0, 133.6, 135.9, 136.3, 137.5, 140.0, 146.8, 148.0, 154.3, 158.0, 164.6, 170.2, 172.4, 176.8. HRMS calcd for $C_{42}H_{47}N_2O_8$ (M+1) 707.3332, found 707.3325. Anal. Calcd for $C_{42}H_{46}N_2O_8$: C, 71.37; H, 6.56; N, 3.96. Found C, 71.09 H, 6.59; N, 3.83.

4.1.13. A diastereomer of 15a (15b). *Compound* **15b** was prepared from **14b** (starting material) in a similar procedure to that described for the preparation of **15a**. White amorphous solid (74% yield). ^{1}H NMR ($CDCl_3$) δ 7.25–7.12 (m, 5H), 7.01 (dd, J=7.7, 1.1 Hz, 1H), 6.79–6.69 (m, 4H), 6.64 (dd, J=7.8, 2.0 Hz, 1H), 6.58–6.51 (m, 2H), 5.96 (br s, 2H), 4.96 (septet, J=6.8 Hz, 1H), 4.90 (d, J=9.8 Hz, 1H), 4.49 (d, J=9.8 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.52–3.43 (m, 1H), 3.21 (t, J=9.8 Hz, 1H), 2.99–2.89 (m, 1H), 2.63–2.53 (m, 1H), 1.34 (s, 9H), 1.18 (d, J=7.0 Hz, 3H), 1.12 (d, J=7.0 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 16.4, 20.7, 21.2, 28.0, 37.4, 40.6, 48.2, 48.8, 51.0, 51.7, 55.3, 64.3, 81.3, 101.1, 108.2, 108.4, 112.8, 115.7, 121.8, 123.4, 127.6, 128.4, 129.3, 129.4, 132.9, 133.7, 136.1, 136.2, 137.4, 139.6, 146.8, 148.0, 154.4, 157.7, 164.7, 170.2, 172.3, 176.8. HRMS calcd for $C_{42}H_{47}N_2O_8$ (M+1) 707.3332, found 707.3329. Anal. Calcd for $C_{42}H_{46}N_2O_8$: C, 71.37; H, 6.56; N, 3.96. Found C, 71.15 H, 6.57; N, 3.83.

4.1.14. (5*RS*,6*SR*,7*SR*)-7-[2-(2-Carboxypropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)-2-*iso*-propylaminocyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (3a). *Compound* **15a** (3.40 g, 4.81 mmol) were dissolved with TFA (50 ml) and stirred for 4 h at room temperature. After TFA was removed in vacuo, water was added to the residue and the compound was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$ to $CHCl_3$–MeOH=10:1) to yield the monoester as a white amorphous solid (2.94 g, 94%). ^{1}H NMR ($CDCl_3$) δ 7.25–7.09 (m, 5H), 7.01 (d, J=7.9 Hz, 1H), 6.76–6.53 (m, 7H), 5.94 (br s, 2H), 4.95 (septet, J=6.8 Hz, 1H), 4.93 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.28 (t, J=9.6 Hz, 1H), 3.09–2.78 (m, 3H), 1.22 (d, J=6.8 Hz, 3H), 1.12 (d, J=6.8 Hz, 3H), 1.11 (d, J=6.8 Hz, 3H). HRMS calcd for $C_{38}H_{39}N_2O_8$ (M+1) 651.2706, found 651.2699. A quantity of 50 ml (200 mmol) of 4 M NaOH solution was added to a solution of monoester (2.94 g, 4.52 mmol) in MeOH (70 ml) and the mixture was stirred under reflux overnight. After cooling to room temperature, 4 N HCl was added drop-wise to the mixture until it reached pH 2–3. The mixture was then extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=1:2 to $CHCl_3$–MeOH=10:1) to give **3a** as a white solid (1.79 g, 74%). Mp 158–160 °C. ^{1}H NMR (acetone-d^6) δ 7.08 (d, J=8.5 Hz, 1H), 7.05 (d, J=8.3 Hz, 1H), 6.88–6.72 (m, 5H), 6.38 (d, J=8.5 Hz, 1H), 6.00 (s, 2H), 5.20 (br s, 1H), 4.90 (d, J=9.5 Hz, 1H), 4.47 (d, J=8.9 Hz, 1H), 3.87–3.75 (m, 1H), 3.75 (s, 3H), 3.29 (dd, J=9.5, 8.9 Hz, 1H), 3.17–3.10 (m, 1H), 3.00–2.80 (m, 2H), 1.22 (d, J=6.5 Hz, 3H), 1.13 (d, J=6.3 Hz, 3H), 1.10 (d, J=6.3 Hz, 3H). ^{13}C NMR (acetone-d^6) δ 17.8, 22.8, 22.9, 38.6, 42.6, 43.4, 50.3, 52.0, 55.2, 63.7, 101.8, 106.8, 108.7, 108.9, 113.3, 115.8, 122.2, 125.7, 130.3, 133.8, 135.0, 138.4, 140.7, 147.2, 148.6, 158.6, 159.6, 162.8, 174.9, 176.7. HRMS calcd for $C_{30}H_{33}N_2O_7$ (M+1) 533.2288, found 533.2282. Anal. Calcd for $C_{30}H_{32}N_2O_7 \cdot 0.5\ H_2O$: C, 66.53; H, 6.14; N, 5.17. Found C, 66.55 H, 6.28; N, 5.01.

4.1.15. A diastereomer of 3a (3b). A volume of 2 ml of 6 M NaOH solution (12 mmol) was added to a solution of **15b** (85 mg, 0.120 mmol) in MeOH (4 ml) and the mixture was

stirred under reflux overnight. After cooling to room temperature, 6 N HCl was added to the mixture until it reached pH 2–3. Insoluble material was collected by filtration and the filtrate was extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue and the insoluble material were combined and purified by silica gel column chromatography ($CHCl_3$–MeOH=10:0 to 9:1) to give **3b** as a pale brown solid (43 mg, 67%). Mp 137–141 °C. ^{1}H NMR (CD_3OD) δ 7.33 (d, J=8.8 Hz, 1H), 6.94 (d, J=7.8 Hz, 1H), 6.83–6.75 (m, 5H), 6.68 (d, J=8.8 Hz, 1H), 5.92 (s, 2H), 5.16–5.05 (m, 1H), 4.48 (d, J=8.4 Hz, 1H), 3.90–3.80 (m, 1H), 3.76 (s, 3H), 3.28–3.20 (m, 1H), 3.14–3.06 (m, 1H), 2.85 (dd, J=14.6, 7.0 Hz, 1H), 2.73–2.62 (m, 1H), 1.30–1.23 (m, 3H), 1.21 (d, J=6.3 Hz, 3H), 1.14 (d, J=6.3 Hz, 3H). ^{13}C NMR (CD_3OD) δ 18.3, 22.3, 22.6, 37.5, 43.2, 45.1, 52.8, 55.7, 65.4, 102.4, 109.1, 109.2, 110.6, 114.0, 116.0, 122.4, 127.8, 130.3, 132.6, 137.2, 139.9, 141.8, 148.2, 149.4, 156.0, 156.2, 159.9, 176.1, 180.5. HRMS calcd for $C_{30}H_{33}N_2O_7$ (M+1) 533.2288, found 533.2295. Anal. Calcd for $C_{30}H_{32}N_2O_7 \cdot 0.5\ H_2CO_3$: C, 65.00; H, 5.90; N, 4.97. Found C, 64.99 H, 6.04; N, 4.94.

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On the non-classical course of Polonowski reactions of *N*-benzylmorpholine-*N*-oxide (NBnMO)

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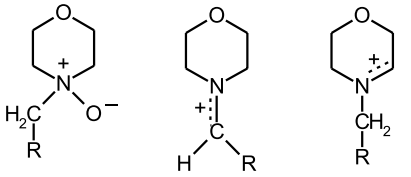
Abstract—The Polonowski reaction of NBnMO (**4**) afforded tropone (**10**) and the novel isoindole **11** besides the expected products benzaldehyde and acetmorpholide, in a temperature-dependent ratio. The reaction proceeded via two primary carbenium–iminium ion intermediates, an *exo*-centered species **5** which underwent a benzylium–tropylium type rearrangement, and a ring-centered species **6**, which reacted further to isoindole **11** by intramolecular electrophilic substitution. The experimental findings were in good agreement with DFT computational data.

1. Introduction

Tertiary amine-*N*-oxide are frequently applied oxidants in organic synthesis,[1] mainly used in combination with catalytic amounts of transition metal catalysts.[2] *N*-Methylmorpholine-*N*-oxide (NMMO, **1**) is moreover used in bulk quantities as a cellulose solvent in the Lyocell process, which is a new and environmentally benign industrial approach to production of man-made cellulosic fibers.[3] NMMO is able to dissolve cellulose directly without chemical derivatization to give a dope which is spun simply into air and water.

In previous studies, we have addressed the chemistry of the Lyocell process[4] and have shown that the NMMO-derived carbenium–iminium ions (**2**, **3**) play a key role in NMMO and Lyocell chemistry. Later we reported on the first example of a carbenium–iminium ion interconversion, which was observed between these two Mannich intermediates. In theory, Polonowski reactions of NMMO would produce the ring-centered, thermodynamically favored **3** as the main product besides small amounts of the *exo*-centered **2**. However, intermediate **3** rearranges into the *exo*-centered **2** via a highly organized transition state involving one molecule of water, the back reaction not being observed,[5] so that the latter intermediate usually predominates. For *N*-benzylmorpholine-*N*-oxide (NBnMO, **4**), which was available from previous NMR studies on conformational equilibria of tertiary amine *N*-oxides,[6] a different behavior was anticipated: first, the corresponding *exo*-cation **5** was supposed to be largely favored from the beginning due to additional charge stabilization at the benzylic position. Second, the rearrangement of ring-centered **6** into **5** would be prevented as the required transition state was strongly disfavored due to steric hindrance imposed by the bulky benzyl group. Even though these expectations proved to be partly true, Polonowski reactions of NBnMO revealed some surprising results, which we wish to report herein, along with related kinetic and computational studies.



1 R = H
4 R = Ph

2 R = H
5 R = Ph

3 R = H
6 R = Ph

2. Results and discussion

Polonowski reactions[7] are intramolecular redox reactions in tertiary aliphatic *N*-oxides. The nitrogen is reduced from the formal oxidation stage −1 to −3, and an α-carbon is oxidized from −2 to ±0. The conversion represents a heterolytic 'self-oxidation' which thus does not require an external oxidant. Polonowski reactions are strictly heterolytic processes.[8] They are induced by *O*-acylation of the

Keywords: Amine *N*-oxides; Polonowski reactions; Carbenium–iminium ions; Rearrangement.
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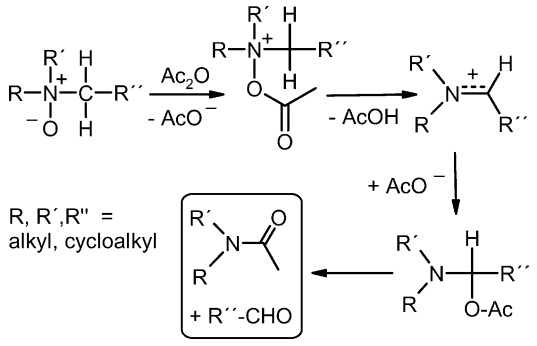
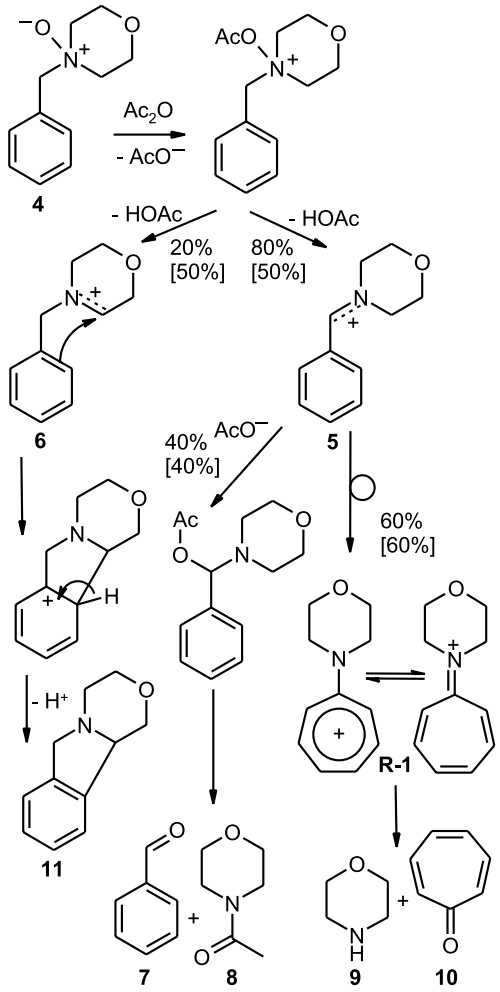
amine *N*-oxide by organic or inorganic acid anhydrides or halides, acetic anhydride being the traditional reagent used. The acylation of the exogenous oxygen lowers the electron density along the N–O bond, and facilitates proton abstraction in α-position to the nitrogen. The classical Polonowski reaction proceeds further with the loss of the respective acid anion, for example, acetate, and simultaneous deprotonation from the α-position in a *trans*-elimination process (Scheme 1). In this step the N–O bond is cleaved, and an iminium ion is generated. Addition of excess acetate in α-position with subsequent N–C bond fission produces the secondary amines in the form of their corresponding acetamides. In the overall process, the amine oxide is dealkylated and acylated, and the α-position of the cleaved alkyl substituent is oxidized to an aldehyde function.[9]



Scheme 1. Classical pathway of the Polonowski reaction.

According to the pathway in Scheme 1, we expected benzaldehyde (**7**) and acetmorpholide (*N*-acetylmorpholine, **8**) to be the main products of the Polonowski reaction between *N*-benzylmorpholine-*N*-oxide (**4**) and acetic anhydride. Indeed, these two compounds were found in equimolar amounts in an approx. 30% yield,[10] but there were three additional main products, however. One of them was morpholine (**9**) in its non-acetylated form in about 50% yield. Surprisingly, it was accompanied by tropone (**10**) in the same amount. In contrast to tropone with its quite simple NMR and mass spectra, identification of the third unexpected product was rather intricate. Finally, the compound was identified as oxazino-isoindole derivative **11**, obtained in 20% yield. Starting from these experimental results we set out to clarify the mechanism of this conversion.

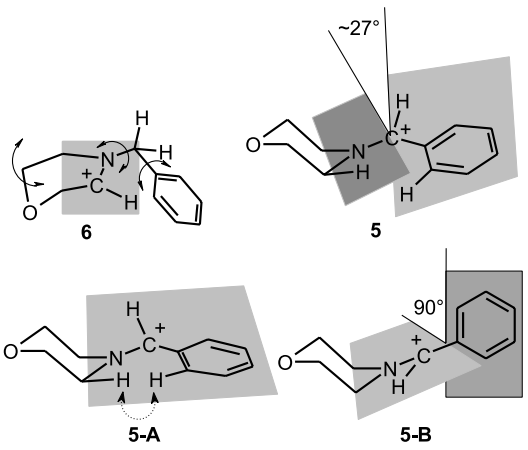
A first valuable clue as to the reaction mechanism was the observed equimolarity between formed benzaldehyde and acetmorpholide on the one hand as well as tropone and morpholine on the other hand, indicating that the first compound couple was formed according to one pathway, and the latter according to a competitive one. Raising the reaction temperature to rt, 35 and 50 °C had no effect on the ratio between the two compound couples, whereas formation of isoindole **11**, was increasingly favored. This indicated that the two compound couples **7/8** and **9/10** originate from one intermediate and **11** from another one which is favored at higher temperatures. From these observations, the overall mechanism as shown in Scheme 2 was developed.



Scheme 2. Non-classical course of the Polonowski reaction of *N*-benzylmorpholine-*N*-oxide (**4**), percentages refer to approx. yields at 0 °C [50 °C].

As the first step in the reaction sequence *N*-benzylmorpholine-*N*-oxide is *O*-acylated by acetic anhydride. Fragmentation of the primary acylation product forms two expected carbenium iminium intermediates, the *exo*-centered (benzyl) cation **5** and the ring-centered **6** (Scheme 2), albeit the latter in surprisingly large amounts. At 0 °C reaction temperature, already about 20% of **6** was produced, and its formation is more and more favored at increasing temperatures. The dependence of the product distribution[11] from the reaction temperature allowed estimating the difference between the free activation energies for formation of either **5** or **6**, which was 12.8 ± 2.3 kJ mol^{-1}, meaning that the activation energy for the formation of **5** was by about 13 kJ mol^{-1} lower than for the formation of **6**.[12]

A possible explanation for these kinetic data was found by means of computational chemistry. In the minimum geometries of both **5** and **6** the positive carbons are sp^2-hybrids with trigonal planar geometry. The morpholinium ring in **6** adopts a twisted chair geometry, as the positively charged carbon has trigonal planar geometry, which anchors the carbenium and the neighboring nitrogen in a rigid structure while the rest of the ring remains flexible (Scheme 3). This flexibility—mainly a flipping of the



Scheme 3. Geometries of the carbenium–iminium ions **5** and **6**. Grey shaded areas indicate in-plane atoms, solid arrows denote conformational flexibility (flipping or bond rotation), dotted arrows sterical hindrance. Hypothetical geometries: **5-A**: phenyl ring in carbenium–iminium plane, maximum benzylic resonance stabilization, but H–H repulsion; **5-B**: phenyl ring perpendicular to carbenium–iminium plane, minimum benzylic resonance stabilization.

conformationally free semi-chair—is increased at increasing temperatures, whereas the rigidity of the carbenium–iminium structure is not influenced. This structural element is the basis of the carbenium–iminium resonance stabilization, which is however only little affected by temperature changes.

The case of intermediate **5**, which actually is a benzyl cation—carbenium–iminium ion hybrid, is different. Apart from the stabilizing carbenium–iminium resonance effect, there is strong additional stabilization by charge delocalization into the aromatic ring. However, for this resonance stabilization to become effective, the aromatic ring, the benzylic CH and the C–N–C element of the morpholine ring must lie in one plane. Optimum charge delocalization into the phenyl moiety is only possible in periplanar benzyl cations (cf. **5-A** in Scheme 3), whereas the positive charge remains localized at the benzyl position in perpendicular benzyl cations (cf. **5-B** in Scheme 3). At equilibrium geometry of **5**, the dihedral angle Ph-2–Ph-1–C_{benzyl}–N is 27° and thus significantly different from 0°, which would guarantee full resonance stabilization. The steric repulsion of the *ortho*-hydrogen in the phenyl ring and the α-hydrogen in the morpholine ring prevents the latter geometry, the H–H distance still being relatively short with 2.08 Å. Thus, the carbenium–iminium ion in **5** does not experience the full additional benzylic resonance stabilization. Moreover, overcoming the rotational barrier of the benzyl cation (the movement from periplanar into perpendicular conformation and further to another periplanar one) becomes more and more easy at higher temperatures. Hence, the net stabilization of the carbenium–iminium ion **5** is decreased since the phenyl moiety is increasingly adopting conformations other than the fully periplanar one, which explains why **5** becomes less stable at higher temperatures. Assuming also that the thermodynamic stabilities of the products go parallel with the activation energies according to the Hammond principle, it becomes clear why the ratio between **5** and **6** is shifted in favor of the latter with increasing temperature, as was experimentally observed. Computations on the transition states leading to **5** and **6** predict an activation energy difference of 14.5 kJ mol^{-1} between the intermediates **5** and **6**, which is in satisfying agreement with the kinetically determined value. The thermodynamic stability of the two carbenium–iminium ions also was assessed by means of DFT computations, which showed that **5** is by 19.2 kJ mol^{-1} more stable than **6**, which is roughly the sixfold of the difference between the two NMMO-derived carbenium–iminium ions **2** and **3** (2.9 kJ mol^{-1}).[5]

Once intermediate **6** was formed, it immediately underwent intramolecular electrophilic substitution to afford isoindole **11**. Apparently, the intramolecular path was much favored over competitive intermolecular ones, as even in the presence of excess methanol, morpholine or trimethylhydroquinone as competing *O*-, *N*-, or *C*-nucleophiles, respectively, only **11** but no trapping products were found. This must be due to a pre-organizational effect, which holds the attacking positive carbenium ion in optimal position for electrophilic attack on the aromatic.

Two competitive pathways start from intermediate **5**: the first one is the classical Polonowski pathway leading to **7** and **8**, the second one constitutes a benzyl-tropylium conversion, a rearrangement which is well known to occur upon fragmentation of substituted aromatics in mass spectrometry. The temperature independence of the ratio between **7** (or **8**) and **9** (or **10**) indicated that the activation energies for the addition of acetate and rearrangement into the tropylium derivative were nearly equal. To support this mechanistic view, we changed the acylating agent to trifluoroacetic anhydride or sulfuryl chloride, since trifluoroacetate or sulfate as the corresponding weakly nucleophilic anions should disfavor the Polonowski pathway thus promoting the competitive tropylium rearrangement. The effect was even stronger than expected: formation of **7** and **8** was completely prevented, and only **9** and **10** was found besides isoindole **11**. It should be noted that the change of the acylating agent affected only the two pathways extending from carbenium—iminium intermediate **5**, but not the pathways leading to it, that is, the ratio between **5** and **6** is not influenced. This is in full agreement with theory: less basic anions, such as trifluoroacetate or sulfate in comparison to acetate, will less efficiently abstract α-protons from acylated **4**. Since this step is required for both **5** and **6** to form, both pathways are equally affected although different protons are abstracted. Thus, the overall reaction rate is lowered, but the ratio between **5** and **6** remains constant. In contrast, only one pathway extending from **5**—the one leading to **7** and **8**—involves the respective anions, and only that one is influenced by changes of the acylating agent.

The driving force for the rearrangement of **5** into the (1-morpholinyl)tropylium cation (**R-1** in Scheme 2) appears to be the high resonance stabilization of the latter. NRT[13] analysis suggests that there is a 54% participation of the tropylium resonance form and a 46% participation of the enamino-cyclohexatrienone canonical structure, which is nearly the 'ideal' 50/50 partition. The mechanism can be assumed to be that of the well-known benzyl–tropylium rearrangement,[14] from which the present case differs only in

the presence of a morpholine ring as the benzylic substituent which additionally stabilizes the primary intermediate **R-1**.

NMMO (**1**) readily undergoes *O*-alkylation by the NMMO-derived carbenium–iminium ions **2** and **3** leading to an autocatalytic degradation cycle.[15] Interestingly, the carbenium–iminium ions derived from NBnMO do not enter a similar path. Evidently, the reaction to the observed products **7**–**11** is energetically favored over *O*-alkylation of NBnMO by either of the carbenium–iminium ions **5** or **6**. The implications of this observation for the stabilization of NMMO solutions will be discussed elsewhere.

3. Conclusions

The Polonowski reaction of *N*-benzylmorpholine-*N*-oxide (**4**) proved to be rather complex. Instead of the expected high yields, only approx. 30% of the two 'traditional' products **7** and **8** were obtained at 0 °C, the majority of the starting material being converted into the novel isoindole **11** and morpholine (**9**)/tropone (**10**). The reaction path and the observed product distribution can be explained by the intermediacy of two competing carbenium–iminium ions **5** and **6**. The differing tolerance of these intermediates towards temperature changes can be utilized to tune the product distribution. The experimental findings agree very well with DFT computational data.

4. Experimental

4.1. General

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G60 (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300.13 MHz, ^{13}C NMR spectra at 75.47 MHz in $CDCl_3$ as the solvent if not stated otherwise and TMS as the internal standard. Data are given in ppm. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra; "d.i." denotes peaks with double intensity.

Computations, as implemented through Spartan Pro 02 by Wavefunction, Inc., Irvine, CA, USA, were carried out on geometries pre-optimized by the semi-empirical PM3 method. For full geometry optimization the widely employed B3LYP hybrid method, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang and Parr[16] parametrized by Becke,[17] was used, along with the double-zeta split valence basis sets 6-31+G*,[18] which includes diffuse functions. Transition states and minima were confirmed by analysis of the calculated vibrational spectrum, and by intrinsic reaction coordinate analysis. For all transition states the number of imaginary frequencies was 1, for all minimum geometries it was 0.

4.1.1. *N*-Benzylmorpholine-*N*-oxide (4). Benzyl chloride (10 mmol) was added dropwise to a solution of morpholine (20 mmol) in chloroform (100 ml). The mixture was stirred for 30 min at room temperature and refluxed for 2 h. After cooling to 0 °C in ice water and addition of *n*-hexane (50 ml), the white, crystalline precipitate formed (morpholinium chloride) was removed by filtration, and the solvents were evaporated under reduced pressure. The residue, crude *N*-benzylmorpholine, was dissolved in ethanol (50 ml) and hydrogen peroxide (30% in H_2O, 5 ml) was added. The mixture was stirred overnight, excess H_2O_2 was destroyed by slowly adding the reaction mixture to a suspension of MnO_2 (10 mg) in ethanol (5 ml). Removal of MnO_2 by filtration and evaporation of the solvent under reduced pressure provided **7**, which was recrystallized from acetone (24% overall yield, 0.47 g, mp 136 °C). The synthesis was repeated and up-scaled to obtain sufficient material. ^{1}H NMR ($CDCl_3$, 0.1 M): δ 2.94 (dd, 2H, N–CH_{eq}), 3.53 (dt, 2H, N–CH_{ax}), 3.78 (dd, 2H, O–CH_{eq}), 4.16 (dt, 2H, O–CH_{ax}), 4.43 (s, 2H, N–CH_2–Ph), 7.44 (m, 3H, Ph), 7.58 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 0.1 M): δ 62.40 (O–CH_2), 64.40 (N–CH_2), 75.96 (N–CH_2–Ph), 129.46 (Ph, d.i., C-3, C-5), 130.26 (Ph, C-1), 130.80 (Ph, C-4), 134.20 (Ph, d.i., C-2, C-6). Anal. calcd for $C_{11}H_{15}NO_2 \cdot H_2O$ (211.27): C 62.54, H 8.11, N 6.63; found C 62.16, H 8.32, N 6.48.

4.2. General experimental procedure for Polonowski reactions of NBnMO

A solution of NBnMO (**4**, 10 mmol) in CH_2Cl_2 (50 ml) was added dropwise to a solution of acetyl chloride or acetic anhydride (10 mmol) in the same solvent (150 ml) under stirring and efficient cooling with an ice/NaCl bath. Also inorganic acid chlorides, such as $POCl_3$ or $SOCl_2$, were used with the same result. (CAUTION! Degradation reactions of amine *N*-oxides are known to easily become uncontrollable![19] Work in an efficient hood and wear appropriate eye protection!). The organic phase was washed thoroughly with a concentrated aqueous sodium hydrogencarbonate solution until evolution of CO_2 ceased, and was dried over $NaSO_4$. Evaporation of the solvent in vacuo yielded a yellow syrup, which was chromatographed on silica gel using *n*-hexane/chloroform (v/v=5:1) to elute the products in the order tropone (**10**), benzaldehyde (**7**), the novel isoindole **11**, acetmorpholide (**8**), and morpholine (**9**). If inorganic acid chlorides were used instead of acetyl chloride or acetic anhydride, no acetmorpholide was found.

4.2.1. Acetmorpholide (8). ^{1}H NMR (DMSO-d_6, 110 °C): δ 2.04 (s, 3H, CH_3), 3.47 (m, 4H, N–CH_2), 3.68 (t, 4H, O–CH_2). ^{13}C NMR: δ 19.7; 47.4; 67.3; 169.4.

4.2.2. Morpholine (9). ^{1}H NMR: δ 1.73 (s, b, 1H, N*H*), 2.87 (m, 4H, N–CH_2, J=4.7 Hz), 3.68 (m, 4H, O–CH_2, J=4.7 Hz). ^{13}C NMR ($CDCl_3$, 0.1 M): δ 46.4, 64.1.

4.2.3. Tropone (10). ^{1}H NMR: δ 6.97–7.17 (m, 6H, CH). ^{13}C NMR: δ 136.7, 136.1, 142.1, 188.1.

4.2.4. 3,4,6,10b-Tetrahydro-1*H*-[1,4]-oxazino[3,4-*a*]isoindole (11). ^{1}H NMR: δ 2.52 (dd, 1H, ^3J=4.4 Hz, ^2J=11.2 Hz, N–CH_2), 2.66 (ddd, 1H, ^3J=4.4, 6.1 Hz, ^2J=11.2 Hz, N–CH_2), 3.55–3.58 (m, 1H, Ar–CH_2–N, O–CH_2–CH_2), 3.63 (m, 1H, O–CH_2–CH), 3.65–3.72 (m, 2H,

Ar–CH_2–N, O–CH_2–CH_2), 3.76 (m, 1H, O–CH_2–CH), 4.31 (t, 1H, ^3J=6.6 Hz), 6.86 (d, 1H, ^3J=7.8 Hz), 7.13 (t, 1H, ^3J=7.8 Hz), 7.29 (t, 1H, ^3J=7.8 Hz), 7.62 (d, 1H, ^3J=7.8 Hz). ^{13}C NMR: δ 46.7 (N–*C*H_2–CH_2), 56.2 (Ar–CH_2–N), 66.0 (N–CH), 66.2 (O–*C*H_2–CH_2), 72.9 (O–*C*H_2–CH), 121.8, 124.1, 125.8, 128.0, 132.4, 140.1. Anal. calcd for $C_{11}H_{13}NO$ (175.23): C 75.40, H 7.48, N 7.99; found C 75.21, H 7.71, N 8.13. Anal. calcd for $C_{11}H_{14}ClNO$ (211.69, hydrochloride of **11**): C 62.41, H 6.67, Cl 16.75, N 6.62; found C 62.36, H 6.83, Cl 16.34, N 6.32.

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10. As minor byproduct, cinnamic acid was found, evidently produced by a Perkin reaction of **7** with Ac_2O.
11. Estimated by the ^{1}H NMR integrals of the crude reaction mixture.
12. With *R* being the ratio **5** and **6** follows: $R=\exp(-(\Delta E_6^{\#}-\Delta E_5^{\#})/RT)$, so that a plot '$\ln R$ versus $1/T$' gives the slope $-\Delta(\Delta E^{\#})/R$, and thus the difference of activation energies.
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Molecular structure of simple mono- and diphenyl *meso*-substituted porphyrin diacids: influence of protonation and substitution on the distorsion

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Abstract—The crystal and molecular structures of three simple porphyrin diacids have been determined from X-ray diffraction data to delineate how the peripheral substituents of the porphyrin affect the overall molecular flexibility. Di-*meso*-substituted $[DPPH_4]^{2+}(CF_3CO_2^-)_2$ and, mono-*meso*-substituted $[MPPH_4]^{2+}(CF_3CO_2^-)_2$ and $[dedmMPPH_4]^{2+}(CF_3CO_2^-)_2$ porphyrin diacids show increasingly saddled core conformation. Some of the spectroscopic properties (NMR and UV–visible) of the porphyrin diacids are also discussed in terms of the observed structures.

1. Introduction

The conformational flexibility of the porphyrin macrocycle may play an important role in controlling the structure–function relationship in many heme proteins.[1,2] Several structural studies have explored the effects of non-planarity on the porphyrin macrocycle using highly substituted porphyrins such as dodecaphenyl- and dodecaalkylporphyrins[3,4] but much less work has been reported with simple porphyrins such as unsubstituted[5] or mono-*meso*-substituted metalloporphyrins.[6] Since the pioneering work of Stone and Fleicher,[7] another approach to study the flexibility of the porphyrin core is based on protonating the porphyrin free bases to form *N*-diprotonated dications, also known as porphyrin diacids.[8–10] Porphyrin diacids typically have non-planar structures with mainly saddle-type distorsions of the porphyrin core, as revealed by X-ray crystallography.[7–14]

In this study, we have used X-ray crystallography to characterize the structure of a 5,15-diarylporphyrin diacid and two mono-arylporphyrin diacids as their trifluoroacetate salts. Although crystallographic structures showing non-planar conformational distorsions in a number of mono- and di-*meso*-substituted porphyrins have been reported, to our knowledge, there is no structural comparison to evaluate the peripheral substitution pattern in a class of relatively unstrained porphyrin diacids. In contrast with previously reported Nickel (II) *meso-tert*-butylporphyrins,[6] an increase of the peripheral substitution leads to a slight decrease of the saddled distorsion. We have also incorporated ^{1}H NMR and UV–visible results since these related data have been used, in some cases, to discuss the flexibility of the porphyrin core in solution.

2. Results and discussion

2.1. Crystal structures of 1, 2 and 3

The porphyrin core of 5,15-(3,5-dimethoxyphenyl)porphyrin $[DPPH_4]^{2+}(CF_3CO_2^-)_2$ **1**, 5-(3,5-dimethoxyphenyl)-porphyrin $[MPPH_4]^{2+}(CF_3CO_2^-)_2$ **2** and 5-(3,4,5-trimethoxyphenyl)-13,17-diethyl-12,18-dimethylporphyrin $[dedmMPPH_4]^{2+}(CF_3CO_2^-)_2$ **3** is saddled as expected for a porphyrin diacid. ORTEP diagrams of **1**, **2** and **3** are presented in Figure 1. The β-carbon atoms of each pyrrole are alternatively displaced above and below the mean porphyrin plane. The magnitudes can be seen in Figure 2, which are formal diagrams of the three porphyrin diacids that show the perpendicular displacement of each atom from the mean plane of the 24-atom core. The deviation follows the order **1** (0.24 Å) < **2** (0.30 Å) ~ **3** (0.31 Å).

The trifluoroacetate ions form hydrogen bonds to the

Keywords: Porphyrin diacids; Structure; Saddled; Flexibility.
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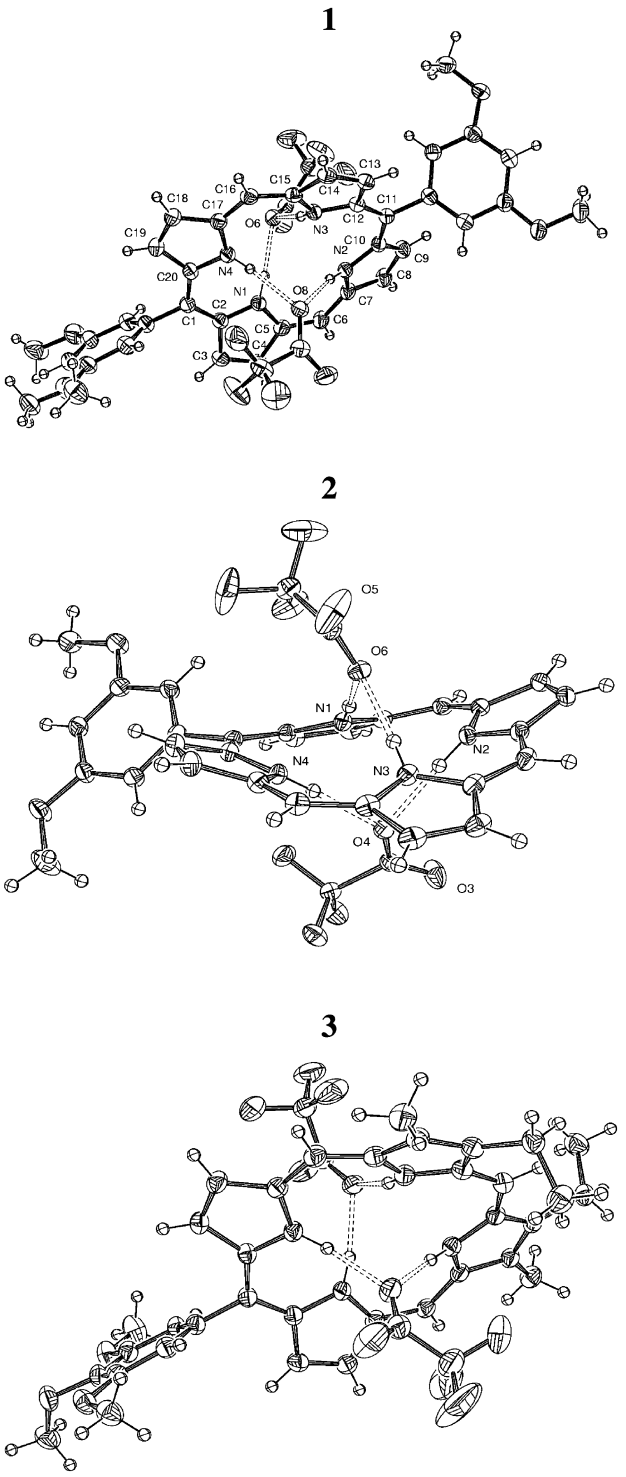

Figure 1. ORTEP diagrams of the structure of the porphyrin diacids **1**, $[DPPH_4]^{2+}(CF_3CO_2^-)_2$, **2** $[MPPH_4]^{2+}(CF_3CO_2^-)_2$ and **3** $[dedmMPPH_4]^{2+}(CF_3CO_2^-)_2$. Thermal ellipsoids are drawn to enclose 50% probability. Dashed lines indicate hydrogen bonds.

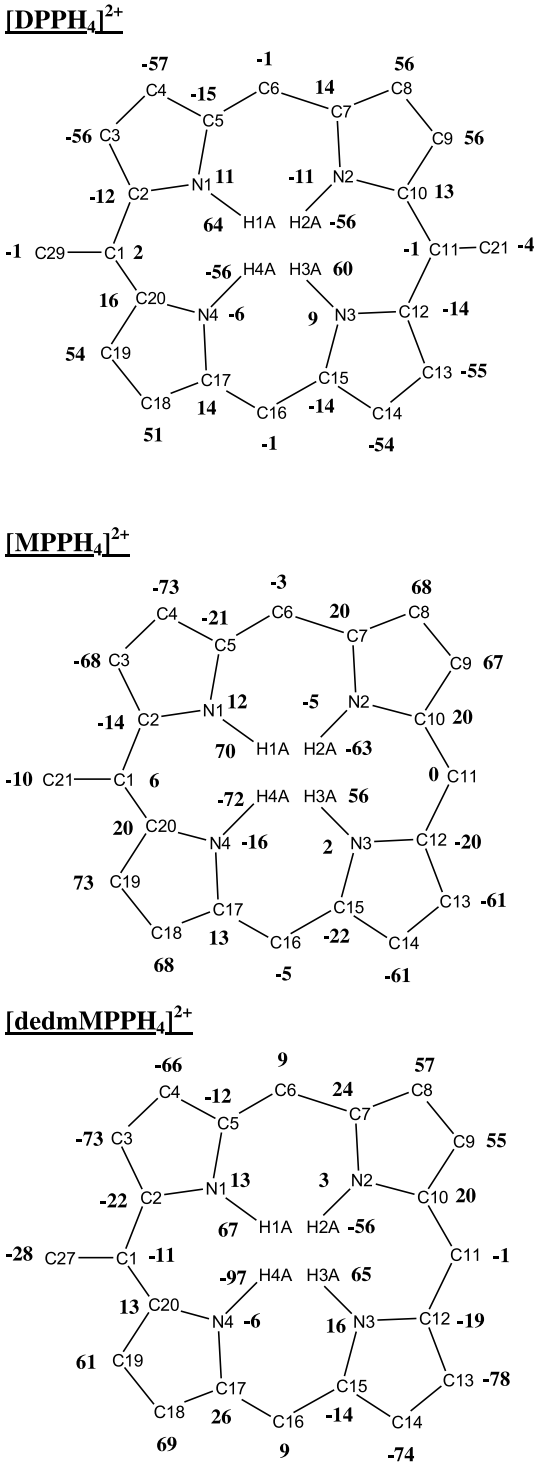

Figure 2. Formal diagrams of the porphyrin diacid cores showing the displacement of the macrocycle atoms from the least-square plane of the 24 atoms ($Å \times 10^2$) and atom numbers.

protons of the porphyrin diacid. The positions of the four inner NH hydrogens atoms are shown in Figure 1 for the three porphyrin diacids. On each porphyrin face, one trifluoroacetic acid anion acts as a monodentate ligand and binds through a carboxyl oxygen to two opposing N–H protons. For the three porphyrins derivatives, the hydrogen bonding H···O range from 1.83 to 2.03 Å. The average values of the N–H···O angle were close to linear with values in the range of 168–176°. Thus, the average value of the hydrogen bond (angle) for each porphyrin are:1.98 Å (170.7°), 1.87 Å (174°), 1.95 Å (171.2°), for $[DPPH_4]^{2+}(CF_3CO_2^-)_2$, $[MPPH_4]^{2+}(CF_3CO_2^-)_2$ and $[dedmMPPH_4]^{2+}(CF_3CO_2^-)_2$, respectively (Table 1).

The pyrrole NH protons are alternately displaced above and

Table 1. Distances (Å) and angles (°) describing the molecular conformations in **1–3**

	N1···N4[a]	N2···N3[a]	N1···N2[b]	N3···N4[b]	C10···C20[a]	C5···C15[b]	Dihedral angles of phenyl groups/ porphyrin plane
$[DPPH_4]^{2+}$	2.969	2.958	3.057	3.028	6.840	6.995	58(1), 56.7(1)
$[MPPH_4]^{2+}$	2.987	2.956	3.039	3.056	6.829	6.971	42.5(1)
$[dedmMPPH_4]^{2+}$	3.002	2.995	3.007	3.013	6.868	6.913	52.3(1)
$DPPH_2$[c]	2.757	2.750	3.055	3.065	6.614	7.118	54.1(1), 54.5(1)

[a,b] Superscripts a and b denote distances perpendicular and parallel to the substituted *meso* positions, respectively.
[c] Ref. [16].

below the 24-atom mean plane. The pyrroles are titled by 17–18.0, 17–24 and 14–25.5° with respect to the porphyrin plane for **1**, **2** and **3**, respectively (Fig. 3).

Correlations exist between increasing macrocycle non-planarity and selected geometric characteristics: some bond lengths and angles are not affected by the distorsion while the increasing of the angles C_m–C_α–C_β and C_α–C_m–C_i and the decreasing of N–C_α–C_m and C_α–C_m–C_α are typical features of the nonplanarity, independent of the way the

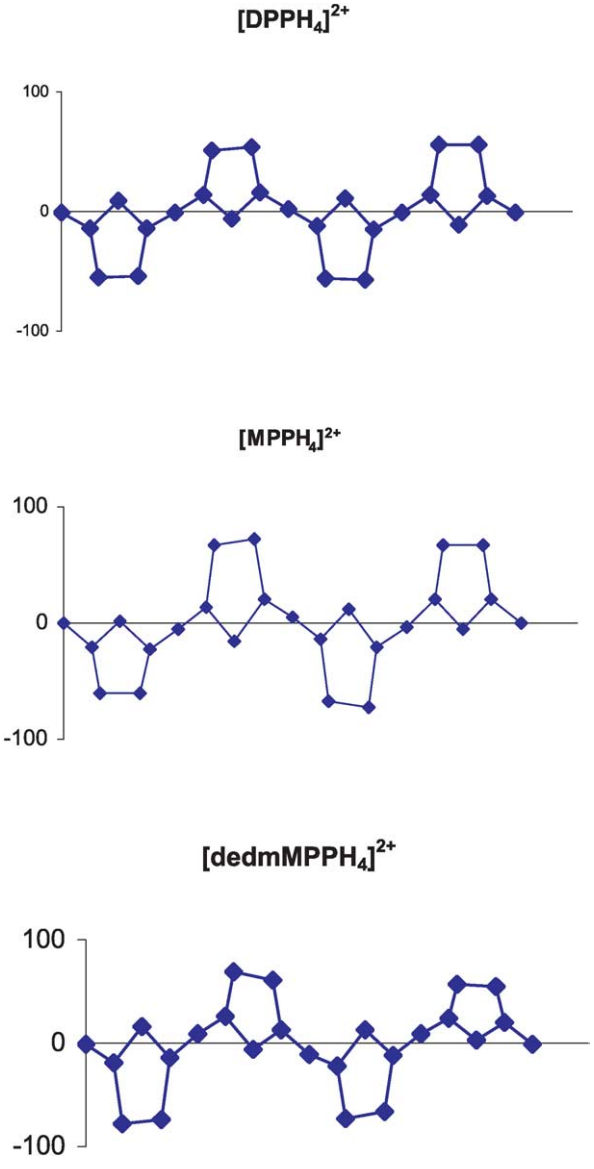

Figure 3. Linear display of the deviations of the macrocycle atoms from the 24-atom mean plane (the horizontal axis is not to scale).

macrocycle is distorted (Table 2). As previously reported,[7–9] a special feature of *meso*-arylporphyrin dications is the decreasing of *meso*-aryl group porphyrin dihedral angles as the magnitude of the saddle distortion increases, although a linear correlation is not possible.[8] The phenyl tilt angles for **1**, **2** and **3** are 56.7–58, 42.5 and 52.3°, respectively.

The porphyrin core displays a weak in-plane distorsion for **1**, **2** and **3** with the N···N distances parallel to the 5,15-axis being ca. ∼0.15, 0.14 and 0.05 Å greater than the N···N distances in the perpendicular direction, respectively. A higher elongation was observed in the X-ray structures of neutral diphenylporphyrin compounds (∼0.30 Å).[15,16]

It should be noted that the *ipso* carbons of the phenyl substituents in **1** do not significantly deviate above and below the molecular plane, in contrast to the observed deviation in similar neutral compounds.[16]

Thus all the herein porphyrin diacids have a saddle shape. In contrast to previously reported Ni porphyrins substituted with *tert*-butyl groups in *meso* position,[6] however, the deformation slightly decreases with an increase of the number of substituents, the two monoarylporphyrin diacids being more saddled than the diarylporphyrin diacid. The loss of symmetry seems to be responsible of that fact: the diphenylporphyrin presents a D_{2h}-saddled porphyrin core whereas the monophenylporphyrins have a C_{2v}-saddled porphyrin core. Moreover, the presence of alkyl-substituents at the beta carbon positions enhances the deviation of the macrocyle from the 24-atom mean plane. Indeed, the *meso* carbons of $[dedmMPPH_4]^{2+}$ present a bigger displacement from planarity.

The average absolute value of the displacement of the carbon beta atoms from the 24-atom mean plane is the best parameter to measure the nonplanarity of the macrocycle (Table 2). The results show the saddled distortion of the diphenyl- and monophenyl-porphyrins is less important than in the $[TPPH_4]^{2+}$ diacid,[7,9,12] which presents an important saddled distortion, but is equivalent to $[TMPH_4]^{2+}$.[9] However, compared to the $[oepH_4]^{2+}\cdot 2[RhCl_2(CO)_2]^-$, which is planar, the porphyrin core in **1**, **2** and **3** presents a sufficient degree of deviation from planarity.

Finally, in these three porphyrin diacids, the saddled conformation seems to result from the steric strain between the four inner protons and the substituents effects, although the packing may also influence slightly the distorsion of the macrocycle.[7]

Table 2. Selected parameters characterizing the extent of the macrocycle deformation of some porphyrin dications

Porphyrins	Δ24 (Å)	ΔCβ (Å)	Aryl tilt angle (°)	C_m–C_α–C_β	C_α–C_m–C_i	N–C_α–C_m	C_α–C_m–C_α
$[DPPH_4]^{2+}(TFA)_2$	0.24	0.54	57.3	126.7	118.3	125.6	125.2
$[MPPH_4]^{2+}(TFA)_2$	0.30	0.67	42.5	127.5	118.2	125.6	124.6
$[dedmMPPH_4]^{2+}(TFA)_2$	0.31	0.66	52.3	126.8	117.4	126.4	124.9
$[TPPH_4]^{2+}(ClO_4^-)_2$[a]	0.42	0.93	26.4	127.9	—	125.9	123.2
$[oepH_4]^{2+}(TFA)_2$[b]	0.33	0.72	—	127.0	—	125.2	127.2
$[TMPH_4]^{2+}(ClO_4^-)_2$[a]	0.31	0.67	63–75	126.7	—	126.2	124.5
$[oepH_4]^{2+}2[RhCl_2(CO)_2]^-$[c]	—	0.1	—	127.4	—	126.4	127.5

[a] Ref. [9].
[b] Ref. [8].
[c] Ref. [11].

2.2. UV–visible spectroscopy

It was commonly believed for a long time that nonplanar distorsions of the porphyrin skeleton bring about significant red shifts in the electronic absorption spectra.[17,18] After some controversial proposal, now it seems accepted that distortions, by themselves do not bring about sizable red shifts effect in the absorption spectra of simple non-transition-metal porphyrins.[19,20] The results presented herein seems confirmed this situation. The peak wavelengths of the three porphyrin diacids and their neutral counterparts are summarized in Table 3. As expected, the three porphyrin diacids show a significant bathochromic shift of the UV–visible absorption, compared to the corresponding neutral precursors. Moreover, there is also a significant bathochromic shift of these absorptions for the diarylporphyrin **1** compared with to the monoaryl porphyrin diacids **2** and **3**. As previously reported, introduction of *meso*-aryl groups will generally lead to a bathochromic shift of all absorptions. This is also observed with the neutral porphyrins. However, this slight bathochromic shift is not correlated to the importance of the saddling. Here less saddled systems show an absorption at longer wavelength, contrary to previously reported with neutral porphyrins.[21]

2.3. ^{1}H NMR

The ^{1}H NMR resonances of the porphyrin diacids **1**, **2** and **3** and the parent neutral porphyrins are collected in Section 4 and are in agreement with previous literature data reported for tetraphenyl porphyrin diacids.[10,18,22,23] As expected, there is a downfield shift of the internal N–H signals upon protonation (~1.5–2 ppm). Many investigations have confirmed that interpretation only based on ring current arguments cannot explain the protonation shifts in porphyrins and have revealed the strong influence of hydrogen-bonding on the chemical shift of the NH protons.[24,25] Since these chemical shifts are also strongly dependent to the trifluoroacetic concentration,[22,23] the deshielding of the N–H resonances cannot be considered as a good marker of the ring distortion and this effect will not be discussed further. The two N–H signals are attributed to two structurally inequivalent pyrrole rings in the unsymmetrically substituted porphyrin diacids **2** ($\delta = -1.29$ and -3.0 ppm) and **3** ($\delta = -1.59$ and -2.92 ppm). The two pyrrole rings bonded to the *meso* carbon to which the substituted phenyl ring is attached constitute one set and the two remaining pyrrole rings connected to a free meso carbon, the second set in the diprotonated system. The separation of N–H lines in dissymmetric porphyrin diacids has been previously reported.[23]

3. Conclusion

The crystal structures of the three simple porphyrin diacids show that the distortion of the porphyrin core depends on the nature of the peripheral substituent. A slightly increased distortion in the saddled mono-phenylporphyrin diacids suggest that this difference is the result of the dissymmetry on the molecular conformation. This conclusion needs to be supported by molecular mechanics calculation.

4. Experimental

4.1. General procedures

Methylene chloride, methanol and pentane were distilled from calcium hydride, magnesium and sodium benzophenone, respectively. Proton NMR spectra were recorded on a Bruker AV 500 (500 MHz) spectrometer at room temperature. Chemical shifts are reported in ppm and referenced to the protonated residual solvent. The porphyrin concentration used for NMR samples was 13 mM in $CDCl_3$ solution (500 μl) with 1% added of trifluoroacetic acid. Spectra were assigned with the aid of HMBC. Visible spectra absorption maxima (nm) and absorption coefficients

Table 3. Selected UV–visible spectroscopic data [nm (ε dm^3 mmol^{-1} cm^{-1})] of porphyrin diacids

	Free porphyrins					Porphyrin dications		
	Soret	IV	III	II	I	Soret	II	I
DPP	407 (400)	502 (18)	536 (4.9)	574 (5.1)	629 (1.4)	424 (182)	569.5 (5.7)	618 (6.9)
MPP	401 (319)	495 (16.8)	526 (2.4)	567.5 (5.2)	621 (0.5)	410 (197)	555.5 (14.01)	602 (6.2)
dedmMPP	404 (230)	500 (16.2)	531.5 (3.9)	569 (5.6)	622 (1.03)	417.5 (125)	559 (14.9)	605 (8.4)
TPP[a]	419 (478)	515 (18.7)	548 (8.1)	592 (5.3)	647 (3.4)	445 (431)	608 (9.0)	661 (50.9)
OEP[b]	399 (163.5)	497 (14.15)	530 (10.59)	568 (6.8)	596 (1.51)	405 (316)	550 (14.7)	595 (7.7)

[a] Ref. [7].
[b] Ref. [24].

(ε) were recorded on an Uvikon XL spectrophotometer using distilled methylene chloride as solvent. ESI mass spectral data were obtained using a HR-MS/MS ZABSpec TOF mass spectrometer.

4.2. Porphyrin synthesis

4.2.1. DPPH$_2$. This synthesis was adapted from previous work.[26] 3,5-dimethoxybenzaldehyde (256 mg, 1.54 mmol) and dipyrromethane (225 mg, 1.54 mmol) were added to 300 ml distilled dichloromethane in a round-bottomed flask. After stirring the solution under a nitrogen stream for 20 min, trifluoroacetic acid (95 µl) was added and the mixture was stirred again at room temperature overnight. A solution of *p*-chloranil (0.5 g in 10 ml CH_2Cl_2) was then added, and the reaction mixture was refluxed for 30 min in an oil bath preheated to 60 °C. Purification of the porphyrin was achieved by flash chromatography with chloroform elution, yielding 353 mg of the desired porphyrin (78%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 10.34 (2H, s, H$_{meso}$), 9.42 and 9.21 (2H, d, J=6 Hz, H$_{\beta pyrr.}$), 7.4 (4H, s, H$_{ortho}$), 6.96 (2H, m, H$_{para}$), 4.03 (12H, s, *m*-OCH_3), −3.12 (2H, br, NH). UV–vis (CH_2Cl_2), λ_{nm} (ε dm^3 mmol^{-1} cm^{-1}): 407 (400), 502 (18), 536 (4.9), 574 (5.1), 629 (1.4). HR-MS (ESI-MS) [$C_{36}H_{31}N_4O_4$ $(M+H)^+$] *m/z*: calcd 583.2345, found 583.2345.

4.2.1.1. [DPPH$_4$]$^{2+}$(CF$_3$COO$^-$)$_2$ 1. ^{1}H NMR (500 MHz, CD_2Cl_2, 1% TFA, ppm): δ 10.86 (2H, s, H$_{meso}$), 9.48 and 9.15 (4H, d, J=4.7 Hz, H$_{\beta pyrr.}$), 7.69 (4H, m, H$_{ortho}$), 7.11 (2H, m, H$_{para}$), 4.11 (12H, s, *m*-OCH_3), −1.72 (4H, br, NH). UV–vis (CH_2Cl_2, 5% TFA), λ_{nm} (ε dm^3 mmol^{-1} cm^{-1}): 424 (182), 569.5 (5.7), 618 (6.9).

4.2.2. MPPH$_2$. This synthesis was adapted from previous work.[27] Pyrrole-2-carboxaldehyde (380 mg, 4.00 mmol), dipyrromethane (300 mg, 2.06 mmol) and 3,5-dimethoxybenzaldehyde (342 mg, 2.06 mmol) were dissolved in 1 L of dry dichloromethane under argon. 100 µL trifluoroacetic acid (1.3 mmol) was added to this solution, and the reaction mixture was shielded from ambient light and stirred for 16 h in the dark. After this time, 1.3 g (5.73 mmol) of DDQ was added and the reaction mixture was stirred for another hour. Then, 1.5 ml triethylamine was added and the solution concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using 2:1 dichloromethane/hexane as eluant. The first fraction was the final product while the second fraction corresponds to the diphenylporphyrin. Recrystallization from dichloromethane/methanol afforded 60 mg (0.13 mmol, 6.3%) of 5-(3,5-dimethoxyphenyl)porphyrin as purple crystals. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 10.36 (2H, s, 10,20-H$_{meso}$), 10.29 (1H, s, 15-H$_{meso}$), 9.51 (4H, dd, ^3J=4 Hz, H$_{\beta pyrr.}$), 9.43 (2H, d, ^3J=4 Hz, H$_{\beta pyrr.}$), 9.22 (2H, d, ^3J=4 Hz, H$_{\beta pyrr.}$), 7.48 (2H, d, H$_{ortho}$), 6.96 (1H, m, H$_{para}$), 4.02 (6H, s, *m*-OCH_3), −3.57 (2H, br, NH). UV–vis (CH_2Cl_2) λ_{nm} (ε dm^3 mmol^{-1} cm^{-1}): 401 (319), 495 (16.8), 526 (2.4), 567.5 (5.2), 621 (0.5). HR-MS (ESI-MS) [$C_{28}H_{23}N_4O_2$ $(M+H)^+$]: calcd 447.1821, found 447.1819.

4.2.2.1. [MPPH$_4$]$^{2+}$(CF$_3$COO$^-$)$_2$ 2. ^{1}H NMR (500 MHz, $CDCl_3$, 1% TFA, ppm): δ 10.94 (2H, s, 10,20-H$_{meso}$), 10.81 (1H, s, 15-H$_{meso}$), 9.71 (4H, dd, ^3J=4.6 Hz, H$_{\beta pyrr.}$), 9.52 (2H, d, ^3J=4.6 Hz, H$_{\beta pyrr.}$), 9.19 (2H, d, ^3J=4.6 Hz, H$_{\beta pyrr.}$), 7.72 (2H, d, ^3J=2 Hz, H$_{ortho}$), 7.14 (1H, t, H$_{para}$), 4.12 (6H, s, *m*-OCH_3), −1.29 (2H, br s, NH), −3 (2H, br s, NH). UV–vis (CH_2Cl_2, 5% vol. TFA) λ_{nm} (ε dm^3 mmol^{-1} cm^{-1}): 410 (197), 555.5 (14), 602 (6.2).

4.2.3. dedmMPPH$_2$. This porphyrin was obtained according to the general procedure involving [2+2] dipyrrole–dipyrrole coupling and adapted from previous work.[28] In a round-bottomed flask, 3,3′-diethyl-4,4′-dimethyldipyrromethane-5,5′-dicarboxylic acid (113 mg, 0.355 mmol) and 5,5′-diformyl-*meso*-(3,4,5-trimethoxyphenyl)dipyrromethane (130 mg, 0.355 mmol) was dissolved in distilled CH_2Cl_2 (120 mL) under argon. To this solution was added trifluoroacetic acid (80 µl, 1.1 mmol) and the reaction mixture was stirred overnight at room temperature and protected from ambient light. After this time, *p*-chloranil (30 mg, 0.12 mmol) was added and the solution was stirred for another hour, treated with triethylamine (1.6 ml, 10.6 mmol) and evaporated. The resulting residue was purified by chromatography with CH_2Cl_2 as eluant. Recrystallization from dichloromethane/pentane afforded 172 mg of 5-(3,4,5-trimethoxyphenyl)-13,17-diethyl-12,18-dimethylporphyrine (0.30 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 10.19 (2H, s, 10,20-H$_{meso}$), 10.06 (1H, s, 15-H$_{meso}$), 9.35 (2H, d, ^3J=4.45 Hz, H$_{\beta pyrr.}$), 9.15 (2H, d, ^3J=4.40 Hz, H$_{\beta pyrr.}$), 7.55 (2H, s, H$_{ortho}$), 4.23 (3H, s, *p*-OCH_3), 4.12 (2H, q, ^3J=7.6 Hz, CH_2-$_{\beta pyrr.}$), 4.03 (6H, s, *m*-OCH_3), 3.66 (6H, s, CH_3-$_{\beta pyrr.}$), 1.93 (6H, t, ^3J=7.7 Hz, CH_3-$_{ethyl}$), −3.19 (1H, br s, NH), −3.44 (1H, br s, NH). UV–vis (CH_2Cl_2) λ_{nm}(ε dm^3 mmol^{-1} cm^{-1}): 404 (230), 500 (16.2), 531.5 (3.9), 569 (5.6), 622 (1.03). HR-MS (ESI-MS) [$C_{35}H_{37}N_4O_3$ $(M+H)^+$]: calcd 561.2865, found 561.2869.

4.2.3.1. [dedmMPPH$_4$]$^{2+}$(CF$_3$COO$^-$)$_2$. ^{1}H NMR (500 MHz, $CDCl_3$, 1% TFA, ppm): δ 10.65 (2H, s, 10,20-H$_{meso}$), 10.38 (1H, s, 15-H$_{meso}$), 9.36 (2H, d, ^3J=4.6 Hz, H$_{\beta pyrr.}$), 9.04 (2H, d, ^3J=4.6 Hz, H$_{\beta pyrr.}$), 7.82 (2H, s, H$_{ortho}$), 4.27 (3H, s, *p*-OCH_3), 4.17 (6H, s, *m*-OCH_3), 4.12 (2H, q, ^3J=7.7 Hz, CH_2-$_{\beta pyrr.}$), 3.66 (6H, s, CH_3-$_{\beta pyrr.}$), 1.77 (6H, t, ^3J=7.7 Hz, CH_3-$_{ethyl}$), −1.59 (2H, br s, NH), −2.92 (2H, s, NH). UV–vis (CH_2Cl_2, 5%vol. TFA) λ_{nm} (ε dm^3 mmol^{-1} cm^{-1}): 417.5 (125), 559 (14.9), 605 (8.4).

4.2.4. Crystallization of porphyrin diacids. For each porphyrin, 40 mg was dissolved in 1 ml of distilled chloroform. 3 equiv of trifluoroacetic acid was added, the red purple solution became green. The solutions were layered with distilled pentane at room temperature. After 1 week, plate-shaped crystals were obtained and suitable for single-crystal X-ray analysis.

4.3. X-ray structure determination

X-ray diffraction data were collected on a NONIUS Kappa CCD with graphite monochromatized Mo Kα radiation (λ= 0.71073 Å). The cell parameters are obtained with Denzo and Scalepack[29] with 10 frames (psi rotation: 1° per frame). All three structures were solved with SIR-97[30] which reveals the non hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined

Table 4. Crystallographic data for **1–3**

	1	**2**	**3**
Empirical formula	$C_{44}H_{34}F_{12}N_4O_{12}$	$C_{32}H_{24}F_6N_4O_6$	$C_{43}H_{40}F_{12}N_4O_{11}$
Formula weight	1038.75	674.55	1016.79
Crystal size (mm)	0.38×0.38×0.24	0.38×0.22×0.18	0.45×0.35×0.32
Temperature (K)	130(1)	120(1)	120(1)
Wavelength (Å)	0.71069	0.71069	0.71069
Crystal system	Triclinic	triclinic	Monoclinic
Space group	P-1	P-1	$P2_1/c$
a (Å)	12.9796(2)	8.52420(10)	13.7355(2)
b (Å)	13.6401(2)	9.17530(10)	17.2426(2)
c (Å)	13.8073(2)	19.2879(3)	20.1298(3)
α (°)	100.3030(10)	84.6690(10)	90
β (°)	101.4180(10)	86.5690(10)	105.9200(10)
γ (°)	101.5990(10)	81.0130(10)	90
V (Å^3)	2285.51(6)	1482.01(3)	4584.60(11)
Z	2	2	4
D_{calc} (mg m^{-3})	1.509	1.512	1.473
μ (mm^{-1})	0.141	0.130	0.137
Total reflections	61753	36279	82767
Independent reflections	10484	6521	10512
Observed reflections [$F^2(2\sigma(F^2)$]	8000	5633	7404
R_{int}	0.0000	0.0186	0.0000
$R1$ [$F^2>2\sigma(F^2)$]	0.0705	0.0415	0.0731
$wR2$ (all data)	0.2188	0.1158	0.2347
Goodness-of-fit on F^2	0.999	1.041	1.030

with SHELXL97[31] by the full-matrix least-square techniques. Atomic scattering factors from International Tables for X-ray Crystallography (1992). Ortep views realized with PLATON98[32]

Crystallographic data are summarized in Table 4.

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Achievement of ring inversion of *myo*-inositol derivatives due to silyloxy/silyloxy repulsion enhanced by the *trans*-substituents on both sides

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Abstract—The introduction of quite bulky trialkyl or diarylalkylsilyl groups into vicinal *trans*-hydroxy groups induced a conformational flip of certain multifunctionalized cyclohexane rings from the usual chair form possessing more equatorial substituents (equatorial-rich chair form) into another chair-form that has more axial substituents (axial-rich chair form). This realization was experimentally revealed by the conformational study of the synthetic *myo*-inositol derivatives possessing two *tert*-butyldimethylsilyl (TBS), two triisopropylsilyl (TIPS), or two *tert*-butyldiphenylsilyl (TBDPS) groups on an adjacent *trans*-diol. Among them, the cyclohexane rings of the 4,5-bis-*O*-TIPS-*myo*-inositol, 4,5-bis-*O*-TBDPS-*myo*-inositol, and 1,2,3,6-tetra-*O*-benzyl-4,5-bis-*O*-TBDPS-*myo*-inositol were in the axial-rich chair form. Comparison of the ring conformations also revealed that the order of the repulsion was OTBDPS/OTBDPS > OTIPS/OTIPS > OTBS/OTBS, and the silyloxy/silyloxy repulsion was enhanced when the two silyloxy groups were placed in the center of the contiguous four equatorial substituents.

1. Introduction

The introduction of bulky trialkyl or diarylalkylsilyl groups into a vicinal hydroxy groups induces a conformational bias due to the repulsion between the two bulky silyloxy groups. The first observation of such a conformational distribution control is the *trans*-1,2-anti orientation of *tert*-butyldimethylsilyloxy groups on acyclic compounds reported by Saito and co-workers (Fig. 1).[1] In 1994, Tius' group found that the silyloxy repulsion also changed the conformation of a tetrahydropyrane ring.[2] The introduction of *tert*-butyldimethylsilyl (TBS) groups into the hydroxy groups on the tetrahydropyrane flipped the ring conformation from the usual chair form possessing more equatorial substituents (equatorial-rich chair form) into another chair-form holding more axial substituents (axial-rich chair form). Since then many conformational flips of tetrahydropyrane rings have occurred due to the introduction of bulky silyl groups thus making effective substrate-controlled stereoselective reactions possible.[3,4]

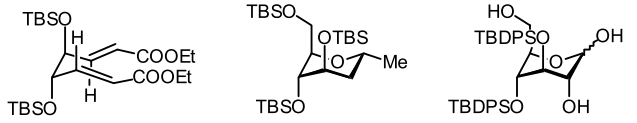

Figure 1. Conformational restrictions of acyclic, tetrahydropyrane, and pyranose derivatives due to the repulsion between adjacent silyloxy groups.[1,2,3f]

Recently, a conformational change in a cyclohexane ring was reported by Marzabadi and co-workers based on the NMR experiments of the *trans*-1,2-bis-silyloxycyclohexanes.[5] They demonstrated that the introduction of triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups into *trans*-1,2-cyclohexanediol favored the 1,2-diaxial

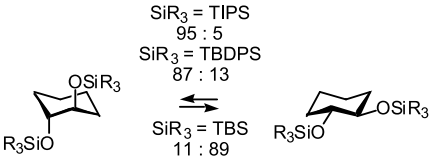

Figure 2. Ring conformation of *trans*-1,2-bis-silyloxycyclohexanes in CD_2Cl_2 at 200 K.[5]

Keywords: Ring conformation; *Myo*-inositol; Axial-rich chair; Silyl protecting groups.
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conformation in the solution (Fig. 2). In contrast, the 1,2-diequatorial conformation was favored when TBS, triphenylsilyl, and other smaller silyl protecting groups were introduced. If the silyl groups could flip a cyclohexane ring possessing other functional groups on the same ring, the conformational control would become an essential and effective synthetic means as well as the flipped sugar chemistry.[4,6] Our objective is accomplishing such a conformational control on a multifunctionalized cyclohexane ring, *myo*-inositol, by introduction of two bulky silyl protecting groups.[7]

Myo-inositol has six hydroxy groups on a cyclohexane ring, and five of them occupy the equatorial positions because the compound is generally in the equatorial-rich chair form (Fig. 3). As the previous ring-inversions shows,[2–6] introduction of the bulky silyl groups into a pair of adjacent *trans*-hydroxy groups—generally these are equatorial—has been crucial to flip the ring. Since *myo*-inositol has one axial hydroxy group, there are two different sets of adjacent *trans*-diols, that is, the 3- and 4-positions and the 4- and 5-positions. For the investigation of a conformational change in the multifunctionalized cyclohexane ring due to the repulsion of two bulky silyloxy groups, we designed *myo*-inositol derivatives possessing two TBS, two TIPS, or two TBDPS groups into the adjacent *trans*-diols (3,4- and 4,5-positions). Thus, we synthesized (±)-3,4-bis-*O*-TBS, TIPS, and TBDPS-*myo*-inositols (**1**–**3**) and the corresponding 4,5-analogues **4**–**6** (Fig. 4), and investigated their ring conformations. The conformations of the synthetic intermediate **1p**–**6p** were also studied. The ring conformations were determined based on the coupling constants in the ^{1}H NMR spectra. When the derivatives afforded single crystals, we also carried out X-ray diffraction studies.

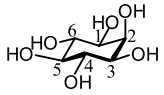


Figure 3. *Myo*-inositol in the equatorial-rich chair form.

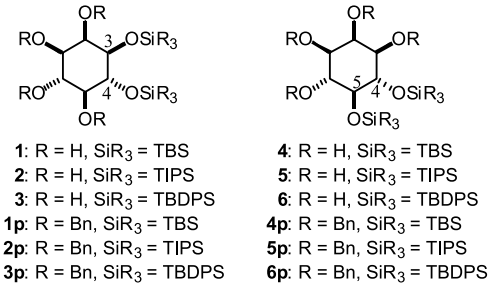
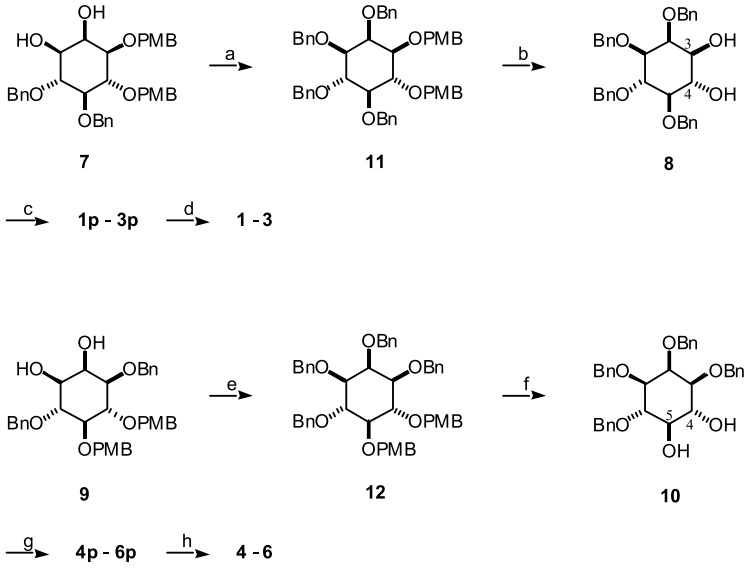


Figure 4. Compounds whose ring conformations were investigated.

2. Results and discussion

2.1. Preparation of the adjacent *trans*-silyloxy derivatives of *myo*-inositol

Scheme 1 shows the syntheses of **1**–**6**. The dibenzylation of (±)-4,5-di-*O*-benzyl-1,6-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**7**)[8] gave the 1,2,5,6-tetrabenzylated derivative **11**, then removal of the two *p*-methoxybenzyl (PMB) groups with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced the 3,4-diol **8**. The protection of the two generated hydroxy groups with TBSOTf, TIPSOTf, and TBDPSOTf[9] gave **1p**, **2p**, and **3p**, respectively, whose benzyl groups were hydrogenated with $Pd(OH)_2$ in THF to give the 3,4-bis-*O*-silylated **1**, **2**, and **3**.[12] The complete removal of the benzyl groups was complicated. These reactions required a long time and sometimes a high hydrogen gas pressure, but the resulting yields of the full debenzylated compounds were not very high. The steric hindrance due to



Scheme 1. Reagents and conditions: (a) NaH, DMF, rt, 2 h, then BnBr, rt, 10 h, 68%, (b) DDQ, 17:1 CH_2Cl_2-H_2O, rt, 45 min, 77%, (c) TBSOTf, 2,6-lutidine, DMF, 100 °C, 1 h, 94% to **1p**; TIPSOTf, 2,6-lutidine, DMF, 100 °C, 12 h, 83% to **2p**; TBDPSOTf, 2,6-lutidine, DMF, 100 °C, 7 h, 85% to **3p**, (d) H_2 (1 atm), $Pd(OH)_2$, THF, rt, 15 days, 12% to **1**; H_2 (1 atm), $Pd(OH)_2$, THF, rt, 17 days, 48% to **2**; H_2 (100 atm), $Pd(OH)_2$, THF, rt, 8 days, 23% to **3**, (e) NaH, DMF, rt, 2 h, then BnBr, rt, 5 h, 98%, (f) DDQ, 17:1 CH_2Cl_2-H_2O, rt, 6 h, 82%, (g) TBSOTf, 2,6-lutidine, DMF, 120 °C, 10 h, 100% to **4p**; TIPSOTf, 2,6-lutidine, DMF, 100 °C, 12 h, 90% to **5p**; TBDPSOTf, 2,6-lutidine, DMF, 100 °C, 1.5 h, 100% to **6p**, (h) H_2 (100 atm), $Pd(OH)_2$, THF, rt, 5 days, 31% to **4**; H_2 (1 atm), $Pd(OH)_2$, THF, rt, 11 days, 35% to **5**; H_2 (1 atm), $Pd(OH)_2$, THF, rt, 10 days, 50% to **6**.

Table 1. ^{1}H NMR coupling constants and dihedral angles of **1–6**, **1p–6p**, **8** and **10**

Compound	$^3J_{HH}$ (Hz) [caluculated dihedral angle (°)]						$^4J_{HH}$ (Hz) (positions)
	H-1–H-2 [H-1–C-1-C-2–H-2]	H-2–H-3 [H-2–C-2–C-3–H-3]	H-3–H-4 [H-3–C-3–C-4–H-4]	H-4–H-5 [H-4–C-4–C-5–H-5]	H-5–H-6 [H-5–C-5–C-6–H-6]	H-6–H-1 [H-6–C-6–C-1–H-1]	
1[a]	2.7 [61]	2.9 [59]	9.5 [162]	9.2 [159]	8.8 [155]	9.0 [157]	—
2[a]	2.9 [59]	2.9 [59]	8.1 [149]	8.1 [149]	8.5 [153]	8.5 [153]	—
3[a]	2.8 [60]	2.7 [61]	7.4 [144]	7.2 [143]	7.6 [146]	7.9 [148]	—
1p[b]	2.1 [68]	2.1 [68]	9.3 [160]	9.0 [157]	9.3 [160]	9.6 [164]	—
2p[b]	1.8 [72]	2.4 [64]	9.3 [160]	8.7 [154]	9.0 [157]	9.3 [160]	—
3p[c]	3.0 [58]	1.8 [72]	8.4 [152]	8.1 [149]	8.4 [152]	8.7 [154]	—
8[c]	2.1 [68]	2.4 [64]	9.3 [160]	9.3 [160]	9.3 [160]	9.6 [164]	—
4[a]	3.4 [54]	3.4 [54]	7.2 [143]	7.1 [142]	7.1 [142]	7.4 [144]	—
5[a]	3.4 [54]	3.4 [54]	3.7 [52]	3.9 [50]	3.8 [51]	3.6 [53]	0.8 (H-3–H-5) 1.7 (H-4–H-6) 1.0 (H-5–H-1)
6[a]	3.3 [55]	3.3 [55]	3.6 [53]	3.3 [55]	3.3 [55]	3.6 [53]	0.9 (H-3–H-5) 1.8 (H-4–H-6) 0.9 (H-5–H-1)
4p[b]	2.4 [64]	2.1 [68]	9.6 [164]	8.7 [154]	9.3 [160]	9.6 [164]	—
5p[b]	2.4 [64]	2.4 [64]	8.4 [152]	7.8 [147]	7.8 [147]	9.0 [157]	—
6p[c]	2.7 [61]	3.6 [53]	3.6 [53]	3.3 [55]	3.6 [53]	4.8 [43]	1.2 (H-4–H-6)
10[c]	2.4 [64]	2.4 [64]	9.6 [164]	9.3 [160]	9.3 [160]	9.6 [164]	—

[a] In CD_3CN.
[b] In $CDCl_3$.
[c] In C_6D_6.

the bulky silyl groups supposedly prevents the approach of the benzyl groups to the surface of the catalyst.[3b,10] Starting from (±)-1,4-di-*O*-benzyl-5,6-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**9**),[11] a similar sequence produced 4,5-bis-*O*-silylated **4p–6p** and **4–6** through the 1,2,3,6-tetrabenzylated derivative **12** and the diol **10**.[12]

2.2. Determination of the ring conformations

Since the original C_s symmetry of the *myo*-inositol was already deformed, the accurate observation of the ^{1}H NMR coupling constants based on both vicinal protons ($^3J_{HH}$) and w-shaped long-range couplings ($^4J_{HH}$) were possible for investigating the ring conformations of **1–6** and **1p–6p**. Table 1 summarizes the coupling constants of **1–6** and **1p–6p** at room temperature and the calculated dihedral angles based on $^3J_{HH}$.[13,14] Although the solution of the Karplus equation has two values for a given coupling constant, the six-membered cyclic structure limits the possible dihedral angles of the vicinal C–H bonds on the ring. The calculated values were confirmed for their validity by assembling molecular models. The coupling constants of **8** and **10**, which are the precursor diols for the corresponding silyl-protected compounds, are also listed for comparison. The coupling constants of the tetraols **1–6** were measured in CD_3CN and those of the tetrabenzyl derivatives **1p–6p** were the data in $CDCl_3$. When the signals heavily overlapped, C_6D_6 was employed.

The assembled molecular models based on the dihedral angles indicated that all the 3,4-bis-*O*-silylated *myo*-inositol derivatives **1–3** and **1p–3p** existed in the equatorial-rich chair form (Fig. 5). The coupling constants of the 3,4-bis-*O*-silylated **1–3** and **1p–3p** were substantially similar to those of the non-silylated diol **8** indicating the large values due to the protons in the 1,2-diaxial relationship at H-3–H-4, H-4–H-5, H-5–H-6, and H-6–H-1. Although the coupling constants of the 3,4-bis-*O*-TBDPS-protected **3** were somewhat smaller than the others, the reduced amount did not indicate a drastic change in the ring conformation. Therefore, the introduction of the bulky silyl protecting groups into the 3,4-hydroxy groups of *myo*-inositol did not change the original equatorial-rich chair form.

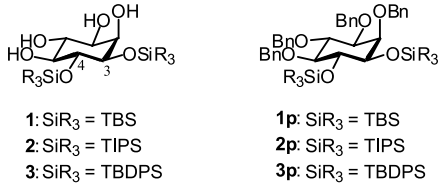


Figure 5. Ring conformation of the 3,4-bis-*O*-silylated *myo*-inositol derivatives.

In contrast, the rings of certain 4,5-bis-*O*-silylated compounds, **5**,**6**, and **6p** existed in the axial-rich chair form (Fig. 6). The coupling constants of these compounds were in the range of 2.7–4.8 Hz (Table 1), and these values indicated that the cyclohexane cores of **5**, **6**, and **6p** were in the axial-rich chair form. The long-range w-couplings due to H-3–H-5, H-4–H-6, and H-5–H-1 supported this conclusion. Furthermore, the X-ray diffraction study elucidated that **6p** existed as the axial-rich chair form in a

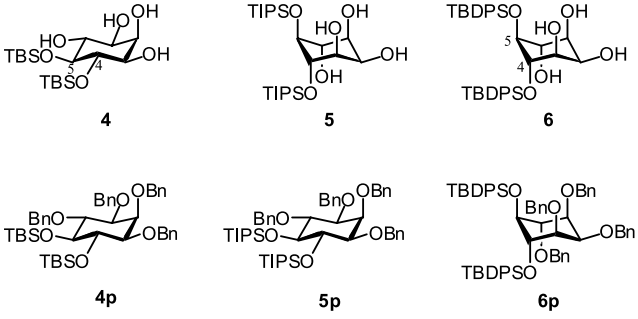


Figure 6. Ring conformation of 4,5-bis-*O*-silylated *myo*-inositol derivatives.

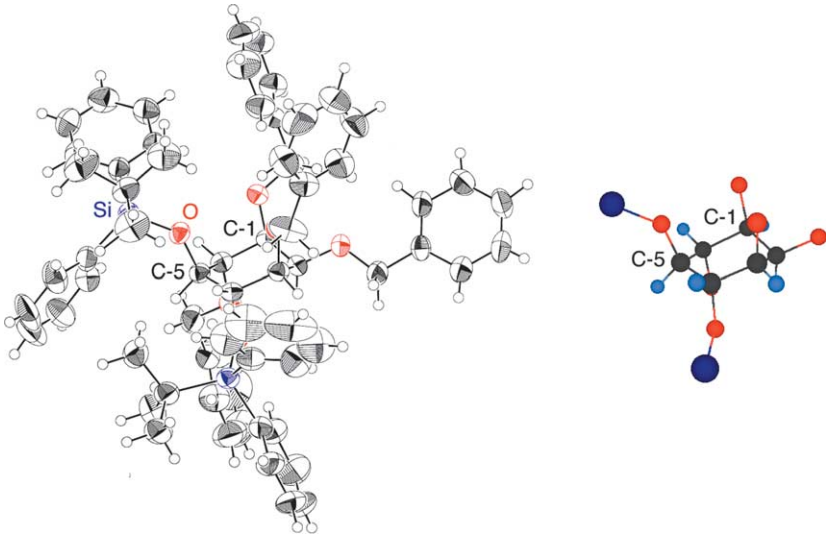


Figure 7. ORTEP drawing and Chem-3D model based on the X-ray diffraction study of **6p**. In the model, the benzyl groups and substituents on the silicon atoms are omitted for clarity.

crystal (Fig. 7). These are the first observations to show that the multifunctionalized cyclohexane rings are able to flip into the axial-rich chair form by the introduction of bulky silyl protections. On the other hand, the tetrabenzylated **4p** and **5p** as well as the tetraol **4** retained the equatorial-rich chair form, although the silyl protections were introduced at the 4,5-positions. The coupling constants of these compounds were generally similar to those of the nonsilylated diol **10** indicating the large values due to the 1,2-diaxial H-3–H-4, H-4–H-5, H-5–H-6, and H-6–H-1.

2.3. Considerations of the ring conformations

Marzabadi's report shows that *trans*-1,2-bis(*tert*-butyldimethylsilyloxy)cyclohexane preferred the equatorial-rich chair form (Fig. 2).[5] At first, we postulated that increasing the functional groups surrounding the *trans*-adjacent OTBS groups would reinforce the steric repulsion of the silyloxy groups and flip the multifunctionalized cyclohexane ring into the axial-rich chair form. Contrary to our expectation, however, all the synthesized bis-*O*-TBS-protected compounds, **1**, **1p**, **4**, and **4p** maintained the original equatorial-rich chair form regardless of the introduced places (3,4- or 4,5-positions) and the presence of the benzyl groups. Therefore, the two OTBS groups are not big enough to induce the ring flip of cyclohexane in solution even when they are placed *trans*-adjacent and even in a multifunctionalized cyclohexane.[15]

When the TIPS groups were introduced to the 4,5-positions, the cyclohexane ring of the tetraol **5** was in the axial-rich chair form, but the ring of the corresponding tetra-benzyl-protected **5p** was in the equatorial-rich chair form. Thus the benzyloxy groups prevented the ring flip more than the hydroxy groups. On the basis of this result, we envisaged that the axial-rich conformation of **5** was stabilized by hydrogen bondings.[16] Because the ring flip of **5** occurred in CD_3CN (Table 1), we changed the solvent to CD_3OD. The result listed in Table 2 indicated that the ring conformation of **5** was still the axial-rich chair form even in methanol. The coupling constants were in the range of 3.1–5.6 Hz. The clear long-range w-coupling due to H-4–H-6 (1.2 Hz) was observed along with small (<1 Hz) w-couplings due to H-1–H-3, H-3–H-5, and H-5–H-1. These small couplings were confirmed by the decoupling experiments because the correlated signals became sharper and taller. On the other hand, each NMR spectrum of the benzyl-protected **5p** in $CDCl_3$, acetone-d_6, and CD_3OD indicated that the equatorial-rich chair form was retained in all cases. These observations demonstrated that the influence of both solvent effects and hydrogen bondings were less marked on these ring conformations.

The introduction of TBDPS groups into the 4,5-hydroxy groups of *myo*-inositol, **6** as well as **6p**, induced complete ring flip into the axial-rich chair form. A comparison of the ring conformations of **4**, **5**, **5p**, and **6p** (Fig. 6) demonstrated that the steric repulsion is OTBDPS/OTBDPS $>$OTIPS/OTIPS$>$OTBS/OTBS. Eliel and Satici reported the conformational energy of monosilyloxycyclohexanes.[17] The population of the axial-rich chair form is 9 and 20% in the TIPS derivative and in the TBDPS derivative, respectively

Table 2. ^{1}H NMR coupling constants and calculated dihedral angles of **5** and **5p** in several solvents

Compound	Solvent	$^3J_{HH}$ (Hz) [calculated dihedral angle (°)]					
		H-1–H-2 [H-1–C-1–C-2–H-2]	H-2–H-3 [H-2–C-2–C-3–H-3]	H-3–H-4 [H-3–C-3–C-4–H-4]	H-4–H-5 [H-4–C-4–C-5–H-5]	H-5–H-6 [H-5–C-5–C-6–H-6]	H-6–H-1 [H-6–C-6–C-1–H-1]
5	CD_3CN	3.4 [54]	3.4 [54]	3.7 [52]	3.9 [50]	3.8 [51]	3.6 [53]
5	CD_3OD	3.1 [57]	3.1 [57]	5.1 [40]	4.4 [46]	4.4 [46]	5.6 [40]
5p	$CDCl_3$	2.4 [64]	2.4 [64]	8.4 [152]	7.8 [147]	7.8 [147]	9.0 [157]
5p	CD_3COCD_3	1.7 [74]	2.1 [68]	9.2 [159]	8.2 [150]	8.4 [152]	9.1 [158]
5p	CD_3OD	2.4 [64]	2.2 [66]	9.0 [157]	8.1 [149]	8.3 [151]	9.0 [157]

(Fig. 8). Therefore, the OTBDPS group is easier to axially orient than the OTIPS group when it is the only substituent on the cyclohexane ring. On the contrary, when these silyloxy groups are placed side by side in a *trans*-adjacent manner, the OTIPS/OTIPS repulsion increased more than that of OTBDPS/OTBDPS (Fig. 2).[5] In the multifunctionalized case, the functionalities except for the silyloxy groups are likely to affect the ring conformation.

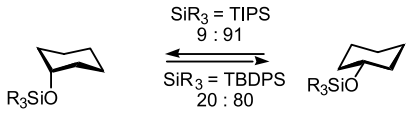


Figure 8. Conformational equilibrium of trialkylsilyloxycyclohexanes in CD_2Cl_2 at 179–188 K.[17]

One of the most important observations is that all the 3,4-bis-*O*-silylated *myo*-inositol derivatives, **1**–**3** and **1p**–**3p** maintained the equatorial-rich chair form in contrast to the ring conformation of the 4,5-bis-*O*-silylated compounds. In *myo*-inositol, both the side-functionalities of the 4- and 5-positions are in the *trans*-relationship. In contrast, one side of the 3,4-bis-*O*-silyloxy derivatives, that is, the 2-position, is in the *cis*-relationship. In these cases, rotation of the C-3–O bond let the bulky silyl group escape into a space in the 2-equatorial direction (Fig. 9) reducing the silyloxy/silyloxy repulsion. In the bis-4,5-*O*-silylated compounds, there is no such space to reduce the repulsion. In the equatorial-rich chair form, the silyloxy/silyloxy repulsion is enhanced when they are located in the center of the contiguous *trans*-hydroxy groups.[15] Because each ring conformation would be the result of a balance between the 1,3-diaxial interactions with the 1,2-diequatorial silyloxy/silyloxy interactions, the bis-4,5-*O*-silylated derivatives, **5**, **6**, and, **6p** are in the axial-rich chair form.

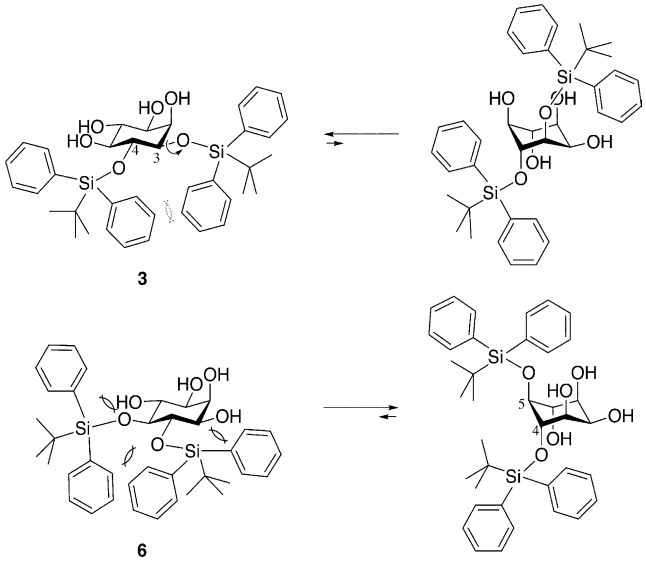


Figure 9.

3. Conclusion

Two adjacent bulky silyloxy groups can flip a cyclohexane-ring into the axial-rich chair form even it is multi-functionalized, as in these reported results. Compounds **5**, **6**, and **6p** are the first axial-rich chair *myo*-inositol derivatives isolated in the pure form, although the ring flip of inositols itself has been previously observed in solution.[18] As well as the famous ring conformation of the *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane reported by Biali and co-workers,[19] the flipped compounds are also the counter examples to the general stability of equatorial-rich chair six-membered rings. It is noteworthy that the introduction and removal of the silyl protecting groups switch the ring conformation, that is, the conformation of the multi-functionalized cyclohexane ring has become controllable.

The cyclohexane-ring of *myo*-inositol was flipped into the axial-rich chair form when the TIPS or TBDPS groups were introduced into the 4- and 5-hydroxy groups. In contrast, when the bulky silyl groups were introduced into the 3- and 4-positions, the equatorial-rich chair forms were retained regardless of the variety of the silyloxy groups. This observation displayed an enhanced silyloxy/silyloxy repulsion as expected due to the oxygen functionalities on both sides of the adjacent silyloxy groups. It may be possible to state that the introduction of TBDPS groups will flip the cyclohexane ring when the silylating vicinal hydroxy groups are in the center of the contiguous four equatorial hydroxy groups.

4. Experimental

4.1. General method and materials

All commercially available reagents were used without further purification. All moisture and air sensitive reactions were performed under a positive pressure of argon in a glassware equipped with rubber septa. The glassware was dried under reduced pressure by heating with a heat-gun before use. When necessary, the solvents and reagents were distilled prior to use and were transferred using a syringe or cannula. The reaction mixture was magnetically stirred.

Thin layer chromatography was performed on Merck precoated silica gel 60 F-254 plates or Merck RP-19 F-254 plates. Column chromatography was performed on Merck silica gel 60 (0.063–0.200 mm) or Merck silica gel 60 230–400 mesh for ordinary phase or Nacalai tesque cosmosil 140C18-PREP for reverse phase. Spots were detected by dipping in a solution of 2% anisaldehyde, 5% H_2SO_4 in EtOH or a solution of 10% phosphomolybdic acid in EtOH followed by heating at ca. 200 °C.

The melting points were determined using a Yanagimoto micro-melting point apparatus. The infrared (IR) spectra were recorded on JASCO FT/IR-5300 or 8000 instruments and the major absorbance bands are all reported in wavenumber (cm^{-1}). The nuclear magnetic resonance (NMR) spectra were recorded on α-JEOL 400, Varian UNITY 300 and JEOL JNM-ECA 300 instruments. The spectral settings for the proton (^1H) NMR were as follows: 8.0 kHz spectral width, 32768 data points, 4.10 sec acquisition time, 0.24 Hz digital resolution for the α-JEOL 400; 4.5 kHz spectral width, 64000 data points, 7.11 sec acquisition time, 0.14 Hz digital resolution for the Varian UNITY 300; and 5.6 kHz spectral width, 32768 data points,

5.81 sec acquisition time, 0.17 Hz digital resolution for the JEOL JNM-ECA 300. Chemical shifts of the NMR spectra are reported in δ units downfield from tetramethylsilane. The ^{1}H NMR data are indicated by a chemical shift with the multiplicity, the coupling constants, the integration, and the assignment in parentheses in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra and the number of carbons in parentheses. When the number of carbons could not be analyzed due to heavy overlapping, the number is not indicated. High-resolution mass spectra (HRMS) were obtained on either JEOL JMS-T100LC or a JEOL JMS-700 spectrometer for electrospray ionization (ESI) or fast atom bombardment ionization (FAB) and are reported in units of mass to charge.

4.2. Preparation of the 3,4-bis-*O*-silylated *myo*-inositol derivatives

4.2.1. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (11). NaH (60% in oil, 180 mg, 4.50 mmol) was added to a stirring solution of 5,6-di-*O*-benzyl-3,4-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**7**)[8] (900 mg, 1.50 mmol) in DMF (5 mL) at room temperature. After stirring for 2 h at room temperature, BnBr (769 mg, 4.50 mmol) was added. After stirring for 10 h at room temperature, the reaction was quenched with saturated NH_4Cl (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was successively washed with water and brine. The combined organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (30 g of SiO_2 eluted with hexane/AcOEt=100/0 to 6/1) to give **11** (791 mg, 68%) as a white powder. mp. 96–98 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3100, 3080, 3030, 2913, 2838, 1615, 1514, 1454, 1358, 1250, 1096, 1036, 824, 733, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.19 (m, 24H), 6.87–6.78 (m, 4H), 4.90 (d, J=10.8 Hz, 1H), 4.87 (s, 4H), 4.83 (d, J=10.5 Hz, 1H), 4.81 (d, J=10.5 Hz, 1H), 4.74 (d, J=10.2 Hz, 1H), 4.65 (d, J=11.7 Hz, 1H), 4.62 (d, J=6.3 Hz, 1H), 4.56 (d, J=4.8 Hz, 1H), 4.53 (d, J=11.1 Hz, 1H), 4.07 (dd, J=9.6, 9.6 Hz, 1H), 4.05 (dd, J=9.6, 9.6 Hz, 1H), 4.00 (dd, J=2.1, 2.1 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.45 (dd, J=9.3, 9.3 Hz, 1H), 3.34 (dd, J=9.9, 2.1 Hz, 1H), 3.32 (dd, J=9.9, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0 (s, 1C), 138.9 (s, 1C), 138.4 (s, 1C), 131.1 (s, 1C), 130.5 (s, 1C), 129.7 (d), 129.1 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 113.7 (d, 4C), 83.7 (d, 1C), 81.7 (d, 1C), 81.4 (d, 1C), 80.9 (d, 1C), 80.7 (d, 1C), 75.8 (t, 1C), 75.5 (t, 1C), 74.4 (d, 1C), 74.1 (t, 1C), 72.7 (t, 1C), 72.4 (t, 1C), 55.2 (q, 2C); HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{50}H_{52}NaO_8$, 803.3560; found, 830.3563.

4.2.2. 1,2,5,6-tetra-*O*-Benzyl-*myo*-inositol (8). DDQ (1.05 g, 4.66 mmol) was added to a stirring solution of **11** (1.66 g, 2.12 mmol) in CH_2Cl_2/H_2O (17/1, 20 mL) at room temperature. After stirring for 45 min at room temperature, the reaction mixture was filtered through a cotton-Celite pad and evaporated. The resulting residue was purified by silica gel chromatography (75 g of SiO_2 eluted with hexane/AcOEt=2/1 to 1/1) to give **8** (885 mg, 77%) as a white powder. mp. 162–164 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3387, 3100, 3080, 3040, 2909, 2890, 1453, 1445, 1354, 1132, 1049, 1026, 727, 694; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.40–7.08 (m, 20H), 4.97 (d, J=11.7 Hz, 2H), 4.94 (d, J=11.1 Hz, 1H), 4.85 (d, J=11.7 Hz, 1H), 4.81 (d, J=11.1 Hz, 1H), 4.74 (d, J=11.7 Hz, 1H), 4.42 (d, J=12.3 Hz, 1H), 4.37 (d, J=12.0 Hz, 1H), 4.15 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.92 (dd, J=9.3, 9.3 Hz, 1H, H-4), 3.84 (dd, J=2.4, 2.1 Hz, 1H, H-2), 3.27 (dd, J=9.3, 9.3 Hz, 1H, H-5), 3.18 (dd, J=9.6, 2.1 Hz, 1H, H-1), 3.15 (dd, J=9.3, 2.4 Hz, 1H, H-3), 2.17 (br, 1H), 2.10 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6 (s, 3C), 138.1 (s, 1C), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.6 (d), 83.0 (d, 1C), 81.4 (d, 1C), 81.3 (d, 1C), 77.2 (d, 1C), 75.7 (t, 1C), 75.4 (t, 1C), 74.8 (t, 1C), 73.9 (d, 1C), 73.1 (t, 1C), 72.1 (d, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{34}H_{37}O_6$, 541.2590; found, 541.2583.

4.2.3. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (1p). TBSOTf (176 mg, 0.665 mmol) was added to a stirring solution of **8** (90 mg, 0.17 mmol) and 2,6-lutidine (356 mg, 3.33 mmol) in DMF (2 mL). After stirring for 1 h at 100 °C, the reaction mixture was cooled to room temperature and diluted with hexane. The mixture was successively washed with water and brine. The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (5 g of SiO_2 eluted with hexane/AcOEt=100/0 to 50/1) to give **1p** (120 mg, 94%) as colorless syrup. IR (NaCl, thin film) ν_{max} (cm^{-1}) 3034, 2930, 2859, 1726, 1456, 1360, 1256, 1130, 1069, 839, 777, 735, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.17 (m, 20H), 5.00–4.64 (m, 8H), 4.11 (dd, J=9.3, 9.0 Hz, 1H, H-4), 4.05 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.85 (dd, J=2.1, 2.1 Hz, 1H, H-2), 3.44 (dd, J=9.6, 2.1 Hz, 1H, H-1), 3.43 (dd, J=9.3, 2.1 Hz, 1H, H-3), 3.25 (dd, J=9.3, 9.0 Hz, 1H, H-5), 0.91 (s, 9H), 0.89 (s, 9H), 0.10–0.00 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0 (s, 1C), 139.4 (s, 1C), 138.9 (s, 1C), 138.5 (s, 1C), 128.4 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.3 (d), 127.1 (d), 127.0 (d), 126.7 (d), 84.3 (d, 1C), 82.6 (d, 1C), 80.9 (d, 1C), 80.2 (d, 1C), 75.7 (t, 1C), 75.2 (t, 1C), 74.6 (t, 1C), 74.5 (d, 1C), 73.2 (d, 1C), 72.8 (t, 1C), 26.5 (q, 6C), 18.4 (s, 2C), 18.1 (s, 1C), −2.9 (q, 1C), −3.6 (q, 1C), −3.7 (q, 1C), −4.2 (q, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{46}H_{65}O_6Si_2$, 769.4320; found, 769.4341.

4.2.4. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-triisopropylsilyl-*myo*-inositol (2p). TIPSOTf (138 mg, 0.450 mmol) was added to a stirring solution of **8** (50 mg, 0.090 mmol) in 2,6-lutidine (248 mg, 2.32 mmol) at 100 °C. After stirring for 12 h at 100 °C, the reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2 (10 mL). The mixture was successively washed with water (3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (15 g of SiO_2 eluted with hexane/AcOEt=100/0 to 30/1) to give **2p** (65 mg, 83%) as colorless syrup. IR (KBr, disk) ν_{max} (cm^{-1}) 3090, 3060, 3020, 2946, 2866, 1458, 1130, 1090, 1065, 1026, 883, 735, 685; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.13 (m, 20H), 5.13 (d, J=11.7 Hz, 1H), 5.08 (d,

J=12.0 Hz, 1H), 4.88 (d, J=10.5 Hz, 1H), 4.74 (d, J=12.0 Hz, 1H), 4.73 (d, J=12.0 Hz, 1H), 4.68 (d, J=12.3 Hz, 1H), 4.66 (d, J=12.0 Hz, 1H), 4.61 (d, J=10.5 Hz, 1H), 4.34 (dd, J=9.3, 8.7 Hz, 1H, H-4), 4.06 (dd, J=9.3, 9.0 Hz, 1H, H-6), 3.95 (dd, J=2.4, 1.8 Hz, 1H, H-2), 3.66 (dd, J=9.3, 1.8 Hz, 1H, H-1), 3.48 (dd, J=9.3, 2.4 Hz, 1H, H-3), 3.27 (dd, J=9.0, 8.7 Hz, 1H, H-5), 1.08–0.99 (m, 42H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.6 (s, 1C), 139.5 (s, 1C), 138.7 (s, 1C), 138.4 (s, 1C), 128.4 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.4 (d), 127.0 (d), 126.8 (d), 126.7 (d), 126.3 (d), 84.2 (d, 1C), 83.3 (d, 1C), 81.6 (d, 1C), 79.4 (d, 1C), 75.4 (t, 1C), 74.5 (d, 1C), 74.1 (t, 1C), 73.9 (d, 1C), 73.7 (t, 1C), 72.8 (t, 1C), 18.5 (q, 3C), 18.4 (q, 9C), 13.8 (d, 6C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{52}H_{77}O_6Si_2$, 853.5259; found, 853.5245.

4.2.5. 1,2,5,6-tetra-*O*-Benzyl-3,4-bis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol (3p). TBDPSOTf (144 mg, 0.371 mmol) was added to a stirring solution of **8** (45 mg, 0.083 mmol) in 2,6-lutidine (178 mg, 1.66 mmol) at 100 °C. After stirring for 7 h at 100 °C, the reaction mixture was cooled to room temperature, and then water (5 mL) was added. The aqueous mixture was extracted with hexane (3× 5 mL). The organic layer was successively washed with water (3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=80/1 to 40/1) to give **3p** (72 mg, 85%) as colorless syrup. IR (KBr, disk) ν_{max} (cm^{-1}) 3069, 3050, 3030, 2932, 2859, 1427, 1360, 1113, 824, 737, 696; ^{1}H NMR (C_6D_6, 300 MHz) δ 8.10–6.65 (m, 40H), 5.03 (dd, J=8.4, 8.1 Hz, 1H, H-4), 4.80 (d, J=12.0 Hz, 1H), 4.73 (d, J=12.0 Hz, 1H), 4.71 (d, J=12.0 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 4.17 (d, J=11.4 Hz, 1H), 4.14 (dd, J=8.4, 1.8 Hz, 1H, H-3), 4.10 (d, J=12.0 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 4.00 (dd, J=8.7, 8.4 Hz, 1H, H-6), 3.96 (d, J=11.7 Hz, 1H), 3.58 (dd, J=3.0, 1.8 Hz, 1H, H-2), 3.46 (dd, J=8.4, 8.1 Hz, 1H, H-5), 3.13 (dd, J=8.7, 3.0 Hz, 1H, H-1), 1.27 (s, 9H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.4 (s, 1C), 139.3 (s, 1C), 138.7 (s, 1C), 138.4 (s, 1C), 136.3 (d, 1C), 136.2 (d, 1C), 135.9 (d, 1C), 135.8 (d, 1C), 135.2 (s, 1C), 135.1 (s, 1C), 133.6 (s, 1C), 133.5 (s, 1C), 129.8 (d), 129.6 (d), 129.0 (d), 128.9 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.2 (d), 127.1 (d), 127.0 (d), 126.7 (d), 126.6 (d), 126.2 (d), 83.7 (d, 1C), 82.6 (d, 1C), 81.3 (d, 1C), 75.9 (d, 1C), 74.7 (d, 1C), 74.6 (d, 1C), 74.5 (t, 1C), 72.7 (t, 1C), 72.3 (t, 1C), 71.9 (t, 1C), 27.5 (q, 3C), 27.2 (q, 3C), 19.9 (s, 1C), 19.2 (s, 1C); HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{66}H_{73}O_6Si_2$, 1017.4946; found, 1017.4961.

4.2.6. 3,4-bis-*O*-*tert*-Butyldimethylsilyl-*myo*-inositol (1).[12] $Pd(OH)_2$ on C (20 wt %, 329 mg, 0.470 mmol) was added to a stirring solution of **1p** (120 mg, 0.160 mmol) in THF (1 mL). The atmosphere of the flask was replaced with H_2, and the mixture was stirred for 15 days under H_2. The reaction mixture was filtered through a cotton-Celite pad, and the filtrate was evaporated. The resulting residue was purified by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=1/1) to give **1** (7.9 mg, 12%) as a white powder. mp. 94–97 °C; IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3574, 3214, 2924, 2884, 2855, 2361, 1643, 1472, 1373, 1256, 1132, 1065, 1018, 860, 835, 777, 721, 669; ^{1}H NMR (400 MHz, CD_3CN) δ 3.87 (dd, J=2.9, 2.7 Hz, 1H, H-2), 3.70 (dd, J=9.0, 8.8 Hz, 1H, H-6), 3.51 (dd, J=9.0, 2.7 Hz, 1H, H-1), 3.47 (dd, J=9.5, 9.2 Hz, 1H, H-4), 3.30 (dd, J=9.5, 2.9 Hz, 1H, H-3), 3.05 (dd, J=9.2, 8.8 Hz, 1H, H-5), 0.91 (s, 9H), 0.90 (s, 9H), 0.11 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.2 (d, 1C), 75.3 (d, 1C), 75.1 (d, 1C), 74.2 (d, 1C), 74.1 (d, 1C), 72.6 (d, 1C), 26.7 (q, 2C), 26.6 (q, 4C), 19.0 (s, 1C), 18.9 (s, 1C), −2.8 (q, 1C), −3.3 (q, 1C), −3.5 (q, 1C), −4.2 (q, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{18}H_{41}O_6Si_2$, 409.2442; found, 409.2439.

4.2.7. 3,4-bis-*O*-Triisopropylsilyl-*myo*-inositol (2).[12] Same procedure as the debenzylation of **1p** was performed starting from **2p** (147 mg, 0.172 mmol) with $Pd(OH)_2$ on C (20 wt%, 363 mg, 0.517 mmol) in THF (1 mL). The reaction needed 17 days. Purification was performed by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=3/1 to 1/1) to give **2** (40 mg, 48%) as colorless syrup. IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3385, 2946, 2868, 2361, 2342, 1466, 1385, 1256, 1121, 1059, 1015, 943, 920, 883, 829, 806, 712, 681, 652; ^{1}H NMR (400 MHz, CD_3CN) δ 3.94 (dd, J=8.1, 8.1 Hz, 1H, H-4), 3.93 (dd, J=2.9, 2.9 Hz, 1H, H-2), 3.77 (dd, J=8.1, 2.9 Hz, 1H, H-3), 3.54 (dd, J=8.5, 8.5 Hz, 1H, H-6), 3.36 (dd, J=8.5, 2.9 Hz, 1H, H-1), 3.20 (dd, J=8.5, 8.1 Hz, 1H, H-5), 1.26–1.08 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.2 (d, 1C), 75.0 (d, 1C), 73.7 (d, 1C), 73.6 (d, 1C), 73.1(d, 1C), 69.5 (d, 1C), 18.4 (q, 4C), 18.3 (q, 8C), 13.2 (d, 3C), 13.1 (d, 3C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{24}H_{53}O_6Si_2$, 493.3381; found, 493.3383.

4.2.8. 3,4-bis-*O*-*tert*-Butyldiphenylsilyl-*myo*-inositol (3).[12] Same procedure as the debenzylation of **1p** was performed starting from **3p** (347 mg, 0.340 mmol) with $Pd(OH)_2$ on C (20 wt%, 719 mg, 1.00 mmol) in THF (2 mL). The reaction needed 8 days. Purification was performed by silica gel chromatography (20 g of SiO_2 eluted with hexane/AcOEt=4/1 to 2/1) to give **3** (52 mg, 23%) as colorless syrup along with 2-*O*-benzyl-3,4-bis-*O*-TBDPS-*myo*-inositol (54 mg, 24%) as pale yellow syrup. Data for **3**: IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3418, 3073, 3050, 2932, 2892, 2859, 1472, 1427, 1113, 1061, 1006, 939, 826, 741, 704; ^{1}H NMR (400 MHz in CD_3CN) δ 7.75–7.66 (m, 8H), 7.45–7.35 (m, 12H), 4.17 (dd, J=7.4, 7.2 Hz, 1H, H-4), 4.14 (dd, J=7.4, 2.7 Hz, 1H, H-3), 3.66 (dd, J=2.8, 2.7 Hz, 1H, H-2), 3.46 (dd, J=7.9, 7.6 Hz, 1H, H-6), 3.33 (dd, J=7.6, 7.2 Hz, 1H, H-5), 3.28 (dd, J=7.9, 2.8 Hz, 1H, H-1), 1.03 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 136.0 (d, 2C), 135.9 (d, 2C), 135.7 (d, 2C), 135.4 (d, 2C), 133.3 (s, 1C), 132.9 (s, 1C), 138.2 (s, 1C), 132.5 (s, 1C), 130.1 (d, 1C), 130.0 (d, 2C), 129.9 (d, 1C), 127.9 (d, 4C), 127.8 (d, 2C), 127.7 (d, 2C), 75.5 (d, 1C), 75.1 (d, 1C), 73.1 (d, 1C), 73.0 (d, 1C), 72.9 (d, 1C), 67.7 (d, 1C), 27.1 (q, 6C), 19.2 (s, 2C); HRMS-FAB (m/z) $[M+Na]^+$ calcd for $C_{38}H_{48}NaO_6Si_2$, 679.2887; found, 679.2886. Data for 2-*O*-benzyl-3,4-bis-*O*-TBDPS-*myo*-inositol: IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3445, 3073, 3050, 2932, 2894, 2859, 1723, 1472, 1428, 1393, 1271, 1111, 1061, 1007, 824, 758, 704, 611; ^{1}H NMR (400 MHz, CD_3CN) δ 7.72–7.63 (m, 8H), 7.45–7.25 (m, 17H), 4.51 (d, J=12.2 Hz, 1H), 4.38 (d, J=12.2 Hz, 1H), 4.33 (dd, J=6.3, 6.3 Hz, 1H, H-4), 4.21 (dd,

J=6.3, 1.5 Hz, 1H, H-3), 3.62–3.56 (br m, 2H, H-1, H-6), 3.52 (br s, 1H, H-2), 3.45 (br m, 1H, H-5), 1.02 (s, 9H), 0.93 (s, 9H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 137.6 (s, 1C), 136.5 (d), 136.2 (d), 136.0 (d), 135.5 (d), 133.0 (s, 1C), 132.0 (s, 1C), 131.9 (s, 1C), 131.8 (s, 1C), 130.1 (d), 129.8 (d), 129.6 (d), 128.3 (d), 127.9 (d), 127.8 (d), 127.7 (d), 127.5 (d), 127.4 (d), 74.7 (d, 1C), 73.5 (d, 1C), 73.1 (d, 2C), 71.6 (d, 2C), 70.4 (t, 1C), 27.0 (q, 3C), 26.8 (q, 3C), 19.0 (s, 1C), 18.9 (s, 1C); HRMS-ESI (*m/z*) $[M+Na]^+$ calcd for $C_{45}H_{54}NaO_6Si_2$, 769.3357; found 769.3327.

4.3. Preparation of the 4,5-bis-*O*-silylated *myo*-inositol derivatives

4.3.1. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (12).[12] NaH (60% in oil, 190 mg, 4.74 mmol) was added to a stirring solution of 3,6-di-*O*-benzyl-4,5-bis-*O*-(4-methoxybenzyl)-*myo*-inositol (**9**)[11] (950 mg, 1.58 mmol) in DMF (5 mL) at room temperature. After stirring for 2 h at room temperature, BnBr (811 mg, 4.74 mmol) was added. After stirring for 5 h at room temperature, the reaction was quenched with saturated NH_4Cl (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was successively washed with water (5 mL), and brine (5 mL). The combined organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (30 g of SiO_2 eluted with hexane/AcOEt=100/1 to 4/1) to give **12** (1.21 g, 98%) as a white powder. mp. 76–78 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3100, 3070, 3030, 3005, 2920, 1615, 1514, 1454, 1360, 1252, 1173, 1130, 1092, 1038, 822, 739, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.25 (m, 26H), 6.84–6.81 (m, 4H), 4.92–4.57 (m, 12H), 4.09–4.01 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.44 (dd, J=9.3, 9.3 Hz, 1H), 3.34 (dd, J=9.3, 9.3 Hz, 1H), 3.33 (dd, J=9.9, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1 (s, 1C), 139.0 (s, 1C), 138.4 (s, 1C), 131.1 (s, 1C), 129.7 (d), 129.4 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.3 (d), 113.8 (d, 8C), 83.5 (d, 1C), 81.8 (d, 1C), 81.5 (d, 1C), 81.0 (d, 2C), 75.8 (t, 1C), 75.6 (t, 1C), 75.5 (t, 1C), 74.4 (d, 1C), 74.1 (t, 1C), 72.8 (t, 2C), 55.3 (q, 2C); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{50}H_{52}NaO_8$, 803.3560; found, 803.3544.

4.3.2. 1,2,3,6-tetra-*O*-Benzyl-*myo*-inositol (10).[12] DDQ (2.67 g, 11.8 mmol) was added to a stirring solution of **22** (4.18 g, 5.35 mmol) in CH_2Cl_2/H_2O (17/1, 50 mL) at room temperature. After stirring for 6 h at room temperature, the reaction mixture was filtered through a cotton-Celite pad. The mixture was diluted with CH_2Cl_2 (100 mL) and successively washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (120 g of SiO_2 eluted with hexane/AcOEt=6/1 to 1/1) to give **10** (2.37 g, 82%) as a white powder. mp. 83–85 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3549, 3422, 3063, 3030, 2899, 1454, 1364, 1200, 1115, 1063, 1030, 731, 696; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.48–7.08 (m, 20H), 4.93 (d, J=11.4 Hz, 1H), 4.90 (d, J=12.3 Hz, 1H), 4.85 (d, J=11.4 Hz, 1H), 4.83 (d, J=12.3 Hz, 1H), 4.50 (d, J=12.0 Hz, 1H), 4.44 (s, 2H), 4.42 (d, J=12.0 Hz, 1H), 4.21 (dd, J=9.6, 9.3 Hz, 1H, H-4), 4.09 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.92 (dd, J=2.4, 2.4 Hz, 1H, H-2), 3.46 (dd, J=9.3, 9.3 Hz, 1H, H-5), 3.17 (dd, J=9.6, 2.4 Hz, 1H, H-1), 3.00 (dd, J=9.6, 2.4 Hz, 1H, H-3); ^{13}C NMR (C_6D_6, 100 MHz) δ 140.8 (s, 1C), 139.7 (s, 1C), 139.2 (s, 2C), 128.7 (d), 128.6 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.5 (d), 81.7 (d, 1C), 81.2 (d, 1C), 80.5 (d, 1C), 75.9 (d, 1C), 75.6 (t, 1C), 75.3 (d, 1C), 74.7 (t, 1C), 73.6 (d, 1C), 72.9 (t, 1C), 72.7 (t, 1C); HRMS-FAB (*m/z*) $[M+H]^+$ calcd for $C_{34}H_{37}O_6$, 541.2590; found, 541.2617.

4.3.3. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (4p). TBSOTf (119 mg, 0.448 mmol) was added to a stirring solution of **10** (50 mg, 0.092 mmol) in 2,6-lutidine (248 mg, 2.32 mmol) at 120 °C. After stirring for 10 h at 120 °C, the reaction mixture was cooled to room temperature. Then the mixture was diluted with water (10 mL). The aqueous mixture was extracted with hexane (3×5 mL) and successively washed with water (3 mL) and brine (3 mL). Then it was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (6 g of SiO_2 eluted with hexane/AcOEt=100/0 to 30/1) to give **4p** (74 mg, 100%) as colorless syrup. IR (NaCl, thin film) ν_{max} (cm^{-1}) 3090, 3060, 3020, 2930, 2857, 1721, 1456, 1362, 1258, 1128, 1071, 1028, 839, 775, 735, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.19 (m, 20H), 5.01 (d, J=11.7 Hz, 1H), 4.81 (d, J=11.7 Hz, 1H), 4.76 (d, J=11.7 Hz, 1H), 4.66 (d, J=11.7 Hz, 1H), 4.60 (d, J=12.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 2H), 4.48 (d, J=11.7 Hz, 1H), 4.11 (dd, J=9.6, 8.7 Hz, 1H, H-4), 3.93 (dd, J=2.4, 2.1 Hz, 1H, H-2), 3.78 (dd, J=9.6, 9.3 Hz, 1H, H-6), 3.43 (dd, J=9.3, 8.7 Hz, 1H, H-5), 3.35 (dd, J=9.6, 2.4 Hz, 1H, H-1), 3.11 (dd, J=9.6, 2.1 Hz, 1H, H-3), 0.89 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.10 (s, 6H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.6 (s, 1C), 139.4 (s, 1C), 138.3 (s, 1C), 138.2 (s, 1C), 128.2 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.0 (d), 126.7 (d), 81.7 (t, 1C), 81.5 (t, 1C), 81.3 (t, 1C), 74.8 (t, 1C), 74.3 (t, 1C), 74.1 (d, 1C), 73.1 (d, 1C), 72.7 (t, 1C), 72.4 (t, 1C), 26.7 (q, 6C), 18.3 (s, 1C), 18.2 (s, 1C), −1.9 (q, 1C), −2.1 (q, 1C), −3.0 (q, 1C), −3.1 (q, 1C); HRMS-FAB (*m/z*) $[M+H]^+$ calcd for $C_{46}H_{65}O_6Si_2$, 769.4320; found, 769.4324.

4.3.4. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-triisopropylsilyl-*myo*-inositol (5p). TIPSOTf (138 mg, 0.450 mmol) was added to a stirring solution of **10** (50 mg, 0.090 mmol) in 2,6-lutidine (248 mg, 2.32 mmol) at 100 °C. After stirring for 12 h at 100 °C, the reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2 (10 mL). It was successively washed with water (3 mL), and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was purified by silica gel chromatography (15 g of SiO_2 eluted with hexane/AcOEt=100/0 to 30/1) to give **5p** (71 mg, 90%) as a white powder. mp. 80–81 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3030, 3000, 2942, 2865, 1638, 1458, 1355, 1127, 1086, 885, 720, 696, 670; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.22 (m, 20H), 5.15 (d, J=12.3 Hz, 1H), 4.82 (d, J=12.3 Hz, 1H), 4.60 (d, J=12.0 Hz, 3H), 4.56 (d, J=11.4 Hz, 1H), 4.48 (d, J=11.4 Hz, 1H), 4.40 (d, J=11.7 Hz, 1H), 4.23 (dd, J=8.4, 7.8 Hz, 1H, H-4), 4.09 (dd, J=2.4, 2.4 Hz, 1H, H-2), 3.88 (dd, J=9.0, 7.8 Hz, 1H,

H-6), 3.68 (dd, J=7.8, 7.8 Hz, 1H, H-5), 3.51 (dd, J=9.0, 2.4 Hz, 1H, H-1), 3.26 (dd, J=8.4, 2.4 Hz, 1H, H-3), 1.13–1.00 (m, 42H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.8 (s, 1C), 139.3 (s, 1C), 138.3 (s, 1C), 138.2 (s, 1C), 128.3 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.2 (d), 127.1 (d), 126.7 (d), 126.5 (d), 82.0 (d, 1C), 81.4 (d, 1C), 81.3 (d, 1C), 76.8 (d, 1C), 74.8 (d, 1C), 73.7 (t, 1C), 73.4 (t, 1C), 72.9 (d, 1C), 72.3 (t, 1C), 71.2 (t, 1C), 18.6 (q, 3C), 18.5 (q, 3C), 18.4 (q, 3C), 18.3 (q, 3C), 13.9 (d, 3C), 13.8 (d, 3C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{52}H_{77}O_6Si_2$, 852.5229; found, 853.5247.

4.3.5. 1,2,3,6-tetra-*O*-Benzyl-4,5-bis-*O*-*tert*-butyldiphenylsilyl-*myo*-inositol (6p). TBDPSOTf (86 mg, 0.22 mmol) was added to a stirring solution of **10** (30 mg, 0.055 mmol) and 2,6-lutidine (118 mg, 1.10 mmol) in DMF (0.5 mL) at 100 °C. After stirring for 1.5 h at 100 °C, the reaction mixture was cooled to room temperature. Water (5 mL) was added and the aqueous mixture was extracted with hexane (3×5 mL). The organic layer was successively washed with water (3 mL) and brine (3 mL). Then it was dried over $MgSO_4$, filtered through a cotton-pad, and evaporated. The resulting residue was successively purified by silica gel chromatography (3 g of SiO_2 eluted with hexane/AcOEt=100/0 to 10/1) and by a reverse phase chromatography (6 g of cosmosil 140C18-PREP eluted with MeOH) to give **6p** (70 mg, 100%) as a white powder. The single crystal used for the X-ray diffraction study was obtained by cooling the hot solution of **6p** in EtOH. mp 115.0–117.0 °C; IR (KBr, disk) ν_{max} (cm^{-1}) 3060, 2920, 2857, 1142, 1117, 1057, 815, 790, 737, 698; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.84–7.05 (m, 40H), 4.78 (ddd, J=3.6, 3.3, 1.2 Hz, 1H, H-4), 4.73 (d, J=11.7 Hz, 1H), 4.59 (d, J=12.3 Hz, 1H), 4.58 (d, J=11.7 Hz, 1H), 4.54 (dd, J=3.6, 3.3 Hz, 1H, H-5), 4.53 (d, J=12.3 Hz, 1H), 4.25 (d, J=12.0 Hz, 1H), 4.23 (d, J=12.3 Hz, 1H), 4.23 (dd, J=3.6, 2.7 Hz, 1H, H-2), 4.15 (ddd, J=4.8, 3.6, 1.2 Hz, 1H, H-6), 4.03 (d, J=12.0 Hz, 1H), 4.02 (d, J=12.3 Hz, 1H), 3.98 (dd, J=4.8, 2.7 Hz, 1H, H-1), 3.76 (dd, J=3.6, 3.6 Hz, 1H, H-3), 1.06 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2 (s, 1C), 139.1 (s, 1C), 134.1 (s, 1C), 134.0 (s, 1C), 129.5 (d), 129.4 (d), 129.3 (d), 129.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.1 (d), 127.0 (d), 126.9 (d), 126.6 (d), 81.1 (d, 1C), 79.1 (d, 1C), 78.2 (d, 1C), 74.6 (d, 1C), 74.4 (d, 1C), 73.9 (d, 1C), 72.6 (t, 1C), 71.8 (t, 1C), 71.7 (t, 1C), 71.1 (t, 1C), 26.8 (q, 6C), 19.3 (s, 1C), 19.1 (s, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{66}H_{73}O_6Si_2$, 1017.4946; found, 1017.4959.

4.3.6. 4,5-bis-*O*-*tert*-Butyldimetylsilyl-*myo*-inositol (4). Same procedure as the debenzylation of **1p** was performed starting from **4p** (720 mg, 0.940 mmol) with $Pd(OH)_2$ on C (20 wt%, 1.97 g, 2.80 mmol) in THF (5 mL). The reaction needed 4 days under 100 atm of H_2 at room temperature. Purification was performed by silica gel chromatography (25 g of SiO_2 eluted with hexane/AcOEt=4/1 to 1/1) to give **4** (118 mg, 31%) as a white powder. mp. 121–123 °C; IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3445, 2932, 2859, 1472, 1389, 1254, 1117, 1053, 937, 837, 777, 692; ^{1}H NMR (400 MHz in CD_3CN) δ 3.86 (dd, J=3.4, 3.4 Hz, 1H, H-2), 3.79 (dd, J=7.2, 7.1 Hz, 1H, H-4), 3.63 (dd, J=7.4, 3.4 Hz, 1H, H-1), 3.62 (dd, J=7.2, 3.4 Hz, 1H, H-3), 3.57 (dd, J=7.4, 7.1 Hz, 1H, H-6), 3.49 (dd, J=7.1, 7.1 Hz, 1H, H-5), 0.91 (s, 18H), 0.12–0.11 (m, 12H); ^{13}C NMR (100 MHz in $CDCl_3$) δ 74.3 (d, 1C), 73.8 (d, 1C), 73.7 (d, 1C), 73.6 (d, 1C), 72.3 (d, 1C), 65.6 (d, 1C), 25.7 (q, 6C), 17.9 (s, 1C), 17.8 (s, 1C), −4.8 (q, 1C), −4.9 (q, 2C), −5.0 (q, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{18}H_{41}O_6Si_2$, 409.2442; found, 409.2449.

4.3.7. 4,5-bis-*O*-Triisopropylsilyl-*myo*-inositol (5). Same procedure as the debenzylation of **1p** was performed starting from **5p** (43 mg, 0.050 mmol) with $Pd(OH)_2$ on C (20 wt%, 106 mg, 0.150 mmol) in THF (1 mL). The reaction needed 11 days. Purification was performed by silica gel chromatography (6 g of SiO_2 eluted with hexane/AcOEt=6/1 to 4/1) to give **5** (8.5 mg, 35%) as a white powder. mp. 86–88 °C; IR (ZnSe, thin film) ν_{max} (cm^{-1}) 3420, 2943, 2868, 2361, 2339, 1464, 1385, 1256, 1061, 883, 825, 764, 683; ^{1}H NMR (400 MHz, CD_3CN) δ 4.27 (ddd, J=3.9, 3.7, 1.7 Hz, 1H, H-4), 4.02 (dddd, J=3.9, 3.8, 1.0, 0.9 Hz, 1H, H-5), 3.96 (ddd, J=3.8, 3.6, 1.7 Hz, 1H, H-6), 3.94 (dd, J=3.4, 3.4 Hz, 1H, H-2), 3.83 (ddd, J=3.7, 3.4, 0.7 Hz, 1H, H-3), 3.80 (ddd, J=3.6, 3.4, 1.0 Hz, 1H, H-1), 1.25–1.10 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.8 (d, 1C), 74.2 (d, 1C), 74.0 (d, 2C), 72.2 (d, 1C), 64.8 (d, 1C), 18.1 (q, 6C), 18.0 (q, 6C), 12.2 (d, 6C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{24}H_{53}O_6Si_2$, 493.3381; found, 493.3384.

4.3.8. 4,5-bis-*O*-*tert*-Butyldiphenylsilyl-*myo*-inositol (6). Same procedure as the debenzylation of **1p** was performed starting from **6p** (490 mg, 0.480 mmol) with $Pd(OH)_2$ on C (20 wt%, 203 mg, 0.290 mmol) in THF (5 mL). The reaction needed 9.5 days. Purification was performed by silica gel chromatography (15 g of SiO_2 eluted with hexane/AcOEt=4/1 to 3/1) to give **6** (149 mg, 50%) as a white powder. mp. 58–61 °C; IR (NaCl, thin film) ν_{max} (cm^{-1}) 3517, 3073, 2930, 2859, 1472, 1427, 1113, 820, 748, 694; ^{1}H NMR (CD_3CN, 300 MHz) δ 7.62–7.58 (m, 2H), 7.53–7.32 (m, 14H), 7.28–7.22 (m, 4H), 4.18 (ddd, J=3.6, 3.3, 1.8 Hz, 1H, H-4), 4.05 (dddd, J=3.3, 3.3, 0.9, 0.9 Hz, 1H, H-5), 4.00 (dd, J=3.3, 3.3 Hz, 1H, H-2), 3.95 (ddd, J=3.6, 3.3, 1.8 Hz, 1H, H-6), 3.84 (dd, J=3.6, 3.3 Hz, 1H, H-1), 3.59 (dd, J=3.6, 3.3 Hz, 1H, H-3), 0.90 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (CD_3CN, 100 MHz) δ 136.7 (d, 4C), 136.6 (d, 2C), 136.5 (d, 2C), 134.2 (s, 1C), 134.0 (s, 1C), 133.8 (s, 1C), 133.7 (s, 1C), 131.0 (d, 1C), 130.9 (d, 2C), 130.7 (d, 1C), 128.8 (d, 2C), 128.7 (d, 2C), 128.6 (d, 4C), 76.5 (d, 1C), 74.9 (d, 1C), 74.8 (d, 1C), 74.6 (d, 1C), 74.4 (d, 1C), 65.9 (d, 1C), 27.2 (q, 6C), 19.6 (s, 1C), 19.5 (s, 1C); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{38}H_{49}O_6Si_2$, 657.3068; found, 657.3039.

4.4. X-ray diffraction study of 6p

X-ray data for **6p** was measured on a MacScience dip image plate diffractometer using graphite-monochromated Mo Kα radiation (l=0.71073 Å). All diagrams and calculations were performed using maXus (Bruker Nonius, Delft & MacScience, Japan). The structure was solved by direct method with SIR-97[20] and refined by a full-matrix least-squares method on F2 with SHELXS-97.[21] Crystallographic data (excluding structure factors) for the structure of **6p** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC

227525. 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 of the analysis are follows: $C_{66}H_{72}O_6Si_2$, $M=1017.46$, crystal size $0.5\times0.3\times0.2$ mm, triclinic, space group $\bar{P}1$, $a=11.75$, $b=13.45$, $c=20.10$ Å, $\alpha=87.80$, $\beta=78.71$, $\gamma=66.80$ Å, $V=2862.55$ Å^3, $Z=2$, $D_{calcd}=1.180$ Mg/m^3, μ(Mo Kα)$=0.113$ mm^{-1}, measured temp. 298 K, reflections collected 9656, independent reflections 9085, $R=0.082$, $wR=0.224$, GOF$=1.164$.

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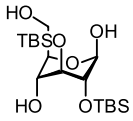

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Dipyridyl/pyridinium thieno[2,3-*b*]thiophenes as new atropisomeric systems. Synthesis, conformational analysis and energy minimization

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Abstract—Synthesis of a new class of cofacially oriented dipyridyl(pyridinium)lthieno[2,3-*b*]thiophenes with or without $-CO_2Et$ and –COMe substituents at C2, and C5 positions of thieno[2,3-*b*]thiophene ring was readily accomplished using a double Dieckman cyclization protocol as the key step. While C2/C5 substituted dipyridylthieno[2,3-*b*]thiophenes exhibited *syn*/*anti* atropisomerism at least up to 70 °C with Arrhenius energy of activation ($\Delta G^{\neq}$) in the range of 17–18 kcal/mol, on the other hand unsubstituted dipyridylthieno[2,3-*b*]thiophene and its bis-*N*-quaternized salt were found to show free conformational rotation with an estimated $\Delta G^{\neq}$ of lower than 10 kcal/mol. Conformational energy minimization using AM1 protocol revealed a slight preference for the *anti* over *syn* isomers. Compared to the unsubstituted dipyridylthieno[2,3-*b*]thiophenes, higher energy barriers to rotation (3.7–5.1 kcal/mol) in substituted dipyridylthieno[2,3-*b*]-thiophenes can be attributed to steric encumbrance resulting from $-CO_2Et$ and –COMe substituents located on the non-rotating thienothiophene platform.

1. Introduction

Conformational dynamics of cofacially oriented 1,8-diaryl naphthalenes is a subject of continuing interest ever since House[1] and Roberts[2] demonstrated the existence of *syn*/*anti* atropisomerism in these systems. The key structural features that have a bearing on the energy barriers to aryl–aryl rotation in various *peri*-diaryl(heteroaryl)naphthalenes include the nature of aryl/heteroaryl rings, transannular distance, location as well as the steric size of substituent(s) on the cofacial rings. While, *peri* di-substituted naphthalenes carrying simple aryl/heteroaryl rings without or with smaller substituents do not exhibit atropisomerism ($\Delta G^{\neq} <$ 15 kcal/mol), the introduction of bulkier substituents at the *ortho*/*meta* positions of the *peri* rings renders rotational barriers sufficiently high ($\Delta G^{\neq} > 15$ kcal/mol) to allow for the detection/isolation of chiral atropisomers.[3] In addition, in recent years, Siegel and several others have elegantly exploited conformationally locked *peri*-diaryl(heteroaryl)-naphthalenes to probe electrostatic, charge transfer and dipole–dipole interaction between the facing rings.[4] Also, torsional angles and hindered aryl–aryl rotation are of crucial revelance in the design of useful materials, for example, axially chiral catalysts,[5] non-linear optic materials,[6] molecular rotors and sensors.[7] Since, efficient synthetic routes to sterically congested *peri* diaryl-naphthalenes are generally tedious[1–3] we deemed it of interest to design newer, easily accessible systems that could deliver stable, axially chiral atropisomers. In this context, we entertained the idea that thieno[2,3-*b*]thiophene system, a 10π analog of naphthalene could also offer a useful platform to develop new atropisomeric systems by placing appropriate rings at the C3 and C4 positions. In continuation of our interest in the structural aspect of 3,4-diarylthienothiophenes,[8] we herein describe the synthesis, dynamic behavior and conformational energy minimization of a new class of atropisomeric systems, exemplified by neutral and ionic 3,4-dipyridyl thienothiophenes **2a–d**. In addition, we also compare the conformational properties of **2a–d** vis-à-vis known 1,8-dipyridyl naphthalenes to get insight into the structure–energy barrier relationship.

2. Results and discussion

Synthesis of **2a–d** (Scheme 1) was readily carried out using

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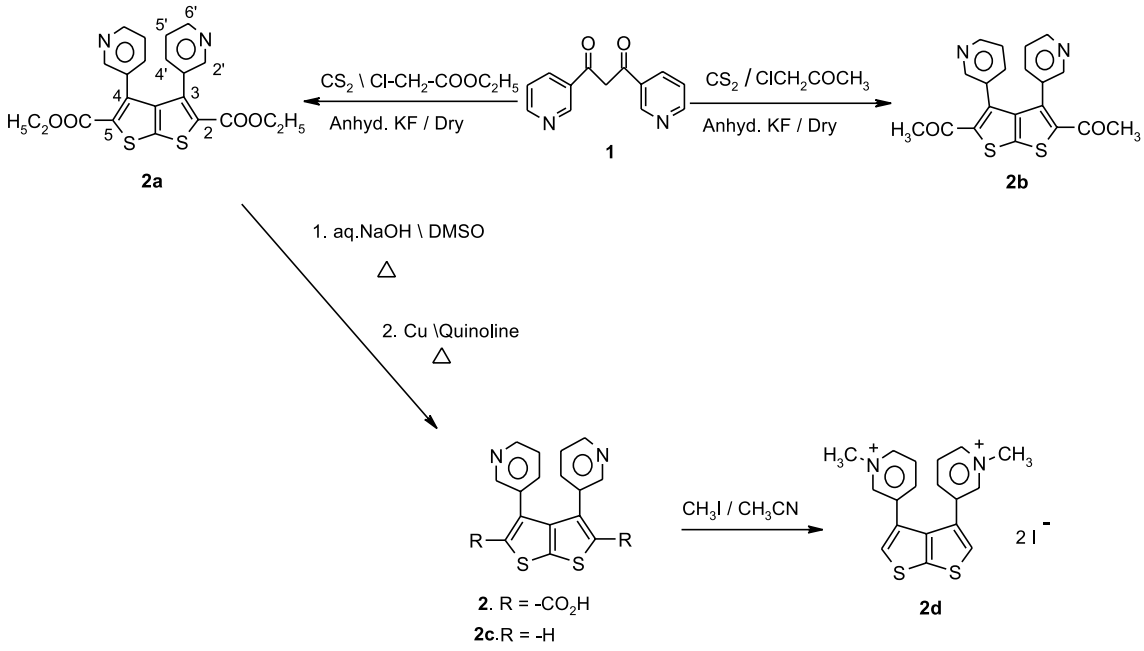


Scheme 1. Synthesis of thienothiophenes **2a–d**.

the double Dieckman type cyclization as the key step by adapting our recently described procedure.[9] The known dipyridyl diketone **1**[10] was condensed with CS_2 and 2 equiv ethyl chloroacetate under anhydrous KF/DMF conditions to afford dipyridyl thienothiophene diester **2a** in one step in an acceptable 28% yield. Similarly, dipyridyl thienothiophene methyl ketone **2b** was prepared in 32% yield by condensing **1** with CS_2 and 2 equiv of chloroacetone under KF/DMF conditions. Hydrolysis of **2a** with aq KOH in DMSO provided, after acidification, the diacid **2** which on decarboxylation (Cu/quinoline, reflux) provided dipyridyl thienothiophene **2c**. Finally, treatment of **2c** with an excess of CH_3I in dry acetonitrile afforded di-*N*-quaternized salt **2d** in almost quantitative yield.

The ^{1}H NMR spectral data for **2a–d** are compiled in Table 1. The proton assignments are based on chemical shifts, spin multiplicities and the expected ring anisotropic effects in *syn*/*anti* isomers. As expected, the pyridyl C4′, C5′ and C6′ protons appeared as ABX type coupling systems. The ambient temperature ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of thienothiophene diester **2a** consisted of two sets of resonances for the pyridyl protons in the ratio of 60:40. These correspond to two chemically non-equivalent ground states of **2a**, namely *syn* and *anti* forms arising from the restricted pyridyl ring rotation on the thienothiophene axis. For the known *peri* dipyridylnaphthalenes, C4′ and C5′ protons in the *anti* isomers are reported to experience a relatively higher ring anisotropic effect than the *syn* isomers.[11] Using this analogy, we have assigned the resonances located at higher fields for C4′ and C5′ protons to the major, *anti* isomers whereas those present at somewhat lower fields belong to the minor, *syn* isomers.

Dynamic ^{1}H NMR analysis of diester **2a** from rt down to −60 °C revealed practically no change in the *anti–syn* ratio. However, ^{1}H NMR spectra measured at higher temperatures (Fig. 1) led to coalescencing of signals around 70 °C giving rise to a single set of resonances due to fast pyridyl ring rotation on the NMR time scale. From $\Delta\nu$ of 54 Hz and the coalescence temperature of 343 K, we determined the rate of inversion (K) for diester **2a** to be 120 s^{-1} with an associated Arrhenius energy of activation ($\Delta G^{\neq}$) of 16.9 kcal/mol.[12] The ambient temperature ^{1}H NMR spectrum of diketone **2b** also exhibited two sets of well resolved NMR signals in 57:43 proportion corresponding to *anti* and

Table 1. ^{1}H NMR (500MHz, $CDCl_3$) of **2a-2d**

H-type	Ratio (60:40)[a]		Ratio (57:43)[a]		**2c**[b]	**2d**[b]
	anti-**2a**	*syn*-**2a**	*anti*-**2b**	*syn*-**2b**		
H-2′	8.20(s)	8.09(s)	8.35(s)	8.20(s)	8.28(s)	9.15(s)
H-4′	7.24(d)	7.35(d)	7.38(d)	7.48(d)	8.36(d)	8.89(d)
H-5′	6.91(dd)	7.00(dd)	7.05(dd)	7.07(dd)	7.08(dd)	7.78(dd)
H-6′	8.25(d)	8.25(d)	8.25(d)	8.31(d)	7.38(d)	8.08(d)
$-C_2H_5$	1.01(t), 4.08(q)	1.01(t), 4.08(q)	—	—	—	—
$-CH_3$	—	—	1.8	1.8	—	—
H2/5	—	—	—	—	7.70(s)	8.10(s)
–NMe	—	—	—	—	—	4.35(s)

[a] Ratio calculated from proton integration of well separated signals.
[b] Compounds **2c** and **2d** showed only a single set of resonances in their ambient temperature NMR spectra.

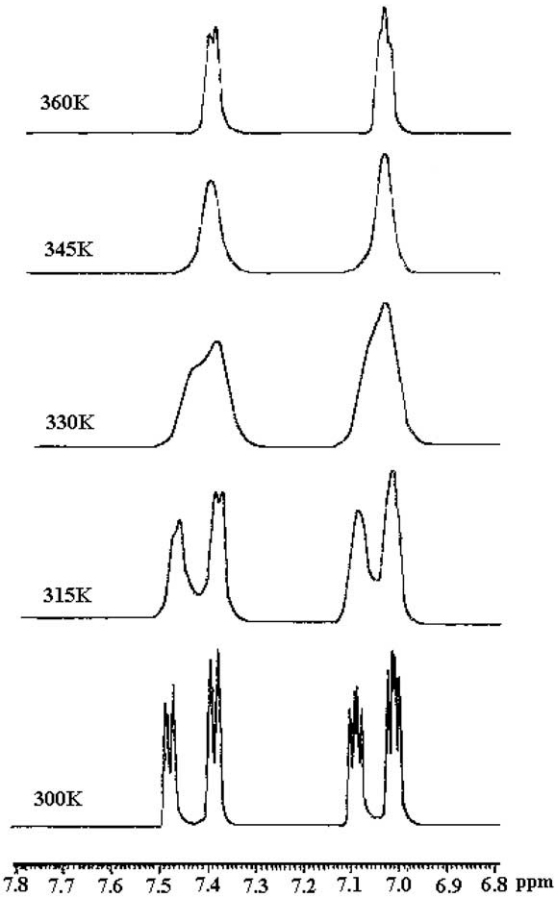


Figure 1. Dynamic ^{1}H NMR spectra of **2a**.

syn atropisomers. Dynamic ^{1}H NMR measurements on **2b** indicated coalescence at 83 °C. From $\Delta\nu$ of 42 Hz, we calculated K of 93 s^{-1} and $\Delta G^{\neq}$ of 17.97 kcal/mol.

In contrast to **2a** and **2b**, the ^{1}H NMR spectrum of unsubstituted dipyridyl thienothiophene **2c** revealed only a single set of signals for pyridyl and thienothiophene ring protons at ambient temperature, thereby implying free ring rotation. Neither increase in the signal multiplicities nor signal broadening was detected in the ^{1}H NMR spectra scanned in the range of 80° to −50 °C. Evidently, the energy barrier to pyridyl rotation for the case of **2c** appears to be significantly lower than that observed for the case of substituted thienothiophenes **2a** and **2b**. Assuming $\Delta\nu$ of 50 Hz, we can estimate the energy barrier to rotation $\Delta G^{\neq}$ for **2c** to be lower than 10 kcal/mol.

Interestingly, even bis *N*–Me salt **2d** carrying methyl substituents on the pyridinium rings also displayed a single set of resonances for the pyridinium ring protons (though, downfield shifted compared to the neutral **2c**, see Table 1), including a sharp singlet for the *N*–CH_3 groups in the temperature range of 80 to −40 °C, with only a slight broadening of signals being observed at −50 °C. The signal broadening seems to result from the sample precipitation at this temperature rather than from slowing down of the conformational process. The temperature independent nature of **2d** clearly points toward unhindered pyridyl ring rotation at least up to −50 °C. However, in contrast to **2c** and **2d**, the known, 1,8-di (3′-pyridyl) naphthalene and its corresponding *N*-methyl salt both at rt have been reported to exist as a mixture of *syn*/*anti* isomers with coalescence occurring at 35 and 100 °C, respectively, indicating sizeable barriers ($\Delta G^{\neq}$ upward of 15 kcal/mol) to ring rotation.[11a,c] Evidently, the presence of methyl substituents on the pyridyl rings in **2d** does not seem to contribute significantly to the conformational energy barrier. In this context, it is noteworthy that rotation of just one of the pyridinium rings would suffice to cause *syn*/*anti* equilibration.[11a,13] Thus, keeping the *N*-methyl groups out of the way, a lower energy pathway for the pyridinium ring rotation in **2d** is conceivable through its unsubstituted i.e. C4′,C5′ face to achieve the required orthogonal (T-shape) transition state, as illustrated in Figure 2.

We speculate that despite the presence of *N*-methyl groups, free ring rotation in **2d** could possibly arise provided there existed a relatively large Van der Waals separation between the cofacial pyridinium rings compared to the *peri* dipyridylnaphthalene analogs mentioned above. If true, this structural factor could override any steric barrier imposed by the *N*-methyl substituents to the rotational process to permit unhindered pyridinium ring rotation in **2d**. In view of the fact that **2c** and **2d** without C2/C5 substituents exist as freely equilibrating systems, the existence of *syn*/*anti* atropisomerism for substituted dipyridylthienothiophenes **2a** and **2b** can be attributed to the steric compression arising from –CO_2Et and –COMe substituents located on the non-rotating thienothiophene framework. In comparison, it is worthy to note that for various *peri*-diaryl (diheteroaryl)naphthalenes, the higher energy barriers owe their origins to the bulky substituents present directly on the rotating *peri* rings.[1–4]

Since, none of **2a–d** gave crystals suitable for single X-ray crystallography, we performed their conformational analysis by semi-empirical molecular orbital calculations using the MOPAC program (Version 5.0).[14] Geometries of *syn* and *anti* conformers of **2a–d** were minimized by means of

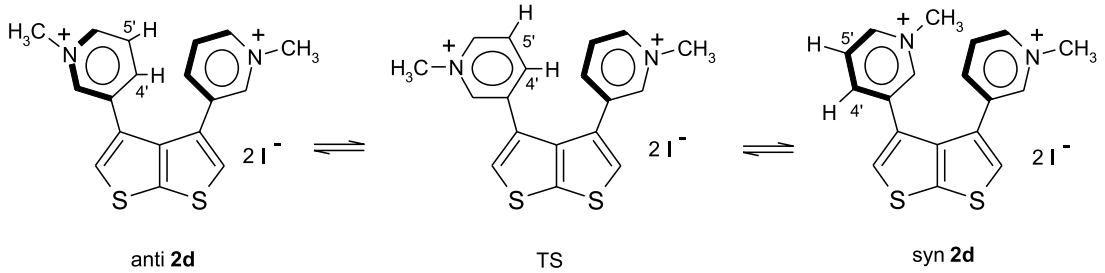


Figure 2. Proposed *syn*/*anti* equilibration of **2d** via T-shaped transition state.

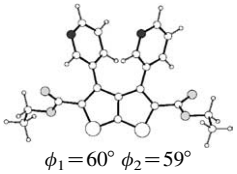
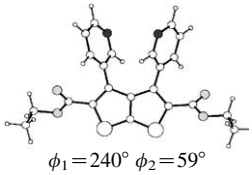
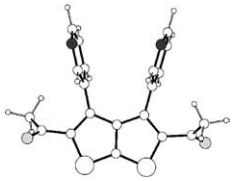
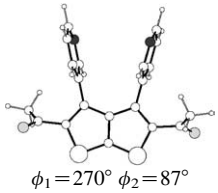
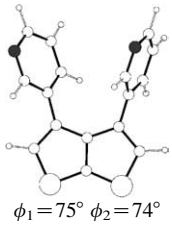
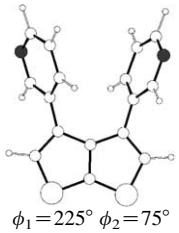
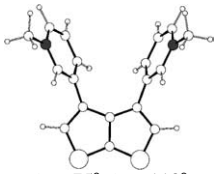
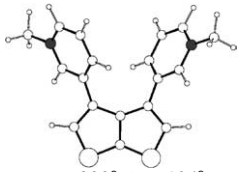
gradient techniques at RHF/AM1 level with MNDO parameters for the sulfur atoms.[15] The ϕ_1 and ϕ_2 refer to dihedral angles involving thienothiophene framework and the C3′/C4′ positions of pyridyl/pyridinium rings, respectively. In these calculations, all parameters except the dihedral angle ϕ_1 were optimized and the heats of formation (ΔH) of various conformers were calculated by rotation of the pyridyl ring (dihedral angle ϕ_1) by steps of 15°. For the case of **2d**, we have excluded the iodide ions from the energy minimization due to their positional uncertainty in the molecule.

In all cases (**2a**–**d**), the *anti*-form is found to be slightly more stable than the *syn*-form. For syn-**2a**, having 2 nitrogens on the same side, one of the lowest energy conformers corresponds to $\phi_1/\phi_2 = 60°/59°$ with calculated $\Delta H = -23.4$ kcal/mol, while for the *anti* isomer, the lowest energy conformer is identified to have $\phi_1/\phi_2 = 240°/59°$ with associated $\Delta H = -24.0$ kcal/mol. From these data, we can infer that for both *syn* and *anti* **2a**, tilt position of pyridyl groups is favored. When one of the pyridyl rings passes through the planar position to the bicycle ($\phi_1 = 180$ or 0°), a situation which corresponds to the T-shaped transition state, an important potential energy barrier of 8.2 kcal/mol is observed. Clearly, this energy barrier is responsible for the observation of *syn*/*anti* atropisomers at ambient temperature.

On the other hand, the lowest energy *syn* **2b** conformer has $\Delta H = 75.9$ kcal/mol when ϕ_1 and ϕ_2 are 90 and 85°, respectively, whereas for *anti* **2b**, the lowest energy conformer ($\Delta H = 75.2$ kcal/mol) possesses ϕ_1 and ϕ_2 of 270 and 87°, respectively. These results suggest that the pyridyl nuclei in both *syn* and *anti* **2b** occupy near perpendicular orientation with respect to the thienothiophene plane. Evidently, the $-COCH_3$ groups seem to offer more pronounced steric interaction with the neighboring pyridyl rings forcing them to assume the perpendicular geometry in both *syn*/*anti* **2b**. In contrast, for the case of *syn*/*anti* **2a** the lower torsional angles are presumably due the presence of relatively less sterically demanding $-CO_2C_2H_5$ groups. Not surprisingly, the potential energy required to achieve the activated complex in **2b** is slightly higher at 9.3 kcal/mol compared to the potential energy barrier of 8.2 kcal/mol computed for **2a**. This is essentially in keeping with the experimental results obtained from the variable temperature ^{1}H NMR analysis.

For **2c** lacking C2/C5 substituents, the *anti* isomer is slightly more stable than the syn isomer by 0.4 kcal/mol and when, one of the pyridyl rings in **2c** passes through the planar position to the bicycle (ϕ_1 of 180 or 0°), a relatively less important potential energy barrier of 4.5 kcal/mol is observed. Thus, unlike **2a** and **2b** for which potential energy barrier is computed in the range of 8.2 to 9.3 kcal/mol, the

Table 2. AM1 generated lowest energy conformation of *syn*/*anti* of **2a**–**2d**

Systems	*syn*	*anti*	ΔH_{syn} (kcal/mol)	ΔH_{anti} (kcal/mol)	Calcd. energy barrier $\Delta\Delta H$ (kcal/mol)
2a	 $\phi_1 = 60°$ $\phi_2 = 59°$	 $\phi_1 = 240°$ $\phi_2 = 59°$	−23.3	−24.0	8.2
2b	 $\phi_1 = 90°$ $\phi_2 = 85°$	 $\phi_1 = 270°$ $\phi_2 = 87°$	75.9	75.2	9.3
2c	 $\phi_1 = 75°$ $\phi_2 = 74°$	 $\phi_1 = 225°$ $\phi_2 = 75°$	142.3	141.9	4.5
2d	 $\phi_1 = 75°$ $\phi_2 = 118°$	 $\phi_1 = 300°$ $\phi_2 = 124°$	498.6	497.8	4.2

The lowest energy *syn* and *anti* conformers were arrived at by rotating ϕ_1 by 15° steps and computing the corresponding ϕ_2.

lower energy of activation for **2c** accounts reasonably well for the existence of free pyridyl ring rotation in this molecule. For the case of bis-*N*-methyl salt **2d**, two potential energy wells corresponding to *syn* and *anti* isomers are discernible, the latter isomer being more stable by ca. 0.8 kcal/mol. Interestingly, when one of the pyridinium rings in **2d** passes through the planar position with respect to the plane of thienothiophene ring, a situation in which the *N*–Me group is directly impinging on the facing ring ($\phi_1=180°$ and $\phi_2=90°$), an important potential energy barrier of 8.4 kcal/mol is calculated. However, when one of the pyridinium rings is passing through the planar position through its unsubstituted face ($\phi_1=0°$ and $\phi_2=90°$, see also Fig. 2), the potential energy barrier is computed to be only 4.2 kcal/mol. Thus, in view of comparable potential energy barriers computed for both **2c** and its *N*-methyl salt **2d**, it is hardly surprising that these molecules exhibit facile ring rotation, a feature that is also supported by their dynamic ^{1}H NMR measurements discussed earlier.

The computer generated *syn*/*anti* structures together with some key computed data of **2a**–**d** are summarized in Table 2. An interesting structural aspect that emerges from the AM1 calculations is the separation between cofacially linked pyridyl rings in these molecules. Thus, on going along the rotation axis, the distance from C3′ to C6′ positions between the cofacial rings for **2c** increases from 3.5 to 5.2 Å, while for **2d**, the corresponding distances register even greater increase from 3.7 to 6.1 Å. In the case of **2d**, this higher ring separation is presumably due to the steric interaction and electrostatic repulsion between the facing *N*-methylpyridinium rings. However, for the sake of comparison, Zoltewicz et al. computed the analogous distances to be 3.14 and 5.51 Å for the bis-*N*-methyl salt of 1,8-di (3′-pyridyl) naphthalene.[11c] Clearly, the pyridyl/pyridinium rings in **2c** and **2d** (more so for the latter case) are relatively more splayed out compared to their naphthalene counterparts. Accordingly, lower energy barriers estimated for the rotation in **2c** and **2d** (<10 kcal/mol) compared to the known, 1,8-di (3′-pyridyl) naphthalene and its corresponding bis-*N*-methyl quaternary salt ($\Delta G^{\neq}$ of ≥ 15 kcal/mol) are not unexpected. These results are also consistent with our recent molecular modeling studies which predicted lower energy barriers to rotation in diarylthienothiophenes relative to their naphthalene counterparts.[8] It is also noteworthy that the presence of $-CO_2C_2H_5$ and $-COCH_3$ groups at C2 and C5 positions of the thienothiophene framework in **2a** and **2b** compresses the facing pyridyl rings slightly inwards as evidenced from the shortening of the distance from C3′ to C6′ between the facing rings to 3.4 and 4.7 Å compared to 3.5 and 5.2 Å computed for the case of unsubstituted **2c**. The additional energy barrier contributed by the $-CO_2C_2H_5$ and $-COCH_3$ substituents in **2a** and **2b** amounts to 3.7 to 5.1 kcal/mol compared to unsubstituted systems **2c** and **2d**. The computed results are therefore consistent with higher energy barriers to rotation found from the dynamic ^{1}H NMR analysis for **2a** and **2b**.

3. Conclusions

New atropisomeric systems based on dipyridyl thienothiophenes have been designed using a simple synthetic protocol. From ^{1}H NMR spectral analysis, compounds **2a** and **2b** with substituents at C2 and C5 positions are found to display *syn*/*anti* atropisomerism with associated $\Delta G^{\neq}$ in the range of 17–18 kcal/mol. Interestingly, unlike *peri*-diaryl(heteroaryl)naphthalenes,[11] the hindered rotation in **2a** and **2b** seems to stem from the steric encumbrance originating from $-CO_2Et$ and –COMe substituents located on the rigid thienothiophene platform rather than on the rotating rings. These results suggest that rotational barriers could be enhanced if the steric bulk of C2/C5 substituents could be increased. Potential, therefore is available to tailor-make axially chiral thienothiophene systems with higher energy barrier to rotation. On the other hand, **2c** and its bis-*N*-methyl salt **2d** lacking C2/C5 substituents revealed *syn*/*anti* equilibration that does not freeze out even at very low temperatures ($\Delta G^{\neq}$ of ≤ 10 kcal/mol). From computational results, the low value of conformational energy barriers (4.2–4.5 kcal/mol) for **2c**–**d** could be attributed to increased cofacial ring separation. Available conformational comparisons indicate that rotational barriers for **2c**–**d** are markedly lower compared to those reported for their naphthalene counterparts.

4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. DMF was dried (CaH_2) and distilled under vacuum. Anhydrous KF was purchased from Aldrich and dried before use. Other reagents and solvents were purchased from S. D. Fine Chemicals Ltd. (India) and used as received. IR spectra were recorded on a Shimadzu FTIR-4200 spectrophotometer as KBr discs. ^{1}H NMR spectra were recorded on Bruker 500 MHz spectrometer with TMS as an internal standard. Coupling constants *J* are given in Hz. ^{13}C NMR spectra (75.5 MHz) were recorded on Bruker AC 300 instrument. Mass spectra were recorded on ZAB 2F HS spectrometer with 70 eV electron impact.

4.1.1. 3,4 Bis-(3-pyridyl) thieno [2,3-*b*] thiophene 2,5 diester 2a. To a solution of dry DMF (20 mL) containing anhydrous KF (8.00 g) were added 1,3-(3′-pyridyl) propan-1,3-dione **1**[10] (2.26 g, 10 mmol) and freshly distilled CS_2 (760 mg) and the reaction mixture vigorously stirred at rt for 6 h. The reaction was cooled to 0–5 °C and ethyl bromoacetate (3.34 g, 20 mmol) dissolved in dry DMF (20 mL) was added dropwise during 1 h. The temperature was allowed to rise to rt and then the reaction heated and stirred at 80–90 °C for 24 h. The reaction mixture was cooled to rt, poured over cold 5% aq NaOH (250 mL) and left overnight for the precipitate to settle. The precipitated solid was filtered, washed with water and then air-dried. Crystallizaton from 1:2 chloroform–hexane gave **2a** as pale yellow needles in 28% yield (1.22 g), mp 175–180 °C. Anal. Calcd for $C_{22}H_{18}N_2O_4S_2$: C, 65.31; H, 3.40; N, 9.52; S, 21.77. Found: C, 65.58; H, 3.49; N, 9.83; S, 22.11. IR (KBr, ν cm^{-1}): 3000, 2950, 2900, 1715, 1685, 1570, 1500, 1480, 1410, 1365, 1295, 1212, 1085, 1015, 900, 815. δ_H ($CDCl_3$)

for 60:40 *anti*/*syn* forms: 1.01 (t, $J=7.5$ Hz), 4.08 (q, $J=7.5$ Hz), 6.91 (dd, $J=8.1$, 5.5 Hz), 7.00 (dd, $J=8.1$, 5.5 Hz), 7.24 (d, $J=8.1$ Hz), 7.35 (d, $J=8.1$ Hz), 8.09 (s), 8.20 (s), 8.25 (d, $J=5.5$ Hz); see Table 1 for ^{1}H NMR assignments. δ_C ($CDCl_3$) 14.3, 60.9, 124.5, 124.7, 126.5, 126.8, 134.4, 136.6, 137.7, 138.2, 147.6, 148.0, 149.1, 149.3, 151.1, 151.2, 168.7 MS (EI) *m*/*z*: 438.

4.1.2. 3,4 Bis-(3-pyridyl) 2,5 diacetyl thieno[2,3-*b*]thiophene 2b. The procedure as described above for **2a** was used except that ethyl bromoacetate was replaced with chloroacetone (1.8 g, 20 mmol). The crude solid product was purified by silica gel column chromatogaphy (elution 1:1 chloroform–pet ether) to afford **2b** as a pale yellow solid in 32% yield (1.2 g), mp 238–240 °C. Anal. Calcd for $C_{20}H_{14}N_2O_2S_2$: C, 63.50; H, 3.70; N, 7.41; S, 16.93. Found: C, 63.29; H, 3.55; N, 7.64; S, 16.80. IR (KBr, ν cm^{-1}): 3000, 2910, 1685, 1570, 1520, 1483, 1410, 1300, 1211, 1195, 1055, 900, 865. δ_H ($CDCl_3$) for 57:43 *anti*/*syn* forms: 1.80 (s), 7.05–7.07 (two overlapping dd), 7.38 (d, $J=7.3$ Hz), 7.48 (d, $J=7.3$ Hz), 8.20 (s), 8.25 (d, $J=5.0$ Hz), 8.31 (d, $J=5.0$ Hz), 8.35 (s); see Table 1 for ^{1}H NMR assignments. δ_C ($CDCl_3$) 22.9, 124.7, 126.8, 126.9, 134.1, 135.1, 135.2, 138.0, 147.8, 148.5, 148.7, 149.3, 151.7, 151.9, 192.4. MS (EI) *m*/*z*: 378.

4.2. Preparation of the diacid 2

Diester **2a** (876 mg, 2 mmol) was dissolved in 20 mL of DMSO to which 10% aq. KOH (10 mL) was added and the reaction heated on a steam bath for 2 h. The reaction mixture was cooled in ice and acidified with 2 M HCl to precipitate the diacid. The product was filtered, washed with cold water and air dried to give the diacid **2** as white solid in 85% yield (650 mg), mp 300–305 °C (dec). IR (KBr, ν cm^{-1}): 3400, 3065, 1682, 1618, 1577, 1507, 1485, 1337, 1281, 1146, 978, 880. Anal. Calcd for $C_{18}H_{10}N_2O_4S_2$: C, 56.54; H, 2.62; N, 7.33; S, 16.75. Found: C, 56.33; H, 2.89; N, 7.54; S, 17.11.

4.2.1. 3,4 Bis-(3′-pyridyl) thieno [2,3-*b*] thiophene (2c). Diacid **2** (382 mg, 1 mmol) was suspended in quinoline (5 mL) and after adding 20 mg of Cu powder, the reaction was stirred and heated at 225–235 °C under N_2 atmosphere for 2 h. The reaction mixture was cooled to rt, diluted with a little chloroform (20 mL) and filtered to remove insoluble residue. Chloroform was first removed by distillation and then quinoline removed under vacuum at 50–60 °C. The residual oily product was purified by SiO_2 column chromatography (eluant: chloroform–hexane 1:4) to provide the required product **2c** as a light yellow solid in 40% yield (115 mg), mp 81–84 °C. IR (KBr, ν cm^{-1}): 2980, 1605, 1556, 1220, 1135, 1087, 1005, 980, 875. Anal. Calcd for $C_{16}H_{10}N_2S_2$: C, 65.31; H, 3.40; N, 9.52; S, 21.77. Found: C, 64.96; H, 3.58; N, 9.81; S, 21.55. δ_H ($CDCl_3$) 7.08 (2H, dd, $J=7.3$, 4.5 Hz), 7.38 (2H, d, $J=7.3$ Hz), 7.70 (2H, s), 8.28 (2H, s), 8.36 (2H, d, $J=4.5$ Hz); see Table 1 for ^{1}H NMR assignments. δ_C ($CDCl_3$) 122.6, 124.2, 126.4, 129.5, 134.9, 135.3, 143.1, 149.4, 150.7. MS (EI) *m*/*z*: 294.

4.2.2. 3,4-Bis(1-methylpyridin-1′-ium-3′-yl)thieno[2,3-*b*]thiophene diiodide (2d). Bis-(3-pyridyl) thieno [2,3-*b*] thiophene **2c** (50.0 mg) was dissolved in dry acetonitrile (1.5 mL). Freshly distilled CH_3I (0.5 mL) was added and the reaction mixture tightly stoppered and left at rt for 48 h whereby a yellow solid was deposited. Solvent was removed by decantation and the solid product washed repeatedly with a little cold acetonitrile (2 mL) and then dried over KOH under vacuum to give the quaternized salt **2d** in almost quantitative yield (95 mg), mp 265–270 °C (dec). IR (KBr, ν cm^{-1}): 3010, 1605, 1443, 1376, 1282, 1220, 1165, 1030, 940, 827. Anal. Calcd for $C_{18}H_{16}N_2S_2I_2$: C, 37.37; H, 2.77; N, 4.84; S, 11.07; I, 43.94. Found: C, 37.66; H, 2.54; N, 5.17; S, 11.44; I, 44.07. δ_H ($CDCl_3$) 4.35 (6H, s), 7.78 (2H, dd, $J=7.1$, 5.1 Hz), 8.08 (2H, d, $J=7.1$ Hz), 8.10 (2H, s), 8.89 (2H, d, $J=5.1$ Hz), 9.15 (2H, s); see Table 1 for ^{1}H NMR assignments. δ_C (DMSO-d_6) 40.6, 124.8, 126.9, 130.1, 136.2, 137.3, 144.7, 151.3, 152.4, 155.5.

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Efficient electrocatalytic addition reactions of allyl phenyl sulfone to electron deficient alkenes

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Abstract—The use of tetraalkylammonium salts as electrolytes has been found to allow the formation of electrogenerated bases of especially high reactivity. Such conditions allow allyl phenyl sulfone to undergo addition to a variety of electron deficient vinyl and propenyl compounds (sulfone, ketone, nitrile, and ester). The additions are catalyzed by electrogenerated bases derived from the reactant itself, rather than via an added pro-base. The nature of the substrate molecule is seen to affect which type of product is formed, leading to an interplay between addition to 1 mol of substrate or to 2 mol of substrate. Yields of 1:1 adducts range from 6 to 81%, while yields of 1:2 adducts range from 57 to 96%.

1. Introduction

The buildup of basicity around the cathode during an electrolytic reduction has long been known. The use of such electrogenerated bases (EGBs) in directed synthesis has been investigated over the last few decades.[1] The applications of EGBs include the electro-activation of both C–H and N–H bonds, with subsequent N–C and C–C bond formation.[2,3] The typical approach has been to provide (usually in stoichiometric amount) an additive (called a pro-base)[4,5] which serves as a precursor to the active base. A relatively novel aspect of the reactions presented here is that, in contrast to most of the earlier applications of EGBs to organic synthesis, one of the reactants (allyl phenyl sulfone) also serves as the pro-base. This use of direct reduction of organic acids is an attractive, simplified approach, which can be utilized in two ways. An ex situ route, often enforced due to competitive substrate reduction.[6] Alternatively, and rather rarely, an in situ route, as is presented here. This approach sees a further layer of experimental simplification, and has been utilized for malonic acid derivatives, for example.[7]

The reactive EGBs formed during reduction lead to exceptionally efficient and highly electrocatalytic additions of allyl phenyl sulfone (via its conjugate base) to a variety of vinyl and propenyl compounds, in which these groups are attached to electron withdrawing groups (sulfone, ketone, nitrile, and ester).

Our previously published work[8] showcased EGB promoted addition of allyl phenyl sulfone to its propenyl isomer, along with its novel reactions with vinyl sulfones to furnish high (90–94%) yields of highly polar molecules in which 1 mol of allyl phenyl sulfone has added consecutively, selectively, and in a linear addition mode to 2 mol of the vinyl sulfone.

The current work initially expands this area to include other vinyl sulfones, obtaining similarly high yields. Competitive addition to two different vinyl sulfones is also examined, allowing for incorporation of a mole each of two sulfones. An attempt has also been made to probe the range of electron-deficient substrates that will allow Michael addition of the electrogenerated[9] conjugate base of allyl phenyl sulfone. The formation of 1:2 adducts (**4**) is seen to be generally limited to vinyl compounds (Fig. 1). The formation of 1:1 adducts (**3**) is mostly seen with propenyl substrates. However, several vinyl compounds yield both product types, the ratio between which is explored, and a mechanism is advanced.

The coupling of simple alkyl groups at the α position of allyl phenyl sulfone has previously been seen (in a two step chemical synthesis).[10] However, the present work represents a large increase in the range of moieties that will couple at the reactive α position. Stoichiometric use of strong bases has been used in related allylic sulfone compounds to affect addition to α,β-unsaturated esters,[11]

Keywords: Catalytic; Electrogenerated base; Carbanion addition; Allyl vinyl sulfone.
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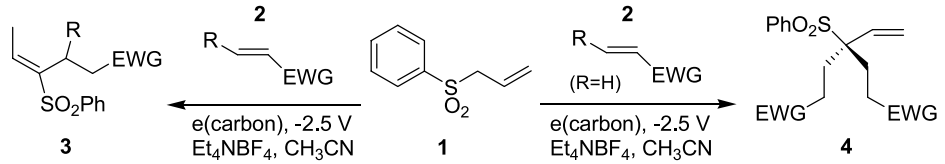


Substrate **2**	R	EWG	Primary product/Yield(%)	Substrate **2**	R	EWG	Primary product/Yield(%)
2a	CH_3	$PhSO_2$	**3a**: 81	**2j**	H	$COCH_2CH_3$	**3j**: 47
2b	H	$PhSO_2$	**4b**: 91	**2k**	CH_3	$COCH_3$	**3k**: 26
2c	H	CH_3PhSO_2	**4c**: 95	**2l**	H	$COOCH_3$	**3l**: 16, **4l**: 18
2d	H	$CH_2CH_3SO_2$	**4d**: 96	**2m**	H	$COOCH_2CH_3$	**3m**: 28, **4m**: 20
2e	H	CH_3SO_2	**4e**: 92	**2n**	H	COOPh	**3n**: 22
2g	H	CN	**4g**: 57	**2o**	CH_3	$COOCH_3$	**3o**: 6
2h	CH_3	CN	**3h**: 26	**2p**	CH_3	$COOCH_2CH_3$	**3p**: 6
2i	H	$COCH_3$	**3i**: 28	**2q**	$COOCH_2CH_3$	$COOCH_2CH_3$	**3q**: 22

Figure 1. Summary of the products formed from the addition of the carbanion of **1** to 1 or 2 mol of various vinyl/propenyl compounds containing electron withdrawing groups (EWGs).

cyclic ketones and nitroalkenes.[12] The conjugate base of the allyl sulfone was produced in a non-electrochemical manner in these latter cases. The environmentally benign nature of this work's electrochemical formation of the reactive carbanion, inherent in the simplified workup and the consumption of electricity as the sole reagent (in catalytic amounts), further adds to the experimental appeal and potential utility of these reactions.

2. Results and discussion

2.1. Addition to vinyl sulfones

A brief account of the facile addition of the conjugate base of allyl phenyl sulfone (substrate **1**), to several vinyl sulfones has been reported from this laboratory.[8] Consequently, the expansion of this work to other vinyl sulfones was a clear next step. Use of ethyl and methyl vinyl sulfone (**2d** and **2e**) as electron-deficient addends unsurprisingly followed a similar pattern of forming high yields of the trimer product, **4** (Table 1).

Table 1. Yields and minimum catalytic factors for cross addition of allyl phenyl sulfone to electron deficient alkenes, leading to exclusive trimer formation

Substrate	Yield (%)	Minimum catalytic factor[a]
2b: Phenyl vinyl sulfone[b]	91	13
2c: Tolyl vinyl sulfone[b]	95	7.4
2d: Ethyl vinyl sulfone	96	17
2e: Methyl vinyl sulfone	92	15

[a] The reactions were monitored for completion in a step-wise fashion, such that the exact amount of charge used to give completion is not known (see experimental data). Therefore, the catalytic factors may be greater than that stated. Catalytic factor based upon total charge used and moles of limiting reagent **1**. Catalytic factors are found using 96,485 °C mol^{-1}.[13]
[b] Previously published results.[8]

These trimers were all produced from reactions with a vinyl sulfone excess of <2.10, over **1**. Indeed when the reaction is run using an excess of **1** at a 1.97:1 ratio (to **2b**), only the trimer (**4b**) and the allyl phenyl sulfone carbanion addition to propenyl phenyl sulfone (**2a**) product (**3a**)[8] are obtained. These products are seen in a 1:1.45 ratio, respectively, in accord with the proposal that exclusive trimer formation occurs until the vinyl substrate is largely consumed, followed by self-addition of the excess **1**.[14]

Attempts to increase the yield of the rather unique cyclic dimer, **5f** (Fig. 2) formed from the addition of **1** to divinyl sulfone (**2f**) proved unsuccessful, with yields of ca. 40%.[8] Yields of the allyl phenyl sulfone self-adduct, **3a**, were similarly not improved beyond 81%.[8] Further expansion to other electron deficient alkenes generally gave a more complicated picture. A mixture of 1:2 and 1:1 adducts were seen, in some cases along with secondary reaction products.

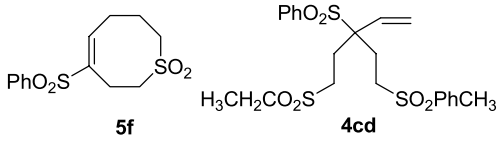


Figure 2. The cyclic 1:1 product, **5f**, formed from α,γ-addition of allyl phenyl sulfone (**1**) to divinyl sulfone (**2f**). An example of a mixed trimer, **4cd**, formed from addition of **1** to 1 mol each of tolyl vinyl sulfone (**2c**) and ethyl vinyl sulfone (**2d**).

2.2. Addition to mixtures of vinyl sulfones

The trimers formed from addition of **1** to vinyl sulfones form readily in near quantitative yields. The reactions also utilize all of the vinyl sulfone substrate prior to formation of **3a**, so that the reactivity of the allyl carbanion to each vinyl sulfone substrate can be probed by competitive addition with two substrates in the reaction. The excess of any one substrate was kept insufficient (below 2) to allow complete reaction with that substrate only. In this way, each reaction yields three trimers, two based on the addition to 2 mol of each substrate, along with a 'mixed' trimer containing 1 mol of each substrate.

The reactivities of the vinyl sulfones (based on product ratios in Table 2) generally follow a pattern which is consistent with the expected relative stabilities of the α-sulfonyl carbanions which would be formed in the nucleophilic addition steps, based upon the relative inductive effects of the four substituents attached to the sulfonyl group (phenyl, tolyl, ethyl, and methyl. Presumably these effects are present in both addition steps (see Fig. 3). These mixed reactions show a reactive rank of **2b**>**2c**>

Table 2. Reactions of allyl phenyl sulfone, **1**, with two vinyl sulfones to yield 'mixed' trimers incorporating all three components

Substrates	Starting ratio where **1** = 1	Products	Product ratio[a]
2b + **2d**	1.52:1.48	**4d**:**4bd**:**4b**	1:3.22:3.42
2c + **2d**	1.50:1.52	**4d**:**4cd**:**4c**	1:2.80:2.30
2c + **2d**	1.01:1.20	**4d**:**4cd**:**4c**	1:1.54:0.77
2b + **2e**	1.51:1.65	**4e**:**4be**:**4b**	1:2.73:2.69
2d + **2e**	1.62:1.60	**4e**:**4de**:**4d**	1:2.03:1.15[b]

A simple mixed trimer is shown in Figure 2.
[a] Based upon NMR integration of vinyl protons.
[b] Based upon LRMS, as vinyl proton NMR were coincident.

2d > **2e**, as judged by the relative amounts of the two 1:2 adducts (the first and third numbers in the product ratios).

2.3. Addition to vinyl/propenyl nitriles

The addition to a vinyl nitrile (**2g**, acrylonitrile) gave reasonable yields of products consisting primarily of the 1:2 adduct (Table 3). The competing formation of the monoadduct can be suppressed by using a slightly higher excess of **2g**. Under these conditions the yield of the trimer, **4g**, is increased to 57%.

Addition to a propenyl nitrile (**2h**, crotononitrile) is seen to be less facile, with yields of the 1:1 product of ca. 25%. The 1:2 adduct is not observed, and indeed the yield of the 1:1 adduct is not increased by using a greater excess of **2h**, even though the yield of the self adduct of **1** (**3a**) is diminished. This is probably due to greater competition from oligomerization reactions engendered by the excess of **2h** (Fig. 4).

2.4. Addition to vinyl/propenyl ketones

The addition to a series of vinyl/propenyl ketones leads to reasonable yields of 1:1 adducts, approaching 50% in the case of ethyl vinyl ketone (Table 4). Yields of 2:1 products are relatively limited (and not seen for **2k**). A secondary reaction of the formed trimers, **4i** and **4j**, leads to an additional product; **6**. This product is formed via an aldol-type cyclization.[15] However, both products **4i** and **6i** are formed in low yields even when the ratio of methyl vinyl ketone (**2i**) is trebled, leaving the 1:1 dimer as the main product. The near four-fold excess of ethyl vinyl ketone does not lead to large yields of **4j** or **6j**, indicating a distinct preference to form the dimer **3j**. It appears that addition to a second mole of ketone is less favored in the ethyl vinyl ketone case. The rationale for this may be steric in nature, or involve the slight differences in acidity of the substrates. An additional curiosity was observed, that use of an old supply of ~90% tech grade methyl vinyl ketone lead to a 45% yield of the 1:1 product (along with 7% of **2a**), presumably the impurities are acidic in nature, protonating the

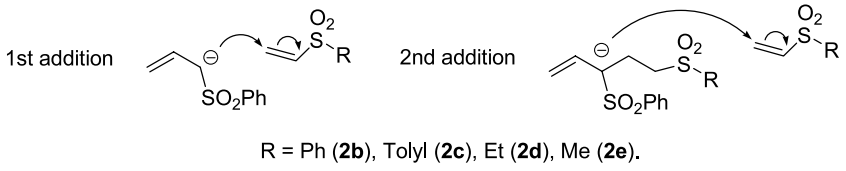


Figure 3. Portions of the reaction mechanism[8] of addition of **1** to vinyl sulfones.

Table 3. Product yields for the addition of **1** to a vinyl and a propenyl nitrile

Substrate	Ratio **1**: substrate	% Yield of 1:1 product (**3**)	% Yield of 1:2 product (**4**)	% Yield of other products	Minimum catalytic factor
2g: Acrylonitrile	1:2.06	6	42	**2a**: 3	25
2g: Acrylonitrile	1:3.09	—	57	—	12
2h: Crotononitrile	1:3.11	26	—	**3a**: 43	16
2h: Crotononitrile	1:5.98	22	—	**3a**: 28	12

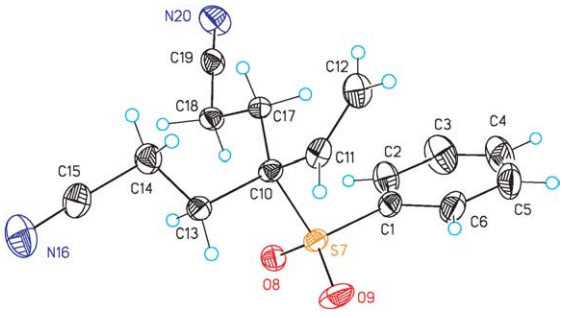
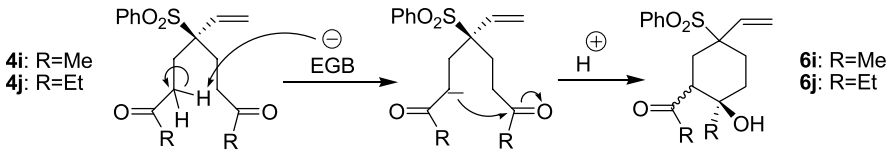


Figure 4. View of **4g** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Table 4. Product yields for the addition of **1** to a series of vinyl and a propenyl ketones

Substrate	Ratio **1**: substrate	% Yield of 1:1 product (**3**)	% Yield of 1:2 derived product	% Yield of other products	Minimum catalytic factor
2i: Methyl vinyl ketone	1:1.00	28	**6i**: 5[a]	**2a**: 7 **3a**: 6	13
2i: Methyl vinyl ketone	1:3.05	18	**6i**: 12[a]	—	11
2j: Ethyl vinyl ketone	1:2.01	27	**6j**: trace	**2a**: 1	6.7
2j: Ethyl vinyl ketone	1:3.84	47	**6j**: trace	—	7.9
2k: Propenyl methyl ketone	1:2.52	26	—	**3a**: ~4	4.2

[a] Two isomers, see Section 4.10 for details.



Scheme 1. Formation of **6** via aldol-type cyclization of **4**.

Table 5. Product yields for the addition of **1** to a series of vinyl esters

Substrate	Ratio **1**: substrate	% Yield of 1:1 product (**3**)	% Yield of 1:2 product (**4**)	% Yield of other products	Minimum catalytic factor
2l: Methyl acrylate	1:2.09	16	18	**2a**: 8 **7l**: 12	2.5
2m: Ethyl acrylate	1:2.09	28	20	**2a**: 8 **3a**: 3 **7m**: 7	4.5
2m: Ethyl acrylate	1:3.08	13	15	**2a**: 2 **7m**: 13	2.0
2n: Phenyl acrylate	1.2.03	22	—	**2a**: 24	1.5

intermediate after one addition. Introduction of small amounts of water into pure **2i** electrolyses, however, did not re-create these results.

Addition to the propenyl ketone studied, **2k**, led to moderate amounts of the 1:1 dimer, the presence of the propenyl group clearly retarding trimer formation. Increases in the excess of **2k** actually reduced yields, at 6:1 no **3k** was formed. This is clearly due to the reactivity of the ketone under these conditions, probably leading to a variety of oligomerization reactions. This reactivity is also indicated by the lowered catalytic factor, as some of the charge is used by the ketone (Scheme 1).

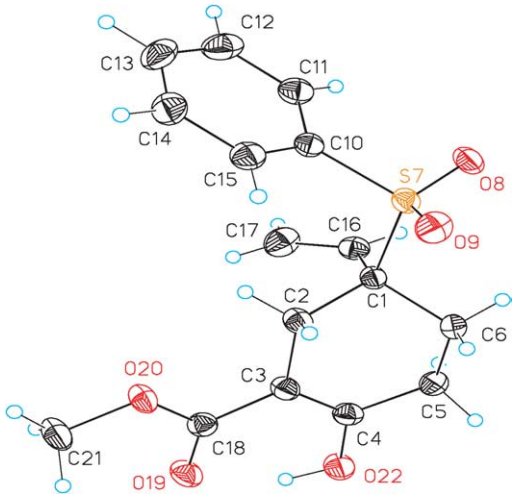


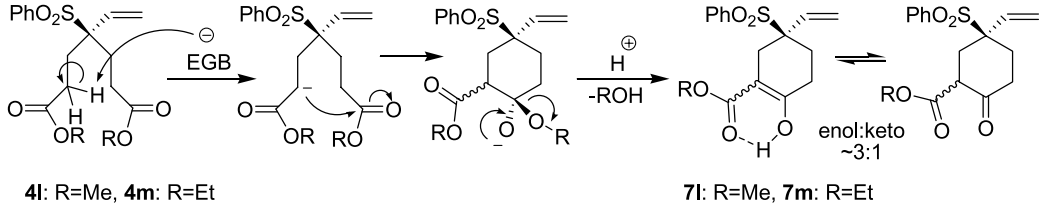
Figure 5. View of **7l** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

2.5. Addition to vinyl esters

The coupling of the allyl phenyl sulfone carbanion to a series of esters yielded both adduct types (1:1 and 1:2) along with the formation of a third product derived from the 1:2 trimer. The catalytic factors seen in all three additions are some of the lowest observed in this work, this taken with the moderate yields, indicates reduction and possible reactivity of the substrates themselves (say, via oligomerization). Addition to methyl and ethyl acrylate generally proceeded to reasonable total product yields around 50% (Table 5). As noted, this yield is made up of three products, with **7** being formed from the cyclization of **4**, and subsequent condensation (loss of an alcohol).

An attempt was made to force the reaction all the way to this cyclic product by increasing the excess (in this case, of ethyl acrylate), and reducing for longer. While **2a** formation is reduced, and no **1** is recovered, there is still some formation of the 1:1 adduct. The yield of the cyclic product is somewhat increased, at the expense of total product yield. This cyclic product is a keto–enol tautomer, with the enol form predominant in ca. 3:1 excess (in *d*-chloroform), while X-ray crystallography shows only the enol form (see Fig. 5). The mechanism for formation of **7** is presented in Scheme 2.

The addition to phenyl acrylate, **2n**, interestingly stops at the 1:1 adduct stage. While this may in part be due to the steric hindrance of the more bulky phenyl group, it may also be appropriate to consider a possible additional electronic basis



Scheme 2. Formation of the keto–enol tautomer **7** via cyclization/condensation (loss of alcohol, MeOH or EtOH).

Table 6. Product yields for the addition of **1** to esters

Substrate	Ratio **1**: substrate	% Yield of 1:1 product (**3**)	% Yield of other products	Minimum catalytic factor
2o: Methyl crotonate	1:2.00	6	**3a**: 57	11
2p: Ethyl crotonate	1:2.09	6	**3a**: 46	8.0
2q: Diethyl maleate	1:1.02	11	**2a**: 20 **3a**: 16	4.0
2q′: Diethyl fumarate	1:1.03	22	**2a**: 4	2.1

relating to the resonance interaction of the phenyl group with the attached ester oxygen. This interaction, which is not present in an alkyl ester, competes with normal ester resonance, making the oxygen atom bound to the phenyl group less electron donating than in the case of an alkyl ester. The net result is that the ester carbonyl group is more electron-deficient than in the case of alkyl esters and better able to stabilize the intermediate carbanion. This would not only enhance the rate of the initial addition, but perhaps retard the rate of the second addition.

If we consider **7** to form via the trimer, we see that while equal amounts of **3m** and **4m** were formed in the electrolysis, there is a slight excess of **4l** formation over **3l** (30%:16%, respectively). This observation, while small in magnitude, falls in line with the previous discussion, by considering ethyl acrylate a small step along the route from methyl acrylate to the extreme case of phenyl acrylate.

2.6. Addition to other esters

The carbanion addition to propenyl esters is rather inefficient, leading to disappointing yields of the 1:1 cross addition product of just 6% in each case (Table 6). It is clear from the reasonable yields of **3a** (ca. 50%) that the addition of the carbanion is much more facile to the in situ formed **2a** than to the higher concentration propenyl ester.

The addition of the allyl phenyl sulfone carbanion to diethyl maleate (**2q**) and diethyl fumarate (**2q′**) leads to formation of the same 1:1 adduct (**3q**). The reaction picture here is rather unclear, firstly it appears that additional reduction time for the fumarate doubled the yield of **3q** whilst restricting **2a** formation (presumably by consuming any that is formed). However, continued reduction generally leads to limited product yields, indicating that the 1:1 adduct may itself be electroreductive under these conditions.[16] Also, increased excess of the maleate/fumarate does not improve yields, a 3:1 excess giving only trace amounts of the 1:1 product. This suggests that **2q**/**2q′** are reducing under these conditions, possibly leading to oligomerization. It may be the more advanced oligomerization in the reaction with the fumarate, inherent in greater reduction time, which consumes any **3a** that is formed. It seems unlikely that any difference in the reactivity of the isomers would lead to formation of **3a** in one case and not the other, particularly as the same 1:1 adduct is formed in both cases.

3. Conclusion

The use of tetraalkylammonium salts as electrolytes has been found to allow the formation of electrogenerated bases of especially high reactivity. Such conditions allow allyl phenyl sulfone to undergo addition, via its carbanion, to a variety of electron deficient vinyl and propenyl compounds (sulfone, ketone, nitrile, and ester). These Michael additions are catalyzed by electrogenerated bases derived from the reactant itself, rather than via an added pro-base. This work clearly displays the variety of substrates to which addition will occur, yet also highlights some important limitations in terms of yields. While several cases approach moderate 50% yields, the products formed from addition to sulfonyl compounds provide the most useful yields from this EGB approach. Mechanisms are advanced to explain the relative yields of dimeric and trimeric products, based upon the nature of the substrate molecule. The mechanisms for the formation of two secondary products from initial trimer products are also discussed. Yields of 1:1 adducts range from 6 to 81%, while yields of 1:2 adducts range from 57 to 96%. Electrocatalytic factors for the majority of reactions are in excess of 10, representing better than 0.1 F mol^{-1} processes.

4. Experimental

4.1. General electrolysis procedure

A typical experiment utilizes 100 mg of allyl phenyl sulfone, **1**, along with the described mole ratio of alkene. Both alkene and **1** are dissolved in 22 mL of electrolyte solution, giving a typical concentration of **1** of 0.025 M, and added to the working electrode (WE) compartment of the electrolysis cell. The electrolyte solution is 0.100 M Et_4NBF_4, in dry acetonitrile. The acetonitrile is distilled fresh for each electrolysis from a reservoir containing phosphorus pentoxide. Electrolyte solution (6 mL) is added to the counter electrode (CE) compartment.

Electrolysis of **1** and substrate was carried out at -2.5 V in each case with stirring under positive nitrogen flow at room temperature. Electrolysis voltages were versus a 'pseudo-standard' silver wire (encased in porous vycor glass) reference electrode (RE).[17] The RE used is seen to have a calibration to SCE of approximately $+0.1$ V, when in 0.1 M Et_4NBF_4 acetonitrile solution. The CE and WE consisted of reticulated vitreous carbon (25 mm$\times$5 mm$\times$5 mm), their corresponding compartments separated by a course frit. The RE was placed within 0.5 cm of the WE. The reaction was stopped when thin-layer chromatography (TLC) indicated that **1** had been consumed. The reactant solution (WE compartment only) then underwent an aqueous workup with sequential washings of dichloromethane (benzene when noted). The organic phase was retained and dried with Na_2SO_4. The dichloromethane was removed by rotary evaporation, with the crude solution being purified by preparative TLC (1 mm thick, elution with ethyl acetate/

petroleum ether mixture, 1:1.5 ratio). Bands were identified, collected by scraping, and extracted with dichloromethane. Filtering removed the silica, with a rotary evaporator again employed to remove the solvent, yielding the desired products.

Notes. In the few cases when **1** was recovered, the yields of products and the catalytic factors are corrected accordingly. PTLC for **4d** and **4e** was not carried out, as NMR/LRMS showed purity, and benzene separation excluded electrolyte. Also these two compounds proved difficult to extract from collected PTLC bands (recovering no **4d** and small amounts of **4e**).

4.2. Analysis

Room temperature ^{1}H NMR spectra were recorded on a Varian Unity+300 as solutions in $CDCl_3$. ^{13}C NMR and COSY spectra were recorded on a Varian Unity Inova 500 spectrometer. Chemical shifts (δ) are relative to tetramethylsilane, and coupling constants (J) are given in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad. X-ray diffraction analyses were conducted using a Nonius Kappa CCD diffractometer. Low-resolution mass spectra (LRMS) were recorded on a Finnigan MAT TSQ-70 mass spectrometer, with high-resolution mass spectra (HRMS) recorded on a VGZAB-2E mass spectrometer.

4.3. Equipment/reagents

A potentiostatic controller, the Electrosynthesis Company (ESC) model 415, was used to control the applied potential. The charge used was tracked by a digital coulometer, ESC model 640. The applied potential was confirmed using a digital multimeter (Wavetek DM7), operating as a potentiometer. The electrode material was Duocel 80 PPI reticulated vitreous carbon. Substrates and electrolyte were used as purchased, from Alfa Aesar, Aldrich, and Lancaster (98–99% purity, except for **2k**: 85 and 90%, which is corrected for in ratio calculations).

4.4. Electrolysis of allyl phenyl sulfone (1) in isolation and with phenyl vinyl sulfone (2b), tolyl vinyl sulfone (2c), and divinyl sulfone (2f)

Electrolysis of 188 mg (0.047 M) of **1** and 88 mg (0.024 M; a 1:1.97 ratio relative to **1**) of **2b** was carried out for 3.5 °C. NMR analysis of the 296 mg of recovered crude gave a **4b**:**3a** ratio of 1:1.45. Other experimental and characterization details for these electrolyses have been previously published,[8] along with X-ray data for **4b** and **5f**. It should be noted that further NOE NMR study of **3a** has shown that the methyl group is *trans* to the phenyl sulfonyl group (as shown in Fig. 1).

4.5. Electrolysis of 1 and ethyl vinyl sulfone (2d)

Electrolysis of 99 mg (0.025 M) of **1** and 136 mg (0.051 M; 2.08:1 ratio relative to **1**) of **2d** was carried out for 3.0 °C. Upon benzene extraction, 221 mg (96%) of **4d** was isolated.

4.5.1. *E*-5,7-Bis(ethylsulfonyl)-3-phenylsulfonyl-2-heptene (4d). ^{1}H NMR (300 MHz, $CDCl_3$): 1.43 (6H, t, 7.5Hz), 2.30 (2H, m), 2.52 (2H, m), 3.06 (6H, m), 3.33 (2H, m), 5.17 (1H, d, J=17.4 Hz), 5.47 (1H, d, J=10.8 Hz), 5.75 (1H, dd, J=10.8, 17.4 Hz), 7.57 (2H, t, J=7.8 Hz), 7.70 (1H, t, J=7.5 Hz), 7.81 (2H, d, J=8.4 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): 6.9 (2C), 21.6 (2C), 46.2 (2C), 48.2 (2C), 67.9, 122.9, 129.2 (2C), 131.0 (2C), 133.5, 134.0, 134.9. LRMS (CI+): 423, 281. HRMS (CI+): calcd; 423.0970, found; 423.0960.

4.6. Electrolysis of 1 and methyl vinyl sulfone (2e)

Electrolysis of 90 mg (0.022 M) of **1** and 108 mg (0.046 M; 2.06:1 ratio relative to **1**) of **2e** was carried out for 3.1 °C. Upon benzene extraction 178 mg (92%) of **4e** was recovered.

4.6.1. *E*-5,7-Bis(methylsulfonyl)-3-phenylsulfonyl-2-heptene (4e). ^{1}H NMR (300 MHz, $CDCl_3$): 2.30 (2H, m), 2.47 (2H, m), 2.99 (6H, s), 3.15 (2H, m), 3.45 (2H, m), 5.16 (1H, d, 17.4Hz), 5.46 (1H, d, J=11.1 Hz), 5.76 (1H, dd, J=11.1, 17.4 Hz), 7.57 (2H, t, J=7.8 Hz), 7.70 (1H, t, J=7.5 Hz), 7.81 (2H, d, J=8.1 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): 22.1 (2C), 41.4 (2C), 49.1 (2C), 67.9, 123.0, 129.3 (2C), 131.0 (2C), 133.4, 134.0, 135.0. LRMS (CI+): 395, 180. HRMS (CI+): calcd; 395.0657, found; 395.0662.

4.7. Electrolysis of 1 with a mixture of two substrates

Electrolysis of 85 mg (0.021 M) of **1**, 119 mg (0.032 M) of **2b**, and 83 mg (0.031 M) of **2d** was carried out for 8.0 °C. This amounted to a 1:1.52:1.48 ratio of **2a**:**2b**:**2d**. NMR analysis of the 368 mg of recovered crude gave a **4d**:**4bd**:**4b** ratio of 1:3.22:3.42 and a **2d**:**2b** ratio of 17.4:1 (no **1**).

Electrolysis of 76 mg (0.019 M) of **1**, 114 mg (0.028 M) of **2c**, and 76 mg (0.029 M) of **2d** was carried out for 8.0 °C. This amounted to a 1:1.50:1.52 ratio of **2a**:**2c**:**2d**. NMR analysis of the 349 mg of recovered crude gave a **4d**:**4cd**:**4c** ratio of 1:2.80:2.30, and a **2d**:**2c** ratio of 11.7:1 (no **1**).

Electrolysis of 68 mg (0.017 M) of **1**, 69 mg (0.017 M) of **2c**, and 54 mg (0.020 M) of **2d** was carried out for 5.0 °C. This amounted to a 1:1.01:1.20 ratio of **2a**:**2c**:**2d**. Upon benzene extraction, NMR analysis of the 206 mg of recovered crude gave a **4d**:**4cd**:**4c** ratio of 1.30:2.00:1, with only **2d** remaining of the three starting materials. PTLC separation gave 32 mg (16%) of **4c** and 62 mg (34%) of **4cd**, along with less than 2 mg of **4d** (see Section 4.1, notes).

4.7.1. 1-Ethylsulfonyl,3-phenylsulfonyl,3-ethenyl,5-tolyl sulfonyl-pentane (4cd). ^{1}H NMR (300 MHz in $CDCl_3$): 1.44 (3H, t. J=7.5 Hz), 2.24 (2H, m), 2.41 (2H, m), 2.48 (3H, s), 3.02 (5H, m), 3.32 (2H, m), 5.10 (1H, d. 17.7Hz), 5.43 (1H, d. J=10.8 Hz), 5.69 (1H, dd, J=10.8, 17.4 Hz), 7.40 (2H, d. J=8.4 Hz), 7.55 (2H, t. J=8.1 Hz), 7.69 (1H, t. J=7.5 Hz), 7.77 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): 6.9, 21.6, 21.9, 22.9, 46.2, 48.1, 50.9, 67.8, 122.8, 128.3 (2C), 129.2 (2C), 130.5 (2C), 131.0 (2C), 133.4, 134.0, 134.8, 135.8, 145.6. LRMS (CI+): 485, 343. HRMS (CI+): calcd; 485.1126, found; 485.1107.

Electrolysis of 79 mg (0.020 M) of **1**, 110 mg (0.030 M) of **2b**, and 76 mg (0.033 M) of **2e** was carried out for 8.0 °C. This amounted to a 1:1.51:1.65 ratio of **2a**:**2b**:**2e**. NMR analysis of the 330 mg of recovered crude product gave a **4e**:**4be**:**4b** ratio of 1:2.73:2.69, and a **2e**:**2b** ratio of 6.64:1 (no **1**).

Electrolysis of 88 mg (0.022 M) of **1**, 93 mg (0.035 M) of **2d**, and 83 mg (0.036 M) of **2e** was carried out for 8.0 °C. This amounted to a 1:1.62:1.60 ratio of **2a**:**2d**:**2e**. NMR analysis of the 348 mg of recovered crude gave a **2d**:**2c** ratio of 1.36:1 (no **1**), but could not distinguish between the three possible trimers. LRMS analysis of the crude was used to arrive at a **4e**:**4de**:**4d** of 1:2.03:1.15.

4.8. Electrolysis of 1 with acrylonitrile (2g)

Electrolysis of 95 mg (0.024 M) of **1** and 57 mg (0.049 M; 2.06:1 ratio relative to **1**) of **2g** was carried out for 2.0 °C. Upon extraction/PTLC 63 mg (42%) of **4g**, 7 mg (6%) of **3g**, and 3 mg (3%) of **2a** were isolated.

Electrolysis of 80 mg (0.020 M) of **1** and 72 mg (0.062 M; 3.09:1 ratio relative to **1**) of **2g** was carried out for 3.5 °C. Upon extraction/PTLC 72 mg (57%) of **4g** was isolated.

Compound **3g**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.98 (3H, d, J=7.2 Hz), 2.59 (4H, s), 7.18 (1H, q. J=7.2 Hz), 7.56 (2H, t, J=7.8 Hz), 7.65 (1H, t, J=7.8 Hz), 7.86 (2H d, J=8.1 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): partial only: 14.8, 22.5, 32.6, 105.9, 128.3 (2C), 129.7 (2C), 133.9, 141.3. LRMS (CI+): 236, 125. HRMS (CI+): calcd; 236.0745, found; 236.0747.

Compound **4g**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.18 (2H, m), 2.36 (2H, m), 2.53 (2H, m), 2.73 (2H, m), 5.14 (1H, d, J=17.4 Hz), 5.53 (1H, d, J=11.1 Hz), 5.74 (1H, dd, J=11.1, 17.4 Hz), 7.60 (2H, t, J=7.8 Hz), 7.75 (3H, m). X-ray crystallography confirms structure (CCDC 254787).

4.9. Electrolysis of 1 with crotononitrile (2h)

Electrolysis of 97 mg (0.024 M) of **1** and 111 mg (0.075 M; 3.11:1 ratio relative to **1**) of **2h** was carried out for 3.3 °C. Upon extraction/PTLC 34 mg (26%) of **3h** and 42 mg (43%) of **3a** were isolated.

Electrolysis of 89 mg (0.022 M) of **1** and 196 mg (0.133 M; 5.98:1 ratio relative to **1**) of **2h** was carried out for 4.0 °C. Upon extraction/PTLC 26.4 mg (22%) of **3h** and 24.6 mg (28%) of **3a** were isolated.

Compound **3h**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.22 (3H, d, J=6.9 Hz), 2.01 (3H, d, J=7.5 Hz), 2.63 (2H, d, J=7.5 Hz) 3.16 (1H, m), 7.11 (1H, q. J=7.5 Hz), 7.56 (2H, m), 7.63 (1H, m), 7.86 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): 15.0, 18.6, 23.5, 30.7, 118.2, 128.1 (2C), 129.6 (2C), 133.7, 140.4, 140.6, 143.0. LRMS (CI+): 250. HRMS (CI+): calcd; 250.0902, found; 250.0904.

4.10. Electrolysis of 1 with methyl vinyl ketone (2i)

Electrolysis of 96 mg (0.024 M) of **1** and 37 mg (0.024 M; 1.00:1 ratio relative to **1**) of **2i** was carried out for 3.0 °C. Upon extraction/PTLC 35.7 mg (28%) of **3i**, 4.1 mg (3%) of **6i** (hydroxyl *syn* to acetyl), 2.8 mg (2%) of **6i** (hydroxyl *anti* to acetyl) and 6.3 mg (7%) of **2a** were isolated. 2.7 mg of **1** was recovered.

Electrolysis of 86 mg (0.021 M) of **1** and 101 mg (0.065 M; 3.05:1 ratio relative to **1**) of **2i** was carried out for 4.0 °C. Upon extraction/PTLC 21 mg (18%) of **3i**, 11 mg (7%) of **6i** (hydroxyl *syn* to acetyl) and 7 mg (5%) of **6i** (hydroxyl *anti* to acetyl) were isolated.

Compound **3i**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.87 (3H, d, J=7.2 Hz), 2.10 (3H, s), 2.44 (2H, t, J=7.2 Hz), 2.69 (2H, t, J=7.2 Hz), 7.03 (1H, q. J=7.2 Hz), 7.53 (2H, m), 7.61 (1H, m), 7.84 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): 14.3, 20.3, 30.1, 42.3, 128.2 (2C), 129.5 (2C), 133.5, 138.5, 139.7, 140.9, 207.4. LRMS (CI+): 253, 168, 125. HRMS (CI+): calcd; 253.0898, found; 253.0890. NOE NMR study of **3i** shows methyl group is *trans* to the phenyl sulfonyl group (as shown in Fig. 1).

Compound **6i** (*hydroxyl syn to acetyl*). ^{1}H NMR (300 MHz, $CDCl_3$): 1.14 (3H, s), 1.25 (1H, m), 1.64 (3H, m), 2.01 (1H, d, J=12 Hz), 2.22 (3H, s), 2.45 (3H, m), 3.74 (1H, d, J=2.4 Hz), 5.24 (1H, d, J=16.8 Hz), 5.64 (2H, m), 7.53 (2H, t, J=7.5 Hz), 7.65 (1H, t, J=7.8 Hz), 7.80 (2H, d, J=7.5 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): 23.8, 27.1, 28.4, 31.1, 34.3, 52.3, 67.4, 68.7, 123.6, 128.5 (2C), 131.0 (2C), 132.8, 133.8, 134.8, 213.8. LRMS (CI+): 323, 305, 181, 163. HRMS (CI+): calcd; 323.1317, found; 323.1325. Configuration of the hydroxyl group with regards to the carbonyl group is inferred from the NMR shift of the hydroxyl group proton.

Compound **6i** (*hydroxyl anti to acetyl*). ^{1}H NMR (300 MHz, $CDCl_3$): partial only: 1.22 (3H, s), 2.22 (3H, s), 2.84 (1H, s), 5.24 (1H, dd, J=1.8, 16.2 Hz), 5.61 (2H, m), 7.52 (2H, m), 7.63 (1H, m), 7.80 (2H, m). ^{13}C NMR (500 MHz, $CDCl_3$): 21.6, 25.7, 28.2, 31.2, 36.8, 54.3, 67.6, 72.1, 123.5, 128.5 (2C), 131.0 (2C), 133.2, 133.9, 134.7, 211.0. LRMS (CI+): 323, 241, 195, 124. HRMS (CI+): calcd; 323.1317, found; 323.1312.

4.11. Electrolysis of 1 with ethyl vinyl ketone (2j)

Electrolysis of 95 mg (0.024 M) of **1** and 88 mg (0.048 M; 2.01:1 ratio relative to **1**) of **2j** was carried out for 7.5 °C. Upon extraction/PTLC 37 mg (27%) of **3j** and 1 mg (1%) of **2a** were isolated, along with a trace amount of **6j** (tentatively assigned).

Electrolysis of 93 mg (0.023 M) of **1** and 165 mg (0.089 M; 3.84:1 ratio relative to **1**) of **2j** was carried out for 6.2 °C. Upon extraction/PTLC 64 mg (47%) of **3j** was isolated, along with a trace amount of **6j** (tentatively assigned).

Compound **3j**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.03 (3H, t, J=7.2 Hz), 1.87 (3H, d, J=7.2 Hz), 2.37 (2H, q, J=7.2 Hz), 2.45 (2H, t, J=7.5 Hz), 2.69 (2H, t, J=7.5 Hz), 7.02 (1H, q. J=7.2 Hz), 7.53 (2H, m), 7.61 (1H, m), 7.84 (2H m). ^{13}C NMR (300 MHz, $CDCl_3$): 7.9, 14.3, 20.3, 36.1, 40.9, 128.2 (2C), 129.4 (2C), 133.5, 138.5, 139.7, 141.0, 210.1. LRMS

(CI+): 267, 209, 191. HRMS (CI+): calcd; 267.1055, found; 267.1062.

Compound **6j**. ^{1}H NMR (300 MHz, $CDCl_3$): partial only: 3.73 (1H, d, J=2.4 Hz).

4.12. Electrolysis of 1 with propenyl methyl ketone (2k)

Electrolysis of 100 mg (0.025 M) of **1** and 137 mg, corrected to 116 mg (0.063 M; 2.52:1 ratio relative to **1**) of **2k** was carried out for 12.6 °C. Upon extraction/PTLC 38 mg (26%) of **3k** and 4 mg (4%) of impure **3a** were isolated.

Compound **3k**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.01 (3H, d, J=6.9 Hz), 1.96 (6H, m), 2.68 (2H, m) 3.35 (1H, m), 6.98 (1H, q. J=7.2 Hz), 7.51 (2H, m), 7.59 (1H, m), 7.83 (2H, m)). ^{13}C NMR (500 MHz, $CDCl_3$): 14.6, 19.0, 28.1, 30.0, 48.2, 127.9 (2C), 129.1 (2C), 133.1, 138.7, 140.9, 145.1, 206.3. LRMS (CI+): 267, 125. HRMS (CI+): calcd; 267.1055, found; 267.1051.

4.13. Electrolysis of 1 with methyl acrylate (2l)

Electrolysis of 85 mg (0.021 M) of **1** and 84 mg (0.044 M; 2.09:1 ratio relative to **1**) of **2l** was carried out for 18.0 °C. Upon extraction/PTLC 22.5 mg (18%) of **3l**, 27 mg (16%) of **4l**, 18.1 mg (12%) of **7l** and 6.4 mg (8%) of **2a** were isolated.

Compound **3l**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.89 (3H, d, J=6.9 Hz), 2.51 (4H, m), 3.65 (3H, s), 7.06 (1H, q. J=7.2 Hz), 7.54 (2H, m), 7.62 (1H, m), 7.85 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): 14.3, 21.7, 32.9, 52.0, 128.3 (2C), 129.5 (2C), 133.5, 139.0, 139.7, 140.5, 172.9. LRMS (CI+): 269. HRMS (CI+): calcd; 269.0848, found; 269.0851.

Compound **4l**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.12 (2H, m), 2.35 (4H, m), 2.65 (2H, m), 3.69 (6H, s), 5.09 (1H, d, J=17.4 Hz), 5.39 (1H, d, J=10.8 Hz), 5.75 (1H, dd, 10.8, J=17.4 Hz), 7.53 (2H, t, J=7.5 Hz), 7.66 (1H, m), 7.80 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): 25.0 (2C), 28.7 (2C), 52.2 (2C), 69.0, 121.7, 128.8 (2C), 130.9 (2C), 132.1, 132.6, 134.9, 173.2 (2C). LRMS (CI+): 355, 213. HRMS (CI+): calcd; 355.1215, found; 355.1219.

Compound **7l**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.92–2.02 (1H-keto, m), 2.15–2.51 (4H-enol, 5H-keto, overlapping m), 2.57 (1H-enol, d, J=15.9 Hz), 2.86 (1H-enol, d, J=15.3 Hz), 3.67 (3H-keto, s), 3.76 (3H-enol, s), 5.10 (1H, d, J=17.4 Hz), 5.44 (1H, d, J=10.8 Hz), 5.71 (1H, dd, 10.8, J=17.4 Hz), 7.55 (2H, t, J=7.8 Hz), 7.67 (1H, t, J=7.2 Hz), 7.84 (2H, d, J=7.8 Hz), 12.08 (1H-enol, s). LRMS (CI+): 323, 181. HRMS (CI+): calcd; 323.0953, found; 323.0943. X-ray crystallography confirms enol structure (CCDC 254677).

4.14. Electrolysis of 1 with ethyl acrylate (2m)

Electrolysis of 87 mg (0.022 M) of **1** and 100 mg (0.045 M; 2.09:1 ratio relative to **1**) of **2m** was carried out for 9.2 °C. Upon extraction/PTLC 34.4 mg (28%) of **3m**, 33.6 mg (20%) of **4m**, 10 mg (7%) of **7m**, 6.6 mg (8%) of **2a** and 2 mg (3%) of **3a** were isolated, along with 8.4 mg of recovered **1**.

Electrolysis of 84 mg (0.021 M) of **1** and 142 mg (0.064 M; 3.08:1 ratio relative to **1**) of **2m** was carried out for 22.2 °C. Upon extraction/PTLC 16.8 mg (13%) of **3m**, 26.1 mg (15%) of **4m**, 19.8 mg (13%) of **7m**, and 1.3 mg (2%) of **2a** were isolated.

Compound **3m**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.23 (3H, t, J=7.2 Hz), 1.89 (3H, d, J=7.2 Hz), 2.49 (4H, m), 4.09 (2H, q, J=7.2 Hz), 7.05 (1H, q. J=7.2 Hz), 7.53 (2H, m), 7.63 (1H, m), 7.85 (2H, m). ^{13}C NMR (500 MHz, $CDCl_3$): 14.1, 14.2, 21.4, 32.9, 60.6, 128.1 (2C), 129.2 (2C), 133.2, 138.7, 139.6, 140.5, 172.2. LRMS (CI+): 283. HRMS (CI+): calcd; 283.1004, found; 283.1004.

Compound **4m**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (6H, t, J=7.2 Hz), 2.11 (2H, m), 2.33 (4H, m), 2.63 (2H, m), 4.14 (4H, q, J=7.2 Hz), 5.09 (1H, d, J=17.7 Hz), 5.38 (1H, d, J=10.8 Hz), 5.75 (1H, dd, J=10.8, 17.7 Hz), 7.52 (2H, t, J=7.5 Hz), 7.65 (1H, m), 7.80 (2H, d, J=7.2 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): 14.2 (2C), 24.8 (2C), 28.7 (2C), 60.8 (2C), 68.9, 121.4, 128.6 (2C), 130.7 (2C), 133.9, 134.8, 135.1, 172.6 (2C). LRMS (CI+): 383, 241. HRMS (CI+): calcd; 383.1528, found; 383.1517.

Compound **7m**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.29 (3H-enol, 3H-keto, overlapping t), 2.14–2.51 (4H-enol, 6H-keto, overlapping m), 2.60 (1H-enol, d, J=16.2 Hz), 2.87 (1H-enol, d, J=15.6 Hz), 4.22 (2H-keto, 2H-enol, m), 5.10 (1H, d, J=17.4 Hz), 5.44 (1H, d, J=10.8 Hz), 5.70 (1H, dd, J=10.8, 17.4 Hz), 7.55 (2H, t, J=7.8 Hz), 7.67 (1H, t, J=7.5 Hz), 7.84 (2H, d, J=7.2 Hz), 12.16 (1H-enol, s). ^{13}C NMR (500 MHz, $CDCl_3$): 14.2, 24.3, 25.1, 25.7, 60.7, 66.2, 94.3, 122.5, 128.5 (2C), 130.8 (2C), 131.9, 133.9, 135.0, 170.1, 171.7. LRMS (CI+): 337, 195. HRMS (CI+): calcd; 337.1110, found; 337.1109.

4.15. Electrolysis of 1 with phenyl acrylate (2n)

Electrolysis of 110 mg (0.027 M) of **1** and 182 mg (0.056 M; 2.03:1 ratio relative to **1**) of **2n** was carried out for 35.0 °C. Upon extraction/PTLC 40.2 mg (22%) of **3n** and 23.9 mg (24%) of **2a** were isolated, along with 9 mg of recovered **1**.

Compound **3n**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.94 (3H, d, J=7.2 Hz), 2.65 (2H, m), 2.78 (2H, m), 7.05 (2H, d, J=8.4 Hz), 7.12 (1H, q. J=6.9 Hz), 7.23 (1H, m), 7.38 (2H, t, J=7.8 Hz), 7.55 (2H, m), 7.64 (1H, m), 7.90 (2H m). ^{13}C NMR (300 MHz, $CDCl_3$): 14.5, 21.5, 32.7, 121.7 (2C), 126.1, 126.2, 128.3 (2C), 129.5 (2C), 129.7 (2C), 129.8, 139.4, 140.3, 171.2. LRMS (CI+): 365, 331, 183. HRMS (CI+): calcd; 331.1004, found; 331.1012.

4.16. Electrolysis of 1 with methyl crotonate (2o)

Electrolysis of 80 mg (0.020 M) of **1** and 88 mg (0.040 M; 2.00:1 ratio relative to **1**) of **2o** was carried out for 4.0 °C. Upon extraction/PTLC 8 mg (6%) of **3o** and 46 mg (58%) of **3a** were isolated.

Compound **3o**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (3H, d, J=7.2 Hz), 1.98 (3H, d, J=6.9 Hz), 2.52 (2H, d, J=7.8 Hz) 3.29 (1H, q, 7.2), 3.54 (3H, s), 7.06 (1H, q. J=7.2 Hz), 7.52 (2H, m), 7.60 (1H, m), 7.85 (2H, m). ^{13}C NMR (500 MHz, $CDCl_3$): 14.6, 18.9, 29.6, 39.1, 51.6, 128.0 (2C), 129.1 (2C), 133.0, 138.8, 140.7, 144.8, 172.0. LRMS (CI+): 283, 251, 141. HRMS (CI+): calcd; 283.1004, found; 283.0995.

4.17. Electrolysis of 1 with ethyl crotonate (2p)

Electrolysis of 87 mg (0.022 M) of **1** and 114 mg (0.045 M; 2.09:1 ratio relative to **1**) of **2p** was carried out for 5.6 °C. Upon extraction/PTLC 8 mg (6%) of **3p** and 40 mg (46%) of **3a** were isolated.

Compound **3p**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.09 (3H, d, J=7.2 Hz), 1.20 (3H, t, J=7.2 Hz), 1.98 (3H, d, J=7.2 Hz), 2.50 (2H, m) 3.29 (1H, m), 4.00 (2H, q, J=7.2 Hz), 7.05 (1H, q. J=7.2 Hz), 7.52 (2H, m), 7.60 (1H, m), 7.86 (2H, m). ^{13}C NMR (500 MHz, $CDCl_3$): 14.1, 14.6, 18.9, 29.6, 39.4, 60.5, 128.0 (2C), 129.1 (2C), 133.0, 138.7, 140.7, 144.9, 171.5. LRMS (CI+): 297, 251. HRMS (CI+): calcd; 297.1161, found; 297.1158.

4.18. Electrolysis of 1 with diethyl maleate (2q), and with diethyl fumarate (2q′)

Electrolysis of 87 mg (0.022 M) of **1** and 84 mg (0.022 M; 1.02:1 ratio relative to **1**) of **2q** was carried out for 10.0 °C. Upon extraction/PTLC 16 mg (11%) of **3q**, 12 mg (16%) of **3a**, and 15.5 mg (20%) of **2a** were isolated, along with 10.5 mg of recovered **1**.

Electrolysis of 99 mg (0.025 M) of **1** and 96 mg (0.025 M; 1.03:1 ratio relative to **1**) of **2q′** was carried out for 20.0 °C. Upon extraction/PTLC 35 mg (22%) of **3q** and 3.6 mg (4%) of **2a** were isolated, along with 18.4 mg of recovered **1**.

Compound **3q**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.01 (3H, t, J=7.2 Hz), 1.23 (3H, t, J=7.2 Hz), 1.90 (3H, d, J=7.5 Hz), 2.45 (1H, dd, 4.5, J=17.1 Hz), 3.05 (1H, dd, 10.2, J=17.1 Hz), 3.91 (2H, m), 4.09 (2H, m), 7.18 (1H, q. J=7.2 Hz), 7.53 (2H, m), 7.62 (1H, m), 7.88 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): 14.1, 14.3, 14.7, 34.8, 39.4, 61.2, 61.7, 128.6 (2C), 129.3 (2C), 133.6, 139.6, 139.7, 141.3, 170.6, 171.3. LRMS (CI+): 355. HRMS (CI+): calcd; 355.1215, found; 353.1222.

4.19. X-ray data

Crystallographic data (excluding structure factors) for **4g** and the enol form of **7l** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 254787 and CCDC 254677, respectively. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Efficient approach to the unknown isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine system by regioselective intramolecular nitrone cycloadditions

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Abstract—An effective approach to the new isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine system was provided by way of an intramolecular nitrone cycloaddition. The required nitrones were built in good yields starting from thiophene-2-carboxylic acids. The same skeleton was achieved in optically active form employing chiral nitrones derived from *N*-α-methylbenzyl- and the *N*-α-hydroxymethylbenzyl-hydroxylamines. The absolute configuration of the products was assigned by X-ray analysis.

1. Introduction

1,3-Dipolar cycloadditions furnish an extensively studied and widely used method for the synthesis of five-membered heterocycles.[1] Among them, those involving nitrones constitute an efficient and versatile entry to isoxazolidines, which in turn represent valuable intermediates in organic synthesis.[2] In particular, the intramolecular nitrone cycloaddition leads directly to isoxazolidines annulated with another ring in a fused or bridged mode. Furthermore, they often benefit from highly regio- and stereoselective outcomes.[3]

Dealing with our interest to the synthesis of nitrogenated heteropolycylic compounds in enantiopure form, we studied the intramolecular cycloadditions of nitrones already containing a heterocyclic unit, namely pyrrole,[4] indole[5] and imidazole,[6] bearing an allylic pendant at the nitrogen atom. At this point, we decided to extend such a synthetic approach by using nitrones having a non-nitrogenated heterocycle skeleton, but endowed with an allylic pendant linked to a ring carbon through a protected amine functionality.

In this paper, we report the results on the intramolecular 1,3-dipolar cycloadditions of thienyl-tethered nitrones derived from the aldehydes **5**, which seemed potentially able to furnish interesting thieno-piperidine derivatives. The latter may well be of interest in view of the pharmacological properties of some thieno-fused azaheterocycles.[7]

2. Results and discussion

Aldehydes **5** were synthesized starting from carboxylic acids of formula **1** by the synthetic sequence depicted in Scheme 1. The first step was the conversion to the acyl azides **2**[8] via the corresponding acyl chlorides. Azides **2** were submitted to Curtius degradation in EtOH, in the absence of water, with the aim to produce directly the carbamates **3**, which were then *N*-allylated by a standard procedure. Finally, a Vilsmeier formylation permitted an entry to the desired aldehydes **5**. It must be noted that this formylation took place exclusively at the C-3 ring carbon in both cases, reasonably because of the *o*,*p*-directing effect of the aminosubstituent which predominates over that of the methyl group of **4a**.

The generation of the suitable nitrones was performed employing the commercially available *N*-benzylhydroxylamine. However, addition of the aldehydes **5** to a suspension containing the *N*-benzylhydroxylamine hydrochloride, $NaHCO_3$ and $MgSO_4$ in diethyl ether at room temperature

Keywords: Nitrones; Intramolecular cycloadditions; Regioselectivity; Fused-ring thiophenes.
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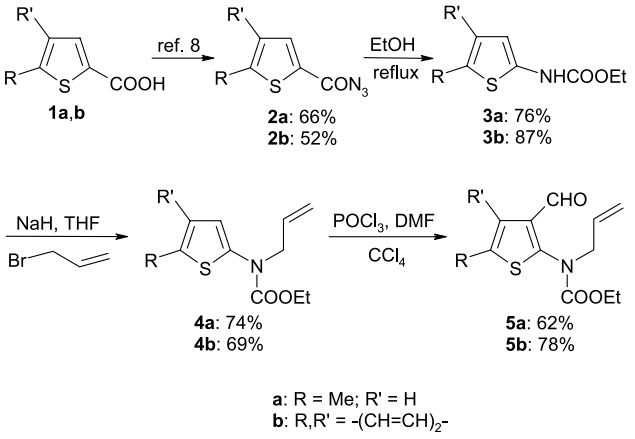
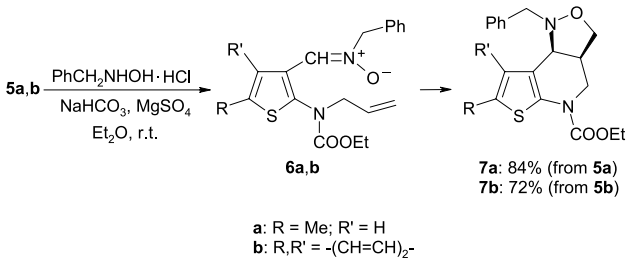


Scheme 1. Preparation of 2-(*N*-allyl-*N*-carbethoxy-amino)-thiophene-3-carbaldehydes.

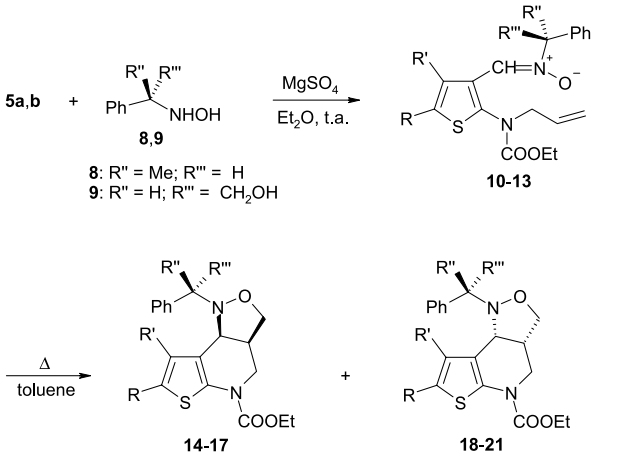
showed somehow different results (Scheme 2). The nitrone **6a** was isolated and characterized and successively cyclized on heating in refluxing toluene. Conversely, the nitrone **6b** directly underwent cyclization at room temperature. This fact does not find a clear explanation, but confirms the subtle interplay of steric and electronic factors in dictating intramolecular nitrone cycloadditions.[9] In every case, a single cycloadduct was obtained in excellent yield. Comprehensive 2D NMR studies have indicated a spatial relationship between the methynic hydrogens, thus establishing a fused-type tricyclic structure with a *cis* ring junction. This means that the cycloaddition proceeded with total regioselectivity and diastereoselectivity.

In the light of the satisfactory trend of the cycloaddition in terms of both selectivity and yields, we directed our attention to the preparation of the related structures in optically active form. The devised way to achieve this goal was to generate nitrones by enantiopure chiral benzyl-type hydroxylamines. In particular, we envisaged the (*R*)-α-methylbenzylhydroxylamine (**8**) and the (*R*)-α-(hydroxymethyl)benzylhydroxylamine (**9**), whose preparations have been described in the literature.[10,11]

The aldehydes **5** showed the same behaviour toward **8** and **9** already noticed with the benzylhydroxylamine, that is only the nitrones derived from **5a** were isolated and fully characterized. However, all the nitrones **10–13** underwent a totally regioselective cycloaddition in agreement to the behaviour of the achiral compounds **6**, but each giving two diastereoisomeric products. Analytical and spectral data of the cycloadduct pairs were in accordance for diastereoisomeric *cis* ring-fused structures (Scheme 3).



Scheme 2. Reaction of aldehydes **5a**,**b** with *N*-benzylhydroxylamine.



Reagents				Nitrones	Products (% yields)
	R	R'	R'' R'''		
5a	Me	H	**8** Me H	**10**	(α*R*,3a*S*,8b*S*)-**14** (42) (α*R*,3a*R*,8b*R*)-**18** (31)
5b	-(CH=CH)$_2$-		**8** Me H	**11**	(α*R*,3a*S*,10c*S*)-**15** (34) (α*R*,3a*R*,10c*R*)-**19** (14)
5a	Me	H	**9** H CH_2OH	**12**	(α*R*,3a*S*,8b*S*)-**16** (17) (α*R*,3a*R*,8b*R*)-**20** (51)
5b	-(CH=CH)$_2$-		**9** H CH_2OH	**13**	(α*R*,3a*S*,10c*S*)-**17** (25) (α*R*,3a*R*,10c*R*)-**21** (54)

Scheme 3. Reaction of aldehydes **5a**,**b** with enantiopure hydroxylamines **8** and **9**.

The absolute stereochemistry of the cycloadducts **14/18**, **16/20** and **17/21** was unequivocally inferred by X-ray diffractometric analysis carried out on the minor products of each pair (Figs. 1–3).[12] In all instances, the relative configuration of the new stereocentres was *cis*, in particular *R*,*R* in the case of the (*R*)-α-methylbenzyl pendant and *S*,*S* in the case of the (*R*)-α-(hydroxymethyl)benzyl one. Unfortunately, neither **15** nor **19** gave crystals suitable for the diffractometric analysis; hence, by analogy with the above evidence, we tentatively assigned the *R*,*R* absolute configuration to **19** as being the minor product with the (*R*)-α-methylbenzyl pendant.

From the point of view of the stereochemistry, it must be noted that a modest asymmetric induction was operative in the case of the *N*-α-methylbenzyl-substituted nitrones **10** and **11**, in line with previous results obtained in intramolecular reactions of nitrones bearing the same chiral

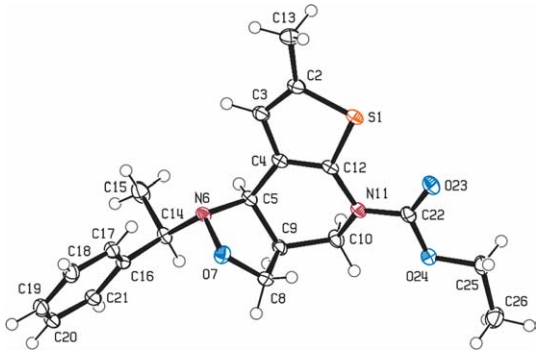


Figure 1. ORTEP plot of **18** at 90 K. Atomic displacement parameters at 50% probability level. H atoms not to scale.

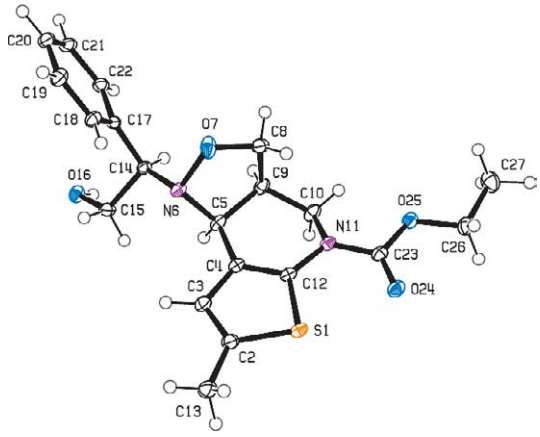


Figure 2. ORTEP plot of **16** at 90 K. Atomic displacement parameters at 50% probability level. H atoms not to scale.

auxiliary.[13] However, the diastereoselectivity increased when the nitrones having the α-(hydroxymethyl)benzyl-pendant were used; in the crude product mixture arising from **12** and **13** the diastereoisomeric ratio was determined to be 75:25 by ^{1}H NMR spectroscopy. The better effectiveness of hydroxylated chiral residue may be reasonably ascribed to the formation of a hydrogen bond with the nitrone oxygen, so making the substrate less flexible and consequently increasing the diastereofacial discrimination of the dipole. Therefore, the allylic moiety approaches the dipole from the face opposite to the phenyl group and the latter is forced to move outside during the rehybridization of the reaction centers, as depicted in Figure 4 representing the suggested transition state for the formation of the major diastereoisomer **20** from **12**.

With the aim to improve the degree of diastereoselectivity and taking into account the known chelating ability[14] of the (*R*)-α-(hydroxymethylbenzyl)hydroxylamine, we carried out the cycloaddition of the nitrone **12** in the presence of metal cations. The reaction was tested with a wide range of Lewis acid [$Zn(OTf)_2$, $Sc(OTf)_2$, $MgBr_2$, $TiCl_4$, $Co(OAc)_2$, AgOAc] and TEA, in different solvents (i.e. CH_2Cl_2 and toluene) and temperatures. Unfortunately, all the experiments gave no improvement of diastereoselectivity or even no reaction, probably because of an excessively strong nitrone oxygen chelation.

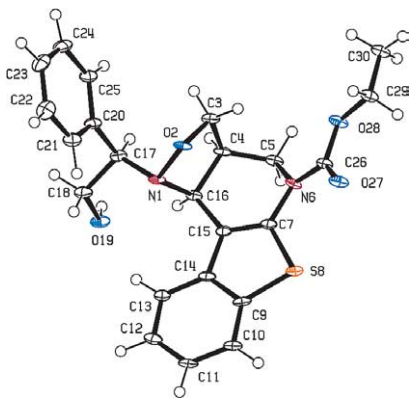


Figure 3. ORTEP plot of **17** at 90 K. Atomic displacement parameters at 50% probability level. H atoms not to scale.

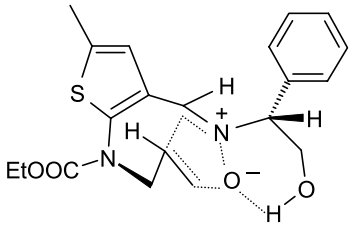


Figure 4. Proposed transition state for the compound **20**.

In conclusion, we have developed a strategy for the synthesis of the new isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine skeleton starting from thiophene-2-carboxylic acids. The three fused-ring system was assembled directly from a nitrone intramolecular cycloaddition.

3. Experimental

3.1. General

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on an AVANCE Bruker 400. Chemical shifts are given in ppm downfield from $SiMe_4$. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT/IR 5300 spectrophotometer. Mass spectra were determined on a WG-70EQ instrument.

3.2. Preparation of acyl azides 2a and 2b

The compounds were prepared as described in the literature.[8a,b]

3.3. General procedure for the preparation of 2-(*N*-carbethoxy-amino)-thiophenes (3a,b)

A solution of **2** (11.7 mmol) in EtOH (20 ml) and toluene (30 ml) was heated to reflux for 24 h. The solvent was evaporated under reduced pressure to give directly **3a**,**b**.

3.3.1. 2-(*N*-Carbethoxy-amino)-5-methyl-thiophene (3a). Yield: 76%. Mp 72–73 °C (cream crystals from diisopropyl ether). IR (nujol): 3246, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.1 Hz), 2.40 (3H, s), 4.24 (2H, q, J=7.1 Hz), 6.41 (1H, d, J=3.6 Hz), 6.46 (1H, d, J=3.6 Hz), 7.03 (1H, br s, missing after deuteriation). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 15.3 (q), 62.0 (t), 113.3 (d), 122.7 (d), 131.9 (s), 137.9 (s), 154.7 (s). Anal. calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56. Found C, 52.01; H, 5.78; N, 7.62.

3.3.2. 2-(*N*-Carbethoxy-amino)-benzothiophene (3b). Yield: 87%. Mp 154–155 °C (white crystals from diisopropyl ether). IR (nujol): 3300, 1691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 6.83 (1H, s), 7.24 (1H, dd, J=7.3, 7.8 Hz), 7.32 (1H, dd, J=7.3, 7.9 Hz), 7.55 (1H, s), 7.60 (1H, d, J=7.9 Hz), 7.73 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9

(q), 62.7 (t), 107.0 (d), 122.2 (d), 122.4 (d), 123.4 (d), 125.0 (d), 135.3 (s), 138.3 (s), 140.4 (s), 153.6 (s). Anal. calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found C, 59.79; H, 4.88; N, 6.12.

3.4. General procedure for the preparation of 2-(*N*-allyl-*N*-carbethoxy-amino)-thiophenes (4a,b)

A solution of **3** (2.4 mmol) in THF (5 ml) was added dropwise to a suspension of 60% NaH (150 mg, 3.6 mmol) in dry THF (33 ml), under nitrogen atmosphere. Allyl bromide (0.42 ml, 4.8 mmol) was added at −5 °C, then the mixture was heated to reflux for 24 h. After cooling to room temperature, H_2O (30 ml) was added. The mixture was extracted with CH_2Cl_2 (2×60 ml) and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **4**.

3.4.1. 2-(*N*-Allyl-*N*-carbethoxy-amino)-5-methyl-thiophene (4a). Yield: 74%. Colourless oil. IR (nujol): 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=6.9 Hz), 2.41 (3H, s), 4.20–4.28 (4H, overlapping), 5.18 (1H, dd, J=1.5, 17.0 Hz), 5.21 (1H, dd, J=1.5, 10.3 Hz), 5.90 (1H, tdd, J=5.6, 10.3, 17.0 Hz), 6.49 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 15.6 (q), 54.7 (t), 62.3 (t), 117.5 (t), 122.8 (d), 126.7 (d), 133.9 (d), 142.0 (s), 146.3 (s), 154.0 (s). Anal. calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found C, 58.61; H, 6.87; N, 6.09.

3.4.2. 2-(*N*-Allyl-*N*-carbethoxy-amino)-benzothiophene (4b). Yield: 69%. Colourless oil. IR (nujol): 1696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=7.1 Hz), 4.33 (2H, q, J=7.1 Hz), 4.48 (2H, d, J=4.8 Hz), 5.26 (1H, d, J=10.2 Hz), 5.29 (1H, d, J=16.4 Hz), 5.97 (1H, tdd, J=4.8, 10.2, 16.4 Hz), 6.85 (1H, s), 7.26 (1H, dd, J=7.3, 7.9 Hz), 7.33 (1H, dd, J=7.3, 7.8 Hz), 7.65 (1H, d, J=7.8 Hz), 7.74 (1H, d, J=7.9 Hz). ^1H NMR (400 MHz, CD_3OD) δ: 1.32 (3H, t, J=7.1 Hz), 4.27 (2H, q, J=7.1 Hz), 4.49 (2H, br s), 5.22 (1H, dd, J=1.1, 10.3 Hz), 5.25 (1H, dd, J=1.1, 17.1 Hz), 5.96 (1H, tdd, J=5.3, 10.3, 17.1 Hz), 6.94 (1H, s), 7.24 (1H, dd, J=7.1, 7.6 Hz), 7.30 (1H, dd, J=7.1, 7.8 Hz), 7.64 (1H, d, J=7.6 Hz), 7.71 (1H, d, J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 60.8 (t), 63.3 (t), 117.8 (t), 122.1 (d), 122.9 (d), 123.8 (d), 124.5 (d), 124.8 (d), 132.8 (d), 137.2 (s), 138.1 (s), 144.8 (s), 154.6 (s). Anal. calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found C, 64.18; H, 5.75; N, 5.22.

3.5. General procedure for the preparation of 2-(*N*-allyl-*N*-carbethoxy-amino)-thiophene-3-carbaldehydes (5a,b)

To a solution of $POCl_3$ (0.82 ml, 8.8 mmol) and DMF (0.90 ml, 12.0 mmol) in CCl_4 (40 ml), cooled at 0 °C, **4** (5.8 mmol) was added. The mixture was heated at reflux for 24 h, then the solvent was removed under reduced pressure. The residue was treated with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (50 ml×3). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified through a silica gel column with light petroleum/AcOEt (10:1) as eluent to afford **5**.

3.5.1. 2-(*N*-Allyl-*N*-carbethoxy-amino)-5-methyl-thiophene-3-carbaldehyde (5a). Yield: 62%. Pale yellow oil. IR (nujol): 1714, 1682 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (3H, t, J=6.9 Hz), 2.44 (3H, s), 4.20 (2H, q, J=6.9 Hz), 4.28 (2H, d, J=6.4 Hz), 5.20 (1H, dd, J=17.0 Hz), 5.23 (1H, dd, J=10.3 Hz), 5.91 (1H, tdd, J=6.4, 10.3, 17.0 Hz), 6.96 (1H, s), 9.71 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (q), 15.7 (q), 55.1 (t), 62.9 (t), 119.6 (t), 121.8 (d), 132.5 (d), 136.3 (s), 137.7 (s), 151.8 (s), 155.0 (s), 183.8 (d). Anal. calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found C, 56.98; H, 6.11; N, 5.42.

3.5.2. 2-(*N*-Allyl-*N*-carbethoxy-amino)-benzothiophene-3-carbaldehyde (5b). Yield: 78%. Pale yellow oil. IR (nujol): 1719, 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 4.21 (2H, q, J=7.0 Hz), 4.38 (2H, d, J=6.4 Hz), 5.10–5.28 (2H, overlapping), 5.94 (1H, tdd, J=6.4, 10.5, 17.1 Hz), 7.38 (1H, dd, J=7.3, 8.1 Hz), 7.46 (1H, dd, J=7.3, 7.8 Hz), 7.74 (1H, d, J=7.8 Hz), 8.61 (1H, d, J=8.1 Hz), 10.05 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 55.4 (t), 63.6 (t), 120.6 (t), 122.4 (d), 125.3 (d), 126.5 (d), 126.6 (d), 129.4 (s), 132.1 (d), 134.8 (s), 136.3 (s), 155.0 (s), 158.5 (s), 184.9 (d). Anal. calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found C, 62.45; H, 5.07; N, 5.02.

3.6. General procedure for the reactions between 5a,b and benzylhydroxylamine

A suspension of benzylhydroxylamine hydrochloride (90 mg, 0.56 mmol), $NaHCO_3$ (138 mg, 1.65 mmol) and $MgSO_4$ (1.13 g, 4.46 mmol) in Et_2O (30 ml) was stirred for 15 min. A solution of **5** (0.44 mmol) in Et_2O (2 ml) was added and the mixture was stirred at r.t. for 24 h. After filtration, the evaporation of the solvent under reduced pressure followed by recrystallization gave **6a** or **7b**.

3.6.1. *N*-Benzyl-*C*-[2-(*N*-carbethoxy-allylamino)-5-methyl-thien-3-yl]nitrone (6a). Yield: 89%. Mp 116–117 °C (cream crystals from diisopropyl ether). IR (nujol): 1711, cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (3H, t, J=6.7 Hz), 2.43 (3H, s), 4.09–4.14 (4H, overlapping), 4.98 (2H, s), 5.10 (1H, d, J=16.5 Hz), 5.14 (1H, d, J=10.3 Hz), 5.72 (1H, tdd, J=6.3, 10.3, 16.5 Hz), 7.13 (1H, s), 7.37–7.45 (5H, overlapping), 8.00 (1H, s), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (q), 16.1 (q), 55.1 (t), 62.9 (t), 70.7 (t), 119.6 (t), 124.2 (d), 127.8 (d), 128.3 (d), 128.7 (d), 129.2 (d), 129.5 (d), 129.6 (d), 132.5 (d), 133.7 (s), 137.1 (s), 137.7 (s), 142.9 (s), 155.5 (s). Anal. calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.81. Found C, 63.57; H, 6.04; N, 7.62.

3.6.2. (3a*R,10c*R**)-1-Benzyl-5-carbethoxy-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (7b).** Yield: 72%. Mp 139–140 °C (white crystals from diisopropyl ether). IR (nujol): 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.42 (3H, br s), 3.25 (1H, br s), 3.88 (1H, br s), 4.12 (4H, br s), 4.32–4.70 (4H, overlapping), 7.19–7.55 (8H, overlapping), 7.73 (1H, br s). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.43 (3H, t, J=7.1 Hz), 3.25 (1H, br s), 3.87 (1H, dd, J=4.9, 8.2 Hz), 3.98–4.25 (4H, overlapping), 4.33–4.52 (4H, overlapping), 7.23 (1H, ddd, J=1.3, 7.2, 7.2 Hz), 7.27–7.32 (2H, overlapping), 7.35 (2H, dd, J=7.2, 7.5 Hz), 7.42 (2H, d, J=7.0 Hz), 7.46 (1H, d, J=7.2 Hz), 7.71 (1H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 40.6 (d), 46.2 (t), 60.1 (d), 60.2 (t), 63.5 (t), 68.6 (t), 121.2 (d), 122.0 (d), 123.6 (d), 124.6 (d), 127.8

(d), 128.7 (d), 129.5 (d), 135.9 (s), 137.4 (s), 138.0 (s), 140.9 (s), 153.8 (s), 155.4 (s). Anal. calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found C, 67.01; H, 5.47; N, 7.22.

3.6.3. Cycloaddition reaction of nitrone 6a. A solution of **6a** (568 mg, 1.6 mmol) in toluene (8 ml) was heated to reflux for 24 h. The solvent was evaporated under reduced pressure to give (3a*R**,8b*R**)-1-benzyl-5-carbethoxy-1,3,3a,4,5,10c-hexahydro-7-methyl-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (**7a**) as a pure colourless oil. Yield: 94%. Oil. IR (nujol): 1697, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.38 (3H, t, $J=7.1$ Hz), 2.38 (3H, s), 3.00 (1H, br s), 3.70 (1H, dd, $J=4.4$, 8.2 Hz), 3.73–3.82 (2H, overlapping), 4.00 (1H, d, $J=13.4$ Hz), 4.11 (1H, dd, $J=4.6$, 12.8 Hz), 4.24–4.31 (2H, overlapping), 4.33 (2H, q, $J=7.1$ Hz), 6.40 (1H, s), 7.30–7.38 (3H, overlapping), 7.42 (2H, d, $J=7.3$ Hz).^1H NMR (400 MHz, DMSO, 100 °C) δ: 1.31 (3H, t, $J=7.1$ Hz), 2.32 (3H, s), 3.11–3.16 (1H, m), 3.57 (1H, dd, $J=4.5$, 8.1 Hz), 3.69 (1H, dd, $J=8.1$, 12.9 Hz), 3.90–4.02 (2H, overlapping), 3.97, 4.14 (2H, sistema AB, $J=13.8$ Hz), 4.21 (1H, dd, $J=8.0$, 8.1 Hz), 4.25 (2H, q, $J=7.1$ Hz), 6.46 (1H, s), 7.30–7.43 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 40.3 (d), 45.2 (t), 61.0 (t), 62.2 (d), 63.0 (t), 68.8 (t), 118.1 (s), 123.2 (d), 127.8 (d), 128.8 (d), 129.3 (d), 131.7 (s), 136.4 (s), 137.9 (s), 153.4 (s). Anal. calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.81. Found C, 63.82; H, 6.01; N, 7.98.

3.7. General procedure for the reactions between 5a,b and 8

A solution of **5** (1.58 mmol), **8** (195 mg, 1.42 mmol), and $MgSO_4$ (1.90 g, 15.8 mmol) in Et_2O (15 ml) was stirred at rt for 72 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with hexane/AcOEt (10:1) as eluent to afford **10** or **15** and **19**.

3.7.1. (*R*)-*N*-(α-Methylbenzyl)-*C*-[5-methyl-2-(*N*-carbethoxy-allylamino)-thien-3-yl] nitrone (10). Yield: 81%. Pale yellow oil. $[\alpha]_D^{23}=+39.2$ ($c=1.00$, EtOH). IR (nujol): 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, br s), 1.84 (3H, d, $J=6.9$ Hz), 2.41 (3H, s), 4.05–4.12 (4H, overlapping), 5.04–5.14 (3H, overlapping), 5.75 (1H, tdd, $J=6.6$, 11.2, 17.2 Hz), 7.20 (1H, s), 7.33–7.40 (3H, overlapping), 7.47 (2H, d, $J=7.6$ Hz), 8.00 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 16.1 (q), 19.2 (q), 55.1 (t), 62.8 (t), 74.9 (d), 119.7 (t), 124.4 (d), 126.8 (d), 127.6 (d), 128.8 (s), 129.1 (d), 129.2 (d), 132.6 (d), 137.1 (s), 138.9 (s), 142.5 (s), 155.7 (s). Anal. calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found C, 64.65; H, 6.36; N, 7.34.

3.7.2. (α*R*,3a*S*,10c*S*)-5-Carbethoxy-1-(α-methylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (15). Yield: 34%. Mp 194–195 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+148.5$ ($c=0.13$, $CHCl_3$). IR (nujol): 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.42 (3H, t, $J=7.1$ Hz), 1.56 (3H, d, $J=6.4$ Hz), 3.25–3.61 (2H, overlapping), 3.93 (1H, dd, $J=5.7$, 5.8 Hz), 3.99 (1H, q, $J=6.4$ Hz), 4.29–4.47 (3H, overlapping), 4.49–4.67 (2H, overlapping), 6.89 (1H, br s), 7.09 (1H, dd, $J=7.3$, 7.7 Hz), 7.16 (1H, dd, $J=7.2$, 7.8 Hz), 7.42 (1H, dd, $J=7.2$, 7.3 Hz), 7.47 (2H, dd, $J=7.1$, 7.5 Hz), 7.53 (2H, d, $J=7.4$ Hz), 7.61 (1H, d, $J=7.9$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 20.5 (q), 41.2 (d), 46.2 (t), 59.3 (d), 63.4 (t), 63.6 (d), 68.0 (t), 121.6 (d), 122.0 (d), 123.5 (d), 124.0 (d), 128.6 (d), 129.0 (d), 129.2 (d), 135.9 (s), 137.1 (s), 140.8 (s), 142.8 (s), 143.3 (s), 154.1 (s). Anal. calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found C, 67.49; H, 5.88; N, 6.98.

3.7.3. (α*R*,3a*R*,10c*R*)-5-Carbethoxy-1-(α-methylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (19). Yield: 14%. Mp 151–152 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=-65.5$ ($c=0.09$, $CHCl_3$). IR (nujol): 1721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.39 (3H, t, $J=7.2$ Hz), 1.68 (3H, d, $J=6.6$ Hz), 3.15–3.24 (1H, m), 3.55–3.62 (1H, m), 3.68 (1H, dd, $J=7.3$, 7.5 Hz), 4.05–4.15 (2H, overlapping), 4.27–4.42 (2H, overlapping), 4.43–4.50 (1H, m), 4.88 (1H, d, $J=7.5$ Hz), 7.22–7.31 (2H, overlapping), 7.32 (2H, dd, $J=6.9$, 7.6 Hz), 7.37 (1H, dd, $J=7.1$, 8.1 Hz), 7.43–7.52 (2H, overlapping), 7.71 (1H, d, $J=7.9$ Hz), 7.84 (1H, d, $J=8.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 22.9 (q), 40.9 (d), 44.8 (t), 58.8 (d), 63.4 (t), 63.6 (d), 67.9 (t), 121.8 (d), 122.0 (d), 123.6 (d), 124.5 (d), 127.8 (d), 128.7 (d), 129.2 (d), 137.1 (s), 140.8 (s), 142.6 (s), 143.3 (s), 143.5 (s), 154.0 (s). Anal. calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found C, 67.55; H, 6.05; N, 6.93.

3.8. Cycloaddition reaction of nitrone 10

A solution of **10** (350 mg, 0.9 mmol) in toluene (8 ml) was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with hexane/AcOEt (10:1) as eluent to give **18** and **14**.

3.8.1. (α*R*,3a*R*,8b*R*)-5-Carbethoxy-7-methyl-1-(α-methylbenzyl)-1,3,3a,4,5,8b-hexahydro-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (18). Yield: 38%. Mp 132–133 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+52.2$ ($c=0.23$, $CHCl_3$). IR (nujol): 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.36 (3H, t, $J=7.1$ Hz), 1.57 (3H, d, $J=6.7$ Hz), 2.41 (3H, s), 2.86 (1H, br s), 3.63 (1H, dd, $J=4.7$, 8.1 Hz), 3.80–3.86 (1H, m), 3.93 (1H, dd, $J=4.7$, 12.9 Hz), 4.03 (1H, dd, $J=7.7$, 7.8 Hz), 4.05–4.12 (2H, overlapping), 4.30 (2H, q, $J=7.1$ Hz), 6.55 (1H, s), 7.29 (1H, d, $J=8.2$ Hz), 7.37 (2H, dd, $J=8.2$, 8.2 Hz), 7.48 (2H, d, $J=8.2$ Hz). ^1H NMR (400 MHz, DMSO, 80 °C) δ: 1.28 (3H, t, $J=7.1$ Hz), 1.41 (3H, d, $J=6.6$ Hz), 2.35 (3H, s), 3.08–3.18 (1H, m), 3.42 (1H, dd, $J=5.2$, 8.0 Hz), 3.76–3.84 (2H, overlapping), 3.97 (1H, dd, $J=8.0$, 8.1 Hz), 4.05 (1H, q, $J=6.6$ Hz), 4.17–4.28 (3H, overlapping), 6.56 (1H, s), 7.24 (1H, d, $J=8.2$ Hz), 7.32 (2H, dd, $J=8.2$, 8.2 Hz), 7.39 (2H, d, $J=8.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 22.3 (q), 41.3 (d), 44.9 (t), 58.7 (d), 62.9 (t), 63.8 (d), 68.2 (t), 120.7 (s), 123.4 (d), 127.7 (d), 128.7 (d), 131.9 (s), 136.2 (s), 142.3 (s), 153.6 (s). Anal. calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found C, 64.54; H, 6.40; N, 7.63.

3.8.2. (α*R*,3a*S*,8b*S*)-5-Carbethoxy-7-methyl-1-(α-methylbenzyl)-1,3,3a,4,5,8b-hexahydro-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (14). Yield: 51%. Mp 164–165 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+27.7$ ($c=$

1.00, $CHCl_3$).IR (nujol): 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.36 (3H, t, J=7.1 Hz), 1.52 (3H, d, J=6.4 Hz), 2.31 (3H, s), 3.18–3.24 (1H, m), 3.59 (1H, br d, J=14.6 Hz), 3.80 (1H, dd, J=5.9, 8.1 Hz), 3.92 (1H, q, J=6.4 Hz), 4.09 (1H, d, J=7.4 Hz), 4.20 (1H, br s), 4.26–4.34 (3H, overlapping), 6.13 (1H, s), 7.32 (1H, d, J=8.2 Hz), 7.38 (2H, dd, J=8.2, 8.2 Hz), 7.45 (2H, d, J=8.2 Hz). ^1H NMR (400 MHz, DMSO, 80 °C) δ: 1.28 (3H, t, J=7.1 Hz), 1.37 (3H, d, J=6.4 Hz), 2.26 (3H, s), 3.22–3.36 (1H, m), 3.57 (1H, dd, J=5.9, 8.1 Hz), 3.61 (1H, dd, J=3.5, 13.2 Hz), 3.94–4.08 (3H, overlapping), 4.18–4.28 (3H, overlapping), 6.08 (1H, s), 7.36 (1H, d, J=8.2 Hz), 7.39 (2H, dd, J=8.2, 8.2 Hz), 7.43 (2H, d, J=8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 21.9 (q), 40.3 (d), 45.0 (t), 60.1 (d), 63.0 (t), 64.1 (d), 68.1 (t), 122.2 (s), 123.1 (d), 128.2 (d), 129.2 (d), 131.7 (s), 136.1 (s), 143.6 (s), 153.8 (s). Anal. calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found C, 64.41; H, 6.68; N, 7.34.

3.9. General procedure for the reactions between 5a,b and 9

A solution of **5** (1.65 mmol), **9** (315 mg, 2.06 mmol) and $MgSO_4$ (2.00 g, 16.5 mmol) in Et_2O (20 ml) was stirred at r.t. for 72 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with hexane/AcOEt (10:1) as eluent to afford **12** or **17** and **21**.

3.9.1. (*R*)-*N*-(α-Hydroxymethylbenzyl)-*C*-[5-methyl-2-(*N*-carbethoxy-allylamino)-thien-3-yl] nitrone (12). Yield: 74%. Pale yellow oil. $[\alpha]_D^{23}=-64.3$ (c=1.00, $CHCl_3$). IR (nujol): 3414, 1726 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, br s), 2.46 (3H, s), 3.80 (1H, br s, missing after deuteriation), 3.92 (1H, dd, J=3.4, 12.2 Hz), 4.01–4.15 (4H, overlapping), 4.53 (1H, dd, J=8.9, 12.2 Hz), 5.01–5.08 (2H, overlapping), 5.10 (1H, d, J=10.2 Hz), 5.73 (1H, tdd, J=6.5, 10.2, 16.8 Hz), 7.18 (1H, s), 7.37–7.42 (3H, overlapping), 7.44–7.48 (2H, overlapping), 7.99 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7 (q), 16.1 (q), 55.1 (t), 62.9 (t), 63.9 (t), 79.9 (d), 119.8 (t), 124.2 (d), 127.9 (d), 128.2 (s), 129.2 (d), 129.3 (d), 129.4 (d), 130.0 (d), 132.4 (d), 135.5 (s), 137.3 (s), 143.7 (s), 155.6 (s). Anal. calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found C, 61.91; H, 6.39; N, 7.11.

3.9.2. (α*R*,3a*S*,10c*S*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (17). Yield: 25%. Mp 197–198 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=+76.8$ (c=0.04, $CHCl_3$). IR (nujol): 3432, 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, br s), 2.47 (1H, br s), 2.83 (1H, br s, missing after deuteriation), 3.45 (1H, br s), 3.65 (1H, dd, J=7.6, 7.6 Hz), 3.77 (1H, dd, J=3.6, 10.2 Hz), 3.94 (1H, dd, J=8.0, 8.2 Hz), 4.12–4.44 (5H, overlapping), 4.83 (1H, br s), 7.29 (1H, dd, J=7.6, 7.7 Hz), 7.38–7.44 (4H, overlapping), 7.48–7.54 (2H, overlapping), 7.74 (2H, d, J=7.4 Hz). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.38 (3H, t, J=7.1 Hz), 2.58 (2H, br s, missing after deuteriation), 3.53 (1H, dd, J=3.5, 9.2 Hz), 3.66 (1H, dd, J=7.6, 7.6 Hz), 3.78 (1H, dd, J=3.6, 10.2 Hz), 3.94 (1H, dd, J=8.0, 8.2 Hz), 4.12–4.44 (5H, overlapping), 4.83 (1H, d, J=7.6 Hz), 7.27 (1H, dd, J=7.6, 7.7 Hz), 7.38–7.44 (4H, overlapping), 7.48–7.54 (2H, overlapping), 7.73 (1H, d, J=7.4 Hz), 7.75 (1H, d, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (q), 40.8 (d), 44.1 (t), 60.1 (d), 63.5 (t), 64.3 (t), 72.5 (d), 68.0 (t), 121.4 (d), 122.2 (d), 123.7 (d), 124.8 (d), 129.0 (d), 129.2 (d), 129.7 (d), 135.9 (s), 137.4 (s), 137.6 (s), 137.7 (s), 139.6 (s), 153.9 (s). Anal. calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60. Found C, 64.90; H, 5.58; N, 6.78.

3.9.3. (α*R*,3a*R*,10c*R*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,10c-hexahydro-benzothieno[2,3-*b*]isoxazolo[3,4-*d*]pyridine (21). Yield: 54%. Mp 170–171 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=-392.0$ (c=0.05, $CHCl_3$). IR (nujol): 3429, 1742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.49 (3H, br s), 2.91 (1H, br s, missing after deuteriation), 3.51 (1H, br s), 3.61 (1H, br s), 3.84–3.90 (1H, m), 3.97 (1H, dd, J=6.9, 7.4 Hz), 4.07 (1H, dd, J=3.6, 6.8 Hz), 4.27–4.40 (3H, overlapping), 4.51–4.62 (3H, overlapping), 6.99–7.22 (3H, overlapping), 7.42–7.58 (5H, overlapping), 7.65 (1H, br s). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.42 (3H, t, J=7.1 Hz), 2.72 (1H, br s, missing after deuteriation), 3.51 (1H, br d, J=13.0 Hz), 3.53–3.59 (1H, m), 3.89 (1H, br d, J=10.2 Hz), 3.96 (1H, dd, J=6.4, 7.8 Hz), 4.06 (1H, dd, J=4.0, 6.4 Hz), 4.26 (1H, dd, J=6.5, 11.7 Hz), 4.32–4.45 (2H, overlapping), 4.48–4.67 (3H, overlapping), 7.10 (1H, br s), 7.16 (1H, ddd, J=1.1, 7.1, 7.1 Hz), 7.20 (1H, ddd, J=1.6, 7.1, 7.1 Hz), 7.41–7.59 (5H, overlapping), 7.64 (1H, dd, J=1.6, 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 40.6 (d), 45.2 (t), 60.1 (d), 63.6 (t), 67.7 (t), 68.2 (t), 69.5 (d), 121.9 (d), 122.4 (d), 123.7 (d), 124.2 (d), 129.1 (d), 129.5 (d), 129.6 (d), 135.5 (s), 136.7 (s), 138.0 (s), 138.1 (s), 141.0 (s), 154.0 (s). Anal. calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60. Found C, 65.06; H, 5.81; N, 6.38.

3.10. Cycloaddition reaction of nitrone 12

A solution of **12** (250 mg, 0.6 mmol) in toluene (8 ml) was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with hexane/AcOEt (5:1) as eluent to give **16** and **20**.

3.10.1. (α*R*,3a*S*,8b*S*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,8b-hexahydro-7-methyl-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (16). Yield: 22%. Mp 131–132 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23}=-72.4$ (c=0.25, $CHCl_3$). IR (nujol): 3447, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.37 (3H, t, J=7.1 Hz), 1.56 (1H, br s, missing after deuteriation), 2.43 (3H, s), 2.61 (1H, br s), 3.64 (1H, dd, J=4.3, 7.8 Hz), 3.67 (1H, dd, J=9.5, 12.7 Hz), 3.70–3.79 (1H, m), 3.90–3.98 (2H, overlapping), 4.04 (1H, br dd, J=4.3, 12.9 Hz), 4.09–4.18 (2H, overlapping), 4.31 (2H, q, J=7.1 Hz), 6.57 (1H, s), 7.36–7.43 (3H, overlapping), 7.49–7.54 (2H, overlapping). ^1H NMR (400 MHz, DMSO, 100 °C) δ: 1.29 (3H, t, J=7.1 Hz), 2.37 (3H, s), 2.97–3.09 (1H, m), 3.44 (1H, dd, J=3.6, 7.3 Hz), 3.63–3.73 (1H, m), 3.78–3.88 (3H, overlapping), 3.91 (1H, dd, J=8.0, 8.0 Hz), 4.00 (1H, dd, J=5.1, 7.3 Hz), 4.23 (2H, q, J=7.1 Hz), 4.46 (1H, d, J=7.2 Hz), 6.63 (1H, s), 7.28–7.34 (3H, overlapping), 7.39–7.44 (2H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 40.4 (d), 44.7 (t), 57.7 (d), 63.0

(t), 64.4 (t), 69.0 (t), 69.4 (d), 122.9 (d), 128.7 (d), 128.8 (d), 129.2 (s), 130.6 (d), 131.8 (s), 136.3 (s), 136.9 (s), 153.3 (s). Anal. calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found C, 61.84; H, 6.08; N, 7.37.

3.10.2. (α*R*,3a*R*,8b*R*)-5-Carbethoxy-1-(α-hydroxymethylbenzyl)-1,3,3a,4,5,8b-hexahydro-7-methyl-isoxazolo[3,4-*d*]thieno[2,3-*b*]pyridine (20). Yield: 68%. Mp 117–118 °C (white crystals from diisopropyl ether). $[\alpha]_D^{23} = -31.1$ ($c=0.24$, $CHCl_3$). IR (nujol): 3455, 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 1.37 (3H, t, $J=7.1$ Hz), 2.33 (3H, s), 2.91–2.96 (1H, m), 3.24–3.32 (1H, m), 3.51–3.57 (1H, m), 3.77 (1H, ddd, $J=3.3$, 8.6, 11.9 Hz), 3.87 (1H, dd, $J=6.8$, 7.7 Hz), 3.99 (1H, dd, $J=3.4$, 6.8 Hz), 4.12–4.20 (2H, overlapping), 4.25–4.37 (3H, overlapping), 4.44 (1H, dd, $J=7.9$, 9.3 Hz), 6.20 (1H, s), 7.35–7.47 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9 (q), 15.2 (q), 40.1 (d), 44.5 (t), 61.0 (d), 63.2 (t), 68.4 (t), 68.9 (t), 69.9 (d), 121.3 (s), 122.7 (d), 128.6 (d), 128.9 (d), 129.5 (d), 132.2 (s), 135.3 (s), 138.6 (s), 153.8 (s). Anal. calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found C, 61.69; H, 6.32; N, 7.07.

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A catalyst- and solvent-free selective approach to biologically important quinazolines and benzo[*g*]quinazoline

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Abstract—A solvent-free and catalyst-free approach towards the selective synthesis of quinazolines and benzo[*g*] quinazolines has been developed using conventional microwave oven with excellent yields and reproducibilty.

1. Introduction

Numerous research papers and several review articles have appeared in literature describing in detail the utilization of iminophosphoranes as reagents and intermediates in organic synthesis.[1] The use of iminophosphoranes has now become a powerful gear in organic synthetic strategies directed towards the construction of nitrogen containing heterocycles. The reactions of iminophosphoranes with carbonyl compounds provide an excellent method for the construction of carbon–nitrogen double bonds[2] via inter and intra molecular aza-Wittig reaction. Their application in the preparation of various heterocycles including pyridine derivatives,[2] polycyclic compounds,[3] benzodiazepines[4] and pharmacologically active alkaloids[5] has also been well archived. On the other hand aza-Wittig type reactions of iminophosphoranes with carbon dioxides, carbon disulphides, isocyanates, isothiocyanates and ketenes render access to functionalised heterocumulenes as highly reactive intermediates able to undergo a pleothera of heterocyclization reactions.[6] Recent work in our laboratory[7] has shown the reactions of *N*-imidoyliminophosphoranes with monosubstituted ketenes and diphenyl ketene resulting exclusively in the formation of pyrimidinones via a [4+2] cycloaddition of the initially formed 1,3-diaza-1,3,5-pentatriene and quinazolines via electrocyclic ring closure, respectively.

Quinazolines have demonstrated an increase in potency over other Tyrosine Kinase inhibitors of 4–5 orders of magnitude for the inhibition of isolated Epidermal Growth Factor (EGF) receptor Tyrosine Kinase and 3–4 orders of magnitude for the inhibition of cellular phosphorylation.[8] They have shown remarkable activity as antitubercular,[9] antiviral[10] and anticancer agents.[11] These have been used as DNA ligands[12] and also have shown binding to benzodiazepines and adenosine receptors.[13] Recent disclosures from our laboratory[14] has shown quinazolines with substituents at second and fourth positions to be potent antibacterial agents and further studies are in progress to explore their medicinal and biological use. The growing medicinal importance of these heterocycles perpetuates to provide strong rationale for the development of synthetic methods for their preparation. These efforts have led to several reviews emphasising the synthesis[15] and biological evaluation of quinazolines. The reactions of *N*-imidoyliminophosphoranes with various aldehydes have been shown to result in a mixture of quinazoline and dihydroquinazoline derivatives in a variable ratio depending upon the nature of aldehydes as well as the employed reaction conditions.[16] The reaction apparently suffers from disadvantages such as longer reaction periods (25–90 h), lower yields, lack of selectivity often leading to a mixture of products and cumbersome workup procedure. As part of our continued interest in the chemistry of azadienes,[17] in a recent communication we have developed a simple and advantageous route for the synthesis of quinazoline derivatives using a domestic microwave oven.[18] Several experiments were performed at various power levels in order to establish the optimum reaction conditions. It was assumed that the initially formed 1,3-diazabuta-1,3-dienes **4** underwent electrocyclic ring closure to dihydroquinazoline as intermediates which on aromatisation led to the quinazoline derivatives **3** (Scheme 1). The products were identified as quinazolines **3** on the basis of analytical data and spectral evidences and by comparison of these with reported melting points in literature.

Keywords: Quinazolines; Benzo[*g*]quinazoline; Catalyst-free; Microwave.
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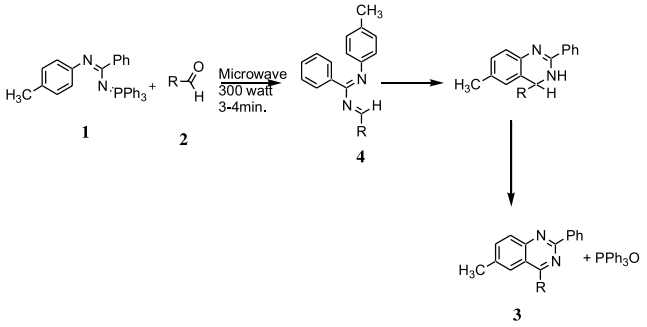


1 2 4 3

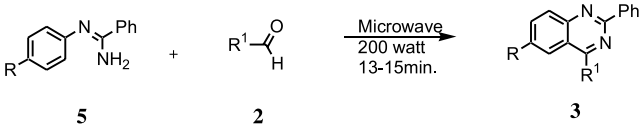
	R	R^1	Yield(%age) (microwave)	Yield(%age) (thermally)
3a	$-CH_3$	C_6H_5	67	--
3b	$-CH_3$	p-O_2N-C_6H_4	64	70
3c	$-CH_3$	p-CH_3O-C_6H_4	59	09
3d	$-CH_3$	p-$Me_2NC_6H_4$	67	--
3e	$-CH_3$	p-Cl-C_6H_4	63	12

Scheme 1.

The spectral evidence involved the absence of a characteristic singlet corresponding to the iminic proton of acyclic 1,3-diazabuta-1,3-diene at $\delta \sim 8.2$ and the absence of characteristic pattern of doublet of doublet of uncyclised *p*-tolyl protons in the ^{1}H NMR spectrum. Interestingly, the formation of dihydroquinazoline derivatives was not observed in reactions of **1** with *para* substituted aromatic aldehydes possessing strong electron donating groups viz. $-OCH_3$ and $-N(CH_3)_2$. This is in contrast to the earlier reports wherein the formation of dihydroquinazoline and their aromatisation was shown to depend on electronic factors.[11] The observed absence of dihydroquinazolines in the present case suggests that the thermal conditions perhaps also play an important role in aromatisation of dihydroquinazolines to quinazolines. The isolation of quinazolines in these reactions still involved their chromatographic separation from triphenylphosphine oxide, resulting in a considerable loss of time and yield.

It was envisaged that this problem may be circumvented by the direct condensation of aldehydes with *N*-arylamidines, without their prior conversion to iminophosphoranes. The reported condensation reactions of *N*-alkylamidines with aldehydes to form 1,3-diazabuta-1,3-dienes invariably employed a Lewis acid catalysts, for example, zinc (II) chloride,[19] titanium(IV) chloride,[20] tin (IV) chloride[21] etc., drastic reaction conditions and cumbersome work up procedures. The stringent reaction conditions employed in these condensation reactions often leading to their irreproducibility[22] and limiting their applicability in organic synthesis. However, there are no literary reports regarding such condensation reactions with *N*-arylamidines even under such adverse reaction conditions.

The reported advantages of microwave assisted reactions[23] prompted us to scrutinize these reactions using a domestic microwave oven and we report herein the solvent-free condensation reactions of *N*-arylamidines **5** with various aldehydes in the absence of any Lewis acid catalyst. Interestingly, these attempts have once again led to the exclusive formation of the desired quinazolines **3** in excellent yields (Scheme 2).

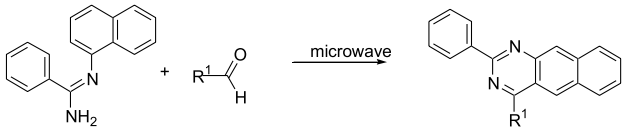


5 2 3

	R	R^1	Yield(%age)
3a	$-CH_3$	C_6H_5	76
3b	$-CH_3$	p-O_2N-C_6H_4	77
3c	$-CH_3$	p-CH_3O-C_6H_4	74
3d	$-CH_3$	p-$Me_2NC_6H_4$	70
3e	$-CH_3$	p-Cl-C_6H_4	73

Scheme 2.

Recently Godde et al. have reported new fluorescent analogs of thymine and cytosine namely benzo[*g*]quinazoline-2,4-(1*H*,3*H*)-dione and (4-amino-1*H*-benzo[*g*]quinazoline-2-one) to probe triple helix formation.[24] When introduced into triplex forming oligonucleotides, this new nucleoside can be used to reveal the protonation state of triplets in triple-stranded structures and thus targets double-stranded DNA through the binding of a short oligonucleotide to homo-purine–homopyrimidine sequences via Hoogsteen (or reverse Hoogsteen) hydrogen bonding.[25,26] Taking this into account, the above methodology has been succesfully extended to the synthesis of benzo[*g*]quinazoline derivatives by carrying out the condensation reactions of *N*-Naphthalen-1-yl-benzamidine[†] with various aldehydes (Scheme 3).



6 7

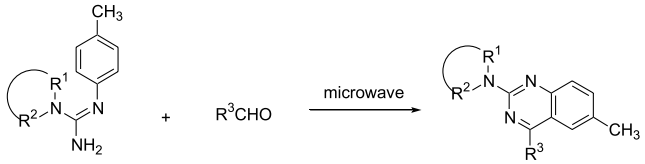
	R^1	%age yield
7a	$-C_6H_5$	72
7b	p-O_2N-C_6H_4	76
7c	p-CH_3O-C_6H_4	78
7d	p-$Me_2NC_6H_4$	80
7e	p-Cl-C_6H_4	72

Scheme 3.

Quinazoline derivatives having a secondary amino functionality at C-2 constitute an important class of medicinal entities acting as α_1 receptor antagonists and antihypertensive agents[27] and the important members include Prazosin and Doxazosin. Prazosin is a prototype of an α_1 receptor antagonist which selectively blocks post synaptic α_1-receptors while having no effects on presynaptic α_2 receptors responsible for the inhibition of norepinephrine release from sympathetic nerve terminals. The compound has been shown to function as a multidrug resistance (MDR) reversal agent and binds to *p*-glycoprotein, a transmembrane transport protein. In view of the above, the present methodology was further extended to the condensation reactions of guanidines **8** with aldehydes resulting once

[†] The preparations should be carried out in an efficient fume cupboard because of highly carcinogenic nature of napthylamine.

again in the exclusive formation of the corresponding 2-*sec*-amino substituted quinazoline derivatives **9** (Scheme 4).



8 **9**

	R^1---------R^2	R^3	Yield (%age)
9a	$(CH_2)_2$-O-$(CH_2)_2$	-C_6H_5	78
9b	$(CH_2)_2$-O-$(CH_2)_2$	*p*-O_2N-C_6H_4	81
9c	$(CH_2)_2$-O-$(CH_2)_2$	*p*-CH_3O-C_6H_4	83
9d	$(CH_2)_2$-O-$(CH_2)_2$	*p*-$(CH_3)_2$-N -C_6H_4	72
9e	$(CH_2)_2$-O-$(CH_2)_2$	*p*-Cl-C_6H_4	78
9f	-----$(CH_2)_4$-----	-C_6H_5	80
9g	-----$(CH_2)_4$-----	*p*-O_2N-C_6H_4	83
9h	-----$(CH_2)_4$----	*p*-CH_3O-C_6H_4	84
9i	-----$(CH_2)_4$-----	*p*-$(CH_3)_2$-N-C_6H_4	74
9*j*	-----$(CH_2)_4$-----	*p*-Cl-C_6H_4	77
9k	------$(CH_2)_5$-----	-C_6H_5	80
9l	------$(CH_2)_5$-----	*p*-O_2N-C_6H_4	84
9m	------$(CH_2)_5$-----	*p*-CH_3O-C_6H_4	78
9n	------$(CH_2)_5$-----	*p*-$(CH_3)_2$-N -C_6H_4	73
9o	------$(CH_2)_5$-----	*p*-Cl-C_6H_4	78

Scheme 4.

Though the reactions reported herein were carried out in a conventional microwave oven, the results were reproducible with excellent yields. Thus, a very simple, convenient, accelerated, less expensive, generalised and high yielding protocol for the selective synthesis of quinazolines and benzo[*g*]quinazolines has been developed.

2. Experimental

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Bruker AC-E 200 (200 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as ppm downfield from TMS and *J* values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. ^{13}C NMR spectra were also recorded on a Bruker AC-200E (50.4 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120) mesh or Harrison Research Chromatotron using 2 mm plates (Silica gel 60 PF254).

2.1. Procedure for the condensation reactions of *N*-imidoyliminophosphoranes with aldehydes

In a typical experiment, *N*-imidoyliminophosphorane **1** was mixed with 1.5 equiv of aldehyde **2** and the mixture was exposed to microwave radiation at a power of 300 W for a period of 3–4 min. The purification of the reaction mixture by flash chromatography resulted in the exclusive isolation of quinazolines **3** in good yields (65–80%).

2.2. Procedure for the condensation reactions of *N*-arylbenzamidine/*N*-naphthylamidines/guanidines with aldehydes

The procedure employed the exposure of microwave radiations to a mixture of *N*-arylbenzamidine/*N*-naphthylamidine/guanidines **5/8/6** and aldehyde **2** (power of 200 W for 13–15 min in 6–7 cycles of 2 min each). The progress of the reaction was monitored by thin layer chromatography (TLC). The isolated product in each case was recrystallized using (1:5) dichloromethane–hexane mixture and characterized as quinazoline **3/9** and benzo[*g*]quinazolines **7** on the basis of spectral evidences.

2.2.1. 6-Methyl-2,4-diphenylquinazoline (3a). Mp 226–227 °C, δ_H (200 MHz): 2.52 (s, 3H, –CH_3); 7.58 (m, 11H, ArH): 8.2 (m, 2H, ArH). δ_c (50.4 MHz): 20.8, 120.8, 121.2, 122.5, 122.9, 123.8, 124.0, 125.7, 126.2, 127.0, 128.3, 129.1, 131.0, 135.0, 155.4, 157.8 *m*/*z* 296 (M^+).

2.2.2. 6-Methyl-4-(4′-nitrophenyl)-2-phenylquinazoline (3b). Lit. mp (189–190 °C)[17b] mp 189–190 °C, δ_H (200 MHz): 2.58 (s, 3H, –CH_3); 7.50–7.53 (m, 3H, ArH); 7.74–7.78 (d, 2H, *J*=8.1 Hz, ArH); 8.02–8.08 (m, 3H, ArH); 8.44–8.48 (d, 2H, *J*=8.1 Hz, ArH); 8.61–8.66 (m, 2H, ArH): δ_c (50.4 MHz) 21.9, 121.2, 123.7, 124.2, 128.4, 128.5, 129.2, 130.4, 130.6, 131.0, 136.3, 137.7, 137.9, 143.9, 148.5, 159.5, 165.0. *m*/*z* 341 (M^+).

2.2.3. 6-Methyl-4-(4′-methoxyphenyl)-2-phenylquinazoline (3c). Lit. mp (160–165 °C)[17b] mp 160–161 °C, δ_H (200 MHz): 2.51 (s, 3H, –CH_3); 3.92 (s, 3H, –OCH_3); 7.09–7.13 (d, 2H, *J*=8.7 Hz, ArH); 7.46–7.54 (m, 3H, ArH); 7.66–7.71 (d, 1H, *J*=10.0 Hz, ArH); 7.85–7.90 (m, 3H, ArH); 8.00–8.05 (d, 1H, *J*=10.2 Hz, ArH) 8.64–8.68 (m, 2H, ArH): δ_c (50.4 MHz) 21.8, 55.3, 113.9, 115.5, 121.5, 123.9, 125.6, 126.6, 127.2, 128.4, 128.8, 130.1, 130.5, 135.4, 136.8, 150.6, 159.4, 160.9. *m*/*z* 326 (M^+).

2.2.4. 6-Methyl-4-(4′-*N*-*N*-dimethylaminophenyl)-2-phenylquinazoline (3d). Mp 212–213 °C. Anal. Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found C, 81.52; H, 6.35; N, 12.13%: δ_H (200 MHz): 2.58 (s, 3H, –CH_3); 3.33 (s, 6H, –$(NCH_3)_2$); 6.91–6.96 (d, 2H, *J*=10.0 Hz, ArH); 7.55 (m, 3H, ArH); 7.74–7.78 (d, 1H, *J*=8.5 Hz, ArH); 7.90–7.95 (d, 2H, *J*=10.0 Hz, ArH); 8.07(m, 2H, ArH); 8.69 (m, 2H, ArH): δ_c (50.4 MHz): 21.2, 40.3, 120.2, 121.0, 122.7,

123.0, 124.5, 125.2, 126.1, 128.2, 128.8, 130.0, 130.5, 132.3, 132.7, 144.5, 150.8, 154.6. *m/z* 339 (M^+).

2.2.5. 4-(4-Chloro-phenyl)-6-methyl-2-phenyl-quinazoline (3e). Lit. mp (181–183 °C)[17b] mp181–183 °C, δ_H (200 MHz): 2.53 (s, 3H, $-CH_3$); 7.05–7.09 (d, 2H, $J=$ 8.4 Hz, ArH); 7.41–7.47 (m, 3H, ArH); 7.65–7.70 (d, 1H, $J=10$ Hz, ArH); 7.84–7.88 (m, 3H, ArH); 8.02–8.06 (d, 1H, $J=10$ Hz, ArH); 8.60–8.64 (m, 2H, ArH): δ_c (50.4 MHz): 21.2, 120.5, 121.7, 122.2, 123.8, 124.6, 125.0, 125.8, 128.3, 128.8, 130.2, 131.1, 133.2, 135.0, 136.7, 156.8, 160.0. *m/z* 330.5 (M^+).

2.2.6. 2,4-Diphenyl-benzo[*g*]quinazoline (7a). Mp 180–181 °C. Anal. Calcd for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43. Found C, 86.93; H, 4.57; N, 8.50%: δ_H (200 MHz): 6.88–6.92 (d, 1H, $J=8.4$ Hz, ArH); 7.27–7.59 (m, 11H, ArH); 7.69–7.73 (d, 1H, $J=8.4$ Hz, ArH); 7.95–8.00 (m, 2H, ArH); 8.91–8.95 (d, 1H, $J=8.4$ Hz, ArH): δ_c (50.4 MHz): 118.7, 124.3, 124.4, 124.5, 125.7, 126.0, 126.7, 127.2, 127.4, 128.2, 128.6, 129.0, 129.8, 130.6, 133.7, 135.4, 137.7, 145.6, 152.8, 155.0. *m/z* 332 (M^+).

2.2.7. 4-(4-Nitro-phenyl)-2-phenyl-benzo[*g*]quinazoline (7b). Mp 155–156 °C. Anal. Calcd for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.13. Found: C, 76.28; H, 3.83; N, 11.41%: δ_H (200 MHz): 6.92–6.96 (d, 1H, $J=8.4$ Hz, ArH); 7.36–7.62 (m, 10H, ArH); 7.69–7.73 (d, 1H, $J=8.4$ Hz, ArH); 7.97–8.02 (m, 2H, ArH); 8.93–8.97 (d, 1H, $J=$ 8.4 Hz, ArH) δ_c (50.4 MHz): 117.9, 124.0, 124.7, 125.5, 126.0, 126.3, 126.6, 127.2, 127.4, 128.0, 128.6, 129.9, 130.1, 133.4, 134.4, 137.0, 140.7, 145.6, 152.0, 155.7. *m/z* 377 (M^+).

2.2.8. 4-(4-Methoxy-phenyl)-2-phenyl-benzo[*g*]quinazoline (7c). Mp 167–168 °C. Anal. Calcd for $C_{25}H_{18}N_2O$: C, 82.85; H, 5.01; N, 7.73. Found C,83.05; H, 4.82; N, 7.64%: δ_H (200 MHz): 3.95 (s, 3H, $-OCH_3$); 6.90–6.94 (d, 1H, $J=$ 8.4 Hz, ArH); 7.36–7.62 (m, 10H, ArH); 7.70–7.74 (d, 1H, $J=8.4$ Hz, ArH); 7.97–8.02 (m, 2H, ArH); 8.92–8.96 (d, 1H, $J=8.4$ Hz, ArH) δ_c (50.4 MHz): 55.3 ($-OCH_3$), 118.0, 122.8, 124.0, 125.4, 126.6, 126.9, 127.6, 127.9, 128.4, 128.6, 129.0, 129.9, 130.4, 133.8, 134.6, 137.0, 140.8, 145.3, 153.0, 156.7. *m/z* 362 (M^+).

2.2.9. Dimethyl-[4-(2-phenyl-benzo[*g*]quinazolin-4-yl)-phenyl]-amine (7d). Mp 198–199 °C. Anal. Calcd for $C_{26}H_{21}N_3$:C, 83.17; H, 5.64; N, 11.19. Found C, 83.37; H, 5.51; N, 11.12%: δ_H (200 *MHz*): 2.90 (s, 6H, $-(NCH_3)_2$); 6.88–6.92 (d, 1H, $J=8.2$ Hz, ArH); 7.42–7.70 (m, 10H, ArH); 7.73–7.77 (d, 1H, $J=8.2$ Hz, ArH); 7.93–7.98 (m, 2H, ArH); 8.94–8.98 (d, 1H, $J=8.4$ Hz, ArH) δ_c (50.4 MHz): 43.2 ($-(NCH_3)_2$); 118.2, 122.5, 124.3, 125.7, 126.8, 127.0, 127.4, 127.9, 128.3, 128.6, 129.3, 129.9, 130.8, 134.0, 134.7, 137.3, 140.2, 145.2, 153.7, 156.9. *m/z* 375 (M^+).

2.2.10. 4-(4-Chloro-phenyl)-2-phenyl-benzo[*g*]quinazoline (7e). Mp 156–158 °C. Anal. Calcd for $C_{24}H_{15}N_2Cl$: C, 78.58; H, 4.12; N, 7.64. Found C, 78.67; H, 4.20; N, 7.45: δ_H (200 MHz): 6.88–6.92 (d, 1H, $J=8.4$ Hz, ArH); 7.40–7.60 (m, 10 H, ArH); 7.72–7.76 (d, 1H, $J=8.2$ Hz, ArH); 7.92–7.97 (m, 2H, ArH); 8.94–8.98 (d, 1H, $J=8.4$ Hz, ArH) δ_c (50.4 MHz): 118.4, 124.3, 124.0, 124.5, 125.2, 125.5, 126.3, 127.0, 127.4, 128.1, 128.3, 129.0, 129.6, 130.5, 133.2, 135.4, 137.0, 145.3, 153.0, 155.3. *m/z* 366.5 (M^+).

2.2.11. 6-Methyl-4-phenyl-2-morpholino-4-yl-quinazoline (9a). Mp 147–148 °C. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found C, 74.97; H, 6.38; N, 13.48% δ_H (200 MHz): 2.41 (s, 3H, $-CH_3$); 3.81–3.86 (m, 4H, $-CH_2-N-CH_2-$); 3.98–4.02 (m, 4H, $-CH_2-O-CH_2-$); 7.54–7.62 (m, 6H, ArH); 7.74–7.76 (m, 2H, ArH): δ_c (50.4 MHz) 21.37 ($-CH_3$); 44.56 ($-CH_2-N-CH_2-$); 66.97 ($-CH_2-O-CH_2-$); 117.7, 126.0, 128.3, 128.5, 129.5, 129.7, 130.0, 131.3, 135.7, 137.9, 160.9, 168.7. *m/z* 305 (M^+).

2.2.12. 6-Methyl-2-morpholin-4-yl-4-(4-nitro-phenyl)-quinazoline (9b). Mp 188–189 °C. Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found C, 65.32; H, 5.27; N, 15.79%: δ_H (200 MHz): 2.40 (s, 3H, $-CH_3$); 3.78–3.84 (m, 4H, $-CH_2-N-CH_2-$); 3.92–3.97 (m, 4H, $-CH_2-O-CH_2-$); 7.70–7.74 (d, 2H, $J=8.1$ Hz, ArH); 8.07–8.12 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J=8.1$ Hz, ArH); δ_c (50.4 MHz): 22.0 ($-CH_3$); 43.6 ($-CH_2-N-CH_2-$); 63.7 ($-CH_2-O-CH_2$); 118.2, 123.5, 124.7, 128.5, 129.3, 130.3, 132.7, 133.8, 134.0, 148.7, 157.5, 163.2. *m/z* 350 (M^+).

2.2.13. 4-(4-Methoxy-phenyl)-6-methyl-2-morpholin-4-yl-quinazoline (9c). Mp 182–183 °C. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found C, 71.76; H, 6.48; N, 12.26%: δ_H (200 MHz): 2.41 (s, 3H, $-CH_3$); 3.81–3.86 (m, 4H, $-CH_2-N-CH_2$); 3.92 (s, 3H, $-OCH_3$); 3.98–4.02 (m, 4H, $-CH_2-O-CH_2-$); 7.08–7.12 (d, 2H, $J=8.2$ Hz, ArH); 7.66–7.71 (d, 1H, $J=10.2$ Hz, ArH); 7.85–7.90 (m, 3H, ArH); 8.01–8.06 (d, 1H, $J=10.3$ Hz, ArH): δ_c (50.4 MHz): 20.8 ($-CH_3$); 42.8 ($-CH_2-N-CH_2-$); 55.0 ($-OCH_3$); 66.9($-CH_2-O-CH_2-$); 118.0, 119.2, 120.8, 121.4, 123.5, 124.7, 125.0, 128.5, 133.0, 144.7, 152.7, 155.8. *m/z* 335 (M^+).

2.2.14. 6-Methyl-4-(4′-*N*-*N*-dimethylaminophenyl)-2-morpholin-4-yl-quinazoline (9d). Mp 198–199 °C. Anal. Calcd for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08. Found C, 72.79; H, 6.48; N, 16.18%: δ_H (200 MHz): 2.45 (s, 3H, $-CH_3$); 2.98 (s, 6H, $-N(CH_3)_2$); 3.80–3.85 (m, 4H, $-CH_2-N-CH_2-$); 3.99–4.03 (m, 4H, $-CH_2-O-CH_2-$); 6.84–6.88 (d, 2H, $J=8.5$ Hz, ArH); 7.43–7.48 (d, 1H, $J=10.0$ Hz, ArH); 7.53–7.58 (d, 1H, $J=10.0$ Hz); 7.74–7.78 (m, 3H, ArH): δ_c (50.4 MHz): 21.2 ($-CH_3$); 40.3 ($-N(CH_3)_2$); 43.6 ($-CH_2-N-CH_2-$); 54.0 ($-CH_2-O-CH_2-$); 120.2, 121.9, 122.0, 123.5, 124.8, 125.7, 128.2, 130.2, 131.7, 142.7, 153.5, 157.5. *m/z* 348 (M^+).

2.2.15. 4-(4-Chloro-phenyl)-6-methyl-2-morpholin-4-yl-quinazoline (9e). Mp 180–181 °C. Anal. Calcd for $C_{19}H_{18}N_3OCl$: C, 67.15; H, 5.34; N, 12.37. Found C, 67.03; H, 5.71; N, 12.21%: δ_H (200 MHz): 2.42 (s, 3H, $-CH_3$); 3.80–3.85 (m, 4H, $-CH_2-N-CH_2-$); 3.92–3.97 (m, 4H, $-CH_2-O-CH_2-$); 7.12–7.16 (d, 2H, $J=8.4$ Hz, ArH); 7.57–7.62 (m, 3H, ArH); 7.84–7.88 (d, 2H, $J=8.4$ Hz, ArH): δ_c (50.4 MHz): 20.7 ($-CH_3$); 43.8 ($-CH_2-N-CH_2-$); 64.9 ($-CH_2-O-CH_2-$); 119.0, 122.3, 123.4, 124.3, 126.2, 126.8, 129.7, 130.8, 131.2, 134.8, 154.7, 157.2. *m/z* 339.5 (M^+).

2.2.16. 6-Methyl-4-phenyl-2-pyrrolidin-1-yl-quinazoline (9f). Mp 140–141 °C. Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found C, 79.02; H, 6.68; N, 14.28%: δ_H (200 MHz): 2.01–2.07 (m, 4H, $-CH_2-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.70–3.76 (m, 4H, $-CH_2-N-CH_2-$); 7.50–7.58 (m, 6H, ArH); 7.70–7.73 (m, 2H, ArH); δ_c (50.4 MHz): 21.1 ($-CH_3$); 24.9 ($-CH_2-CH_2-$); 45.7 ($-CH_2-N-CH_2$); 117.3, 118.2, 120.1, 122.5, 123.3, 125.4, 127.7, 130.2, 135.6, 145.1, 157.9, 166.6. *m/z* 289 (M^+).

2.2.17. 6-Methyl-4-(4-nitro-phenyl)-2-pyrrolidin-1-yl-quinazoline (9g). Mp 154–155 °C. Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found C, 68.48; H, 5.20; N, 16.86%: δ_H (200 MHz): 1.82–1.86 (m, 4H, $-CH_2-N-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.72–3.77 (m, 4H, $-CH_2-N-CH_2-$); 7.70–7.74 (d, 2H, $J=8.2$ Hz, ArH); 8.01–8.07 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J=8.2$ Hz, ArH): δ_c (50.4 MHz): 22.0 (–CH3); 26.2 ($-CH_2-CH_2-$); 48.1 ($-CH_2-N-CH_2-$); 118.2, 119.1, 120.0, 120.8, 123.4, 126.2, 128.5, 130.0, 131.8, 142.7, 153.5, 156.0. *m/z* 334 (M^+).

2.2.18. 6-Methyl-4-(4′-methoxyphenyl)-2-pyrrolidino-1-yl-quinazoline (9h). Mp 147–148 °C. Anal. Calcd for $C_{21}H_{24}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found C, 75.03; H, 6.73; N, 13.12%: δ_H (200 MHz): 2.00–2.07 (m, 4H, $-CH_2-CH_2-$); 2.40 (s, 3H, $-CH_3$); 3.73–3.79 (m, 4H, $-CH_2-N-CH_2-$); 3.92 (s, 3H, $-OCH_3$); 7.03–7.08 (d, 2H, ArH, $J=8.8$ Hz); 7.49–7.64 (m, 3H, ArH); 7.71–7.76 (d, 2H, ArH, $J=8.8$ Hz): δ_c (50.4 MHz): 21.3 ($-CH_3$); 25.5 ($-CH_2-CH_2-$); 47.2 ($-CH_2-N-CH_2$); 55.2 ($-OCH_3$); 113.7, 117.0, 124.6, 126.2, 127.5, 128.7, 130.2, 131.4, 135.6, 150.1, 160.9, 168.6. *m/z* 319 (M^+).

2.2.19. Dimethyl-[4-(6-methyl-2-pyrrolidin-1-yl-quinazolin-4-yl)-phenyl]-amine (9i). Mp 164–165 °C. Anal. Calcd for $C_{21}H_{24}N_4$: C, 75.87; H, 7.28; N, 16.85. Found C, 76.02; H, 7.48; N, 16.43%: δ_H (200 MHz): 2.02–2.06 (m, 4H, $-CH_2-CH_2-$); 2.32 (s, 3H, $-CH_3$); 2.98 (s, 6H, $-N(CH_3)_2$); 3.68–3.73 (m, 4H, $-CH_2-N-CH_2-$); 6.94–6.98 (d, 2H, $J=8.4$ Hz, ArH); 7.52–7.57 (d, 1H, $J=10.2$ Hz, ArH); 7.64–7.69 (d, 1H, $J=10.2$ Hz, ArH); 7.90–7.95 (m, 3H, ArH): δ_c (50.4 MHz): 22.0 ($-CH_3$); 23.8 ($-CH_2-CH_2-$); 39.4 ($-N(CH_3)_2$); 42.7 ($-CH_2-N-CH_2-$); 118.0, 119.2, 123.4, 124.5, 127.2, 128.0, 129.3, 130.1, 132.5, 143.5, 150.7, 157.2. *m/z* 332 (M^+).

2.2.20. 4-(4-Chloro-phenyl)-6-methyl-2-pyrrolidin-1-yl-quinazoline (9J). Mp 157–158 °C. Anal. Calcd for $C_{19}H_{18}N_3Cl$: C, 70.47; H, 5.60; N, 12.98. Found C, 70.86; H, 5.39; N, 12.87%: δ_H (200 MHz): 2.04–2.08 (m, 4H, $-CH_2-CH_2-$); 2.24 (s, 3H, $-CH_3$); 3.64–3.70 (m, 4H, $-CH_2-N-CH_2-$); 6.90–6.94 (d, 2H, $J=8.4$ Hz, ArH); 7.51–7.56 (d, 1H, $J=10.2$ Hz, ArH); 7.64–7.69 (d, 1H, $J=10.2$ Hz, ArH); 7.85–7.90 (m, 3H, ArH): δ_c (50.4 MHz): 20.2 ($-CH_3$); 23.4 ($-CH_2-CH_2-$); 42.7 ($-CH_2-N-CH_2-$); 118.4, 119.0, 122.4, 124.7, 126.2, 128.3, 129.0, 130.1, 133.5, 143.5, 150.9, 156.2. *m/z* 323.5 (M^+).

2.2.21. 6-Methyl-4-phenyl-2-piperidin-1-yl-quinazoline (9k). Mp 137–138 °C. Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found C, 79.28; H, 6.83; N, 13.89%: δ_H (200 MHz): 1.72–1.77 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.38 (s, 3H, $-CH_3$); 3.97–4.02 (m, 4H, $-CH_2-N-CH_2-$); 7.50–7.58 (m, 6H, ArH); 7.70–7.74 (m, 2H, ArH): δ_c (50.4 MHz): 19.3 ($-CH_3$); 25.2 ($-CH_2$); 26.0 ($-CH_2-CH_2-$); 44.4 ($-CH_2-N-CH_2-$); 117.0, 118.3, 120.4, 122.7, 123.4, 125.2, 127.9, 130.0, 135.3, 145.3, 157.7, 166.3. *m/z* 303 (M^+).

2.2.22. 6-Methyl-4-(4-nitro-phenyl)-2-piperidin-1-yl-quinazoline (9l). Mp 160–162 °C. Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found C, 68.80; H, 5.87; N, 15.96%: δ_H (200 MHz): 1.70–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.41 (s, 3H, $-CH_3$); 3.98–4.03 (m, 4H, $-CH_2-N-CH_2-$); 7.70–7.74 (d, 2H, $J=8.2$ Hz, ArH); 8.02–8.08 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J=8.2$ Hz, ArH): δ_c (50.4 MHz): 19.3 ($-CH_3$); 25.2 ($-CH_2$); 26.0 ($-CH_2-CH_2-$); 44.4 ($-CH_2-N-CH_2-$); 118.0, 123.5, 124.4, 128.7, 129.2, 130.4, 132.8, 133.9, 134.3, 148.5, 157.3, 163.0. *m/z* 348 (M^+).

2.2.23. 4-(4-Methoxy-phenyl)-6-methyl-2-piperidin-1-yl-quinazoline (9m). Mp 140–141 °C. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found C, 75.47; H, 6.98; N, 12.78%: δ_H (200 MHz): 1.70–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.90 (s, 3H, $-OCH_3$); 3.98–4.03 (m, 4H, $-CH_2-N-CH_2-$); 6.88–6.92 (d, 2H, $J=8.2$ Hz, ArH); 7.38–7.43 (d, 1H, $J=10.3$ Hz, ArH); 7.52–7.57 (d, 1H, $J=10.3$ Hz, ArH); 7.75–7.79 (m, 3H, ArH): δ_c (50.4 MHz): 19.7 ($-CH_3$); 25.0 ($-CH_2$); 25.9 ($-CH_2-CH_2-$); 44.8 ($-CH_2-N-CH_2-$); 55.0 ($-OCH_3$); 119.8, 120.7, 121.2, 122.7, 123.0, 124.5, 127.8, 132.8, 133.0, 145.0, 152.4, 157.4 *m/z* 333 (M^+).

2.2.24. 6-Methyl-4-(4′-*N*-*N*-dimethylaminophenyl)-2-piperidin-1-yl-quinazoline (9n). Mp 143–144 °C. Anal. Calcd for $C_{22}H_{26}N_4$: C, 76.27; H, 7.56; N, 16.17. Found C, 76.43; H, 7.72; N, 15.93%: δ_H (200 MHz): 1.70–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.41 (s, 3H, $-CH_3$); 2.93 (s, 6H, $-N(CH_3)_2$); 3.98–4.03 (m, 4H, $-CH_2-N-CH_2-$); 6.84–6.88 (d, 2H, $J=8.2$ Hz, ArH); 7.43–7.48 (d, 1H, $J=10.3$ Hz, ArH); 7.53–7.58 (d, 1H, $J=10.3$ Hz, ArH); 7.74–7.78 (m, 3H, ArH) δ_c (50.4 MHz): 21.3 ($-CH_3$); 25.0 ($-CH_2$); 25.7, ($-CH_2-CH_2-$); 39.3 ($-N(CH_3)_2$); 44.9 (CH_2-N-CH_2-); 118.5, 119.3, 120.2, 125.6, 125.8, 126.3, 130.8, 131.3, 134.9, 146.3, 154.3, 158.7. *m/z* 346 (M^+).

2.2.25. 4-(4-Chloro-phenyl)-6-methyl-2-piperidin-1-yl-quinazoline (9o). Mp 156–157 °C. Anal. Calcd for $C_{20}H_{20}N_3Cl$: C, 71.10; H, 5.97; N, 12.44. Found C, 71.03; H, 6.04; N, 12.51%: δ_H (200 MHz): 1.69–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.41 (s, 3H, $-CH_3$); 3.98–4.02 (m, 4H, $-CH_2-N-CH_2-$); 6.90–6.94 (d, 2H, $J=8.2$ Hz, ArH); 7.43–7.48 (d, 1H, $J=10.3$ Hz, ArH); 7.57–7.62 (d, 1H, $J=10.3$ Hz, ArH); 7.74–7.78 (m, 3H, ArH) δ_c(50.4 MHz): 21.3 ($-CH_3$); 25.0 ($-CH_2$); 25.7, ($-CH_2-CH_2-$); 44.2 (CH_2-N-CH_2-); 118.0, 119.3, 120.5, 123.6, 125.8, 126.7, 130.0, 131.2, 133.9, 147.3, 154.3, 158.7. *m/z* 337.5 (M^+).

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Room temperature ionic liquid promoted improved and rapid synthesis of 2,4,5-triaryl imidazoles from aryl aldehydes and 1,2-diketones or α-hydroxyketone

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Abstract—An improved and rapid one-pot synthesis of 2,4,5-triaryl imidazoles in a room temperature ionic liquid is described, which does not need any added catalyst. Different ionic liquids based on 1-*n*-butyl and 1,3-di-*n*-butyl imidazolium salts were screened and their efficacy in terms of acidity and polarity have been correlated with yields and reaction period. The one-pot methodology resulting in excellent isolated yields in short reaction times is characterized by simple work up procedures and efficient recovery and recycling of the ionic liquid, which acts as a promoter.

1. Introduction

The development of a simple, efficient and general synthetic method for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. In 1858 Debus[1] reported the reaction between glyoxal and ammonia, a reaction that pioneered a novel synthetic route to imidazole. Over the century, the importance of imidazoles in biological system has attracted much interest due to their chemical and biochemical properties. Even today, 147 years later, research in imidazole chemistry continues unabated. Compounds with imidazole ring system have many pharmacological properties and play important roles in biochemical process.[2] Many of the substituted imidazoles are known as inhibitors of P38 MAP kinase,[3] fungicides and herbicides,[4] plant growth regulators[5] and therapeutic agents.[6] Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related N-heterocyclic carbenes (NHC).[7,8]

There are several methods reported in literature for the synthesis of imidazoles such as hetero-Cope rearrangement,[9] four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin,[10] reaction of N-(2-oxo)-amides with ammonium trifluroacetate,[11] 1,2-aminoalcohols in the presence of PCl_5,[12] diketones, aldehyde, amine and ammonium acetate in phosphoric acid,[13] in acetic acid,[14] organo catalyst in acetic acid[15] as well as H_2SO_4,[16] DMSO.[17] Several micro-wave (MW) assisted syntheses of imidazoles from 1,2-diketones and aldehydes in the presence of a variety of catalysts have been recently reported. These include MW/silica-gel,[18] MW/silica-gel/H-Y,[19] MW/Al_2O_3,[20] MW/acetic acid,[21] in DMF.[22] The condensation of α-hydroxy ketones with aldehydes and ammonium acetate on solid supported silica gel or alumina in the presence of MW has been reported recently.[23]

Many of the synthetic protocols for imidazoles reported so far suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and often expensive acid catalysts. Moreover, the synthesis of these heterocycles have been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off.

One of the biggest problems posed to the chemical industry is to continuously deal with the fact that all chemical plants

Keywords: 2,4,5-Triaryl imidazoles; Ionic liquid (IL); Ammonium acetate; Benzaldehydes; 1,2-Diketones; α-Hydroxyketone.
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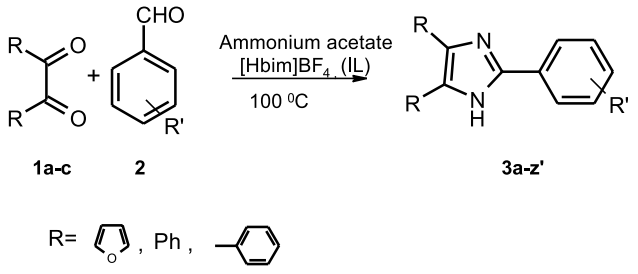
rely heavily on toxic, hazardous and flammable organic solvents. Organic solvents used in most of the synthetic processes in chemical industries evaporate into the atmosphere with detrimental effects on the environment as well as human health. Most of the time, these volatile organic solvents are expensive to purchase, difficult to recycle or reuse, and impractical to dispose of without incurring substantial costs and/or adversely affecting the environment and/or personnel.

Recently, room temperature ionic liquids (RTILs) have attracted much attention as promising alternative 'green' solvents to hazardous traditional organic solvents, due to their properties such as non-flammability, negligible vapour pressure, high thermal stability, solvating ability and easy recyclability.[7] They have the potential to be highly polar yet non-coordinating. In addition to the above-mentioned salient features of ionic liquids (ILs) as reaction media, we have also recently shown that they can promote and catalyze important organic transformations under ambient conditions without the need for any added catalyst or ligand. The reactions investigated by us are Heck and Suzuki reactions,[24] bromination of aromatics,[25] Friedlander heteroannulation,[26] synthesis of benzodiazepines, benzimidazoles and benzthiazole,[27] which proceed with significantly enhanced reaction rates, high regioselectivity and excellent isolated yields.

As part of an ongoing development of efficient protocols for the preparation of biologically active heterocycles from common intermediates using RTILs, we herein report for the first time, a one-pot condensation of 1,2-diketones or α-hydroxy ketone, aromatic aldehydes and ammonium acetate in the IL, 1-butyl imidazolium tetrafluoroborate ([Hbim]BF_4) which afforded a diverse array of 2,4,5-triaryl imidazoles in excellent isolated yields in the absence of any added catalyst.



Scheme 1.

Table 1. Synthesis of imidazole **3k** in [bbim] X

ILs	pK_a[a]	E_T (30) (kcal mol^{-1})[28]	Yield[b] (%)
[bbim]ClO_4	−11	76.34	21
[bbim]Br	−9	66.49	27
[bbim]Cl	−7	68.89	29
[bbim]BF_4	0.5	75.73	43

[a] The pK_a values of the parent acid of the anions.[29]
[b] Isolated yield after column chromatography.

2. Results

2.1. Synthesis of 2,4,5-triaryl imidazoles from 1,2-diketones

Ionic liquids (ILs) based on 1,3-di-*n*-butyl imidazolium salts [bbim]X and *N*-butyl imidazolium salts [Hbim]X with varying basicity of anions were tested as solvents and promoters for the typical reaction of 1,2-diphenyl-ethane-1,2-dione (**1b**) with *p*-anisaldehyde in the absence of any added catalyst to afford 2-(4-methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole (**3k**) (Scheme 1). The reactions in the various ILs were carried out at 100 °C for 24 h. The yield data are recorded in Tables 1 and 2.

The polarity of different ionic liquids based on 1,3-di-*n*-butyl imidazolium salts and 1-*n*-butyl imidazolium salts were evaluated using Reichardt's dye as per the procedure reported.[28] The pK_a values are those of the parent acid of the anions and taken from literature.[29]

It was observed that for a typical reaction of **1b** with *p*-anisaldehyde at the reaction temperature of 90 °C, the conversion does not go beyond 45% even after 24 h and at 130 °C the IL decomposed to give a black charry material. Hence, a reaction temperature of 100 °C was found to be optimum.

It becomes evident from these results, that the IL [Hbim]BF_4 afforded the best results. Consequently, all further studies were conducted using this IL as the reaction medium and promoter to generate a variety of imidazoles (**3a**–**z′**) by the reaction of 1, 2-di-furan-2-yl-ethane-1,2-dione (**1a**), 1,2-diphenyl-ethane-1,2-dione (**1b**) and 1,2-di-*p*-toluyl-ethane-1,2-dione (**1c**) with benzaldehydes (**2**), and ammonium acetate, respectively at 100 °C (Scheme 1).

The results are recorded in Table 3. All the reactions proceed to completion at the time indicated in the Table 3 and the yield data are for the isolated products after column chromatography. All the compounds were well characterized by melting point, IR, ^{1}H NMR and ^{13}C NMR. Their elemental analyses were in conformity with their structures.

Table 2. Synthesis of imidazole **3k** in [Hbim]X

ILs	pK_a[a]	Chemical shift –NH proton δ ppm	E_T (30) (kcal mol^{-1})[28]	Yield[b] (%)
[Hbim]ClO_4	−11	11.83	63.82	61
[Hbim]Br	−9	12.17	73.68	81
[Hbim]Cl	−7	12.22	73.59	80
[Hbim]BF_4	0.5	14.59	74.35	95

[a] The pK_a values of the parent acid of the anions.[29]
[b] Isolated yield after column chromatography.

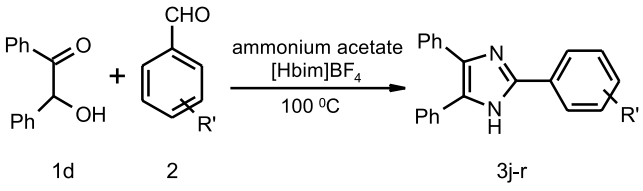
Table 3. Syntheses of imidazoles **3a–z′** from 1,2-diketones

Sr. no.	Imidazole **3**			Time (min)	Yield[a] (%)
	R	R′	**3a–z′**		
1	*o*-Furyl	H	**3a**	25	93
2	*o*-Furyl	*p*-OMe	**3b**	25	94
3	*o*-Furyl	*o*-OH	**3c**	35	92
4	*o*-Furyl	*p*-OH	**3d**	40	93
5	*o*-Furyl	*o*-Cl	**3e**	70	85
6	*o*-Furyl	*p*-Br	**3f**	65	92
7	*o*-Furyl	*o*-OH, *m*-OMe	**3g**	70	88
8	*o*-Furyl	*m*-OMe, *p*-OH	**3h**	75	85
9	*o*-Furyl	*p*-NO_2	**3i**	70	87
10	Phenyl	H	**3j**	60	95
11	Phenyl	*p*-OMe	**3k**	60	95
12	Phenyl	*o*-OH	**3l**	70	93
13	Phenyl	*p*-OH	**3m**	90	94
14	Phenyl	*o*-Cl	**3n**	70	96
15	Phenyl	*p*-Br	**3o**	65	95
16	Phenyl	*o*-OH, *m*-OMe	**3p**	60	95
17	Phenyl	*m*-OMe, *p*-OH	**3q**	70	87
18	Phenyl	*p*-NO_2	**3r**	60	94
19	*p*-Tolyl	H	**3s**	60	91
20	*p*-Tolyl	*p*-OMe	**3t**	60	88
21	*p*-Tolyl	*o*-OH	**3u**	70	90
22	*p*-Tolyl	*p*-OH	**3v**	100	93
23	*p*-Tolyl	*o*-Cl	**3w**	110	98
24	*p*-Tolyl	*p*-Br	**3x**	95	87
25	*p*-Tolyl	*o*-OH, *m*-OMe	**3y**	110	91
26	*p*-Tolyl	*m*-OMe, *p*-OH	**3z**	120	87
27	*p*-Tolyl	*p*-NO_2	**3z′**	70	87

[a] Isolated yield after column chromatography.

2.2. Synthesis of 2,4,5-triaryl imidazoles from α-hydroxy ketone, benzoin (1d)

Although there are several papers reporting the synthesis of tri-substituted imidazoles using 1,2-diketones, there are very few reports in the literature using α-hydroxyl-ketone as starting material. We found that our methodology works very well even for a α-hydroxyl-ketone such as benzoin (**1d**) under similar conditions to those used for the 1,2-diketones (Scheme 2). The results are summarized in Table 4.



Scheme 2.

3. Discussion

It is important to note that in all the cases, imidazoles were precipitated on dilution of the reaction mixtures with water and were isolated by a simple filtration. The dried product thus obtained showed a single spot on TLC and was pure enough for all practical purposes. The aqueous filtrate was then subjected to distillation at 80 °C under reduced pressure (10 mmHg) for 4 h to recover the IL almost

Table 4. Synthesis of imidazoles **3j–r** from benzoin

Sr. no.	Imidazole **3**			Time (min)	Yield[a] (%)
	R	R′	**3j–r**		
1	Phenyl	H	**3j**	60	95
2	Phenyl	*p*-OMe	**3k**	60	95
3	Phenyl	*o*-OH	**3l**	70	93
4	Phenyl	*p*-OH	**3m**	90	94
5	Phenyl	*o*-Cl	**3n**	70	96
6	Phenyl	*p*-Br	**3o**	65	95
7	Phenyl	*o*-OH, *m*-OMe	**3p**	60	95
8	Phenyl	*m*-OMe, *p*-OH	**3q**	70	87
9	Phenyl	*p*-NO_2	**3r**	60	94

[a] Isolated yield after column chromatography.

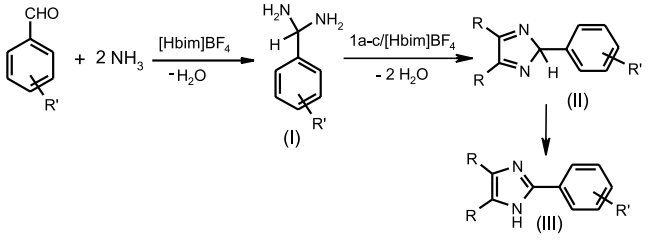
completely. The IL, thus recovered could be reused three times without loss of activity for the typical reaction of **1b** or **1d** with anisaldehyde.

The 2,4,5-triaryl imidazoles have been obtained in excellent isolated yields in relatively short reaction times. It can be observed that the process tolerates both electron donating and electron withdrawing substituents on the aldehyde. This methodology also gives the imidazoles using the 1,2-diketone or α-hydroxy ketone in more or less the same yield and same reaction period. It is worth noting here that 1,2-diketones such as benzil (**1b**) are usually prepared from benzoins catalysed by various toxic oxidants.[30] Consequently, the direct use of benzoin (**1d**) in our methodology constitutes a significant improvement in the synthesis of tri-substituted imidazoles towards green chemistry.

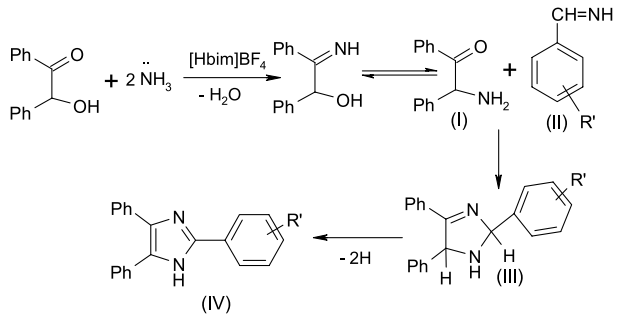
A typical reaction of **1b** with anisaldehyde under similar conditions in the absence of a catalyst using molecular solvents such as ethanol, toluene, DMF, DMSO showed no conversion beyond 30% even after 24 h and acetic acid gave 80% conversion only even after 6 h, thus highlighting the role of the IL in promoting the reaction.

The efficacy of the ILs to promote these heterocyclization reactions was correlated to the basicity of the anions of the ILs as well as the polarity of ionic liquids. The polarity of ionic liquids in terms of E_T values was measured by using Reichardt's dye as reported earlier.[28] It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (Tables 1 and 2). This correlation was also evident when the yield of **3k** was compared with –NH proton chemical shifts of the ILs indicative of the Bronsted acidities of the [Hbim] ILs (Table 2). The yield of **3k** increases progressively not only with increasing Bronsted acidity of the ILs as indicated by the increasing downfield shift of the NH proton but also with increasing polarity of these ILs as indicated by their E_T values.

The IL, [Hbim]BF_4 has promoted this heterocyclization reaction by virtue of its inherent Brønsted acidity conferred by the most acidic –N–H hydrogen [chemical shift δ ppm = 14.6]. This makes the IL capable of bonding with the carbonyl oxygen increasing the reactivities of the parent carbonyl compounds. Evidence in the form of significant ^{13}C NMR and IR spectral shifts of the carbonyl group by its



Scheme 3.



Scheme 4.

interaction with [Hbim]BF_4 has already been given in a previous communication by us.[31] Based on this, the following probable mechanisms may be postulated for this methodology as shown in Schemes 3 and 4. In both the mechanisms, the IL promotes the splitting of ammonium acetate to generate the ammonia required for the initial condensation.

For the postulated mechanism starting from 1,2-diketone (Scheme 3). The IL may facilitate the formation of a diamine intermediate I, which under Brønsted acid catalysis of the IL condenses with the carbonyl carbons of the 1,2-diketone followed by dehydration to afford the imino intermediate II, which rearranges to the required tri-aryl imidazole III.

A probable mechanism for the synthesis involving benzoin may be postulated as shown above (Scheme 4). It is highly probable that the Brønsted acidity of the IL may have promoted the formation of α-amino ketone I, aryl aldimine II, their subsequent condensation and intramolecular cyclization to the imidazoline III which dehydrogenates to the triaryl imidazoles IV. It was thought that the dissolved oxygen in the IL may have brought about the formal oxidation of the imidazoline III. However, this possibility was discounted by subjecting the IL to a degassing protocol using an ultrasonic cleaning bath (Transsonic Model T710DH) at 40 KHz in the degassing mode at a reduced pressure of 15 mmHg for 2 h. The degassed IL was well flushed with argon and the typical reaction of benzoin with benzaldehyde was performed in it using an inert atmosphere of argon. Even under such conditions, no trace of the formation of the imidazoline III was observed (TLC and ^{1}H NMR) and the triarylimidazole **3j** was obtained in excellent isolated yield (95%). It seems probable that apparently the fully conjugated nature of the product results in rapid oxidation in this case aided by the large chemical window and polarity of the IL.

Alternatively, the probability of benzoin itself undergoing oxidation under these conditions to benzil was explored. Thus, a solution of benzoin in the degassed IL was heated at 100 °C for 1 h in an atmosphere of argon. To our surprise, benzoin was converted to benzil in 85% isolated yield. The benzil so formed then can follow the pathway shown in Scheme 3 to afford the triaryl imidazoles. Further work is in progress to establish the role of the IL in such oxidations.

4. Conclusion

In conclusion, we have developed a mild, convenient and efficient protocol for the synthesis of biologically active 2,4,5-triaryl imidazoles via the condensation of 1,2-diketones and α-hydroxy ketones such as benzoin with aromatic aldehydes and ammonium acetate using a room temperature ionic liquid as a recyclable medium as well as promoter. The process gives rise to excellent isolated yields of 2,4,5-triaryl imidazoles in short reaction times (25–120 min). The reaction times achieved are shorter than those hitherto reported under thermal conditions excluding those wherein microwave assisted synthesis are carried out. Consequently, this methodology becomes an efficient strategy for the rapid synthesis of highly substituted imidazole libraries in a recyclable homogeneous medium in the absence of a catalyst. The corresponding reaction in molecular solvents under similar conditions in the absence of a catalyst are sluggish and poor yielding, highlighting the role of the IL in promoting this novel one-pot methodology. The experimental procedure, combining the features of simple isolation procedure, efficient recovery, and recycling of IL and the absence of a catalyst makes this an environmentally benign methodology amenable for scale up.

5. Experimental

5.1. General

NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$/DMSO-d_6 with TMS as an internal standard. Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer. Polarity of ILs was recorded on Lambda EZ 201, using Reichardt's dye. Melting points were recorded in open capillary and were uncorrected. All solvents and chemicals were of research grade and were used as obtained from Merck and Lancaster.

5.2. Typical procedure for synthesis of 2,4,5-triaryl imidazoles from 1,2-diketones or α-hydroxyketone

The ILs were prepared as per the procedure reported by us earlier.[26]

A mixture of 1,2-diketones (**1a**, **1b** or **1c**) or the α-hydroxyketone (benzoin) (**1d**) (4 mmol), substituted aldehydes (**2**, 4 mmol), ammonium acetate (10 equiv) and $[Hbim]BF_4$ (4 mmol) was heated at 100 °C with good stirring for the appropriate time mentioned in Tables 3 and 4. The completion of reaction was monitored by TLC using 25% ethyl acetate in petroleum ether. After completion of reaction, the reaction mixture was diluted with water (25 ml). The solid imidazole products, which separated out, were filtered, washed with water and dried. The crude products, thus isolated, were pure (single spot on TLC). They were subjected to further purification by chromatography through a column of silica-gel using 25% EtOAc in petroleum ether as eluent to yield the desired substituted imidazoles in excellent yields of 84–95% and were fully characterized.

The aqueous layer consisting of the IL was subjected to distillation (80 °C at 10 mmHg) for 4 h to remove water, leaving behind the IL $[Hbim]BF_4$ (recovery 98%), which was recycled.

5.3. Spectral data for compounds 3a–z′

5.3.1. 4,5-Difuran-2-yl-2-phenyl-1*H*-imidazole (3a). Mp 218 °C; IR (cm^{-1}) 718, 890, 1448, 1602, 3058; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.13–6.18 (dd, $J=7.5$ Hz, 2H), 6.85–6.89 (d, $J=8$ Hz, 2H), 7.18 (s, 2H), 7.22–7.48 (m, 5H), 12.42 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 106.9, 110.7, 123.9, 125.6, 127.7, 127.9, 128.9, 140.2, 146.1, 146.3; $C_{17}H_{12}N_2O_2$ (276): calcd C, 73.91, H, 4.34, N, 10.14; found C, 73.82, H, 4.24, N, 10.10.

5.3.2. 4,5-Difuran-2-yl-2(4-methoxy-phenyl-1*H*-imidazole (3b). Mp 198 °C; IR (cm^{-1}) 708, 880, 1508, 1610, 3105; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.75 (s, 3H), 6.14–6.19 (dd, $J=8$ Hz, 2H), 6.83–6.86 (dd, $J=8.5$ Hz, 2H), 7.16 (s, 2H), 7.41 (dd, $J=8$ Hz, 2H), 7.79–7.82 (dd, $J=8$ Hz, 2H), 12.53 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 54.5, 105.2, 111.6, 114.6, 128.0, 128.8, 142.2, 154.1, 162.0; $C_{18}H_{14}N_2O_3$ (306): calcd C, 70.58, H, 4.61, N, 9.15; found C, 70.42, H, 4.52, N, 9.10.

5.3.3. 2-(4,5-Difuran-2-yl-1*H*-imidazole-2yl)-phenol (3c). Mp 235 °C; IR (cm^{-1}) 718, 870, 1416, 1615, 3108, 3528; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.13–6.16 (dd, $J=7$ Hz, 2H), 6.18–6.23 (dd, $J=8.3$ Hz, 2H) 6.85–7.15 (m, 4H) 7.16 (s, 2H), 12.38 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 115.3, 121.6, 122.8, 124.5, 126.8, 127.3, 130.1, 135.1, 146.5; $C_{17}H_{12}N_2O_3$ (292): calcd C, 69.86, H, 4.10, N, 9.58; found C, 69.58, H, 3.92, N, 9.75.

5.3.4. 4-(4,5-Difuran-2-yl-1*H*-imidazole-2yl)-phenol (3d). Mp 223 °C; IR (cm^{-1}) 715, 860, 1416, 1615, 3108, 3550; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.14–6.18 (dd, $J=8$ Hz, 2H), 6.49–6.61 (dd, $J=7.5$ Hz, 2H) 6.85–6.89 (dd, $J=7$ Hz, 2H), 7.16 (s, 2H), 7.23–7.28 (dd, $J=8$ Hz, 2H), 12.41 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 116.3, 121.6, 123.4, 130.1, 134.9, 146.4; $C_{17}H_{12}N_2O_3$ (292): calcd C, 69.86, H, 4.1, N, 9.58; found C, 69.68, H, 3.91, N, 9.73.

5.3.5. 2-(2-Chloro-phenyl) 4,5-difuran-1*H*-imidazole (3e). Mp 240 °C; IR (cm^{-1}) 716, 865, 1420, 1618, 3110; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.31–6.39 (dd, $J=7$ Hz, 4H), 7.31–7.40 (d, $J=7$ Hz, 2H) 7.16–7.42 (m, 4H) 12.58 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 105, 111.6, 122.1, 127.1, 128.4, 129.9, 132.1, 135.9, 136.9, 142.2, 154.1; $C_{17}H_{11}N_2O_2Cl$ (311): calcd C, 65.59, H, 3.53, N, 9.0; found C, 65.48, H, 3.49, N, 8.93.

5.3.6. 2-(4-Bromo-phenyl) 4,5-difuran-1*H*-imidazole (3f). Mp 228 °C; IR (cm^{-1}) 708, 1416, 1608, 3108; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.28–6.33 (dd, $J=7$ Hz, 4H), 7.3–7.4 (d, $J=7$ Hz, 2H), 7.54–7.58 (d, $J=8.22$ Hz, 2H), 8.02–8.06 (d, $J=8.60$ Hz, 2H), 12.78 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 105.8, 111.6, 122.1, 127.1, 128.4, 129.4, 129.9, 132.1, 135.5, 136.4, 142.2, 154.2; $C_{17}H_{11}N_2O_2Br$ (355): calcd C, 57.46, H, 3.09, N, 7.88; found, C, 57.32, H, 2.98, N, 7.81.

5.3.7. 2-(4,5-Difuran-1*H*-imidazol-2-yl)-6-methoxy phenol (3g). Mp 238 °C; IR (cm^{-1}) 715, 864, 1416, 1610, 3130, 3600; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.65 (s, 3H), 6.30–6.33 (dd, $J=7$ Hz, 4H), 7.31–7.40 (d, $J=7$ Hz, 2H), 7.55–7.58 (m, 3H), 12.71 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 105.2, 111.6, 115.5, 120.2, 122.6, 124.2, 127.1, 140.1, 152.3, 156.2; $C_{18}H_{14}N_2O_4$ (322): calcd C, 67.08, H, 4.34, N, 8.69; found C, 66.98, H, 4.29, N, 8. 62.

5.3.8. 2-(4,5-Difuran-1*H*-imidazol-2-yl)-2-methoxy phenol (3h). Mp 225 °C; IR (cm^{-1}) 715, 864, 1416, 1610, 3130, 3600; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.87 (s, 3H), 6.47–6.49 (dd, $J=5$ Hz, 2H), 7.30–7.40 (d, $J=7$ Hz, 2H), 7.55–7.58 (m, 3H), 12.72 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 105.0, 111.6, 115.5, 120.0, 122.6, 124.0, 127.1, 140.1, 152.0, 156.0; $C_{18}H_{14}N_2O_4$ (322): calcd C, 67.08, H, 4.34, N, 8.69; found C, 66.98, H, 4.29, N, 8.62.

5.3.9. 2-(4-Nitro-phenyl) 4,5-difuran-1*H*-imidazole (3i). Mp 208 °C (decomposes); IR (cm^{-1}) 718, 865, 1408, 1605, 3120; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.29–6.33 (dd, $J=7.5$ Hz, 4H), 7.31–7.40 (d, $J=7$ Hz, 2H), 7.78–7.79 (d, $J=9$ Hz, 2H), 8.51–853 (d, $J=9$ Hz, 2H), 12.69 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 105.3, 111.6, 122.3, 124.1, 127.9, 136.3, 142.3, 142.6, 148.4, 154.4; $C_{17}H_{11}N_3O_4$ (321): calcd C, 63.55, H, 3.42, N, 13.08; found C, 63.45, H, 3.38, N, 12.98.

5.3.10. 2,4,5-Triphenyl-1*H*-imidazole (3j). Mp 269 (275[32]) °C; IR (cm^{-1}) 1216, 1638, 2470, 2993, 3434; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ 7.42–8.12 (m, 15H), 12.61 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): $\delta=122.1$, 127.2, 128.5, 129.1, 136.5; $C_{21}H_{16}N_2$ (296): calcd C, 85.11, H, 5.44, N, 9.45; found C, 85, H, 5.28, N, 9.35.

5.3.11. 2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole (3k). Mp 222 °C; IR (cm^{-1}) 1216, 1636, 2465, 2893, 3428; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.85 (s, 3H), 6.93–6.96 (d, $J=8.8$ Hz, 2H), 7.25–7.59 (m, 10H), 8.02–8.05 (d, $J=8.8$ Hz, 2H), 12.52 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 54.6, 113.2, 122.7, 126.3, 126.5, 127.4, 127.6, 132.8, 145.7, 159.1; $C_{22}H_{18}N_2O$ (326): calcd C, 80.96, H, 5.56, N, 8.58; found C, 80.85, H, 5.48, N, 8.38.

5.3.12. 2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-phenol (3l). Mp 205 °C; IR (cm^{-1}) 1216, 1638, 2465, 2998, 3432, 3596; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.87–6.95 (d, $J=7.5$ Hz, 2H), 6.97–7.01 (d, $J=8.06$ Hz, 2H), 7.17–7.23 (m, 10H), 12.74 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 112.7, 116.4, 118.1, 124.8, 126.8, 127.4, 127.8, 129.1, 145.7, 156.6; $C_{21}H_{16}N_2O$ (312): calcd C, 80.75, H, 5.16, N, 8.97; found C, 80.62, H, 5.08, N, 8.85.

5.3.13. 4-(4,5-Diphenyl-1*H*-imidazol-2-yl)-phenol (3m). Mp 233 °C; IR (cm^{-1}) 1216, 1638, 2465, 2998, 3432, 3596; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 6.93–6.97 (d, $J=8$ Hz, 2H), 7.52–7.87 (m, 10H), 7.88–7.92 (d, $J=8.5$ Hz, 2H), 12.58 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 113.7, 119.9, 125.1, 125.3, 126.1, 126.5, 144.7, 159.2; $C_{21}H_{16}N_2O$ (312): calcd C, 80.75, H, 5.16, N, 8.97; found C, 80.68, H, 5.05, N, 8.90.

5.3.14. 2-(2-Chloro-phenyl)-4,5-diphenyl-1*H*-imidazole (3n). Mp 188 °C; IR (cm^{-1}) 1216, 1638, 2470, 2993, 3434; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 7.27–7.37 (m, 10H), 7.45–7.49 (dd, $J=9$ Hz, 1H), 7.57–7.59 (d, $J=8$ Hz, 2H), 8.02–8.05 (dd, $J=8.79$ Hz, 1H), 12.5 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 125.4, 125.6, 126.5, 126.9, 127.2, 128.4, 128.6, 128.8, 129.6, 130.1, 130.5, 142.2; $C_{21}H_{15}ClN_2$ (330): calcd C, 76.24, H, 4.57, N, 8.47; found C, 76.12, H, 4.49, N, 8. 38.

5.3.15. 2-(4-Bromo-phenyl)-4,5-diphenyl-1*H*-imidazole (3o). Mp 248 °C; IR (cm^{-1}) 1261, 1645, 2255, 2473, 3417; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 7.25–7.48 (m, 10H), 7.50–7.52 (d, $J=8$ Hz, 2H), 7.80–7.92 (d, $J=8.6$ Hz, 2H), 12.49 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 120.1, 125.5, 126.3, 126.7, 127.1, 128.1, 129.5, 129.9, 130.5, 143.3; $C_{21}H_{15}BrN_2$ (374): calcd C, 67.21, H, 4.03, N, 7.47; found C, 67.10, H, 3.95, N, 7. 32.

5.3.16. 2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-6-methoxy phenol (3p). Mp 170 °C; IR (cm^{-1}) 1253, 1654, 2925, 3412, 3610; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.86 (s, 3H), 6.82–6.85 (m, 3H), 7.29–7.32 (m, 5H), 7.53–7.55 (m, 5H), 12.5 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 54.7, 110.9, 112.1, 155.6, 117.1, 126.3, 126.7, 127.3, 127.4, 129.8, 145.1, 146.1, 147.3; $C_{22}H_{18}N_2O_2$ (342): calcd C, 77.17, H, 5.30, N, 8.18; found C, 77.08, H, 5.18, N, 8.02.

5.3.17. 2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-2-methoxy phenol (3q). Mp 197 °C; IR (cm^{-1}) 1230, 1450, 1605, 2924, 3512, 3614; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 3.80 (s, 3H), 6.75–6.69 (d, $J=8.22$ Hz, 1H), 7.11–7.19 (m, 5H), 7.22–7.23 (d, $J=8.1$ Hz, 1H), 7.40–7.45 (m, 5H), 7.55–7.56 (d, $J=8$ Hz, 1H), 12.52 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 55.1, 108.5, 114.6, 118.1, 121.1, 126.2, 127.3, 127.5, 132.3, 146.3, 146.8; $C_{22}H_{18}N_2O_2$ (342): calcd C, 77.17, H, 5.30, N, 8.18; found C, 77.05, H, 5.18, N, 8.02.

5.3.18. 2-(4-Nitro-phenyl)-4,5-diphenyl-1*H*-imidazole (3r). Mp 196 °C (decomposes); IR (cm^{-1}) 845, 1443, 1522, 1540, 1602, 3056; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 7.25–7.57 (m, 10H), 7.78 (d, $J=9$ Hz, 2H), 8.50 (d, $J=9$ Hz, 2H), 12.59 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 122.7, 124.2 127.3, 127.6, 132.8, 146.7, 160.8; $C_{21}H_{15}N_3O_2$ (341): calcd C 73.88, H 4.43, N 12.31; found C 73.85, H 4.38, N 12.25.

5.3.19. 2-Phenyl-4,5-di-*p*-tolyl-1*H*-imidazole (3s). Mp 254 °C; IR (cm^{-1}) 1216, 1638, 2465, 2998, 3432; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.36 (s, 6H), 7.14–7.34 (m, 8H), 7.35–7.38 (m, 5H), 12.56 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.7, 124.1, 126.4, 126.6, 127.1, 127.5, 127.7, 128.3, 129.1, 129.2, 135.1; $C_{23}H_{20}N_2$ (324): calcd C, 85.15, H, 6.21, N, 8.63; found C, 85, H, 6.11, N, 8. 50.

5.3.20. 2-(4-Methoxy-phenyl)-4,5-di-*p*-tolyl-1*H*-imidazole (3t). Mp 243 °C; IR (cm^{-1}) 1216, 1638, 2475, 2988, 3430; ^1H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.37 (s, 6H), 3.86 (s, 3H), 6.94–6.96 (d, $J=8.25$ Hz, 2H), 7.13–7.15 (m, 4H), 7.46–7.48 (m, 4H), 8.03–8.05 (d, $J=8.25$ Hz, 2H),

12.59 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 20.2, 54.3, 112.9, 122.6, 126.1, 126.9, 128.1, 135.4, 145.1, 158.6; $C_{24}H_{22}N_2O$ (354): calcd C, 81.33, H, 6.26, N, 7.90; found C, 81.20, H, 6.11, N, 7.58.

5.3.21. 2-(4,5-Di-*p*-tolyl-1*H*-imidazol-2-yl) phenol (3u). Mp 223 °C; IR (cm^{-1}) 1216, 1638, 2465, 2998, 3432, 3596; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.36 (s, 6H), 6.85–6.90 (t, J=8.3 Hz, 1H), 6.95–6.98 (d, J=8.06 Hz, 1H), 7.14–7.17 (m, 4H), 7.21–7.23 (d, J=7.33 Hz, 1H), 7.43–7.46 (m, 4H), 7.96–7.99 (d, J=8.06 Hz, 1H), 12.84 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.7, 114.2, 118.5, 126.1, 126.5, 126.8, 127.6, 127.7, 127.9, 129.7, 135.5, 144.4, 157.2; $C_{23}H_{20}N_2O$ (340): calcd C, 81.15, H, 5.92, N, 8.23; found C, 81.05, H, 5.81, N, 8.18.

5.3.22. 4-(4,5-Di-*p*-tolyl-1*H*-imidazol-2-yl) phenol (3v). Mp 218 °C; IR (cm^{-1}) 1216, 1638, 2465, 2975, 3422, 3610; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.38 (s, 6H), 6.88–6.92 (d, J=8.61 Hz, 2H), 7.15–7.19 (m, 4H), 7.41–7.45 (m, 4H), 7.91–7.96 (d, J=8.61 Hz, 2H), 12.77 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.7, 114.2, 118.5, 126.1, 126.5, 126.8, 127.6, 127.7, 127.9, 129.7, 135.5, 144.4, 157.2; $C_{23}H_{20}N_2O$ (340): calcd C, 81.15, H, 5.92, N, 8.23; found C, 81.10, H, 5.85, N, 8.18.

5.3.23. 2-(2-Chlor-phenyl)-4,5-di-*p*-tolyl-1*H*-imidazole (3w). Mp 195 °C; IR (cm^{-1}) 1216, 1638, 2465, 2998, 3432; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.39 (s, 6H), 7.27–7.37 (m, 8H), 7.45–7.49 (dd, J=9 Hz, 1H), 7.57–7.59 (d, 2H), 8.02–8.05 (dd, J=8.79 Hz, 1H), 12.54 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.6, 125.4, 125.6, 126.5, 126.9, 127.2, 128.4, 128.7, 128.8, 129.7, 130.1, 130.6, 142.2; $C_{23}H_{19}ClN_2$ (358): calcd C, 76.98, H, 5.34, N, 7.81; found C, 76.88, H, 5.28, N, 7.72.

5.3.24. 2-(4-Bromo-phenyl)-4,5-di-*p*-tolyl-1*H*-imidazole (3x). Mp 215 °C; IR (cm^{-1}) 1216, 1638, 2465, 2978, 3432; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.35 (s, 6H), 7.11–7.15 (m, 4H), 7.42–7.46 (m, 4H), 7.54–7.58 (d, J=8.22 Hz, 2H), 8.02–8.06 (d, J=8.60 Hz, 2H), 12.78 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.4, 119.8, 125.4, 126.1, 127.3, 129.8, 134.7, 142.8; $C_{23}H_{19}BrN_2$ (402): calcd C, 68.49, H, 4.75, N, 6.95; found C, 68.38, H, 4.68, N, 6.82.

5.3.25. 2-(4,5-Di-*p*-tolyl-1*H*-imidazol-2-yl)-6-methoxy-phenol (3y). Mp 230 °C; IR (cm^{-1}) 1216, 1638, 2475, 2978, 3442, 3616; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.36 (s, 6H), 3.79 (s, 3H), 6.82–6.85 (m, 3H), 7.31–7.34 (m, 4H), 7.55–7.58 (m, 4H), 12.71 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.4, 54.7, 110.9, 112.1, 155.6, 117.1, 126.3, 126.7, 127.3, 127.4, 129.8, 145.1, 146.1, 147.3; $C_{24}H_{22}N_2O_2$ (370): calcd C, 77.81, H, 5.99, N, 7.56; found C, 77.68; H, 5.89, N, 7.47.

5.3.26. 4-(4,5-Di-*p*-tolyl-1*H*-imidazol-2-yl)-2-methoxy-phenol (3z). Mp 245 °C; IR (cm^{-1}) 1216, 1638, 2475, 2988, 3422, 3616; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.37 (s, 6H), 3.80 (s, 3H), 6.75–6.69 (d, J=8.22 Hz, 1H), 7.14–7.19 (m, 4H), 7.23–7.25 (d, J=8.7 Hz, 1H), 7.43–7.47 (m, 4H), 7.56–7.57 (d, J=8.3 Hz, 1H), 12.72 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 19.4, 55.1, 108.7, 114.7, 118.1, 121.2, 126.3, 127.3, 127.5, 132.3, 146.4, 146.9; $C_{24}H_{22}N_2O_2$ (370): calcd C, 77.81, H, 5.99, N, 7.56; found C, 77.72; H, 5.89, N, 7.47.

5.3.27. 2-(4-Nitro-phenyl)-4,5-di-*p*-tolyl-1*H*-imidazole (3z′). Mp 198 °C (decomposes); IR (cm^{-1}) 845, 1443, 1522, 1540, 1602, 3056; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 2.37 (s, 6H) 7.25–7.57 (m, 8H), 7.78 (d, J=9 Hz, 2H), 8.5 (d, J=9 Hz, 2H), 12.59 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz) δ 122.8, 124.3, 127.3, 127.6, 132.8, 146.7, 160.8; $C_{23}H_{20}N_3O_2$ (370): calcd C, 74.58, H, 5.44, N, 11.34; found C, 74.49, H, 5.40, N, 11.28.

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Electron depleted bis(methylene)cyclobutenes: sulfinyl and sulfonyl substitution

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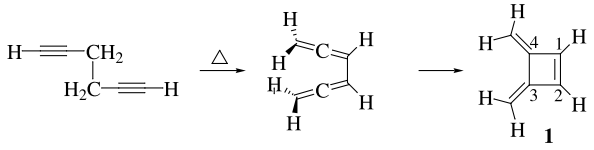
Abstract—Double [2,3] sigmatropic rearrangements of bis(propargyl sulfenates) to bis(allenic sulfoxides) and of bis(propargyl sulfinates) to bis(allenic sulfones) are shown to be a convenient and effective method for the preparation of conjugated diallene systems bearing two electron withdrawing trihalomethyl sulfoxide or sulfone substituents either on C-1 and C-6, or on C-3 and C-4. Such substituents are further shown to facilitate cyclization to bis(methylene)cyclobutenes, and to stabilize the latter. The electron withdrawing group substitution on the exocyclic methylene extremities proved more effective than similar substitution on the endocyclic double bond.

1. Introduction

3,4-Bis(methylene)cyclobutene (BMCB, **1**) is an isomer of benzene and formally an alternant hydrocarbon. As such, it is unique in exhibiting a surprisingly large dipole moment (0.616 ± 0.002 D).[1] Clearly, the nature of the polarization is to shift electronic charge from the ring towards the exocyclic methylenes, thus mitigating cyclic 4*e* anti-aromaticity and the associated energy penalty. Surprisingly, little experimental work has been reported on the parent system or on derivatives bearing functional substituents.[2] The most frequently used approach to BMCB system involves the electrocyclic ring closure of a 1,2,4,5-tetraene (i.e., conjugated diallene) structure (Scheme 1). The latter is usually accessed by the Cope rearrangement of a 1,5-hexadiyne, and at the high temperatures generally required for this rearrangement, the diallene is not isolated since the rate constant for its ring closure is greater than that for its formation.[3,4] Though it may perhaps be counter-intuitive, Pasto has already emphasized that by the thermodynamic criterion BMCB is more stable than diallene.[5] Nevertheless, BMCB does suffer from kinetic instability as a result of the intra-molecular charge separation. Thus, BMCB in solution is very sensitive to air oxidation and readily polymerizes.[3,6]



Scheme 1.

Obviously the study of the chemistry of the BMCB system and its diverse synthetic potential would be facilitated if kinetically stable representatives were readily available, especially ones bearing easily manipulated and synthetically useful functional groups. It seemed clear to us that electron withdrawing groups, if appended to the exocyclic methylenes, should stabilize the BMCB structure both thermodynamically and kinetically and should also facilitate its formation.

Methodology necessary to readily achieve the desired goal was in fact indigenous to our laboratory. We had, in the past, discovered the highly stereoselective facile [2,3]-sigmatropic rearrangements of allylic sulfenates and sulfinates to allylic sulfoxides[7] and sulfones,[8] respectively, and extended them to propargylic systems which yielded the corresponding allenic sulfoxides and sulfones.[9] In this report we detail the successful extension to similarly bis-substituted dipropargyl structures which, by double [2,3]-sigmatropic rearrangement, lead to the functionalized conjugated diallenes. Cyclization of the latter gave BMCBs bearing the above mentioned electron attracting, and in fact stabilizing substituents.[10]

Keywords: Bis(methylene)cyclobutenes; Diallenes; [2,3]-Sigmatropic rearrangements.
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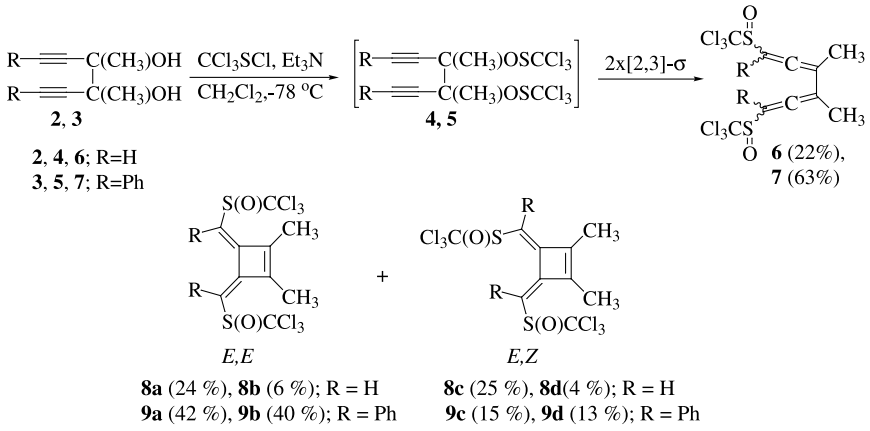


Scheme 2.

2. Results and discussion

2.1. Bis(methylene)cyclobutenes: exocyclic methylene sulfinyl substitution

The diols 3,4-dihydroxy-3,4-dimethyl-1,5-hexadiyne, (**2**), and 3,4-dihydroxy-3,4-dimethyl-1,6-diphenyl-1,5-hexadiyne (**3**), were prepared by standard procedures, each as an approximately equimolar mixture of the *meso* and *racemic* forms.[11] Whereas attempts to separate the diastereoisomers of **2** failed, flash-chromatography of crude **3** yielded the pure racemate, **3a** (mp 122–124 °C) and the *meso* isomer **3b** (mp 68–70 °C). The reaction of each of the diols, **2** (racemate+*meso*), **3a** and **3b** with trichloromethanesulfenyl chloride (triethylamine, −78 °C) resulted in the complete rearrangement of the first formed propargylsulfenate esters **4** or **5** to the diallenic disulfoxides (**6**; **7**) and in part, by subsequent cyclization, to 3,4-bis(methylene)-cyclobutenes (**8**; **9**) (Scheme 2), as detailed below.

In the case of **2**, after 20 min at −78 °C, NMR spectroscopy analysis showed that cyclobutenes **8** constituted 78% of the crude product, and isolation of the remaining diallene **6** (~22%) was thwarted by its continuing transformation to **8**. Following total conversion of **6**, chromatography lead to the isolation of four isomeric 3,4-bis(methylene)cyclobutenes, **8a** (24%), **8b** (6%), **8c** (50%), **8d** (8%).

Under the same reaction conditions, the crude product from **3a** contained no remaining diallene, and upon chromatographic separation yielded approximately equal amounts of **9a** and **9b** (total yield 82%). In contrast, the crude product derived from **3b**, even after 1 h at −78 °C, was still the diallene **7** (hexane insoluble; isolated yield 63%; mp 124–126 °C). However, in CH_2Cl_2 solution at ambient temperature (ca. 3.5 h) **7** transformed into a mixture of cyclobutenes **9c** (15%) and **9d** (13%) accompanied by polymer. These were separated by chromatography. In Table 1, we list those of the NMR spectroscopic data, which will serve us in the discussion of the structures of each of the eight BMCBs mentioned heretofore.

In the substituted 3,4-bis(methylene)cyclobutene **8** (and similarly in **9**) each of the exocyclic double bonds could independently have an *E* or a *Z* substitution pattern. Additionally the two sulfur atoms of the sulfoxide functions are independent chiral centers. As the molecule is composed of two halves of the same constitution only ten stereoismers are possible, and these divide into two *meso* compounds and four racemates (see Table 2). However, as detailed above, only four of the six were in fact obtained in each system, **8** and **9**, and in differing yields. The structures of **8a**, **9a** and **9c** were established by X-ray crystallography. These are shown in Figures 1–3.

The two exocyclic double bonds in both **8a** and **9a** are clearly *E*, and both structures possess a two fold rotational axis of symmetry. These compounds configuration of both sulfur atoms in each, is the same. They are therefore to be identified as racemates. As demanded by the symmetry of their X-ray structures (Figs. 1 and 2), there is only one signal for each type of hydrogen and of carbon in the NMR spectra of **8a** and of **9a** (Table 1). This symmetry feature is also evident in the NMR spectra of **8b** and of **9b**, and the

Table 1. Some NMR data of bis(methylene)cyclobutenes **8** and **9**

	δ ^{1}H				δ ^{13}C							
	C*H*		CH_3		*C*H$_3$		*C*S		*C*=CS		*C*CH$_3$	
	E	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
8a	6.05	—	2.27	—	14.17	—	109.49	—	155.35	—	161.54	—
8b	6.01	—	2.27	—	14.44	—	109.28	—	155.39	—	161.75	—
8c	5.97	6.34	2.28	2.09	14.67	10.87	110.05	114.04	154.89	155.76	161.94	161.36
8d	5.94	6.36	2.28	2.11	14.60	10.93	110.38	114.24	155.02	155.47	162.05	161.29
9a	—	—	2.39	—	16.02	—	107.71	—	153.12	—	159.95	—
9b	—	—	2.41	—	16.22	—	108.61	—	152.49	—	160.68	—
9c	—	—	2.33	1.45	16.18	12.54	124.46	126.38	154.86	151.98	161.51	160.11
9d	—	—	2.33	1.34	16.47	12.47	125.07	127.99	153.96	152.37	162.35	160.05

Table 2. Stereochemical isomers of **8** and **9**

Entry	$C_{(3)}$=C···S(O)		$C_{(4)}$=C···S(O)		*rac/meso*	Corresponds to
(i)	*Z*	(*R*/*S*)	*E*	(*R*/*S*)	*rac*	{**8d** or **8c**}, **9c**
(ii)	*Z*	(*R*/*S*)	*E*	(*S*/*R*)	*rac*	{**8c** or **8d**}, **9d**
(iii)	*E*	(*R*/*S*)	*E*	(*R*/*S*)	*rac*	**8a**, **9a**
(iv)	*E*	(*R*/*S*)	*E*	(*S*/*R*)	*meso*	**8b**, **9b**
(v)	*Z*	(*R*/*S*)	*Z*	(*R*/*S*)	*rac*	—
(vi)	*Z*	(*R*/*S*)	*Z*	(*S*/*R*)	*meso*	—

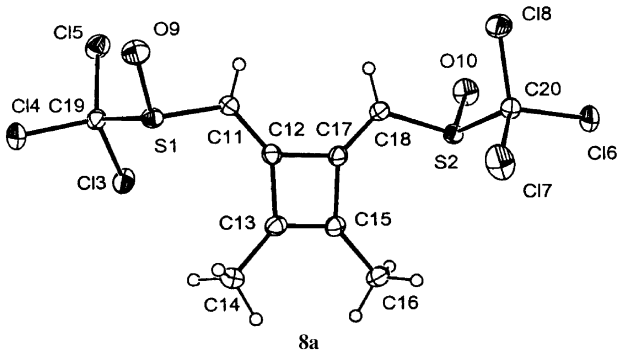


Figure 1. Crystal structures of (3*E*,4*E*)-1,2-dimethyl-3,4-bis{[(trichloromethyl)sulfinyl]methylene}-cyclobutene, **8a**.

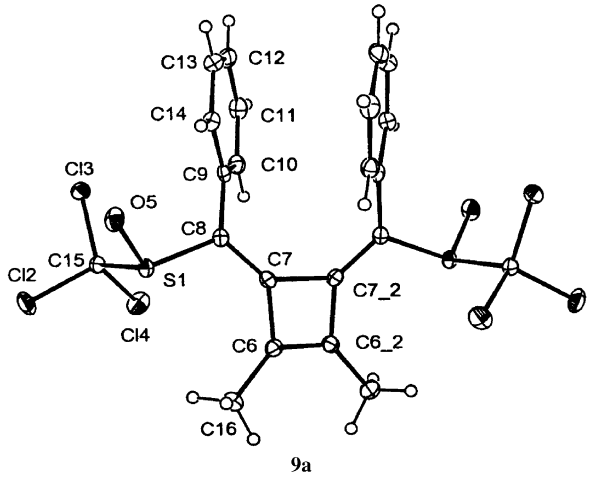


Figure 2. Crystal structures of {[(*E*)-(4*E*)-2,3-dimethyl-4-{phenyl[(trichloromethyl)sulfinyl]methylene}cyclobut-2-en-1-ylidene)[(trichloromethyl)sulfinyl]methyl}benzene, **9a**.

chemical shifts are similar to those of **8a** and **9a**, respectively. It may therefore be concluded that the relevant double bonds in **8b** and **9b** are also *E*,*E*. Only the relative configurations of the two sulfoxide groups distinguish **8b** from **8a**, and **9b** from **9a**. By elimination (Table 2), **8b** and **9b** must be *meso*.

The X-ray structure of **9c** (Fig. 3) showed that this compound, in contrast to the four BMCBs discussed above, has one exocyclic double bond of *E*, and one of *Z* configuration. This is in keeping with its NMR spectrum which shows two absorptions of each type of hydrogen and carbon. Likewise, compounds **8c**, **8d**, and **9d** all have two absorptions in the NMR for each type of hydrogen and

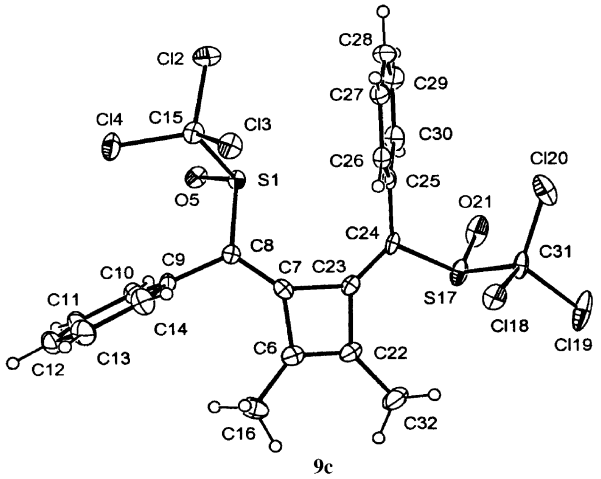
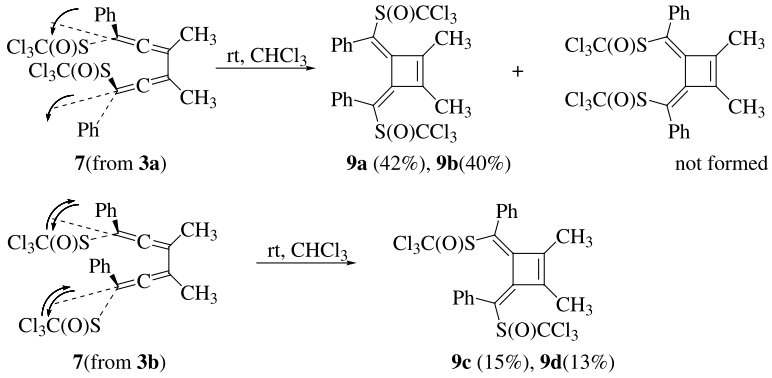


Figure 3. Crystal structures of {[(*E*)-(4*Z*)-2,3-dimethyl-4-{phenyl[(trichloromethyl)sulfinyl]methylene}cyclobut-2-en-1-ylidene)[(trichloromethyl)sulfinyl]methyl}benzene, **9c**.

carbon, showing that also in these compounds the two halves of each are dissimilar, one exocyclic double bond in each being *E*, and the other *Z*. The difference in structure within each pair (**8c**–**8d**; **9c**–**9d**) is restricted to the sulfoxide configurations. Further examination of the crystal structure of **9c** reveals that in each of the two enantiomeric molecules present the configurations of the two sulfoxide functions are the same (i.e., either both *R* or both *S*). In other words, **9c** is the racemate of stereochemistry assigned to it in Table 2. By elimination **9d** must have the stereochemistry assigned in the same Table. For **9a** and **9b** the proton resonances of both the C-1 and the C-2 pendant methyl groups are at $\delta \sim 2.4$. In these *E*,*E*-compounds both phenyl groups are at the mouth of the 'bay' formed by the exocyclic double bonds, and distanced from said methyl groups. For the *E*,*Z*-compounds **9c** and **9d** the methyl resonances are one at δ 2.33 and the other at δ 1.45/1.34 (see Table 1). Thus, the former value belongs to the methyls in the moieties having the *E* double bonds, while the latter values are assignable to the methyls shielded by the proximate phenyls on the exocyclic *Z* double bond.

By similar comparison of methyl group resonance in the series **8a**–**d** (cf. also **9a**–**b**) it may be concluded that those with δ 2.09 (in **8c**) and 2.11 (in **8d**) are the ones proximate to the *Z* double bond, and this proved in accord with connectivity determinations by 2D NMR. The steric congestion created in the placement of one phenyl group and one –S(O)CCl_3 group in the 'bay' regions of **9c** and **9d**

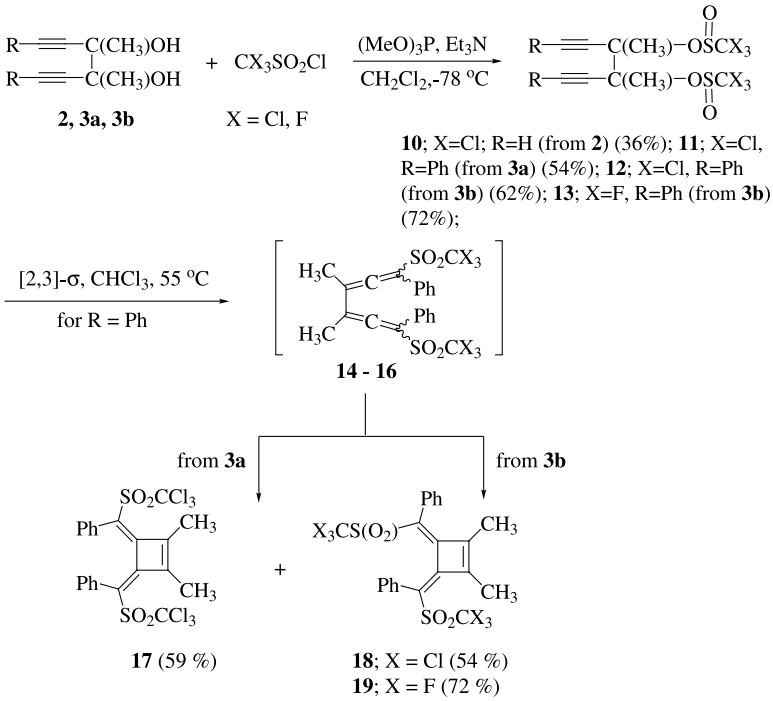


Scheme 3.

is presumably responsible for slowing the cyclization of the diallene **7** (derived from **3b**) and permitting competing polymerization. No product in which both exocyclic double bonds have *Z* configuration was isolated in either series. Such a structure would require both trichloromethylsulfinyl groups to occupy positions in the bay area, and this is precluded by their steric requirements.

In contrast to the Cope rearrangement at elevated temperatures which was most commonly used in the past to convert 1,5-hexadiyne systems into diallenes and thereafter into BMCBs, the present 'one-pot' synthesis utilizes the convenient low temperature conversion of readily accessible bis(propargylic alcohols) to bis-sulfenates followed by their rapid in situ double [2,3]-sigmatropic rearrangement to bis(allene sulfoxides) and subsequent electrocyclization to BMCB bis-sulfoxides. The symmetry permitted path for said sigmatropic rearrangement is suprafacial.[12] Consequently, the reaction of both propargylic moieties of the *meso*-disulfenate **5b**, converts it into a diallene whose overall stereochemistry, focusing for the moment on allene axial chirality and ignoring the sulfoxide group chiralities, is of the *meso* type, one allenic arm (originating from the $S_{(C)}$-sulfenate) having *M* helicity, and the other (originating from the $R_{(C)}$-sulfenate) having *P* helicity. In view of the distance between two sulfoxide functions it is reasonable to assume that the configuration of the one produced in the first sigmatropic rearrangement does not determine the configuration of the other produced in the second. In all, *meso*-**5b** may thus generate two *meso* and one *racemic* isomer of **7** (=**7b**). Similar stereochemical analysis shows that the [2,3]-sigmatropic migrations in the *rac*-disulfenate **5a** may yield three different racemates of constitution **7** (=**7a**).

The stereochemistry of the cyclization of substituted diallene to a BMCB has been studied previously and found to proceed stereospecifically in a conrotatory manner even at elevated temperatures, in keeping with orbital symmetry considerations.[3,13–16] Application of this finding to the present study shows that the 3,4-bis(methylene)-cyclobutenes in which the exocyclic double bonds are both *E* were produced from the diol racemates via *racemic*



Scheme 4.

diallenes, while those in which one double bond is *E* and the other is *Z* originate in the *meso* diols via *P*,*M*-diallenes. The steps leading to the various isomers of **8** and **9** are shown in Scheme 3.

The BMCBs **8a–d** and **9a–d**, bearing electron withdrawing groups on the exocyclic methylenes, lived up to expectations and proved stable upon chromatography as well in air, and even in solution, for months.

2.2. Bis(methylene)cyclobutenes: exocyclic methylene sulfonyl substitution

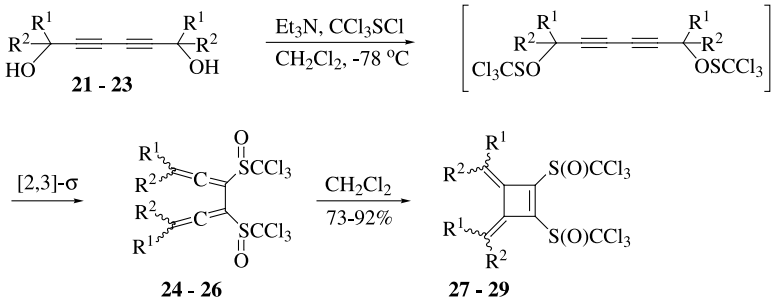
Proceeding from the utilization of the sulfenate-to-sulfoxide rearrangement, to that of the sulfinate-to-sulfone rearrangement, we prepared the bis(trichloromethanesulfinates) of **2** (racemate+*meso*), of **3a** and of **3b**, as well as the bis(trifluoromethanesulfinate) of **3b**, by the method of Klunder and Sharpless (Scheme 4).[17] All of these bis(propargyl sulfinate esters) **10–13** proved stable at room temperature and could be purified from extraneous material by chromatography on silica gel. This however failed in all cases to separate the stereoisomers produced by the introduction of the two additional stereogenic sulfur atoms. In the case of **10**, the bis(trichloromethanesulfinates) obtained from **2**, the ^{13}C NMR spectrum indicated the presence of all possible four racemates and two *meso* isomers. The mixture of bis(trichloromethanesulfinates) **11**, derived from **3a**, may contain three racemates, and it was accompanied by, and separated from 1-methyl-2-methylene-4-phenyl-1-(phenylethynyl)but-3-ynyl trichloromethanesulfinate **20**, a by-product of elimination of trichloromethane sulfonic acid. The bis(trichloromethanesulfinates) **12**, and the bis(trifluoromethanesulfinate) **13**, both prepared from the *meso* diol **3b**, may each contain two *meso* isomers and one racemate. No effort was invested in trying to separate these mixtures of isomers at this stage, since in the sulfone substituted BMCBs, which were the goal of the reaction sequence, the stereogenicity of the sulfur atoms is lost, and the chirality at the carbon atoms is translated into geometrical isomerism.

In our original investigations of the propargyl sulfinate to allenic sulfone rearrangement we found that it requires much higher temperatures than the corresponding sulfenate-to-sulfoxide rearrangement.[9] Thus it required heating at ~55°C for 12 h in chloroform solution to complete rearrangement of **11** and of **12**. The formation of the intermediate allenes could be detected by NMR spectroscopy, but they were not isolated because of their rapid cyclization to BMCBs. In keeping with our findings in the case of the sulfoxide substituted BMCBs, **11**, derived from *racemic* **3a**, gave only a single isomer **17**, of *E*,*E*-configuration of the two exocyclic double bonds, whereas **12**, derived from *meso* **3b** gave a single isomer **18** of *E*,*Z*-configuration. Likewise **13**, prepared from bis(trifluoromethanesulfonyl)ester of **3b**, by refluxing in chloroform solution for ~7 h yielded a single isomer **19** possessing the *E*,*Z*-configuration. Most surprisingly, **10** did not undergo the [2,3]-sigmatropic rearrangement in refluxing chloroform for 26 h. Refluxing in acetonitrile caused decomposition. Obviously the stabilizing effect of the phenyl substituent on the transition state is necessary in these cases to reduce the temperature required for rearrangement below the decomposition temperature.

Not surprisingly, the BMCBs **17–19** were found to be stable under the conditions detailed for **8** and **9**.

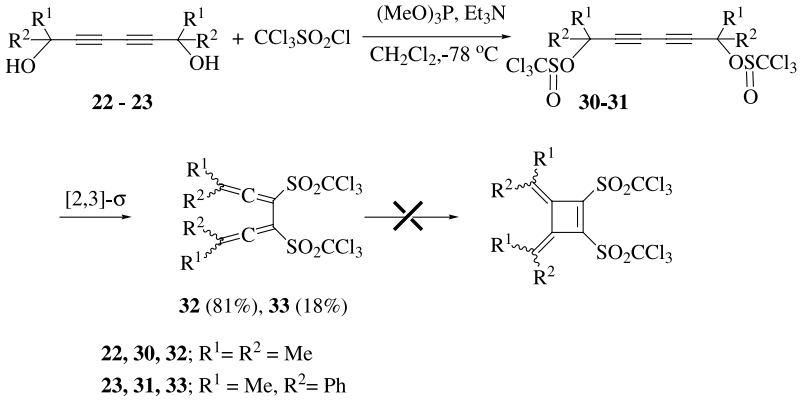
2.3. Bis(methylene)cyclobutenes: endocyclic double bond sulfinyl substitution

The question naturally presented itself whether electron-withdrawing substitution on carbons 1 and 2 of the ring would be equally effective in stabilizing the BMCB system. To investigate this we prepared 3,5-octadiyn-2,7-diol (**21**), 2,7-dimethyl-3,5-octadiyn-2,7-diol (**22**), and 2,7-diphenyl-3,5-octadiyn-2,7-diol (**23**), by oxidative coupling of the respective propargyl alcohols (Glaser reaction).[18] The diols **21** and **23** thus obtained were mixtures of the racemate and the *meso* isomer. These diols were all converted into their bis(trichloromethanesulfenate) esters (trichloromethanesulfenyl chloride, Et_3N, −78 °C) which underwent spontaneous [2,3]-sigmatropic rearrangement to the 4,5-bis-trichloromethansulfinyl-2,3,5,6-octatetraenes **24–26**, respectively, and subsequent cyclization to the respective BMCBs, **27**, **28**, **29** (Scheme 5). The suprafacial nature of the sigmatropic rearrangement dictates that in the present cases a carbon atom of *R* chirality in the diol (and its sulfenate ester) engenders an allene arm of *M* helicity while



21, 24, 27; R^1= H, R^2= Me
22, 25, 28; R^1= R^2 = Me
23, 26, 29; R^1 = Me, R^2= Ph

Scheme 5.



Scheme 6.

S chirality leads to *P* helicity. In keeping with the stereoanalysis above regarding the formation of the diallenes, and since **21** was a mixture of *meso*+ racemate, product **24** may contain up to four racemates and two *meso* isomers. The same is true for **26**. The possible constituents of **25**, derived from **22**, wherein only the two sulfur atoms are stereogenic, are limited to one *meso* isomer and one racemate. As noted for **6**, and also in the case of **24**, the diallene bearing only one substituent at each extremity cyclized rapidly; too rapidly in the present instance to permit meaningful NMR spectroscopic characterization of this mixture of diallene stereoisomers. In contrast, the diallenes **25** and **26**, being fully substituted at their extremities (cf. **7**), require one to two hours for complete cyclization, and NMR spectroscopic data could be gathered.

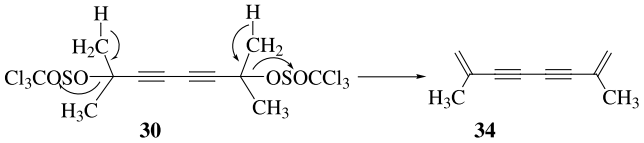
Since, as detailed above, the diallenes **24**–**26** were obtained as mixtures of stereoisomers, so were their cyclization products **27**–**29.** Attempts at chromatographic separation of the isomeric BMCBs lead to decomposition in every case. The isomeric composition of **27**–**29** was therefore determined by 2D NMR spectroscopy analysis only. However, as already noted above, such analysis distinguishes only *Z*–*E* isomerism of the exocyclic double bonds, but is insensitive to stereoisomerism of the sulfoxide functions. Thus BMCB **28**, obtained from **22** via **25** in 90% yield, showed only one set of ^{1}H and ^{13}C NMR signals though its two sulfur atoms are chiral centers and it is presumed to be a mixture of racemate and *meso* isomer. Unexpectedly, it also possessed a sharp melting point (68–69 °C). The cyclization of **24** gave **27**, which ignoring sulfur chirality, appeared in the NMR spectrum as a mixture of three BMCBs isomeric about the exocyclic double bonds, in the ratios of 5/5/1 (total yield, 73%). These were assigned the respective structures *E*,*Z* (presumably derived from *meso* **21**), *E*,*E* and *Z*,*Z* (these two presumably derived from *racemic* **21**). Similarly, the mixed product **29** derived from the diol **23** via **26** possessed an NMR spectrum showing the presence of three *E*–*Z* isomeric compound types in the ratios 1/7/2 (total yield 92%).

Returning to the question of relative stability, BMCBs **27**, **28**, **29** proved to be much less stable than **8** or **9**. Not only did they decompose upon chromatography, but they also underwent polymerization and oxidation upon exposure to air for a few days. However, when compared to descriptions in the literature it appears that they are somewhat more stable than BMCBs lacking electron-withdrawing groups.

2.4. Bis(methylene)cyclobutenes: endocyclic double bond sulfonyl substitution

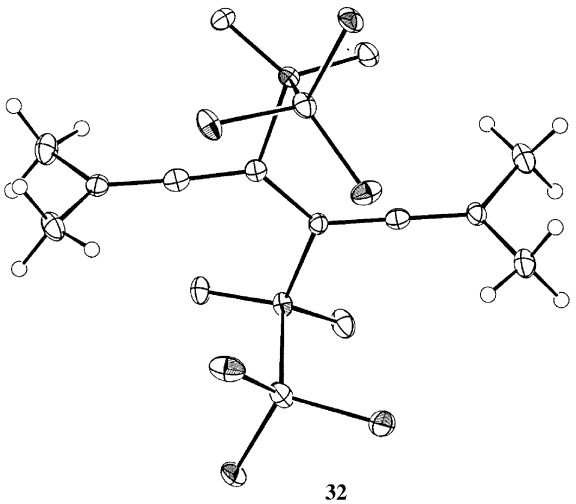
In an attempt to prepare BMCBs bearing the more effective sulfones electron withdrawing groups on C-1 and C-2, we converted the diols **22** and **23** into their respective bis(trichloromethanesulfinates) **30** and **31** using Klunder–Sharpless conditions[17] (Scheme 6).

Purification of **30** was achieved by repeated washing with hexane, since upon chromatography partial rearrangement to the diallene **32** was accompanied by elimination yielding **34** (Scheme 7). Complete conversion of **30** to **32** was achieved by heating a dilute chloroform solution at 60 °C for 3 h. X-ray crystallographic determination of the structure of **32** showed that, as expected (see above), it adopted an 'extended' conformation (Fig. 4). In the case of **23** the production of **31** was accompanied in situ by its partial rearrangement to the diallene **33**. Only the latter was isolated in poor yield upon chromatography of the crude product. Unlike the diallenyl sulfones **14** and **15**, the diallenyl sulfones **32** and **33** did not cyclize to BMCBs even in refluxing chloroform solution. Elimination of the trichloromethanesulfinyl groups took precedence. Thus, **30** showed 66% conversion to the previously identified **34**[19] after 2 h. The mixture of products from **33** was not characterized.



Scheme 7.

It is thus appears that while *cis* 1,2-bis(trichloromethylsulfinyl) substituents in **27**–**29** can sterically accommodate each other, the replacement of the sulfoxide by sulfone function makes such accommodation difficult. Compounds having vicinal *cis*-phenyl sulphonyl substituents at a double bond are known,[20] but a trichloromethyl group is sterically more demanding than a phenyl group, as also shown by the



32

Figure 4. Crystal structure of 2,7-dimethyl-4,5-bis[(trichloromethyl)sulfonyl]octa-2,3,5,6-tetraene, **32**.

formation of the *E*,*E*-isomer of **9a**, **9b** (vide infra), but not of the *Z*,*Z*-isomer.[†]

3. Conclusions

The facile [2,3]-sigmatropic rearrangements of propargylic sulfenates to allenyl sulfoxides and propargylic sulfinates to allenyl sulfones has been enlisted to prepare conjugated diallenes bearing trihalomethyl sulfoxide and sulfone substituents. These electron withdrawing groups have been found to greatly facilitate ring closure of the diallenes to bis(methylene)cyclobutenes, and to stabilize the latter kinetically, and presumably also thermodynamically. In the unsubstituted bis(methylene)cyclobutene antiaromaticity is mitigated by expelling electronic charge from the ring to the exocyclic methylene carbons. Consequently, it is to be expected that electron-accepting groups on these carbons will be more effective in stabilizing the system than similar electron withdrawing substituents on the ring carbons. This expectation was in fact borne out in our findings.

4. Experimental

4.1. General

Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected IR spectra were recorded on a Nicolet 60 SXB FTIR instruments. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-300 or DMX-600 spectrometers, using TMS as internal standard. Chemical shifts are reported in ppm downfield from tetramethylsilane. High-resolution mass spectra were obtained on a VG-Fison AutoSpec instrument and other mass spectra on a Finnigan GC/MS 4021, by using chemical ionization (CI) or electron impact (EI). Column chromatography was performed with Merck silica gel 60 (230–240 mesh). All solvents and reagents were obtained from Aldrich or Fluka and used without further purification with the following exception: CH_2Cl_2 was distilled from P_2O_5.

4.2. General procedure for the preparation of diallenes 6

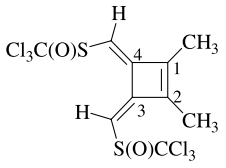
To a solution of the corresponding diynediol (1 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C trichloromethanesulfenyl chloride (0.22 mL, 2 mmol) and triethylamine (0.28 mL, 2 mmol) were added simultaneously via syringes and the reaction mixture was allowed to stir at the same temperature for 30 min. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and rapidly washed with cold 3% aq HCl (20 mL), cold saturated $NaHCO_3$ (20 mL), cold brine (20 mL) and evaporated under reduced pressure. The residue was triturated with small quantities of hexane and immediately analyzed by NMR spectroscopy.

4.2.1. 3,4-Dimethyl-1,6-bis[(trichloromethyl)sulfinyl]-hexa-1,2,4,5-tetraene, 6. Diallene **6** was obtained as a mixture with the corresponding bis(methylene)cyclobutenes **8**. Viscous oil, yield 22% (by NMR). δ_H (300 MHz, $CDCl_3$) 2.01 (6H, d, $J=1.5$ Hz), 6.52 (2H, q, $J=1.5$ Hz); δ_C (75 MHz, $CDCl_3$) 16.3 (CH_3), 99.5 (CH), 106.7 (CCl_3), 108.5 (C-3,4), 206.6 (C-2,5).

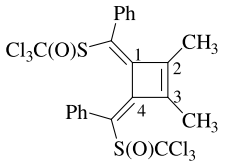
4.2.2. {3,4-Dimethyl-6-phenyl-1,6-bis[(trichloromethyl)-sulfinyl]hexa-1,2,4,5-tetraenyl}benzene, 7 (from diol 3b). Colorless crystals, mp 124–126 °C, yield 0.37 g (63%). δ_H (300 MHz, $CDCl_3$) 2.05 (6H, s), 7.33–7.50 (10H, m); δ_C (75 MHz, $CDCl_3$)16.9 (CH_3), 109.3 (CCl_3), 113.4 (C-3,4), 118.2 (C-1,6), 127.8 (*C*H), 128.6 (*C*H), 129. 2 (*C*H), 131.6 (C), 206.1 (C-2,5).

4.3. General procedure for the preparation of 3,4-bis(methylene)cyclobutenes 8a–d and 9a–d

These compounds were obtained using the above procedure described for allenes **6** and **7** with the exception that the reaction time was extended. In the case of cyclobutenes **8** the reaction mixture was kept at room temperature for an additional 1 h, and for cyclobutenes **9**—for 3.5 h. Isomeric cyclobutenes were separated by flash chromatography with EtOAc/hexane 1:8, samples for X-ray were recrystallized from ethyl acetate–hexane.



8c,d



9c,d

4.3.1. (3*E*,4*E*)-1,2-Dimethyl-3,4-bis{[(trichloromethyl)-sulfinyl]methylene}-cyclobutene, 8a (from diol 2). Colorless crystals, mp 168–169 °C, yield 0.105 g (24%). ν_{max} (KBr) 830, 910, 1089, 1447, 1573, 1626 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.27 (6H, s), 6.05 (2H, s); δ_C (75 MHz, $CDCl_3$) 14.2 (CH_3), 107.7 (CCl_3), 109.5 (*C*H=), 155.4 (C-3,4), 161.5 (C-1,2); *m/z* (CI, CH_4) 434

[†] Preliminary experiments with the diallene 2,7-dimethyl-4,5-bis(diethoxyphosphinyl)-2,3,5,6-octatetraene[21] showed that it does ring close to the BMCB bearing vicinal diethyl phosphonate ester grouping carbons 1 and 2, albeit under relatively vigorous conditions (4 days, ~100 °C, toluene sol.).

(MH^+, 11.2), 317 (55.6), 200.0 (100), 183.0 (30.6), 153.0 (29), 135.0 (44); HRMS ($C_{10}H_9$ $Cl^{35}{}_6O_2S_2$): calcd 434.8175; found 434.8164.

4.3.2. (3*E*,4*E*)-1,2-Dimethyl-3,4-bis{[(trichloromethyl)-sulfinyl]methylene}-cyclobutene, 8b (from diol 2). Colorless crystals, mp 58–60 °C, yield 0.026 g (6%). ν_{max} (KBr) 838, 1089, 1573, 1626 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.27 (6H, s), 6.01 (2H, s); δ_C (150 MHz, $CDCl_3$) 14.4 (*C*H_3), 107.9 (*C*Cl_3), 109.3 (*C*H), 155.4 (C-3,4), 161.8 (C-1,2); HRMS ($C_{10}H_9$ $Cl^{35}{}_6O_2S_2$): calcd 434.8175; found 434.8164.

4.3.3. (3*E*,4*Z*)-1,2-Dimethyl-3,4-bis{[(trichloromethyl)-sulfinyl]methylene}-cyclobutene, 8c (from diol 2). Colorless crystals, mp 146–148 °C, yield 0.109 g (25%). ν_{max} (KBr) 735, 932, 1396, 1439, 1577 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.10 (3H, s, C*H*$_3$–C-1), 2.28 (3H, s, C*H*$_3$–C-2), 5.97 (1H, s, C*H*=C-3), 6.34 (1H, s, C*H*=C-4); δ_C (150 MHz, $CDCl_3$) 10.9 (*C*H_3–C-1), 14.7 (*C*H_3–C-2), 107.8 (*C*Cl_3–S(O)CHC-3), 107.9 (*C*Cl_3–S(O)CHC-4), 110.1 (*C*H=C-3), 114.0 (*C*H=C-4), 154.9 (C-3), 155.8 (C-4), 161.4 (C-1), 161.9 (C-2); *m*/*z* (%) (CI, CH_4): 434 (MH^+, 22.6), 317 (100), 200 (11.8), 153 (17.3), 135 (26.9), 121 (34.6); HRMS ($C_{10}H_9$ $Cl^{35}{}_6O_2S_2$): calcd 434.8175; found 434.8195.

4.3.4. (3*E*,4*Z*)-1,2-Dimethyl-3,4-bis{[(trichloromethyl)-sulfinyl]methylene}-cyclobutene, 8d (from diol 2). Colorless crystals, mp 80–82 °C, yield 0.017 g (4%). ν_{max} (KBr) 811, 1107, 1591, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.10 (3H, s, C*H*$_3$–C-1), 2.27 (3H, s, C*H*$_3$–C-2), 5.93 (1H, s, C*H*=C-3), 6.37 (1H, s, C*H*=C-4); δ_C (75 MHz, $CDCl_3$) 10.9 (*C*H_3–C-1), 14.7 (*C*H_3–C-2), 107.8 (*C*Cl_3–S(O)CHC-3), 107.9 (*C*Cl_3–S(O)CHC-4), 110.1 (*C*H=C-3), 114.0 (*C*H=C-4), 154.9 (C-3), 155.8 (C-4), 161.4 (C-1), 161.9 (C-2); *m*/*z* (%) (CI, CH_4) 434 (MH^+, 7.1), 318 (54.2), 229 (22.2), 200 (73.5), 183 (74.8), 168 (18.5), 153 (39.0), 136 (100), 121 (33.9), 117 (75.7); HRMS ($C_{10}H_9$ $Cl^{35}{}_6O_2S_2$): calcd 434.8175; found 434.8173.

4.3.5. {[(*E*)-(4*E*)-2,3-Dimethyl-4-{phenyl[(trichloromethyl)sulfinyl]methylene}cyclobut-2-en-1-ylidene)[(trichloromethyl)sulfinyl]methyl}benzene, 9a (from diol 3a). Colorless crystals, mp 164–165 °C, yield 0.247 g (42%). ν_{max} (KBr) 1044, 1254, 1451, 1585 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.39 (6H, s), 6.65–7.21 (10H, m); δ_C (150 MHz, $CDCl_3$) 16.0 (*C*H_3), 107.7 (*C*Cl_3), 126.2 (C), 128.0 (*C*H), 129.0 (*C*H), 130.5 (*C*H), 131.6 (C), 153.1 (C-1,4), 160.0 (C-2,3); *m*/*z* (%) (FAB) 586.8 (MH^+, 6.8), 513 (14.3), 419 (19.5), 304 (100), 289 (47.2), 255 (34.2), 201 (40.5), 189 (15.6).

4.3.6. {[(*E*)-(4*E*)-2,3-Dimethyl-4-{phenyl[(trichloromethyl)sulfinyl]methylene}cyclobut-2-en-1-ylidene)[(trichloromethyl)sulfinyl]methyl}benzene, 9b (from diol 3a). Colorless crystals, mp 158–159 °C, yield 0.236 g (40%). ν_{max} (KBr) 1052, 1268, 1440, 1596 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.41 (6H, s), 6.84–6.89 (8H, m), 6.98–7.02 (4H, m); δ_C (150 MHz, $CDCl_3$) 16.2 (*C*H_3), 108.7 (*C*Cl_3), 126.3 (C), 127.7 (*C*H), 128.8 (*C*H), 131.3 (*C*H), 132.7 (C), 152.5 (C-1,4), 160.7 (C-2,3); *m*/*z* (%) (FAB) 586.9 (MH^+, 6.1), 304 (100), 286 (5.7), 255 (7.0), 154 (12.3), 136 (10.9).

4.3.7. {[(*E*)-(4*Z*)-2,3-Dimethyl-4-{phenyl[(trichloromethyl)sulfinyl]methylene}cyclobut-2-en-1-ylidene)[(trichloromethyl)sulfinyl]methyl}benzene, 9c (from diol 3b). Colorless crystals, mp 128–130°C, yield 0.088 g (15%). ν_{max} (KBr): 898, 1285, 1431, 1568 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.46 (3H, s), 2.33 (3H, s), 7.23–7.38 (6H, m), 7.43–7.55 (4H, m); δ_C (150 MHz, $CDCl_3$) 12.5 (*C*H_3), 16.2 (*C*H_3), 107.7 (*C*Cl_3), 107.8 (*C*Cl_3),124.6 (C), 126.5 (C), 127.4 (*C*H), 128.1 (C), 128.5 (*C*H), 128.9 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 129.8 (C), 130.3 (*C*H), 132.2 (*C*H), 132.5 (*C*H), 132.8 (*C*H), 152.0 and 154.9 (C-1,4), 160.1 and 161.5 (C-2,3); *m*/*z* (%) (CI, CH_4) 586.9 (MH^+, 3.5), 471 (13.5), 404 (12.6), 369 (15.5), 351 (18.7), 334 (14.3), 320 (74.5), 304 (55.6), 288 (100), 256 (23.9), 169 (22), 131 (28); HRMS ($C_{22}H_{17}^{35}Cl_6O_2S_2$): calcd 586.8801; found 586.8827.

4.3.8. {[(*E*)-(4*Z*)-2,3-Dimethyl-4-{phenyl[(trichloromethyl)sulfinyl]methylene}cyclobut-2-en-1-ylidene)[(trichloromethyl)sulfinyl]methyl}benzene, 9d (from diol 3b). Colorless crystals, mp 164–166°C, yield 0.076 g (13%). ν_{max} (KBr): 915, 1268, 1431, 1586 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.34 (3H, s), 2.33 (3H, s), 7.30–7.56 (10H, m); δ_C (150 MHz, $CDCl_3$) 12.5 (*C*H_3), 16.5 (*C*H_3), 125.1 (C), 127.6 (*C*H), 128.0 (C), 128.3 (*C*H), 128.5 (*C*H), 128.7 (C), 129.2 (*C*H), 130.3 (*C*H), 132.3 (*C*H), 132.4 (*C*H), 132.7 (*C*H), 152.5 and 154.1 (C-1,4), 160.2 and 162.5 (C-2,3); *m*/*z* (%) (CI, CH_4) 586.9 (MH^+, 7.3), 471 (41), 406 (26), 371 (37), 353 (55), 337 (56), 321 (74), 304 (81), 288 (100), 273 (22), 256 (17); HRMS ($C_{22}H_{17}^{35}Cl_6O_2S_2$): calcd 586.8801; found 586.8770.

4.4. General procedure for the preparation of bis-(trihalomethanesulfinates) 10–13

To a solution of the corresponding diynediol (1 mmol) and trihalomethanesulfonyl chloride (3 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C, triethylamine (0.42 mL, 3 mmol) and trimethyl phosphite (0.35 mL, 3 mmol) were added simultaneously via syringes and the reaction mixture was allowed to stir at the above temperature for 30 min and an additional 2 hr at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 3% aq HCl (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL) and evaporated under reduced pressure. After purification by column chromatography (hexane/EtOAc 10:1) each of the sulfinates **10–13** was obtained as a mixture of stereoisomers.

4.4.1. 1-Ethynyl-1,2-dimethyl-2-{[(trichloromethyl)sulfinyl]oxy}but-3-ynyl trichloromethane-sulfinate, 10 (from diol 2). Colorless solid, total yield of isomers 0.169 g (36%),. ν_{max} (KBr): 910, 1181, 1379, 1448, 1740, 2135, 2270 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.90–2.02 (m, superposition of C*H*$_3$-peaks of all isomers), 3.09–3.12 (m, superposition of C*H*-peaks of all isomers); δ_C (75 MHz, $CDCl_3$) 24.6 (*C*H_3), 24.8 (*C*H_3), 24.9 (*C*H_3), 25.0 (*C*H_3), 25.1 (*C*H_3), 25.4 (*C*H_3), 25.6 (*C*H_3), 25.8 (*C*H_3), 25.8 (*C*H_3), 78.0 (C), 78.0 (C), 78.3 (C),78.5 (C), 82.4 (C), 82.5 (C), 82.6 (CH), 82.7 (C), 82.8 (C), 82.9 (*C*H), 108.5 (*C*Cl_3); *m*/*z* (%) (FAB) 466.9 (M^+, 34.7), 341 (25), 327 (51), 285 (100); HRMS ($C_9H_8Cl_3O_2S$) ($M-CCl_3SO_2$)$^+$: calcd 284.9310; found 284.9322.

4.4.2. 1,2-Dimethyl-4-phenyl-1-(phenylethynyl)-2-{[(trichloromethyl)sulfinyl]oxy}but-3-ynyl trichloromethanesulfinate, 11 (from diol 3a). Total yield of isomers 0.335 g (54%), colorless solid. ν_{max} (KBr): 866, 1054, 1277, 1466 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.00 (CH_3, s), 2.03 (CH_3, s), 2.08 (CH_3, s), 7.33–7.58 (10H,m); δ_C (75 MHz, $CDCl_3$) 24.7 (*C*H_3), 25.3 (*C*H_3), 25.7 (*C*H_3), 83.8 (C), 84.0 (C), 84.2 (C), 84.3 (C), 84.4 (C), 94.3 (C), 94.6 (C), 94.6 (C), 109.1 (*C*Cl_3), 109.1 (*C*Cl_3), 120.7 (C), 128.7 (*C*H), 130.0 (*C*H), 130.0 (*C*H), 132.2 (*C*H), 132.2 (*C*H); *m/z* (%) (CI, CH_4) 618.9 (MH^+, 9.1), 592.4 (44.5), 520.9 (100), 504.9 (33.1), 486.9 (33.5), 466.9 (90), 454.9 (80.5); HRMS ($C_{22}H_{17}Cl_6O_4S_2$) calcd 618.8699; found 618.8698.

4.4.3. 1,2-Dimethyl-4-phenyl-1-(phenylethynyl)-2-{[(trichloromethyl)sulfinyl]oxy}but-3-ynyl trichloromethanesulfinate, 12 (from diol 3b). Total yield of isomers 0.385 g (62%), colorless solid. ν_{max} (KBr): 924, 1044, 1173, 1450 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.01 (CH_3, s), 2.07 (CH_3, s), 2.11 (CH_3, s), 7.38–7.43 (6H, m), 7.53–7.60 (4H, m); δ_C (75 MHz, $CDCl_3$) 24.9 (*C*H_3), 26.0 (*C*H_3), 26.2 (*C*H_3), 83.4 (C), 83.5 (C), 83.5 (C), 83.6 (C), 83.8 (C), 83.8 (C), 84.1 (C), 84.2 (C), 94.2 (C), 94.3 (C), 94.3 (C), 94.3 (C), 108.6 (*C*Cl_3), 108.7 (*C*Cl_3), 120.4 (C), 120.4 (C), 120.5 (C), 128.4 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 129.8 (*C*H), 131.8 (*C*H), 131.9 (*C*H), 131.9 (*C*H), 132.0 (*C*H); *m/z* (%) (CI, CH_4) 618.9 (MH^+, 0.62), 439 (100), 403 (14.9), 373 (19.3), 367 (28.7), 354 (21.2), 348 (28); HRMS ($C_{22}H_{17}Cl_6O_4S_2$): calcd 618.8699; found 618.8726.

4.4.4. 1,2-Dimethyl-4-phenyl-1-(phenylethynyl)-2-{[(trifluoromethyl)sulfinyl]oxy}but-3-ynyl trifluoromethanesulfinate, 13 (from diol 3b). Prepared by the above procedure from diol **3b** and trifluoromethane sulfonyl chloride; total yield of isomers 0.376 g (72%), colorless solid. ν_{max} (KBr): 924, 1044, 1173, 1362, 1450, 2225 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.87 (CH_3, s), 1.99 (CH_3, s), 2.04 (CH_3, s), 7.32–7.60 (10H, m); δ_C (75 MHz, $CDCl_3$) 24.4 (*C*H_3), 25.5 (*C*H_3), 26.1 (*C*H_3), 82.6 (C), 82.7 (C), 82.9 (C), 84.2 (C), 84.5 (C), 84.9 (C), 94.7 (C), 95.6 (C), 119.8 (C), 120.1 (C), 120.3 (C), 126.6 (C), 127.7 (C), 128.5 (*C*H), 128.6 (*C*H), 130.0 (*C*H), 130.1 (*C*H), 130.2 (*C*H), 132.0 (*C*H), 132.3 (*C*H), 132.9 (C); *m/z* (%) (CI, CH_4) 523 (MH^+, 12.3), 391 (100), 320 (97.4), 289 (48.7), 255 (91), 229 (37.9), 135 (79.8), 105 (43.2); HRMS ($C_{22}H_{17}F_6O_4S_2$): calcd 523.0472; found 523.0493.

4.5. General procedure for the preparation of 3,4-bis(methylene)cyclobutenes 17–19

A solution of the corresponding bis-sulfinate, **11**–**13**, (0.5 mmol) in dry $CHCl_3$ (10 mL), was heated at ~55 °C for specified time in each case. The solvent was removed under reduced pressure and the solid residue recrystallized from hexane.

4.5.1. {(*E*)-((4*E*)-2,3-Dimethyl-4-{phenyl[trichloromethyl)sulfonyl]methylene}cyclobut-2-en-1-ylidene)-[(trichloromethyl)sulfonyl]methyl}benzene, 17. Obtained upon heating of solution of **11** for 12 h. White crystals, mp 235 °C (d), yield 0.183 g (59%). ν_{max} (KBr): 701, 803, 1158, 1345 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.53 (6H, s), 6.82–6.6.86 (4H, m), 6.93–6.99 (4H, m), 7.11–7.7.17 (2H, m); δ_C (75 MHz, $CDCl_3$) 15.3 (*C*H_3), 105.4 (C), 109.3 (C), 115.1 (C), 128.1 (*C*H), 129.00 (*C*H), 131.8 (*C*H), 158.0 (C-1,4), 166.4 (C-2,3); *m/z* (%) (CI, CH_4) 618.9 (MH^+, 3.5), 592.9 (34.1), 577.1 (100), 542.9 (17.6), 520.9 (65.4), 506.9 (21.8), 486.9 (23.7); HRMS ($C_{22}H_{17}Cl_6O_4S_2$): calcd 618.8699; found 618.8701.

4.5.2. {(*E*)-((4*Z*)-2,3-Dimethyl-4-{phenyl[trichloromethyl)sulfonyl]methylene}cyclobut-2-en-1-ylidene)-[(trichloromethyl)sulfonyl]methyl}benzene, 18. Obtained upon heating of solution of **12** for 12 h. White crystals, mp 210 °C (d), yield 0.279 g (90%). ν_{max} (KBr): 821, 915, 1156, 1225, 1353, 1560 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.43 (3H, s), 2.43 (3H, s), 7.33–7.45 (6H, m), 7.50–7.54 (2H, m), 7.63–7.68 (2H, m); δ_C (75 MHz, $CDCl_3$) 12.0 (*C*H_3), 15.0 (*C*H_3), 104.3 (*C*Cl_3), 105.5 (*C*Cl_3), 114.4 (C), 117.7 (C), 127.5 (*C*H), 127.9 (C), 128.1 (*C*H), 130.0 (*C*H), 130.5 (*C*H), 131.6 (C), 132.6 (*C*H), 133.8 (*C*H), 155.1 and 156.4 (C-1,4), 161.3 and 165.6 (C-2,3); *m/z* (%) (CI, CH_4) 617.9 (M^+, 4.6), 520.9 (100), 484.9 (19.7), 467.9 (23.4); HRMS ($C_{22}H_{16}Cl_6O_4S_2$): calcd 617.8621; found 617.8615.

4.5.3. {(*E*)-((4*Z*)-2,3-Dimethyl-4-{phenyl[trifluoromethyl)sulfonyl]methylene}cyclobut-2-en-1-ylidene)-[(trifluoromethyl)sulfonyl]methyl}benzene, 19. Obtained upon heating of solution of **13** for 7 h. White crystals, mp 146–148 °C, yield 0.188 g (72%). ν_{max} (KBr) 756, 1119, 1219, 1367, 1568 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.43 (3H, s), 2.35 (3H, s), 7.36–7.48 (10H, m); δ_C (150 MHz, $CDCl_3$) 11.9 (*C*H_3–C-2), 14.82 (*C*H_3–C-3), 115.1 (*C*=C-4), 119.0 (*C*=C-1), 119.2 (*C*F_3, q, $^1J_{CF}$=320 Hz), 120.3 (*C*F_3, q, $^1J_{CF}$=320 Hz), 128.1 (*C*H), 128.5 (C-*ipso*), 128.8, (*C*H), 130.7 (*C*H), 130.8 (*C*H), 131.9 (C-*ipso*), 132.3 (*C*H), 132.9 (*C*H), 154.7 (C-1), 156.0 (C-4), 162.4 (C-2), 166.0 (C-3); *m/z* (%) (CI, CH_4) 522 (M^+, 1.7), 389 (100), 272 (10.9), 256 (72.9), 241 (13.2), 131 (23.3); HRMS ($C_{22}H_{16}F_6O_4S_2$): calcd 522.0394; found 522.0394.

4.5.4. 1-Methyl-2-methylene-4-phenyl-1-(phenylethynyl)but-3-ynyl trichloromethanesulfinate, 20. The title compound was obtained from diol **3a** as a mixture with sulfinate **11** and separated from the latter by column chromatography (hexane–EtOAc 10:1). Viscous oil, yield 0.035 g (8%). ν_{max} (KBr): 1070, 1156, 1276, 1371, 1448, 1491 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.78 (3H, s), 5.57 (1H, d, J=1 Hz), 5.93 (1H, d, J=1 Hz), 7.29–7.33 (6H, m), 7.44–7.50 (4H, m); δ_C (150 MHz, $CDCl_3$) 29.8 (*C*H_3), 70.3 (C), 85.4 (C), 86.5 (C), 90.7 (C), 92.3 (C), 104.8 (C), 120.7 (*C*H_2), 122.6 (C), 123.0 (C), 128.4 (*C*H), 128.5 (*C*H), 128.7 (*C*H), 131.8 (*C*H), 131.9 (*C*H), 136.1 (C=); *m/z* (%) (CI, CH_4) 618.9 (MH^+, 9.1), 592.4 (44.5), 520.9 (100), 504.9 (33.1), 486.9 (33.5), 466.9 (90), 454.9 (80.5); HRMS ($C_{22}H_{17}Cl_6O_4S_2$): calcd 618.8699; found 618.8698.

Diallenes **24**–**26**[‡,22] were obtained from the corresponding diols **21**–**23** according to the procedure described above for the preparation of diallenes **6** and **7**.

[‡] Preliminary and incomplete data reported for 24-26[22] was found subsequently to be incorrect. The spectra had been determined on samples which had undergone partial cyclization.

4.5.5. 2,7-Dimethyl-4,5-bis[(trichloromethyl)sulfinyl]-octa-2,3,5,6-tetraene, 25 (from diol 22). White solid, mp 90–94 °C, yield 0.471 g (80%) (total for two diastereomers). ν_{max} (KBr): 791, 809, 1114, 1325, 1943 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.90 (3H, s), 1.93 (3H, s), 1.94 (3H, s), 2.00 (3H, s); δ_C (75 MHz, $CDCl_3$) 19.2 (CH_3), 19.5 (CH_3), 19.2 (CH_3), 19.6 (CH_3), 103.6 and 104.9 (C-2,7), 107.4 and 107.6 (CCl_3), 113.0 and 114.4 (C-4,5), 202.3 and 203.7 (C-3,6).

4.5.6. {1-Methyl-6-phenyl-3,4-bis[(trichloromethyl)sulfinylhepta-1,2,4,5-tetraenyl}benzene, 26 (from diol 23). White solid, mp 110–112 °C, yield 0.40 g (68%) (total for two isomers). ν_{max} (KBr): 919, 1063, 1242, 1492, 1960 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.32 (CH_3, s), 2.36 (CH_3, s), 2.37 (CH_3, s), 7.31–7.53 (10H, m); δ_C (75 MHz, $CDCl_3$) 17.1 (CH_3), 17.3 (CH_3), 17.7 (CH_3), 108.2 (C), 108.4 (C), 109.3 (C), 118.6 and 119.2 (C-4,5), 126.9 (CH), 127.0 (CH), 127.3 (CH), 128.9 (CH), 128.9 (CH), 129.7 (CH), 133.1 (C), 133.2 (C), 206.9 and 207.9 (C-3,6).

Cyclobutenes **27–29** were obtained as mixtures of isomers from the corresponding diols **21–23** via the diallenes **24–26** according the procedure described above for the preparation of cyclobutenes **8** and **9**.

4.5.7. 3,4-Diethylidene-1,2-bis[(trichloromethyl)sulfinyl]cyclobutene, 27 (from diol 21). NMR data showed the presence of three geometric isomers (ignoring sulfur chirality), one unsymmetrical and two symmetrical, in the ratio 1:1:0.2. White solid, yield 0.319 g (73%) (total for three isomers). ν_{max} (KBr): 993, 1293, 1345, 1680, 2204 cm^{-1}; *m/z* (%) (CI, CH_4) 434.8 (MH^+, 9), 400.8 (24.7), 352.9 (32.8), 317 (41.1), 247 (100), 219 (69.3), 201 (45.3), 176.9 (74.8), 116.9 (99.4); HRMS ($C_{10}H_9Cl_6O_2S_2$): calcd 434.8175; found 434.8167.

E,Z-isomer. δ_H (600 MHz, $CDCl_3$) 1.86 (3H, d, J=7.5 Hz), 1.93 (3H, d, J=7.5 Hz), 5.59 (1H, q, J=7.5 Hz), 6.02 (1H, q, J=7.5 Hz); δ_C (150 MHz, $CDCl_3$) 11.7 and 13.5, (CH_3), 84.3 and 91.0 (C-1,2), 99.40 and 99.5 (CCl_3), 119.5 and 119.8 (CH), 139.6 and 140.0 (C-3,4); first symmetrical isomer (major): δ_H (600 MHz, $CDCl_3$) 1.91 (6H, d, J= 7.5 Hz), 5.54 (2H, q, J=7.5 Hz); δ_C (150 MHz, $CDCl_3$) 11.8 (CH_3), 86.3 (C-1,2), 99.5 (CCl_3), 119.6 (CH), 139.6 (C-3,4); second symmetrical isomer (minor): δ_H (600 MHz, $CDCl_3$) 1.89 (6H, d, J=7.5 Hz), 6.06 (2H, q, J=7.5 Hz); δ_C (150 MHz, $CDCl_3$) 13.6 (CH_3), 84.3 (C-1,2), 99.4 (CCl_3), 119.6 (CH), 140.0 (C-3,4).

4.5.8. 3,4-Bis(1-methylethylidene)-1,2-bis[(trichloromethyl)sulfinyl]cyclobutene, 28 (from diol 22). White solid, mp 68–69 °C, yield 0.418 g (90%). ν_{max} (KBr): 937, 1092, 1233, 1305, 1374, 1441 cm^{-1}; *m/z* (%) (CI, CH_4) 461.8 (MH^+, 53.30, 296.9 ($(MH-CCl_3SO)^+$, 33.1), 268.9 (13.9), 232.9 (68.7), 198 (25.1), 180.1 (50.5), 167.1 (38.4), 155.1 (67.8); HRMS ($C_{12}H_{12}Cl_6O_2S_2$): calcd 461.8409; found 461.8408; δ_H (600 MHz, $CDCl_3$) 1.9 (6H, s), 1.99 (6H, s); δ_C (150 MHz, $CDCl_3$) 17.8 and 21.2 (CH_3), 89.5 (C-1,2), 99.5 (CCl_3), 129.0 (C), 135.2 (C-3,4).

4.5.9. 1-{4-(1-Phenylethylidene)-2,3-bis[(trichloromethyl)sulfinyl]cyclobut-2-en-1-ylidene} ethyl)benzene, 29 (from diol 23). NMR data showed the presence of three geometric isomers (ignoring sulfur chirality), one unsymmetrical and two symmetrical, in the ratio 1:2:7. White solid, yield 0.542 g (92%) (total for three isomers). ν_{max} (KBr): 769, 812, 898, 1044, 1130, 1250, 1448, 1499 cm^{-1}; *m/z* (%) (CI, CH_4) 586.9 (MH^+, 0.8), 460.0 (16.4), 439.0 (12.0), 352.1 (78.2), 337 (36.8), 321.1 (94.7), 305.1 (21.6), 259.2 (47.8), 245.1 (40.4), 232 (51.6), 215.1 (32.2), 189.0 (27.1), 139.1 (100), 132.1 (41.5), 121.1 (44.6), 105.5 (90.3); HRMS ($C_{22}H_{16}Cl_6O_2S_2$): calcd 585.8722; found 585.8729.

δ_H (600 MHz, $CDCl_3$) *E,Z*-isomer: 2.05 (3H, s), 2.37 (3H, s), 7.25–7.53 (10H, m); first symmetrical isomer (major): 2.28 (6H, s), 7.25–7.27 (6H, m), 7.31–7.7.33 (4H, m); second symmetrical isomer (minor): 2.36 (6H, s), 7.25–7.53 (10H, m); δ_C (75 MHz, $CDCl_3$) (for three isomers): 15.4 (CH_3), 18.3 (CH_3), 21.3 (CH_3), 89.5 (C), 92.7 (C), 98.5 (C), 99.8 (C), 109.9 (C), 128.2 (CH), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.7 (CH), 128.3 (CH), 132.8 (C), 136.2 (C), 136.7 (C), 137.6 (C), 139.1 (C).

4.5.10. 1,1,6-Trimethyl-6-{[(trichloromethyl)sulfinyl]-oxy}hepta-2,4-diynyl trichloromethane sulfinate, 30. The title compound was obtained from the diol **22** (as a mixture of *dl* and *meso* due to sulfur chirality) by the procedure described above for the preparation of bis-(trichloromethanesulfinates) **10–13**. After the usual work-up the crude sulfinate was triturated with hexane (3×20 mL). Yellow-white solid, mp 63–64 °C, yield 0.166 g (67%). ν_{max} (KBr): 847, 1044, 1190, 1290, 1371, 1456 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.8 (6H, s), 1.84 (6H, s); δ_C (75 MHz, $CDCl_3$) 29.9 (CH_3), 30.2 (CH_3), 72.2 (C), 78.3 (C), 80.2 (C), 108.0 (CCl_3); *m/z* (%) (CI, CH_4) 494.8 (MH^+, 7.9), 349 (90), 315 (71.9), 293 (79), 275 (45), 243 (55); HRMS ($C_{12}H_{13}Cl_6O_4S_2$): calcd 494.8386; found 494.8361.

4.5.11. 2,7-Dimethyl-4,5-bis[(trichloromethyl)sulfonyl]-octa-2,3,5,6-tetraene, 32. A solution of bis-sulfinate **30** (*dl* and *meso*) (0.16 g, 0.32 mmol) in dry $CHCl_3$ (100 mL) was heated under reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was subject to column chromatography (hexane/EtOAc 10:1). White crystals, mp 166–168 °C, yield 0.134 g (81%). ν_{max} (KBr): 924, 1164, 1353, 1955 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.96 (12H, s); δ_C (75 MHz, $CDCl_3$) 19.0 (CH_3), 95.5 (C-4,5), 104.8 (CCl_3), 110.2 (C-2,7), 214.1 (C-3,6); *m/z* (%) (CI, CH_4) 494.8 (MH^+, 2.7), 312.9 (47.8), 249 (91.3), 213 (14), 179 (18.7), 167 (50), 131 (100), 116.9 (14.3); HRMS ($C_{12}H_{13}Cl_6O_4S_2$): calcd 494.8386; found 494.8399.

4.5.12. {1-Methyl-6-phenyl-3,4-bis{(trichloromethyl)sulfonyl]hepta-1,2,4,5-tetraenyl}benzene, 33. Treatment of diol **23** (*dl* and *meso*) (0.145 g, 0.5 mmol) at −78 °C with trichloromethanesulfonyl chloride, triethylamine and trimethyl phosphite according the procedure used for the preparation of sulfinates **10–13** resulted in the formation of the mixture of the sulfinate, 1-methyl-1,6-diphenyl-6-{[(trichloromethyl)sulfinyl]oxy}hepta-2,4-diynyl trichloromethanesulfinate **31** and the rearranged sulfone **33**. The latter was isolated after column chromatography (hexane/EtOAc 10:1). White crystals, mp 130–132 °C, yield 0.056 g (18%); ν_{max} (KBr): 1156, 1370, 1964 cm^{-1}; δ_H (300 MHz,

$CDCl_3$) 2.41 (6H, s), 7.38–7.49 (10H, m); δ_C (75 MHz, $CDCl_3$) 15.9 (CH_3), 98.8 (C-3,4), 105.0 (CCl_3), 114.6 (C-1,6), 127.3 (*C*H), 129.0 (*C*H), 129.8 (*C*H), 131.3 (C), 217.9 (C-2,5); *m/z* (%) (CI, CH_4) 437 ($(M-SO_2CCl_3)^+$, 24.3), 320.1 (31.6), 256 (100); HRMS ($C_{21}H_{16}Cl_3O_2S$): calcd 436.9936; found 436.9929.

4.6. X-ray structure determination

The X-ray diffraction measurements were carried out at 115 K on a Nonius Kappa-CCD diffractometer, using Mo Kα ($\lambda=0.7107$ Å) radiation. The structures were solved by direct methods (SIR-92) and refined by full-matrix least-squares (SHELXL-97). Non-hydrogen atoms were treated anisotropically. The hydrogen atoms were located in calculated positions to correspond to standard bond lengths and angles. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with Cambridge Crystallographic Center as supplementary publication numbers CCDC-245831 to CCDC-245834 for **8a**, **9a**, **9c** and **32**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Acknowledgements

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Chemistry of 3-arylindenones: behavior in superacids and photodimerization

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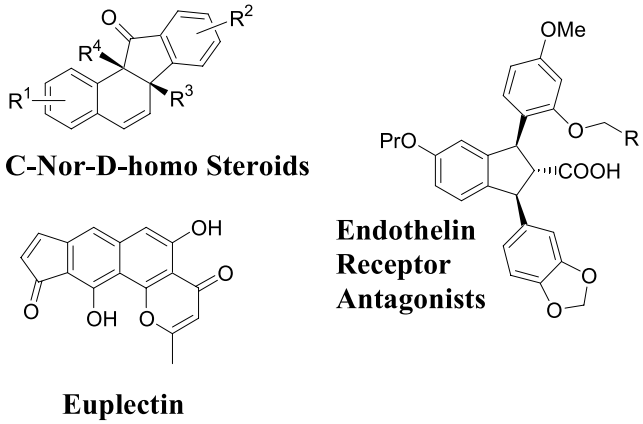
Abstract—In superacids HSO_3F and CF_3SO_3H, it has been found that 3-arylindenones are very stable and exist as a doubly protonated species. NMR showed protonation both at the oxygen of the carbonyl group and at the C2 carbon of the indenone system. 3-Arylindenones proved however very sensitive to heat and light. Their [2+2] photodimerization under daylight has been studied.

1. Introduction

Due to their unique combination of functionalities, indenones are interesting compounds *per se* and key intermediates towards indanones,[1] indenes,[2] or more complex compounds. Indenones have been used as starting materials for the synthesis of various bioactive products such as C-nor-D-homosteroids,[3] estrogen-binding receptors,[4] gibberellins,[5] and more recently non-peptidic antagonists of endothelin receptors (Scheme 1).[6] Indenones have also been used for the synthesis of compounds such as indanones, photochromic indenone oxides,[7] 2,4- and 3,4-disubstituted 1-naphthols[8] (Scheme 1). The indenone unit is also present in a few natural products.[9]



Scheme 1.

Several indenone syntheses have thus been developed and we recently described a new, fast and very efficient synthesis of 3-arylindenones.[10] In this account, we report on the reactivity of these compounds, in superacids and in the presence of light.

2. Results and discussion

2.1. 3-Arylindenones in superacids, an NMR study

Activation of organic compounds in superacids[11] is the most efficient way to generate and investigate carbocations,[12,13] cation-radicals,[14] and other long-lived charged intermediates[15]. Solvation in superacids, with weak nucleophile counterpart, leads to the stabilization of highly electron-deficient species behaving as electrophiles or even superelectrophiles.[16]

To the best of our knowledge, the behavior of indenones **1** (Scheme 2) in these conditions has never been studied. In superacids, one would expect the formation of a species protonated at the oxygen atom of the carbonyl group (**2** in Scheme 2). However, in strong superacids, the formation of diprotonated species can also be envisaged via the so-called superelectrophilic solvation.[17] Such an entity would be doubly protonated at the oxygen and at the terminal carbon of the enone system (**3** in Scheme 2). Therefore, the investigation of 3-arylindenones in superacids offers a

Keywords: Superacid; Dications; Indenone; Truxone.
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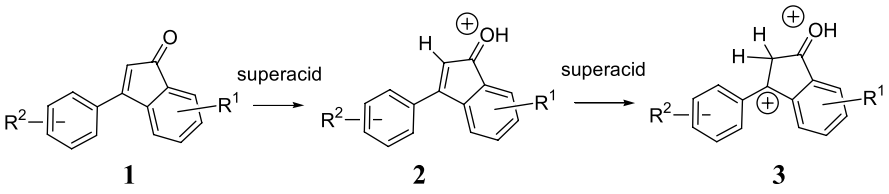


Scheme 2.

Table 1. ^{1}H NMR data of indenones **1a–d** in $CDCl_3$ at 25 °C and dicationic species **3a–d** in CF_3SO_3H at −30 °C

	Me	Proton on C^2	Indenone Aryl part	Aryl substituent of indenone[a]
1a	3.82; 3.86	5.84 (1H)	6.77dd; 7.08d; 7.26d	6.98(2H, d); 7.62(2H, d)
3a	4.25; 4.48	5.07 (2H)	8.10(2H, br.); 8.84s	7.52; 7.60 8.47; 9.04
1b	2.26; 2.28; 3.87	5.85 (1H)	7.13s; 7.27s	7.01(2H, d); 7.63(2H, d)
3b	2.72; 2.82; 4.56	5.05 (2H)	8.47s; 8.70s	7.57; 7.64s; 8.51; 9.19
1c	2.42	5.97 (1H)	7.30m; 7.38dd; 7.39d; 7.52dd	7.32d(2H, d); 7.58d(2H, d)
3c	3.03	5.36 (2H)	8.62(2H, br.); 8.68dd; 8.76d	8.03(2H); 9.06(2H)
1d	3.86	5.95 (1H)	7.30m; 7.38d; 7.39d; 7.52dd	7.02(2H, d); 7.65(2H, d)
3d	4.52	5.05 (2H)	8.32; 8.56; 8.63; 8.81	7.53(2H); 9.10(1H); 8.45(1H)

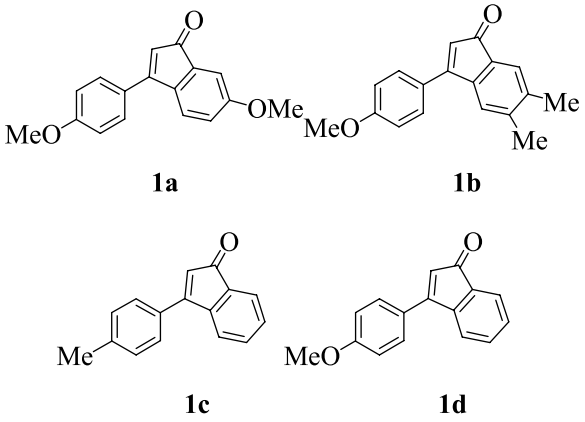
[a] All protons of this aryl ring appear as broad singlets in triflic acid at −30 °C.

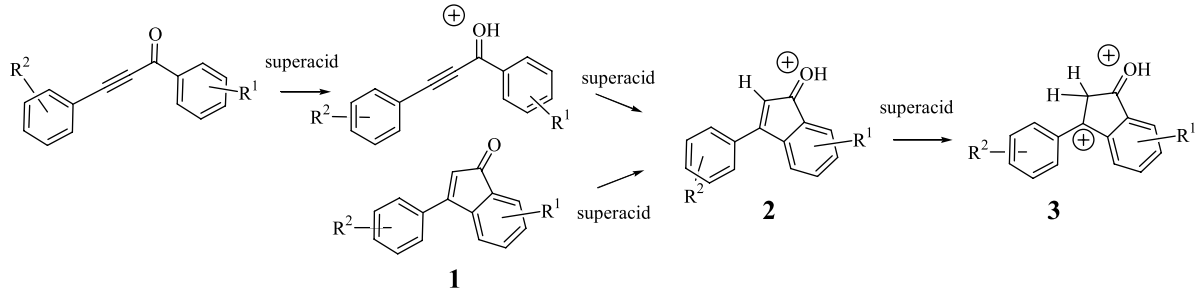
Table 2. ^{13}C NMR typical data for indenones **1a–d** in $CDCl_3$ 25 °C and dicationic species **3a–d** in CF_3SO_3H at −30 °C

	Me	C1	C2	C3
1a	55.4; 55.7	196.7	122.6	163.3
3a	58.7; 60.9	217.1	45.7	183.7
1b	19.8; 20.5; 55.4	197.5	121.1	162.3
3b	21.4; 22.7; 61.9	214.3	45.01	186.2
1c	21.5	197.1	122.5	162.6
3c	27.1	216.0	46.5	182.2
1d	55.5	197.1	122.6	162.8
3d	61.7	216.5	44.3	186.7

unique opportunity to study such dicationic species and investigate the superelectrophilic activation.

Several 3-arylindenones **1a–d** were thus dissolved in various superacids and placed in NMR tubes. Their behavior was then monitored by NMR. ^{1}H NMR and ^{13}C NMR spectra of these compounds in CF_3SO_3H at −30 °C are reported in Tables 1 and 2, respectively, as well as their spectra in $CDCl_3$ for comparison. Although only ^{13}C–^{1}H decoupled spectra were reported in Table 2, exact assignments of signals in ^{13}C NMR spectra have been made on the basis of multiplets analysis of ^{13}C–^{1}H coupled NMR spectra.





Scheme 3.

In comparison with the starting indenones, the NMR spectra of indenones **1a–d** in triflic acid show a strong deshielding of all nuclei but one. Integrations of the ^{1}H signal are in accordance with the double protonation of the carbonyl group and the adjacent double bond (Scheme 3, species 3). The spectral data in HSO_3F at −80 °C were found very similar. Delocalization of the positive charge on carbon C3 into the phenyl substituent induces a partial π-bond character to the phenyl-C3 bond, evidenced by non-equivalent *o*,*m*-nuclei (Fig. 1) due to slow rotation at the NMR time scale. The assignment of protons Hc/c′ and Hd/d′ is based on previous works on the protonation of acetophenones.[18] Surprisingly, the life-time of some of these diprotonated species was sufficient to allow their observation by NMR during several hours even at room temperature. An example is given in Figure 1. The O-protonation is not observed due to a fast proton exchange[19] at −30 °C but taking into account both ^{1}H and ^{13}C chemical shifts the presence of the dicharged species is clearly evidenced.

It is worth noting that diprotonated species like 3 could also be obtained when the corresponding 1,3-diarylpropynones were used as starting material (Scheme 3), the efficiency of the transformation depending on the nature of the substituent.[20]

2.2. 3-Arylindenones [2+2] photodimerization

Indene (Scheme 4, X=H_2, R^1,R^2=H)[21] and its derivatives bearing a chloride substituent (X=H_2, R^1=H, R^2=Cl or R^1=Cl, R^1=H)[22] are known to photodimerize. These photochemical reactions require UV light and the presence of sensitizers. The yields are quite low (<40%) and provide with a mixture of products among which diastereomeric and regioisomeric dimers (Scheme 4).

With an enone system known to photoreact with alkenes, ketones or enones,[23] indenones should also be prone to photodimerization. Surprisingly, a literature survey revealed only a single example of such reaction. In an attempt to synthesize a natural product,[24] Joshi et al. tried a [2+2] cycloaddition between 3-acetoxyindenone and a protected quinone. Instead of the expected adduct, they isolated after UV irradiation an indenone dimer, which was characterized by X-ray diffraction.[25] Other papers mentioned the probable formation of a dimer from 3-benzylthioindenone[26] and from 2-phenylindenone[27] but without any characterization.

With various 3-arylindenones in hands, we thus looked at their behavior in the presence of light. 3-Arylindenones

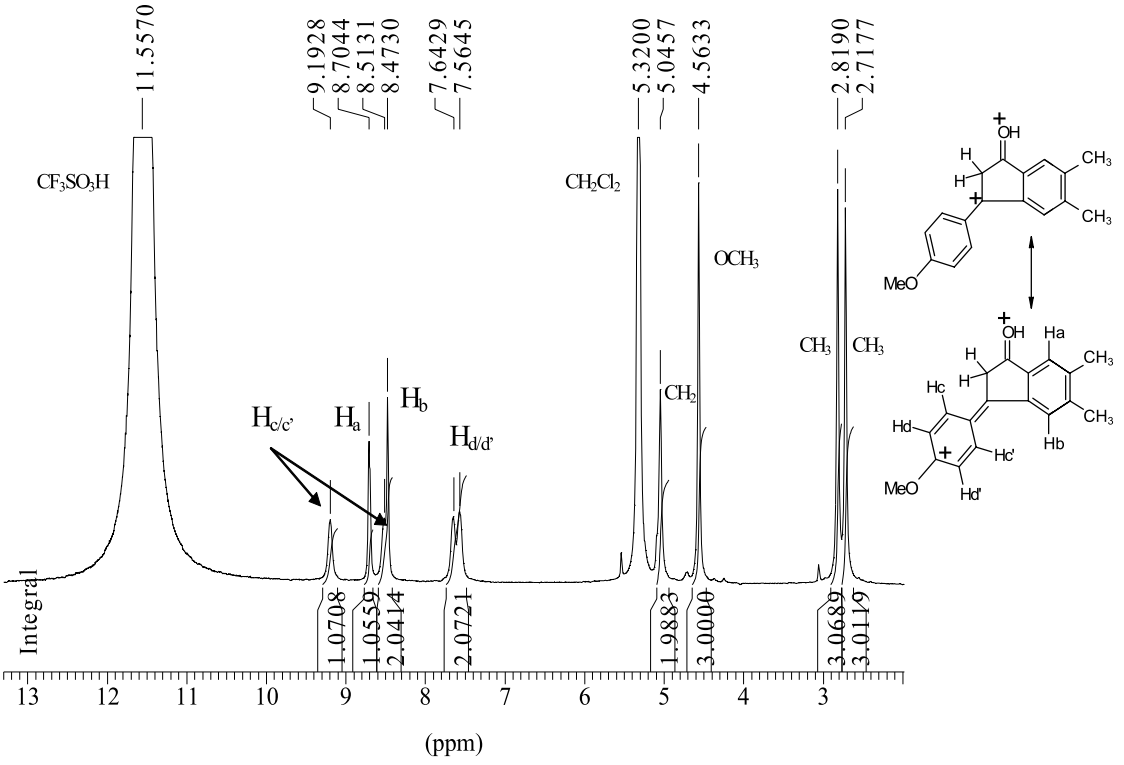
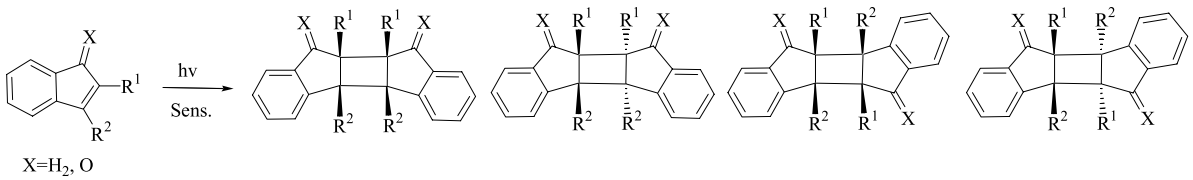


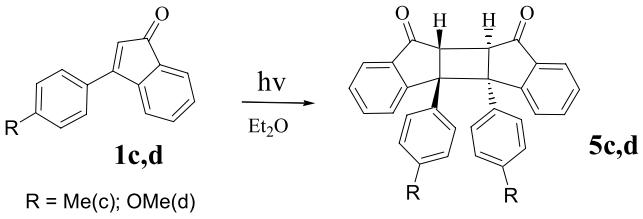
Figure 1. Proton NMR spectra of dicationic form **3b** in triflic acid at −30 °C.



Scheme 4.

proved to be more or less sensitive to light, some were even so sensitive that daylight must be excluded during their handling, especially during chromatography. Not so surprisingly, the most sensitive bear an electron-donating substituent at the para position of their 3-phenyl group.

So, **1c–d** were smoothly converted to **5c–d** in good yield after 3 days in ethereal solutions under day light (Scheme 5). It is worth noting that the initial color of the indenone solution gradually faded away under these conditions. Evaporation of diethyl ether left solids, which upon recrystallization gave a single dimer with excellent yields (70%).



Scheme 5.

NMR spectra of compounds **5c** and **5d** indicated a symmetric structure. They exhibited proton singlet signal, respectively, at 3.57 and 3.60 ppm linked to tertiary carbon at 50.5 and 50.7 ppm, respectively (C^{9a} C^{9b}) as well as quaternary carbon at, respectively, 59.6 and 59.9 ppm (C^{4b} C^{4c}) and a single carbonyl carbon at 202.9 and 203.0, respectively. These values were close to the one described for the only known indenone dimer (singlet at 3.20 ppm and doublet at 51.4 ppm). Since four isomeric structures are expected (Scheme 5), it was nevertheless difficult to definitively assign one with the data available.

The exact structure of compound **5d** was eventually determined by X-ray analysis. We failed to grow a single crystal for compound **5c** suitable for X-ray analysis but, on the basis of the resemblance of NMR spectra of both compounds, the same stereochemical structure is suggested. Therefore, the photoadducts derived from 3-arylindenones possess a *syn-trans*-truxone like structures (Fig. 2).

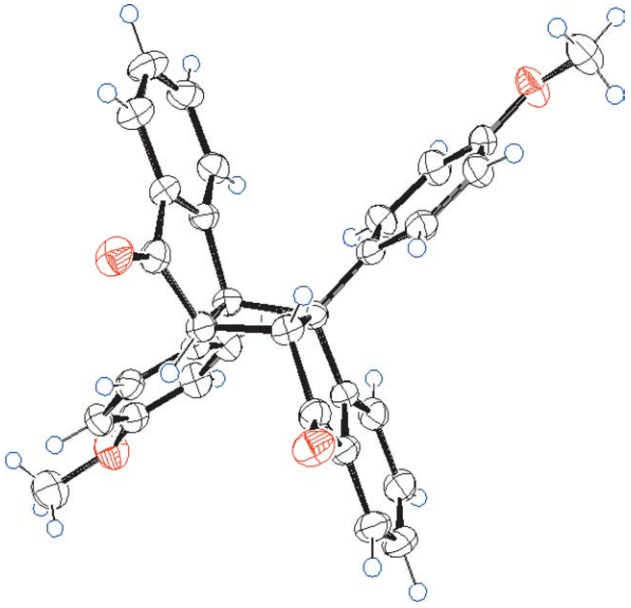
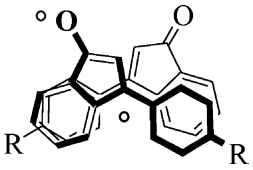


Figure 2. Structure of the truxone **5d**.

These results are in agreement with the known model for the photochemical cycloaddition of enones to alkenes. Reacting in its triplet excited state, the enone system behaves as a biradical and exhibits a polarity complementary to its ground state.[23] Therefore, a reaction between the polarized triplet excited state and a strongly polarized ground state such as indenones should go through a first C–C bond formation linking the end of the enones leading to a biradical which collapses through a second C–C bond formation. This process leads to a head-to-head adduct, the stereochemistry of which is usually governed by steric interactions. However, with 3-arylindenones, π-stacking in the exciplex could play a role and would thus favor a *syn-trans*-adduct (Scheme 6).



Scheme 6.

3. Conclusion

The reactivity of 3-arylindenones has been investigated in order to better know this important and useful class of compounds. Two major reactions have been studied here. When dissolved in superacids, 3-arylindenones evolved to a very stable species which has been characterized by ^1H and ^{13}C NMR as the O,C-diprotonated form of 3-arylindenones. Under daylight, 3-arylindenones readily dimerize to give [2+2] adducts, having a *syn-trans* truxone-like structure as established by NMR and X-ray.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra of compounds **1a–d** and **5c**,**d** were recorded on spectrometer Brucker AVANCE 300 (working frequencies 300 and 75 MHz, respectively). The residual proton-solvent peaks: $CDCl_3$ (δ 7.25 ppm) for ^1H spectra, $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR spectra were used as internal references. Spectral measurements in HSO_3F at −80 °C and in CF_3SO_3H at −30 °C were performed on spectrometer Brucker AVANCE 400 (frequencies 400 for ^1H and 100 MHz for ^{13}C NMR spectra). Spectra in the superacids were referenced to the signal of CH_2Cl_2 added as internal standard (δ 5.32 ppm for ^1H andδ 53.8 ppm for ^{13}C NMR spectra). Mass spectra (electron impact, ionisation energy 70 eV) were measured on instrument TSQ 700 Finnigan MAT.

Purity of the starting and obtained compounds was controlled by TLC on the plates Silufol UV-254. Preparative separation and purification of reaction products were

carried out by column chromatography on silica-gel Merck 60 eluted with gradient mixtures of ether-hexanes. Yields of products were determined after chromatography.

4.2. Protonation of indenones in superacids

General technique for generation of the ions in superacids: 5–30 mg of substrate **1a–d** were added to 0.8–1 ml of HSO_3F (mp −89 °C) frozen in NMR tube at ∼−110 °C (ethanol–liquid nitrogen bath). Temperature was raised up to −78 °C and a Teflon capillary with internal diameter 1 mm was entered to the bottom of the NMR tube, passing through it a weak flow of argon during 5–15 min. in order to obtain a homogeneous solution. The capillary was then removed and internal standard CH_2Cl_2 was added. Similarly, solutions could be prepared in CF_3SO_3H by addition of 5–30 mg of substrate **1a–d** to 0.8–1 ml CF_3SO_3H (mp −34 °C) frozen in NMR tube at −78 °C. The subsequent homogenization of the mixture was performed at −30 °C. NMR spectra were then recorded at −30 °C (Tables 1 and 2).

4.2.1. O,C-Diprotonated form 3a derived from 6-methoxy-3-(4-methoxyphenyl)indenone. ^{1}H NMR (300 MHz, CF_3SO_3H): δ 4.25 s (3H, OMe), 4.48 s (3H, OMe), 5.07 s (2H, CH_2), 7.52 s (1H arom.), 7.60 s (1H arom.), 8.10 s (2H arom.), 8.47 s (1H arom.), 8.84 s (1H arom.), 9.04 s (1H arom.). ^{13}C NMR (75 MHz, CF_3SO_3H): δ 45.7 (CH_2), 58.7, 60.9, 130.3, 134.1, 137.0, 142.4, 142.7, 145.5, 148.1, 171.7, 174.2, 183.7 (C^3), 217.1 (C=OH^+).

4.2.2. O,C-Diprotonated form 3b derived from 3-(4-methoxyphenyl)-5,6-dimethylindenone. ^{1}H NMR (300 MHz, CF_3SO_3H): δ 2.72 s (3H, Me), 2.82 s (3H, Me), 4.56 s (3H, OMe), 5.05 s (2H, CH_2), 7.57 s (1H arom.), 7.64 s (1H arom.), 8.47 s (1H arom.), 8.51 s (1H arom.), 8.70 s (1H arom.), 9.19 s (1H arom.). ^{13}C NMR (75 MHz, CF_3SO_3H): δ 21.4, 22.7, 45.0 (CH_2), 61.9, 131.6, 132.9, 135.6, 136.2, 148.7, 145.9, 162.1, 174.2, 186.2 (C^3), 214.3 (C=OH^+).

4.2.3. O,C-Diprotonated form 3c derived from 3-(4-methylphenyl)-indenone. ^{1}H NMR (300 MHz, CF_3SO_3H): δ 2.62 s (3H, Me), 5.35 s (2H, CH_2), 8.03 s (2H arom.), 8.62 s (2H arom.), 8.68 dd (1H arom.), 8.76 d (1H arom.), 9.06 s (2H arom.). ^{13}C NMR (75 MHz, CF_3SO_3H): δ 22.28, 46.5 (CH_2), 131.8, 132.3, 135.4, 136.9, 145.0, 146.9, 148.7, 171.7, 182.2 (C^3), 216.0 (C=OH^+).

4.2.4. O,C-Diprotonated form 3d derived from 3-(4-methoxyphenyl)-indenone. ^{1}H NMR (300 MHz, CF_3SO_3H): δ 4.52 s (3H, OMe), 5.05 s (2H, CH_2), 7.53 s (2H arom.), 8.32 s (1H arom.), 8.45 s (1H arom.), 8.56 s (1H arom.), 8.63 s (1H arom.), 8.81 s (1H arom.), 9.10 s (1H arom.). ^{13}C NMR (75 MHz, CF_3SO_3H): δ 44.3 (CH_2), 61.7, 131.5, 132.4, 134.0, 137.1, 140.0, 146.6, 149.9, 171.7, 186.7 (C^3), 216.5 (C=OH^+).

4.3. General procedure for the transformation of indenones into dimers

3-arylindenone **1c,d** (0.25 mmol) dissolved in ether (50 ml) was left 3 days at room temperature under daylight. During this time, the initially colored solutions completely bleached. The evolution of the transformation was monitored by TLC. Ether was then evaporated under vacuum and solids formed. The dimers **5c,d** were obtained pure after recrystallization from MeOH. Yields: 67% (**5c**), 72% (**5d**).

4.3.1. (4b*R,4c*R**,9a*S**,9b*S**)-4b,4c-Bis(4-methylphenyl)-9,10-dioxoindano[2′,3″:4,3]cyclo-buta[1,2-*b*]-indan 5c.** Mp 133–135 °C with decomposition. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 3.60 (s, 2H), 7.02 (d, J=8.0 Hz, 4H), 7.17 (d, J=8.0 Hz, 4H), 7.28–7.42 (m, 6H), 7.76–7.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.89, 50.48 (C^{9a}, C^{9b}), 59.90 (C^{4b},C^{4c}), 124.36, 127.12, 128.34, 129.08, 129.43, 134.11, 136.69, 136.85, 136.90, 155.55, 202.97. MS: *m/z* (I. rel., %) 440 (42) M+, 423 (81), 349 (100), 220 (23). Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.25; H, 5.49. Found: C, 86.83; H, 5.50.

4.3.2. (4b*R,4c*R**,9a*S**,9b*S**)-4b,4c-Bis(4-methoxyphenyl)-9,10-dioxoindano[2′,3′:4,3]cyclo-buta[1,2-*b*]-indan 5d.** Mp 178–180 °C with decomposition. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 2H), 3.72 (s, 6H), 6.74 (d, J=8.8 Hz, 4H), 7.17 (d, J=8.8 Hz, 4H), 7.29–7.37 (m, 6H), 7.76–7.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.66 (C^{9a}, C^{9b}), 55.18, 59.61 (C^{4b},C^{4c}), 113.70, 124.39, 128.34, 128.38, 129.36, 131.77, 134.11, 136.89, 155.61, 158.47, 202.94. MS: *m/z* (I. rel., %) 472 (28) M+, 454 (45), 364 (100), 236 (48). Anal. Calcd for $C_{32}H_{24}O_4$: C, 81.34; H, 5.12. Found: C, 79.99; H, 5.30.

Crystal data. $C_{33}H_{28}O_5$ (**5d**+1 molecule of methanol), M=504.59, monoclinic, a=12.9243(2), b=28.4039(8), c=9.0628(2), U=2695.5(1) Å^3, T=173 K, space group $C12/c1$, Z=4, μ(Mo K$_\alpha$)=0.083 mm^{-1}, 7230 reflections measured, 1679 unique (R_{int}=0.062) which were used in all calculations. The final $wR(F^2)$ was 0.088 (all data).

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An assessment of the technique of simultaneous cooling in conjunction with microwave heating for organic synthesis

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Abstract—In the light of the controversy in the area and since reports using simultaneous cooling in conjunction with microwave heating are appearing in the literature, we were keen to assess the methodology, looking at temperature measurement issues as well as the use of the technique in three classes of reaction, namely a Heck coupling, a Diels–Alder cycloaddition and a Michael addition. We present our initial findings here.

1. Introduction

Microwave-promoted synthesis is an area of increasing research interest as evidenced by the number of papers and recent reviews appearing in the literature.[1,2] As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. Much of the work in the field to date has been conducted using modified domestic microwave ovens. There are, however, problems associated with this, in particular poor reproducibility of reactions and the fact that it is hard to control the reaction precisely. With the advent of scientific focused microwave systems, many of these problems can be overcome. Using these scientific microwaves it is possible to control the temperature, pressure, microwave power and reaction times very easily and with a high degree of reproducibility. A concept that has generated debate over the last year is that of simultaneous cooling, a method patented by CEM Corporation as PowerMAX.[3] This allows for simultaneous cooling of a reaction with compressed air whilst heating it with a substantial microwave power. In principle, it allows for higher levels of microwave energy to be introduced into a reaction whilst maintaining the mixture at a particular temperature. It has been suggested that this can result in higher product yields and new pathways that were previously unattainable. There have been criticisms leveled at the technique, in particular focusing on whether the measurement of the reaction temperature is accurate. There are two ways of measuring the temperature of a reaction mixture in a microwave reaction, either by use of an IR temperature sensor located outside the reaction vessel or a fiber-optic probe inserted into the reaction vessel. Critics claim that when using external temperature measurement it is possible to, in effect, 'trick' the temperature sensor when using simultaneous cooling; the temperature read being significantly lower than the actual bulk temperature in the reaction vessel. Therefore, the difference in reactivity could be attributed simply to the difference in reaction temperature.

In the light of the controversy in the area and since reports using simultaneous cooling are appearing in the literature,[4–6] we were keen to assess the methodology, looking at the temperature measurement issue as well as the use of simultaneous cooling in three classes of reaction, namely a Heck coupling, a Diels–Alder cycloaddition and a Michael addition. We present our initial findings here.

2. Results and discussion

2.1. Assessment of temperature measurement

The first objective of our studies was to obtain temperature, pressure and microwave power profiles for microwave heating of common solvents both with and without simultaneous cooling using a fiber-optic probe inserted into the reaction vessel. Repeating the studies with the external IR sensor would thus enable us to compare the two possible temperature measurement methods. We chose water, hexane, DMF and DMSO as solvents for study since they span a wide polarity range and thus would heat at

Keywords: Microwave; Water; Heck coupling; Diels–Alder reaction; Michael addition.
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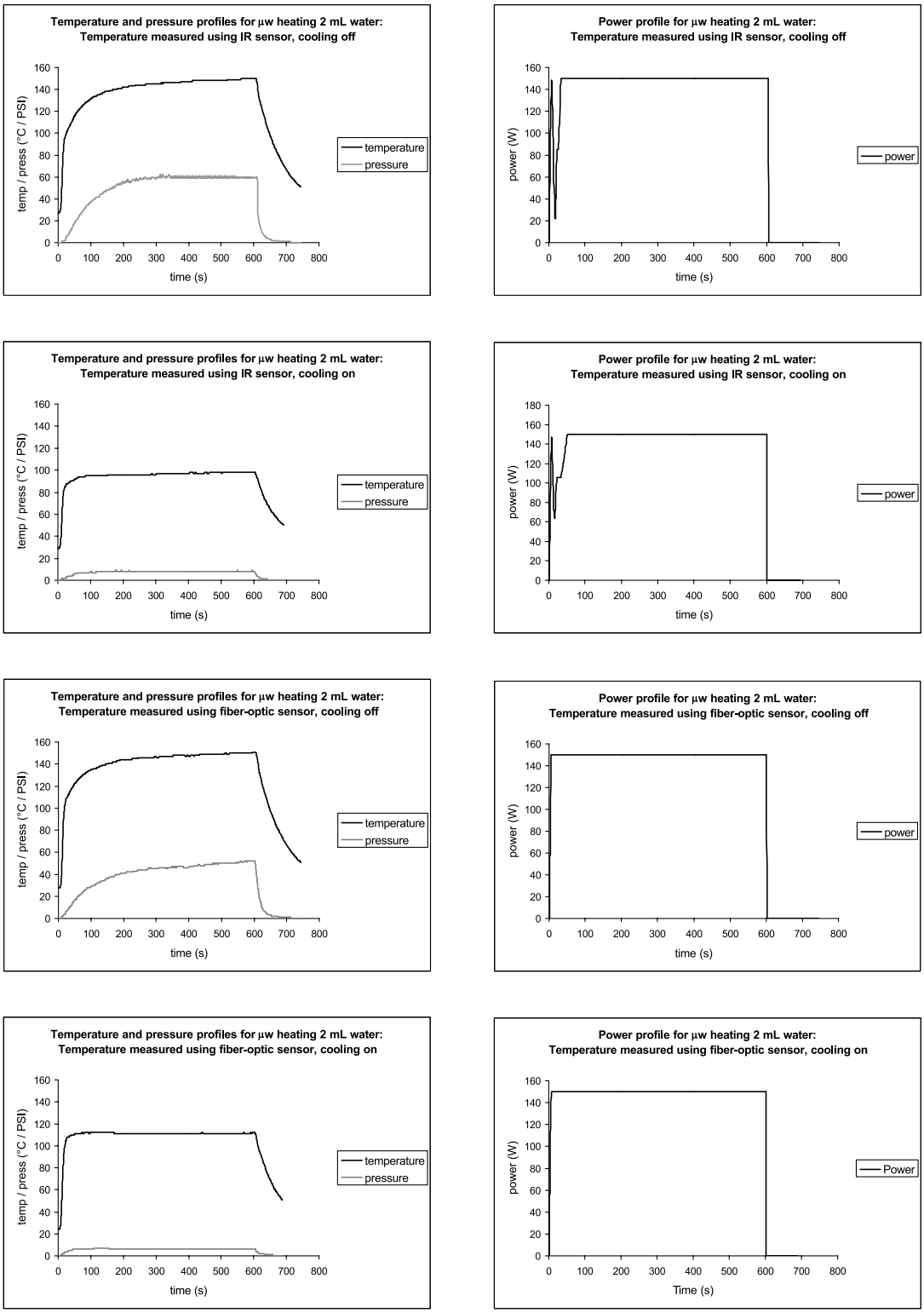


Figure 1. Heating 2 mL water to 150 °C measuring the temperature using an IR sensor or a fiber optic device with simultaneous cooling off and on.

different rates under microwave irradiation. In addition, they are all media that have been used for microwave-promoted organic synthesis. A good measure of how rapidly a solvent will be heated by microwave irradiation is its dielectric loss value (ε'), the higher the value the more efficiently the solvent converts microwave energy in to thermal energy and hence the faster the temperature will rise. Values for DMSO, water, DMF and hexane are 37.13, 9.89, 6.07 and 0.038, respectively. The temperature, pressure and microwave power profiles for the four solvents are shown in Figures 1–4. In each set of experiments, 2 mL of the solvent was heated in a 10 mL sealed tube to a target

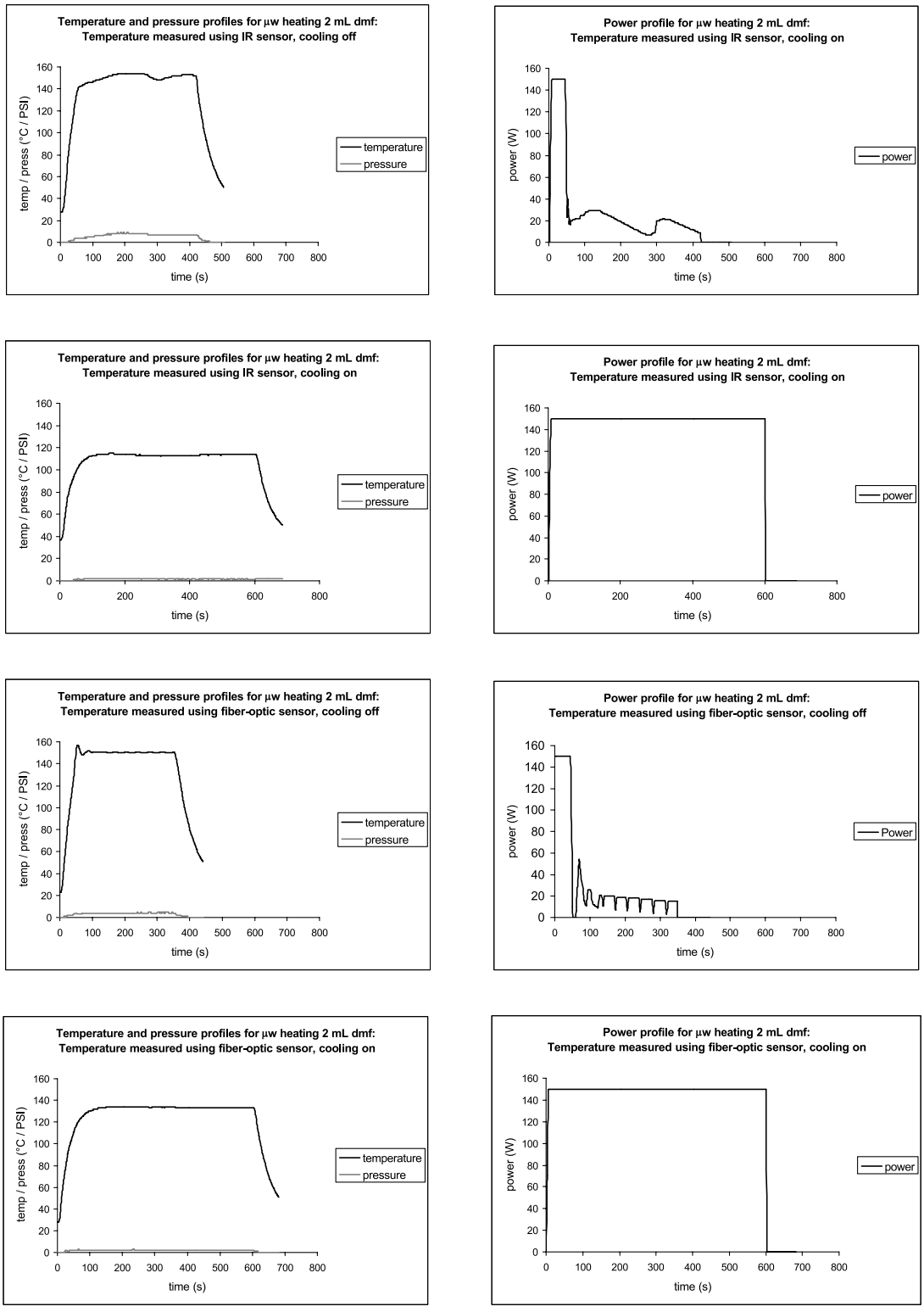


Figure 2. Heating 2 mL DMF to 150 °C measuring the temperature using an IR sensor or a fiber optic device with simultaneous cooling off and on.

temperature of 150 °C, with the exception of hexane which was heated to a target temperature of 100 °C. Initial microwave irradiation of 150 W was used, the apparatus being programmed to ramp from rt to the target temperature over 5 min. Once this temperature was reached, the reaction mixture was held at this temperature for a further 5 min. The effects of simultaneous cooling are clearly evident; when cooling is applied, more microwave power is delivered to the reaction vessel than when the cooling is off. With cooling off, all four solvents reach the target temperature during the microwave irradiation time. However, with cooling on, of the four solvents screened, only DMSO

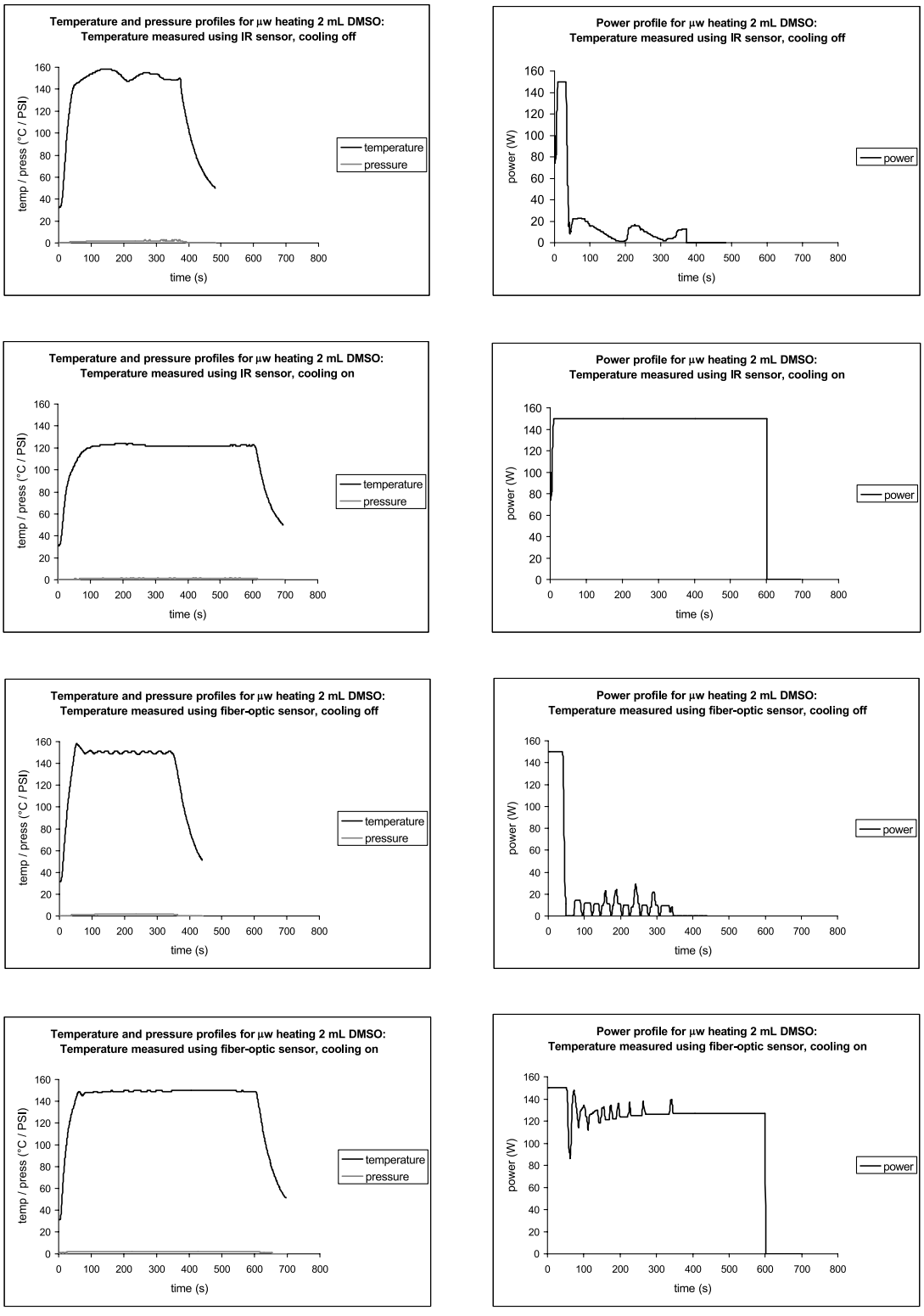


Figure 3. Heating 2 mL DMSO to 150 °C measuring the temperature using an IR sensor or a fiber optic device with simultaneous cooling off and on.

reaches the target temperature during the 5 min ramp time. Water reaches around 100 °C and DMF around 130 °C. Of note is that for water, DMF and DMSO there is a difference of around 10–20 °C between the temperatures measured using the IR sensor and the internal fiber-optic device with simultaneous cooling on, the fiber-optic recording the higher temperature. This is clear from the temperature/time profiles (Fig. 5). The situation with hexane is more marked. Due to its low polarity and dielectric loss constant, hexane heats up very slowly under microwave irradiation. Indeed it is the heating of the glass reaction tube that leads to the heating of the solvent by conduction/convection.

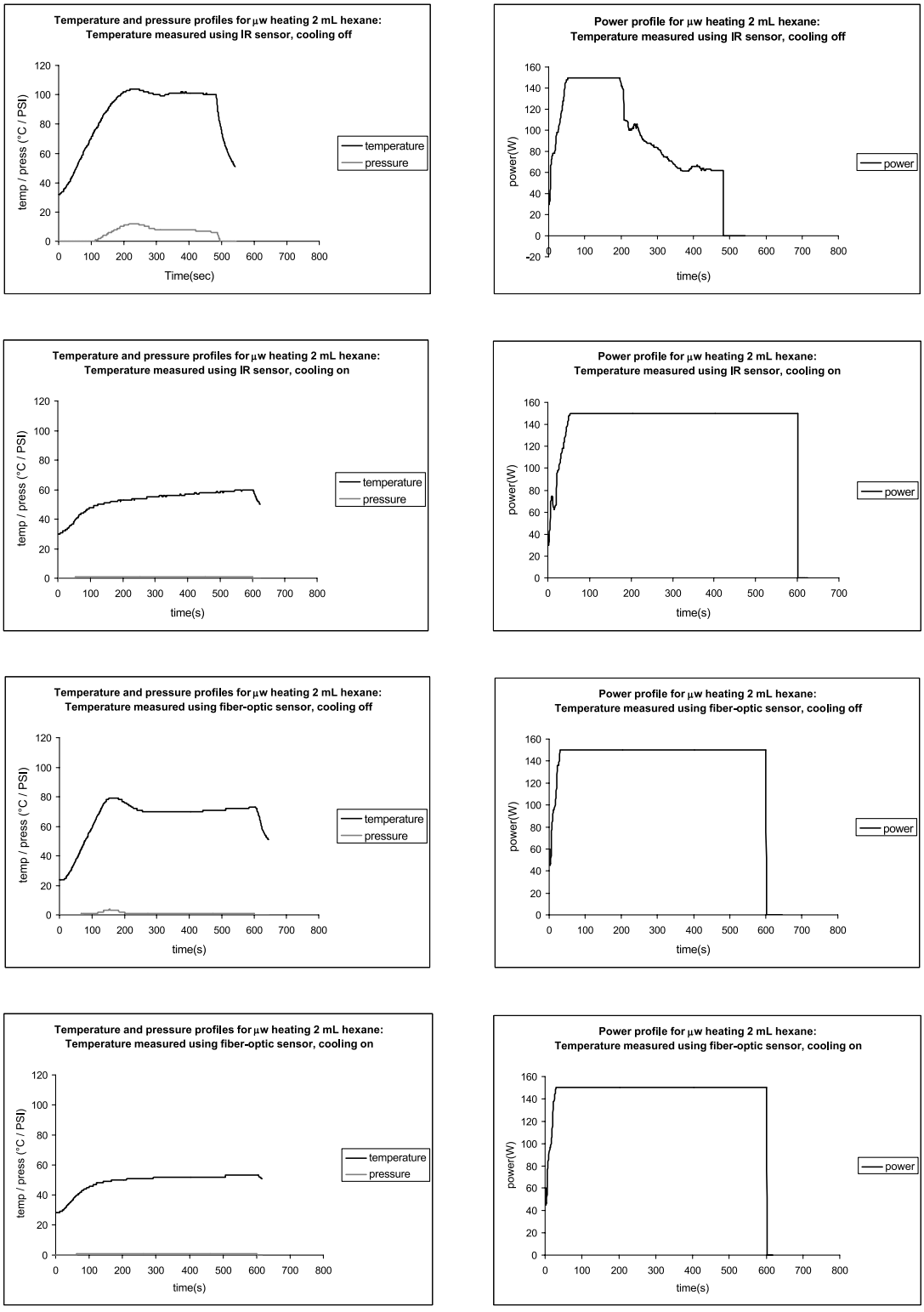


Figure 4. Heating 2 mL hexane to 100 °C measuring the temperature using an IR sensor or a fiber optic device with simultaneous cooling off and on.

Therefore, this approximates more to conventional heating than microwave heating. Using the IR sensor, the solvent is recorded to reach the target temperature of 100 °C after approximately 4 min. With cooling on, again measuring using the IR sensor, the maximum temperature recorded is 60 °C. Using the internal fiber optic system, with cooling off the reaction mixture reaches no higher than 70 °C and with cooling on, 52 °C. The differences in this case can be attributed to the fact that the IR sensor is, in effect, measuring the temperature of the reaction tube and the fiber optic is measuring that of the solvent itself.

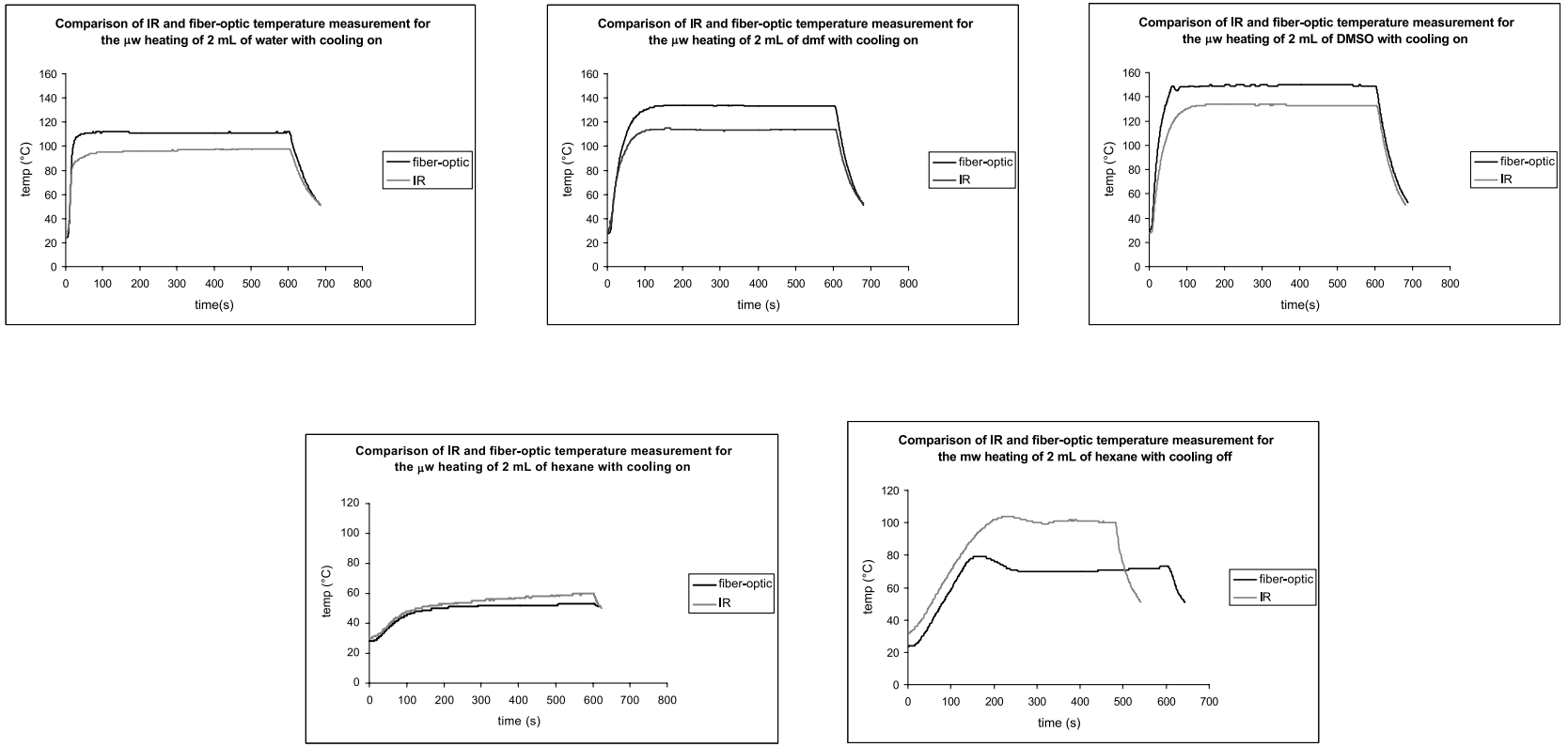
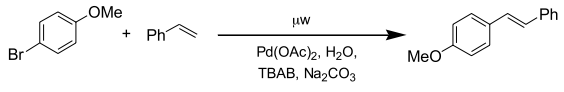


Figure 5. Superimposition of temperature/time profiles for water, DMF, DMSO and hexane measuring the temperature using an IR sensor or a fiber optic device with simultaneous cooling on.

2.2. Studies of reactions

Having made comparisons of the two temperature measurement methods, we turned our attention to the effects of simultaneous cooling on organic transformations.

2.2.1. Heck reaction. Our first reaction for examination was a Heck coupling in water using palladium acetate as a catalyst. The concept of efficient and selective synthesis in water has been exemplified as the rates, yields and selectivity observed for many reactions in water have begun to match, or in many cases, surpass those in organic solvents.[7] In contrast to many other solvents, water not only provides a medium for solution chemistry but often participates in elementary chemical events on a molecular scale. Water also offers practical advantages over organic solvents. It is cheap, readily available, non-toxic and non-flammable. There have been a number of reports of Heck couplings using water or water/organic solvent mixtures as solvent.[8,9] Palladium acetate has been used as a catalyst previously. Beletskaya and co-workers have shown that the coupling of acrylic acid and acrylonitrile with aryl halides can be effected in neat water or in DMF–water or HMPA–water mixtures at 70–100 °C with good yields.[10] The reaction can be performed under milder conditions upon addition of potassium acetate. Jeffery and co-workers have shown that reactions involving water-insoluble substrates can be efficiently performed in water, in the presence of a combination of an alkali metal carbonate and a quaternary ammonium salt.[11] Microwave heating has been used for the Heck reaction before, a range of solvents and catalysts being used.[12] We chose 4-bromoanisole and styrene as substrates because we knew from previous work that the yield from this reaction was dependent on temperature and did not always reach completion.[13] This therefore would give us an indication as to the effects, if any, of simultaneous cooling (Scheme 1).



Scheme 1.

The reactions were run using sodium carbonate as base and with the addition of tetrabutylammonium bromide (TBAB) as a phase-transfer agent to facilitate the solvation of the organic substrates in the water. We ran the reaction at two different 'set' temperatures, 100 and 150 °C, first with cooling off and then with cooling on. We performed each of the reactions using the fiber optic device for temperature measurement and with an initial microwave power of 150 W. The temperature was ramped to the desired point where it was held for a further 5 min. The product yields and total microwave power inputs are shown in Table 1 and heating profiles in Figure 6. At first glance it seems like there is a slight yield-enhancing effect when using simultaneous cooling in the reaction when running at 150 °C (Table 1, entries 3 and 4) but negligible at 100 °C (Table 1, entries 1 and 2). However, a closer look at the heating profiles shows that the reactions run with cooling on take a longer time to reach the target temperature as compared to those when the cooling is off. This is clearly shown by superimposing the cooling on and cooling off temperature/time profiles as is done in Figure 7. We re-ran the reactions at 150 °C but this time with no set ramp time. Instead we simply ran both the reaction with cooling on and that with cooling off for a set total time of 10 min (Table 1, entries 5 and 6). Heating profiles are shown in Figure 8. We find that the product yield is now higher in the case of cooling on but the difference is only 5% as compared to 17% when running a program with a set ramp time. To compare microwave heating with conventional heating, we repeated the reactions but using an oil bath instead of the microwave apparatus. Reactions were run by placing the reaction mixture contained in a glass tube identical to that using the microwave heating experiments into an oil bath pre-heated to the desired temperature and holding it there for 10 min before removing and cooling. We find that yields are substantially lower when using conventional heating which is not unexpected given the precedent for this in the literature (Table 1, entries 7 and 8).

If the amount of microwave power has an effect on the reaction then it would be expected that if the power was increased then so would the product yield. To probe this we performed the Heck coupling using 10, 20 and then 30 W of microwave power. To achieve this we set the target temperature to 200 °C, something we knew could not be attained during a 10 min reaction time. We therefore were able to obtain full power using both cooling on and cooling off. The only difference therefore is the maximum temperature attained. We obtained yield data for all the experiments and these and the total microwave power inputs

Table 1. The Heck coupling of 4-bromoanisole and styrene in water using microwave heating with and without simultaneous cooling

Entry	Temparature/°C	Cooling	Yield/%	Total μw power/W[a]
1[b]	100	No	10	4470
2[b]	100	Yes	12	27,830
3[b]	150	No	83	19,257
4[b]	150	Yes	100	59,832
5[c]	150	No	75	22,481
6[c]	150	Yes	80	76,826
7[d]	100	—	0	—
8[d]	150	—	35	—

[a] Power delivered by the magnetron. Obtained by integrating the power versus time profile.
[b] Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to the target temperature where it was then held for 5 min.
[c] Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to the target temperature where it was then held until a total reaction time of 10 min had elapsed.
[d] Performed using conventional heating. Reaction time of 10 min.

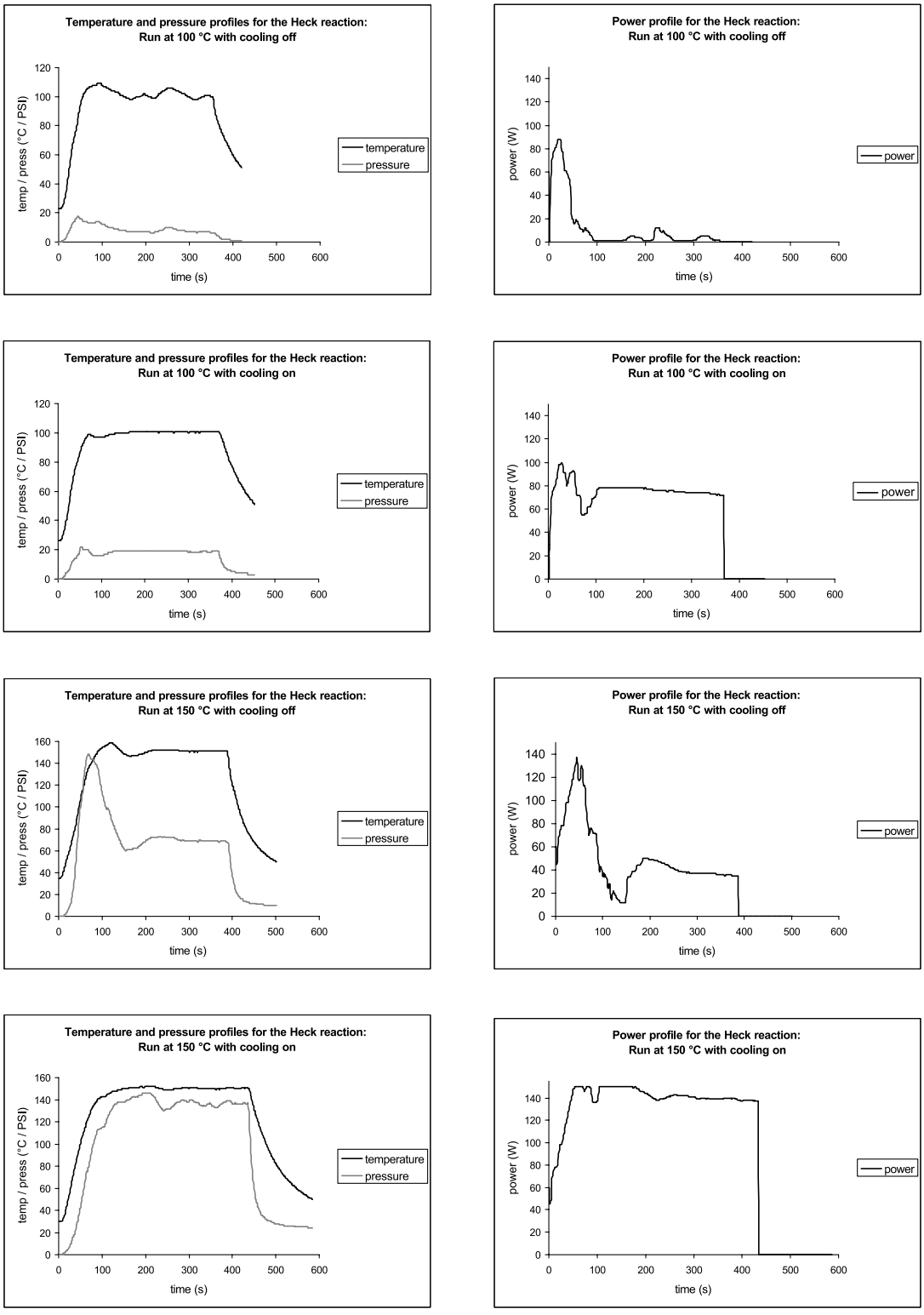


Figure 6. Heating profiles for the Heck coupling of 4-bromoanisole and styrene in water using microwave heating with and without simultaneous cooling.

are shown in Table 2.[14] The heating profiles are shown in Figure 9.

Not surprisingly, the reactions run with cooling off attain a higher maximum temperature and product yields are higher in these cases (Table 2, entries 1, 3 and 5). It is interesting to compare the yields not only within Table 2 but also with those from the reactions run at 100 °C and 150 °C in Table 1. The maximum temperature reached in the reaction run at 10 W with cooling off (Table 2, entry 1) is the same as that reached at 30 W with cooling on (Table 2, entry 6) but there is a negligible difference in product yield despite the total

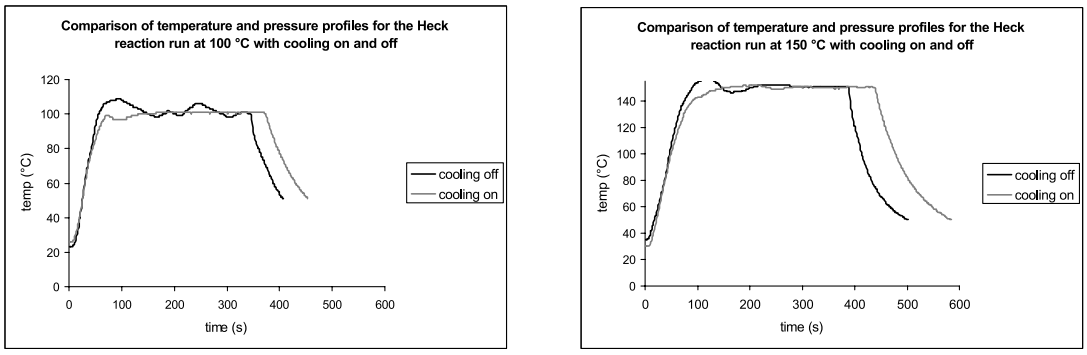


Figure 7. Superimposition of temperature/time profiles for the Heck coupling of 4-bromoanisole and styrene in water using microwave heating with and without simultaneous cooling.

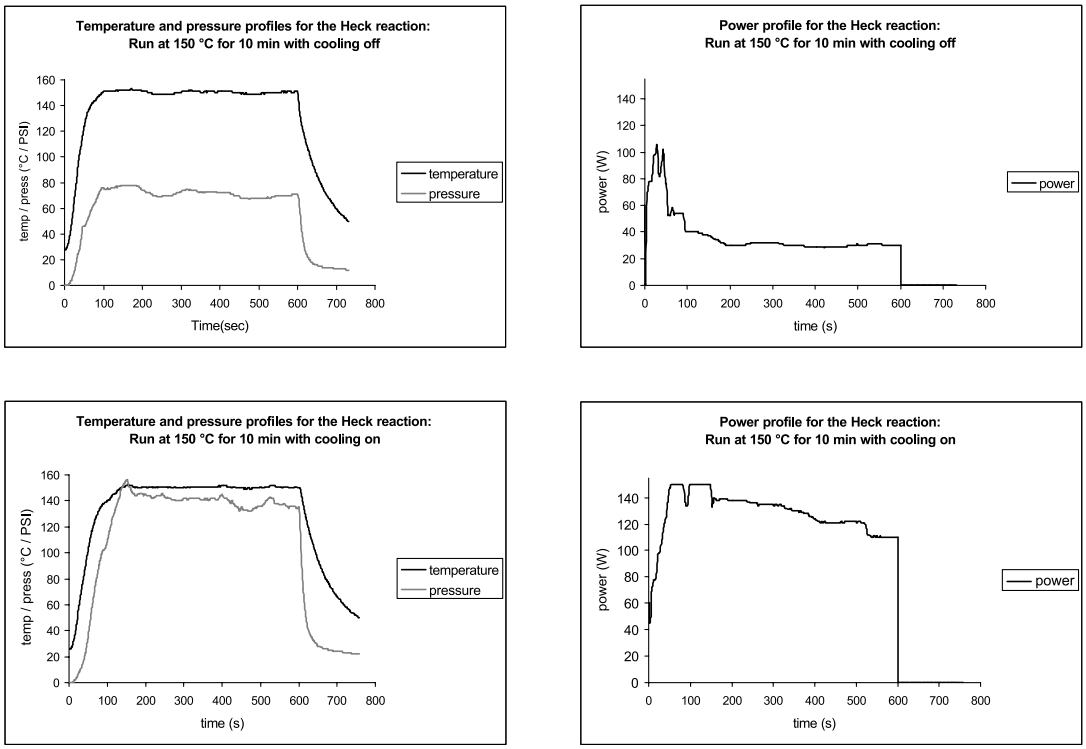


Figure 8. Heating profiles for the Heck coupling of 4-bromoanisole and styrene in water using microwave heating for a 10 min reaction time with and without simultaneous cooling.

Table 2. The Heck coupling of 4-bromoanisole and styrene in water using microwave heating with and without simultaneous cooling with constant microwave power[a]

Entry	Power/W	Cooling	Product yield/%	Maximum temperature reached/°C	Total μw power/W[b]
1	10	No	15	122	5978
2	10	Yes	9	74	6007
3	20	No	19	139	11,966
4	20	Yes	10	111	12,000
5	30	No	58[c]	154	17,919
6	30	Yes	19	122	17,913

[a] Microwave irradiation of the desired power was used, the temperature being set to ramp from rt to 200 °C or until a total reaction time of 10 min had elapsed at which point the reaction mixture was cooled to rt.
[b] Power delivered by the magnetron. Obtained by integrating the power versus time profile.
[c] Loss of material noted.

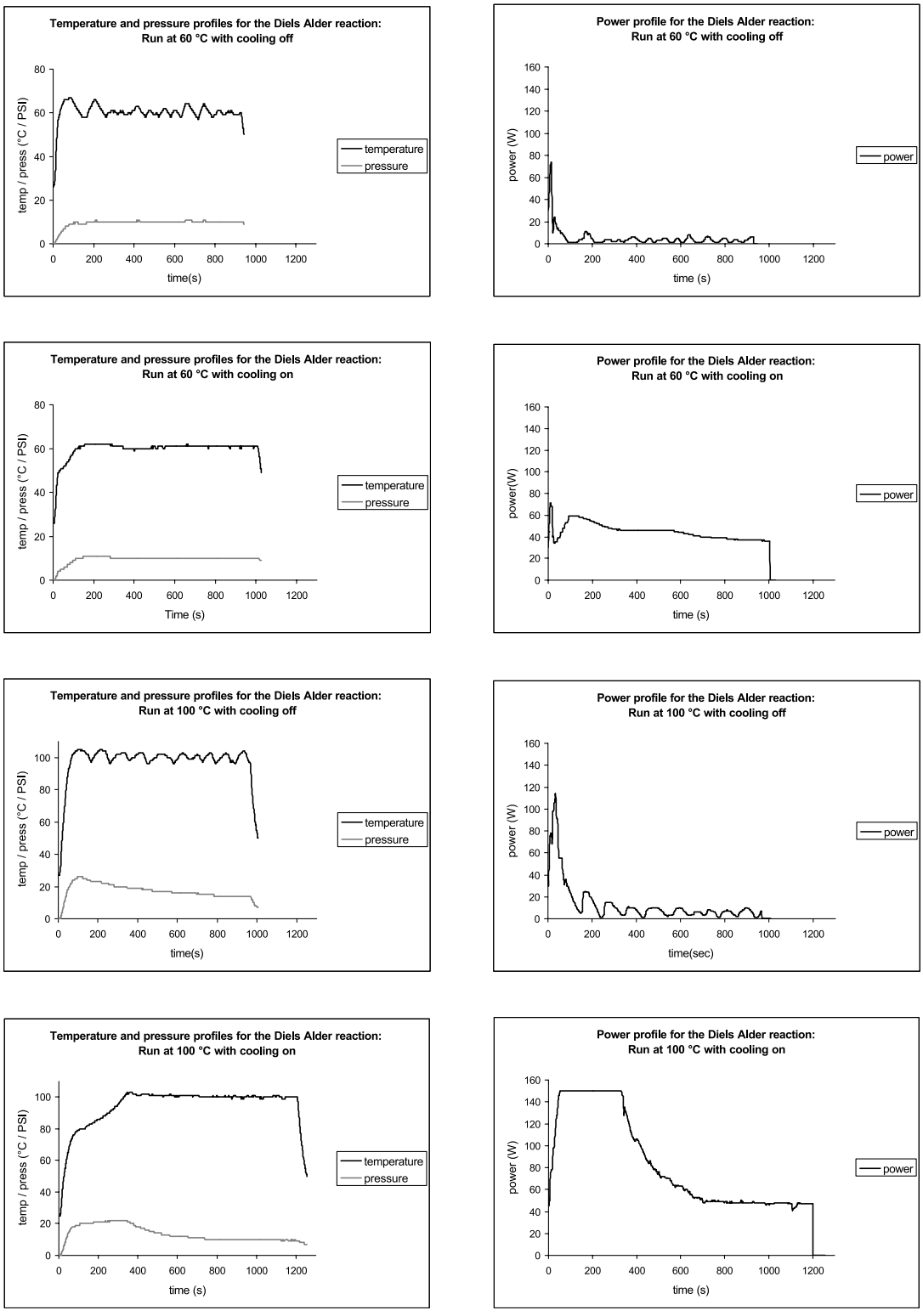
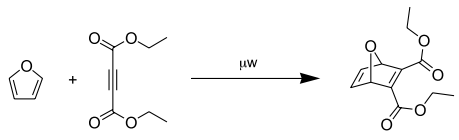


Figure 9. Heating profiles for the Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating with and without simultaneous cooling.



Scheme 2.

input of three times as much power (5978 W for 10 W cooling off and 17,913 W for 30 W cooling on). The maximum temperature reached in the reaction run at 20 W with cooling on is 111 °C and a product yield of 10% is obtained (Table 2, entry 4). The total microwave power input for this reaction is 12,000 W. This can be compared

Table 3. The Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating with and without simultaneous cooling

Entry	Temperature/°C	Cooling	Yield/%	Total μw power/W[a]
1[b]	60	No	0	4524
2[b]	60	Yes	15	45,160
3[b]	100	No	38	12,672
4[b]	100	Yes	94	100,725
5[c]	60	No	11	8086
6[c]	60	Yes	26	60,090
7[c]	100	No	48	16,254
8[c]	100	Yes	57	89,491
9[d]	100	—	28	
10[d]	150	—	70	

[a] Power delivered by the magnetron. Obtained by integrating the power versus time profile.
[b] Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to the target temperature where it was then held for 15 min.
[c] Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to the target temperature where it was then held until a total reaction time of 20 min had elapsed.
[d] Performed using conventional heating. Reaction time of 20 min.

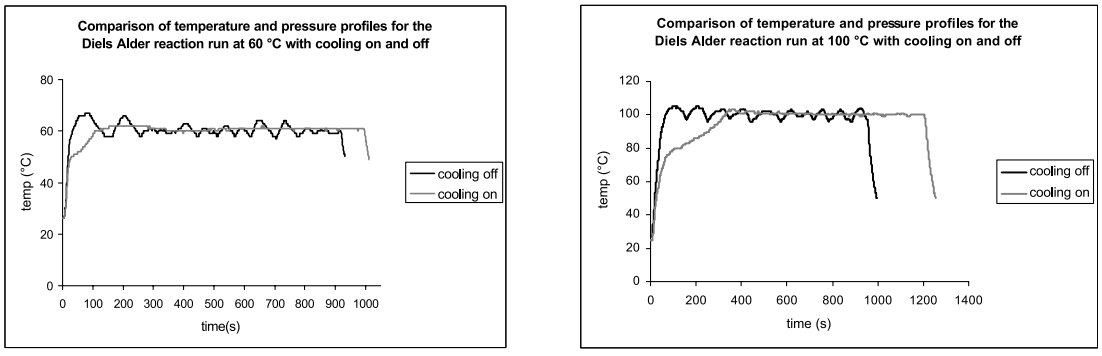


Figure 10. Superimposition of temperature/time profiles for the Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating with and without simultaneous cooling.

with the experiment run at 100 °C with cooling on which has a total microwave power input of 27,830 W and where a product yield of 12% is obtained (Table 1, entry 2).

2.2.2. Diels–Alder cycloaddition. Since the start of the field of microwave-assisted synthesis, the far shorter times reported for reactions as compared to those using 'conventional' heating have sparked debate into the nature of the microwave heating.[15] The acceleration of reactions could simply be an effect of the thermal energy generated by the microwaves interacting with the substrates or could be an effect specific to microwave heating. In most cases, the observed differences between microwave and conventional heating can be attributed to simple thermal effects. Proponents of non-thermal microwave effects suggest that, if polar solvents are used (either protic or aprotic), the main interaction that occurs in microwave heating is between the microwaves and the solvent. Energy transfer is from the solvent molecules to the reagents and any specific microwave effects would be masked by this. Therefore microwave effects are most likely to be observed under solvent-free conditions. Loupy and co-workers have proposed a rationalization of microwave effects in organic synthesis based on mechanistic considerations.[16] If the polarity of a system is enhanced from the ground state to the transition state, it can result in an acceleration due to an increase in material-wave interactions during the course of the reaction. They cite a range of examples and suggest that non-thermal effects are most frequently encountered in unimolecular or bimolecular reactions between neutral molecules and anionic reactions of tight ion pairs. We therefore decided to screen two solvent-free reactions using the CEM PowerMAX methodology, one where non-thermal effects are thought not to manifest themselves and one where there is the possibility of non-thermal effects. This would give us a deeper insight into the validity of the simultaneous cooling methodology and also allow us to probe any non-thermal effects since, if they manifest themselves, there should be a correlation between product yield and microwave power.

We first studied a Diels–Alder cycloaddition. The use of microwave heating for the acceleration of Diels–Alder reactions has attracted much attention over recent years[17] and a number of reports have suggested non-thermal microwave effects are responsible for the rate enhancements seen.[18] We performed the reaction between furan and diethylacetylene dicarboxylate at 60 and 150 °C with and without simultaneous cooling using an initial microwave power of 150 W (Scheme 2).

In our first experiments we again wanted to see the effect of setting a ramp time followed by a fixed hold time so the temperature was ramped to the desired point where it was held for a further 15 min. Product yields are shown in Table 3, entries 1–4 and heating profiles in Figure 9. A clear

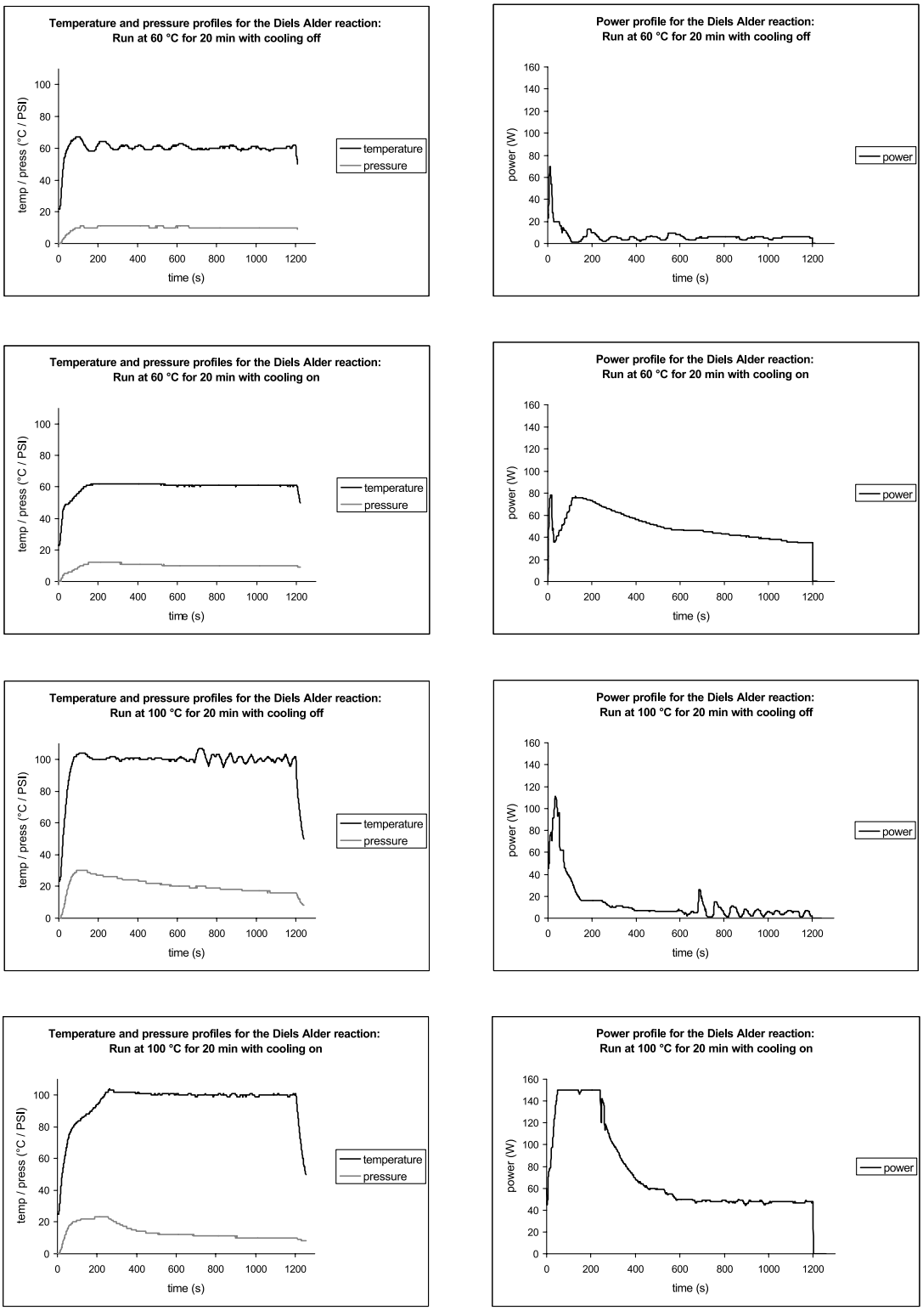


Figure 11. Heating profiles for the Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating for a 20 min reaction time with and without simultaneous cooling.

difference between cooling off and cooling on is observed at both temperatures; significantly higher yields of product being obtained when simultaneous cooling is used. However, if the temperature/time profiles are superimposed (Fig. 10), just as with the Heck reaction again a time differential is observed; the experiments with simultaneous cooling on running for greater overall times due to the longer time required to ramp the reaction mixture to the desired temperature. This effect is even more marked in the case of the Diels–Alder reaction. At 60 °C, with cooling

Table 4. The Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating with and without simultaneous cooling with constant microwave power[a]

Entry	Power/W	Cooling	Product yield/%	Maximum temperature reached/°C	Total μw power/W[b]
1	10	No	43	97	11,997
2	10	Yes	0	46	11,897
3	20	No	48	147	23,960
4	50	No	0[c]	190	59,002
5	50	Yes	40	79	59,877
6	70	Yes	44	101	83,856
7	100	Yes	26[c]	153	119,778

[a] Microwave irradiation of the desired power was used, the temperature being set to ramp from rt to 200 °C until a total reaction time of 20 min had elapsed at which point the reaction mixture was cooled to rt.
[b] Power delivered by the magnetron. Obtained by integrating the power versus time profile.
[c] Loss of material noted.

on, the reaction was run for an additional 90 s and, at 100 °C, an additional 4.3 min. This again highlights the importance of taking into account the total reaction time when comparing results obtained with simultaneous cooling with those using conventional microwave heating methods. We repeated the reactions at both temperatures but using a fixed reaction time of 20 min. Product yields are shown in Table 3, entries 5–8 and heating profiles in Figure 11. At both temperatures, an increase in product yield in the region of 10–15% is observed when simultaneous cooling is used. This difference could be attributed to the fact that, in this reaction, competitive decomposition of the product is a problem. With simultaneous cooling it could be that the lifetime of the product can be extended and this manifests itself in the higher observed product yield.

We performed the Diels–Alder reaction using a fixed microwave power, as we did in the Heck reaction. Again, to achieve this we set the target temperature to 200 °C, something we knew could not be attained. We therefore were able to obtain full power using both cooling on and cooling off. We obtained yield data for all the experiments and these and the total microwave power inputs are shown in Table 4. The heating profiles are shown in Figure 12.

The first point that can be drawn from the data in Table 4 is that bulk temperature is important, regardless of any 'hot spots' generated in the reaction. Below around 50 °C, no reaction is observed and above 150 °C decomposition becomes a major problem. We find that the maximum temperature reached using 10 W with cooling off is similar to that obtained using 70 W with cooling on. Product yields are similar for these two reactions but the power delivered from the magnetron is very different (11,997 W for 10 W cooling off vs 83,856 for 70 W cooling on). These data again suggest that bulk temperature may be the key factor. However, when comparing the results obtained using 20 W cooling off and 100 W cooling on, although a similar final temperature is reached, the power is much higher in the case of the latter and this is accompanied by significant product decomposition.

To probe the reaction further, we re-ran experiments using a total reaction time of 5 min as compared to 20 min since, if product decomposition was a problem, running the reaction for a shorter time should indicate this. We first ran the reaction at a fixed temperature of 115 °C and then at different fixed powers. The results are shown in Tables 5 and 6 and heating profiles in Figures 13 and 14. At 115 °C, the product yields with cooling off and on are almost identical, 58 and 54%, respectively. This is in fact not all that unexpected giving that the total power delivered in these two reactions is almost identical. Running the reaction at fixed power again shows that bulk temperature is important, similar observations being made as when running the reaction for 20 min.

2.2.3. Michael addition. The third reaction we studied was the 1,4-Michael addition of methyl acrylate with imidazole, again under solvent-free conditions. The reaction of imidazole and ethyl acrylate has been reported by Martin-Aranda and co-workers using microwave heating in a domestic apparatus using basic clays as catalysts.[19] In this report the authors show that, when using microwave heating, significantly higher yields of the product are formed as compared to conventional heating for the same time. It has also been shown that microwave heating accelerates the Michael addition of primary and cyclic secondary amines to acrylic esters.[20] The use of microwave heating for intramolecular Michael additions has been reported. A range of ortho-aminochalcones have been cyclised to tetrahydroquinolines using a clay support.[21] The work has also been carried out using silica supports.[22] Microwave-promoted Michael reactions also have been the subject of a number of recent studies bringing together synthesis and calculations.[23] Also, microwave activation of an asymmetric Michael reaction has been studied and unexpected selectivity when using chiral alpha-alkoxy imines reported (Scheme 3).[24]

We have studied the microwave-reaction reaction between imidazole and methyl acrylate before.[25] We replaced the clays used by Martin-Aranda and co-workers with triethylamine and found that using a mixture of toluene and an ionic liquid (used to heat the reaction mixture rapidly) we were able to prepare the desired product in 2 min in an isolated yield of 75%. During the reaction, a microwave power of 100 W was used and the temperature of the mixture held at 200 °C. In control experiments, the reaction was repeated firstly in the absence of the ionic liquid and secondly in the absence of toluene and in both cases it was found that after the same time (2 min at 100 W microwave power) there was no product formed. As a starting point for our new, solvent-free, studies we investigated the addition using

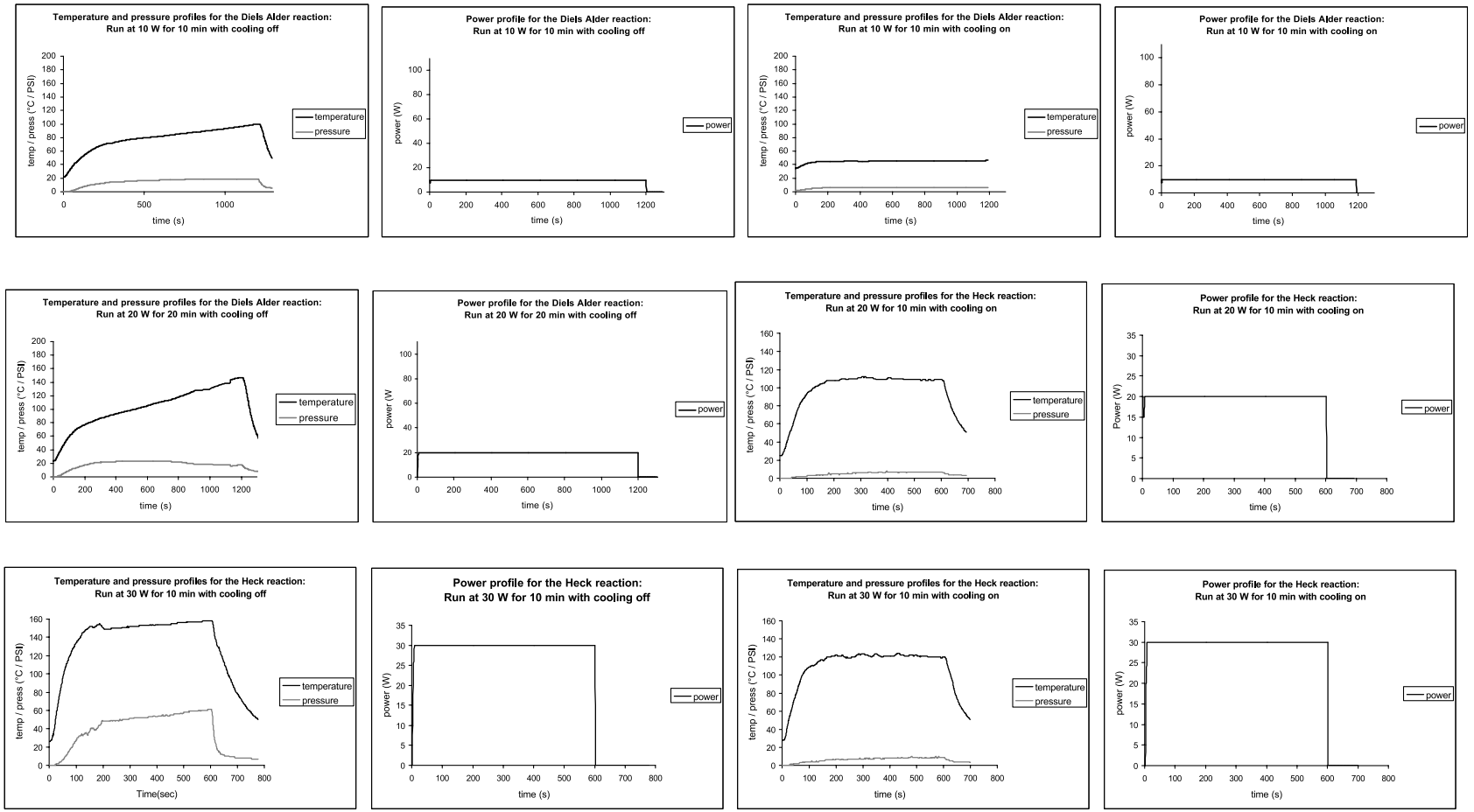


Figure 12. Heating profiles for the Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating with and without simultaneous cooling with constant microwave power run for 20 min.

Table 5. The Diels–Alder reaction between furan and diethylacetylene dicarboxylate at 115 °C using microwave heating with and without simultaneous cooling[a]

Entry	Cooling	Yield/%	Total μw power/W[b]
1	No	58	22,076
2	Yes	54	22,335

[a] Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to 115 °C where it was then held for 5 min.
[b] Power delivered by the magnetron. Obtained by integrating the power versus time profile.

triethylamine as a base, running the reaction for 10 min at 150 °C. We obtained an 87% yield of the desired product. Extending the reaction time to 15 min leads to a decrease in product yield due to competitive decomposition of the product. We subsequently discovered that the reaction in fact occurs in the absence of any added base. We ran the reaction at 100 and 150 °C for a fixed time of 15 min with simultaneous cooling on and off, using an initial microwave power of 150 W. We also performed the reaction using conventional heating. Product yields are summarized in Tables 7 and 8 and heating profiles for the microwave reactions are shown in Figures 15 and 16. As with the Diels–Alder reaction, here in the Michael addition studied the product yields obtained with simultaneous cooling on are some 10–15% higher than with the cooling off. Again it could be that the lifetime of the product can be extended when using simultaneous cooling resulting in a higher product yield. Interestingly the product yields obtained using conventional heating are in fact higher than those when using microwave heating. Put together, these results point towards there being no non-thermal microwave effect manifesting itself in this reaction despite the prediction that there should be.

3. Summary

We have presented here our initial assessment of the

Table 6. The Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating for 5 min with and without simultaneous cooling with constant microwave power[a]

Entry	Power/W	Cooling	Product yield/%	Maximum temperature reached/°C	Total μw power/W[b]
1	20	No	6	77	5980
2	20	Yes	0	50	5962
3	30	No	22	105	8957
4	50	No	39	125	14,917
5	50	Yes	7	76	14,878

[a] Microwave irradiation of the desired power was used, the temperature being set to ramp from rt to 200 °C or until a total reaction time of 5 min had elapsed at which point the reaction mixture was cooled to rt.
[b] Power delivered by the magnetron. Obtained by integrating the power versus time profile.

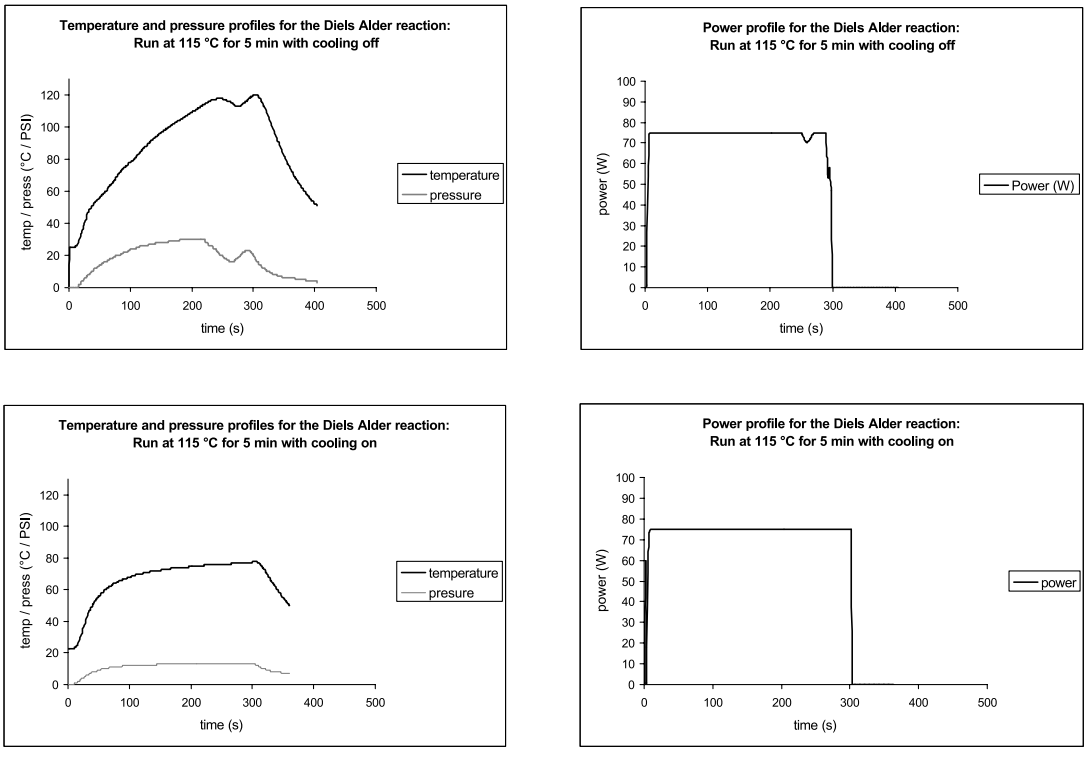


Figure 13. Heating profiles for the Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating for a 5 min reaction time with and without simultaneous cooling.

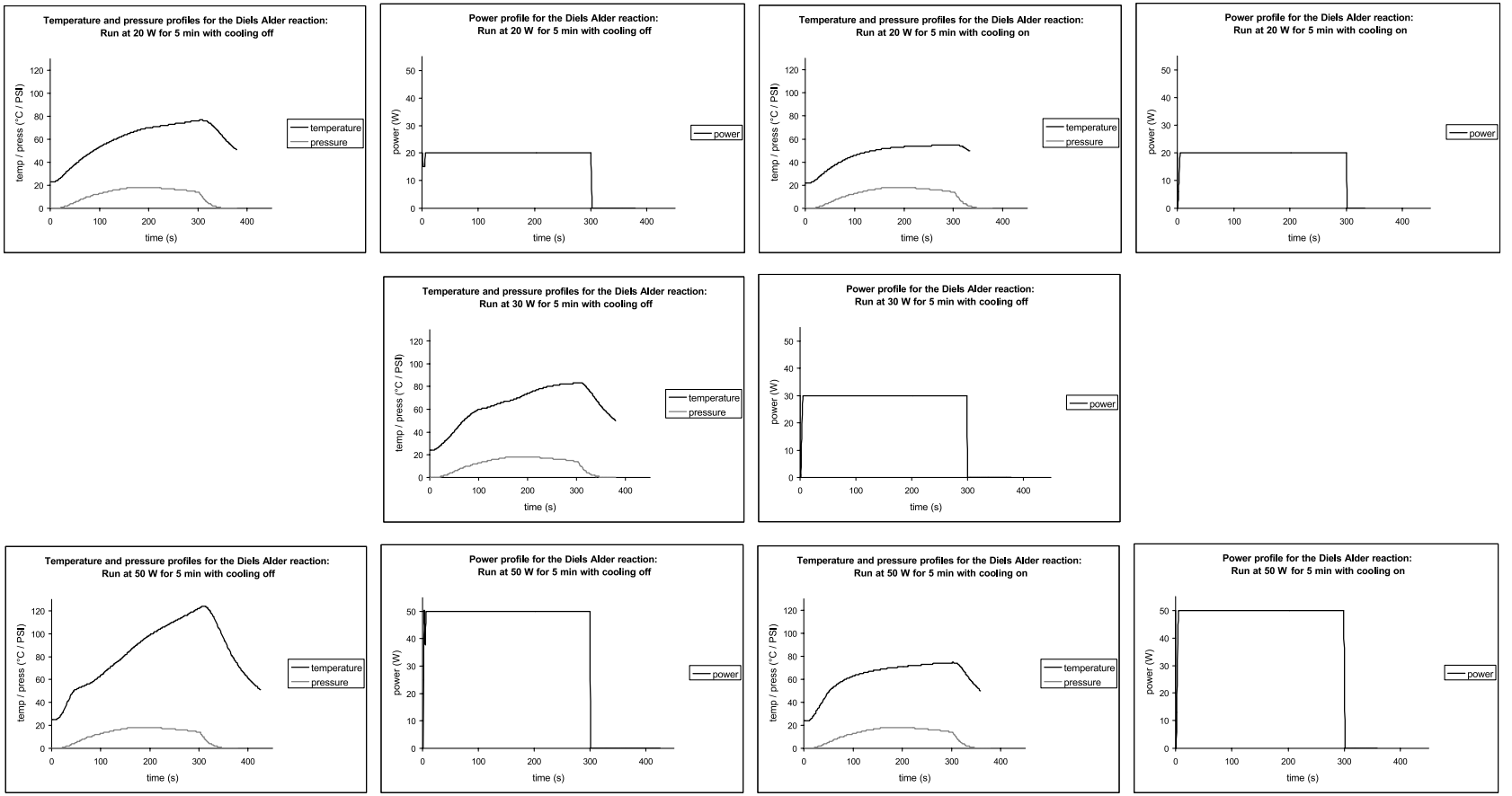


Figure 14. Heating profiles for the Diels–Alder reaction between furan and diethylacetylene dicarboxylate using microwave heating with and without simultaneous cooling with constant microwave power run for 5 min.

Scheme 3.

methodology of simultaneous cooling whilst microwave heating, looking at temperature measurement issues as well as the use of simultaneous cooling in three classes of reaction. When using simultaneous cooling, we find that it is important to monitor the temperature of a reaction mixture accurately and this involves the use of a fiber-optic temperature measurement set-up. Using IR temperature measurement, because of the air passing over the reaction vessel, the temperature recorded is lower than the bulk temperature of the reaction mixture. In our first reaction of study, the Heck coupling of 4-bromoanisole and styrene, we do not see any significant differences in product yield between experiments run with simultaneous cooling on and off. In the second class of reaction studied, the Diels–Alder cycloaddition between furan and diethylacetylene dicarboxylate, an increase in product yield of around 10–15% is obtained if cooling is on as compared to when it is off during the course of the reaction. Decomposition of the desired product is a problem associated with this reaction and could be the explanation for this difference. In the third class of reaction, the Michael addition of methyl acrylate to imidazole, product yields obtained with simultaneous cooling on are 10–15% higher than with the cooling off. Again, it could be that the lifetime of the product can be extended when using simultaneous cooling. In all of the reactions we have studied here, we see no evidence for non-thermal microwave effects manifesting themselves.

We believe that the technique of simultaneous cooling does have potential uses not only in synthetic organic chemistry but also in connection with studies of non-thermal microwave effects. It is possible to compare one microwave-promoted reaction with another at a different power, which has more credence than comparing microwave-promoted reactions with conventional heating since, in the case of the latter we believe that a fair comparison cannot often be made. We are continuing our studies in the area and our results will be reported in due course.

4. Experimental

4.1. General experimental

Unless noted otherwise, all materials were obtained from commercial suppliers and used without further purification. All reactions were carried out in air. Microwave reactions were conducted using a focused microwave unit. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure is controlled by a load cell connected to the vessel either via a 14-gauge needle, which penetrates just below the septum surface or directly from the vessel. The temperature of the contents of the vessel was monitored either using a calibrated infrared temperature control mounted under the reaction vessel or a fiber-optic probe inserted into the reaction vessel by means of a sapphire immersion well. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating

Table 7. The Michael addition reaction of imidazole and methyl acrylate using microwave heating with and without simultaneous cooling

Entry	Temperature/°C	Cooling	Yield/%	Total μw power/W[a]
1[b]	100	No	79	3030
2[b]	100	Yes	91	14,815
3[b]	150	No	61	8154
4[b]	150	Yes	72	38,910
5[c]	100	—	94	—
6[c]	150	—	89	—

[a] Power delivered by the magnetron. Obtained by integrating the power versus time profile.
[b] Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to the target temperature where it was then held until a total reaction time of 10 min had elapsed.
[c] Performed using conventional heating. Reaction time of 10 min.

Table 8. The Michael addition reaction of imidazole and methyl acrylate using microwave heating with and without simultaneous cooling with constant microwave power[a]

Entry	Power/W	Cooling	Product yield/%	Maximum temperature reached/°C	Total μw power/W[b]
1	3	No	88	117	1795
2	3	Yes	48	82	1795
3	5	No	78	114	2988
4	5	Yes	79[c]	100	2994
5	10	No	40	222	5722
6	10	Yes	95	118	5997

[a] Microwave irradiation of the desired power was used, the temperature being set to ramp from rt to 200 °C or until a total reaction time of 10 min had elapsed at which point the reaction mixture was cooled to rt.
[b] Power delivered by the magnetron. Obtained by integrating the power versus time profile.
[c] Loss of material noted.

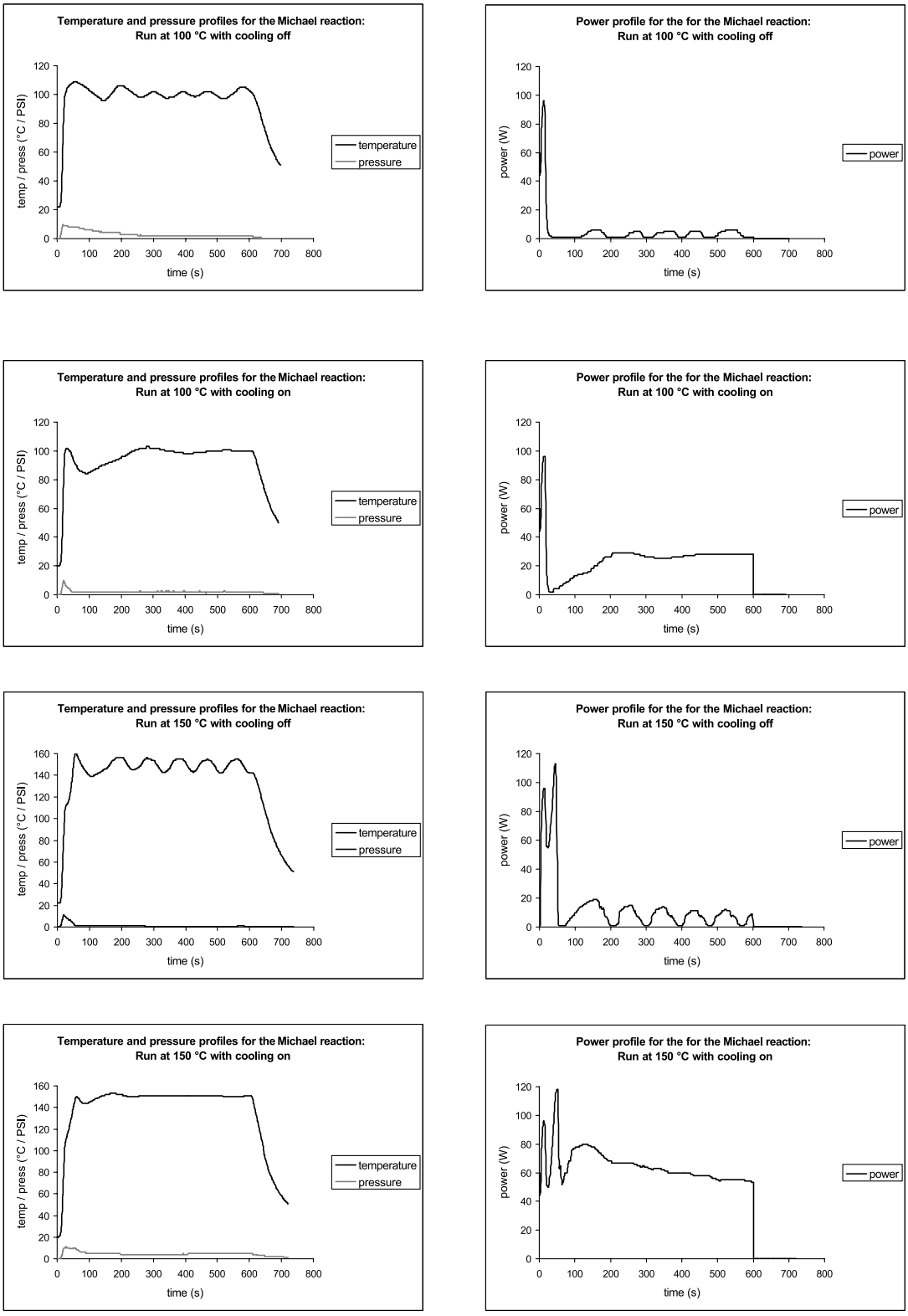


Figure 15. Heating profiles for the Michael addition reaction between imidazole and methyl acrylate using microwave heating a 10 min reaction time with and without simultaneous cooling.

magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were recorded using commercially available software provided by the microwave manufacturer. ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a 300 MHz spectrometer. All yields reported are determined by integration of NMR signals relative to an internal standard.

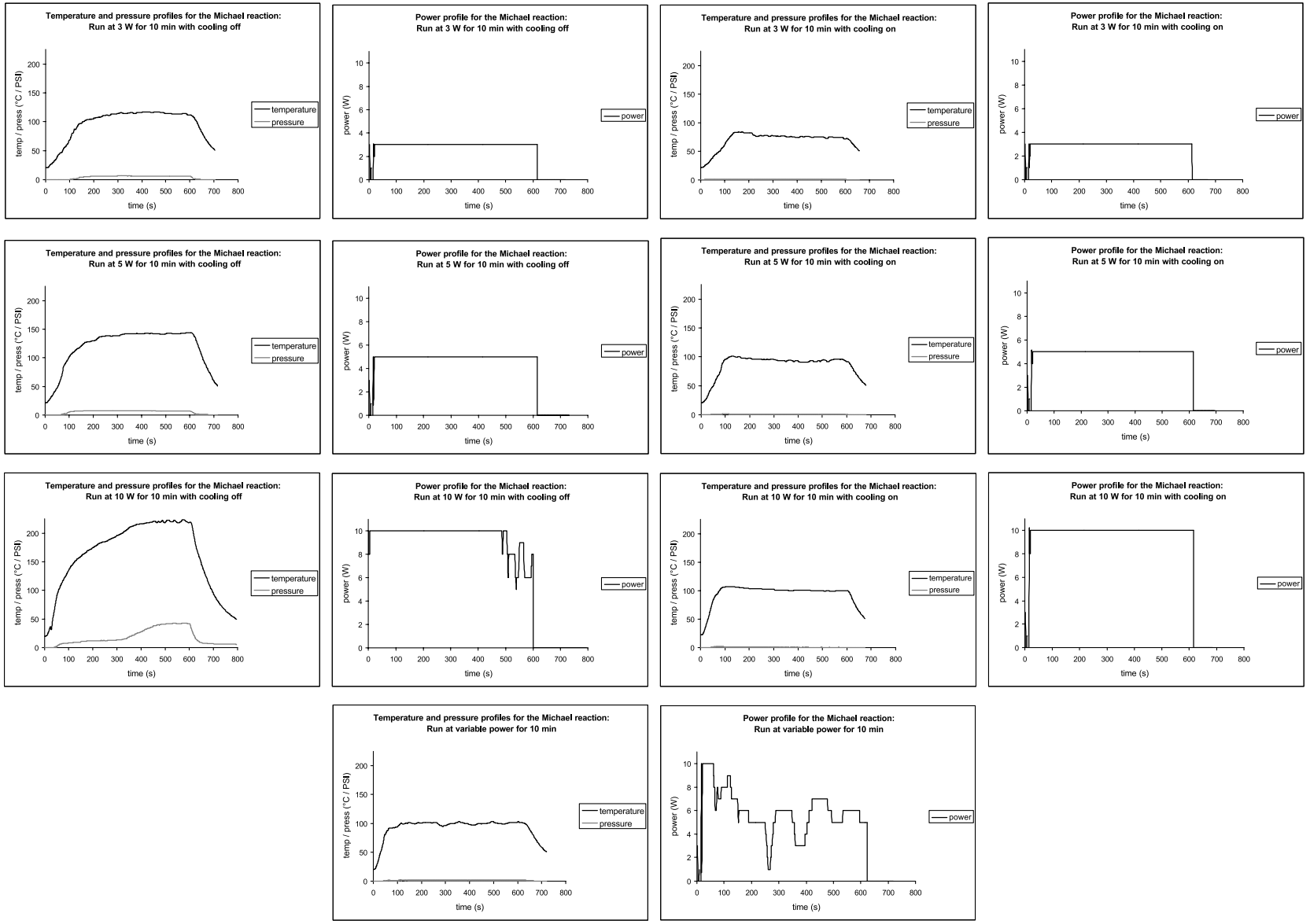


Figure 16. Heating profiles for the Michael addition reaction between imidazole and methyl acrylate using microwave heating with and without simultaneous cooling with constant microwave power.

4.2. Temperature measurement studies

To a microwave vessel containing a Teflon-coated magnetic stirrer bar was added 2 mL of the desired solvent for study. The vessel was then sealed and the experiment undertaken. For safety, the maximum pressure and temperature were set to 200 psi and 300 °C, respectively. A microwave irradiation power of 150 W was used. The apparatus was set to attain a target temperature of 150 °C, with the exception of hexane which was heated to a target temperature of 100 °C, the apparatus being programmed to ramped from rt to this target temperature over 5 min. Once the temperature was reached, the reaction mixture was held for a further 5 min. Experiments were run firstly with simultaneous cooling off and then, after letting the solvent return to rt, repeating with simultaneous cooling on.

4.3. Heck coupling between 4-bromoanisole and styrene at fixed temperature

In a 10 mL glass tube was placed 4-bromoanisole (1.0 mmol, 187 mg, 0.128 mL), styrene (1.5 mmol, 156 mg, 0.173 mL), Na_2CO_3 (392 mg, 3.7 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), palladium acetate (0.0045 mmol, 1 mg, 0.4 mol%), 2 mL water and a magnetic stir bar. The vessel was sealed with a septum, shaken vigorously (essential) and placed into the microwave cavity. Microwave irradiation of 150 W was used, the temperature being ramped from rt to the desired temperature. Once this was reached, the reaction mixture was held at this temperature until a total irradiation time of 10 min had elapsed. After allowing the mixture to cool to rt, the reaction vessel was opened and the contents poured into a separating funnel. Water (30 mL) and ethyl acetate (30 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with ether, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in-vacuuo leaving the crude product. Characterised by comparison of NMR data with that in the literature.[26]

4.4. Heck coupling between 4-bromoanisole and styrene at fixed power

A microwave tube was loaded, sealed and shaken as with the fixed temperature experiments. Microwave irradiation of the desired power was used, the temperature threshold being set at 200 °C. The reaction mixture was irradiated for a fixed time of 10 min. After allowing the mixture to cool to rt, the reaction vessel was opened and worked-up as with the fixed time experiments.

4.5. Diels–Alder reaction between diethylacetylene dicarboxylate and furan at fixed temperature

In a 10 mL glass tube was placed furan (3.7 mmol, 265 mg, 0.28 mL), diethylacetylene dicarboxylate (3.7 mmol, 633 mg, 0.59 mL) and a magnetic stir bar. The vessel was sealed with a septum, and placed into the microwave cavity. An initial microwave power of 150 W was used, the temperature being ramped from rt to the desired temperature. Once this was reached, the reaction mixture was held at this temperature until a total irradiation time of 20 min had elapsed. After allowing the mixture to cool to rt, the reaction vessel was opened and the crude product removed directly from the tube.

4.6. Diels–Alder reaction between diethylacetylene dicarboxylate and furan at fixed power

A microwave tube was loaded and sealed as with the fixed temperature experiments. Microwave irradiation of the desired power was used, the temperature threshold being set at 200 °C. The reaction mixture was irradiated for a fixed time of 20 min. After allowing the mixture to cool to rt, the reaction vessel was opened and the crude product removed directly from the tube.

4.7. Michael addition reaction between imidazole and methyl acrylate at fixed temperature

In a 10 mL glass tube was placed imidazole (11 mmol, 768 mg), methyl acrylate (11 mmol, 972 mg, 1.0 mL) and a magnetic stir bar. The vessel was sealed with a septum, and placed into the microwave cavity. An initial microwave power of 150 W was used, the temperature being ramped from rt to the desired temperature. Once this was reached, the reaction mixture was held at this temperature until a total irradiation time of 10 min had elapsed. After allowing the mixture to cool to rt, the reaction vessel was opened and the crude product removed directly from the tube. Characterised by comparison of NMR data with that in the literature.[23]

4.8. Michael addition reaction between imidazole and methyl acrylate at fixed power

A microwave tube was loaded and sealed as with the fixed temperature experiments. Microwave irradiation of the desired power was used, the temperature threshold being set at 200 °C. The reaction mixture was irradiated for a fixed time of 10 min. After allowing the mixture to cool to rt, the reaction vessel was opened and the crude product removed directly from the tube.

Acknowledgements

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The deoxygenation of sulfoxide mediated by the Ph_3P/Lewis acid combination and the application to the kinetic resolution of racemic phosphines using optically active sulfoxide

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Abstract—It was found that the combination of $Ph_3P/TiCl_4$ was an effective promoter for the deoxygenation of sulfoxides and gave the corresponding sulfides in good yield (up to 97%) under mild conditions. This method was applied to the reaction between racemic phosphines and (*R*)-methyl *p*-tolyl sulfoxide, and it was found that the kinetic resolution was achieved in moderate selectivities.

1. Introduction

Sulfinyl group is one of the most important functional groups in organic synthesis and there are many reports of stereoselective reactions using sulfinyl group as a chiral auxiliary with high stereoselectivity.[1] The sulfinyl group is usually eliminated in two steps; first, the sulfoxide is deoxygenated to sulfide, and after that, the sulfide is removed by catalytic hydrogenation or other chemical means.[2] So, until now, many kinds of methods of the deoxygenation of sulfoxides have been developed; using metal hydride reagents ($LiAlH_4$, $NaBH_4$, etc.), low-valent metallic species ($SnCl_2$, VCl_2, $TiCl_3$ etc.), halide ions (HI, TMSI, TiI_4 etc.) and so on.[3,4] And phosphines were also known as reductants for sulfoxides.[4a,b] For example, the deoxygenation of diphenyl sulfoxide was mediated by Ph_3P, in the presence of $BF_3\cdot OEt_2$, under acetic acid reflux condition. However, in these cases, the drastic conditions were required and the ranges of substrates were limited. Therefore, it was desired the development of the deoxygenations using phosphines, which proceeded under mild conditions and had high generalities of substrates.

On the other hand, we have recently investigated the reaction mediated by the combination of phosphine and Lewis acid and it has been already reported that the several reactions proceeded in good yield with high stereoselectivity using this combination.[5,6] For example, the reduction of various α-bromocarboxylic acid derivatives proceeded in good yield under mild conditions,[5a] and the reduction of 1,2-dicarbonyl compounds was smoothly mediated by the $Ph_3P/AlBr_3$ combination.[5e] We herein would like to describe the deoxygenation of sulfoxides mediated by the phosphine and Lewis acid combination under mild conditions. Moreover, we would like to show the application to the kinetic resolution of racemic phosphines.

2. Results and discussion

2.1. The deoxygenation of sulfoxide

First, we examined the deoxygenation of diphenyl sulfoxide (**1a**) using the combination of Ph_3P and several Lewis acids, such as $AlCl_3$, $BF_3\cdot OEt_2$, $SnCl_4$ and $TiCl_4$, in CH_2Cl_2 at room temperature. Among Lewis acids examined, it was found that only $TiCl_4$ gave a good result. However, under these conditions, the deoxygenation of other aliphatic sulfoxides could not proceed in satisfied yield. So, we examined the effect of solvents in the deoxygenation of dibenzyl sulfoxide (**1b**) using Ph_3P and $TiCl_4$ combination. Then, it was found that THF was the most effectively solvent and the highest yield (96%) was achieved.

Under the optimized conditions, the deoxygenation of several kinds of sulfoxides was carried out. The results are summarized in Table 1.

As can be seen from Table 1, it was found that the deoxygenation of sulfoxides was effectively mediated by this combination. Moreover, it should be noted that even if

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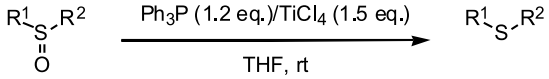
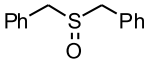
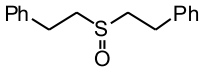
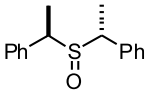
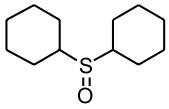
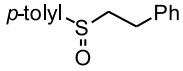
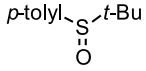
Table 1. The deoxygenation of sulfoxides using the combination of $Ph_3P/TiCl_4$



Entry	Substrate		Time (h)	Yield (%)[a]
1	**1a**		24	88
2	**1b**		2	96
3			24	88[b]
4	**1c**		1	92
5	**1d**		24	78
6	**1e**		2	67
7	**1f**		14	96
8	**1g**		2	97
9[c]	**1h**		14	90

[a] Isolated yields.
[b] Reaction was carried out using 0.5 equiv of $TiCl_4$.
[c] Reaction was carried out at 60 °C

the substrates possessed the bulky substituents, namely secondary or tertiary alkyl sulfoxides, the reaction proceeded smoothly in good yield (entries 5, 7, 9). And the reaction was also found to proceed in 88% yield using a catalytic amount of $TiCl_4$ (0.5 equiv) although the reaction rate was slower than that of the reaction using excess $TiCl_4$ (entries 2 and 3).

In summary, we found that the deoxygenation of sulfoxides smoothly proceeded in the presence of the Ph_3P and $TiCl_4$ combination in THF at room temperature and that this deoxygenation had high generalities.

2.2. Kinetic resolution of racemic phosphines

It is possible to consider this reaction, deoxygenation of sulfoxides, as the oxidation of the phosphine using the sulfoxide and Lewis acid combination. So, if the optically active sulfoxide is used with Lewis acid, it is assumed that this reaction can be applied to the asymmetric oxidation. Namely, it is expected that the kinetic resolution of racemic phosphines can be achieved to give the optically active phosphines. The optically active phosphines have many important roles in organic syntheses, especially in the transition metal catalyzed asymmetric reactions.[7] Therefore, a lot of methods for preparation of optically active phosphines have been developed. Recently, the kinetic resolution of planar chiral ferrocenyl phosphine was reported using selenoxide having an optically active binaphthyl skeleton.[8] But there were few reports to obtain the optically active phosphines using such a kinetic resolution. Then, we examined the kinetic resolution of racemic phosphines using optically active sulfoxides and Lewis acid combinations.

Initially, we carried out the kinetic resolution of racemic methyl(1-naphthyl)phenylphosphine using the combination of (*R*)-methyl *p*-tolyl sulfoxide (**2a**) and $TiCl_4$ in THF. Then, the reaction was found to proceed smoothly to give (*S*)-methyl(1-naphthyl)phenylphosphine in 32% yield with 18% ee.

Next, we screened a variety of optically active sulfoxides (Fig. 1) and $TiCl_4$ combination in the kinetic resolution of racemic methyl(1-naphthyl)phenylphosphine. Among the sulfoxides examined (**2a**–**e**), it was found that the highest enantioselectivity was achieved in the case of using (*R*)-methyl *p*-tolyl sulfoxide (**2a**). So, under these conditions, kinetic resolution of several sorts of racemic phosphines (**3a**–**e**) was carried out. The results are summarized in Table 2.

As shown in Table 2, the moderate enantioselectivity could be achieved in the reaction of P-chiral phosphine derivatives (**3a**, **3b**), the planer chiral phosphine (**3d**) and even the phosphine having a chiral center on neighboring carbon

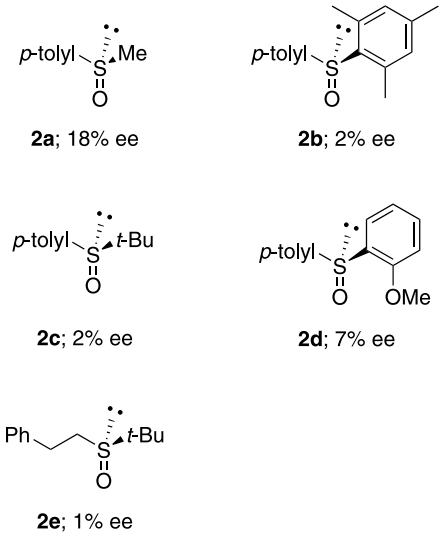


Figure 1. The used sulfoxide and the enantiomeric excess of methyl(1-naphthyl)phenylphosphine resolved by the sulfoxide.

atom (**3c**). Among them, it was noticed that the better results were obtained in the reaction of phosphines possessing the coordinating group (**3b**, **3d**).

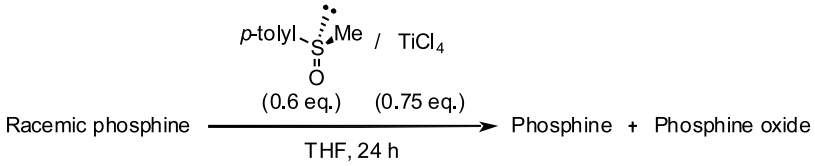
2.3. Mechanism

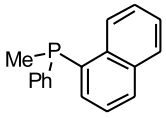
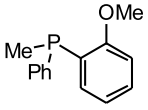
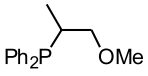
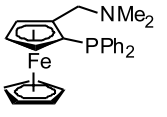
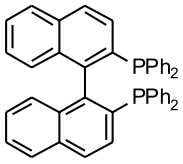
The mechanism of the kinetic resolution of methyl-(1-naphthyl)phenylphosphine (**3a**) could be explained as follows (Scheme 1): first, $TiCl_4$ coordinated the oxygen atom of (*R*)-methyl *p*-tolyl sulfoxide (**2a**). After that, phosphine (**3a**) attacked sulfur atom from behind the lone pair and then the intermediate (**4a**) and (**4b**) were formed. However, the formation of the intermediate (**4b**) was more disadvantageous than the formation of the intermediate (**4a**) because of the steric repulsion between naphthyl substituent and *p*-tolyl substituent. So, the reaction prefers to go through the intermediate (**4a**) to give the intermediate (**5**) and the (*S*)-methyl(1-naphthyl)phenylphosphine oxide was formed preferably.

3. Conclusion

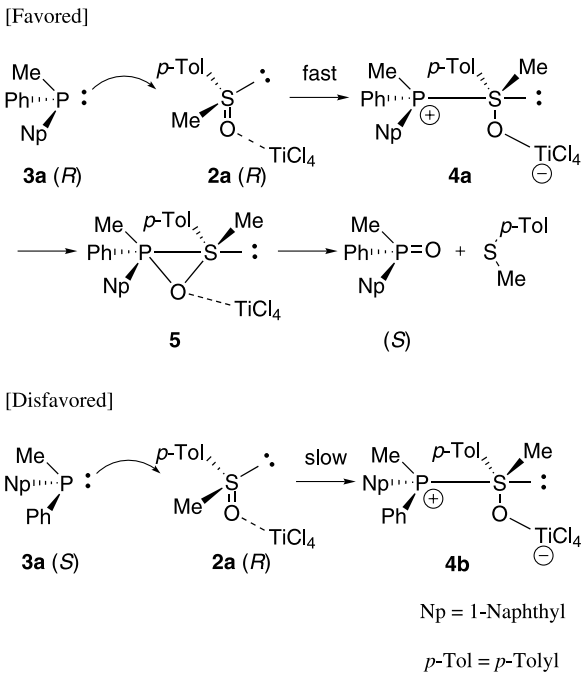
We found that the deoxygenation of many kinds of sulfoxides was effectively promoted by the combination of

Table 2. The kinetic resolution of several racemic phosphines mediated by the combination of (*R*)-methyl *p*-tolyl sulfoxide and $TiCl_4$



Entry	Substrate		Temperature (°C)[a]	Phosphine		
				Yield (%)[b]	ee (%)	Ref.
1	**3a**		−40	32	18 (*S*)[c,d]	18b
2	**3b**		0	37	23 (*S*)[e]	19
3	**3c**		0	21	12 (*S*)[f]	20
4	**3d**		0	34	26 (*R*)[f]	21
5	**3e**		rt	49	4 (*S*)[f]	22a

[a] These were the lowest temperatures to be able to carry out the reaction.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Daicel Chiralcel OJ).
[d] The corresponding phosphine oxide was obtained in 59% yield with 14% (*S*) ee.
[e] Determined by chiral HPLC analysis (Daicel Chiralcel OJ) of the corresponding phosphine–borane.
[f] Determined by optical rotation.



Scheme 1.

Ph_3P and $TiCl_4$ under mild conditions in good yield. This reaction was found to be a very useful reaction in organic synthesis because of the easy operation, mild conditions and high generalities of substrates. Moreover, it was found that the (*R*)-methyl *p*-tolyl sulfoxide/$TiCl_4$ combination was the effective promoter for the kinetic resolution of several types of racemic phosphines. Further examination of the kinetic resolution is now in progress.

4. Experimental

4.1. General

The starting materials (**1a**, **1b**, **1e**) and reagents, purchased from commercial suppliers, were used after standard purification. Solvents were dried over sodium or molecular sieves, and were distilled before use. The reaction flasks were flame-dried under a steam of argon. Preparative TLC (PTLC) was carried out with Wakogel B-5F. ^{1}H NMR spectra were recorded on a Varian Mercury 300 at 300 MHz using tetramethylsilane as an internal standard. Optical rotations were recorded on a JASCO DIP-360. Analytical HPLC was performed using a Daicel Chiralcel OJ column with the detector wavelength at 254 nm. Sulfoxides (**1c**,[9] **1d**,[10] **1f**,[11] **1g**,[12] **1h**[13]), enantiomerically pure sulfoxides (**2a**,[14] **2b**,[15] **2c**,[13] **2d**,[16] **2e**[17]) and phosphines (**3a**,[18] **3b**,[19] **3c**,[20] **3d**,[21] **3e**[22]) were prepared according to the literature procedures. $TiCl_4$ was used as a 3 mol/L solution in hexane.

4.2. General procedure for the deoxygenation of sulfoxide

To a solution of sulfoxide (0.20 mmol) and $TiCl_4$ (0.3 mmol) in THF (2.5 mL) was added a solution of triphenylphosphine (0.24 mmol) in THF (1.5 mL) and the mixture was stirred at appropriate temperature under an argon atmosphere. The reaction was quenched with saturated sodium hydrogencarbonate (10 mL), and the mixture was extracted with ether (3×10 mL). The combined ether layers were washed with brine (1×10 mL) and dried over Na_2SO_4. This organic layer was filtered and evaporated under reduced pressure, and then the crude product was purified by preparative TLC to give the corresponding sulfide. All sulfides are known compounds and were characterized by a comparison of their spectral data with those of authentic samples prepared or those from the literature (Table 1).[9–11,23,24]

4.3. General procedure for kinetic resolution

To a solution of (*R*)-methyl *p*-tolyl sulfoxide (0.12 mmol) and $TiCl_4$ (0.15 mmol) in THF (2 mL) was added a solution of racemic phosphine (0.2 mmol) in THF (1 mL) and the mixture was stirred at appropriate temperature under an argon atmosphere. The reaction was quenched with aqueous 1 N NaOH (10 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4. This organic layer was filtered and evaporated under reduced pressure, and then the crude product was purified by preparative TLC to give the desired chiral phosphines. Absolute configurations and enantiomeric excess of all products were determined by a comparison of their optical rotation or HPLC analysis with those of the literature (Table 2).[18b–22a]

4.3.1. (*S*)-Methyl(1-naphthyl)phenylphosphine (3a). The enantiomeric excess was determined as 18% by an HPLC analysis using chiral column: Daicel Chiralcel OJ, hexane: 2-propanol=93:7, 0.6 mL/min, 10.3 min (*R*), 13.9 min (*S*). The absolute configuration was determined as *S* by a comparison of their optical rotation with that of the literature.[25]

4.3.2. (*S*)-Methyl(1-naphthyl)phenylphosphine oxide.[18b] The enantiomeric excess and absolute configuration were determined as 14% (*S*) by an HPLC analysis using chiral column: Daicel Chiralcel OJ, hexane:2-propanol=90:10, 0.6 mL/min, 19.4 min (*S*), 24.0 min (*R*).

4.3.3. (*S*)-2-Methoxyphenyl(methyl)phenylphosphine (3b). The enantiomeric excess and absolute configuration were determined as 23% (*S*) by an HPLC analysis of the corresponding phoshphine–borane using chiral column: Daicel Chiralcel OJ, hexane:2-propanol=90:10, 0.5 mL/min, 17.2 min (*S*), 32.9 min (*R*).[18b]

4.3.4. (*S*)-(2-Methoxy-1-methylethyl)diphenylphosphine (3c). The enantiomeric excess was determined as 12% by an optical rotation; $[\alpha]_D=-2.8$ (*c* 0.432, CH_2Cl_2). Lit;[20] $[\alpha]_D=+23.5$ (*c* 1, CH_2Cl_2) of an (*R*)-isomer.

4.3.5. (*R*)-[2-(*N*,*N*-Dimethylaminomethyl)ferrocenyl]diphenylphosphine (3d). The enantiomeric excess was determined as 26% by an optical rotation; $[\alpha]_D=+84$ (*c* 0.3, $CHCl_3$). Lit;[21] $[\alpha]_D=+324$ (*c* 0.5, $CHCl_3$).

4.3.6. (*S*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (3e). The enantiomeric excess was determined as 4% by

an optical rotation; $[\alpha]_D = -8.5$ (*c* 0.15, benzene). Lit;[22a] $[\alpha]_D = -229$ (*c* 0.31, benzene).

Acknowledgements

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Diels–Alder reactions of highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives: further chemistry of pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{4,9}]dodeca-5,8,11-triene

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Abstract—A study of the trapping of highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives (generated from a 1,2-diiodo precursor on reaction with *t*-BuLi, 0.45% sodium amalgam and molten sodium) with different dienes (11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene, 1,3-diphenylisobenzofuran, 2,5-dimethylfuran and furan) is presented. Byproducts from the trapping of pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{4,9}]dodeca-5,8,11-triene with 1,3-diphenylisobenzofuran have been synthesized and fully characterized, including an X-ray diffraction analysis. Also, the above triene has been cross coupled with 3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1(5)ene to give a tetrasecododecahedratetraene derivative.

1. Introduction

We have described the generation of highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives (**1**) (Fig. 1) from 1,2-diiodo precursors (**5**) by reaction with molten sodium in boiling 1,4-dioxane, a reaction that usually gives diene dimers (**3**) via cyclobutane dimers (**2**).[1] As byproducts, dihydrodimers (**7**) and products derived from the addition of the pyramidalized alkene to the solvent (**4**), have been observed.[2] To trap these alkenes as Diels–Alder adducts,

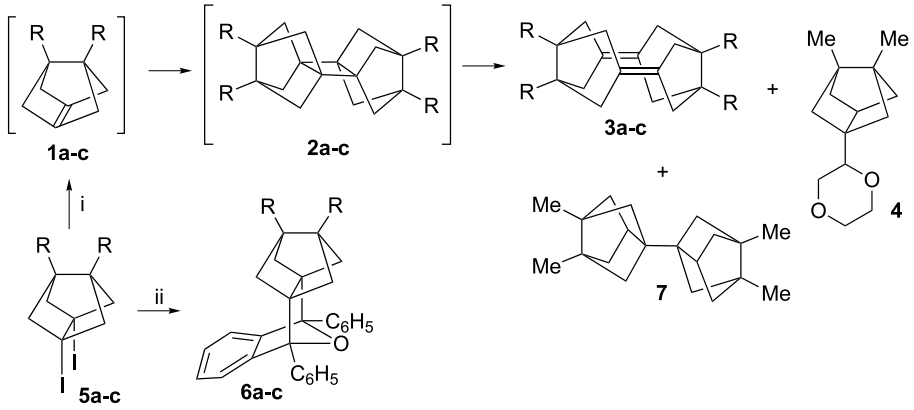

Figure 1. Reactivity of highly pyramidalized alkenes **1a–c**. a, R=H; b, R=Me; c, R,R=–OC(CH$_3$)$_2$O–. (i) molten sodium, 1,4-dioxane, reflux; (ii) *t*-BuLi, 1,3-diphenylisobenzofuran, **8**, THF, −78 °C.

Keywords: Cage compounds; Pyramidalized alkenes; Diels–Alder reaction; DFT calculations.
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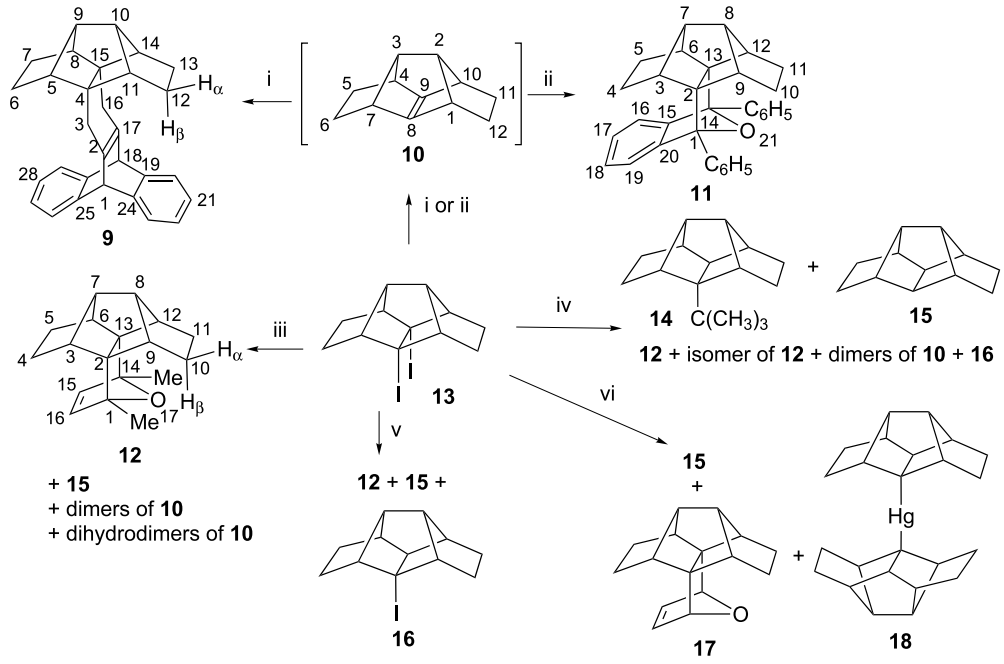


Scheme 1. (i) 0.45% Na(Hg), 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene (**19**), 1,4-dioxane, room temperature, 44%; (ii) 0.45% Na(Hg), **8**, 1,4-dioxane, room temperature, 61%; (iii) molten Na, 2,5-dimethylfuran (**20**), 1,4-dioxane, reflux, 26% **12**; (iv) **20**, *t*-BuLi, hexanes/THF, −67 °C; (v) 0.45% Na(Hg), **20**, room temperature, **12**: 21%. (vi) 0.45% Na(Hg), furan (**21**), room temperature, 30%.

reactive dienes such as 1,3-diphenylisobenzofuran (**8**) and 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene (**19**) have usually been employed. The pyramidalized alkene is generated in these cases by reaction of the 1,2-diiodide **5** with *t*-BuLi in anhydrous THF at low temperature (dry ice–acetone bath). A small excess of the reactive diene (20%) is enough to obtain good yields of the corresponding Diels–Alder adducts. In the last reactions, the pyramidalized alkene is not generated by reduction of the diiodide **5** with molten sodium to prevent the reduction of the dienes. The generation of other highly pyramidalized alkenes by reaction of 1,2-dihalides with sodium amalgam have also been described.[3] However, these conditions are not adequate for the preparation of diene dimers of alkenes **1**, probably because of the low concentration of the highly pyramidalized alkene present in the reaction medium at a given moment.[4]

2. Results and discussion

In this article we describe the trapping of three tricyclo[3.3.0.$0^{3,7}$]oct-1(5)-ene derivatives (alkenes **1b**, **10** and **26**, Figure 1 and Schemes 1 and 3, respectively) with different dienes (reactive dienes such as **8** and **19**, or much less reactive dienes, such as 2,5-dimethylfuran (**20**) and furan (**21**)), generating the pyramidalized alkenes from 1,2-diiodides under different reaction conditions, depending on the kind of diene used. Also, further chemistry of pentacyclo[6.4.0.$0^{2,10}$.$0^{3,7}$.$0^{4,9}$]dodeca-5,8,11-triene, **26**, such as its cross coupling with **1b** to give tetrasecododecahedratetraene derivative **31** is described.

First, the reactivity of pyramidalized alkene **10** was studied (Scheme 1). Reaction of diiodide **13** with 0.45% sodium amalgam in the presence of diene **8** (20% molar excess) gave the Diels–Alder adduct **11** in 61% yield.

When the above reaction was carried out in the presence of diene **19** (20% molar excess), instead of **8**, a mixture containing mainly the expected Diels–Alder adduct **9** and starting diene **19** was obtained. This mixture was reacted with a slight excess of maleic anhydride to transform diene **19** into the corresponding more polar Diels–Alder adduct. From the new mixture, **9** could be easily isolated (43% yield) by column chromatography on elution with hexane. The yield of **9** is somewhat lower than that of **11**, what may be indicative of the lower reactivity of diene **19** as compared with **8**.

The trapping of the pyramidalized alkene **10** with a much less reactive diene, 2,5-dimethylfuran (**20**), was studied under different reaction conditions. Reaction of diiodide **13** with molten sodium in boiling 1,4-dioxane in the presence of a huge excess of diene **20** gave a mixture containing mainly the expected Diels–Alder adduct **12** (45.6% area ratio (a.r.) by GC/MS), together with the known reduction product **15**[5] (13.8% a.r.). Two dimers and three dihydrodimers of **10** (22.7% global a.r.) of unknown structure and a small amount of the starting diiodide **13** (2.8% a.r.) were also observed. From this mixture, adduct **12** could be obtained in low yield (26%) by column chromatography. Alternatively, reaction of diiodide **13** with 0.45% sodium amalgam at room temperature, using diene **20** as the solvent, gave a mixture containing mainly the reduction product **15** (22.2% a.r.), the known monoiodo product **16**[6] (32.3% a.r.) and adduct **12** (23.8% a.r.). Two products, whose molecular ion ($M^{\cdot+}$ = 190) suggest them to be dimers—2H of **20** (3.2 and 14.3% a.r.'s), were also detected. Adduct **12** could be isolated from this mixture by column chromatography in 21% yield. Finally, reaction of diiodide **13** with *t*-BuLi in

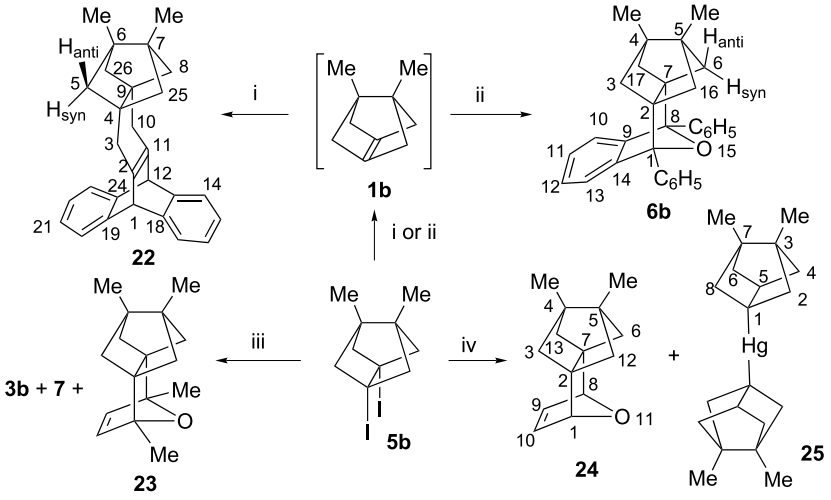
anhydrous THF in the presence of a slight excess of **20** (33% molar excess) gave a mixture containing mainly the known product **14**[5] (31.8% a.r. by GC/MS), derived from the addition of *t*-BuLi to alkene **10** followed by hydrolysis, two dimers of **10** of unknown structure (38.6% global a.r.) and the expected Diels–Alder adduct **12** (14.2% a.r.). When the above reaction was carried out in the presence of a huge excess of diene **20** and 2 equiv of *t*-BuLi, the obtained mixture contained the following components (% a.r. by GC/MS): diiodide **13** (39.2% a.r.) together with the reduction product **15** (3.5%), **14** (10.6%), adduct **12** (26.0%) plus an isomer of **12** (11.2%). When a greater excess of *t*-BuLi (4 equiv) was used in the above reaction, a mixture containing the following components (% a.r.) was obtained: **13** (35.6%), **15** (2.6%), **14** (3.7%), iodide **16** (16.4%), adduct **12** (11.1%), isomer of **12** (19.0%). These results suggest that *t*-BuLi is reacting with diene **20**. In fact, the isomer of **12**, formed in increasing amounts on increasing the amounts of diene **20** and *t*-BuLi, might reasonably be a product formed by addition of 2,5-dimethyl-3-furyllithium to alkene **10**, followed by hydrolysis. No attempts were made to separate these complex mixtures.

For the trapping of alkene **10** with furan (**21**), diiodide **13** was reacted with 0.45% sodium amalgam at room temperature using **21** as the solvent. From this reaction, a mixture containing mainly the expected adduct (**17**) (49.4% a.r. by GC/MS), the known reduction product **15**[5] (17.3% a.r.) and a product whose MS spectra suggests it to be the dialkylmercury derivative **18** (28% a.r.) was obtained. From this mixture, adduct **17** could be obtained in 30% yield by distillation under reduced pressure. Although we were not able to isolate compound **18**, its structure is closely related to that of compound **25**, obtained from diiodide **3b** under similar reaction conditions, a compound that could be isolated in very low yield and characterized by ^{1}H NMR and HRMS (Scheme 2). The use of molten sodium in boiling 1,4-dioxane to trap pyramidalized alkenes with furan was not considered due to the volatility of this diene. Also, the use of *t*-BuLi in this reaction was considered not adequate since it is known that furan can be readily lithiated by organolithium reagents.[7]

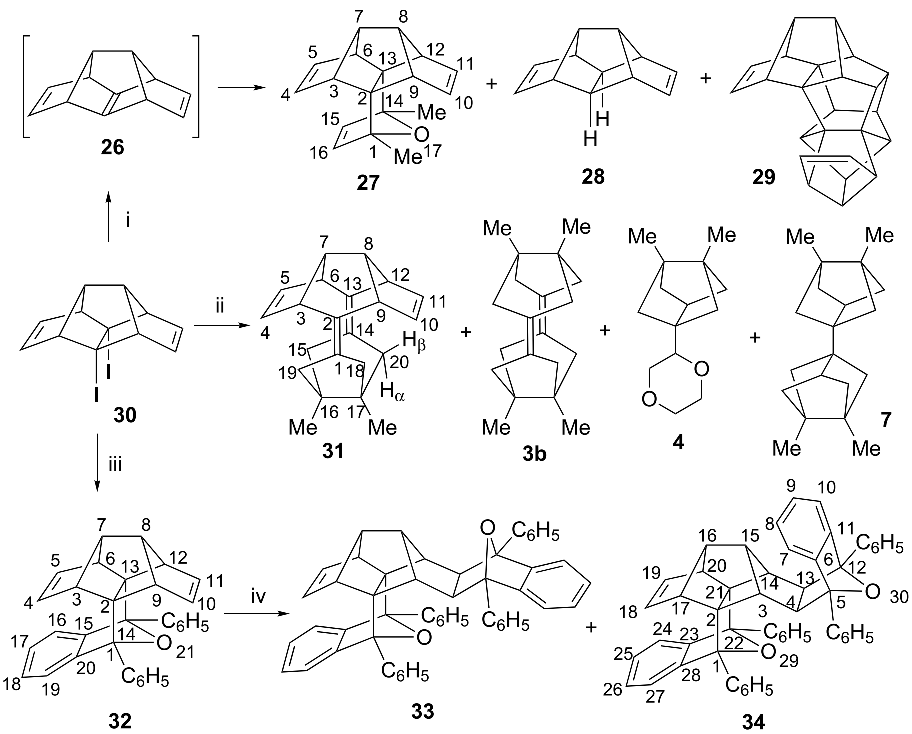
We had previously described the trapping of alkene **1b**, generated from diiodide **5b** by reaction with *t*-BuLi in anhydrous THF, with the reactive dienes **8** and **19** and had isolated the corresponding Diels–Alder adducts **6b** and **22** in good yields. When diiodide **5b** was reacted with 0.45% sodium amalgam in anhydrous 1,4-dioxane in the presence of a slight excess (20% molar) of dienes **8** and **19**, the corresponding adducts **6b** (68% yield) and **22** (43% yield) were isolated, as described before for adducts **8** and **9**, respectively (Scheme 2). The yields of these reactions are somewhat lower than those obtained by using *t*-BuLi to generate the intermediate pyramidalized alkene **1b** (75% for **6b** and 67% for **22**).[1a] As before, the trapping of **1b** with diene **19** (43%) seems to be less effective than its trapping with diene **8** (68%).

For the trapping of **1b** with diene **20**, diiodide **5b** was reacted with molten sodium in boiling dioxane in the presence of a huge excess of diene. After the workup, a mixture containing mainly the expected Diels–Alder adduct **23** (87.8% a.r. by GC/MS) was obtained. Minor amounts of the known compounds **7** (7.0% a.r.) and **3b** (2.6% a.r.) were also observed by GC/MS. From this mixture, pure **23** (21% yield) was isolated by distillation. As before, when diiodide **5b** was reacted with 0.45% sodium amalgam using furan as the solvent, a mixture containing the expected adduct **24** (52.3% a.r.) and the bis-alkyl-mercury product **25** (22.2% a.r., respectively) was obtained. From this mixture, pure adduct **24** (38% yield) and a minimum amount of pure **25** (1% yield) were obtained by column chromatography and further purification by crystallization, in the last case.

We also performed the reaction of diiodide **30** with molten sodium in boiling 1,4-dioxane in the presence of a huge excess of diene **20** (Scheme 3). The crude reaction mixture was analyzed by GC/MS and showed to contain the expected adduct **27** (71.4% a.r.) as the main product together with the known reduction product **28**[8] (21.4% a.r.) and the known dimer **29**[9] (2.7% a.r.), derived from the pyramidalized alkene **26**. Pure **28** (20% yield) was isolated from this mixture by distillation. Sublimation of the residue of this distillation gave pure **27** (12% yield).



Scheme 2. (i) 0.45% Na(Hg), **19**, 1,4-dioxane, room temperature, 43%; (ii) 0.45% Na(Hg), **8**, 1,4-dioxane, room temperature, 68%; (iii) molten Na, **20**, 1,4-dioxane, reflux, 21%; (iv) 0.45% Na(Hg), **21**, room temperature, **24**: 38%, **25**: 1%.



Scheme 3. Reactivity of highly pyramidalized **26**. (i) **20**, molten Na, 1,4-dioxane, reflux, 27%; (ii) **3b**, ratio **30**/**3b** = 1:5, molten Na, 1,4-dioxane, reflux, **31**: 25%; (iii) *t*-BuLi, *n*-pentane, THF, **8**, −67 °C, 63%; (iv) **8**, toluene, reflux, **33**: 54%; **34**: 5%.

The yield of the Diels–Alder adducts in the above reactions seems to depend mainly on the reactivity of the diene, better yields being obtained with reactive dienes (**8** and **19**) than with poorly reactive dienes (**20** and **21**). The lower reactivity of the last dienes may be partially compensated by using them in huge excess. The choice of the reducing agent is mainly dictated by the stability of the diene under the specific reduction conditions. Thus, molten sodium is not a convenient reducing agent when dienes **8** and **19** are used since both can be reduced under these conditions. Similarly, *t*-BuLi is not a convenient reagent when using furan or 2,5-dimethylfuran as dienes. The more general reducing agent seems to be sodium amalgam, although the yields of the adducts with reactive dienes are somewhat lower than those obtained using *t*-BuLi.

Ab initio and DFT calculations show that the HOMO/LUMO energy gap in pyramidalized alkenes is much lower than in normal alkenes.[4,10,11] This is due to a slight increase of their HOMO energy and to a high decrease of their LUMO energy, due to two factors: (a) pyramidalization of the carbon atoms, which reduces the energy of both HOMO and LUMO orbitals and (b) reduced overlapping of the hybridized atomic orbitals, which increases the energy of the HOMO, but reduces the energy of the LUMO. TCSCF/6-31G(d)//HF/6-31G(d) calculations show a low contribution of a diradical resonance structure in highly pyramidalized alkenes, which in the case of tricyclo-[3.3.0.0^{3,7}]oct-1(5)-ene derivatives (pyramidalization angle, $\Phi = 61.7°$) is around 11%, much lower than the values calculated for anti-Bredt alkenes, such as homocubenes (around 57% diradical character) and dehydroquadricyclanes (around 60% diradical character).[12,13] However, UB3LYP/6-311+G(3df,2p) calculations gives for tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene a $\langle S^2 \rangle = 0$, clearly indicating absence of diradical character. On the other hand, UB3LYP/6-311+G(3df,2p) calculations show that the energy of tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene in its diradical triplet state is 13.8 kcal/mol higher than that in its ground state. So, an initially formed hypothetical triplet 1,2-diradical species should reasonably turn into its ground state.

Although, the nature of the initially formed reactive species generated from a 1,2-diiodide on reaction with *t*-BuLi, sodium amalgam or molten sodium could be different, it seems reasonable that the same species, the pyramidalized alkene, is implied in the formation of the ‘Diels–Alder’ adducts.

The formation of much of the byproducts detected in the trapping reactions of pyramidalized alkenes with different dienes using molten sodium or sodium amalgam may be explained by electron transfer from the metal to the intermediate pyramidalized alkene to give a radical anion. Then: (a) hydrogen transfer followed by protonation would give reduction products, such as **15** or **28**; (b) coupling with mercury followed by protonation would give bis-alkylmercury derivatives, such as **18** or **25**; (c) dimerization followed by protonation would give dihydrodimers, such as **7**. The detection of a significant amount of the monoiodo compound **16** in the reaction of diiodide **13** with sodium amalgam in the presence of diene **20**, is indicative of stepwise reduction of the diiodo derivatives with the reasonable formation of intermediate monoiodo radicals, which by hydrogen abstraction would give monoiodo compounds, such as **16**. The formation of dimers of the pyramidalized alkene or of compound **4** does not require the

reduction of the alkene. The formation of products such as **14** in the reaction of diiodide **13** with *t*-BuLi is well documented.[14]

Moreover, we had previously described the reaction of diiodide **30** with *t*-BuLi in the presence of diene **8**, and had obtained the adduct **32**.[9] In one batch of the above reaction we isolated a minor amount of a compound that seemed to be a product derived from the reaction of **32** and diene **8**. Its formation would imply a new Diels–Alder reaction of diene **8** with a simple olefin. However, it is known that 2-norbornene and related compounds may participate as dienophiles in Diels–Alder reactions.[15] To obtain enough amount of this product for its full characterization, we carried out a reaction between adduct **32** and diene **8** (20% molar excess) in toluene under reflux. From this reaction we isolated the main component by column chromatography, which was fully characterized by spectroscopic means, including an X-ray diffraction analysis, as adduct **33** (54% yield).[16]

A second fraction contained a mixture of **33** and another adduct (**34**) and a third fraction contained a mixture of **34** and products of double condensation. From the last fraction, part of **34** and all of the double reaction product precipitated on crystallization from *n*-pentane. The mother liquors from this crystallization contained pure **34** which was isolated by evaporation of the solvent (5% isolated yield) and fully characterized by spectroscopic means including NOESY, $^{1}H/^{1}H$ COSY and $^{1}H/^{13}C$ HETCOR [one bond (hsqc sequence) and long range (hmbc sequence)] experiments and HRMS.

Worthy of note, the stereochemistry of adduct **34** is clearly deduced from the ^{1}H NMR spectrum in which the signal of 15-H appears at δ −0.62 ppm, 3.01 ppm upfield shifted with respect to 16-H of **34** and 3.18 ppm upfield shifted with respect to 15-H of **33**, an effect that is due to the proximity of 15-H to the benzene ring defined by the atoms C6 to C11.[17] Preferential formation of adduct **33**, i.e. (a) selectivity for the C═C double bond closer to the oxygen atom of **32**, (b) *exo*-stereoselectivity of the dienophile and (c) *exo*-approach of diene and dienophile, may be easily explained on steric grounds.

As it was previously observed in a related case,[2b] the ^{1}H and ^{13}C NMR spectra of compounds **33** and **34** are temperature dependent due to the slow rotation of the 1(22)-phenyl groups around the C_{ipso}–C1(22) bonds. At 298 K, the H_{ortho}, H_{meta}, C_{ortho} and C_{meta} atoms of the 1(22)-phenyl groups appear as broad signals. At 248 K the ^{1}H NMR spectra of **33** showed two doublets for the H_{ortho} and two pseudotriplets for the H_{meta} protons of those phenyl groups. At 313 K these protons appear as a broad signal, but the complexity of the spectra in the aromatic region precluded a precise determination of the coalescence temperature. A similar situation was also observed in the ^{1}H NMR spectra of **34**.

As a matter of fact, the byproduct isolated in the preparation of **32** so far described coincides with **34**, the minor Diels–Alder adduct of the present reaction.

Finally, to extend the reactivity of the pyramidalized alkene **26**,[9] we performed its cross coupling with another pyramidalized alkene (**1b**). A mixture of diiodides **30** and **3b** in the ratio of 1:5 was reacted with molten sodium in boiling 1,4-dioxane obtaining a crude product containing the tetraene cross product **31**, the known diene dimer **3b**,[1a] dihydrodimer **7**[2] and the addition product of alkene **1b** and 1,4-dioxane (**4**)[2] (21.0:47.0:14.0:7.0 a.r.'s, respectively, by GC/MS). Column chromatography of this mixture allowed the isolation of pure **31** (25% yield) and pure **7** (10% yield from **5b**). Other fractions contained mixtures of products that could not be fully separated.[18]

Compound **31** is a tetrasecododecahedratetraene derivative that was fully characterized by spectroscopic means and HRMS. Figure 2 shows the minimum energy conformation calculated for **31** by using B3LYP/6-31G(d) method. The C═C double bonds at positions 1 and 13 are slightly pyramidalized with the following pyramidalization angles [C1(14), 12.5°; C2(13), 12.8°], the distance between C1 and C14 (2.957 Å) being longer than that between C2 and C13 (2.901 Å). Moreover, the minimum energy conformation of **31** belongs to the C_{2v} symmetry point group.

All of the new compounds herein described were fully characterized by spectroscopic means (IR, ^{1}H and ^{13}C NMR, MS) and elemental analysis or HRMS. Assignments given for the NMR spectra are based on DEPT, COSY $^{1}H/^{1}H$, HETCOR $^{1}H/^{13}C$ (HSQC and HMBC sequences for one bond and long range heterocorrelations, respectively) and NOESY experiments for selected compounds.

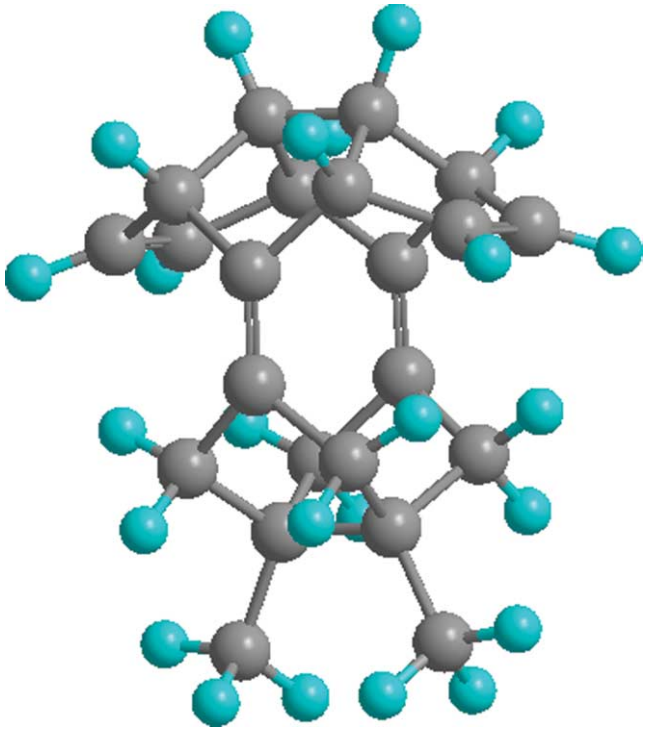


Figure 2. C_{2v} Minimum energy conformation [B3LYP/6-31G(d)] of tetrasecododecahedratetraene, **31**.

3. Conclusions

In conclusion, highly pyramidalized alkenes can be generated and trapped as Diels–Alder adducts with different kind of dienes, by reaction of 1,2-diiodides with *t*-BuLi, molten sodium or sodium amalgam in the presence of the diene. Most of the byproducts isolated from these reactions suggest that the pyramidalized alkene can be further reduced by molten sodium or sodium amalgam. A tetrasecododecahedratetraene (**31**) has been obtained in a convergent way by cross coupling of two highly pyramidalized alkenes (**1b** and **26**).

4. Computational details

All quantum-mechanical calculations were carried out at Becke's three-parameter hybrid functional with the Lee, Yang and Parr correlation functional (B3LYP) level[19] using the 6-31G(d) basis set for **31** and the 6-311+G(3df,2p) basis set for **1a**, as implemented in Gaussian 03 on a Compaq HPC320 computer.[20] Geometry optimizations were undertaken using appropriate symmetry constraints and default convergence limits. The minimum energy nature of the optimized structures was verified from vibrational frequency analysis (Fig. 3).

5. Experimental

5.1. General

Melting points were determined with a MFB 595010 M Gallenkamp melting point apparatus. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ in the following spectrometers: ^{1}H NMR (500 MHz, Varian VXR 500), ^{13}C NMR (75.4 MHz, Varian Gemini 300). 600 MHz ^{1}H and 100.5 MHz ^{13}C NMR spectra of compounds **33** and **34** were performed in a Bruker Digital Avance 600 MHz spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to internal tetramethylsilane (TMS). The multiplicity of the signals is: s, singlet; d, doublet; t, triplet, q, quartet, m, multiplet; or their combinations. Diastereotopic methylene protons in tricyclo[3.3.0.0^{3,7}]octane derivatives are referred as H_α/H_β or H_{syn}/H_{anti} as shown in the corresponding structures. IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model 1600; only the more intense absorption bands are given. UV spectra were recorded on a Perkin Elmer Lambda 2 UV/VIS spectrometer. Routine MS spectra were taken on a Hewlett-Packard 5988A spectrometer, the sample was introduced directly or through a gas chromatograph, Hewlett-Packard model 5890 Series II, equipped with a 30-meter HP-5 (5% diphenyl-95% dimethylpolysiloxane) column (conditions: 10 psi, initial temperature: 35 °C (2 min), then heating at a rate of 8 °C/min till 300 °C, then isothermic] and the electron impact technique (70 eV). Only significant ions are given: those with higher relative abundance, except for the ions with higher *m*/*z* values. HRMS were performed on a Micromass Autospec spectrometer. Neutral aluminum oxide (MN), Brockmann activity 1 or silica gel SDS 60 (35–70 μm) was utilized for the standard and flash column chromatography, respectively. NMR and routine MS spectra were performed at the *Serveis Científico-Tècnics* of the University of Barcelona, while high resolution mass spectra and elemental analyses were carried out at the Mass Spectrometry Laboratory of the University of Santiago de Compostela (Spain) and at the Microanalysis Service of the IIQAB (C.S.I.C, Barcelona, Spain), respectively.

5.1.1. Decacyclo[16.6.6.0^{2,17}.0^{4,11}.0^{4,15}.0^{5,9}.0^{8,15}.0^{10,14}.0^{19,24}.0^{25,30}]triaconta-2(17),19,21,23,25,27,29-heptaene (9). Sodium amalgam (0.45%) was prepared by addition of Na (0.30 g, 13 mmol) to mercury (63.7 g). The magnetically stirred mixture was heated with a bunsen flame under an argon atmosphere until sodium melted. The amalgam was allowed to cool to room temperature and a solution of diiodide **13** (412 mg, 1.00 mmol) and 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene (**19**) (276 mg, 1.20 mmol) in anhydrous 1,4-dioxane (7 mL) was added and the mixture was stirred for 24 h at room temperature. The mixture was diluted with diethyl ether (50 mL) and filtered through Celite®, washing the filter content with diethyl ether (2×50 mL). The combined filtrate and washings were concentrated under reduced pressure to give a solid residue (448 mg), containing mainly adduct **9** and the starting diene **19** (GC/MS and ^{1}H NMR) (ratio **9**/**19**=1.2:1 by ^{1}H NMR). The above mixture was reacted with maleic anhydride (80 mg, 0.83 mmol) in refluxing 1,4-dioxane (8 mL) for 5 h. The solution was concentrated to dryness under reduced pressure and the residue (534 mg) was submitted to column chromatography [silica gel (26 g), hexane] to give pure Diels–Alder adduct **9** (170 mg, 44% yield), as a white solid. An analytical sample was obtained by crystallization from a mixture hexane/CH_2Cl_2. Mp 223–224.5 °C; IR (KBr) ν: 2954, 2916, 2872, 2861, 2826, 1456, 1446, 1286, 1203, 1168, 783, 736, 624, 613 cm^{-1}; ^{1}H NMR δ: 0.92 [m, 4H, 6(7,12,13)-H_β], 1.08–1.13 [m, 4H, 6(7,12,13)-H_α], 1.78 [m, 4H, 5(8,11,14)-H], 2.13 [m, 2H, 9(10)-H], 2.14 [s, 4H, 3(16)-H_2], 4.73 [s, 2H, 1(18)-H], 6.91 [m, 4H, 21(22,27,28)-H], 7.23 [m, 4H, 20(23,26,29)-H]; ^{13}C NMR δ: 21.5 [CH_2, C6(7,12,13)], 26.6 [CH_2, C3(16)], 47.5 [CH, C9(10)], 49.2 [C, C4(15)], 56.6 [CH, C1(18)], 58.1 [CH, C5(8,11,14)], 122.2 [CH, C20(23,26,29)], 124.1 [CH, C21(22,27,28)], 141.6 [C, C2(17)], 146.3 [C, C19(24,25,30)]. MS (EI), *m*/*z* (%): 389 (11), 388 ($M^{\cdot+}$, 34), 216 (22), 215 (17), 210 (17), 179 (28), 129 (100). Elemental analysis: calcd for $C_{30}H_{28}\cdot 0.02\ CH_2Cl_2$ (390.25): C 92.39, H 7.24. Found: C 92.27, H 7.30.

5.1.2. 1,14-Diphenyl-21-oxaoctacyclo[12.6.1.0^{2,9}.0^{2,13}.0^{3,7}.0^{6,13}.0^{8,12}.0^{15,20}]henicosa-15,17,19-triene (11). This reaction was carried out in a similar manner to that described for **9**. To the same amount of 0.45% sodium amalgam, diiodide **13** (412 mg, 1.00 mmol), 1,3-diphenylisobenzofuran (**8**) (324 mg, 1.20 mmol) and anhydrous 1,4-dioxane (7 mL) were successively added and the mixture was stirred at room temperature for 24 h under an Ar atmosphere. The mixture was diluted with diethyl ether (50 mL) and filtered through Celite®, washing the filter content with diethyl ether (2×50 mL). The combined filtrate and washings were concentrated under reduced pressure to give a solid residue (475 mg), which crystallized from a mixture hexane/CH_2Cl_2 gave pure adduct **11**

(263 mg, 61% yield), whose spectroscopic data were coincidental with those previously described.[5]

5.1.3. 1,14-Dimethyl-17-oxaheptacyclo[12.2.1.$0^{2,9}$.$0^{2,13}$.$0^{3,7}$.$0^{6,13}$.$0^{8,12}$]heptadec-15-ene (12).

5.1.3.1. By reaction of diiodide 13 with molten sodium in the presence of 2,5-dimethylfuran (20). A solution of diiodide **13** (412 mg, 1.00 mmol) in a mixture of 2,5-dimethylfuran (**20**, 2.2 mL, 20 mmol) and 1,4-dioxane (2 mL) was rapidly added under argon to molten sodium (200 mg, 8.7 mmol) in boiling 1,4-dioxane (4 mL), and the mixture was heated under reflux for 4 h. The reaction mixture was allowed to cool to room temperature and filtered, and the filter content was washed with diethyl ether (3×8 mL). Concentration of the combined filtrate and washings gave a brown oily residue (181 mg), which analyzed by GC/MS showed the presence of the expected Diels–Alder adduct **12** (retention time (r.t.), 23.4 min, 45.6% a.r.] and the known reduction product **15**[5] (r.t. 14.7 min, 13.8% a.r.) as the main components. Minor amounts of two different dimers ($M^{\cdot+}$=316; r.t. 32.3 and 33.2 min) and three dihydrodimers of **10** of unknown structure ($M^{\cdot+}$=318; r.t. 32.4, 32.9 and 33.4 min) (22.7% total a.r.) and starting diiodide **13** (r.t. 26.8 min, 2.8% a.r.) were also detected. Column chromatography of this residue (neutral aluminum oxide (4 g), hexane) gave pure **12** (66 mg, 26% yield). An analytical sample of **12** was obtained as a white solid by crystallization from *n*-pentane. Mp 160–162 °C; IR (KBr) ν: 2932, 2899, 2854, 1461, 1373, 1314, 1301, 1281, 1204, 1132, 1031, 850, 800, 745, 663, 632 cm^{-1}; ^1H NMR δ: 1.24–1.29 [m, 2H, 4(5)-H_β], 1.30–1.40 [m, 2H, 4(5)-H_α], 1.40–1.45 [m, 2H, 10(11)-H_α], 1.47 [s, 6H, 1(14)-CH_3], 1.85–1.95 [m, 2H, 10(11)-H_β], 2.03 [pseudo q, J=2.5 Hz, 2H, 3(6)-H], 2.18 [pseudo q, J=2.5 Hz, 2H, 9(12)-H], 2.31 (dt, J=4.5 Hz, J'=2.5 Hz, 1H, 8-H), 2.35 (dt, J=4.5 Hz, J'=2.5 Hz, 1H, 7-H), 6.31 [s, 2H, 15(16)-H]; ^{13}C NMR (100.5 MHz) δ: 17.0 [CH_3, 1(14)-CH_3], 23.8 [CH_2, C10(11)], 23.9 [CH_2, C4(5)], 48.4 (CH, C8), 52.2 (CH, C7), 53.2 [CH, C3(6)], 53.7 [CH, C9(12)], 65.0 [C, C2(13)], 85.8 [C, C1(14)], 139.9 [CH, C15(16)]; MS (EI), *m*/*z* (%): 255 (22), 254 ($M^{\cdot+}$, 100), 239 [$(M-CH_3)^+$, 29], 226 [$(M-CO)^{\cdot+}$, 19], 225 (18), 212 (18), 211 [$(M-CH_3-CO)^+$, 94], 145 (43), 143 (46), 131 (45) 130 (74), 129 (81), 128 (53), 117 (55), 115 (69), 91 (70). Elemental analysis: calcd for $C_{18}H_{22}O$ (254.37): C 84.99, H 8.72. Found: C 84.99, H 8.77.

5.1.3.2. By reaction of diiodide 13 with Na(Hg) in the presence of diene 20. This reaction was carried out in a similar manner to that described for **9**, starting from the same amount of 0.45% Na (Hg), diiodide **13** (412 mg, 1.00 mmol) and diene **20** (7 mL, 65 mmol). After the same workup, the combined filtrate and washings were concentrated by distillation through a 10-cm Vigreux column and atmospheric pressure and the excess of diene **20** was eliminated by distillation in a rotary microdistillation equipment at 70 °C/20 Torr. The residue (282 mg), analyzed by GC/MS, showed the presence of three main components: the reduction product **15**[5] (r.t. 14.7 min, 22.2% a.r.) the known monoiodo product **16**[6] (r.t. 20.9 min, 32.3% a.r.) and the expected Diels–Alder adduct **12** (r.t. 23.4 min, 23.8% a.r.). Two products (r.t. 16.2 min (3.2% a.r.) and 16.7 min (14.3% a.r.), $M^{\cdot+}$=190), probably dimers of 2,5-dimethylfuran—2H were also observed. Column chromatography [neutral aluminum oxide (2 g), hexane] of this mixture gave pure **12** (53 mg, 21% yield).

5.1.3.3. By reaction of diiodide 13 with *t*-BuLi in the presence of diene 20. To a cold (−67 °C) solution of diiodide **13** (103 mg, 0.25 mmol) and diene **20** (35 μL, 0.33 mmol) in anhydrous THF (4 mL), a solution of *t*-BuLi (1.7 M in *n*-pentane, 0.5 mL, 0.85 mmol) was dropwise added. After 30 min at −67 °C, the mixture was allowed to heat to room temperature, methanol (2 mL) and water (10 mL) were added and it was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to give a yellow oily residue (44 mg), which analyzed by GC/MS showed to be a complex mixture containing a small amount of the expected adduct **12** (r.t. 23.4 min, 14.2% a.r.). Products of molecular mass corresponding to dimers of **10** (r.t. 32.3 min (8.9% a.r.), and 33.2 min (29.7% a.r.), $M^{\cdot+}$=316), the known product **14**,[5] derived from the addition of *t*-BuLi to alkene **10** (r.t. 20.7 min (31.8% a.r.), $M^{\cdot+}$=216), and some starting diiodide **13** (r.t. 26.8 min, 8.7% a.r.) were also observed.

When this reaction was carried out as before, starting from diiodide **13** (412 mg, 1.00 mmol) but using a huge amount of diene **20** (2.2 mL, 20 mmol) in anhydrous THF (2 mL) and some excess of *t*-BuLi (1.5 M in hexanes, 1.33 mL, 2.0 mmol), a mixture (302 mg) was obtained, which analyzed by GC/MS showed the presence of the following main components (% a.r.): **15** (3.5%), **14** (10.6%), **12** (26.0%), isomer of **12** (r.t. 24.6 min, 11.2%) and diiodide **13** (39.2%).

When this reaction was carried out as before, using the same excess of diene **20** and a higher excess of *t*-BuLi (1.5 M in hexanes, 2.7 mL, 4.0 mmol), a mixture (380 mg) was obtained, which analyzed by GC/MS showed the presence of the following main components (% a.r.): **15** (2.6%), **14** (3.7%), **16** (16.4%), **12** (11.1%), isomer of **12** (19.4%) and diiodide **13** (35.6%).

5.1.4. 17-Oxaheptacyclo[12.2.1.$0^{2,9}$.$0^{2,13}$.$0^{3,7}$.$0^{6,13}$.$0^{8,12}$]heptadec-15-ene (17).

This reaction was carried out in a similar manner to that described for **9**, starting from the same amount of 0.45% Na(Hg), diiodide **13** (412 mg, 1.00 mmol) and furan (**21**, 7 mL, 96 mmol). After the workup, a colorless oily residue (213 mg) was obtained, which analyzed by GC/MS showed the presence of the expected Diels–Alder adduct **17** as the main component (r.t. 21.9 min, 49.4% a.r.). The known reduction product **15**[5] (r.t. 14.7 min, 17.3% a.r.) and a product of probable structure **18**, closely related to **25** (r.t. 33.3 min, 28.0% a.r.) were also detected. This residue was distilled on a rotary microdistillation equipment at 70–150 °C/1–2 Torr, to give slightly impure **17** as a white solid (69 mg, 30% approximate yield). An analytical sample of **17** was obtained by crystallization from diethyl ether. Mp 111–112 °C; IR (KBr) ν: 2950, 2939, 2896, 2857, 1461, 1438, 1312, 1294, 1282, 1204, 1151, 1004, 986, 878, 838, 729, 708 cm^{-1}; ^1H NMR δ: 1.22–1.27 [m, 2H, 4(5)-H_β], 1.36–1.42 [complex signal, 4H, 4(5)-H_α and 10(11)-H_α], 1.74–1.79 [m, 2H, 10(11)-H_β], 2.08 [m, 2H, 3(6)-H], 2.18 [m, 2H, 9(12)-H], 2.30 (m, 1H,

8-H), 2.38 (m, 1H, 7-H), 4.50 [s, 2H, 1(14)-H], 6.55 [s, 2H, 15(16)-H]; ^{13}C NMR (100.5 MHz) δ: 23.7 [CH_2, C4(5)], 23.8 [CH_2, C10(11)], 48.1 (CH, C8), 52.8 [CH, C3(6)], 53.0 (CH, C7), 54.1 [CH, C9(12)], 60.9 [C, C2(13)], 78.5 [C, C1(14)], 135.6 [CH, C15(16)]; MS (EI), *m/z* (%): 227 (16), 226 ($M^{\cdot+}$, 94), 225 [$(M-H)^+$, 17], 211 (17), 198 (52), 146 (62), 141 (52), 132 (55) 131 (66), 130 (71), 129 (100), 128 (64), 117 (79), 115 (72), 106 (65), 91 (91), 77 (61), 67 (51). Elemental analysis: calcd for $C_{16}H_{18}O$ (226.32): C 84.91, H 8.02. Found: C 84.95, H 8.10. **18**: MS (EI), *m/z* (%): [520 (0.5), 519 (0.4), 518 (0.4), 517 (0.3) ($M^{\cdot+}$)], 160 (14), 159 [$(C_{12}H_{15})^+$, 100], 158 (30), 131 (32), 129 (32), 117 (75), 91 (33), 79 (31).

5.1.5. 6,7-Dimethyloctacyclo[10.6.6.1^{4,7}.1^{6,9}.0^{2,11}.0^{4,9}.0^{13,18}.0^{19,24}]hexacosa-2(11),13,15,17,19,21,23-heptaene (22). This reaction was carried out in a similar manner to that described for **9**. Starting from the same amount of sodium amalgam, diiodide **5b** (388 mg, 1.00 mmol) and diene **19** (276 mg, 1.20 mmol) in anhydrous 1,4-dioxane (7 mL), after a similar workup, a solid residue (444 mg), containing mainly **22** (r.t. 33.3 min, 65.0% a.r.) and the starting diene **19** (r.t. 23.0 min, 22.0% a.r.) was obtained. As for **9**, the above mixture containing approximately 0.47 mmol of diene **18** was reacted with maleic anhydride (55 mg, 0.55 mmol) in refluxing 1,4-dioxane (8 mL) for 5 h. The solution was concentrated to dryness under reduced pressure and the residue (484 mg) was submitted to column chromatography (silica gel (25 g), hexane) to give pure Diels–Alder adduct **22** (155 mg, 43% yield), whose spectroscopic data were coincidental with those previously described.[1a]

5.1.6. 4,5-Dimethyl-1,8-diphenyl-15-oxahexacyclo[6.6.1.1^{2,5}.1^{4,7}.0^{2,7}.0^{9,14}]heptadeca-9,11,13-triene (6b). This reaction was carried out in a similar manner to that described for **11**, starting from the same amount of 0.45% sodium amalgam, diiodide **5b** (388 mg, 1.00 mmol), diene **8** (324 mg, 1.2 mmol) and anhydrous 1,4-dioxane (7 mL). After a similar workup, a solid residue (501 mg) was obtained, which was submitted to column chromatography (silica gel (50 g), hexane/AcOEt mixtures). On elution with hexane/AcOEt in the ratio of 95:5, pure **6b** (276 mg, 68% yield) was obtained, whose spectroscopic data were coincidental with those previously reported.[1a]

5.1.7. 1,4,5,8-Tetramethyl-11-oxapentacyclo[6.2.1.1^{2,5}.1^{4,7}.0^{2,7}]tridec-9-ene (23). This reaction was carried out in a similar manner to that described for **12** (under Section 5.1.3.1), starting from a solution of diiodide **5b** (388 mg, 1.00 mmol) in diene **20** (2.2 mL, 20 mmol) and molten sodium (190 mg, 8.3 mmol) in boiling 1,4-dioxane (4 mL). After heating the mixture under reflux for 4 h and a similar workup, a brown oily residue (118 mg) was obtained, which analyzed by GC/MS showed the presence of **23** as the main component (r.t. 16.9 min, 87.8% a.r., 45% approximate yield), with **7** (r.t. 22.2 min, 7.0% a.r.) and **3b** (r.t. 25.9 min, 2.6% a.r.) as minor components. This residue was distilled in a rotary microdistillation equipment at 70 °C/2 Torr to give pure **23** as a colorless oil (48 mg, 21% yield). IR (KBr) ν: 2952, 2878, 1475, 1458, 1377, 1284, 1132, 860, 746, 710 cm^{-1}; ^{1}H NMR δ: 1.10 (s, 3H, 4-CH_3), 1.16 (s, 3H, 5-CH_3), 1.21 [m, 2H, 3(13)-H_{syn}], 1.34 [m, 2H, 3(13)-H_{anti}], 1.42 [s, 6H, 1(8)-CH_3], 1.45 [m, 2H, 6(12)-H_{anti}], 1.64 [m, 2H, 6(12)-H_{syn}], 6.20 [s, 2H, 9(10)-H]; ^{13}C NMR (50.3 MHz) δ: 15.9 [CH_3, 1(8)-CH_3], 17.3 (CH_3, 4-CH_3), 17.5 (CH_3, 5-CH_3), 52.1 [CH_2, C3(13)], 52.4 (C, C4), 52.8 (C, C5), 53.2 [CH_2, C6(12)], 65.8 [C, C2(7)], 84.9 [C, C1(8)], 139.9 [CH, C9(10)]. MS (EI), *m/z* (%): 230 ($M^{\cdot+}$, 9), 215 [$(M-CH_3)^+$, 100], 212 (26), 197 (38), 187 (59), 159 (49), 157 (67), 156 (66), 145 (65), 141 (55), 131 (49), 121 (44), 119 (71), 105 (45), 91 (75), 77 (54). Elemental analysis: calcd for $C_{16}H_{22}O$ (230.35): C 83.43, H 9.63. Found: C 83.50, H 9.67.

5.1.8. 4,5-Dimethyl-11-oxapentacyclo[6.2.1.1^{2,5}.1^{4,7}.0^{2,7}]-tridec-9-ene (24) and bis(3,7-dimethyltricyclo[3.3.0.0^{3,7}]-oct-1-yl)mercury (25). This reaction was carried out in a similar manner to that described for **17**. From the same amount of 0.45% sodium amalgam, diiodide **5b** (388 mg, 1.00 mmol) in diene **21** (7 mL, 96 mmol), after a similar workup, a colorless oil (178 mg) was obtained, which analyzed by GC/MS spectrometry showed to contain compounds **24** (r.t. 17.7 min, 52.3% a.r.) and **25** (r.t. 30.2 min, 22.2% a.r.) as the main components. Column chromatography of the above mixture (neutral aluminum oxide (5.4 g), hexane/AcOEt mixtures) gave in order of elution: (a) eluting with hexane: a mixture of products containing **25** (43 mg), and (b) eluting with a mixture hexane/AcOEt in the ratio of 98:2: **24** (77 mg, 38% yield). Pure **25** (3 mg, 1% yield) was obtained from the fraction eluted with hexane by crystallization from MeOH/AcOEt in the ratio of 7:3. The analytical sample of **24** was obtained as a low melting point white solid by distillation on a rotary microdistillation equipment at 55–60 °C/2 Torr. Mp 42–43 °C; IR (KBr) ν: 2966, 2927, 2875, 1477, 1464, 1448, 1304, 1293, 1226, 1037, 994, 930, 888, 852, 774, 722, 697 cm^{-1}; ^{1}H NMR δ: 1.10 (s, 3H, 4-CH_3), 1.15 (s, 3H, 5-CH_3), 1.20 [m, 2H, 3(13)-H_{syn}], 1.39 [m, 2H, 3(13)-H_{anti}], 1.54 [m, 2H, 6(12)-H_{anti}], 1.67 [m, 2H, 6(12)-H_{syn}], 4.64 [s, 2H, 1(8)-H], 6.37 [s, 2H, 9(10)-H]; ^{13}C NMR δ: 17.2 (CH_3, 4-CH_3), 17.3 (CH_3, 5-CH_3), 52.2 (C) and 52.3 (C) (C4 and C5), 52.3 [CH_2, C3(13)], 54.6 [CH_2, C6(12)], 61.2 [C, C2(7)], 78.7 [CH, C1(8)], 135.6 [CH, C9(10)]. MS (EI), *m/z* (%): 202 ($M^{\cdot+}$, 5), 187 [$(M-CH_3)^+$, 14], 169 (10), 160 (10), 159 (34), 147 (65), 146 (50), 145 (50), 133 (38), 131 (50), 119 (67), 117 (48), 105 (41), 91 (100), 79 (41), 77 (50). Elemental analysis: calcd for $C_{14}H_{18}O$ (202.30): C 83.12, H 8.97. Found: C 83.30, H 8.99. Analytical and spectroscopic data of **25**: ^{1}H NMR δ: 1.10 [s, 12H, 3(3′,7,7′)-CH_3], 1.34 (complex signal, 8H) and 1.64 (complex signal, 8H) [2(2′,8,8′)-H_2 and 4(4′,6,6′)-H_2], 2.04 [broad s, 2H, 5(5′)-H]; MS (EI), *m/z* (%): [472 (0.5), 471 (0.3), 470 (0.4), 469 (0.3) ($M^{\cdot+}$)] 135 [$(C_{10}H_{15})^+$, 57], 134 (28), 119 (30), 107 (31), 93 (100), 91 (30), 79 (31). HRMS (CI, CH_4) calcd for $(C_{20}H_{30}{}^{202}Hg)^{\cdot+}$: 472.2054. Found: 472.2053

5.1.9. 1,14-Dimethyl-17-oxaheptacyclo[12.2.1.0^{2,9}.0^{2,13}.0^{3,7}.0^{6,13}.0^{8,12}]heptadeca-4,10,15-triene (27). This reaction was carried out in a similar manner to that described for **12** (under Section 5.1.3.1) starting from molten sodium (190 mg, 8.7 mmol) in boiling 1,4-dioxane (4 mL) and diiodide **30** (408 mg, 1.00 mmol) and diene **20** (2.15 mL, 20 mmol) in 1,4-dioxane (1 mL). After the usual workup, a brown oily residue (167 mg) was obtained, which analyzed by GC/MS showed to contain the expected Diels–Alder

adduct **27** (r.t. 29.1 min, 71.4% a.r.) and the known products **28** (r.t. 13.5 min, 21.4% a.r.)[8,9] and **29** (r.t. 30.1 min, 2.7% a.r.)[9] as the main products. This residue was distilled in a rotary microdistillation equipment giving a fraction distilled at 60 °C/2 Torr, corresponding to **28** (31 mg, 20% yield). The residue of this distillation, sublimed at 80–90 °C/1 Torr, gave **27** as a white solid (29 mg, 12% yield). A second crop of the sublimation contained slightly impure **27** (43 mg). Mp 165.5–167 °C (sublimed); IR (KBr) ν: 3052, 2986, 2951, 1582, 1439, 1374, 1338, 1315, 1239, 1208, 1189, 1175, 1149, 1127, 920, 877, 856, 838, 780, 758, 744, 702 cm^{-1}; ^1H NMR δ: 1.33 [s, 6H, 1(14)-CH_3], 2.59 [dt, J=4.2 Hz, J'=2.8 Hz, 1H, 8-H], 2.66 [dt, J=4.2 Hz, J'=2.8 Hz, 1H, 7-H], 2.70 [dt, J=2.8 Hz, J'=2.0 Hz, 2H, 3(6)-H], 2.98 [dt, J=2.8 Hz, J'=2.0 Hz, 2H, 9(12)-H], 5.52 [t, J=2.0 Hz, 2H, 4(5)-H], 5.70 [s, 2H, 15(16)-H], 6.08 [t, J=2.0 Hz, 2H, 10(11)-H]; ^{13}C NMR (100.5 MHz) δ: 17.0 [CH_3, 1(14)-CH_3], 60.2 [CH, C3(6)], 61.2 (CH, C8), 61.3 [CH, C9(12)], 64.7 (CH, C7), 71.2 [C, C2(13)], 86.4 [C, C1(14)], 132.3 [CH, C4(5)], 133.1 [CH, C10(11)], 139.7 [CH, C15(16)]; MS (EI), m/z (%): 250 ($M^{\cdot+}$, 42), 249 [$(M-H)^+$, 32], 235 [$(M-CH_3)^+$, 50], 207 [$(M-CH_3-CO)^+$, 82], 193 (30), 192 (100), 191 (73), 185 (56), 179 (53), 178 (45), 165 (83), 153 (89), 152 (72), 128 (57), 115 (67). Elemental analysis: calcd for $C_{18}H_{18}O\cdot 0.2\ H_2O$ (253.94): C 85.14, H 7.30. Found: C 85.37, H 7.26.

5.1.10. 16,17-Dimethylheptacyclo[14.2.1.1^{14,17}.0^{2,9}.0^{3,7}.0^{6,13}.0^{8,12}]icosa-4,10-diene (31). A mixture of diiodides **30** (102 mg, 0.25 mmol) and **3b** (485 mg, 12.2 mmol) was rapidly added under argon to molten sodium (280 mg, 12.2 mmol) in boiling 1,4-dioxane (5.1 mL) and the mixture was heated under reflux for 4 h. The reaction mixture was allowed to cool to room temperature, filtered and the filter content was washed with diethyl ether (3×5 mL). Concentration of the combined filtrate and washings gave a brown residue (216 mg), which analyzed by GC/MS showed the presence of the cross diene product **31** (r.t. 30.8 min, 21.0% a.r.) and the known products **3b** (r.t. 25.9 min, 47.0% a.r.),[1a] **7** (r.t. 22.2 min, 14.0% a.r.)[2] and **4** (r.t. 19.6 min, 7.0% a.r.),[2] as the main components. This residue was submitted to column chromatography [neutral aluminum oxide (27 g), hexane]. In order of elution, **7** (17 mg, 10% yield from **5b**), a mixture of **3b**, **7** plus other minor products (53 mg), pure **31** (18 mg, 25% yield from **30**), slightly impure **31** (22 mg) were successively eluted. An analytical sample of **31** was obtained as a white solid by crystallization from *n*-pentane. Mp 115–116 °C; IR (KBr) ν: 3042, 3014, 2960, 2889, 2862, 2828, 1664, 1650, 1464, 1438, 1336, 1261, 1248, 1100, 951, 882, 797, 742 cm^{-1}; UV (*n*-pentane) λ max. 208 nm (ε=8.900). ^1H NMR δ: 1.01 [s, 6H, 16(17)-CH_3], 1.54, [m, 4H, 15(18,19,20)-H_α], 3.02 [m, 2H, 7(8)-H], 3.40 [complex signal, 8H, 15(18,19,20)-H_β and 3(6,9,12)-H], 6.21 [d, J=1.5 Hz, 4H, 4(5,10,11)-H]; ^{13}C NMR (100.5 MHz) δ: 24.7 [CH_3, 16(17)-CH_3], 40.3 [C, C16(17)], 43.5 [CH_2, C15(18,19,20)], 53.0 [CH, C7(8)], 58.6 [CH, C3(6,9,12)], 134.5 [C, C1(14)], 136.2 [CH, C4(5,10,11)], 139.9 [C, C2(13)]. MS (EI), m/z (%): 289 (25), 288 ($M^{\cdot+}$, 100), 273 [$(M-CH_3)^+$, 20], 179 (18), 165 (19), 129 (23), 115 (20), 91 (22). HRMS (EI) calcd for $(C_{22}H_{24})^{\cdot+}$: 288.1878. Found: 288.1865.

5.1.11. (1*R*,2*S*,3*R*,4*S*,5*R*,12*S*,13*R*,14*S*,17*R*,20*S*,21*R*,22*S*)-1,5,12,22-Tetraphenyl-29,30-dioxaundecacyclo[20.6.1.1^{5,12}.0^{2,17}.0^{2,21}.0^{3,15}.0^{4,13}.0^{6,11}.0^{14,21}.0^{16,20}.0^{23,28}]triaconta-6,8,10,18,23,25,27-heptaene (33) and (1*R*,2*S*,3*R*,4*S*,5*S*,12*R*,13*R*,14*S*,17*R*,20*S*,21*R*,22*S*)-1,5,12,22-Tetraphenyl-29,30-dioxaundecacyclo[20.6.1.1^{5,12}.0^{2,17}.0^{2,21}.0^{3,15}.0^{4,13}.0^{6,11}.0^{14,21}.0^{16,20}.0^{23,28}]triaconta-6,8,10,18,23,25,27-heptaene (34). A mixture of compound **32** (42.4 mg, 0.10 mmol) and diene **8** (32.4 mg, 0.12 mmol) in toluene (2 mL) was heated under reflux following the reaction by TLC. After 5 h, the reaction mixture was allowed to cool to room temperature, concentrated to dryness under reduced pressure and the brown residue thus obtained was submitted to column chromatography (neutral aluminum oxide (8 g), mixture of hexane/AcOEt in the ratio of 98:2). In order of elution, adduct **33** (37.1 mg, 54% yield), a complex mixture containing adducts **33** and **34** in the ratio of 1:1 (8.7 mg), and a mixture of adduct **34** and products of double Diels–Alder reaction (15.1 mg) were eluted. The last mixture was crystallized from *n*-pentane. The precipitated solid was shown to be a mixture of **34** and the double Diels–Alder products, while evaporation of the solvent from the mother liquors under reduced pressure gave pure **34** (3.2 mg, 5% yield). The analytical samples of **33** and **34** were obtained by crystallization from *n*-pentane. Analytical and spectroscopic data of **33**: Mp>290 °C (dec.). IR (KBr) ν: 3062, 3024, 2954, 1602, 1497, 1456, 1447, 1302, 984, 934, 886, 768, 746, 701, 668 cm^{-1}; ^1H NMR (600 MHz, 298 K) δ: 2.46 [d, J=3.0 Hz, 2H, 3(14)-H], 2.55–2.56 [complex signal, 4H, 15-H, 16-H, 17(20)-H], 2.75 [s, 2H, 4(13)-H], 4.69 [m, 2H, 18(19)-H], 6.63 [m, 2H, 24(27)-H], 6.69 [m, 2H, 7(10)-H], 6.95–6.99 [complex signal, 8H, 8(9)-H, 25(26)-H, H_{ortho} 5(12)-phenyl], 7.29–7.36 [complex signal, 6H, H_{meta} 5(12)-phenyl and H_{para} 5(12)-phenyl] 7.38–7.70 [complex signal, 10H, Ar-H 1(22)-phenyl]; partial ^1H NMR (600 MHz, 248 K) δ: 7.43 (d, J=7.2 Hz, 2H) and 7.63 (d, J=7.2 Hz, 2H) [H_{ortho} 1(22)-phenyl], 7.48 (pseudo t, J=7.2 Hz, 2H) and 7.57 (pseudo t, J=7.2 Hz, 2H) [H_{meta} 1(22)-phenyl], 7.52 [t, J=7.2 Hz, 2H, H_{para} 1(22)-phenyl]. Partial ^1H NMR (600 MHz, 313 K) δ: 7.51 [broad signal, Ar-H 1(22)-phenyl]. ^{13}C NMR (100.5 MHz) δ: 43.7 (CH, C15), 49.5 [CH, C4(13)], 57.7 [CH, C17(20)], 59.6 [CH, C3(14)], 68.3 [C, C2(21)], 69.2 (CH, C16), 87.8 [C, C1(22)], 90.6 [C, C5(12)], 118.0 [CH, C7(10)], 119.4 [CH, C24(27)], 125.5–126.5 (broad signal, CH) and 126.5–127.2 (broad signal, CH) [C_{ortho} 1(22)-phenyl], 125.9 [CH, C_{ortho} 5(12)-phenyl], 126.0 [CH, C8(9)], 126.3 [CH, C18(19)], 126.6 [CH, C25(26)], 126.8 (CH) and 127.4 (CH) [C_{para} 1(22)-phenyl and 5(12)-phenyl], 127.5–128.5 (broad signal, CH) and 128.5–129.3 (broad signal, CH) [C_{meta} 1(22)-phenyl], 128.0 [CH, C_{meta} 5(12)-phenyl], 137.9 [C, C_{ipso} 5(12)-phenyl], 138.5 [C, C_{ipso} 1(22)-phenyl], 148.6 [C, C23(28)], 149.0 [C, C6(11)]. MS (EI), m/z (%): 695 [$(M+H)^+$, 0.1], 677 [$(M-OH)^+$, 0.3], 424 [$(M-C_{20}H_{14}O)^{\cdot+}$, 1], 271 (23), 270 [$(C_{20}H_{14}O)^{\cdot+}$, 100], 241 (7), 105 (6). Elemental analysis: calcd for $C_{52}H_{38}O_2$ (694.87): C 89.88, H 5.51. Found: C 90.11, H 5.49. Analytical and spectroscopic data of **34**: Mp>255 °C (dec.). IR (KBr) ν: 3061, 3027, 2949, 1602, 1497, 1457, 1448, 1302, 985, 933, 883, 746, 699, 676 cm^{-1}; ^1H NMR (600 MHz, 298 K) δ: −0.62 (dt, J=4.8 Hz, J'=3.0 Hz, 1H, 15-H), 2.39 (dt, J=4.8 Hz, J'=3.0 Hz, 1H, 16-H), 2.49 [d, J=3.0 Hz, 2H, 3(14)-H], 2.62 [m, 2H, 17(20)-H], 3.59 [s, 2H, 4(13)-H], 4.77 [t, J=1.8 Hz, 2H, 18(19)-H], 6.62 [m,

2H, 7(10)-H], 6.72 [m, 2H, 24(27)-H], 6.77 [dd, $J=7.2$ Hz, $J'=1.2$ Hz, 4H, H_{ortho} 5(12)-phenyl], 7.00 [m, 2H, 25(26)-H], 7.08 [m, 2H, 8(9)-H], 7.10 [t, $J=7.8$ Hz, 4H, H_{meta} 5(12)-phenyl], 7.22 [t, $J=7.8$ Hz, 2H, H_{para} 5(12)-phenyl], 7.43 (broad signal, 2H) and 7.69 (broad signal, 2H) [H_{meta} 1(22)-phenyl], 7.53 [t, $J=7.8$ Hz, 2H, H_{para} 1(22)-phenyl], 7.62 (broad signal, 2H) and 7.82 (broad signal, 2H) [H_{ortho} 1(22)-phenyl]; partial ^{1}H NMR (600 MHz, 273 K) δ: 7.43 (t, $J=7.2$ Hz, 2H) and 7.70 (t, $J=7.2$ Hz, 2H) [H_{meta} 1(22)-phenyl], 7.55 [tt, $J=7.5$ Hz, $J'=1.5$ Hz, 2H, H_{para} 1(22)-phenyl], 7.62 (d, $J=7.2$ Hz, 2H) and 7.82 (d, $J=7.2$ Hz, 2H) [H_{ortho} 1(22)-phenyl]; Partial ^{1}H NMR (600 MHz, 323 K) δ: 7.3–7.9 [broad signal, Ar-H 1(22)-phenyl]. ^{13}C NMR (100.5 MHz) δ: 42.8 (CH, C15), 48.3 [CH, C4(13)], 57.6 [CH, C17(20)], 59.2 [CH, C3(14)], 68.8 (CH, C16), 70.0 [C, C2(21)], 87.8 [C, C1(22)], 90.5 [C, C5(12)], 119.5 [CH, C24(27)], 120.1 [CH, C7(10)], 125.2 (CH) and 127.0 (CH) [C_{ortho} 1(22)-phenyl], 126.5 [CH, C18(19)], 126.7 [CH, C25(26)], 126.8 [CH, C8(9)], 127.5 [CH, C_{para} 1(22)-phenyl], 127.7 [CH, C_{para} 5(12)-phenyl], 127.9 [CH, C_{ortho} and C_{meta} 5(12)-phenyl], 128.1 (CH) and 129.6 (CH) [C_{meta} 1(22)-phenyl], 138.3 [C, C_{ipso} 5(12)-phenyl], 138.6 [C, C_{ipso} 1(22)-phenyl], 148.5 [C, C23(28)], 148.7 [C, C6(11)]. MS (CI, CH_4), *m/z* (%): 695 [$(M+H)^+$, 1], 677 [$(M-OH)^+$, 1], 425 [$(M-C_{20}H_{14}O+H)^+$, 4], 271 (63), 270 [$(C_{20}H_{14}O)^{\cdot+}$, 100], 105 (31), 79 (22). HRMS (CI, CH_4) calcd for $(C_{52}H_{38}O_2+H)^+$: 695.2950. Found: 695.2953.

5.2. X-ray crystal-structure determination of 33.[16]

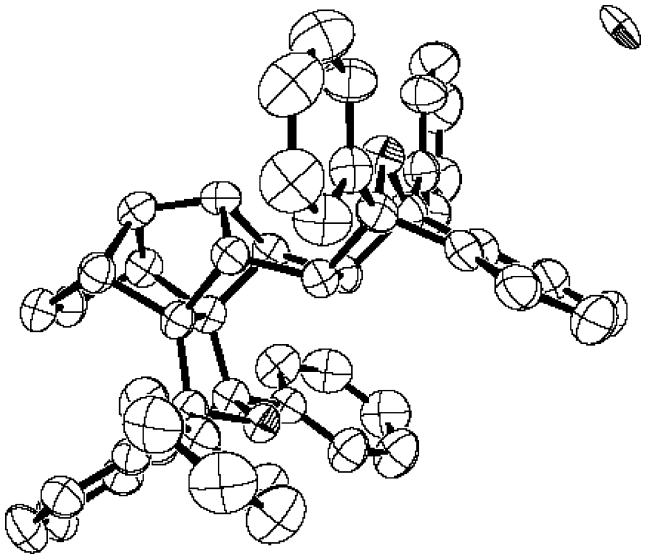


Figure 3. Crystal structure (ORTEP) of adduct **33**. Hydrogen atoms have been omitted to simplify the structure. Water of crystallization is also observed.

A prismatic crystal ($0.1\times0.1\times0.2$ mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from automatic centering of 8622 reflections ($3<\theta<31°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. 14,964 reflections were measured in the range $3.30\leq\theta\leq28.88°$. 2656 of which were non-equivalent by symmetry [R_{int}(on I)=0.050]. 2116 reflections were assumed as observed applying the condition $I>2\sigma(I)$. Lorentz polarization but no absorption corrections were made. The structure was solved by direct methods, using SHELXS computer program[21] and refined by full-matrix least-squares method with SHELX97 computer program,[22] using 2656 reflections (very negative intensities were not assumed). The function minimized was $\Sigma w||F_o|^2-|F_c|^2|^2$, where $w=[\sigma^2(I)+(0.0630P)^2]^{-1}$, and $P=(|F_o|^2+2|F_c|^2)/3$, f, f' and f'' were taken from the literature.[23] The chirality of the structure was defined from the Flack coefficient, which is equal to 2.5(13) for the given results.[24] 38 H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which are linked. The final R(on F) factor was 0.0425, wR(on $|F|^2$)=0.0952 and goodness of fit=0.972 for all observed reflections. Max. shift/esd=0.00, mean shift/esd=0.00. Max. and min. peaks in final difference synthesis was 0.431 and -0.212 e Å^{-3}, respectively. [$C_{52}H_{38}O_2\cdot2(H_2O)$], $M_r=730.86$, orthorhombic, space group $Cmc2_1$, $a=18.3248$ (11), $b=14.5762(9)$, $c=14.6750(10)$, $\alpha=90$, $\beta=90$, $\gamma=90°$, $V=3919.8(4)$ Å^3, $Z=4$, $F(000)=1544$, $\rho_{calcd}=1.238$ g cm^{-3}; crystal dimensions (mm), $0.1\times0.1\times0.2$ mm; μ (Mo Kα) linear absorption coefficient=0.077 mm^{-1}; $T=293(2)$ K; 2656 reflections and 260 parameters were used for the full matrix.

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An efficient method for the synthesis of methyl 11α-amino-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate

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Abstract—The synthesis of methyl 11α-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate, methyl 11β-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate and methyl 11α-amino-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate have been achieved. Mechanistic aspects for the decomposition of steroidal azidoketones to its enamines are discussed.

1. Introduction

Among the numerous HIV-1 protease inhibitors, the most active inhibitors contain hydroxyethylamine or the related carbonyl equivalent. Marples and co-workers have designed[1] novel steroidal inhibitors of HIV-1 protease, having such types of amino-alcohols and amino-ketones namely, 11-amino-12-hydroxy/keto-steroids **1** and **2** based upon bile acids and estra 1,3,5 (10)-trienes, respectively, with the help of X-ray crystallographic data[2] and molecular modeling (Fig. 1). The attempted synthesis of these amino-steroids failed[1] due to problems in the decomposition of α-azidoketones. Such types of decomposition is observed in both alicyclic[3,4] as well as steroidal[1,4–6] α-azidoketones.

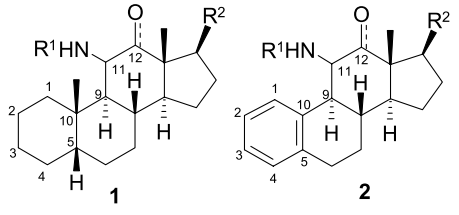

Figure 1. Proposed HIV-1 protease inhibitors.

Steroids with C-11 functionality are crucial for biological activity and are observed in a number of drug molecules including steroid hormones.[7] Stereoselective C-11 functionalization in the steroids is one of the challenging targets for synthetic organic chemists as it involves severe steric interactions caused by the C-18 and C-19 angular methyl groups. In this paper, we wish to report a successful synthesis of methyl 11α-amino-3α,7 α-diacetoxy-12-oxo-5β-cholan-24-oate **18** from the corresponding methyl 11α-azido-3α,7 α-diacetoxy-12-oxo-5β-cholan-24-oate **13** and unstable methyl 11β-azido-3α,7 α-diacetoxy-12-oxo-5β-cholan-24-oate **14**. A generalized mechanism for the decomposition of steroidal azidoketones **13** and **14** is also discussed.

2. Results and discussion

Recently, Marples and co-worker reported[1] the synthesis of a steroidal enamine, methyl 11-amino-3α-benzyloxy-12-oxo-5β-chol-9, 11-en-24-oate **7** from 11α-bromo compound **3**. Compound **3** on treatment with NaN_3 in DMSO at 100 °C for 48 h afforded the steroidal enamine **7** instead of the expected β-azido compound **4** (Fig. 2). They proposed the formation of enamine **7** through the intermediates **4**, **5** and **6** with the expulsion of nitrogen gas. Thus, the synthesis of 11-aminosteroids with a specific stereogenic center at C-11 was not realized by Marples et al. This compound **7** is reported[1] to possess modest activity against HIV-1 protease.

In the course of our studies on the synthesis of steroidal protease inhibitors we prepared methyl 11α-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **10** (71% yield) and

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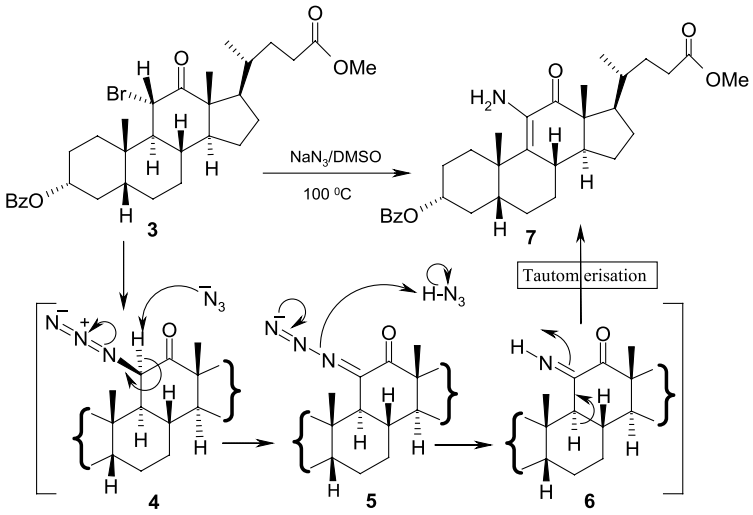
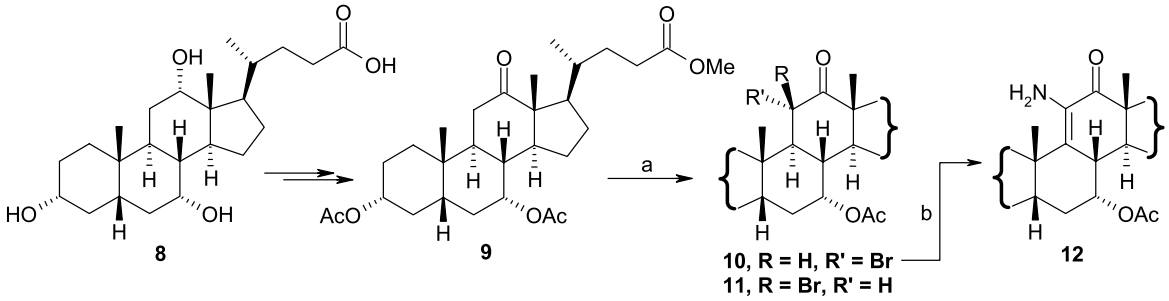


Figure 2. Proposed mechanism for the formation of steroidal enamine **7**.



Scheme 1. Reagents and conditions: (a) Br_2, benzene, 28 °C, 96 h, 95%. (b) NaN_3 (12 equiv), DMF, 100 °C, 48 h, 72%.

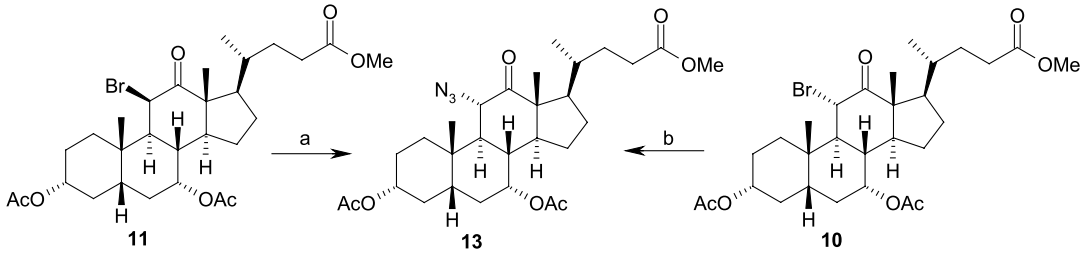
methyl 11β-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **11** (24% yield) from cholic acid **8** following the literature procedures[8–12] (Scheme 1).

Starting from the α-bromo ketone **10** and following the procedure of Marples et al.,[1] using DMF as solvent in place of DMSO we synthesized steroidal enamine, methyl 11-amino-3α,7α-diacetoxy-12-oxo-5β-chol-9, 11-en-24-oate **12** in 72% yield (Scheme 1). However, our main aim was to synthesize the hitherto unknown 11-amino steroids.

Substitutions α to carbonyl groups are known to follow S_N2 mechanism[13,14] and exposure of compound **11** with 5 equiv of NaN_3 in DMF at 28 °C for 8 h furnished the azido compound **13** in 85% yield (Scheme 2). Treatment of epimeric α-bromo compound **10** with 5 equiv of NaN_3 in DMF at 60 °C for 16 h surprisingly resulted in the formation of the same azido compound **13** in 98% yield.

The assignment of the stereochemistry at C-11 of compound **13** was supported by the ^{1}H NMR spectrum in which the C-11 proton appeared as a doublet (δ 4.06 ppm, $J=10.8$ Hz) due to *trans* diaxial coupling between the C-11 and C-9 protons (Table 1). This was confirmed by single crystal X-ray analysis (Fig. 3).

In addition, 11α-bromo-12-keto compound **10** under mild reaction conditions [slight excess of NaN_3 (1.2 equiv) at 60 °C for 4 h] afforded the unstable 11β-azido-12-keto compound **14** in 64% yield (Scheme 3). The assignment of stereochemistry at C-11 of compound **14** was supported by the ^{1}H NMR spectrum in which the C-11 proton appeared as



Scheme 2. Reagents and conditions: (a) NaN_3 (5 equiv), DMF, 28 °C, 8 h, 85%. (b) NaN_3 (5 equiv), DMF, 60 °C, 16 h, 98%.

Table 1. Some representative ^{1}H and ^{13}C NMR spectroscopy chemical shifts

Compound number	^{1}H NMR, δ ppm and coupling constants J in Hz						^{13}C NMR, δ ppm C-12 Carbonyl carbon
	18-CH_3	19-CH_3	21-CH_3	9-H	11-H	1-H_e	
9	1.03	1.03	0.85 d, J=6.0	—	—	—	213.3
10	1.04	1.22	0.86 d, J=5.9	2.79 dd, J=10.7	5.01 d, J=10.7	2.90 dt, J=15.4, 3.0	202.3
11	1.36	1.38	0.93 d, J=6.4	2.64 dd, J=11.7, 5.9	4.42 d, J=5.9	—	203.4
13	1.02	1.15	0.88 d, J=6.4	—	4.06 d, J=10.8	2.48 dt, J=14.6, 3.0	207.0
14	1.25	1.26	0.92 d, J=6.3	—	4.14 d, J=5.5	—	206.7
18	1.01	1.19	0.85 d, J=6.5	—	3.76 d, J=9.3	2.72 dt, J=14.1, 3.0	214.1

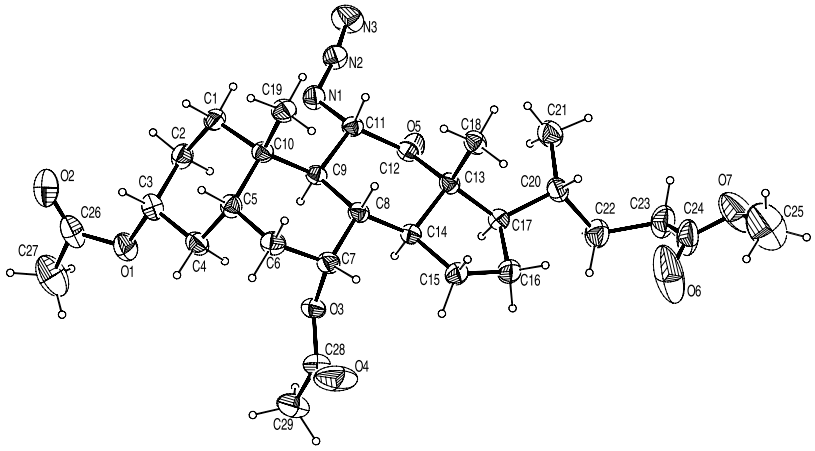


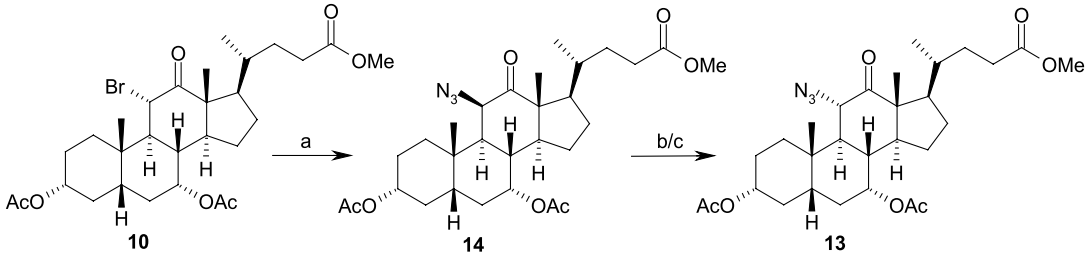
Figure 3. ORTEP[15] view of compound **13**.

a doublet (δ 4.14 ppm, J=5.5 Hz) due to *cis* coupling between the C-11 and C-9 protons (Table 1). The structure of compound **14** was unambiguously confirmed by single crystal X-ray analysis (Fig. 4).

The isolated 11β-azido-12-keto compound **14**, on treatment with 1.2 equiv of NaN_3 in DMF at 60 °C for 9 h furnished the relatively stable 11α-azido-12-keto compound **13** in excellent yield (98%). A similar transformation of compound **14** to compound **13** was observed with KOAc in DMF (Scheme 3). In these cases NaN_3 and KOAc act as a base to promote epimerisation to the more stable compound.[16] However, no epimerisation was observed when compound **14** was treated under similar conditions in DMF alone or in the presence of protic acids such as *p*-toluenesulfonic acid and camphorsulfonic acid. Thus, compound **13** can be obtained via two routes (a) in a single step from 11α-bromo compound **10** following harsh conditions (Scheme 2) or (b) from 11β-azido compound **14** following milder conditions (Scheme 3).

In related work, Heathcock and co-workers prepared the 2α-azidocholestan-3-one **17** from 2α-bromo ketone **15**.[17] When we treated 2α-bromocholestan-3-one **15**[18] with NaN_3 (1.2 equiv) in DMF at 28 °C for 2 h, we isolated the known 2α-azidocholestan-3-one **17** in 89% yield (Scheme 4). We propose the formation of 2α-azidocholestan-3-one **17** from 2α-bromocholestan-3-one **15** by base (NaN_3) catalyzed epimerisation[16] of unisolated 2β-azidocholestan-3-one **16**.

11α-Azido-12-keto compound **13** on catalytic hydrogenation using 10% Pd/C was readily converted into



Scheme 3. Reagents and conditions: (a) NaN_3 (1.2 equiv), DMF, 60 °C, 4 h, 64%. (b) NaN_3 (1.2 equiv), DMF, 60 °C, 9 h, 98%. (c) KOAc (1.2 equiv), DMF, 60 °C, 9 h, 98%.

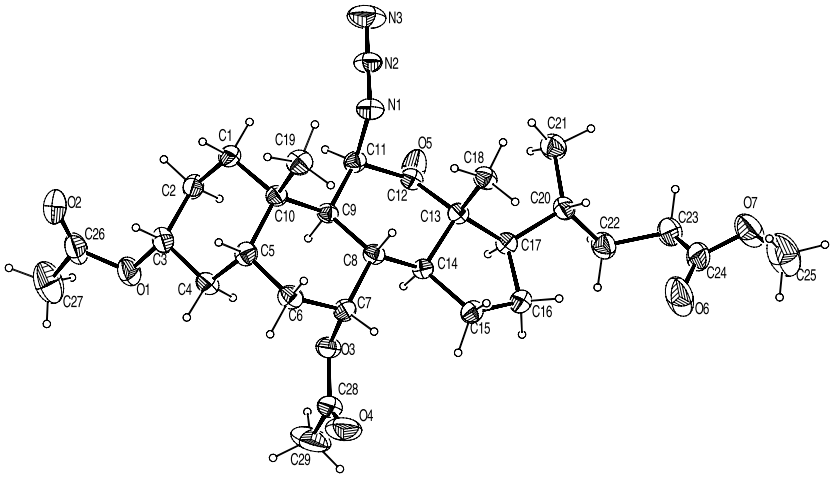
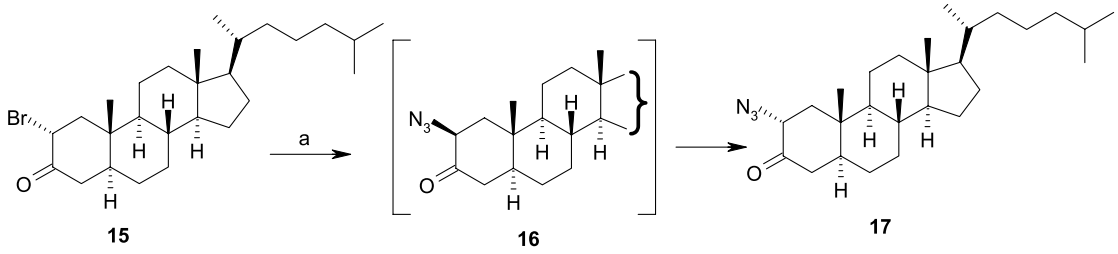


Figure 4. ORTEP view of compound **14**.



Scheme 4. Reagents and conditions: (a) NaN_3 (1.2 equiv), DMF, 28 °C, 2 h, 89%.

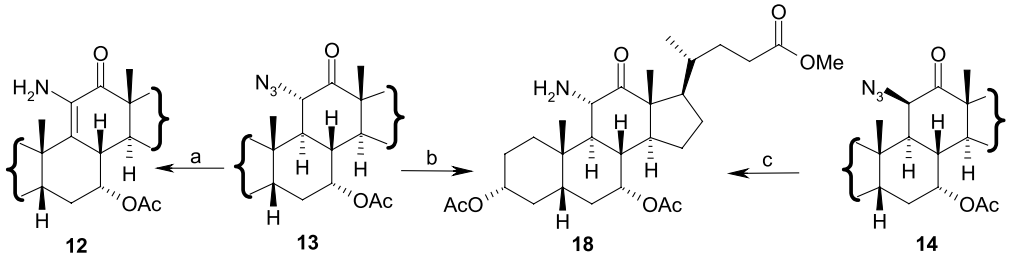
the desired 11α-amino-12-keto compound **18** in 97% yield (Scheme 5).

There was a strong absorption at 3529 cm^{-1} in the IR spectrum of compound **18** attributed to the NH_2 group while in the ^1H NMR spectrum, the C-11 proton appeared as a doublet ($J=9.3$ Hz) at δ_H 3.76 ppm due to *trans* diaxial coupling with the C-9 proton. The structure of 11α-amino-12-keto compound **18** was confirmed by single crystal X-ray analysis (Fig. 5).

Treatment of 11β-azido-12-keto compound **14** with excess of Pd/C and high pressure (40–80 psi) of H_2 in ethanol or ethyl acetate resulted in the recovery of the starting compound **14**. Attempted reduction of the 11β-azide functionality in compound **14** by excess of LAH in THF or dioxane reduced the 3,7 diacetate and 24-methylester functionality with no effect on the 11-azido-12-keto functionality. However, treatment of 11β-azido-12-keto compound **14** with triphenylphosphine in THF[19] followed by aqueous work-up gave the 11α-amino-12-keto compound **18** in 80% yield (Scheme 5). This reaction clearly proceeds with epimerisation.

3. Spectroscopic discussion

Some interesting observations can be made on the ^1H NMR and ^{13}C NMR of the bromo ketones (**10**, **11**), azido ketones (**13**, **14**) and amino ketone **18** with respect to the starting 12-keto compound **9**. Deshielding of C-19 methyl group was observed with 11α-bromo compound **10**, 11α-azido compound **13** and 11α-amino compound **18** in comparison with the starting 12-keto compound **9** (Fig. 6, Table 1). While deshielding effect on both the C-18 and C-19 methyl's was observed with 11β-bromo compound **11** and 11β-azido



Scheme 5. Reagents and conditions: (a) NaN_3 (10 equiv), DMF, 100 °C, 36 h, 67%. (b) H_2/Pd–C, ethyl acetate, 40 psi, 28 °C, 5 h, 95%. (c) PPh_3, THF, H_2O, 28 °C, 48 h, 80%.

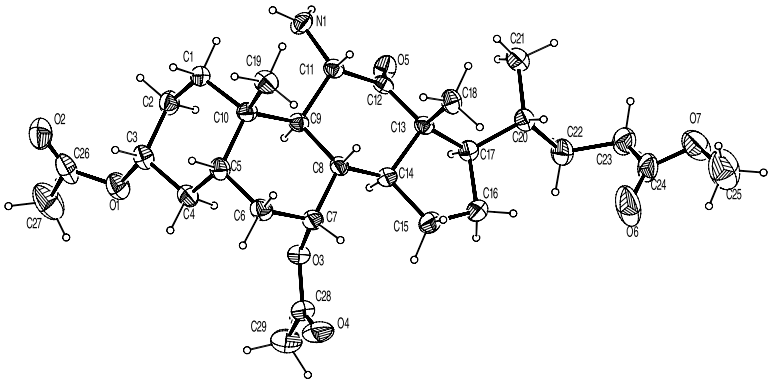


Figure 5. ORTEP view of compound **18**.

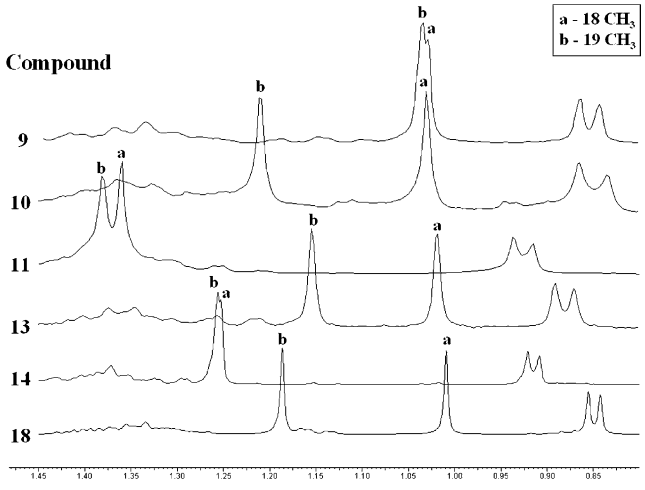


Figure 6. Partial ^{1}H NMR spectra of compounds **9**, **10**, **11** **13**, **14** and **18** showing the effect of C-11 substitution on C-21 and C-18, C-19 angular methyl groups.

compound **14**. These observations showed a pronounced effect of bromine, azide or amine functionality through space on the chemical shifts of C-18 and C-19 methyl protons.

Carbonyl resonance of C-12 in compound **9** appeared at 213.3 ppm. As expected,[20] marked upfield shift (shielding) of about 10 ppm was observed for carbonyl resonances in 11-bromo-12-keto compounds **10** (202.3) and **11** (203.4). Similar type of upfield shift of about 6 ppm was observed for 11-azido-12-keto compounds **13** (207.0) and **14** (206.7).

4. Conclusion

In conclusion, we have demonstrated that 11α-bromo compound **10** on treatment with NaN_3 is converted into 11β-azido compound **14**. In the presence of base, compound **14** epimerized to the thermodynamically more stable 11α-azido compound **13**. Compound **13** on further treatment with NaN_3 under drastic conditions is transformed into the steroidal enamine **12**. The stereoselective synthesis of 11α-amino steroid **18** has been achieved.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded at 500/300 and 125/75 MHz, respectively. Commercially available reagents were used without further purification. All reactions were monitored by TLC with silica gel coated plates; spots were visualized by UV light and/or with dipping in a phosphomolybdic acid solution and charring on a hot plate. Column chromatography was carried out using 60–120 mesh silica gel at atmospheric pressure. Infrared (IR) spectra were recorded in Nujol or $CHCl_3$. Only diagnostic bands are reported on cm^{-1} scale. All concentrations are given in g/100 mL for the optical rotation measurements. Usual work-up means, the organic extract was washed successively with water (2 times), brine (1 time) and dried over Na_2SO_4. Evaporation of the organic extract afforded the crude product, which was purified by column chromatography.

5.1.1. Methyl 3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (9). Compound **9** was synthesized in overall good yield starting from cholic acid **8** using the literature procedures.[21] White solid, mp 178 °C (EtOAc/hexane, lit.[21] mp 178–179 °C); IR and NMR spectroscopic data is consistent with that reported in the literature. δ_C (50 MHz, $CDCl_3$) 11.4, 18.4, 21.3, 21.3, 23.6, 26.5, 27.2, 30.3, 31.1, 31.1, 34.4, 34.8, 35.4, 35.4, 37.5, 37.8, 37.8, 40.5, 46.4, 51.2, 53.0, 57.0, 70.4, 73.4, 170.0, 170.3, 174.2, 213.3.

5.1.2. Methyl 11α-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (10) and methyl 11β-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (11). To a solution of **9** (1.008 g, 2 mmol) in benzene (10 mL), a bromine solution (1 mL, 2 M in benzene) was slowly added with stirring, at 30 °C in the dark. After 4 days, TLC analysis showed the total consumption of the starting material. The reaction mixture was worked up in the usual way to afford the crude product. The residue was chromatographed on silica gel (20% EtOAc/hexane) to yield the β-bromo compound **11** (0.25 g, 24%) as crystalline solid, mp 189 °C (EtOAc/hexane, lit.[12] mp 190–191 °C); $[\alpha]_D^{25} = +19.20$ (*c* 1.25, $CHCl_3$, lit.[12] $[\alpha]_D = +15.9$); IR and NMR spectroscopic data is consistent with that reported in the literature. δ_C (75 MHz, $CDCl_3$) 15.5, 18.1, 21.2, 21.2, 23.7, 24.6, 26.9,

27.3, 30.4, 30.6, 31.1, 33.7, 34.6, 35.6, 35.8, 36.9, 39.9, 43.8, 47.4, 51.3, 52.0, 52.2, 56.3, 70.6, 73.1, 169.6, 170.3, 174.3, 203.4; and α-bromo compound **10** (0.83 g, 71%) as white crystalline solid, mp 220 °C (EtOAc/hexane, lit.[12] mp 223–224 °C). $[\alpha]_D^{25}=+43.3$ (*c* 1.20, $CHCl_3$, lit.[12] $[\alpha]_D=+40.7$); IR and NMR spectroscopic data is consistent with that reported in the literature. δ_C (75 MHz, $CDCl_3$) 10.7, 17.9, 20.8, 20.8, 22.3, 23.7, 26.6, 27.7, 29.8, 30.6, 31.3, 34.8, 35.0, 36.5, 37.5, 37.5, 39.5, 41.7, 46.1, 47.6, 50.8, 50.8, 55.9, 57.6, 70.3, 72.9, 169.4, 170.0, 173.8, 202.3.

5.1.3. Methyl 11-amino-3α,7α-diacetoxy-12-oxo-5β-chol-9, 11-en-24-oate (12) from compound (10). To a solution of methyl 11α-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **10** (0.15 g, 0.257 mmol) in dry DMF (5 mL) was added solid sodium azide (0.2 g, 3.1 mmol). The reaction mixture was stirred at 100 °C for 48 h and it was poured into crushed ice. It was extracted with EtOAc (3×50 mL), washed with cold water (2×25 mL), brine (20 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford crude product. Purification by column chromatography on silica gel (1% MeOH/CH_2Cl_2) produced compound **12** as a yellowish solid (0.096 g, 72%), mp 65–68 °C; [found C, 66.96; H, 8.56; N, 2.74. $C_{29}H_{45}NO_7$ requires C, 67.27; H, 8.39; N, 2.71]; R_f (5% MeOH/CH_2Cl_2) 0.44; $[\alpha]_D^{25}=+20.00$ (*c* 2.5, $CHCl_3$); ν_{max} (Nujol) 3500, 3365, 2923, 1730, 1685, 1604 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.94 (s, 3H, C*H*$_3$-18), 0.99 (d, *J*=6.1 Hz, 3H, C*H*$_3$-21), 1.28 (s, 3H, C*H*$_3$-19), 1.98 (s, 6H, OCOC*H*$_3$×2), 3.64 (s, 3H, COOC*H*$_3$), 4.71 (m, 1H, C*H*-3), 5.00 (m, 1H, C*H*-7); δ_C (125 MHz, $CDCl_3$) 10.3, 19.2, 21.3, 21.3, 23.7, 25.5, 26.6, 27.4, 30.0, 30.5, 31.3, 32.0, 35.2, 35.6, 40.5, 40.7, 42.6, 45.9, 47.8, 51.3, 51.6, 70.6, 73.0, 126.6, 135.3, 170.3, 170.4, 174.5, 202.4; MS (LCMS) *m/z* 541 (M^++23), 519.00 (M^++1) base peak.

5.1.4. Compound (12) from compound (13). To a solution of methyl 11α-azido-3α,7α-diacetoxy-12-keto-5β-cholan-24-oate **16** (0.1 g, 0.183 mmol) in dry DMF (5 mL) was added solid sodium azide (0.12 g, 1.83 mmol). The reaction mixture was then stirred at 100 °C for 36 h. This was further worked up and purified as described above to yield compound **12** (0.064 g, 67% yield).

5.1.5. Methyl 11α-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (13) from compound (10). To a solution of methyl 11α-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **10** (0.1 g, 0.172 mmol) in dry DMF (5 mL) was added solid sodium azide (0.056 g, 0.86 mmol). The reaction mixture was stirred at 60 °C for 16 h and allowed to cool to room temperature. It was then poured into H_2O (50 mL) and extracted with Et_2O (3×50 mL). The organic extract was washed with cold water (2×25 mL) followed by brine (20 mL) and it was dried over Na_2SO_4. Solvent was evaporated under reduced pressure to afford crude product. Purification by column chromatography on silica gel (10% EtOAc/hexane) afforded compound **13** (0.092 g, 98%) as a white crystalline solid, mp 213 °C (CH_2Cl_2/hexane); [found C, 63.68; H, 7.91; N, 7.63. $C_{29}H_{43}N_3O_7$ requires C, 63.81; H, 7.96; N, 7.70]; R_f (40% EtOAc/hexane) 0.44; $[\alpha]_D^{28}=+61.68$ (*c* 1.07, $CHCl_3$); ν_{max} (Nujol) 2922, 2108, 1740, 1722 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (d, *J*=6.4 Hz, 3H, C*H*$_3$-21), 1.02 (s, 3H, C*H*$_3$-18), 1.15 (s, 3H, C*H*$_3$-19), 2.02 (s, 3H, OCOC*H*$_3$), 2.04 (s, 3H, OCOC*H*$_3$), 2.48 (dt, *J*=14.6, 3.0 Hz, 1H, C*H*$_e$-1), 3.66 (s, 3H, COOC*H*$_3$), 4.06 (d, *J*=10.8 Hz, 1H, C*H*-11), 4.58 (m, 1H, C*H*-3), 4.96 (bs, 1H, C*H*-7); δ_C (75 MHz, $CDCl_3$) 10.7, 18.3, 21.2, 21.2, 22.7, 23.9, 27.0, 27.4, 30.1, 30.9, 31.4, 35.2, 35.2, 37.0, 37.2, 37.9, 41.6, 42.9, 47.0, 51.3, 51.7, 56.1, 64.4, 70.4, 73.4, 169.8, 170.6, 174.1, 207.0.

5.1.6. Compound (13) from compound (14). To a solution of methyl 11β-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **14** (0.05 g, 0.092 mmol) in dry DMF (2 mL) was added solid sodium azide (0.007 g, 0.11 mmol)/potassium acetate (0.011 g, 0.11 mmol). The reaction mixture was then stirred at 60 °C for 9 h for the complete conversion of β-azide to α-azide (TLC). This was worked up and purified as described above to yield compound **13** in quantitative yield.

5.1.7. Compound (13) from compound (11). To a solution of methyl 11β-bromo-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **11** (0.05 g, 0.086 mmol) in dry DMF (2 mL) was added solid sodium azide (0.028 g, 0.43 mmol). The reaction mixture was then stirred at 28 °C for 8 h. This was further worked up and purified as described above to yield compound **13** (0.04 g, 85% yield).

5.1.8. Methyl 11β-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (14). To a solution of methyl 3α,7α-diacetoxy-11α-bromo-12-oxo-5β-cholan-24-oate **10** (0.18 g, 0.3 mmol) in dry DMF (10 mL) was added solid sodium azide (0.023 g, 0.36 mmol). The reaction mixture was then stirred at 60 °C for 4 h. It was then diluted with H_2O (50 mL) and extracted with Et_2O (3×50 mL). The organic layer was washed with cold water (2×20 mL), brine (20 mL) and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to give 0.17 g of crude product. Purification by column chromatography, on silica gel (10% EtOAc/hexane), furnished compound **14** (0.105 g, 64%) as white solid, mp 181 °C (CH_2Cl_2/hexane); [found C, 63.83; H, 8.04; N, 7.24. $C_{29}H_{43}N_3O_7$ requires C, 63.81; H, 7.96; N, 7.70]; R_f (40% EtOAc/hexane) 0.50; $[\alpha]_D^{27}=+98.61$ (*c* 1.44, $CHCl_3$); ν_{max} (Nujol) 2910, 2108, 1738, 1715 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.92 (d, *J*=6.3 Hz, 3H, C*H*$_3$-21), 1.25 (s, 3H, C*H*$_3$-18), 1.26 (s, 3H, C*H*$_3$-19), 2.03 (s, 6H, OCOC*H*$_3$×2), 3.67 (s, 3H, COOC*H*$_3$), 4.14 (d, *J*=5.5 Hz, 1H, C*H*-11), 4.60 (m, 1H, C*H*-3), 5.01 (bs, 1H, C*H*-7); δ_C (125 MHz, $CDCl_3$) 10.3, 18.7, 21.3, 21.3, 23.6, 25.2, 27.0, 27.1, 30.4, 30.8, 31.2, 34.3, 34.6, 35.4, 35.5, 36.0, 39.3, 43.1, 47.2, 51.4, 52.7, 56.4, 69.0, 70.7, 73.3, 169.8, 170.4, 174.4, 206.7; MS (LCMS) *m/z* 546.02 (M^++1), 506.02, 227.05.

5.1.9. Methyl 11α-amino-3α,7α-diacetoxy-12-keto-5β-cholan-24-oate (18) from compound (13). Methyl 11α-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **13** (0.25 g, 0.46 mmol) in EtOAc (15 mL) was hydrogenated at 28 °C and 40 psi pressure using 10% Pd/C (25 mg) for 5 h. After filtration of the catalyst and evaporation of the solvent, afforded compound **18** (0.224 g, 95%) as foamy solid, mp 154 °C (EtOAc/hexane); [found C, 66.77; H, 9.14; N, 2.72 $C_{29}H_{45}NO_7$ requires C, 67.01; H, 8.74; N, 2.69]; R_f

(5% MeOH/CH_2Cl_2) 0.55; $[\alpha]_D^{28} = +61.84$ (*c* 1.52, $CHCl_3$); ν_{max} (Nujol) 3389, 2954, 1731, 1714 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.85 (d, $J=6.5$ Hz, 3H, C*H*$_3$-21), 1.01 (s, 3H, C*H*$_3$-18), 1.19 (s, 3H, C*H*$_3$-19), 2.01 (s, 3H, OCOC*H*$_3$), 2.02 (s, 3H, OCOC*H*$_3$), 2.27 (m, 1H), 2.40 (m, 1H), 2.72 (dt, $J=$ 14.1, 3.0 Hz, 1H, C*H*$_e$-1), 3.66 (s, 3H, COOC*H*$_3$), 3.76 (d, $J=10.0$ Hz, 1H, C*H*-11), 4.64 (m, 1H, C*H*-3), 4.94 (bs, 1H, C*H*-7); δ_C (125 MHz, $CDCl_3$) 11.0, 18.5, 21.4, 21.4, 23.1, 24.3, 27.4, 28.0, 30.4, 31.2, 31.8, 35.4, 35.4, 37.6, 37.8, 38.5, 42.2, 46.0, 47.3, 51.4, 52.3, 56.0, 57.0, 71.0, 74.0, 170.1, 170.6, 174.5, 214.1; MS (LCMS) *m/z* 520.03 ($M^+ + 1$) base peak, 227.05.

5.1.10. Methyl 11α-amino-3α,7α-diacetoxy-12-keto-5β-cholan-24-oate (18) from compound (14). A solution of methyl 11β-azido-3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate **14** (0.11 g, 0.2 mmol) was stirred with triphenylphosphine (0.08 g, 0.3 mmol) in dry THF (5 mL) for 24 h. Water (0.1 mL) was added and the solvent was removed after additional 24 h. After dilution with EtOAc (100 mL), the organic layer was separated, washed with water (2× 20 mL), brine (20 mL), dried and solvent was evaporated under reduced pressure. Chromatography of the residue on alumina (10% EtOAc/hexane) afforded compound **18** (0.08 g, 80%) as white solid.

5.1.11. 2α-Azidocholestan-3-one (17) from 2α-bromocholestan-3-one (15). To a solution of 2α-bromocholestan-3-one **16** (0.233 g, 0.5 mmol) in dry DMF (15 mL) was added solid sodium azide (0.039 g, 0.6 mmol). The reaction mixture was stirred at 28 °C for 2 h. This was worked up and purified as usual to afford compound **17** (0.19 g, 89%)as white solid, mp 145 °C (EtOAc/hexane, lit.[16] mp 147–150 °C). Spectroscopic data is consistent with that reported in the literature.

5.2. X-ray crystallographic data

Single crystals of all the compounds **13**, **14** and **18** obtained from ethyl acetate–petroleum ether mixture. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer at room temperature. All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97[22] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The details of the crystal structure determination and the refinements of all the compounds are given in the supporting information.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-253328 (for compound **13**), CCDC-253329 (for compound **14**) and CCDC-253330 (for compound **18**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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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.2005.01.073

^1H and ^{13}C NMR spectra of all the compounds, X-ray crystallographic data and detailed computational section.

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