ELSEVIER

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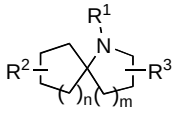
Contents

REPORT



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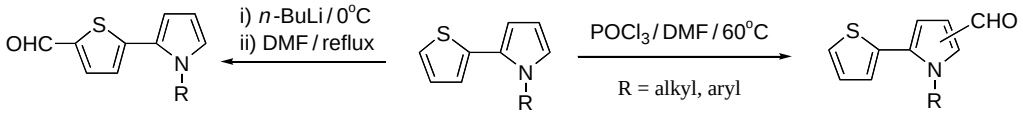

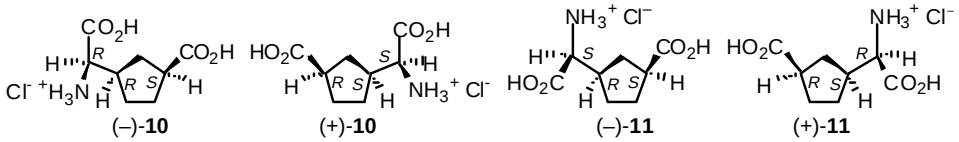

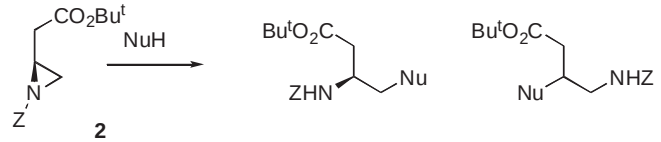

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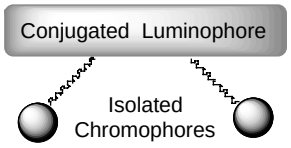

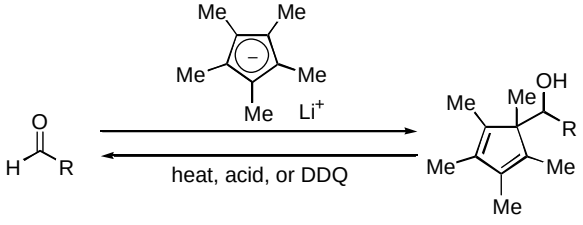

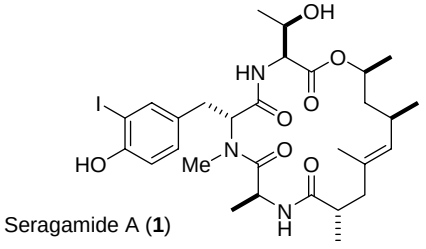

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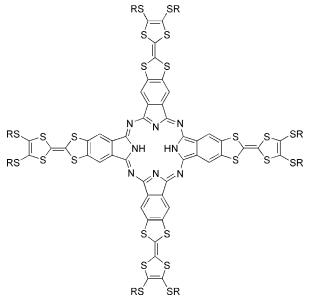
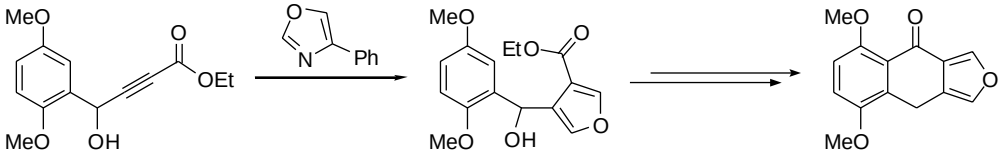
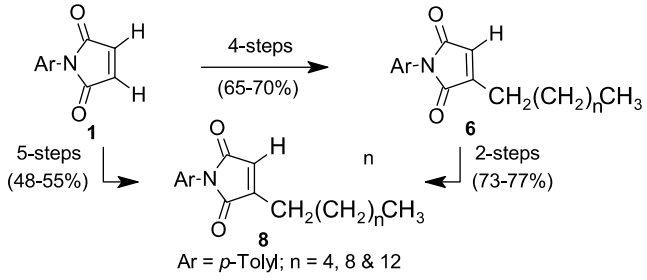
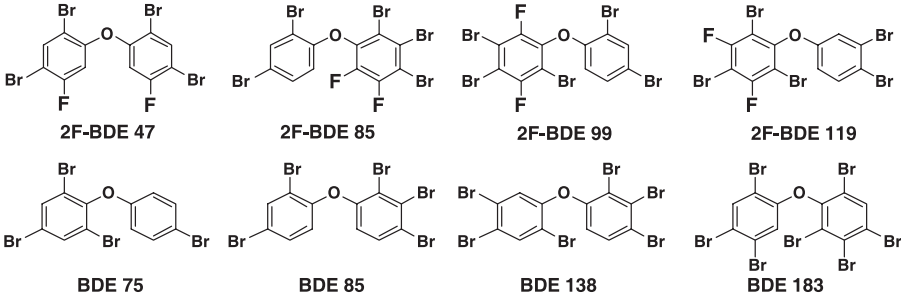
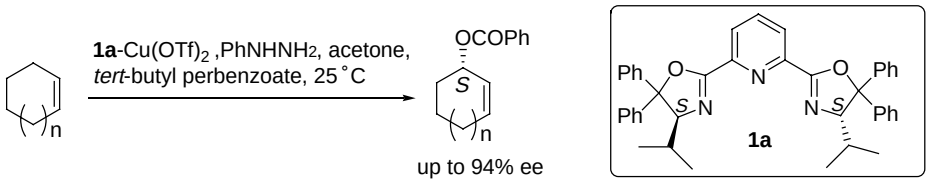
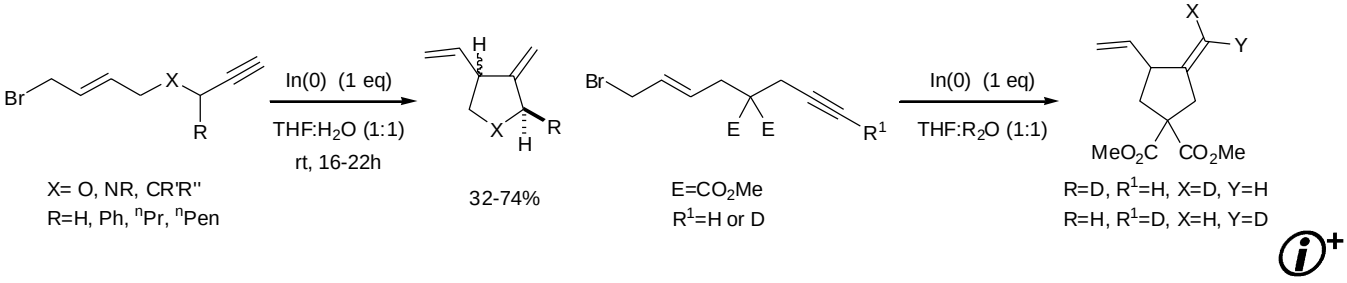


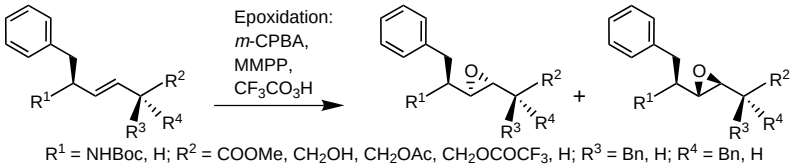


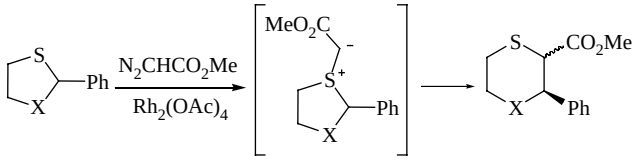


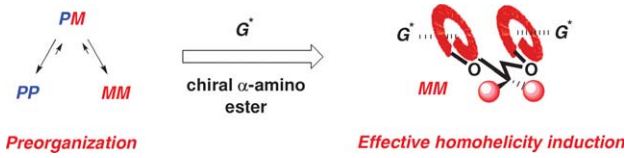


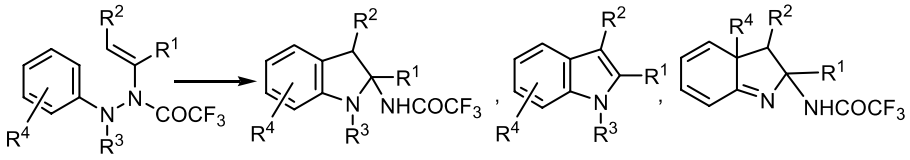


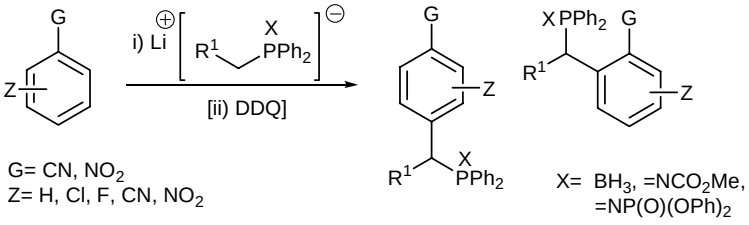


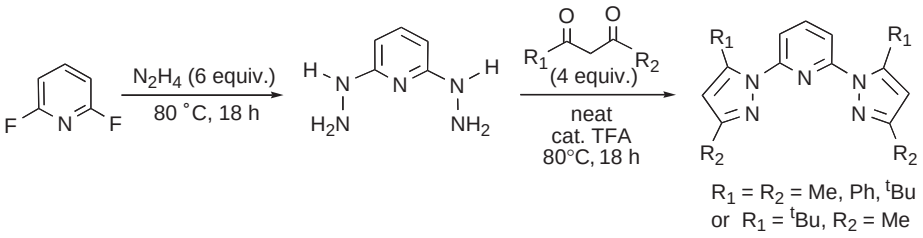


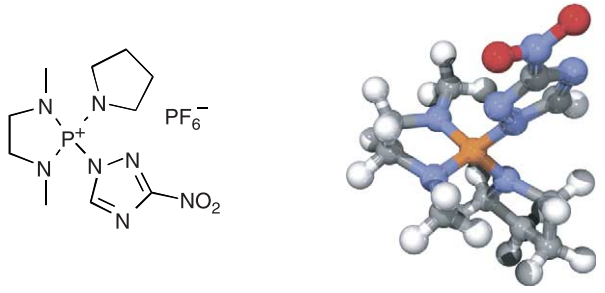


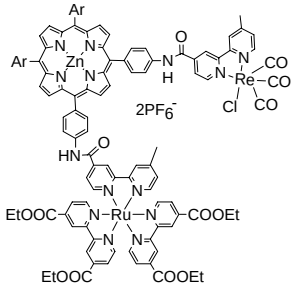


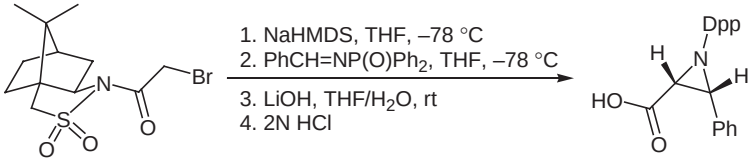


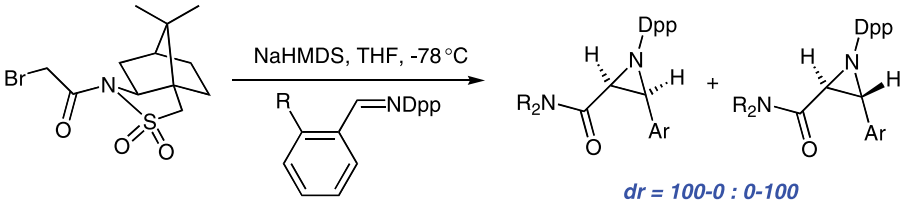


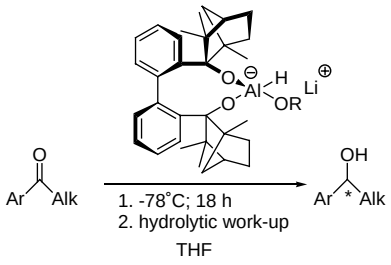




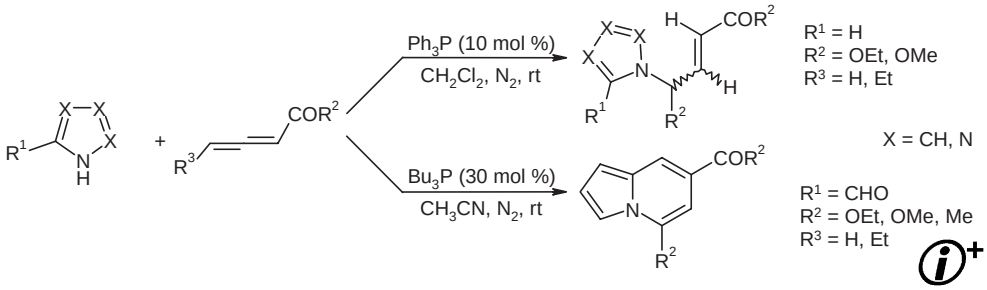


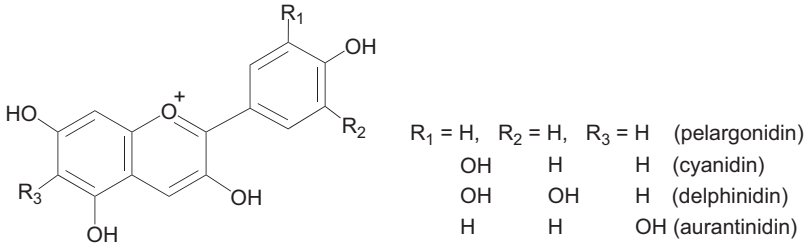




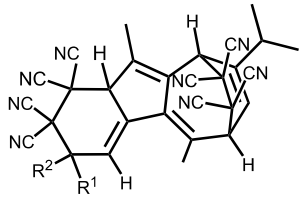


Efficient method for functional allylation of azoles has been developed using phosphine-catalyzed reactions with electron-deficient allenes. This metal free catalytic methodology has been extended to addition–cyclization reactions for the preparation of substituted indolizines.

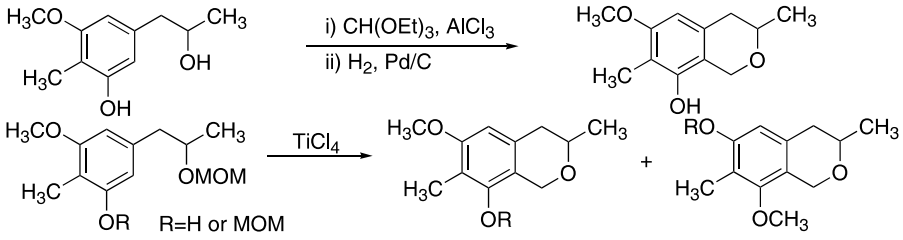


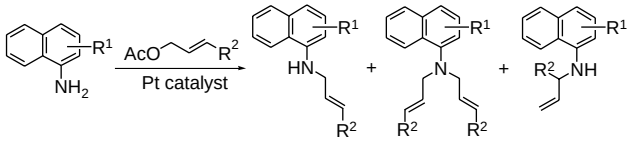


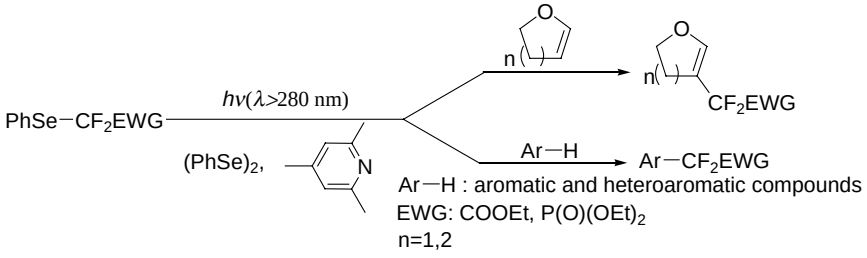
Reactions of the title ethylene derivatives **1** and **2** with TCNE in benzene at 25 °C for 24 h under argon give new cycloaddition compounds **3** (from **1**) and **4** (from **2**), respectively, in 66 and 87% isolated yields. Comparative studies on the above reactions as well as the spectroscopic properties of the unique products **3** and **4**, possessing interesting molecular structures, are reported.



3 and **4**
3 : R^1 = 3–guaiazulenyl, R^2 = H
4 : $R^1 = R^2 = p$–$CH_3OC_6H_4$–







*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Recent approaches to the construction of 1-azaspiro[4.5]decanes and related 1-azaspirocycles

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Contents

Keywords: Azaspirocyclic ring systems; Spirocycles; 3° Carbon center.

Abbreviations: Ac, acetyl; AIBN, azobisisobutyronitrile(2,2′-azo(2-methylpropionitrile)); Ar, aryl; Bn, benzyl; Boc, *t*-butoxycarbonyl; Bu, butyl; Cbz, benzyloxycarbonyl; Cy, cyclohexyl; DBB, di-*t*-butylbiphenylide; DBU, diazadicycloundecane; DIB, di(acetoxyl)iodobenzene; DMAP, 4-dimethylaminopyridine; DMSO, dimethylsulfoxide; DPPA, diphenylphosphorylazide; DTBHN, di-*t*-butylhyponitrite; Et, ethyl; h, hours; HMDS, hexamethyldisilazide; H–W–E, Horner–Wadsworth–Emmons Reaction; LA, arbitrary Lewis acid; LDA, lithium di(isopropyl)amide; Me, methyl; MOM, methoxymethyl; MS, molecular sieve; NMO, *N*-methyl morpholine *N*-oxide; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NPS, *N*-phenylselenylsuccinimide; Ph, phenyl; PMB, *p*-methoxybenzyl; Pr, propyl; rt, room temperature; SEM, 2-(trimethylsilyl)ethoxymethyl; SIMes, 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene; TBAF, tetrabutylammonium fluoride; TBS, *t*-butyldimethylsilyl; TBDPS, *t*-butyldiphenylsilyl; TMS, trimethylsilyl; Tf, trifluoromethanesulfonate; TFA, trifluoroacetic acid; THF, tetrahydrofuran; tol, toluyl; TMG, tetramethylguanidine; TPAP, tetrapropylammonium perruthenate; Ts, *p*-toluenesulfonyl.

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1. Introduction

Natural products are embedded with structural motifs that inspire practitioners of synthetic organic chemistry. The development of new synthetic methods and strategies for the construction of these motifs is a continuing focus of interest for our community. In assessing the strengths and weaknesses of a synthetic approach, criteria that can be used to evaluate each method include conciseness, efficiency, functional group compatibility, cost, 'elegance' as well as other factors. Although in practice each method has its own pros and cons, the instructive value for each is substantial. These studies define within specific contexts 'achievable' and, perhaps more importantly, 'unachievable' processes. 'Unachievable' transformations or strategies present problems that require further examination and, hopefully, innovation.

The 1-azaspiro[4.5]decane ring system, along with related structures such as the 1-azaspiro[5.5]undecane, 1-azaspiro[4.4]nonane and 6-azaspiro[4.5]decane ring systems, represent structural motifs that can be termed, despite obvious nomenclature inaccuracies, as '1-azaspirocycles' (Fig. 1). These cyclic systems incorporate two rings connected by a spiro ring fusion containing a nitrogen atom adjacent to the ring junction. This structural motif has been observed in a number of alkaloid natural products (starred atoms in structures in Fig. 2).

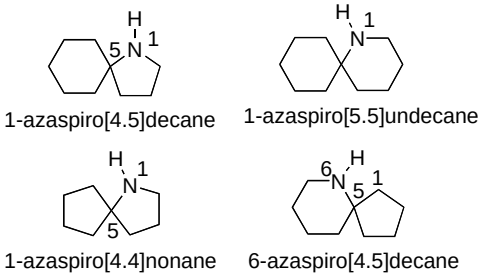


Figure 1. 1-Azaspiro[4.5]decane and structurally related '1-azaspirocycles'.

This ring system is not only observed in natural products that have served as synthetic targets for a number of years, such as histrionicotoxin,[1] cephalotaxine[2] and erythrina alkaloids[3] as exemplified by erysotramidine and cocculidine (Fig. 2), but also within natural products whose structures have only recently been reported. Examples of these compounds include halichlorine,[4] pinnaic acid (not pictured),[5] TAN1251A,[6] FR901483[7] and members of the cylindricine family such as fasicularin,[8] cylindricine A[9] and lepadiformine.[10]

A number of methods have been described recently for the construction of azaspirocyclic ring systems, especially within the context of synthetic approaches to targets in Figure 1. The synthesis of spirocycles that contain more than one heteroatom as exemplified within the natural products in Figure 3 will not be covered in this review.

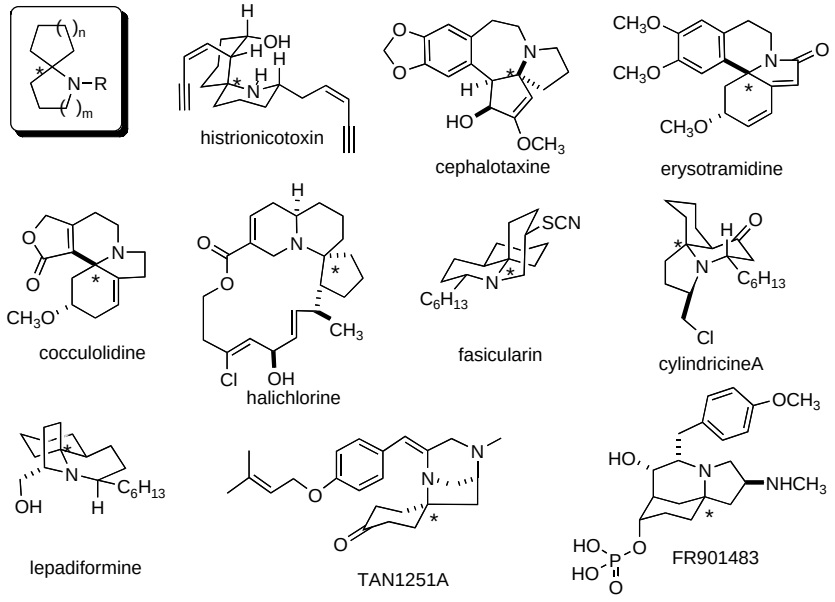


Figure 2. Alkaloids that contain 1-azaspirocycle motifs.

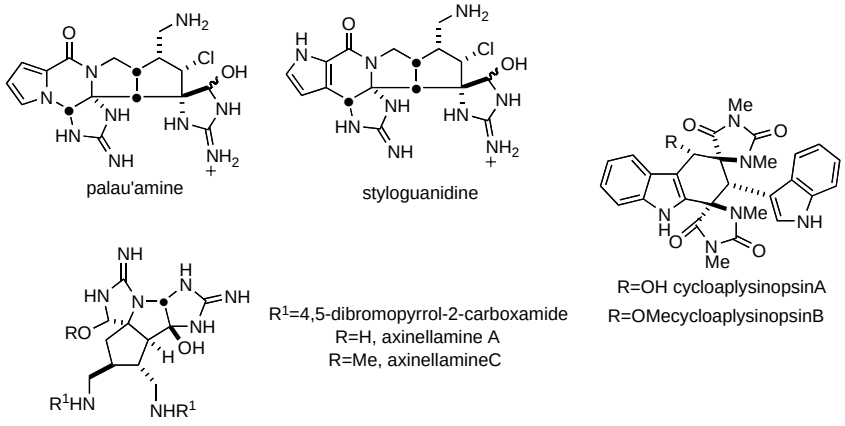


Figure 3. Alkaloids with spirocycle substructures not covered in this review.

Recent reviews dealing with aspects of this general topic are available.[11] This report will present recent developments to provide an overview of the diverse strategies for the construction of these azaspirocyclic structural motifs.

1.1. Organization

In considering a route to construct 1-azaspirocyclic motifs, two synthetic challenges must be considered. The first problem is the construction of the 3° carbon center bearing the nitrogen atom that will ultimately become the spirocycle ring junction. This carbon is often a stereogenic center, thus necessitating stereochemical control in its formation. The second issue is the installation of the 'rings' of the spirocyclic system. By defining these two synthetic problems, approaches to 1-azaspirocycles can be divided into three general possibilities (Fig. 4). The first two strategies require a two-step process where the 3° carbon center and the spirocycle are each constructed in separate events. The establishment of the 3° carbon center could be achieved in an early step, and a subsequent discrete step would close the heterocycle of the spirocyclic system (path a). Formation of the 3° stereogenic center could also conceivably be followed by carbocycle formation in a two-step process (path b). A third approach is to combine both the generation of the 3° stereogenic center and the formation of the spirocyclic ring system within the same reaction (path c). This account is organized on the basis of these three approaches to the formation of 1-azaspirocycles.

2. Approaches that construct the 3° center, then close the heterocycle

In determining a synthetic approach to a 1-azaspirocycle, a useful solution is to break the synthetic challenge into two parts. In this section, the two-step strategy in which the 3° center is established followed by formation of the heterocycle to generate the spiro-ring system is presented. By necessity, installation of the carbon atom bearing the nitrogen atom must precede the formation of the spirocycle. As such, methods that can generate a 3° stereogenic center bearing a nitrogen functionality are used. Common methods to perform this transformation include the Curtius

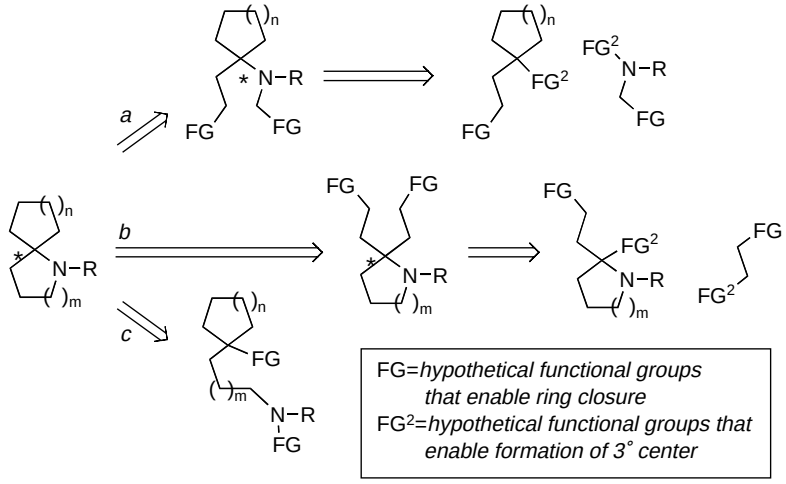
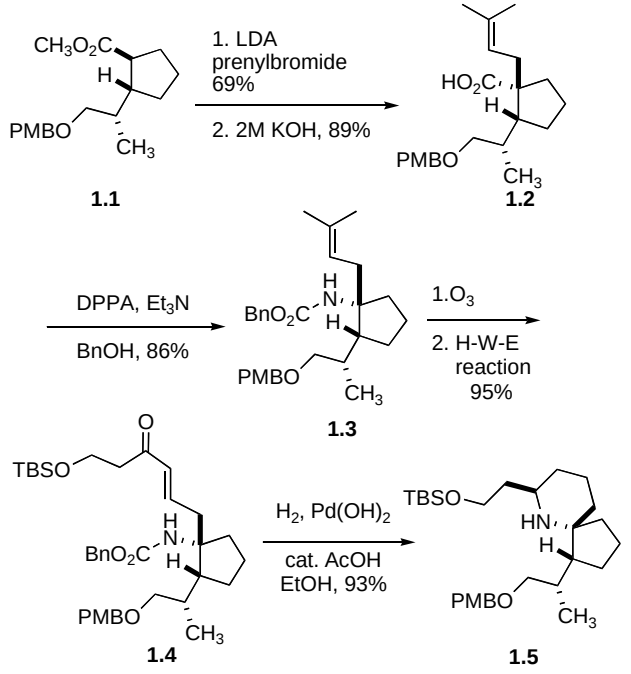


Figure 4. Approaches to target ring system.

rearrangement, addition of organometallic reagents (e.g., Grignard reagents) to imines, or conjugate addition reactions using amine nucleophiles. With formation of the 3° center complete, the heterocyclic ring must be constructed. This can be performed using C–C bond forming reactions such as ring closing metathesis. However, as C–N bond forming processes are comparatively easy, these procedures are often used, as well. Typical examples are reductive amination reactions or lactamization reactions.

2.1. Curtius rearrangement–reductive amination

A classic method of establishing a 3° stereogenic center attached to an amine-derived functional group is the Curtius rearrangement. In the Arimoto route, ester **1.1** was sequentially treated with LDA followed by prenyl bromide to establish the 4° carbon stereocenter in **1.2** (Scheme 1).

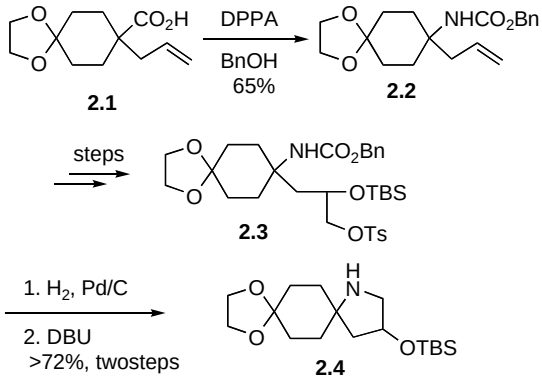


Scheme 1. The arimoto route.

Saponification of the methyl ester followed by reaction with diphenylphosphoryl azide (DPPA), triethylamine and benzyl alcohol produced benzyl carbamate **1.3** in 71% yield.[12] Oxidative cleavage of the alkene followed by a Horner–Wadsworth–Emmons reaction led to ketone **1.4** in good yield. The C–N bond completing the spirocyclic ring system was established using reductive amination. Catalytic hydrogenation of **1.4** smoothly provided **1.5**, reducing the iminium ion intermediate on the least hindered face of the heterocycle.

2.2. Curtius rearrangement–N-alkylation

The 3° stereocenter in **2.2** was similarly established using a Curtius rearrangement (Scheme 2). The conversion of **2.2** to 1° tosylate **2.3** utilized standard procedures. The benzyl carbamate function in **2.3** was deprotected (H_2, Pd/C) and subsequently treated, without purification, with DBU to smoothly produce the desired spirocycle **2.4** in >72% yield (over two steps) from **2.3**.[13]

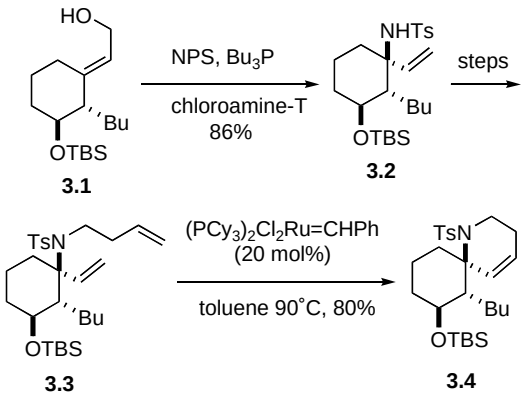


Scheme 2. The Nagumo/Kawahara route.

2.3. Sigmatropic rearrangement–ring closing metathesis

The reaction of allylic alcohol **3.1** with *N*-phenylselenylsuccinimide (NPS) in the presence of tributylphosphine and chloroamine T smoothly produced, via a [2,3] sigmatropic

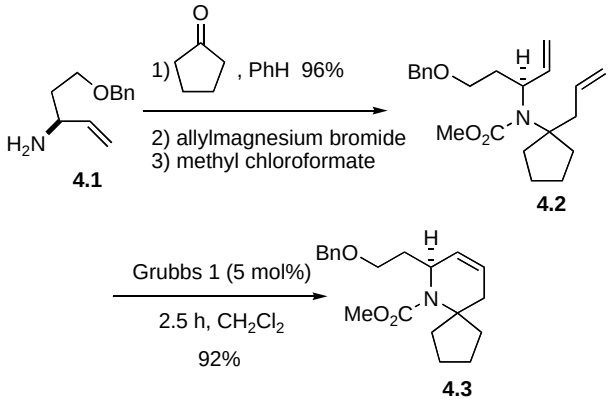
rearrangement, allylic sulfonamide **3.2** in 86% yield, establishing the required 3° stereocenter (Scheme 3).[14] N-alkylation followed by ring closing metathesis using $(PCy_3)_2$ $Cl_2Ru{=}CHPh$ (the Grubbs 'first-generation' precatalyst, 'Grubbs 1') produced spirocycle **3.4** in 80% yield.[15] This material was used in a synthesis of perhydrohistrionicotoxin.



Scheme 3. The Tanner route.

2.4. Imine addition–ring closing metathesis

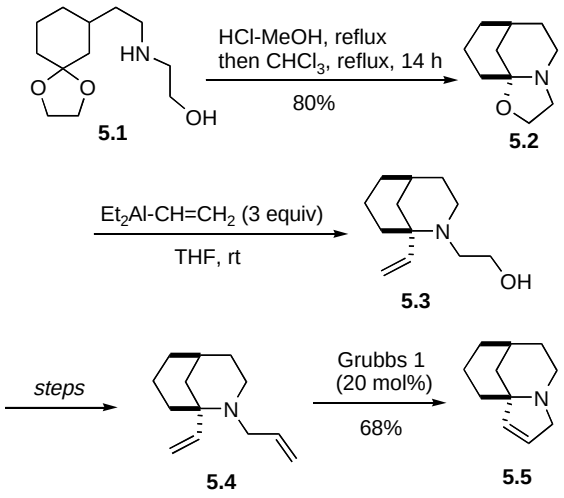
Imine formation using **4.1** and cyclopentanone was followed by the sequential addition of allyl magnesium bromide and methyl chloroformate (Scheme 4). Subjecting alkene **4.2** to the Grubbs 1 precatalyst produced spirocycle **4.3** in 92% yield. Protection of the amine function as its methyl carbamate was important as the corresponding reaction using a free amine in the metathesis substrate required a 60% 'catalyst' load using an acid-copromoter to produce only 33% of cyclized product after 20 days.[16]



Scheme 4. The Wright route.

2.5. Iminium ion addition–ring closing metathesis

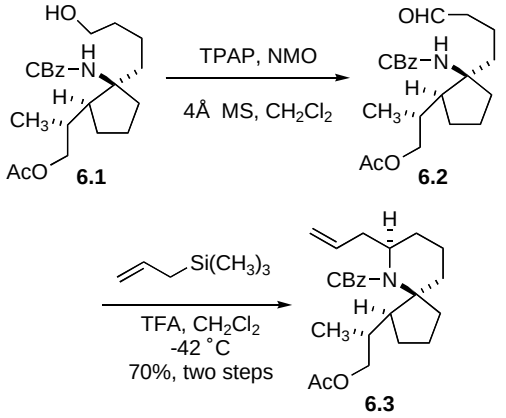
The Kibayashi group presented the following construction of a bridged spirocycle-containing ring system of FR901483 (Scheme 5).[17] Intramolecular transketalization of **5.1** provided bridged ring system **5.2**. Addition of a vinyl group to the iminium ion generated in situ from **5.2** was accomplished using vinyldiethylalane to produce **5.3**. Subsequent manipulation of **5.3** resulted in **5.4**. Ring closing metathesis of **5.4** using a 20 mol% catalyst loading of the Grubbs 1 precatalyst produced **5.5** in 68% yield.



Scheme 5. The Kibayashi metathesis route.

2.6. Not disclosed-iminium ion addition

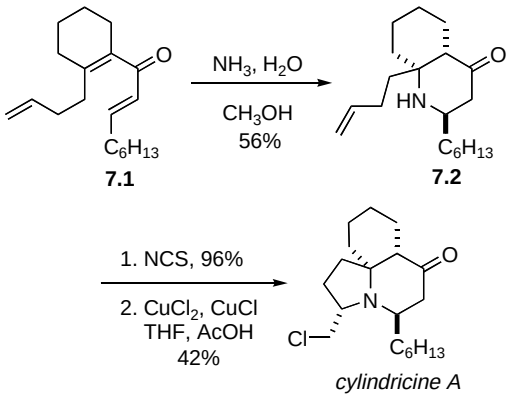
In a preparation of a spirocyclic ring system related to halichlorine, the following sequence was disclosed (Scheme 6).[18] The oxidation of alcohol **6.1** (the preparation was not disclosed) was followed by treatment of aldehyde **6.2** with trifluoroacetic acid and allyltrimethylsilane. The *N*-carbamoyl iminium ion that was formed in situ reacted with allyltrimethylsilane to form azaspirocycle **6.3** in 70% yield as a single diastereomer. The diastereoselectivity of the addition reaction was rationalized via an axial attack on the less hindered face of the *N*-carbamoyl iminium ion.



Scheme 6. The Forsyth route.

2.7. Conjugate addition–radical cyclization

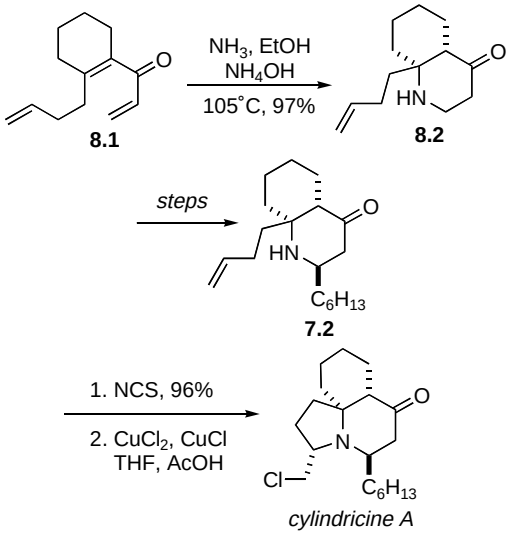
In early syntheses of cylindricines A and B, the 3° stereogenic center of the spirocycle in the natural product was established using a conjugate addition sequence of ammonia to bis-enone **7.1** (Scheme 7).[19] N-chlorination was followed by radical cyclization, using the procedure



Scheme 7. The Snider approach to the cylindricines.

established by Stella,[20] to form the spirocyclic structure within these alkaloids.

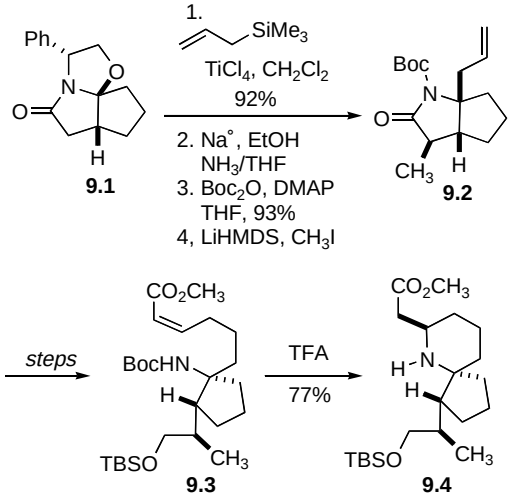
Heathcock and Liu used a conceptually similar approach in another cylindricine synthesis (Scheme 8).[21] A conjugate addition of ammonia to **8.1** installed the required 3° stereocenter. After subsequent manipulation of **8.2**, a Stella procedure was used to form the spirocycle in the natural product.



Scheme 8. The Heathcock route to the cylindricines.

2.8. Iminium ion addition–conjugate addition

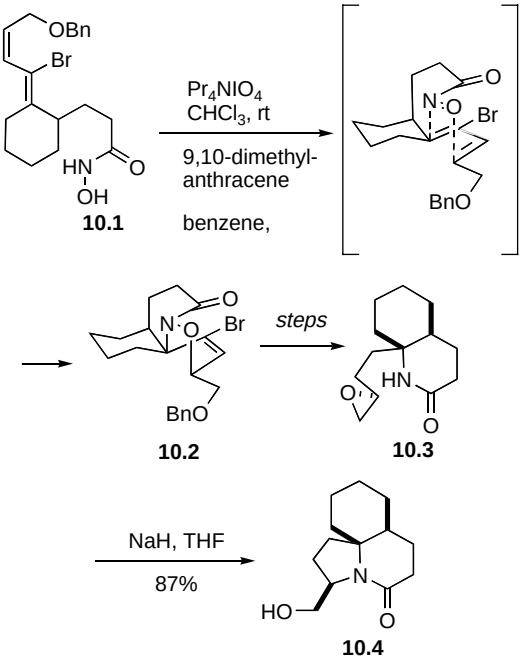
The bias of a [3.3.0] bicyclic ring system was used to ensure control in establishing the stereochemistry of the 3° center in Danishefsky's approach to halichlorine and pinnaic acid (Scheme 9).[22] Titanium tetrachloride promoted addition of allyltrimethylsilane to lactam **9.1** established the stereochemistry of what would become the 3° stereocenter of the natural product. This process was followed by several functional group manipulations to produce enoate **9.3**. Deprotection of the *t*-butylcarbamate group within **9.3** initiated spontaneous intramolecular conjugate addition to the enoate, producing **9.4** in 77% yield.



Scheme 9. The Danishefsky route.

2.9. Cycloaddition–N-alkylation

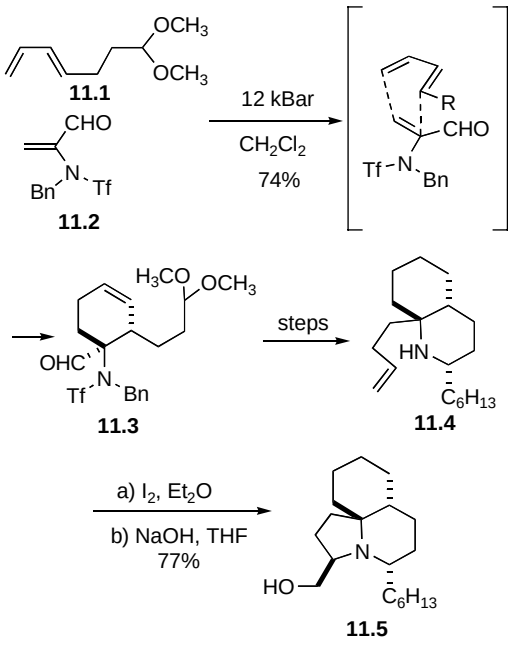
In an early approach to lepadiformine, an *N*-acyl nitroso Diels–Alder reaction was used to establish the 3° center in a stereocontrolled manner (Scheme 10).[23] The major stereochemical result of the cycloaddition reaction can be rationalized by the minimization of $A^{1,3}$ strain between the nitroso containing side chain and the bromine substituent on the diene within **10.1**. Several steps led to the eventual formation of **10.3**. Closure of the spirocyclic ring occurred uneventfully as treatment of **10.3** with NaH in THF led to the requisite spirocycle in 87% yield.



Scheme 10. The Kibayashi *N*-acyl nitroso Diels–Alder route.

2.10. [4+2] Cycloaddition–iodoamination of an alkene

An alternative cycloddition-based approach towards lepadiformine was implemented by the Funk group

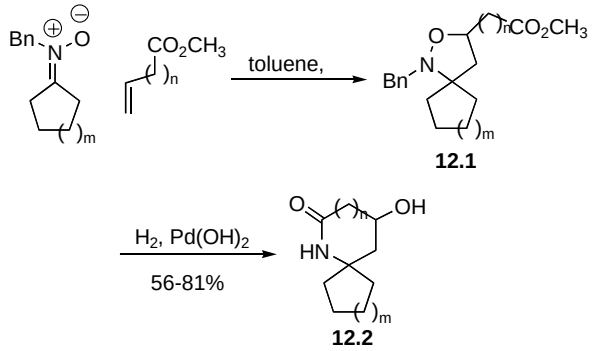


Scheme 11. The Funk α-amidoacrolein cycloaddition route.

(Scheme 11).[24] Specifically, a Diels–Alder reaction between diene **11.1** and dienophile **11.2** under high pressure produced functionalized cyclohexene **11.3** in 74% yield, establishing the requisite 3° center for the spirocycle. Elaboration of **11.3** provided **11.4**, which upon treatment of iodine underwent a smooth cyclization to form the spirocyclic ring system within **11.5**. A very similar transformation was used by the Funk group to establish the spirocyclic ring system of fasicularin.

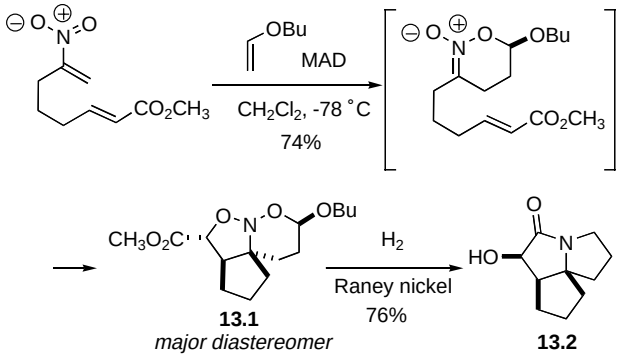
2.11. [3+2] Cycloaddition–amide bond formation

In the late 1980s, the Funk group devised a route to spirocyclic ring systems (Scheme 12).[25] Specifically, a [3+2] dipolar cycloaddition was used to establish the 3° center required in the spirocycle. Hydrogenolysis of the N–O bond followed by spontaneous lactamization resulted in the formation of azaspirocycles of type **12.2**. This procedure was adapted in a more complex setting by the Snider group in a recent synthesis of (−)-FR901483.[26]



Scheme 12. The Funk dipolar cycloaddition route.

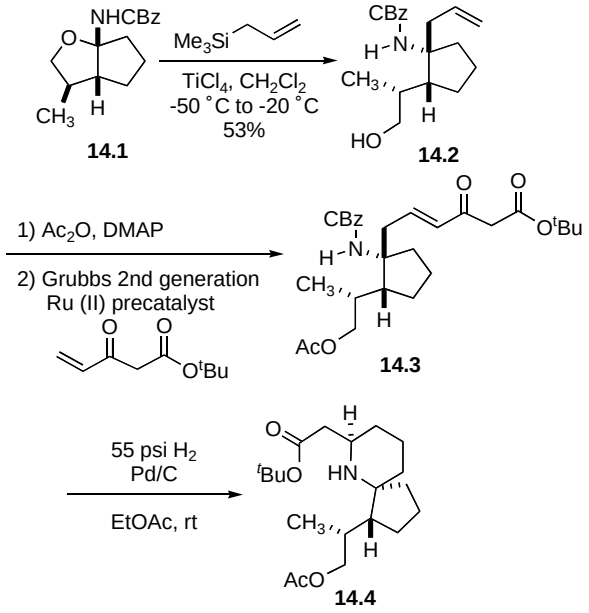
A tandem hetero-[4+2]/[3+2] cycloaddition sequence formed heterocycle **13.1** (Scheme 13).[27] Reductive cleavage of the N–O bonds in this instance resulted in a one-pot reductive amination–lactamization sequence, leading to the efficient formation of the azaspirocycle ring system in **13.2**.



Scheme 13. The Denmark route.

2.12. Iminium ion addition–reductive amination

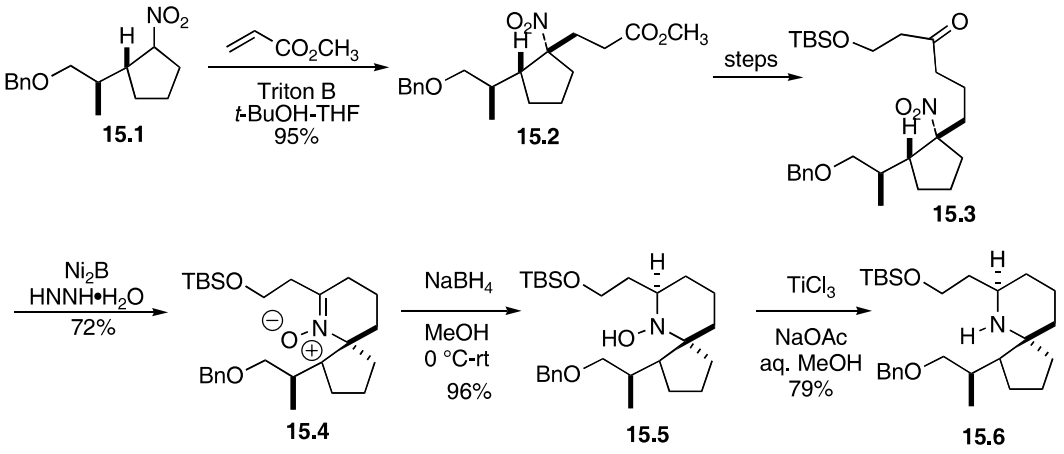
The Heathcock approach to halichlorine and the pinnaic acids outlined in Scheme 14 used the following protocol.[28] Allylsilane addition to **14.1** mediated by titanium tetrachloride gave adduct **14.2**. With the 3° center of the spirocycle established, acetylation and cross-metathesis provided **14.3**, which served as a precursor to reductive amination. Hydrogenation of **14.3** over palladium on carbon provided **14.4**, an intermediate in the Heathcock synthesis.



Scheme 14. The Heathcock route to halichlorine/pinnaic acid.

2.13. Nitroalkane alkylation–imine reduction

Conjugate addition of the anion derived from the nitro function in **15.1** to methyl acrylate resulted in the formation of **15.2** in 95% yield (Scheme 15).

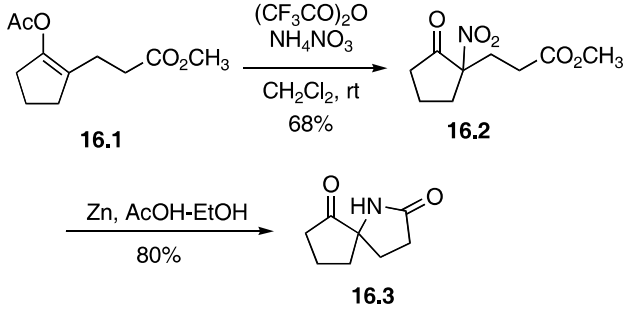


Scheme 15. The Zhao route.

The relative stereochemistry of **15.2** was a result of electrophile approach to the less-hindered face of the anion of **15.1**. Functional group manipulation led to **15.3**. Formation of the spiro compound necessitated three steps. Reduction using nickel boride and hydrazine hydrate generated nitrone **15.4**. Further reduction using sodium borohydride followed by titanium trichloride produced spirocycle **15.6** in good yield.[29] Bonjoch reported a conceptually similar approach.[30] A recent approach to the erythrinan alkaloids also used an alkylation reaction as the key step to establish the critical 3° stereocenter.[31]

2.14. Electrophilic nitration–amide bond formation

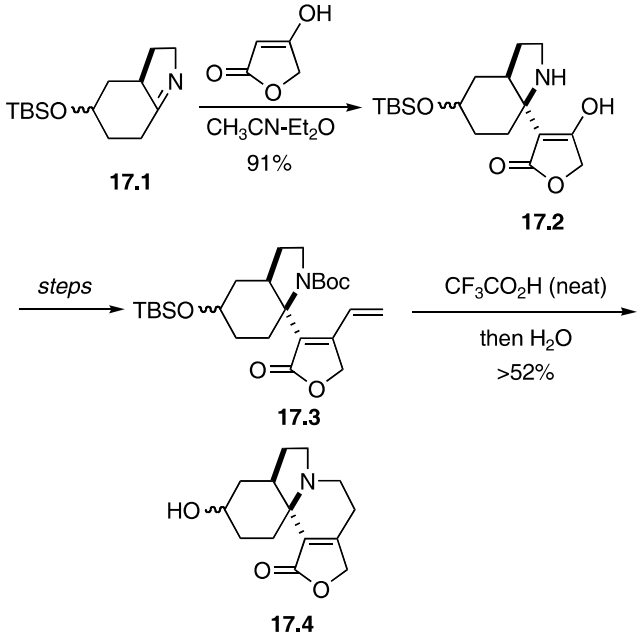
A straightforward approach to azaspirocycles utilized the installation of a nitro function adjacent to a ketone carbonyl moiety using enol acetate **16.1** as a key precursor (Scheme 16).[32] Treatment of **16.1** with ammonium nitrate in the presence of trifluoroacetic anhydride gave ketone **16.2**. Chemoselective reduction of the nitro functional group using Zn in acidic ethanol led to spontaneous amide bond formation to provide **16.3**.



Scheme 16. The Nagasaka route.

2.15. Imine addition–conjugate addition

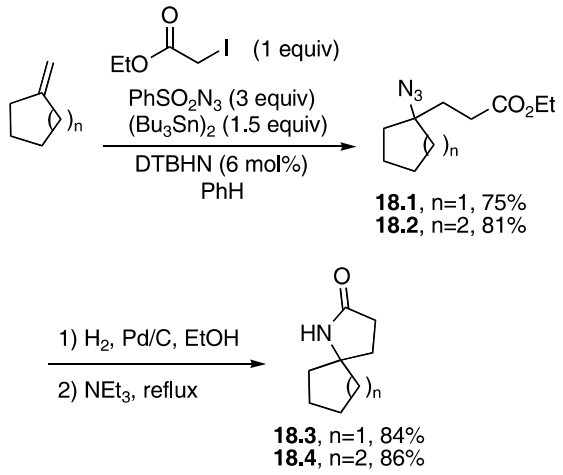
The reaction of imine **17.1** with tetronic acid in an acetonitrile–ether mixture produced adduct **17.2** in excellent yield (Scheme 17).[33] This procedure established the 3° center in the target structure. Compound **17.2** was converted to **17.3** using standard manipulations. Deprotection of the carbamate protecting group using trifluoroacetic acid led to spontaneous 1,6-addition to furnish spirocycle **17.4**.



Scheme 17. The Kitahara route.

2.16. Radical addition to alkene–lactamization

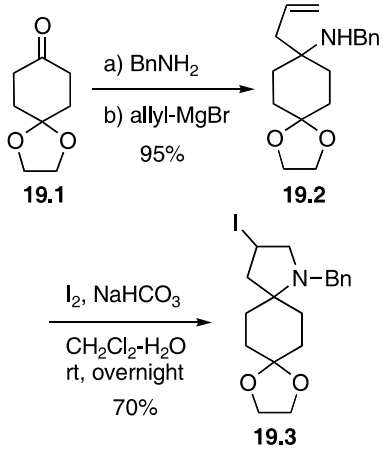
An interesting reaction that results in the addition of azide and methylenecarboxyl functions across alkenes through radical intermediates sets the stage for an azaspirocycle synthesis (Scheme 18).[34] The reaction of methylenecyclopentane or methylenecyclohexane with ethyl 2-iodoacetate, phenylsulfonylazide, and hexabutyldistannane in the presence of di-*tert*-butylhyponitrite (DTBHN) provided azides **18.1** or **18.2** in very good yields. The catalytic reduction of the azide function was followed by lactamization to provide spirocycles **18.3** and **18.4**, each process occurring in excellent yield.



Scheme 18. The Renaud route.

2.17. Imine addition–N-alkylation

In the context of a synthetic approach towards FR901843, Bonjoch and co-workers allylated the intermediary benzylimine produced from **19.1** (Scheme 19). The reaction of the alkene function in **19.2** with iodine then induced an iodoamination to provide alkylated amine **19.3** in excellent yield.[35]



Scheme 19. The Bonjoch route.

3. Approaches that construct the 3° center, then close the carbocycle

After the 3° stereocenter is set, the spirocyclic ring system could be made using C–C bond forming reactions in building the carbocyclic unit of the spirocycle. Efficient procedures such as ring closing metathesis, enamine alkylation or enolate condensation processes are effectively used.

3.1. Lactamization–Claisen condensation

An efficient sequence involving well-established reactions was used by the Fukuyama group in their efforts towards FR901483 (Scheme 20).[36] Nitromethane was induced to undergo multiple conjugate addition reactions upon its treatment with excess methyl acrylate under the influence of catalytic DBU. Reduction of the nitro function and cyclization produced lactam **20.1**. Dieckmann cyclization followed by saponification and decarboxylation produced ketone **20.2**.

3.2. Enolate alkylation–ring closing metathesis

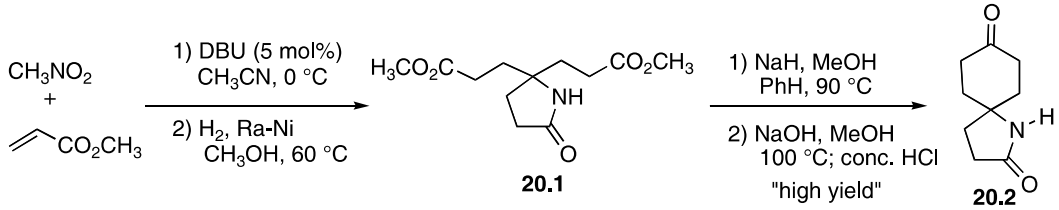
The 3° center of a compound used in a program directed toward the synthesis of halichlorine was established by the desymmetrization of meso diester **21.1** (Scheme 21).[37] Reaction of **21.1** with chiral base **21.2** followed by addition of allyl bromide produced allylated diester **21.3**. Elaboration of **21.3** using straightforward procedures culminated in the formation of **21.4**. Treatment of **21.4** with (SIMes)PCy_3-Cl_2Ru=HPh, a Grubbs second generation precatalyst, produced the spirocycle **21.5** in 80% yield.

3.3. Enolate alkylation–radical addition to an alkene

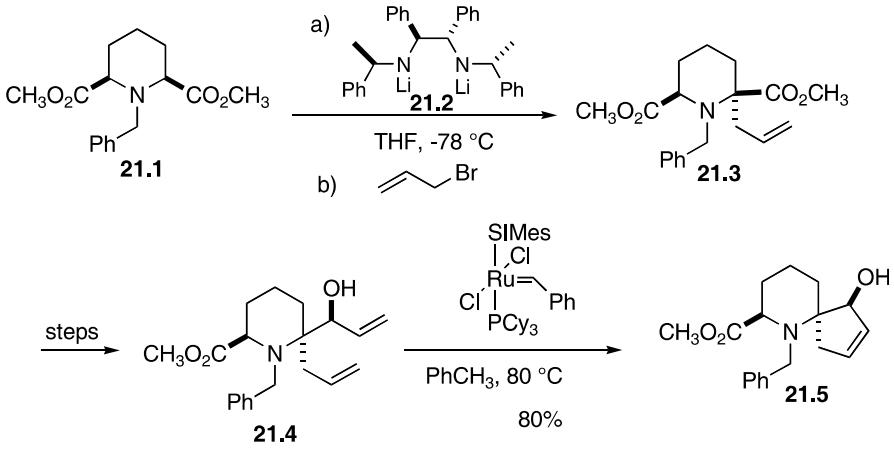
After installing chirality in the same fashion as the Simpkins route to provide **21.3**, the Clive group performed a number of chemical transformations to procure **22.1**, an advanced synthetic intermediate towards halichlorine (Scheme 22).[38] Subjection of **22.1** to the conditions of tri-*n*-butyltin hydride and AIBN generated a mixture of compounds, **22.2** and **22.3**, that had undergone cyclization. Enone **22.3** was the major component within the reaction mixture (46 or 67%, depending on the diastereomer (not known) of **22.1** used as the starting material).

3.4. C–H insertion–conjugate addition

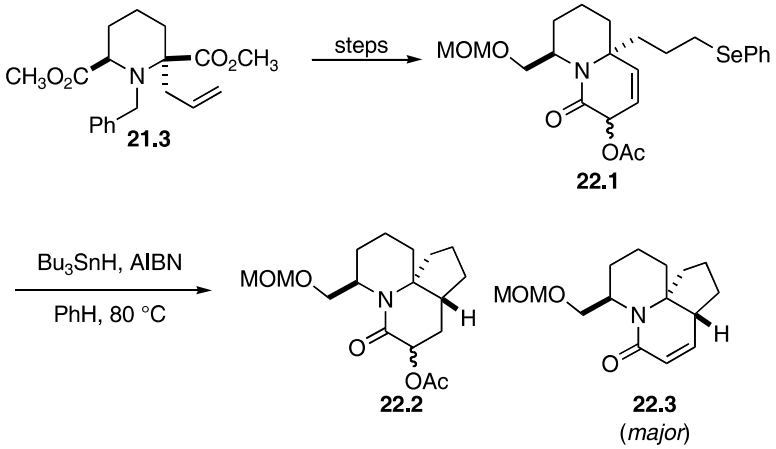
Alkynyliodonium salt **23.1**, upon reaction with sodium *p*-toluenesulfonate, suffered a conjugate addition reaction to produce, after α-elimination, an intermediate represented simplistically as **23.2** (Scheme 23).[39] This carbene-like intermediate underwent a 1,5 C–H insertion process to produce bicycle **23.3**. This process thus established the 3° stereogenic center required for the spirocycle synthesis. In the event, treatment of **23.3** with magnesium bromide induced a smooth 1,4-addition reaction of the alkylstannane to the doubly activated alkene, generating an azaspirocycle. This compound was elaborated to the core structure of halichlorine.



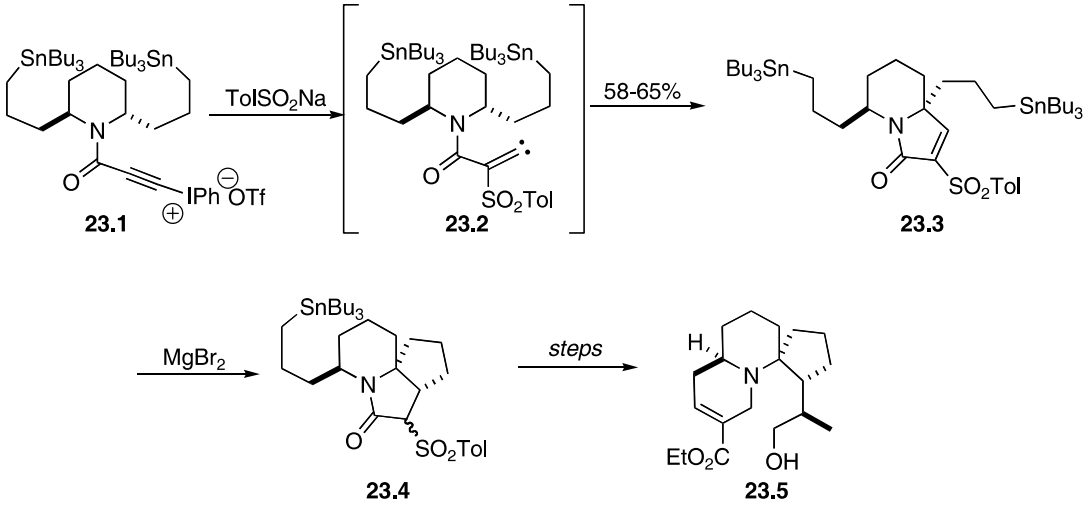
Scheme 20. The Fukuyama route.



Scheme 21. The Simpkins route.



Scheme 22. The Clive desymmetrization approach.



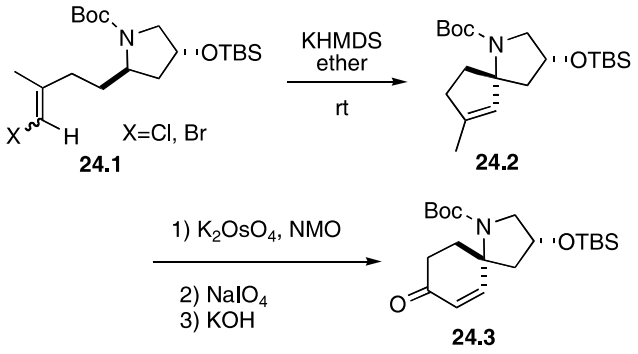
Scheme 23. The Feldman route.

3.5. C–H insertion–aldol condensation

In a somewhat related sequence, the reaction of vinylhalides **24.1** with potassium hexamethyldisilazide produced an intermediary carbene that undergoes C–H insertion to produce spirocycle **24.2** (Scheme 24).[40] This compound was further elaborated by oxidative cleavage of the alkene in **24.2** followed by aldol condensation to produce functionalized cyclohexanone **24.3**.

3.6. Imine addition–alkylation

In the context of synthetic approaches to marine alkaloids, the Kibayashi group has developed a number of routes to



Scheme 24. The Hayes route.

azaspirocycles. This specific procedure involved the addition of allylmagnesium bromide to imine **25.1** under the influence of boron–trifluoride etherate to generate amine **25.2** as a single diastereomer (Scheme 25).[41] Standard manipulations of **25.2** produced **25.3**. This compound, upon reaction with pyrollidine to generate an enamine, underwent a smooth cyclization reaction to produce, after hydrolysis, aldehyde **25.4**.

3.7. Enolate alkylation–carbonyl addition

A recent approach to cephalotaxine utilized an interesting alkylation–carbonyl addition sequence (Scheme 26).[42] The 3° stereocenter of the target spirocycle was established by enolate alkylation within a constrained [3.3.0] bicyclic ring system. With the 3° center in **26.2** established, functional group manipulations provided vinyl iodides **26.3** or **26.4**. Intramolecular carbonyl addition of the vinyl iodide function to the carbonyl group in each case was promoted by trimethylsilyltributylstannane and cesium fluoride. In each case the reactions proceeded very well, providing the target spirocycles in good yields.

3.8. Enolate acylation–ring closing metathesis

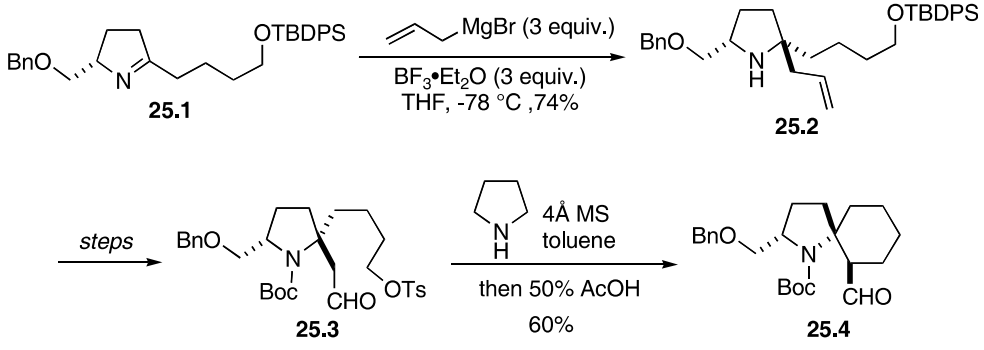
Ring closing metathesis provided the crucial spirocycle in the construction of the ring-system of lepadiformine (Scheme 27).[43] Reaction of the extended silyl enol ether derived from **27.1** with trimethylorthoformate provided **27.2** in excellent yield. Acetal hydrolysis and carbonyl addition then provided diene **27.3**. Closure of the carbocyclic system of the spirocycle was accomplished using standard ring closing metathesis technology. Functional group manipulations provided spirocycle **27.4**.

3.9. Nitrile anion alkylation–Thorpe/Zeigler cyclization

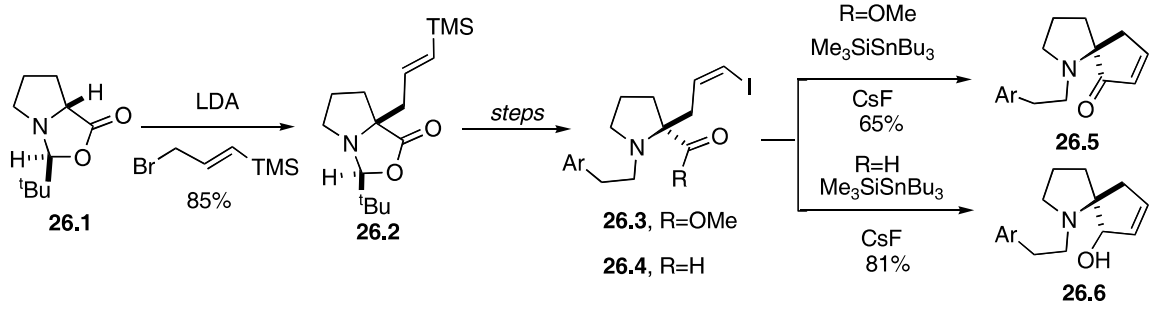
Electrochemical installation of a nitrile function adjacent to the amine moiety in **28.1** allowed for its further functionalization, yielding a spirocycle in the following manner (Scheme 28).[44] Deprotonation and alkylation of **28.2** was followed by conversation to bis-nitrile **28.3**. Thorpe/Zeigler cyclization under the influence of LDA produced spirocycle **28.4** in 70% yield. A thematically related sequence (anion alkylation–aldol condensation) was used in a recent approach to cephalotaxine.[45]

4. Approaches that construct 3° center and spirocycle in the same step

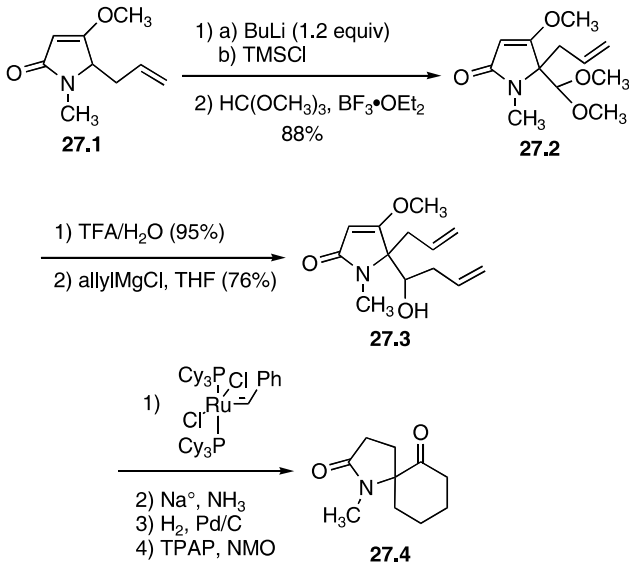
The last general strategies to be presented are those that generate the 3° stereocenter of the spirocycle in conjunction with the two rings of the spirocycle. As these require only one synthetic step, these procedures can have a benefit of efficiency. However, the gain in efficiency can be limited by



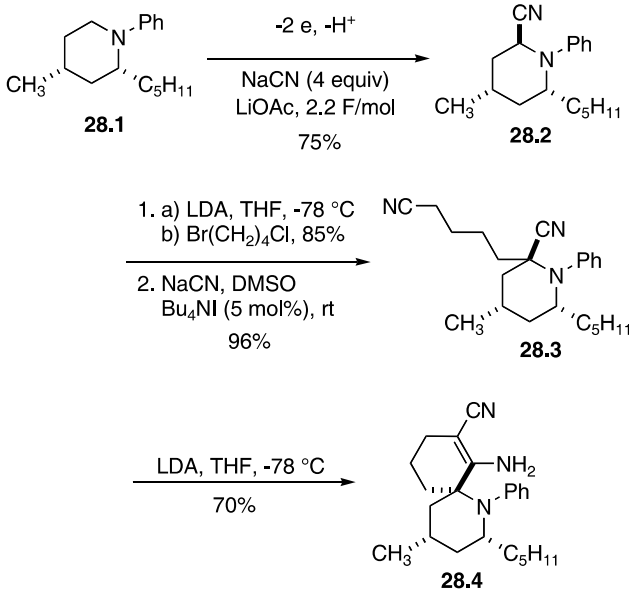
Scheme 25. The Kibayashi route.



Scheme 26. The Mori route.



Scheme 27. The Hunter route.

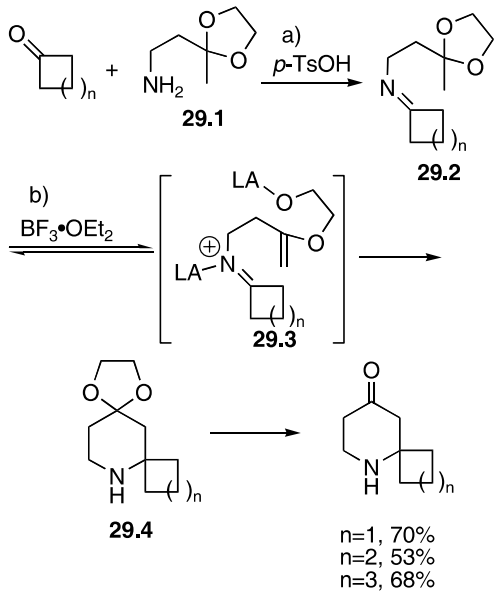


Scheme 28. The Hurvois route.

reaction scope (e.g., the heterocycle or carbocycle ring size) in certain instances.

4.1. Addition to iminium ions

4.1.1. Mannich reaction. The condensation of a cyclic ketone and amine **29.1** under acidic conditions formed, as expected, imine **29.2** (Scheme 29). Although no subsequent productive reaction occurred using *p*-toluenesulfonic acid, the addition of BF_3–OEt_2 (1.5 equiv) then, in sequence, activated the imine and formed (under equilibrating conditions) an enol ether represented as **29.3**. The closure of the spirocycle led to ketals of type **29.4** that can be deprotected using standard chemistry.[46]

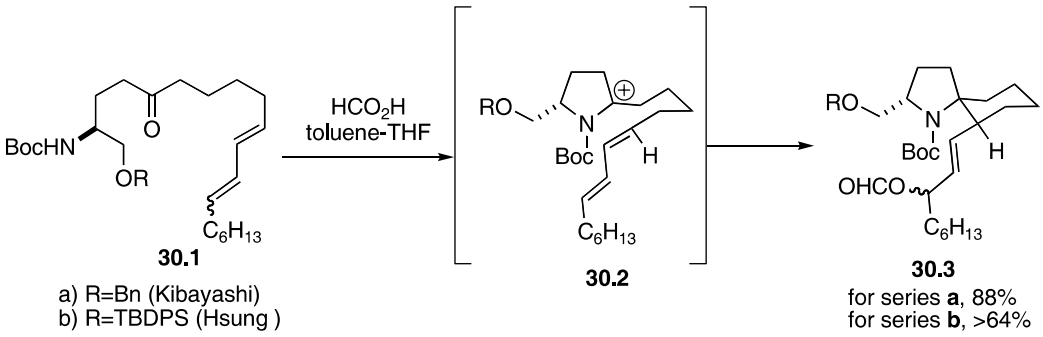


Scheme 29. The Troin route.

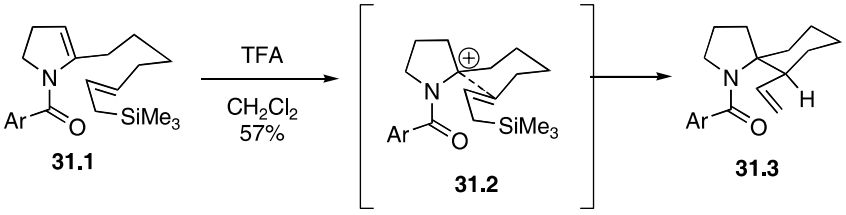
4.1.2. Alkene addition to iminium ions. The cyclization of nucleophilic alkenes onto transiently formed azacarbenium ions is a well-recognized method to form a C–N and C–C bond in the same reaction vessel. The Kibayashi and Hsung groups have each independently used this protocol to generate synthetic intermediates for the construction of lepadiformine and the cylindricines (Scheme 30). In each case, structurally similar substrates (differing in protecting group; the Hsung substrate was described as a stereoisomeric mixture of alkenes at the indicated position) were subjected to similar cyclization conditions using formic acid in a toluene–THF mixture. In each case, in situ formation of the *N*-carbamoyl azacarbenium ion **30.2** led to 'conjugate spirocyclization.' Cyclization was followed by quenching of the intermediate allyl cation to form allylic formate **30.3**.[47,48]

The Hsung and Kibayashi studies also demonstrated that simple alkenes were not nucleophilic enough to capture transiently formed azacarbenium ions. It had been established by Weinreb's group that a more nucleophilic alkene such as an allyltrimethylsilane was sufficiently reactive to capture those electrophiles (Scheme 31).[49] The reaction of enamide **31.1** with trifluoroacetic acid produced an azacarbenium ion that was intercepted by a pendant allylic silane. On the basis of the stereochemistry of **31.3**, the reaction was believed to proceed through a chair topology as represented by structure **31.2**.

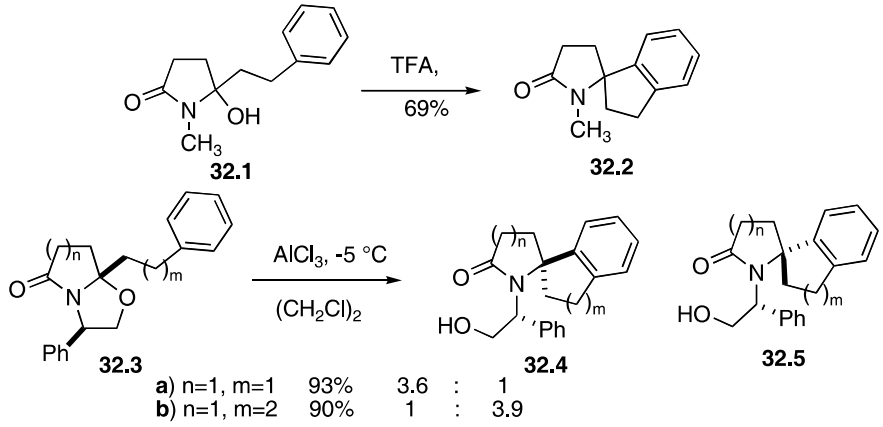
4.1.3. Nucleophilic arenes. Arene nucleophiles were used in the early reports of addition reactions to *N*-acyliminium ions. Further studies examined the problem of stereochemical induction in the spirocycle forming step.[50] The use of chiral auxiliaries attached to the nitrogen atom within substrates similar to **32.1** did not generate products of high de. (Scheme 32). Conversely, acetals of type **32.3** reacted smoothly upon treatment with aluminum chloride at 5 °C to give spirocyclic products **32.4** and **32.5** with modest diastereoselectivities (~3:1). Interestingly, the diastereoselectivity of the ring-forming event was strongly dependant on the size of the ring being produced. Formation



Scheme 30. Kibayashi and Hsung diene addition route.



Scheme 31. The Weinreb allylsilane approach.



Scheme 32. The Vernon route.

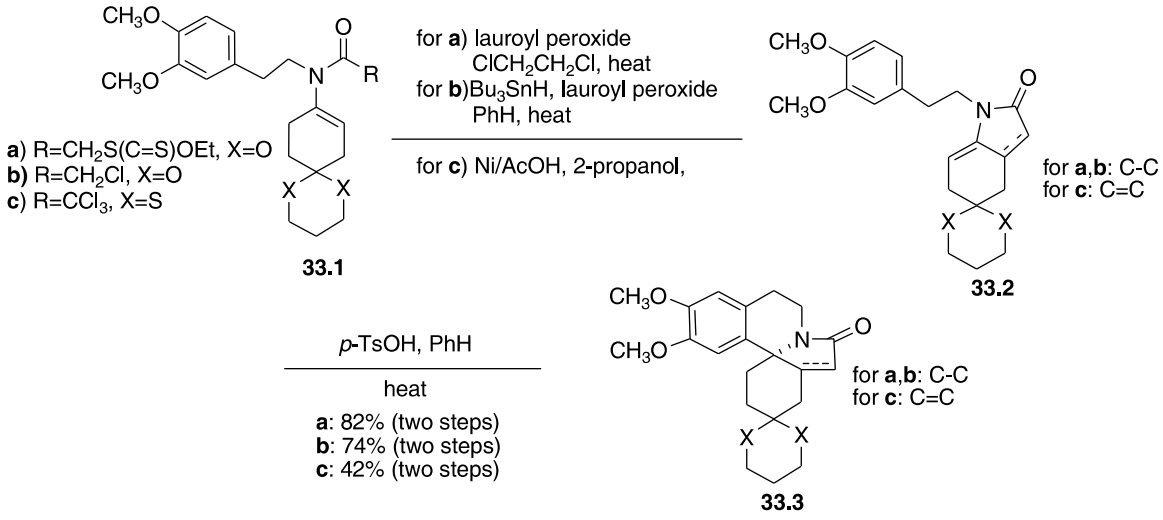
of a five-membered ring generated **32.4a** as the major diastereomer. In contrast, the cyclization of the homologous substrate yielded **32.5b** as the preferred product. A rationale for this observation was not provided.

This process has been exploited extensively in the construction of the erythrinan ring skeletons. Some recent examples are given in Scheme 33.[51] Formation of the critical bicycle **33.2** was accomplished by subjecting starting materials **33.1** to conditions amenable for radical generation. With enamide **33.2** in hand, its conversion to the designated spirocycle target was accomplished in a straightforward manner using catalytic *p*-toluenesulfonic acid in benzene. A mechanistically similar, highly diastereoselective route to the same ring system using an acetal as a chiral auxiliary (cf. to Scheme 32) proceeded in high yield.[52]

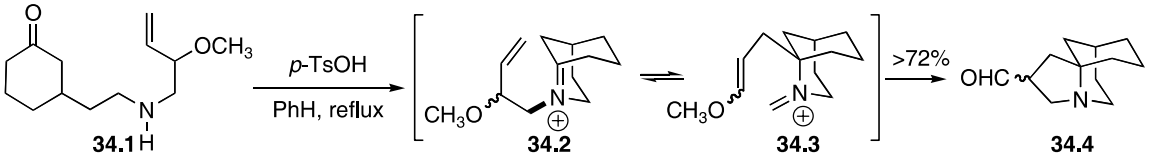
4.1.4. Tandem sigmatropic–aza-Prins process. The formation of a bridgehead iminium ion set the stage for a tandem [3,3] sigmatropic rearrangement followed by an aza-Prins process (Scheme 34).[53] Upon treatment of ketone **34.1** with *p*-toluenesulfonic acid in benzene, the intermediate ketiminium ion **34.2** rearranged to the alternate iminium ion **34.3**. This species suffered intramolecular attack from the pendant enol ether, to produce, after workup a mixture of diastereomeric aldehydes in 72% yield.

4.1.5. Attack on bromonium or iodonium ion intermediates. In the context of a recent cephalotaxine construction, the following sequence was used to build the azaspirocyclic core structure (Scheme 35).[54] The reaction of **35.1** with titanium tetrachloride in an acetic acid–dichloromethane mixture presumably formed an iminium ion in situ that suffered attack from the nearby β-keto ester to ultimately result in the formation of **35.2** in excellent yield (97%). Alternatively, subjection of **35.1** to *N*-iodosuccinimide and titanium tetrachloride generated enone **35.3**. This reaction was thought to proceed through an intermediate in which an iodide atom is located β to the ketone carbonyl moiety.

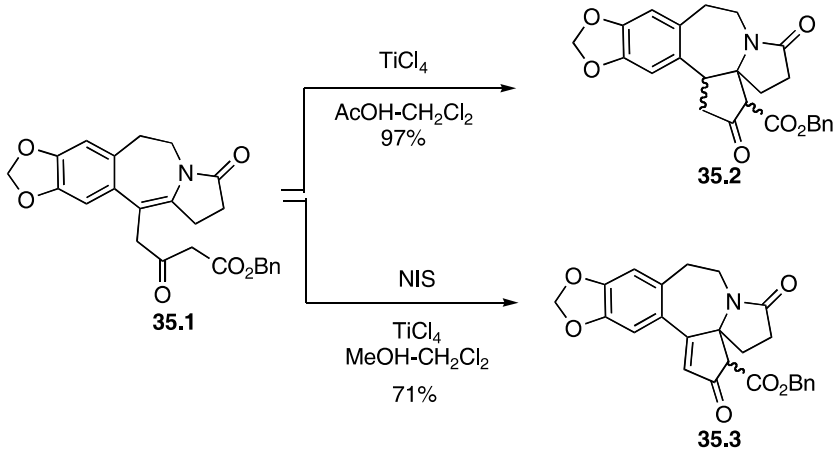
A recent efficient approach to the erythrina alkaloids utilized the attack of a nucleophilic arene to a bromonium



Scheme 33. The Zard/Ishibashi route.



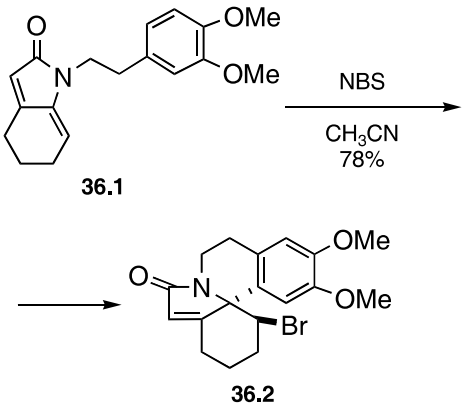
Scheme 34. The Brummond route.



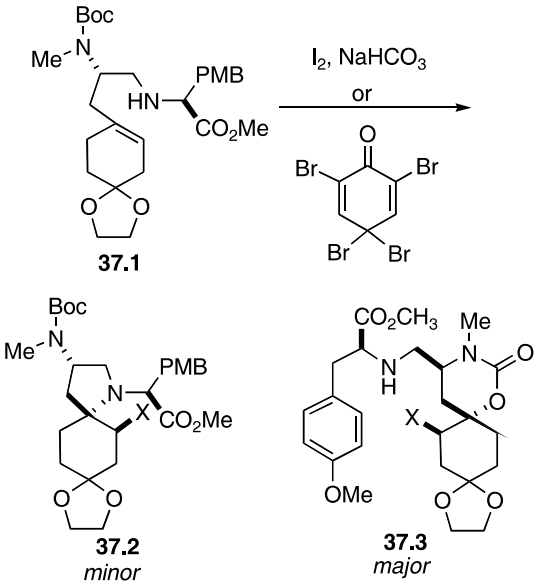
Scheme 35. The Nagasaka route.

ion-containing intermediate (Scheme 36).[55] *N*-Bromosuccinimide in acetonitrile induced a smooth cyclization of enamide **36.1** to produce tetracycle **36.2** in 78% yield. This process was strongly dependant on the solvent, as the use of dichloromethane resulted in the formation of a β-bromoenamide. This product was ultimately used in a construction of erysotramidine.

Spirocyclization of **37.1** occurred upon treatment with either iodine (with sodium bicarbonate) or 2,4,4,6-tetrabromo-2,5-cyclohexadienone (an electrophilic bromine source) to give the desired azaspirocycle **37.2** as the minor component in the reaction mixture (Scheme 37). The major product resulted from interception of the putative halonium ion species with the carbonyl atom of the *t*-butylcarbamate in **37.1**.[56]

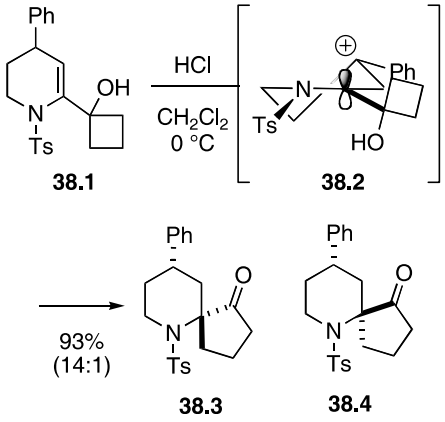


Scheme 36. The Padwa route.



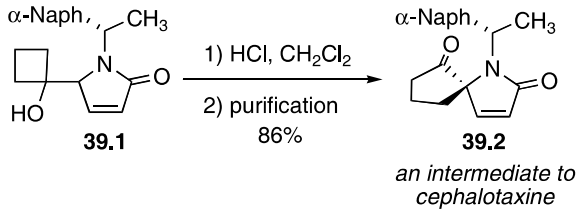
Scheme 37. The Bonjoch route.

4.1.6. Ring expansions. The use of semipinacol rearrangement reactions to form azaspirocycles has been a significant research interest of the Dake group.[57] Protonation of the double bond in **38.1** using concentrated hydrochloric acid at 0 °C generated a putative azacarbenium ion (represented by **38.2**). A 1,2-alkyl shift with concomitant C=O π-bond formation generated azaspirocycles **38.3** and **38.4** in 93% yield as a 14:1 ratio of diastereomers. The diastereoselectivity was rationalized by considering a transition state in which (a) the phenyl group is oriented in a pseudoequatorial orientation and (b) the 1,2-alkyl migration occurs from the 'axial' direction via a chair-like topology (Scheme 38).



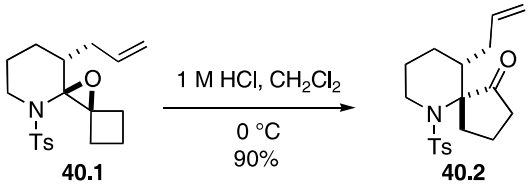
Scheme 38. The Dake routed.

A variant of this reaction was utilized by the Royer group in the synthesis of cephalotaxine and its derivatives (Scheme 39).[58] Reaction of lactam **39.1** with concentrated hydrochloric acid resulted in formation of ring-expanded products in ~80% diastereomeric excess. Purification of this mixture enabled a recovery of 86% of pure diastereomer **39.2**. This compound served as a key intermediate in their cephalotaxine construction.



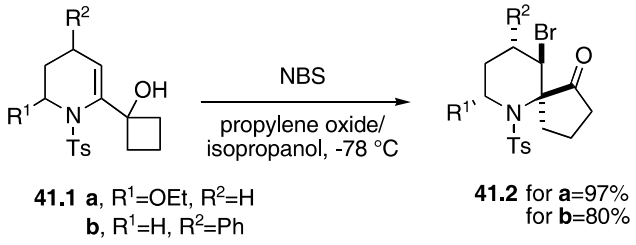
Scheme 39.

A related acid-promoted expansion of epoxide **40.1** smoothly formed azaspirocycle **40.2** in 90% yield (Scheme 40).[59] Noteworthy features for this process are (a) the formation of a spirocycle with an alkyl substituent on the carbon adjacent to the spirocyclic center and (b) the high diastereoselectivity of the process—the migrating alkyl group approaches the face opposite the adjacent alkyl group.



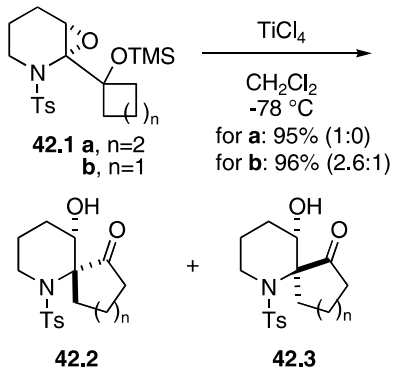
Scheme 40.

Semipinacol rearrangements forming azaspirocycles can also be performed using an electropositive halogen source (Scheme 41).[57b,60] As an example, **41.1a**, when subjected to a slight excess of *N*-bromosuccinimide (NBS) promptly underwent ring expansion to provide ketone **41.2a** in 97% yield. That the *N*-ethoxyaminal did not react is a testament to the mildness of these reaction conditions. In addition, substrates that have substituents at C-4 or C-6 of the heterocycle undergo highly diastereoselective reactions. In these cases, the indicated diastereomers are the only materials observed in the product mixture.



Scheme 41.

Investigations into siloxy-epoxide semipinacol processes uncovered some interesting observations (Scheme 42). For example, the ring expansion of **42.1a** using titanium tetrachloride generated cyclohexanone **42.2a** as a single observable diastereomer in 95% yield.[59] A related process was used to generate an intermediate used in a formal construction of fasicularin.[61] In contrast, the ring expansion of **42.1b** generated a 2.6:1 mixture of diastereomeric ring expansion products **42.2b** and **42.3b**, albeit in good yield (96%).



Scheme 42.

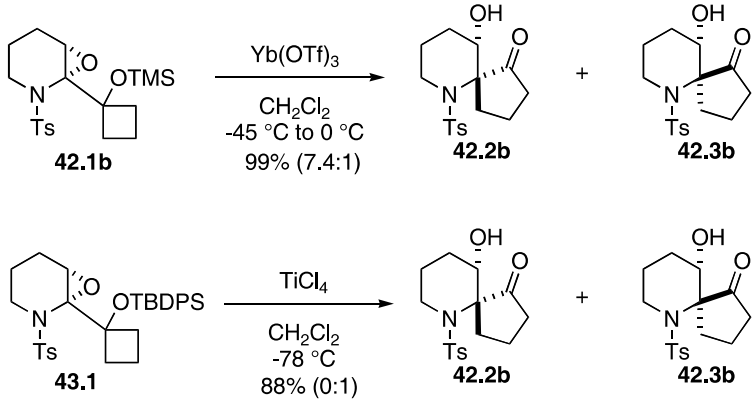
Fortunately, somewhat more selective processes forming **42.2b** or **42.3b** were uncovered by modifying the reaction parameters (Scheme 43). Treatment of **42.1b** with ytterbium(-III) triflate generated **42.2b** as the major product in a 7.4:1 mixture in 99% yield. Conversely, using a *tert*-butyldiphenylsilyl ether in the starting material (**43.1**) using titanium tetrachloride (identical conditions as that for **42.1a**) produced the alternate diastereomer as the only product in 88% yield.

4.1.7. Ring reorganization processes. A recent construction of cephalotaxine used a ring reorganization strategy to establish the azaspirocycle (Scheme 44).[62] A Wacker oxidation and aldol-type condensation was used to form azaspirocycle **44.2**. The ring system was then modified by treatment of **44.2** with zinc metal in acetic acid at 100 °C. Presumably proceeding through an azirdinium ion such as **44.3**, the reorganization process (ring expansion–ring contraction) formed the cephalotaxine skeleton **44.4** in 65% yield.

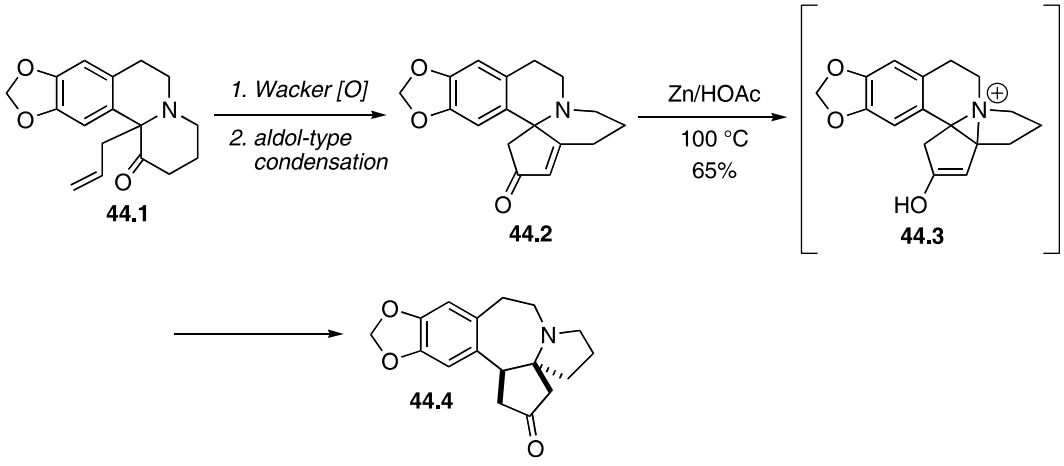
4.2. Cycloaddition strategies

4.2.1. Hetero Diels–Alder reaction. The reaction of Danishefsky's diene with imines generated in situ from amines and cyclic ketones such as **45.1** provided straightforward access to azaspirocycles (Scheme 45).[63] Although the success of the reaction did not depend on whether the imine was preformed or utilized in situ, the efficiency of the process was dependent on the size of the substituent (R^2) on nitrogen. As the diene was interpreted to approach from the equatorial face of the imine, larger substituents (R^2) on the nitrogen atom were detrimental to the process.

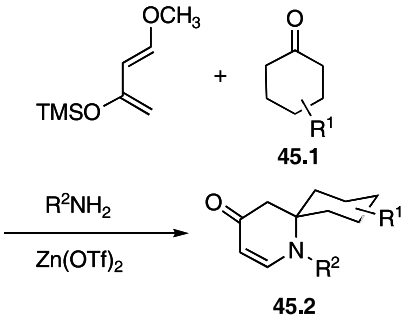
4.2.2. [3+2] Azaallyl cycloaddition. The Pearson group has disclosed fascinating cycloaddition strategies to approach these azaspirocycle ring systems (Scheme 46).[64] Imine formation between **46.1** and **46.2** using trimethylaluminum occurred smoothly. Tin–lithium exchange using butyllithium generated a 2-azaallyl anion that underwent cycloaddition with an electron rich alkene such as vinyl



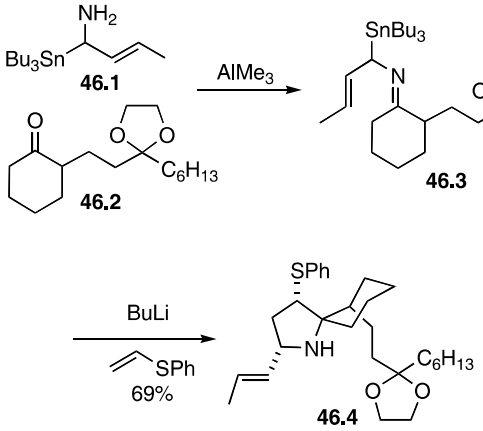
Scheme 43.



Scheme 44.



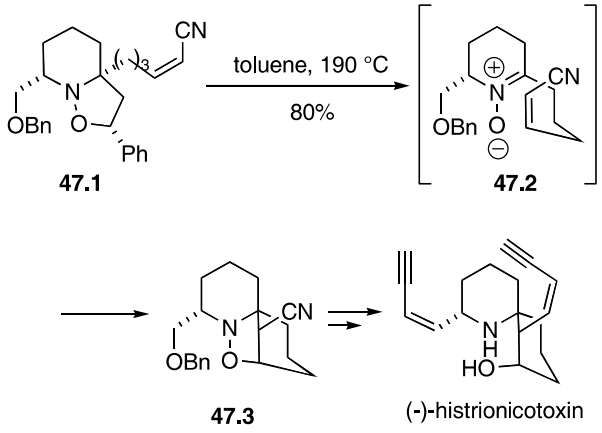
Scheme 45. The Oh approach.



Scheme 46. The Pearson azaallyl cycloaddition route.

phenyl sulfide. Cycloaddition on the face opposite the side chain generated azaspirocycle **46.4**. This work was the first to establish the relative configuration of lepadiformine.

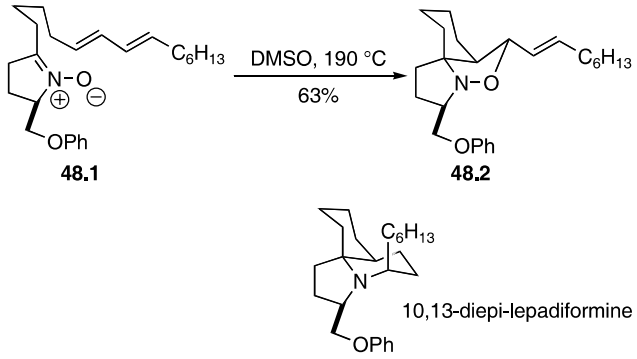
4.2.3. [3+2] Nitrone–alkene cycloadditions. A number of approaches to the azaspirocyclic core of histrionicotoxin utilizing [3+2] cycloadditions have been unsuccessful because of the formation of an undesired regioisomer as the major product.[65] Holmes and co-workers provided a useful and elegant solution to this problem (Scheme 47).[66] Heating **47.1** resulted in the loss of styrene to generate nitrone **47.2** in situ. This nitrone underwent cycloaddition in a regio- and stereochemically defined sense to produce **47.3**



Scheme 47.

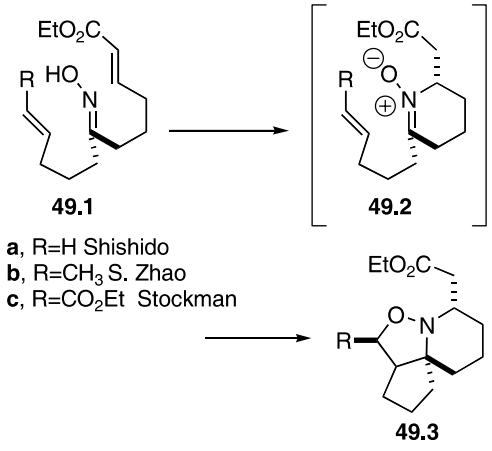
in 80% yield. The use of an α,β unsaturated nitrile was crucial to ensure the appropriate regiochemical result.

Weinreb utilized a [3+2] cycloaddition process to access the skeleton of lepadiformine (Scheme 48).[67] To that end, heating **48.1** in DMSO led to smooth formation of spirocycle **48.2**. This process was used to generate an intermediate used in a synthesis of epimers of lepadiformine, clues that helped to establish the structural and stereochemical identity of the natural product.



Scheme 48. The Weinreb nitrone cycloaddition route.

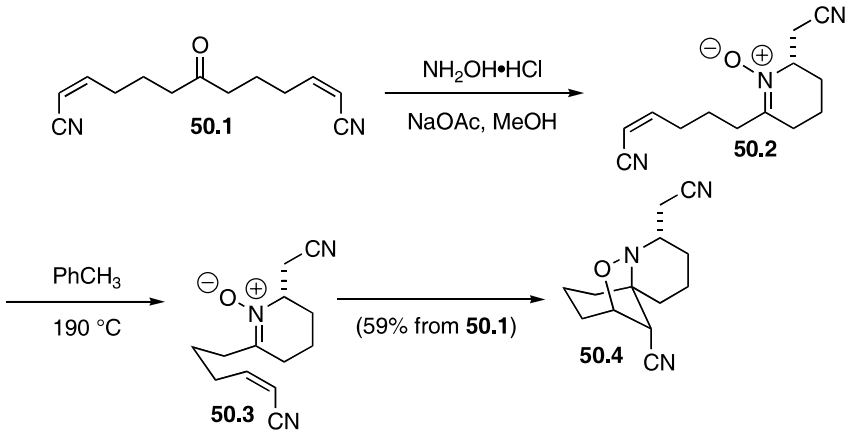
Related approaches to the halichlorine/pinnaic acid core have been developed independently in the Shishido, Zhao and Stockman groups (Scheme 49).[68] At its core, the approach consists of the in situ formation of a 1,3-dipole generated by conjugate addition of the nitrogen atom of an oxime of general structure **49.1** into an adjacent Michael acceptor. At this stage, [3+2] cycloaddition proceeds to generate the requisite azaspirocycle-containing intermediate **49.3**.



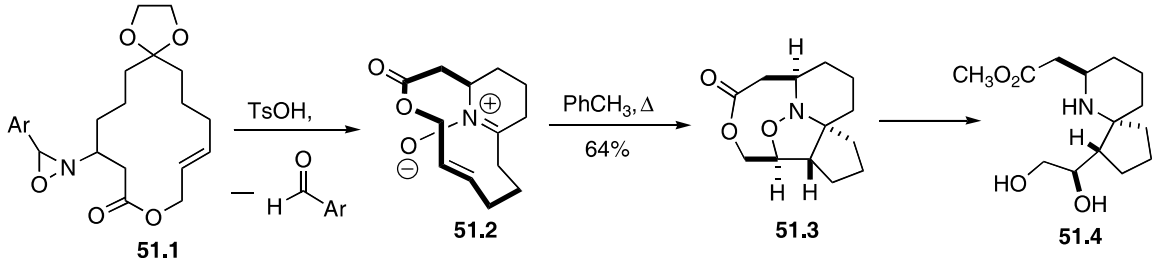
Scheme 49.

Stockman expanded this idea further.[69] His interest in two-directional synthesis led to his use of bis-*Z*-configured enenitrile **50.1** to generate, in rapid fashion, a common intermediate to that used in the Holmes' construction of histrionicotoxin (Scheme 50).

White and co-workers utilized a nitrone–alkene cycloaddition in a perceptive context as a synthetic approach towards the halichlorine/pinnaic acid spirocyclic core



Scheme 50. The Stockman route.



Scheme 51. The White approach.

(Scheme 51).[70] Deprotection of the ketal function within **51.1** under acidic conditions accompanied by concomitant cleavage of aldehyde enabled the generation of nitrone **51.2**. Transannular cycloaddition produced tetracycle **51.3**. Subsequent functional group manipulations produced the desired spirocycle **51.4**.

4.3. Other concerted reactions

Oxidation of hydroxylamine **52.1** led to the generation of *N*-acylnitroso compound **52.2**. The juxtaposition of the nitroso functional group and the alkene in **52.2** resulted in a nitroso-ene process (Scheme 52). This reaction established the azaspirocyclic ring system appropriately functionalized for its conversion to the ring system of halichlorine.[71]

The Knoevanagel condensation of iminium ion **53.1** and lactone **53.2** initiated a cascade process (Scheme 53). After condensation, an electrocyclic ring closure of **53.3** lead to spirocycle **53.4** in good yield. The hydrogenation of the double bond in **53.4** to produce **53.5** was the first in a series of reactions to produce 2-epi-perhydrohistrionicotoxin.[72]

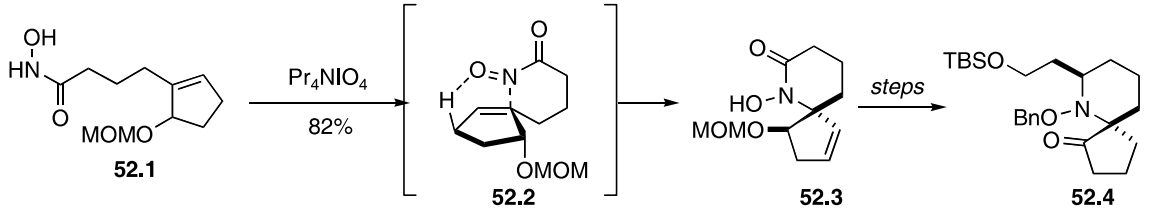
4.4. Intramolecular conjugate addition

In the Molander approach to the spirocycles, a double intramolecular conjugate addition reaction was used to establish both the 3° center and the spirocyclic ring system of the cylindricines in one step (Scheme 54).[73]

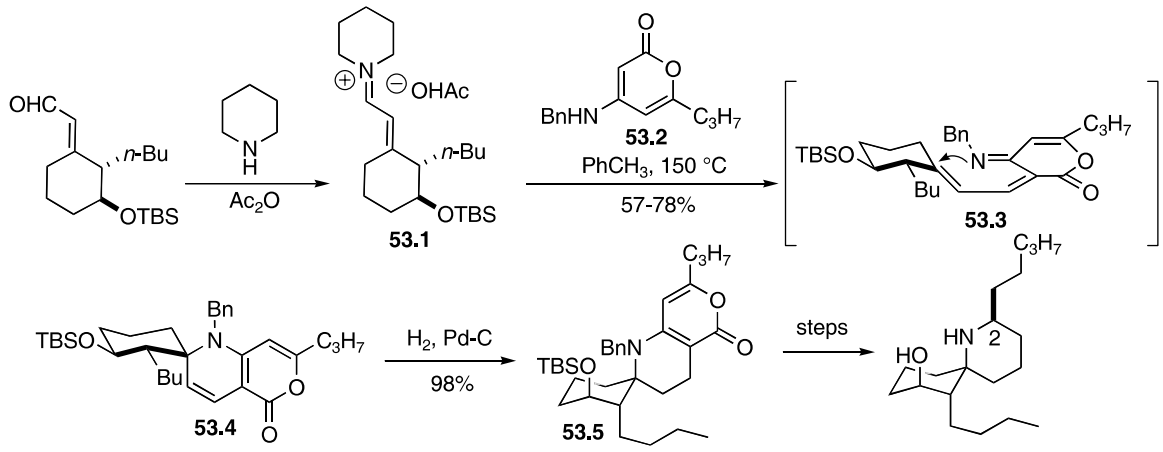
The Tietze group used a domino amide-bond formation–intramolecular conjugate addition reaction to generate spirocycles such as **55.3** (Scheme 55). Yields ranged from moderate to excellent, and the reaction was found to proceed particularly well with unhindered amines.[74]

4.5. Dearomatizations

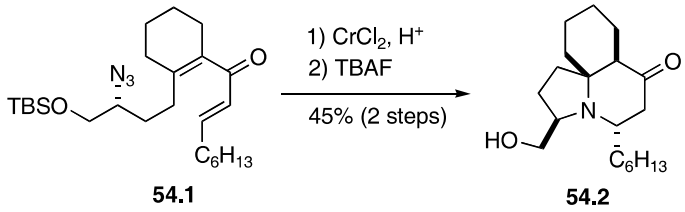
4.5.1. Electrophilic addition processes. The interaction between silver salts and *N*-chloro-*N*-methoxyamides generates an intermediary azetidium ion that, if juxtaposed with an appropriate nucleophile, will suffer nucleophilic attack. In the case of amide **56.1**, this reaction proceeded to generate azaspirocycle **56.2** in



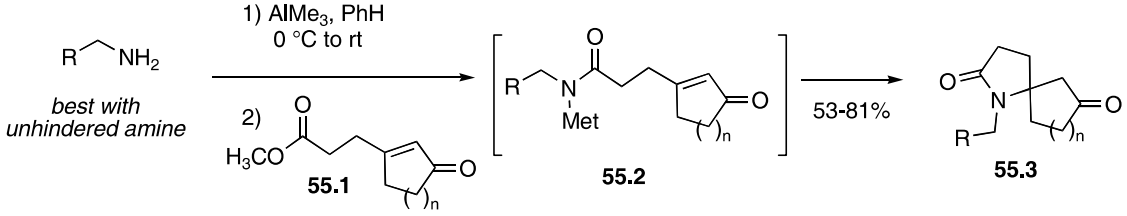
Scheme 52. The Kibayashi nitroso-ene approach.



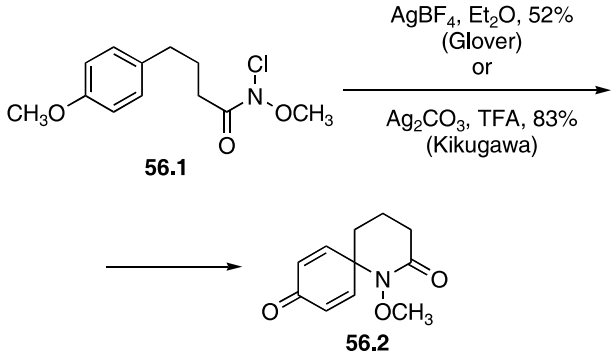
Scheme 53. The Hsung '3+3' annulation route.



Scheme 54. The Molander route.



Scheme 55. The Tietze route.



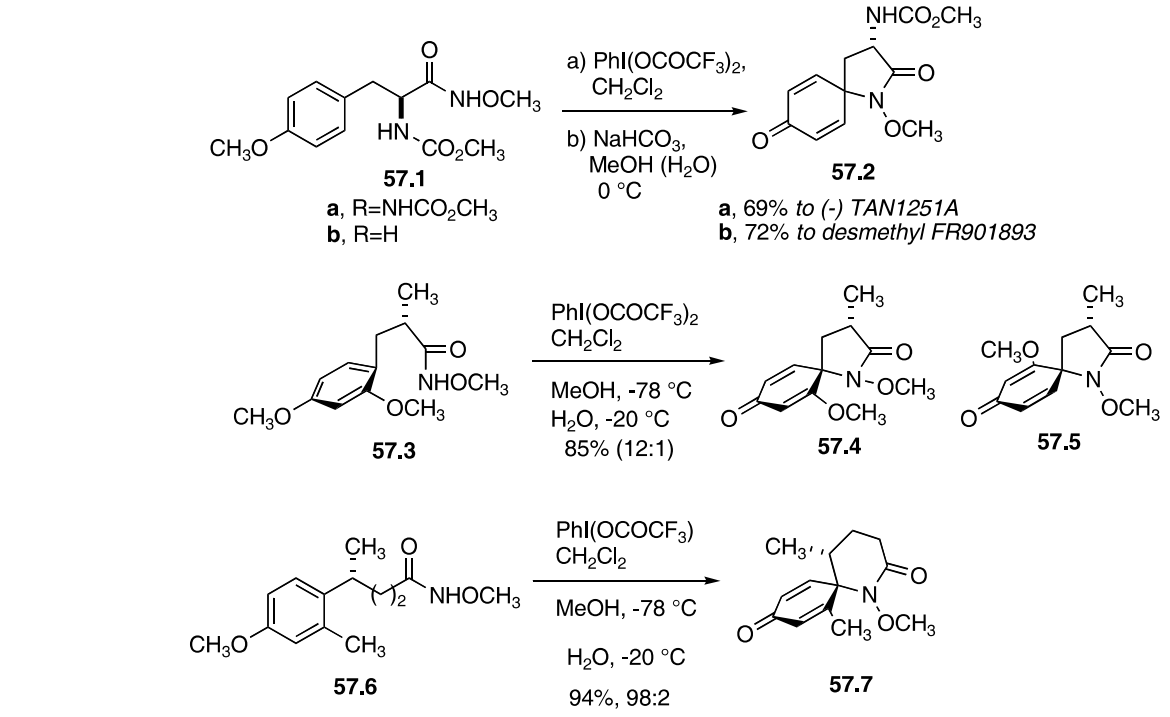
Scheme 56. Dearomatizing route to spirocycles.

excellent yield (Scheme 56).[75] The *p*-methoxy group is necessary as it directs *para* rather than alternative *ortho* attack of the aromatic ring.

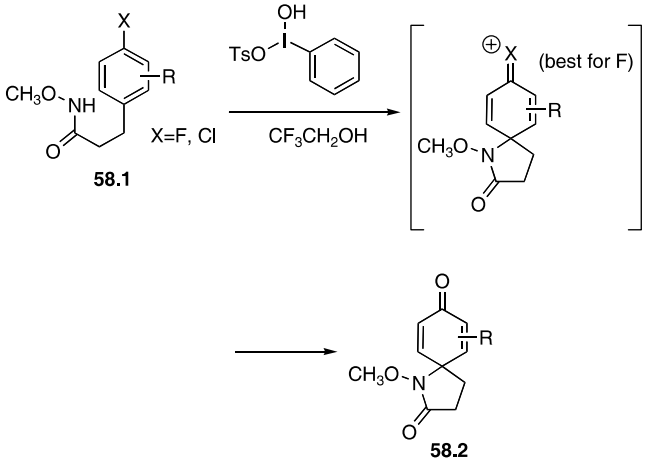
Wardrop and his group have recently expanded upon this concept.[76] In these cases, the use of the phenyliodinebis(trifluoroacetate) (PIFA), a hypervalent iodine reagent, leads to the formation of an identical type of compound (Scheme 57). This reagent system avoids *N*-chlorinated intermediates and aromatic chlorination. These compounds undergo attack by pendant electron-rich arenes. In certain cases, the diastereoselectivity can be quite good. These reactions have been used to generate key intermediates in the synthesis of desmethylamino FR901483 and (−)-TAN 1251A.

In a recent development, the Kikugawa group has uncovered that *p*-halo substrates can be induced to cyclize using hydroxy(*p*-toluenesulfonyloxy)iodobenzene as the oxidant (Scheme 58).[77] The reaction is most efficient using fluoroarenes as substrates.

4.5.2. Nucleophilic addition to arenes. The interaction between diacetoxyiodobenzene (DIB) and phenols in polar solvents produces an electrophilic species that can engage amide equivalents such as imino ethers in an intramolecular manner (Scheme 59).[78] As a specific example, the reaction of phenol **59.1** with DIB produces a transient electrophile that rapidly reacts with its pendant imidate moiety. The putative transient structure is then hydrolyzed with water, and acetylation furnishes the spirocycle **59.3**.[79] Indoles can also be used as internal nucleophiles.[80]



Scheme 57. The Wardrop route.



Scheme 58. The Kikugawa route.

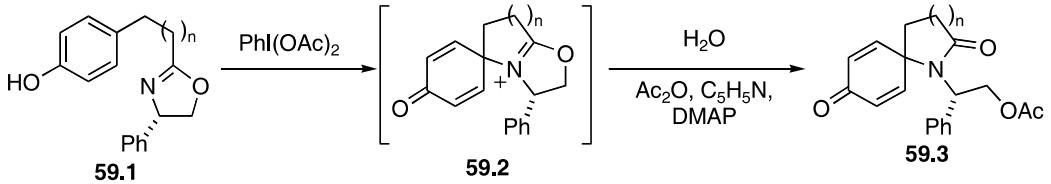
Secondary amines will also react in this context, but the yields are somewhat reduced (Scheme 60).[81] The selection of solvent can be crucial—the cyclization of **60.1** proceeded in highest yield using hexafluoroisopropanol. A similar observation was uncovered in a synthetic approach to TAN1251A (Scheme 61).[82]

This process proceeds particularly well using sulfonamide nucleophiles (Scheme 62).[83] A construction of the cylindricine alkaloids utilized a methanesulfonyl function in a dual role. It served as a protecting group and as a means to desymmetrize the dienone in the reaction product.[84] In general, though, cyclizations to form heterocyclic rings larger than five-membered are low yielding. Recently, an important, two-step variation of this methodology has been described that solves that particular problem. On appropriately functionalized substrates, intermolecular addition of nitriles to the intermediate electrophiles can be followed by a simple amide N-alkylation process to generate spirocycles in which the heterocyclic ring is larger than five-membered.[85]

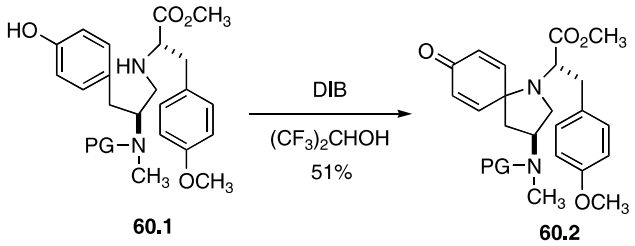
4.6. Radical cyclizations

In an approach to the azaspirocyclic core of halichlorine and the pinnaic acids, the reaction of the intermediary radical generated from **63.1** resulted in the formation of the fused ring system in **63.2** (Scheme 63).[86] This result presumably derived from 6-*endo* addition to the enamide, followed by expulsion of *p*-toluenesulfinate anion. In contrast, the radical initiation of **63.3** resulted in the smooth formation of spirocycle **63.4**.

Treatment of **64.1** with tri-*n*-butyltin hydride and AIBN leads to spirocycles **64.2** and **64.3** in excellent yield

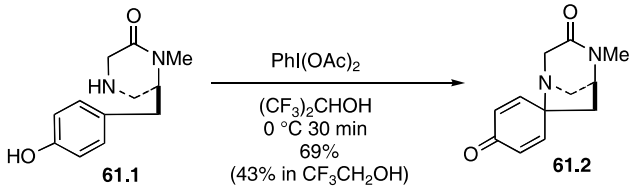


Scheme 59. The Ciufolini route.



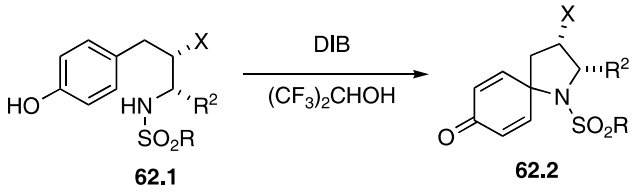
60.1 60.2

Scheme 60. The Sorensen approach.



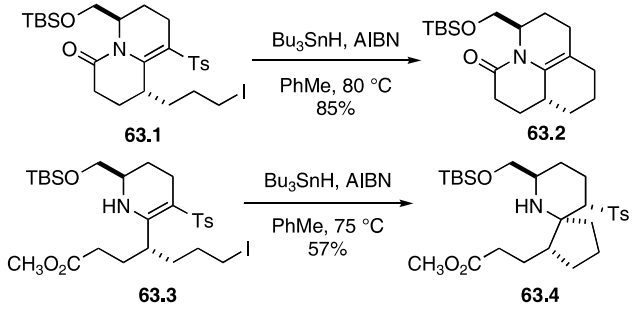
61.1 61.2

Scheme 61.



62.1 62.2

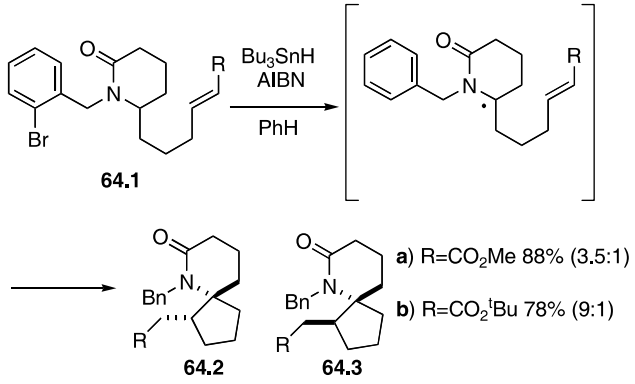
Scheme 62. The Ciufolini sulfonamide approach.



63.1 63.2 63.3 63.4

Scheme 63. The Clive approach.

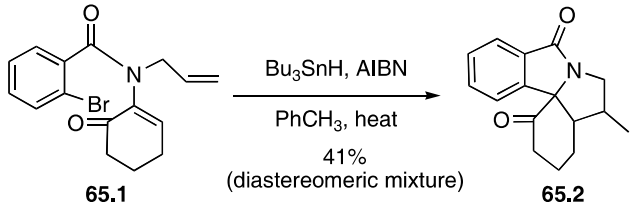
(Scheme 64).[87] After generation of an aryl radical, a 1,5-hydrogen abstraction generated a radical adjacent to the nitrogen atom. Cyclization in a 5-*exo* mode then produced the spirocycles.



64.1 64.2 64.3

Scheme 64. The Ihara route.

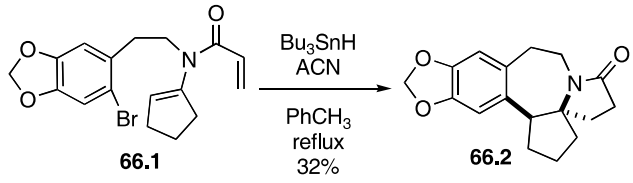
Spirocycles related to the erythrinan skeleton were formed, albeit in low yield and as a diastereomeric mixture, using a tandem bond-forming process via radical intermediates (Scheme 65).[88] As might be expected, initial 6-*endo* cyclization competed with the desired 5-*exo* cyclization process.



65.1 65.2

Scheme 65. The Parsons' approach.

A recent approach to cephalotaxine utilized a radical-mediated 7-*endo* cyclization reaction (Scheme 66).[89] Treatment of aryl bromide **66.1** with tri-*n*-butyl tin hydride generated the requisite natural product skeleton in **66.2** in 32% yield.



66.1 66.2

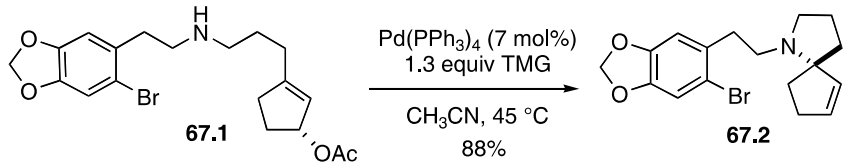
Scheme 66. The Ishibashi route.

4.7. Metal catalysis

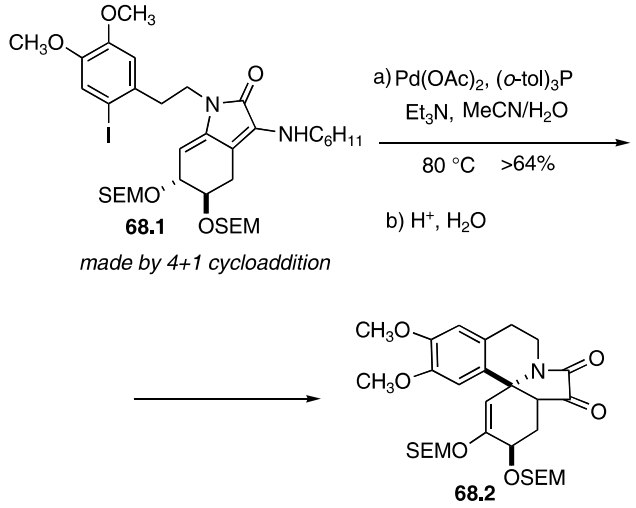
A recent construction of cephalotaxine utilized the following sequence to generate the required spirocycle (Scheme 67). Palladium(0) catalyzed allylic alkylation of amine **67.1** generated spiro compound **67.2** in excellent yield.[90] The aryl bromide function was a necessity for success—attempted reactions with the corresponding aryl iodide did not produce the desired spirocycle. In addition, the reaction temperature was key. Heating the reaction above 50 °C resulted in incomplete conversion, perhaps because of a competing process involving the haloarene.

The Rigby group recently investigated a synthetic approach to erythrinan alkaloids that incorporate a Pd(0) catalyzed Heck reaction as a key process (Scheme 68).[91] The stereochemistry of the spirocycle junction was established using the stereochemistry of the allylic siloxy function in **68.1**. The combination of catalytic palladium(II) acetate and tri-*o*-tolylphosphine in the presence of triethylamine generated a palladium(0) complex in situ that undergoes oxidative insertion into the aryl iodide bond. The sequence of migratory insertion (preferentially a *syn* process) followed by β-hydride elimination (also preferentially a *syn* process) thus defined the stereochemistry of the spirocycle ring junction. Initial unsuccessful studies utilized TBS ethers in place of the sterically less hindering SEM ethers.

Ring closing metathesis reactions have been used in two-step 1-azaspirocycle formation (vida supra). A process that utilizes

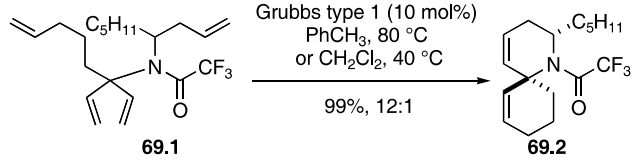


Scheme 67. The Tietze allylic alkylation route.



Scheme 68. The Rigby approach.

metathesis chemistry to generate both the heterocycle and the carbocycle of the spirocycle in a single step has been developed (Scheme 69).[92] This process proceeds with good diastereoselectivity (12:1 favoring **69.2**). The diastereoselectivity increases further when the metathesis chemistry is carried out in two discrete steps. The heterocycle is formed first through metathesis, then the carbocycle.



Scheme 69. The Harrity route.

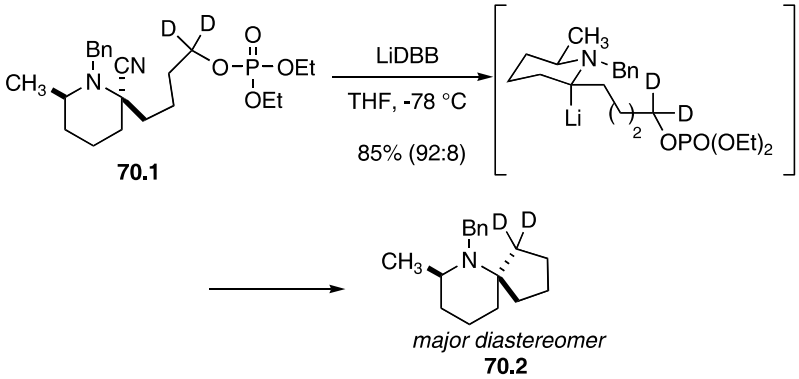
4.8. Miscellaneous

4.8.1. Intramolecular nucleophilic substitution. Rychnovsky's reductive decyanation/lithiation–electrophilic trapping protocol has recently been used for the construction of 1-azaspirocycles (Scheme 70).[93] In an interesting study, the treatment of deuterated substrate **70.1** with lithium di-*tert*-butylbiphenylide presumably produced predominantly axially lithiated α-aminoorganolithium intermediate. Cyclization proceeds with retention of configuration to produce **70.2** in 85% yield.

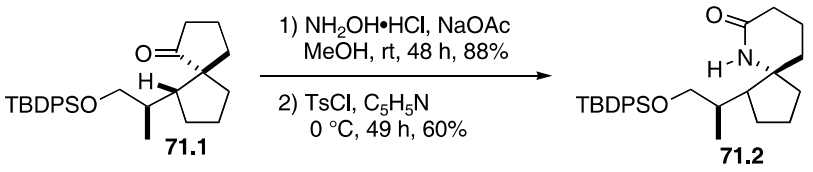
4.8.2. Beckmann rearrangement. Although it necessitates the stereocontrolled construction of a quaternary center, the conversion of an 'all-carbon' spirocyclic system to one containing a heteroatom can be a useful process. A recent example of this process was described by Pilli (Scheme 71).[94] In the event, ketone **71.1** was converted to its corresponding oxime using hydroxylamine in the presence of sodium acetate. Reaction of the hydroxylamine with *p*-toluenesulfonyl chloride with pyridine initiated a Beckmann rearrangement to produce amide **71.2** in 60% yield.

4.8.3. Nazarov reaction. An ingenious method for the installation of an embedded spirocyclic system utilized a Nazarov cyclization (Scheme 72).[95] Specifically, the treatment of the vinylogous amide **72.1** with diethylaluminum chloride induced cyclization to produce **72.2** in good yield.

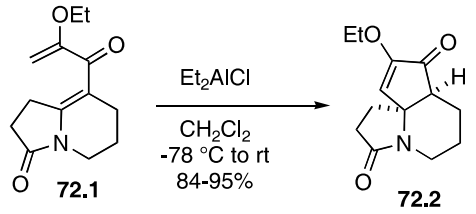
4.8.4. Photochemical cycloaddition–fragmentation. A photochemical formal [5+2] cycloaddition was used to build three rings common to cephalotaxine (Scheme 73).[96] The irradiation of a solution of **73.1** in toluene generated an excited state species (represented by **73.2**) that is presumably organized via hydrogen bonding. After a [2+2] cycloaddition between the C=N bond of the imide-ol tautomer of **73.1** and the pendant alkene, spontaneous fragmentation of **73.3** produced the cephalotaxine ring system within **73.4**.



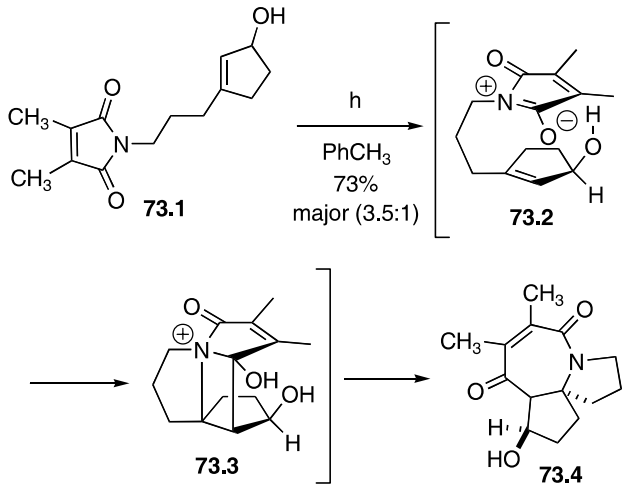
Scheme 70. The Rychnovsky approach.



Scheme 71. The Pilli route.



Scheme 72. The Cha route.



Scheme 73. The Booker-Milburn approach.

5. Concluding remarks

The wide range of approaches presented in the preceding schemes is a clear demonstration of the inspiration of 1-azaspirocycles for synthetic organic chemists. In most cases, a method was developed in order to solve a specific synthetic problem, generally within the context of a total synthesis exercise. These solutions, taken as a whole, help to set new boundaries for the organic chemist. Even so, the prospect of future developments that will enable the synthesis of these motifs within any structural context in a highly selective, economical manner, is an exciting one.

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Biographical sketch

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Synthesis of formyl-thienylpyrroles: versatile building blocks for NLO materials

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Abstract—Several formyl-substituted 1-alkyl(aryl)-2-(2′-thienyl)pyrroles **3–7** were synthesized by functionalization of the pyrrole or thiophene ring of thienylpyrroles **2** using different methods: Vilsmeier formylation or metalation followed by reaction with DMF.

1. Introduction

Formylation is a key process in organic synthesis, with the resulting aldehyde function being a 'crossroads' intermediate. Not surprisingly, a large number of methods have been developed for this reaction. Reagents for electrophilic formylation are mostly of the form $Y–CH{=}X^+$. Thus the reactions attributed to Vilsmeier ($ClCH{=}NR_2^+$), Rieche (e.g., $MeOCHCl_2 \rightarrow MeO{=}CHCl^+$), Gatterman ($Zn[CN]_2$/$HCl \rightarrow HC{=}NH_2^{2+}$), Gatterman–Koch (CO/HCl/Lewis acid $\rightarrow HC{=}O^+$) and even Duff ($CH_2{=}NH_2^+$— followed by dehydrogenation of initially formed RCH_2NH_2) all fit this pattern.[1]

Organolithiums are beyond any doubt the most useful metalated heterocycles. Usually they are prepared by direct deprotonation of acidic hydrogens using strong bases or, particulary useful in the case of the less acidic sites in aromatic rings, by halogen exchange between a halogenated heterocycle and an organolithium compound or lithium metal. Another frequent alternative is the so-called *ortho*-lithiation or 'directed *ortho*-metalation' (DoM), which is the metalation of an aromatic ring adjacent to a heteroatom-containing functional group by providing the lithium base with a point of coordination, thus increasing reactivity close to the coordination site. The lithiated species generated by all these methods are able to react with all kinds of electrophiles.[2–3]

Vilsmeier formylation and metalation followed by quenching with DMF constitute the most significant routes for the preparation of formyl-substituted pyrroles and thiophenes.[4–5]

The formyl-derivatives obtained can further react to afford more complex molecules, which have made of formyl-thiophenes and formyl-pyrroles some of the most important molecules to be used as building blocks in biological active compounds, supramolecular chemistry and molecular electronics.[6–25]

During the last years we have been concerned with the studies of several organic and organometallic compounds such as oligothiophenes, thienylpyrroles, thienylphthalazines, thienyl and bithienyl–Mo complexes bearing donor and electron acceptor units motivated by their potential applications in optical and electronic devices.[25–34] Recently, we have investigated donor–acceptor substituted thienylpyrroles. Due to their solvatochromic, electrochemical and non-linear optical properties, donor–acceptor thienylpyrrole derivatives could be used for the manufacture of semiconductor materials or materials with strong non-linear optical (NLO) properties.[28–31] Conjugated 1-(alkyl)aryl-2-(2′-thienyl)pyrroles, as strong π-electron donor moieties functionalized with the formyl-group on the thiophene or on the pyrrole moiety, could be used as precursors in the preparation of functional π-conjugated systems with several applications (e.g., NLO).

As part of our continuing interest in non-linear optical material, in this paper, we describe the synthesis of formyl-thienylpyrroles, **3–7** prepared from 1-propyl-2-(2′-thienyl)-pyrrole **2a** and 1-aryl-2-(2′-thienyl)pyrroles **2b–f**.[35]

Keywords: Formyl-substituted thienylpyrroles; Reactivity studies; Vilsmeier formylation; Metalation; UV–visible spectroscopy.
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2. Results and discussion

2.1. Synthesis

2.1.1. Synthesis of 1-*n*-propyl-2-(2′-thienyl)pyrrole 2a. In order to compare the reactivity of 1-alkyl- and 1-aryl-2-(2′-thienyl)pyrroles through the Vilsmeier reaction and through the metalation followed by quenching with DMF, 1-propyl-2-(2′-thienyl)pyrrole **2a** was synthesized from *N*-propyl-4-(2′-thienyl)-4-oxobutanamide **1a** using a combination of the Friedel–Crafts and the Lawesson reactions.[35,36] Direct amidation of 4-oxo-(2′-thienyl)butanoic acid[36] with propylamine was carried out through DCC–BtOH mediated reaction. Amide **1a** was obtained as a colourless solid in good yield (80%).

Recently, we have demonstrated that the reaction of secondary aryl-(2′-thienyl)-4-oxobutanamides with Lawesson's reagent (LR) can yield thienylpyrroles and/or bithiophenes in different ratios depending on the substituent(s) of the precursor arylamines.[35] In the case of the secondary *n*-propyl amide **1a**, treatment with an equimolar amount of LR gave only the thienylpyrrole **2a** in 47% yield.

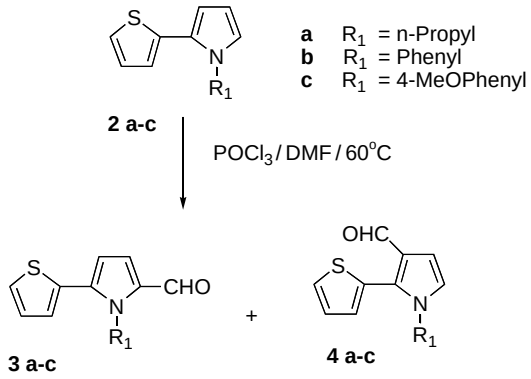
2.1.2. Vilsmeier formylation. Electrophilic substitution reactions of thienylpyrroles were found to be very selective. According to earlier reports, the pyrrole nitrogen atom has a greater ability to delocalize the positive charge of σ-complexes than the sulfur atom in thiophene; pyrrole is therefore considerably more reactive towards electrophilic substitution than thiophene. Even when both α-positions of the pyrrole ring are occupied, electrophilic substitution will preferentially occur in the β-position of the pyrrole ring rather than the α-position of the thiophene ring.[4,37–40] The reactivity of these systems has been demonstrated with the use of electrophilic reactions producing derivatives with the electrophile substituted primarily on the pyrrole ring.[28–31,39–46]

To our knowledge, there is only one previous study describing the formylation of thienylpyrroles and this study was performed through the Vilsmeier–Haack reaction on the simple 2-(2′-thienyl)pyrrole and 2-(3′-thienyl)-pyrrole. Bouka et al. obtained exclusively derivatives formylated on the α-position of the pyrrole ring.[40]

Therefore, we decided to study the reactivity of different thienylpyrroles bearing *N*-alkyl or *N*-aryl groups on the pyrrole ring through the Vilsmeier–Haack reaction and metalation followed by reaction with DMF.

Accordingly, Vilsmeier formylation of thienylpyrroles **2a–c** proceeded selectively in the pyrrole ring to form the corresponding formyl-substituted thienylpyrroles **3–4**.

In our studies of Vilsmeier–Haack formylation of 1-propyl-2-(2′-thienyl)pyrrole **2a**, the 5-position of the pyrrole ring was found to be much more reactive than the 3-position. The Vilsmeier–Haack formylation of **2a**, with DMF/$POCl_3$ at 60 °C for 2 h produced a mixture of 5-formyl- **3a** (63%), and 3-formyl- derivative **4a**, in lower yield (5%) (Table 1, entries 1–2). Under the same experimental conditions 1-aryl-2-(2′-thienyl)pyrroles **2b–c** behave quite differently giving a mixture of the 5- and 3-formyl-derivatives in similar yields. Formylation of **2b** gave a mixture of **3b** (19%) and **4b** (22%), (Table 1, entries 3–4) and formylation of **2c** gave a mixture of **3c** (12%) and **4c** (10%). In comparison to alkylpyrrole **2a** the formyl derivatives of 1-aryl-2-(2′-thienyl)pyrroles **2b–c** were obtained in lower yields (Scheme 1).



Scheme 1. Synthesis of formyl-thienylpyrroles **3–4** from thienylpyrroles **2** by Vilsmeier formylation.

In order to interpret the results obtained we consider several factors: (i) an appreciably larger nucleophilicity of the pyrrole ring compared to that of thiophene; (ii) a decrease in the electron density in the pyrrole ring due to the competitive conjugation of the *N*-aryl group with the unshared electron pair on nitrogen and also due to its negative inductive effect; (iii) possible steric influence due to the *n*-propyl group for attack at the α-position of the pyrrole ring.[44]

3-Substituted pyrroles are the most difficult to synthesize since most electrophilic aromatic substitution reactions and lithiation reactions of *N*-substituted pyrroles occur at the 2-position and so functionalization at the 3-position of

Table 1. Yields, ^{1}H NMR, IR and UV–visible data of formyl-thienylpyrroles **3–4**

Entry	Pyrrole	Formyl-pyrrole	Yield (%)	δ_H (ppm)[a]	IR υ_{CHO} (cm^{-1})	λ_{max} (nm) (ε)[b]
1	**2a**	**3a**	63	9.54	1658	321.5 (24,650)
2	**2a**	**4a**	5	9.54	1662	293.5 (5440)
3	**2b**	**3b**	19	9.39	1660	340.5 (20,100)
4	**2b**	**4b**	22	9.82[c]	1661	325.0 (7440)
5	**2c**	**3c**	12	9.38	1655	343.0 (21,559)
6	**2c**	**4c**	10	9.81[c]	1661	—

[a] For the C*H*O proton of formyl-thienylpyrroles **3–4** (300 MHz, $CDCl_3$).
[b] All the UV–visible spectra were run in ethanol.
[c] For the C*H*O proton of formyl-thienylpyrroles **3–4** (300 MHz, acetone-d_6).

pyrrole is a challenging goal in synthetic research. Bulky substituents on the nitrogen atom promote 3-substitution. This observation led to new approaches to the synthesis of 3-substituted pyrroles, as these are normally found only as by products in reactions leading predominantly to 2-substitution.[47–49] As 3-formyl *N*-arylpyrroles are key synthetic intermediates to highly biologically active compounds the preparation of new derivatives, even in fair yields, still remains an attractive goal.[10–11,44,46]

The structures of formyl-substituted pyrrole derivatives **3–4** were unambiguously confirmed by their analytical and spectral data. In the ^{1}H NMR spectrum of 5-formyl-substituted pyrrole derivatives **3a–c** two signals at about 6.40–6.64 and 6.96–7.17 ppm were detected. Both signals appear as doublets with coupling constants of 4.2–4.5 Hz indicating the presence of two adjacent protons (3-H and 4-H) at the corresponding pyrrole moiety. In the ^{1}H NMR spectrum of 3-formyl-substituted pyrrole derivatives **4a–c** two signals at about 6.47–6.79 and 6.78–7.19 ppm were detected. Both signals appear as doublets with coupling constants of 3.0–3.3 Hz. These signals were attributed to the 5-H and 4-H in the pyrrole moiety. The position of the formyl group in pyrrole derivatives **4a–c** was also confirmed through the analysis of 2D NOESY spectra. Thus, the 2D NOESY spectra of compounds **4a–c** shows a cross peak of the pyrrole ring 4-H with the formyl group and also a cross peak of the formyl group with the thiophene ring 3′-H. On the contrary, the 2D NOESY spectrum of compound **4a** shows a cross peak of the NCH_2 protons of the *n*-propyl group with the 5-H proton of the pyrrole ring but there is no cross peak of the pyrrole ring 5-H with the formyl group. This is taken as evidence for the attachment of the formyl group at ring position 3. In all the ^{1}H NMR spectra of formyl-substituted pyrrole derivatives **3a–c** and **4a–c** three signals at about 6.90–7.20 (multiplet), 6.72–7.20 (double doublet) and 7.19–7.63 (double doublet) were detected. These signals were attributed, respectively, to the 4′, 3′ and 5′-H protons in the thiophene moiety.

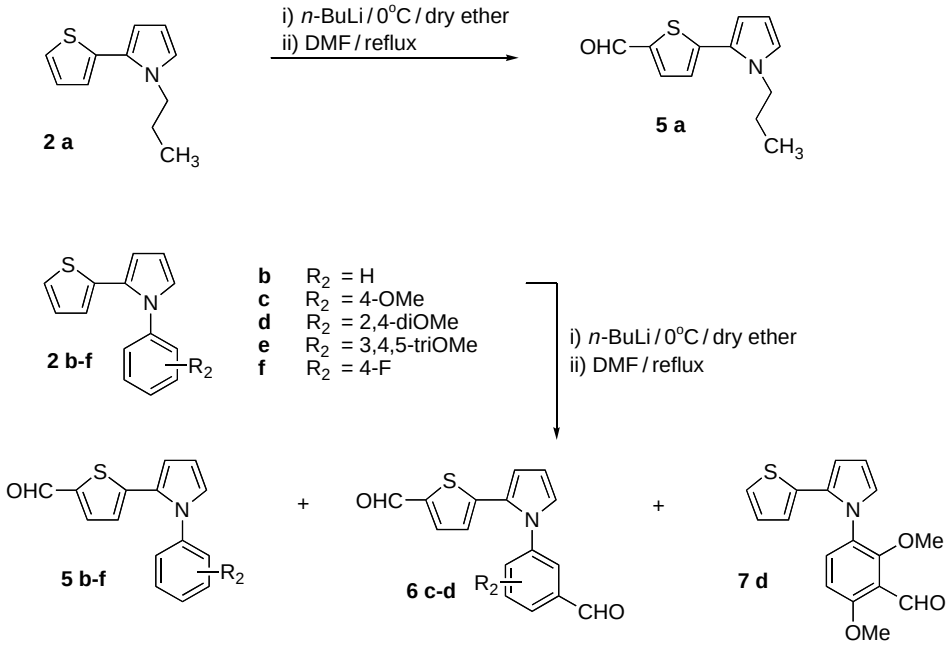
2.1.3. Metalation followed by reaction with DMF. As (5′-formyl-2′-thienyl)pyrroles could not be synthesized solely by the Vilsmeier–Haack reaction, we tried to prepare these compounds by lithiation followed by treatment with DMF.

The electron-rich five member aromatic *N*-substituted pyrrole, furan and thiophene are lithiated at C-2 by direct deprotonation with a lithium-containing base. Several authors have reported the α-lithiation of *N*-arylpyrroles using different experimental conditions: *n*-BuLi-TMEDA chelate, *n*-BuLi-*t*BuOK (LiCKOR) superbase, *tert*-BuLi-secondary amides, Na/dry ether/0 °C/*tert*-BuLi, *tert*-BuLi/−78 °C/THF, *n*-BuLi/THF/−78 °C, *n*-BuLi-TMEDA/THF/−75 °C.[49–54]

Recently, novel methods for site-selective lithiation in α or benzylic positions of 1-(methoxyphenyl), 1-(chlorophenyl), 1-(bromophenyl), 1-(trifluoromethylphenyl) and 1-(methylphenyl)pyrroles have also been reported.[55–59]

To our knowledge, the formylation of thienylpyrroles through lithiation followed by quenching with DMF has not been previously reported, and success would open the way to a new range of formyl-functionalized thienylpyrroles.

The metalation of thienylpyrroles **2** was carried out with *n*-BuLi in dry ether at 0 °C for 1 h. Subsequently, the organolithium derivatives were converted to the corresponding formyl compounds, by addition of DMF followed by refluxing the mixture for 1 h (Scheme 2, Table 2). In order to compare the reactivity of pyrroles **2** under



Scheme 2. Synthesis of formyl-thienylpyrroles **5–7** from thienylpyrroles **2** by metalation followed by reaction with DMF.

Table 2. Yields, ^{1}H NMR, IR and UV–visible data of formyl-thienylpyrroles **5–7**

Entry	Pyrrole	λ_{max} (nm) (ε)[a]	Formyl-pyrrole	Yield (%)	δ_H (ppm)[b]	IR υ_{CHO} (cm^{-1})	λ_{max} (nm) (ε)[a]
1	**2a**	291.0 (1800)	**5a**	68	9.87	1659	374.0 (9474)
2	**2b**	294.5 (9208)	**5b**	78	9.75	1659	374.0 (19,180)
3	**2c**	290.0 (11,410)	**5c**	63	9.74	1659	379.0 (18,613)
4	**2c**	—	**6c**	5	9.81,[c] 10.48[c]	1659, 1684	374.0 (10,605)
5	**2d**	286.5 (10,093)	**5d**	48, 34[d]	9.73	1652	384.5 (18,158)
6	**2d**	—	**6d**	18[d]	9.75, 10.45	1657, 1690	377.0 (16,040)
7	**2d**	—	**7d**	8, 14[d]	10.45	1693	—
8	**2e**	281.5 (8477)	**5e**	12	9.77	1659	377.0 (11,860)
9	**2f**	289.5 (7939)	**5f**	25	9.75	1659	373.5 (15,191)

[a] All the UV–visible spectra were run in ethanol.
[b] For the C*H*O proton of formyl-thienylpyrroles **5–7** (300 MHz, $CDCl_3$).
[c] For the C*H*O proton of formyl-thienylpyrroles **5–7** (300 MHz, acetone-d_6).
[d] Yields for compounds **5d–7d** obtained for 2 h of lithiation followed by 2 h of reaction with DMF.

the experimental conditions described above, the reaction time studied for all derivatives (for the metalation and for the reaction with DMF) was 1 h. As a consequence of the limited reaction time, in some cases, unreacted starting materials remained in the reaction mixtures.

Through this method thienylpyrroles **2a–b** and **2e–f** were selectively lithiated at the α-position of the thiophene ring giving formyl-derivatives **5a–b** and **5e–f**.

The methoxy group is known as a moderately strong *ortho* directing substituent with electron withdrawal and electron donor properties.[3,55,60] At the same time, for compounds **2c–d** the 4-methoxy and the 2,4-dimethoxy group(s) have an α-directing effect in the aromatic ring. Consequently, the formylation of the aromatic ring was also observed for thienylpyrroles **2c–d** (Table 2, entries 4, 6 and 7, compounds **6c–d**, **7d**) due to the *ortho* directing effect of the methoxy groups (Scheme 2) giving a mixture of several formylated derivatives with 2-(5′-formyl-2′-thienyl)-pyrroles **5c–d** being the major products.

For compound **2d** we studied also the effect of the reaction time for the metalation step and for the reaction with DMF. Metalation of thienylpyrrole **2d** for 2 h followed by 2 h of reflux with DMF gave a mixture of 4 compounds: thienylpyrrole **2d** (18%), 1-(2″,4″-dimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5d** (34%), 1-(3″-formyl-2″,4″-dimethoxyphenyl)-2-(2′-thienyl)pyrrole **7d** (14%) and 1-(3″-formyl-2″,4″-dimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **6d** (18%) (Table 2, entries 5–7). The experiment showed that, instead of improving the yield of compound **5d** we obtained the diformylated compound **6d** and a higher yield for the formyl-aryl derivative **7d** as a result of the increase of the reaction time.

Compounds **5e** and **5f** were obtained but in lower yields. It should be recorded that we could not isolate any benzylic formyl product from these reactions.

^{1}H NMR spectra of (5′-formyl-2′-thienyl)pyrrole derivatives **5a–f** showed two signals at about 6.61–7.12 and 7.49–7.71 ppm. Both signals appear as doublets with coupling constants of 3.9–4.2 Hz indicating the presence of two adjacent protons (3′-H and 4′-H) at the corresponding thiophene moiety. In all the ^{1}H NMR spectra of formyl-substituted thiophene derivatives **5a–f** three signals at about 6.20–6.42 (multiplet) 6.53–6.77 (double doublet), and 6.82–6.97 (multiplet) were detected. These signals were attributed, respectively, to the 4, 3 and 5-H protons in the pyrrole moiety.

2.2. UV–visible study of formyl-substituted thienylpyrroles

The electronic spectra of formyl-thienylpyrrole derivatives were recorded in ethanol (Tables 1–2).

All the formyl-substituted thienylpyrroles **3–7** synthesized exhibit intense absorptions in the UV–visible range. The position of these absorptions is influenced by the structure of the compounds, for example, by the substituent on the nitrogen atom of the pyrrole ring and by the position of substitution of the formyl group on the thiophene, pyrrole or on the aromatic ring(s).

Communication between the electron donating and accepting termini can be evaluated by comparing the λ_{max} values. Dramatic differences in energy occur upon formyl-substitution of thienylpyrroles **2**. For example, thienylpyrrole **2d** (λ_{max}=286.5 nm) is shifted 98 nm upon formyl substitution (formyl- derivative **5d**, λ_{max}= 384.5 nm) (Table 2, entry 5). This effect has been attributed to the stabilization of LUMO by the electron-withdrawing groups.[61] The influence of the substituent on the nitrogen atom of the pyrrole ring is demonstrated by comparison of the absorption maxima of compounds **5a** and **5d** as the longest wavelength transition is shifted from 374.0 nm in 1-(*n*-propyl)-2-(5′-formyl-2′-thienyl)pyrrole **5a** (Table 2, entry 1) to 384.5 nm for 1-(2″,4″-dimethoxy-phenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5d** (Table 2, entry 5). The influence of the position of the formyl group on the pyrrole ring on λ_{max} of absorption for formyl derivatives **3** and **4** is noteworthy. The difference in λ_{max} values ($\Delta\lambda_{max}$) between compounds (**3a–b** and **4a–b**) is in the range of 15–28 nm (Table 1, entries 1–4). As expected, the presence of the formyl group on the 5-position of the pyrrole ring (**3a–3b**), relative to the same acceptor group in the 3-position (**4a–4b**), results in a bathochromic shift in the λ_{max} of absorption for **3a–3b** due to more extensive electron delocalization.

3. Conclusions

Starting from the readily available thienylpyrroles **2**, commercial reagents and simple and convenient procedures were used to synthesize new formyl-thienylpyrroles in fair to good yields, via two methods: Vilsmeier formylation and lithiation followed by reaction with DMF.

Vilsmeier–Haack formylation of **2** was made at the 3- and 5-positions on the pyrrole ring to give compounds **3–4**. These results are in accordance with the greater nucleophilicity of the pyrrole ring versus the thiophene ring as has been shown earlier in the case of the tricyanovinylation reaction and azo coupling reaction of 1-alkyl(aryl)-2-(2′-thienyl)pyrroles **2**.[28,29]

The lithiation of thienylpyrroles **2a–b** and **2e–f**, followed by quenching with DMF, occurred selectively on the α-position of the thiophene ring giving formyl derivatives **5a–b** and **5e–f**. For compounds **2c–d** with methoxy group(s) on the aryl ring was obtained a mixture of formyl-derivatives **5c–d**, **6c–d** and **7d** with the formyl group on the thiophene ring and/or on the aryl ring. The major compounds formed were (5′-formyl-2′- thienyl)pyrroles **5c–d**.

The formyl-derivatives **3–7** studied exhibit an absorption band in the UV–visible range influenced by the structure of the compounds: the type of substituent on the nitrogen atom of the pyrrole ring and also by the position of the formyl group on the thiophene or on the pyrrole ring.

The conjugated formyl derivatives of 1-alkyl(aryl)-2-(2′-thienyl)pyrroles will be used in the future, as precursors in the preparation of compounds with a stronger electronwithdrawing group for potential applications in NLO.[22,25]

4. Experimental

4.1. General

^{1}H NMR spectra were obtained on a Varian Unity Plus Spectrometer at 300 MHz and ^{13}C NMR spectra were determinated on a Varian Unity Plus Spectrometer at 75.4 MHz using the solvent peak as internal reference. The solvents are indicated in parenthesis before the chemical shift values (δ relative to TMS). Mps were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. UV–visible absorption spectra were obtained using a Shimadzu UV/2501PC spectrophotometer. EI mass spectra EI (70 eV) and HRMS were run on a Unicam GC–MS 120. Elemental analysis was carried out on a Leco CHNS-932. Column chromatography was performed on Merck silica gel 60 (Art 9385). Light petroleum refers to solvent boiling in the range 40–60 °C.

The synthesis of 1-aryl-2-(2′-thienyl)pyrroles **2b–f** has been described elsewhere.[35]

4.2. Synthesis of 1-propyl-2-(2′-thienyl)pyrrole 2a

(i) Synthesis of *N*-propyl-4-(2′-thienyl)-4-oxobutanamide **1a**. Amide **1a** was obtained using the experimental method described in Refs. 35, 36, by reacting 4-oxo-(2-thienyl)-butanoic acid (5.4 mmol) in CH_2Cl_2 with 1,3-dicyclohexylcarbodiimide (7.1 mmol) and BtOH (7.1 mmol) and adding propylamine (5.4 mmol) at rt.

4.2.1. *N*-Propyl-4-(2′-thienyl)-4-oxobutanamide 1a. Colourless solid (80%). Mp: 96.2–97.6 °C (EtOH). IR (liquid film) ν 3311 (NH), 3029, 1661 (C═O), 1645 (C═O), 1552, 1523, 1420, 1397, 1248, 1179, 1063, 983, 954, 910, 851, 717 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.2 Hz, CH_3), 1.52 (m, 2H, CH_2CH_3), 2.61 (t, 2H, J=7.8 Hz, $CONHCH_2$), 5.78 (br s, 1H, N*H*), 7.13–7.15 (m, 1H, 4′-H), 7.65 (dd, 1H, J=5.1, 1.2 Hz, 5′-H), 7.78 (dd, 1H, J=3.7, 1.2 Hz, 3′-H). ^{13}C NMR ($CDCl_3$) δ 11.30, 22.76, 30.26, 34.62, 41.27, 128.16, 132.23, 133.73, 143.59, 171.71, 192.09. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.63; H, 6.72; N, 6.22; S, 14.23. Found: C, 58.63; H, 6.71; N, 6.23; S, 13.98.

(ii) Reaction of amide **1a** with Lawesson's reagent. Thienylpyrrole **2a** was obtained using the experimental method described in Refs. 35, 36, by heating the amide **1a** (2.3 mmol) in toluene (12 ml) with the Lawesson reagent (2.3 mmol) at reflux during 30 min.

4.2.2. 1-Propyl-2-(2′-thienyl)pyrrole 2a. Orange oil (47%). UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 291.0 (1803), 225.5 (2054). IR (liquid film) ν 3102, 2964, 2932, 2874, 1508, 1470, 1430, 1383, 1345, 1299, 1234, 1201, 1108, 1070, 941, 896, 844, 783, 711, 613 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.2 Hz, $(CH_2)_2CH_3$), 1.65–1.68 (m, 2H, $CH_2CH_2CH_3$), 3.97 (t, 2H, J=7.2 Hz, NCH_2), 6.17–6.22 (m, 1H, 4-H), 6.31 (dd, 1H, J=3.6, 1.8 Hz, 3-H), 6.76–6.88 (m, 1H, 5-H), 7.01 (dd, 1H, J=3.6, 1.2 Hz, 3′-H), 7.06–7.09 (m, 1H, 4′-H), 7.29 (dd, 1H, J=5.1, 1.2 Hz, 5′-H). ^{13}C NMR ($CDCl_3$) δ 11.17, 24.74, 48.99, 107.71, 110.16, 122.68, 124.71, 125.29, 126.28, 127.16, 134.97. MS (EI) *m*/*z* (%): 191 (M$^+$, 100), 162 (50), 149 (34), 130 (7), 121 (13), 111 (40), 104 (15). HRMS: *m*/*z* (EI) for: $C_{11}H_{13}NS$; calcd 191.0768; found: 191.0763.

4.2.3. General procedure for the synthesis of formyl derivatives 3–4 of 1-alkyl(aryl)-2-(2′-thienyl)pyrroles 2a–c through Vilsmeier formylation. $POCl_3$ (0.46 mmol) was added to DMF (0.46 mmol) at 0 °C and the mixture was stirred for 15 min at 0 °C. After this time pyrroles **2** (0.39 mmol) dissolved in DMF (1 ml) were added dropwise with stirring. The reaction mixture was then heated 2 h at 60 °C. The solution was then poured slowly into 5 ml saturated sodium acetate aqueous solution and stirred 30 min. The organic layer was diluted with ether, washed with saturated $NaHCO_3$ aqueous solution, and dried with anhydrous $MgSO_4$. Evaporation of the organic extract under reduced pressure gave a mixture of 5-formyl- **3** and 3-formylpyrroles **4**, which were purified by 'flash' chromatography on silica with increasing amounts of ether in light petroleum as eluent.

Vilsmeier formylation of **2a** gave a mixture of 5-formyl-1-propyl-2-(2′-thienyl)pyrrole **3a** and 3-formyl-1-propyl-2-(2′-thienyl)pyrrole **4a**. The first component eluted was 5-formyl-1-propyl-2-(2′-thienyl)pyrrole **3a** as a green oil (63%). UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}), 321.5

(24,650). IR (liquid film): ν 2964, 1658 (C=O), 1509, 1473, 1428, 1396, 1314, 1294, 1251, 1225, 1198, 1154, 1042, 847, 776, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J=7.5$ Hz, $(CH_2)_2CH_3$), 1.70–1.82 (m, 2H, $CH_2CH_2CH_3$), 4.41 (t, 2H, $J=7.8$ Hz, NCH_2), 6.40 (d, 1H, $J=4.2$ Hz, 3-H), 6.96 (d, 1H, $J=4.2$ Hz, 4-H), 7.12–7.16 (m, 1H, 4′-H), 7.18 (dd, 1H, $J=3.6$, 1.2 Hz, 3′-H), 7.44 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 9.54 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 10.80, 24.68, 47.50, 111.89, 124.73 (two overlapped signals), 127.00, 127.42, 127.59, 132.17, 132.51, 136.36. MS (EI) *m/z* (%): 219 (M^+, 100), 218 (21), 204 (16), 202 (74), 190 (28), 177 (80), 176 (77), 162 (18), 148 (16), 121 (30), 104 (7). HRMS: (EI) *m/z* (%) for $C_{12}H_{13}NOS$; calcd 219.0718; found 219.0720. The second component eluted was 3-formyl-1-propyl-2-(2′-thienyl)pyrrole **4a** as a brown oil (5%). UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$), 293.5 (5440), 248.0 (10,388), 211.0 (8678). IR (liquid film): ν 1662 (C=O), 1485, 1446, 1382, 1257, 849, 765, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, $J=7.5$ Hz, $(CH_2)_2CH_3$), 1.65–1.82 (m, 2H, $CH_2CH_2CH_3$), 3.87 (t, 2H, $J=7.2$ Hz, NCH_2), 6.47 (d, 1H, $J=3.3$ Hz, 5-H), 6.78 (d, 1H, $J=3.3$ Hz, 4-H), 7.13–7.20 (m, 2H, 3′and 4′-H), 7.54 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 9.54 (s, 1H, CHO). MS (EI) *m/z* (%): 219 (M^+, 100), 218 (19), 190 (12), 174 (11), 162 (24), 149 (10), 130 (4), 121 (6), 104 (7), 89 (5). HRMS: (EI) *m/z* (%) for $C_{12}H_{13}NOS$; calcd 219.0718; found 219.0708.

Vilsmeier formylation of **2b** gave a mixture of 5-formyl-1-phenyl-2-(2′-thienyl)pyrrole **3b** and 3-formyl-1-phenyl-2-(2′-thienyl)pyrrole **4b**. The first component eluted was 5-formyl-1-phenyl-2-(2′-thienyl)pyrrole **3b** as a pale yellow solid (19%). Mp: 72.6–73.9 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$), 340.5 (20,100), 253.0 (8630). IR (liquid film): ν 1660 (CHO), 1596, 1511, 1497, 1469, 1433, 1406, 1361, 1318, 1046, 847, 775, 695, 547 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.64 (d, 1H, $J=4.2$ Hz, 3-H), 6.72 (dd, 1H, $J=3.9$, 1.2 Hz, 3′-H), 6.86–6.90 (m, 1H, 4′-H), 7.17 (d, 1H, $J=4.2$ Hz, 4-H), 7.19 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 7.33–7.39 (m, 2H, 2×Ar-*H*), 7.49–7.56 (m, 3H, 3×Ar-*H*), 9.39 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 109.72, 110.96, 120.51, 126.43, 126.62, 127.21, 128.87, 129.34, 129.46, 132.66, 136.45, 137.15, 178.76. MS (EI) *m/z* (%): 253 (M^+, 100), 225 (12), 175 (11), 147 (10), 121 (20), 77 (12). HRMS: (EI) *m/z* (%) for $C_{15}H_{11}NOS$; calcd 253.0561; found 253.0558. The second component eluted was 3-formyl-1-phenyl-2-(2′-thienyl)pyrrole **4b** as a pale yellow solid (22%). Mp: 106.9–107.8 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 325.0 (7440). IR (liquid film): ν 1661 (CHO), 1596, 1496, 1473, 1449, 1413, 1241, 848, 762, 695 cm^{-1}. ^1H NMR (acetone-d_6) δ 6.79 (d, 1H, $J=3.0$ Hz, 5-H), 7.10–7.13 (m, 1H, 4′-H), 7.15–7.19 (m, 2H, 4-H and 3′-H), 7.30–7.36 (m, 2H, 2×Ar-*H*), 7.43–7.49 (m, 3H, 3×Ar-*H*), 7.63 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 9.82 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 108.14, 110.95, 125.44, 126.27, 127.09, 128.20, 128.48, 129.18, 130.61, 132.66, 134.92, 138.60, 186.76. MS (EI) *m/z* (%): 253 (M^+, 100), 224 (19), 209 (14), 180 (5), 121 (11), 77 (22). HRMS: (EI) *m/z* (%) for $C_{15}H_{11}NOS$; calcd 253.0561; found 253.0576.

Vilsmeyer formylation of **2c** gave a mixture of 5-formyl-1-(4″-methoxyphenyl)-2-(2′-thienyl)pyrrole **3c** and 3-formyl-1-(4″-methoxyphenyl)-2-(2′-thienyl)pyrrole **4c**. The first component eluted was 5-formyl-1-phenyl-2-(2′-thienyl)pyrrole **3c** as a yellow solid (12%). Mp: 110.5–111.9 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$), 343.0 (21,559), 257.5 (8165), 226.5 (14,668). IR (liquid film): ν 1655 (CHO), 1512, 1495, 1395, 1337, 1319, 1248, 1230, 1193, 1162, 1103, 1052, 832, 805, 779, 765, 709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H, OCH_3), 6.63 (d, 1H, $J=4.5$ Hz, 3-H), 6.80 (dd, 1H, $J=3.8$, 1.2 Hz, 3′-H), 6.88–6.92 (m, 1H, 4′-H), 7.00 (d, 2H, $J=9.0$ Hz, 2×Ar-*H*), 7.15 (d, 1H, $J=4.5$ Hz, 4-H), 7.19 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 7.26 (d, 2H, $J=9.0$ Hz, 2×Ar-*H*), 9.38 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 55.49, 110.58, 114.45, 120.38, 126.41, 126.51, 127.16, 129.54, 129.88, 132.71, 134.76, 136.69, 160.17, 178.88. MS (EI) *m/z* (%): 283 (M^+, 100), 254 (19), 240 (30), 175 (48), 147 (18), 121 (16), 108 (6). HRMS: (EI) *m/z* (%) for $C_{16}H_{13}NO_2S$; calcd 283.0667; found 283.0664. Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.83; H, 4.69; N, 4.94; S, 11.33. Found: C, 67.58; H, 4.96; N, 4.91; S, 10.82. The second component eluted was 3-formyl-1-(4″-methoxyphenyl)-2-(2′-thienyl)pyrrole **4c** as pale yellow solid (10%). Mp: 99.7–101.0 °C. IR (liquid film): ν 1661 (CHO), 1512, 1449, 1300, 1242, 1028, 835, 763 cm^{-1}. ^1H NMR (acetone-d_6) δ 3.86 (s, 3H, OCH_3), 6.76 (d, 1H, $J=3.0$ Hz, 5-H), 7.00 (d, 2H, $J=9.0$ Hz, 2×Ar-*H*), 7.08 (dd, 1H, $J=3.0$, 1.0 Hz, 4-H), 7.09–7.13 (m, 1H, 4′-H), 7.16 (dd, 1H, $J=3.4$, 1.2 Hz, 3′-H), 7.25 (d, 2H, $J=9.0$ Hz, 2×Ar-*H*), 7.61 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 9.81 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 55.46, 107.85, 114.24, 125.43, 125.68, 127.03, 127.55, 128.40, 129.54, 129.90, 130.51, 131.47, 135.23, 186.71. MS (EI) *m/z* (%): 283 (M^+, 100), 254 (13), 240 (26), 210 (5), 175 (11), 121 (8). HRMS: (EI) *m/z* (%) for $C_{16}H_{13}NO_2S$; calcd 283.0667; found 283.0666. Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.83; H, 4.59; N, 4.94; S, 11.33. Found: C, 67.64; H, 4.98; N, 4.91; S, 11.03.

4.2.4. General procedure for the synthesis of formyl-derivatives of 1-alkyl(aryl)-2-(2′-thienyl)pyrroles 2a–f, via metalation with *n*-BuLi followed by reaction with DMF. A 2.5 M solution of *n*-BuLi in hexanes (0.44 ml, 1.1 mmol) was dropped under Ar at 0 °C to a stirred solution of thienylpyrroles **2** (1.0 mmol) in anhydrous ether. The reaction mixture was then stirred 1 h at 0 °C and was allowed to stand 15 min at rt. DMF (0.05 ml, 1.0 mmol) dissolved in anhydrous ether (2 ml) was added dropwise at rt. The mixture was heated at reflux for 1 h. The mixture was poured into water (20 ml) and extracted with (3×50 ml) of ethyl acetate. The combined organic extracts were washed with H_2O (100 ml), dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to give the crude 1-alkyl(aryl)-2-(5′-formyl-2′-thienyl)pyrroles **5** or a mixture of formyl-derivatives **5**, **6** and **7**, which were purified by 'flash' chromatography on silica with increasing amounts of ether in light petroleum as eluent.

Metalation of thienylpyrrole **2a** followed by a reaction with DMF gave a mixture of **2a** and 1-propyl-2-(5′-formyl-2′-thienyl)pyrrole **5a**. The first compound eluted was thienylpyrrole **2a** (19%). The second compound eluted was 1-propyl-2-(5′-formyl-2′-thienyl)pyrrole **5a** as an orange oil (68%). UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 374.0 (9474). IR (liquid film): ν 1659 (C=O), 1554, 1513, 1475, 1436, 1381, 1283, 1229, 1061, 941, 808, 724, 668, 611, 506 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, $J=7.5$ Hz,

(CH_2)$_2$CH_3), 1.77–1.90 (m, 2H, $CH_2CH_2CH_3$), 4.08 (t, 2H, J=7.5 Hz, NCH_2), 6.20–6.22 (m, 1H, 4-H), 6.53 (dd, 1H, J=3.9, 1.8 Hz, 3-H), 6.82–6.86 (m, 1H, 5-H), 7.12 (d, 1H, J=3.9 Hz, 3′-H), 7.71 (d, 1H, J=3.9 Hz, 4′-H), 9.87 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 11.06, 24.61, 49.64, 108.70, 112.38, 112.44, 125.56, 125.70, 137.22, 140.94, 145.32, 182.54. MS (EI) *m*/*z* (%): 219 (M^+, 100), 218 (9), 191 (19), 177 (26), 176 (23), 162 (17), 148 (7), 104 (7), 78 (2). HRMS: (EI) *m*/*z* (%) for $C_{12}H_{13}NOS$; calcd 219.0718; found 219.0718.

Metalation of thienylpyrrole **2b** followed by a reaction with DMF gave a mixture of **2b** and 1-phenyl-2-(5′-formyl-2′-thienyl)pyrrole **5b**. The first compound eluted was thienylpyrrole **2b** (9%). The second compound eluted was 1-phenyl-2-(5′-formyl-2′-thienyl)pyrrole **5b** as a dark orange oil (78%). UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 374.0 (19,180), 260.0 (7000). IR (liquid film): ν 1659 (CHO), 1597, 1498, 1461, 1438, 1230, 1062, 916, 802, 724, 696, 667 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.36–6.38 (m, 1H, 4-H), 6.61 (d, 1H, J=4.2 Hz, 3′-H), 6.71 (dd, 1H, J=3.6, 1.5 Hz, 3-H), 6.94–6.97 (m, 1H, 5-H), 7.28–7.33 (m, 2H, 2×Ar-*H*), 7.42–7.47 (m, 3H, 3×Ar-*H*), 7.49 (d, 1H, J=4.2 Hz, 4′-H), 9.75 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 109.99, 113.05, 124.42, 126.88, 126.94, 128.42, 129.40 (two overlapped signals), 136.88, 139.38, 140.73, 145.25, 182.49. Anal. Calcd for $C_{15}H_{11}NOS$: C, 71.13; H, 4.35; N, 5.53; S, 12.67. Found: C, 70.98; H, 4.54; N, 5.58; S, 12.69.

Metalation of thienylpyrrole **2c** followed by a reaction with DMF gave a mixture of 1-(4″-methoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5c** and 1-(3″-formyl-4″-methoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **6c**. The first compound eluted was 1-(4″-methoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5c** as a green solid (63%). Mp: 96.6–97.4 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 379.0 (18,613), 270.0 inf. (6000), 230.5 (16,603), 203.5 (24,294). IR (liquid film): ν 1659 (CHO), 1609, 1539, 1515, 1462, 1444, 1412, 1299, 1250, 1231, 1182, 1169, 1158, 1106, 1061, 917, 836, 797, 755, 724, 666, 619 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H, OCH_3), δ 6.32–6.36 (m, 1H, 4-H), 6.67 (d, 1H, J=4.2 Hz, 3′-H), 6.70 (dd, 1H, J=3.6, 1.8 Hz, 3-H), 6.88–6.91 (m, 1H, 5-H), 6.95 (d, 2H, J=9.0 Hz, 2×Ar-*H*), 7.22 (d, 2H, J=9.0 Hz, 2×Ar-*H*), 7.49 (d, 1H, J=4.2 Hz, 4′-H), 9.74 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 55.45, 109.63, 112.33, 114.41, 124.02, 127.13, 127.19, 128.21, 132.04, 136.98, 140.43, 145.32, 159.52, 182.46. MS (EI) *m*/*z* (%): 283 (M^+, 100), 268 (54), 240 (6), 121 (8), 103 (5). HRMS: (EI) *m*/*z* (%) for $C_{16}H_{13}NO_2S$; calcd 283.0667; found 283.0665. Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.83; H, 4.59; N, 4.94; S, 11.33. Found: C, 67.78; H, 4.82; N, 5.02; S, 11.25. The second compound eluted was 1-(3″-formyl-4″-methoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **6c** as a orange oil (5%). UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 374.0 (10,605), 270.0 inf. (5000). IR (liquid film): ν 1684 (C═O), 1659 (C═O), 1611, 1499, 1462, 1394, 1273, 1234, 1122, 1019, 869, 817, 755, 726, 666 cm^{-1}. ^{1}H NMR (acetone-d_6) δ 4.11 (s, 3H, OCH_3), 6.37–6.40 (m, 1H, 4-H), 6.80 (dd, 1H, J=3.8, 1.2 Hz, 3-H), 6.91 (d, 1H, J=3.9 Hz, 3′-H), 7.09–7.11 (m, 1H, 5-H), 7.41 (d, 2H, J=8.7 Hz, 5″-H), 7.65 (dd, 1H, J=8.7, 2.4 Hz, 6″-H), 7.69 (d, 1H, J=2.4 Hz, 2″-H), 7.75 (d, 1H, J=3.9 Hz, 4′-H), 9.81 (s, 1H, C*H*O), 10.48 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 56.06, 110.18, 112.56, 112.92, 124.49, 125.07, 126.56, 127.02, 127.07, 132.36, 134.26, 137.01, 140.92, 144.81, 161.43, 182.53, 188.68. MS (EI) *m*/*z* (%): 311 (M^+, 100), 285 (5), 268 (30), 235 (6). HRMS: (EI) *m*/*z* (%) for $C_{17}H_{13}NO_3S$; calcd 311.0616; found 311.0625.

Metalation of thienylpyrrole **2d** followed by a reaction with DMF gave a mixture of thienylpyrrole **2d**, 1-(2″,4″-dimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5d** and 1-(3″-formyl-2″,4″-dimethoxyphenyl)-2-(2′-thienyl)pyrrole **7d**. The first compound eluted was pyrrole **2d** as a green solid (40%). The second component eluted was 1-(3″-formyl-2″,4″-dimethoxyphenyl)-2-(2′-thienyl)pyrrole **7d** as a dark green oil (8%). IR (liquid film): ν 3108, 1693 (C═O), 1659, 1581, 1492, 1442, 1397, 1334, 1288, 1232, 1186, 1164, 1121, 1096, 1013, 948, 842, 814, 716 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.33–6.38 (m, 1H, 4-H), 6.54 (dd, 1H, J=4.2, 1.8 Hz, 3-H), 6.70 (dd, 1H, J=3.6, 1.2 Hz, 3′-H), 6.75 (d, 1H, J=9.0 Hz, 6″-H or 5″-H), 6.80–6.83 (m, 1H, 5-H), 6.86–6.90 (m, 1H, 4′-H), 7.08 (dd, 1H, J=5.1, 1.2 Hz, 5′-H), 7.42 (d, 1H, J=9.0 Hz, 6″-H or 5″-H), 10.45 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 56.28, 61.44, 106.44, 109.59, 109.72, 119.05, 123.71, 123.88, 125.04, 125.72, 127.07, 128.54, 134.70, 135.92, 158.82, 161.18, 189.14. MS (EI) *m*/*z* (%): 313 (M^+, 100), 298 (17), 284 (13), 270 (9), 255 (5), 121 (9). HRMS: (EI) *m*/*z* (%) for $C_{17}H_{15}NO_3S$; calcd 313.0772; found 313.0785. The third compound eluted was 1-(2″,4″-dimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5d** as a dark green oil (48%). UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 384.5 (18,158), 277.5 (6264), 233.0 (1312), 207.0 (30,609). IR (liquid film): ν 2962, 2838, 1652 (CHO), 1613, 1589, 1541, 1516, 1462, 1443, 1416, 1383, 1306, 1286, 1260, 1232, 1210, 1161, 1135, 1092, 1062, 1046, 1030, 928, 911, 803, 728 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.34–6.38 (m, 1H, 4-H), 6.52–6.58 (m, 2H, 3″-H and 5″-H), 6.74 (dd, 1H, J=3.9, 1.8 Hz, 3-H), 6.80–6.84 (m, 2H, 3′-H and 5-H), 7.17 (d, 1H, J=9.3 Hz, 6″-H), 7.51 (d, 1H, J=4.2 Hz, 4′-H), 9.73 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 55.54, 55.69, 99.72, 104.41, 109.56, 111.33, 121.03, 123.11, 127.34, 128.00, 129.78, 137.08, 140.00, 145.78, 156.40, 161.39, 182.51. MS (EI) *m*/*z* (%): 313 (M^+, 100), 270 (8), 255 (8). HRMS: (EI) *m*/*z* (%) for $C_{17}H_{15}NO_3S$; calcd 313.0773; found 313.0770. Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.79; N, 4.47; S, 10.24. Found: C, 65.14; H, 5.07; N, 4.58; S, 10.04.

Metalation of thienylpyrrole **2d** during 2 h followed by 2 h of reflux with DMF gave a mixture of 4 compounds: thienylpyrrole **2d** (18%), 1-(2″,4″-dimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5d** (34%), 1-(3″-formyl-2″,4″-dimethoxyphenyl)-2-(2′-thienyl)pyrrole **7d** (14%) and 1-(3″-formyl-2″,4″-dimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **6d** as a dark orange oil (18%). UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 377.0 (16,040), 260.5 (14,720). IR (liquid film): ν 1690 (C═O), 1657 (C═O), 1492, 1461, 1288, 1231, 1094, 1019, 812, 608 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.39–6.42 (m, 1H, 4-H), 6.77 (dd, 1H, J=3.6, 1.5 Hz, 3-H), 6.82 (d, 1H, J=9.0 Hz, 5″-H), 6.85–6.90 (m, 2H, 3′-H and 5-H), 7.46 (d, 1H, J=9.0 Hz, 6″-H), 7.54 (d, 1H, J=4.2 Hz, 4′-H), 9.75 (s, 1H, C*H*O), 10.45 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 56.35, 61.79, 106.96, 110.46, 112.23, 119.37, 123.62,

125.26, 127.47, 127.87, 135.43, 137.30, 140.62, 144.74, 158.44, 161.99, 182.49, 188.79. MS (EI) *m/z* (%): 341 (M^+, 100), 326 (7), 312 (13), 298 (7), 83 (9). HRMS: (EI) *m/z* (%) for $C_{18}H_{15}NO_4S$; calcd 341.0722; found 341.0710.

1-(3″,4″,5″-Trimethoxyphenyl)-2-(5′-formyl-2′-thienyl)-pyrrole **5e**. Metalation of thienylpyrrole **2e** followed by a reaction with DMF gave a mixture of thienylpyrrole **2e** and 1-(3″,4″,5″-trimethoxyphenyl)-2-(5′-formyl-2′-thienyl)-pyrrole **5e**. The first component eluted was thienylpyrrole **2e** as a pale green solid (40%). The second component eluted was 1-(3″,4″,5″-trimethoxyphenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5e** as a yellow solid (12%). Mp: 113.5–114.7 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 377.0 (11,860), 265.0 inf. (6820). IR (liquid film): ν 2935, 1659 (CHO), 1596, 1507, 1463, 1417, 1262, 1230, 1127, 1066, 1033, 1004, 840, 808, 727, 668 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79 (s, 6H, 2×OCH_3), 3.92 (s, 3H, OCH_3), 6.34–6.37 (m, 1H, 4-H), 6.52 (br s, 2H, 2″and 6″-H), 6.66 (d, 1H, J= 4.2 Hz, 3′-H), 6.71 (dd, 1H, J=3.8, 1.5 Hz, 3-H), 6.89–6.93 (m, 1H, 5-H), 7.52 (d, 1H, J=3.9 Hz, 4′-H), 9.77 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ 55.45, 109.63, 112.33, 114.41, 124.02, 127.13, 127.19, 128.21, 132.04, 136.98, 140.43, 145.32, 159.52, 182.46. MS (EI) *m/z* (%): 343 (M^+, 100), 328 (50), 300 (6). HRMS: (EI) *m/z* (%) for $C_{18}H_{17}NO_4S$; calcd 343.0878; found 343.0896.

1-(4″-Fluorophenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5f**. Metalation of thienylpyrrole **2f** followed by a reaction with DMF gave a mixture of thienylpyrrole **2f** and 1-(4″-fluorophenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5f**. The first component eluted was thienylpyrrole **2f** as a pale yellow solid (15%). The second component eluted was the 1-(4″-fluorophenyl)-2-(5′-formyl-2′-thienyl)pyrrole **5f** as a brown solid (25%). Mp: 112–114 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 373.5 (15,191), 257.6 (6386), 226.0 (8830), 204.0 (17,041). IR (liquid film): ν 1659 (CHO), 1511, 1462, 1439, 1412, 1349, 1221, 1189, 1154, 1094, 1061, 1039, 916, 842 cm^{-}.[1] ^1H NMR ($CDCl_3$) δ 6.30–6.40 (m, 1H, 4-H), 6.63 (d, 1H, J=4.2 Hz, 3′-H), 6.65–6.75 (m, 1H, 3-H), 6.85–6.90 (m, 1H, 5-H), 7.13 (t_{ap}, 2H, J=8.4 Hz, 3″ and 5″-H), 7.25–7.35 (m, 2H, 2″ and 6″-H), 7.49 (d, 1H, J=4.2 Hz, 4′-H), 9.75 (s, 1H, C*H*O). MS (EI) *m/z* (%): 271 (M^+, 100), 243 (3), 242 (8), 209 (5), 198 (6), 185 (5), 150 (9), 133 (6), 121 (6), 95 (5), 75 (4). HRMS: (EI) *m/z* (%) for $C_{15}H_{10}FNOS$; calcd 271.0467; found 271.0465.

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Chemoenzymatic resolution of epimeric *cis* 3-carboxycyclopentylglycine derivatives

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Abstract—Epimeric 3-carboxycyclopentylglycines (+)-**10**/(−)-**10** and (+)-**11**/(−)-**11** were efficiently prepared by the way of a sequence of Diels–Alder and retro-Claisen reactions. The synthesis incorporates a concise and inexpensive chemoenzymatic resolution of racemic compounds **4**,**5a**, the *N*,*O*-protected derivatives of amino acids **10**,**11**. Systematic screening with different enzymes and microorganisms was performed to select a very efficient catalyst for the separation of the racemic mixtures. The reaction conditions allowing deprotection of both ester and amino functions and to avoiding epimerization processes were studied. Enantiomers (i.e., (+)-**10**/(−)-**10** and (+)-**11**/(−)-**11**) were obtained in high enantiopurity. The absolute configuration of all stereocenters was unequivocally assigned.

1. Introduction

Unnatural amino acids have been recognized as major tools for the preparation of peptidomimetics with enhanced biological activity and proteolytic resistance. One of the modern approaches towards the synthesis of modified peptides is the incorporation of non-proteinogenic amino acids into the peptide backbone.[1] This is a powerful strategy to overcome the problem that peptides are generally flexible and do not take the defined conformation necessary for function.

3-Carboxycyclopentylglycines are very promising amino acids to be used in this field since they are non-proteinogenic amino acids containing conformational constraints. Furthermore, the skeleton of both 2-aminoadipic acid and 2-aminopimelic acid, two natural amino acids of biological importance, is included in their structure.[2–5] Heterosubstituted 3-carboxycyclopentylglycines were prepared and their biological activity toward neuraminidase was evaluated.[6] Recently, we reported on the chiral preparation of epimeric 1*S*,3*R*,1′*R*- and 1*S*,3*R*,1′*S*-(benzoylamino-ethoxycarbonylmethyl)cyclopentanecarboxylic acid derivatives **6** and **7** (Scheme 3) characterized by the cis relationship between the two carbon residues.[7]

Chiral synthesis is a powerful tool to produce a chiral compound, but there are some limitations such as the expensive chiral reagents, the necessity to repeat the synthetic protocol twice when both enantiomers are needed, and most of all and in most cases, the difficulty of separating the diasteromers. For these reasons, one alternative approach to overcome all these limitations is the enzymatic separation of racemic compounds and, in particular, of amino acids. In fact, isolated enzymes or microbial cells can catalyse the stereoselective hydrolysis of amino acids with *N*-protected amide group or *O*-protected ester group.[8] High selectivity and mild and safe conditions are typical. In particular, the use of whole microbial cells often shows good performance with regard to stability and selectivity and is advantageous to access intracellular esterase activity.[9]

The importance of amino acid chirality in biological interactions is well known. The impossibility to forecast a priori the biological activity of a single stereoisomer requests the availability of both pure enantiomers. For this reason, considering the potential biological interest of the above amino acids and the perspective of using the 3-carboxycyclopentylglycines in peptide syntheses, racemic epimers (±)-**4** and (±)-**5a** were prepared and the synthetic

Keywords: 3-Carboxycyclopentylglycines; Enzymatic resolution; *Aspergillus melleus*; Absolute configuration.
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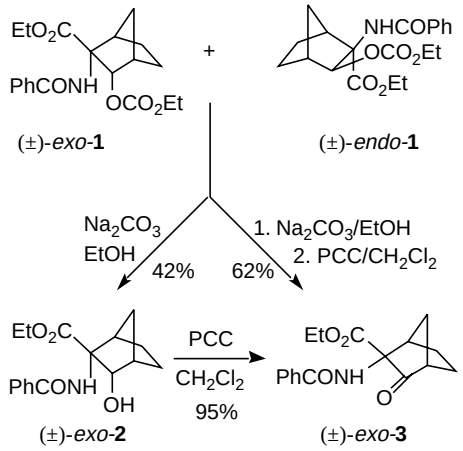
protocol for their preparation was considerably improved.[10] The chemoenzymatic resolution of each epimer (±)-**4** and (±)-**5a** was planned. Systematic screening with different enzymes and microorganisms was performed to select a very efficient catalyst for the separation of the racemic mixtures.

Furthermore, the absolute configuration of each stereocenter in the above amino acids was assigned taking advantage of the availability of chiral derivatives **6** and **7**.

2. Results

The key starting material for the preparation of the epimeric 3-carboxy-cyclopentylglycines **4**,**5a** is the racemic ethyl 2-benzoylamino-3-oxo-bicylo[2.2.1]heptane-2-carboxylate (±)-*exo*-**3** (Scheme 1).



Scheme 1.

The synthesis of the corresponding methyl ester, was already reported by us[11] but a more efficient protocol is described here which allowed to minimize us the reaction steps, to avoid chromatographic purifications and to improve the reaction yield (53% instead of 35%).

A mixture of the norbornane derivatives (±)-*exo*-**1** and (±)-*endo*-**1** (70:30) was the starting material for the preparation of **3**. (Scheme 1) The selective deprotection of the C-3 carbonate of the exo compound, using sodium carbonate in ethanol at room temperature, gave the 3-hydroxy derivative (±)-*exo*-**2** which was easily separated from the endo carbonate (±)-**1**. Compound (±)-*exo*-**2** was isolated in 42% yield and than oxidized to ketone (±)-*exo*-**3** (95%) using pyridinium chlorocromate (PCC). Alternatively, the oxidation reaction was performed directly on the mixture of alcohol (±)-*exo*-**2** and carbonate (±)-*endo*-**1**.

Ethyl 2-phenyl-5-oxo-oxazol-4-methylene-carbonate and cyclopentadiene were the starting reagents used for the synthesis of norbornane ring via a Diels–Alder reaction. Here, we prepared the ketone (±)-*exo*-**3** in four steps and 53% overall yield. This protocol allowed us to avoid one chromatographic step and, importantly, to perform an easier separation of carbonate *endo*-**1** from the ketone *exo*-**3**.

β-Ketoester (±)-*exo*-**3** was then transformed into a mixture of epimeric cyclopentylglycines (±)-**4** and (±)-**5a** (1:1; 82%) by a base catalysed retro-Claisen reaction (pyridine/water at reflux; 1:1) which ensured the cis relationship between the two carbon residues on the ring (Scheme 2).

2.1. Enzymatic resolution

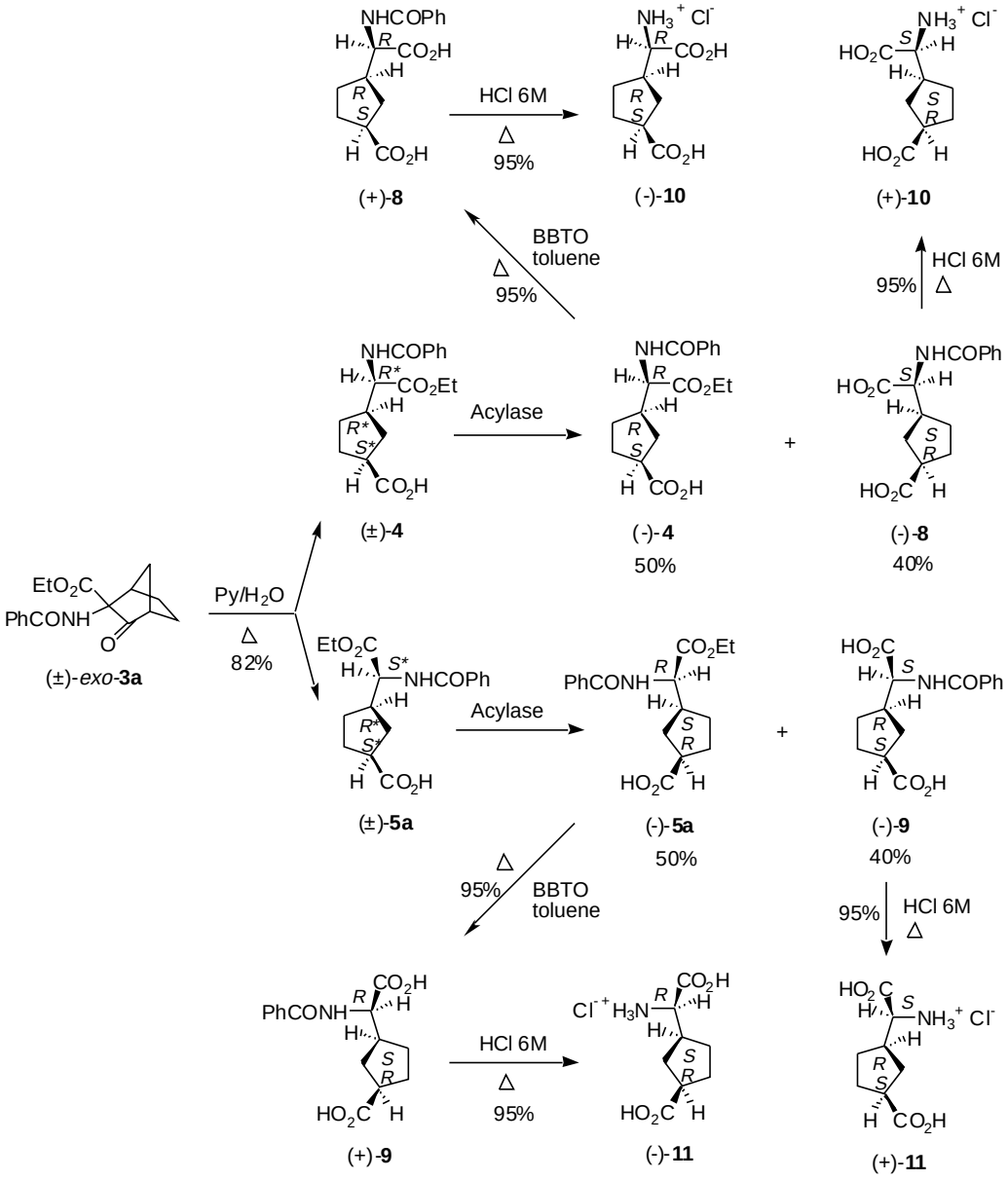
Aiming to obtain the enantiopure amino acids, an enzymatic study was performed starting from racemic compound (±)-**5a**. Twelve enzymes (lipases, acylases, proteases) and fifty microorganisms (yeasts, bacteria) belonging to different genera were tested. The screening was carried out using miniaturized systems and TLC as analytical technique allowing an evaluation of the activity of a large number of biocatalysts in a short time. Different enzymes and microbial cells were able to selectively hydrolyze the ester function of the cyclopentylglycine **5a** to obtain compound *S*-**9**. The enantiomeric excess was evaluated by chiral HPLC and the results are summarized in Table 1. The hydrolysis of the amide function was never observed.

As shown in Table 1, the best results were achieved by using PPL and acylase from *Aspergillus melleus*. In both cases it was possible to obtain the complete resolution of racemic (±)-**5a**. After the extraction of the reaction mixture, the bicarboxylic acid (−)-**9** was separated from the ester (−)-**5a** (50%, $[\alpha]_D^{25}$ −22) by simple crystallization from dichloromethane. (Scheme 2) Enantiopure acid (−)-**9** ($[\alpha]_D^{25}$ −14.5) was obtained in 40% yield. The same results were obtained starting from (±)-**4**. Enantiopure acid (−)-**8** ($[\alpha]_D^{25}$ −20) was separated from the ester (−)-**4** (50%, $[\alpha]_D^{25}$ −11) by crystallization. (Scheme 2) Interestingly, a different reaction rate was observed starting from two epimers, with the 1*S**,3*R**,1′*R** epimer being more reactive (24 h) than 1*S**,3*R**,1′*S** one (48 h).

The acylase from *Aspergillus melleus* was also most active also at low concentration (5 mg/mL) for both racemic compounds. For this reason this enzyme was selected for the semi-preparative resolution (250 mg) of both (±)-**4** and (±)-**5a** (Scheme 2).

One problem of biotransformations carried out with enzymes is the formation of emulsions during the work-up of the crude reaction mixture. For this reason we screened whole cells and the best results were found using *Pichia etchellsii* MIM and *Saccharomyces cerevisiae* ZEUS. (Table 1) This result appears very interesting in the perspective of scaling up the process to the gram scale.

Recently, we have synthesised the chiral epimeric cyclopentylglycines (+)-**6** and (+)-**7**. Since their separation had been achieved by semi-preparative HPLC, which required the use of considerable amounts of solvent and long times, we planned their separation using enzymes. This target was successfully achieved using a lipase from *Candida cylindracea*, which gave the best selectivity. In fact, this enzyme is both regioselective and stereoselective. It hydrolysed only the methyl ester function of stereoisomer (+)-**7** in 72 h with a diastereomeric excess of 97% and molar conversion of 49%. After column chromatography it was easily possible to obtain the pure compound (−)-**5b**



Scheme 2.

(30%, $[\alpha]_D^{25}$ −8) and the methyl ester derivative (+)-**6** (40%) (Scheme 3). Considering that both epimer **6** and **7** have the same 1-*S* stereocenter, we conclude that the remote amino acid function controls the selectivity of the enzyme.

2.2. Deprotection of the amino acid function

The deprotection of the ester and amide functions in compounds **4**,**5a** was critical because a partial epimerization of the amino acid C-α occurred when performing the above hydrolysis in standard conditions (see below). To avoid this problem, different reaction conditions were tested starting from the racemic (±)-**4** and (±)-**5a**. Results are summarized in Table 2 (Scheme 2).

The selective deprotection of the ester function of both (±)-**4** and (±)-**5a** with LiOH in MeOH at room temperature gave a mixture of epimeric amino acids (±)-**8** and (±)-**9**, respectively, in the ratio indicated in the Table (entries 1, 2).

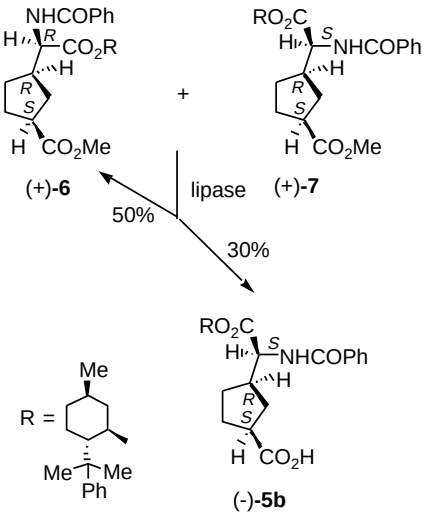
The epimerization was also observed by hydrolysis of the ester function of (±)-**5a** with BBr_3 (entry 3).[12] Attempts to first hydrolyze the amide function using Na_2O_2[13] gave only the hydrolysis of the ester function with epimerization (entry 4). Finally, the best result was achieved by using a catalytic amount of bis-tributyltin oxide (BBTO)[14] in refluxing toluene (entry 5). Compound (±)-**9** was obtained from **5a** with a small amount of **8** (7%). The direct hydrolysis of both ester and amide function of (±)-**5a** with 6 M HCl at reflux was possible and a mixture of amino acids **11** and **10** was obtained due to the epimerization process (entry 6). Instead, the hydrolysis (6 M HCl) of the amide function of the free bicarboxylic compounds did not undergo epimerization. In fact, starting from the mixture of acids **9**/**8** (93:7) the mixture of amino acids **11** and **10** was obtained in the same ratio (entry 7).

We can conclude that it is impossible to completely avoid the epimerization process in compounds in which both

Table 1. Hydrolysis of ester of racemic compound (±)-**5a** with different microbial cells or isolated enzymes

Microorganism	ee S (%)[a]	ee P (%)[a]	Molar conversion (%)[a]	E[a]	Time (h)
Streptomyces sp. 27	74	90	45	42	24
Streptomyces sp. 52	22	51	30	3,8	48
Streptomyces sp. 103	24	>99	29	>200	24
Streptomyces sp. 34	4	68	6	5,5	144
Pichia etchellsii MIM	36	>99	26	>200	4
Pichia etchellsii MIM	>99	80	56	65	24
Saccaromyces cerevisiae Zeus	66	>99	40	>200	4
Saccaromyces cerevisiae Zeus	>99	/	/	/	24
Geobacillus thermoleovorans ATCC 43513	41	42	49	3,6	24
Papaine	93	93	50	94	24
Papaine	>99	84	54	84	96
Acylase from *Aspergillus melleus*	>99	95	51	>200	24
Acylase from *Aspergillus melleus*	>99	84	54	84	96
Acylase from *Asp.* sp.	88	92	49	69	4
Acylase from *Asp.* sp.	>99	83	55	78	24
Porcine pancreatic lipase	77	>99	44	>200	4
Porcine pancreatic lipase	>99	99	50	>200	24

[a] Conversion and enantioselectivity factor (E) calculated from the ee of the substrate (ee S) and the product (ee P).



Scheme 3.

the amino and the carboxy groups are protected, probably because of the high acidity of the amino acid α-hydrogen. Instead, starting from the *N*-protected acids this problem is overcome.

With this information in mind, the chiral esters (−)-**4** and (−)-**5a** were hydrolyzed with BBTO. Bicarboxylic compounds (+)-**8** (de 86%) and (+)-**9** (de 86%) were obtained, respectively.

The hydrolysis of the amide function of the single stereomers (+)-**8**, (−)-**8**, (+)-**9** and (−)-**9** to the corresponding amino acids (−)-**10** (de 86%, $[\alpha]_D^{25}$ −4), (+)-**10** ($[\alpha]_D^{25}$ +5), (−)-**11** (de 86%, $[\alpha]_D^{25}$ −10) and (+)-**11** ($[\alpha]_D^{25}$ +11) was performed using 6 M HCl.

The absolute configuration of all stereocenters of bicarboxylic acids **8** and **9** was unequivocally assigned by correlation of the [α] values with authentic samples. We found that starting both from **7**,[7] by hydrolysis, and from (±)-**5a**, by enzymatic resolution, the same epimer (−)-*S*-**9** was obtained. The same *S* selectivity of the enzymes was observed in the case of compound (±)-**4**. Epimer (−)-*S*-**8** was obtained, having the opposite optical rotation with respect to that found for compound obtained through the chiral synthesis.

3. Conclusion

In conclusion, a highly efficient protocol for the preparation of four enantiopure stereoisomers of the 3-carboxycyclopentylglycine derivatives **10**,**11** was achieved starting from the racemic 3-oxo-norbornaneamino acid derivative **3**. The enzymatic separation of protected cyclopentylglycine

Table 2. Chemical deprotection of amino acid function

Entry	Reagent	Reaction conditions	Yield (%)	Products[a] (ratio)
1	(±)-**4**	LiOH/MeOH, 25 °C	80	**8/9** (86:14) [b]
2	(±)-**5a**	LiOH/MeOH, 25 °C	80	**9/8** (86:14)[b]
3	(±)-**5a**	BBr_3/CH_2Cl_2, 25 °C	75	**9/8** (85:15) [b]
4	(±)-**5a**	Na_2O_2/H_2O, 50 °C	80	**9/8** (80:20) [b]
5	(±)-**5a**	BBTO/toluene/reflux	95	**9/8** (93:7) [b]
6	(±)-**5a**	6 M HCl, reflux	95	**11/10** (87:13) [c]
7	(±)-**9/8** (93:7)	6 M HCl, reflux	95	**11/10** (93:7) [c]

[a] Isolated compounds.
[b] HPLC determination.
[c] ^{13}C NMR determination.

derivatives, obtained in high enantiomeric purity, was assured using the acylase from *Aspergillus melleus*, which also operates on semipreparative scale.

4. Experimental

4.1. General

Melting points were measured with a Büchi B-540 heating unit and are not corrected. NMR spectra were recorded with an AVANCE 500 Bruker at 500 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts, relative to TMS as internal standard, are given in δ values. IR spectra were taken with a Perkin–Elmer 1725X FT-IR spectrophotometer. $[\alpha]_D^{25}$ were measured with a Perkin–Elmer MODEL343 Plus Polarimeter. Ethanol-free CH_2Cl_2 was used in all experiments.

4.1.1. 'One Pot' synthesis of ethyl (1*R,2*R**,4*S**)-2-benzoylamino-3-oxo-bicyclo[2.2.1]heptane-2-carboxylate *exo*-3.** Compounds *exo*-**1a** and *endo*-**1a** were prepared according to known procedures.[11] Without the separation of diastereomers, the mixture of norbornane esters (5 g, 13.3 mmol, 7:3) was treated with lyophilized Na_2CO_3 (1.37 g, 13.3 mmol) in EtOH (50 mL) at room temperature under stirring for 24 h (TLC: CH_2Cl_2/Et_2O, 2:1). Na_2CO_3 was filtered over a Celite column and the alcohol was evaporated. Unreacted compound *endo*-**1** (1.2 g, 24%) was separated from hydroxy compound *exo*-**2** by column chromatography on silica gel (CH_2Cl_2/Et_2O, 10:1; R_f: *endo*-**1**=0.51, *exo*-**2**=0.37). Pure compound *exo*-**2** (1.7 g, 42%) was obtained after crystallization. Alternatively, the mixture of *endo*-**1** and *exo*-**2**, after filtration over Celite, was directly oxidized. Both, hydroxy compound *exo*-**3** and a mixture of *endo*-**2**/*exo*-**3** were treated under nitrogen atmosphere with PCC (6 mmol×1 mmol of reagent) in CH_2Cl_2 (80 mL). The solution, was stirred at room temperature for 2 h (TLC: cyclohexane/AcOEt, 1:1). The reaction mixture was filtered through a silica gel column (cyclohexane/AcOEt, 70:30). Starting from pure *exo*-**2** (1.7 g, 5.6 mmol), ketone *exo*-**3** (1.6 g, 95%) was obtained. Compound *exo*-**3** (2.58 g, 62%) and carbonate *endo*-**1** (1.25 g, 25%) (R_f: *exo*-**3**=0.6, *endo*-**1**=0.2) were isolated starting from the mixture of *endo*-**1**/*exo*-**2** (5 g, 13.3 mmol, 7:3). Mp 160 °C (cyclohexane/AcOEt). IR: ν_{max} 3320, 1720, 1700, 1640 cm^{-1}; ^{1}H NMR δ 7.83–7.42 (m, 5H, ArH), 6.69 (s, 1H, exch., NH), 4.30–4.10 (m, 2H, CH_2O), 3.73 (br s, 1H, H-4), 2.81 (dd, J=5.1, 1.2 Hz, 1H, H-1), 2.53, 1.83 (AB system, J=9.9 Hz, 2H, H-7), 2.06–1.94 (m, 1H, H-5), 1.75–1.28 (m, 3H, H-5, H-6), 1.22 (t, J=7.3 Hz, 3H, Me); ^{13}C NMR δ 14.3, 22.1, 27.6, 34.8, 44.4, 48.3, 62.5, 72.0, 127.4, 128.9, 132.3, 133.6, 166.3, 168.2, 210.2. Anal. Calcd: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.38; N, 4.62.

4.2. General procedure for the retro-Claisen reaction of ketone *exo*-3

Pure ketone *exo*-**3** (301 mg, 1 mmol) was dissolved in pyridine (3 mL) and H_2O (1.5 mL). The reaction mixture was heated at reflux for 3 h (TLC: CH_2Cl_2/Et_2O, 2:1). The solvent was evaporated and the residue was taken up with a HCl solution (10%, 10 mL) which was then extracted with a mixture of THF/AcOEt (7.5 mL, 1:1). The organic layer was separated and dried over Na_2SO_4 giving a mixture of the two diastereomeric amino acid derivatives **4** and **5a** (1:1, 260 mg, 82%). Compounds (±)-**4** from (±)-**5a** were separate by flash chromatography (CH_2Cl_2/Et_2O/AcOH, 5:1:0.1, R_f: **4**=0.4, **5a**=0.32).

4.2.1. (1*S,3*R**,1′*R**) 3-(Benzoylamino-ethoxycarbonyl-methyl)cyclopentanecarboxylic acid (±)-4.** 95 °C. (CH_2Cl_2/Et_2O). IR: ν_{max} 3340, 1732, 1700, 1668 cm^{-1}; ^{1}H NMR δ 7.88–7.40 (m, 5H, ArH), 7.12 (d, J=8.1 Hz, 1H, exch., NH), 4.89 (dd, J=8.1, 5.1 Hz, 1H, CHN), 4.25 (q, J=7.0 Hz, 2H, CH_2O), 2.99–2.83 (m, 1H, H-1), 2.78–2.53 (m, 1H, H-3), 2.10–1.60 (m, 6H, H-2, H-4, H-5), 1.32 (t, J=7.0 Hz, 3H, Me); ^{13}C NMR δ 181.6, 172.5, 168.1, 134.3, 132.1, 129.0, 127.6, 61.9, 55.0, 43.2, 42.5, 30.9, 30.3, 28.7, 14.6. Anal. Calcd: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.87; H, 6.59; N, 4.31.

4.2.2. (1*S,3*R**,1′*S**) 3-(Benzoylamino-ethoxycarbonyl-methyl)cyclopentanecarboxylic acid (±)-5a.** Mp 134 °C (CH_2Cl_2/iPr_2O). IR: ν_{max} 3340, 1730, 1700, 1665 cm^{-1}; ^{1}H NMR δ 7.85–7.42 (m, 5H, ArH), 6.87 (d, J=7.7 Hz, 1H, exch., NH), 4.88 (dd, J=8.0, 5.9 Hz, 1H, CHN), 4.26 (q, J=7.0 Hz, 2H, CH_2O), 2.93–2.80 (m, 1H, H-1), 2.80–2.45 (m, 1H, H-3), 2.30–1.60 (m, 6H, H-2, H-4, H-5), 1.32 (t, J=7.0 Hz, 3H, Me); ^{13}C NMR δ 181.7. 172.4, 168.1, 134.2, 132.2, 129.0, 127.5, 62.0, 55.1, 43.4, 43.1, 32.7, 29.4, 27.8, 14.6. Anal. Calcd: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.89; H, 6.60; N, 4.33.

4.3. Media and culture conditions

Strains from an official collection (ATCC, American Type Culture Collection), from our collection (MIM, Microbiologia Industriale Milano) and *Streptomyces* kindly furnished by Prof. Flavia Marinelli were employed. The active biocatalysts are reported in Table 1. Yeasts were routinely maintained on malt extract (8 g/L, agar 15 g/L pH 5,5), non filamentous bacteria on Difco nutrient broth (8 g/L, agar 15 g/L, pH 7) and *Streptomyces* on oatmeal agar (60 g/L corn flaks, agar 20 g/L, pH 7). To obtain cells for biotransformations, microorganisms were cultured on different media: (a) yeast: malt extract 15 g/L, yeast extract 5 g/L, pH 5.8; (b) *Geobacillus* CYSP medium (casytone 15 g/L yeast extract 5 g/L, soytone3 g/L, peptone 2 g/L, $MgSO_4\cdot 7H_2O$ 15 mg/L, $FeCl_3\cdot 6H_2O$ 116 mg/L, $MnCl_2\cdot 4H_2O$ 20 mg/L, pH 7); (c) *Streptomyces*: AF/MS medium (glucose 20 g/L, yeast extract 2 g/L, soy meal 8 g/L, NaCl 4 g/L, $CaCO_3$ 1 g/L, pH 7). The cultures were inoculated into a 100 mL Erlenmeyer flask containing 20 mL of medium and incubated at 28 °C (45 °C for *Geobacillus*) for 24–48 h in the case of yeast and *Geobacillus* and 96 h for *Actinomyces*. The biomass production was carried out on rotary shaker at 200 rpm.

4.4. Biotransformations

The screening was carried out in 24 well microtitre plates (125×5×18 mm). Isolated enzyme or cells harvested by centrifugation were suspended (20 mg dry weight/mL) in a phosphate buffer (0.1 M, pH 7.0) and put into the wells. A mixture of (±)-**5a** or (±)-**4** (final concentration 4 mg/mL)

or of diastereomers **6** and **7** (final concentration 2 mg/mL) was directly added. The plates were incubated at 28 °C on a rotary shaker. The biotransformation was monitored by TLC at different times. To detect the enantiomeric excess, the biotransformations were carried out in a 10 mL screw capped test tube with the biocatalyst suspended in 5 mL of buffer and the samples were analysed by chiral HPLC. The diastereoisomeric excess was detected by reverse phase HPLC.

4.5. Analytical methods

In the Screening phase, 200 μL of the sample were brought to pH 2 with HCl and extracted with ethyl acetate and analysed by thin-layer chromatography ($CHCl_3$/Et_2O/AcOH, 50:25:1). The enantiomeric excess and the molar conversion were determined by chiral HPLC analysis (Chiralcel OD: hexane/*i*PrOH/TFA, 85:15:1; $T=25$ °C; flow=0,5 mL/min; $\lambda=230$ nm). The samples (0.5 mL) were brought to pH 2 with HCl and extracted twice with an equal volume of ethyl acetate. The organic phases were dried over Na_2SO_4, the solvent was removed and the sample was analysed. The diastereomeric excess for compounds **6** and **7** was determined by reverse phase HPLC analysis (Hypersil ODS: MeCN/H_2O, 70:30; $T=25$ °C; flow=1 mL/min; $\lambda=254$ nm).

4.6. Semipreparative biotransformations

Resolution of (±)-**4** *and* (±)-**5a**. Semi preparative resolution of mixture (±)-**4** or (±)-**5a** (250 mg, 0.8 mmol) was carried out resuspending acylase from *Aspergillus melleus* (5 mg/mL) in a phosphate buffer (0.1 M, pH 7.0, 60 mL). After 24 h (**5a**: HPLC monitoring) or 48 h (**4**, HPLC monitoring) the reaction was treated with HCl (pH 2) and extracted three times with ethyl acetate. The organic phase was separated and dried over Na_2SO_4 and the solvent removed under vacuum. The acid (−)-**8** (93 mg, 40%) or (−)-**9** (93 mg, 40%) was separated from unreacted compound (−)-**4** (125 mg, 50%) or (−)-**5a** (125 mg, 50%), respectively, by crystallization with CH_2Cl_2 (15 mL).

Resolution of **6**,**7**. A mixture of **6**,**7** (50 mg) was treated with lipase from *Candida cylindracea* (17 mg/mL) resuspended in phosphate buffer (0.1 M, pH 7.0) in the presence of MeCN (10%). The biotransformation systems were incubated at 30 °C under magnetic stirring. After 72 h the reaction mixture was extracted three times with ethyl acetate. The organic phase was separated and dried over Na_2SO_4 and the solvent removed under vacuum. Pure compound **5b** (15 mg, 30%) was separated from **6** (25 mg, 50%) by column chromatography ($CHCl_3$, Et_2O, 2:1).

4.6.1. 3-(Benzoylamino-carboxy-methyl)-cyclopentane-carboxylic acids.

(1*R*,3*S*,1′*S*) (−)-**8**. Mp 210 °C (CH_2Cl_2). $[\alpha]_D^{25}$ −20 (*c* 1, MeOH).

(1*S*,3*R*,1′*S*) (−)-**9**. Mp 193 °C (CH_2Cl_2). $[\alpha]_D^{25}$ −14.5 (*c* 1, MeOH) [Mp 193 °C (CH_2Cl_2); $[\alpha]_D^{25}$ −14.5 (*c* 1, MeOH)].[7]

4.6.2. 1*S*,3*R*,1′*S*-(Benzoylamino-(−)-8-phenylmenthoxy-carbonyl-methyl)cyclopentanecarboxylic acid (−)-5b.

Oil. $[\alpha]_D^{25}$ −8 (*c* 1, $CHCl_3$). IR (nujol) cm^{-1} 3300, 1725, 1660; ^1H NMR δ 7.82–7.78 (m, 2H, ArH), 7.52–7.16 (m, 8H, ArH), 6.58 (d, $J=8.0$ Hz, 1H, exch., NH), 4.87–4.79 (m, 1H, OCH), 4.17 (dd, $J=8.0$, 5.5 Hz, 1H, CHN), 2.79–2.71 (m, 1H, H-1), 2.17–0.79 (m, 15H, H-2, H-3, H-4, H-5, CH_{2menth}, CH_{menth}), 1.31 (s, 3H, Me), 1.21 (s, 3H, Me), 0.87 (d, $J=6.4$ Hz, 3H, Me); ^{13}C NMR δ ($CDCl_3$) 180.0, 171.4, 167.5, 151.7, 134.5, 131.8, 128.8, 128.3, 127.3, 125.5, 76.2, 54.2, 50.8, 43.0, 42.9, 41.6, 39.7, 34.7, 32.9, 31.5, 29.9, 27.1, 26,7, 24.4, 22.0. Anal. Calcd: C, 73.63; H, 7.77; N, 2.77. Found: C, 73.59; H, 7.80; N, 2.70.

4.7. General procedure for the deprotection of carboxylic group

Method (*a*). To a solution of compound (±)-**4**, or (±)-**5a** (319 mg, 1 mmol) in MeOH (4 mL), LiOH (48 mg, 2 mmol) was added. The reaction was stirred at room temperature for 24 h and extracted with AcOEt (3×4 mL). The aqueous layer was acidified with 2 M HCl (3 mL) and extracted with THF/AcOEt (1:1, 3×4 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to obtain the free carboxylic derivative ((±)-**4**: **8/9**, 86:14, 80%; (±)-**5a**: **9/8**, 86:14, 80%).

Method (*b*). In a sealed tube a solution of compound (±)-**5a**, or (−)-**5a** or (−)-**4** (319 mg, 1 mmol) and BBTO (1.19 g, 2 mmol) in toluene (10 mL) was stirred at 110 °C for 48 h. The solvent was removed under vacuum, the residue was taken up with AcOEt (10 mL) and extracted with a saturated solution of $NaHCO_3$ (3×5 mL). The aqueous layer was acidified with 2 N HCl (4 mL) and extracted with THF/AcOEt (1:1, 3×5 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give the free carboxylic acid derivative ((±)-**5a**: **9/8**, 93:7, 90%; (−)-**5a**: (+)-**9**/(−)-**8**, 93:7, 90%; (−)-**4**: (+)-**8**/(−)-**9**, 93:7, 90%).

4.7.1. 3-(Benzoylamino-carboxymethyl)cyclopentane-carboxylic acid.

(1*S*,3*R*,1′*R*) (+)-**8**. Mp 200 °C. (CH_2Cl_2); $[\alpha]_D^{25}$ +17.5 (*c* 1, MeOH). [210 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +20 (*c* 1, MeOH)].[7]

(1*R*,3*S*,1′*R*) (+)-**9**. Mp 189 °C. $[\alpha]_D^{25}$ +12 (*c* 1, MeOH).

4.7.2. 3-(Amino-carboxymethyl)cyclopentanecarboxylic acid hydrochloride.

In a sealed tube, pure compound (−)-**8**, or (−)-**9**, or a mixture of (+)-**8**/(−)-**9**, or of (+)-**9**/(−)-**8** (93:7) or their corresponding racemic mixture (291 mg, 1 mmol) was suspended in HCl (6 M, 3 mL) and heated at 105 °C for 12 h. The reaction mixture was cooled at 0 °C and the precipitated benzoic acid was filtered. The aqueous layer was washed with Et_2O (3×2 mL) and evaporated under vacuum giving the pure amino acid hydrochloride **10** or **11** (159 mg, 85%).

(1*R*,3*S*,1′*S*) (+)-**10**. Oil. $[\alpha]_D^{25}$ +5 (*c* 1, H_2O).

(1*S*,3*R*,1′*R*) (−)-**10**. Oil. $[\alpha]_D^{25}$ −4 (*c* 1, H_2O); [oil, $[\alpha]_D^{25}$ −5 (*c* 1, H_2O)].[7]

(1*S*,3*R*,1′*S*) (+)-**11**. Oil. $[\alpha]_D^{25}$ +11 (*c* 1, H_2O); [oil; $[\alpha]_D^{25}$ +9 (*c* 1, H_2O)].[7]

(1*R*,3*S*,1′*R*) (−)-**11**. Oil. $[\alpha]_D^{25}$ −10 (*c* 1, H_2O).

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Aziridines derived from amino acids as synthons in pseudopeptide synthesis

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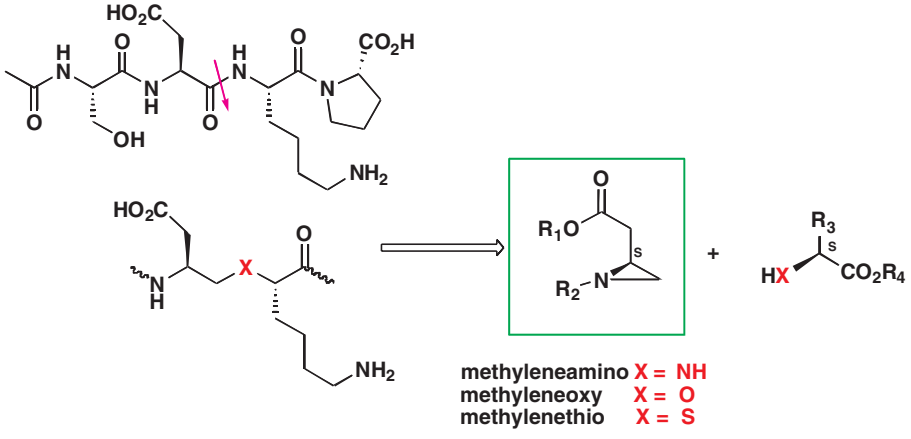
Abstract—The reactivity of the *Z*-protected aziridine derived from aspartic acid has been studied with various *N*- and *O*-nucleophiles. The optimized reaction conditions allow quick and easy access to 1, 2-diamines or amino alcohols. In the case of opening with *N*-nucleophiles, very good regioselectivity was observed. Use of an α-amino ester as the nucleophile yielded a methyleneamino pseudodipeptide.

1. Introduction

During the course of our ongoing study concerning the tetrapeptide Ac-Ser-Asp-Lys-Pro-OH extracted from bone marrow,[1] we were interested in preparing various analogues, which would be stable towards proteolysis.[2] A common approach to achieve this goal is to replace the hydrolyzable peptide bond by a surrogate bond.[3] Among the number of possibilities reported in the literature, the methyleneamino, methyleneoxy and methylenethio pseudopeptides have retained our attention. Of the three, only the former has been extensively used since a fully described methology is available for its preparation.[4] Examples of the two other surrogates are scarce as there is no general methodology for their synthesis. In principle, these three pseudopeptides could be obtained from a common precursor, namely an aziridine, which could be opened by amino acids or peptide esters or analogues (α-hydroxy or α-thio esters) as shown in Scheme 1. A preliminary report exploring the reactivity of the aziridine derived from an aspartic acid derivative with amines has shown the feasability of this approach with respect to the methyleneamino analogue.[5]

Aziridines as reactive intermediates have drawn considerable interest in the last decade.[6] They can be opened by



Scheme 1. Preparation of pseudodipeptides through opening of an aziridine by an α-amino, α-hydroxy or α-thio ester.

Keywords: Methyleneamino pseudopeptide; *Z*-Substituted aziridine opening; Microwaves; β-Amino alcohols; β-Amino acids.
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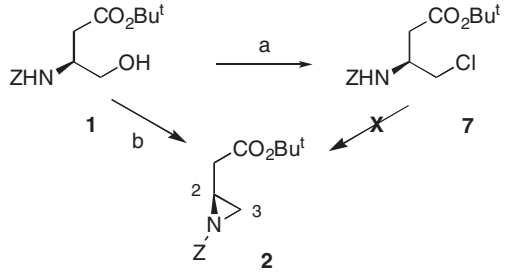
a variety of amine, alcohol, thiol or carbon nucleophiles. Their reactivity depends greatly on the nature of the substituent on the nitrogen. Thus, *N*-sulfonylaziridines react very readily with nucleophiles.[7] Using the chiral pool, optically active aziridines can be easily obtained from α-amino alcohols and many reports deal with aziridines derived from serine. There are, however, fewer papers dealing with aziridines derived from other amino acids.[8] Our purpose was to prepare derivatives, which could be used directly for peptide synthesis from amino acids having common protecting groups such as *t*-butyl and benzyl via the use of aziridines (Scheme 1).

We first addressed the question of the reactivity of *N*-benzyloxycarbonyl protected aziridines by studying aziridine **2** obtained from *Z*-Asp(OBu^t)-ol. This molecule bearing a *tert*-butyl ester on the side chain was reacted with various *N*-nucleophiles after screening of different mild reaction conditions. The reaction of **2** with oxygenated and sulfur nucleophiles was studied afterwards.

2. Results

2.1. Preparation of aziridine 2

Aziridine **2** was synthesized from the amino alcohol *Z*-L-Asp(OBu^t)-ol **1**.[9] This alcohol, obtained from commercial *Z*-L-Asp(OBu^t)-OH was treated either under Mitsunobu conditions (PPh_3, DEAD, THF) or with methanesulfonyl chloride in the presence of diisopropylethylamine (Scheme 2).[8] Only the Mitsunobu reaction yielded aziridine **2**. The mesylation of alcohol **1** followed by reflux with DIPEA gave the chloride **7** as the sole product. This chloride resisted further treatment with various bases (K_2CO_3, $KHCO_3$, $NaHSO_3$, AgO, KF, NaH), which gave either no reaction or decomposition.



Scheme 2. Synthesis of aziridine **2** (a): MsCl, DIPEA, THF, reflux, 20 h, 90%; (b): PPh_3, DEAD, THF, 0 °C, 30 min, rt, 18 h, 60–90%.

2.2. Ring opening of aziridine 2 with *N*-nucleophiles

2.2.1. With simple amines. We first applied conditions taken from the literature.[10] All the reactions were run in refluxing acetonitrile with 1.2 equiv of nucleophile and 1 equiv of $LiClO_4$[†] (Method A, entries 1, 3, 5). Most of the reactions were completed in 22–29 h and were quite regioselective yielding an approximately 1:10 ratio of **4**:**3** along with some tertiary amine **5** resulting from the attack of secondary amine **3** on aziridine **2** as shown in Table 1 (entries 1, 3, 4). In order to avoid the formation of **5**, we used an excess of nucleophile (3 equiv) in the following reactions.

Microwave-assisted organic synthesis has proven very efficient in shortening reaction times and increasing yields of sluggish reactions.[11] We used microwave irradiation to accelerate the reaction of **2** with amines and sealed tubes, which allowed reaction temperatures higher than the solvent or reagent boiling points. The screening of other reactions conditions (different solvents (toluene, THF) or catalysts ($Yb(OTf)_3$,[12] $MgClO_4$, $LiBF_4$, $Sc(OTf)_3$[13]) did not provide any benefit. However, the amount of $LiClO_4$ could be reduced to 0.5 equiv without reduction of yield whereas the use of 0.2 equiv decreased the rate of the reaction. Finally, the best reaction conditions were found to be 3 equiv of nucleophile in acetonitrile at 100 °C with 0.5 equiv $LiClO_4$[†] as catalyst in sealed tubes under microwave irradiation (Method B).

The aziridine opening reaction with simple amines (Table 1, entries 1–8) displayed very good regioselectivity except for benzylhydroxylamine (entry 5) where **3** and **4** were obtained in a ratio of 4:1, respectively. In all cases, the attack took place on the less substituted carbon. In some cases (entries 7 and 8), no product **4** resulting from attack at C-2 was isolated. Microwave activation gave satisfactory results considerably increasing the rate of the reactions (entries 1 and 2 and entries 3 and 4) while giving better yields. The reactions were generally completed within 1 h (entries 4, 7–8). The tertiary amine **5** was not obtained when a larger excess of nucleophile (3 equiv) was used (entries 7 and 8).

The 1, 2-diamino compounds **3** and **4** are valuable synthetic intermediates as their various protecting groups may be selectively cleaved before further elaboration.

2.2.2. Opening of 2 with other *N*-nucleophiles and amino acid esters (entries 9–11). When **2** was treated with the free bases of glycine *tert*-butyl ester or lysine methyl ester, **3** was obtained in good yield as the only regioisomer in the case of the latter (entry 10) whereas a slight amount of **4** could be isolated in the case of the former nucleophile (entry 9).

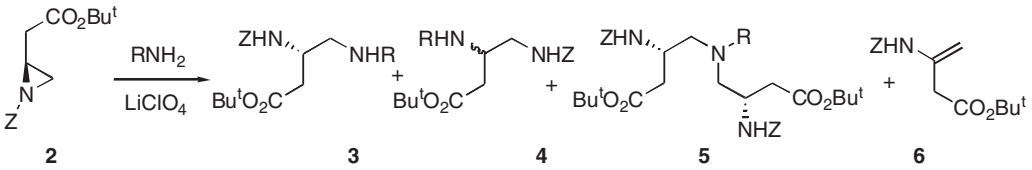
Treatment of **2** with NaN_3 (2 equiv) in CH_3CN/H_2O yielded only one regioisomer **3**, along with some elimination product **6** (29%) (entry 11).

2.3. Ring opening of aziridine 2 with *O*-nucleophiles

2.3.1. With alcohols (Scheme 3). Whereas, a wealth of catalysts is known to promote the opening of aziridines with *N*-nucleophiles, there are only a few described for their opening with *O*-nucleophiles, namely Lewis acids.[6] The most widely used catalyst is boron trifluoride etherate ($BF_3 \cdot OEt_2$), though $Yb(OTf)_3$[14] and $Sn(OTf)_2$[15] have also been reported for cases in which the alcohol nucleophile is used as the solvent. More recently, CAN[7b] has been used to catalyze the opening of tosyl aziridines also when using the alcohol as the solvent.

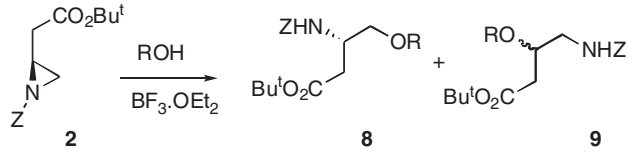
[†] Lithium perchlorate in organic solvents is a potential explosive hazard. It must be handled in small amounts and with appropriate care.

Table 1. Reaction of **2** with *N*-nucleophiles



Entry	Nucleophile (equiv)	Method[a]	Time (h)	Yield (**3**+**4**) (%)[b]	Ratio **4**:**3**	Yield **5** (%)[b]
1	$PhCH_2NH_2$ (1.1)	A	22	60	1:11	3
2	$PhCH_2NH_2$ (3)	B	0.5	85	1:14	
3	CH_2=CH–CH_2–NH_2 (1.5)	A	29	60	1:11	6
4	CH_2=CH–CH_2–NH_2 (1.5)	A[c]	2	70	1:8	10
5	$PhCH_2$–ONH_2 (1.2)	A	22	76	1:4	
6	$PhCH_2OCONHNH_2$ (2.4)	A	8 days	67	1:14	2
7	$(OEt)_2CHCH_2NH_2$ (3)	B	0.5	82	[d]	
8	*p*-MeO–$PhCH_2NH_2$ (3)	B	0.3	88	[d]	
9	$H_2NCH_2CO_2Bu^t$ (3)	B	1	80	1:26	
10	H-Lys(Boc)-OMe (1.2)	A	18	82	[d]	5
11	NaN_3 (2)	B	1.1	47	[d,e]	

[a] Method A: aziridine **2** (0.3 mmol), amine (1.2 equiv) and $LiClO^4$ (1 equiv) in refluxing acetonitrile (1.5 mL). Method B: aziridine **2** (0.2 mmol), amine (3 equiv) and $LiClO_4$ (0.5 equiv) in acetonitrile (1 mL) in sealed tubes under microwave irradiation T=100 °C, power: 40 W.
[b] Yields of purified products.
[c] Same conditions as entry 3, except that the reaction mixture in sealed tubes was subjected to microwave irradiation T=80 °C, power: 40 W.
[d] No product **4** was isolated.
[e] Elimination product **6**: 29%.

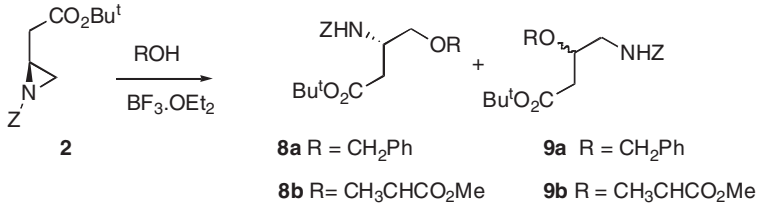


Scheme 3. Ring opening of **2** with alcohols.

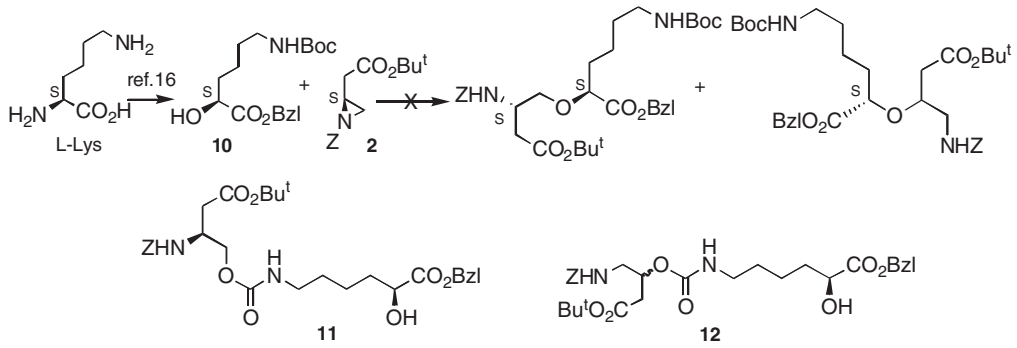
2.3.1.1. Reaction of 2 with benzyl alcohol. A first experiment run with 2 equiv of benzyl alcohol and 0.5 equiv of $BF_3 \cdot OEt_2$ catalyst at 0 °C for 1 h and at room temperature overnight provided a 46% yield of **8a** and **9a** in a 1:1 ratio. A additional experiment run at −30 °C with only 0.1 equiv of $BF_3 \cdot OEt_2$ improved the yield (74%) while giving the same ratio of regioisomers. Different sets of conditions were then investigated aiming to achieve better regioselectivity in favor of **8**. The use of bentonite yielded modest overall yields (40%) of **8a** and **9a** in a 1:1 ratio for reactions run at 130 °C in toluene or 100 °C without solvent under microwave activation. Montmorillonite KSF or K10 were not useful as catalysts either at room temperature in CH_2Cl_2 or in refluxing CH_3CN. Silica gel under solvent free conditions was totally inefficient.

2.3.1.2. With secondary alcohols. We then used methyl lactate as a model of an α-hydroxy ester nucleophile. In the presence of $BF_3 \cdot OEt_2$ (0.2 equiv) as the catalyst (Scheme 4), the two regioisomers **8b** and **9b** were obtained in 56% yield and in a 1.5:1 ratio. Keeping in mind our goal of preparing methyleneoxypseudodipeptides, we also used as nucleophile the benzyl ester of (2*S*)-6-(*tert*-butylcarboxylamino)-2-hydroxy-hexanoic acid **10** obtained through nitrous deamination of L-lysine followed by protection of the amino and carboxylic functions with the corresponding protecting groups (Scheme 5).[16] Using the same conditions as described above, no product corresponding to the expected mass could be isolated. Numerous attempts to improve these reaction conditions by varying the ratios of the reagents or the reaction temperature consistently gave the same results, that is, a reaction mixture the mass and NMR spectra of which indicated the loss of a *t*-butyl group. Careful HPLC analysis indicated a 7:3 ratio of two products and allowed the isolation of sufficient amounts for their identification. 2D NMR analysis established their structures as being two regioisomers **11** (major) and **12** (minor) as shown in Scheme 5. Although the Boc group is known to react in an intramolecular fashion with aziridines,[19] there is no literature precedence for such an intermolecular reaction to the best of our knowledge.

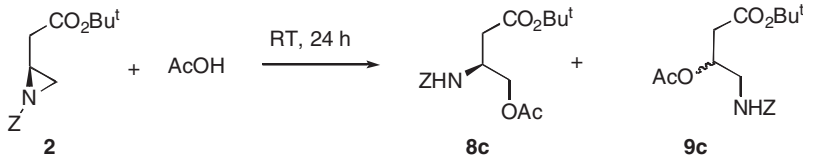
2.3.2. With acetic acid.[17] The opening of aziridine **2** with AcOH (5 equiv) at room temperature for 24 h yielded two compounds **8c** and **9c**, which could not be easily separated on silica gel. Acetylation of the alcohol **1** with acetic anhydride and DMAP allowed identification of **8c** in the



Scheme 4. Ring opening of **2** with primary and secondary alcohols.



Scheme 5. Opening of **2** with (2*S*)-2-hydroxy 6-amino hexanoic acid derivative **10**.

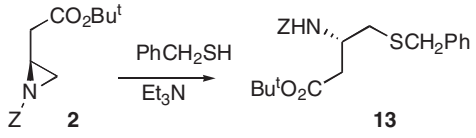


Scheme 6. Opening of **2** with acetic acid.

HPLC chromatogram of the mixture. The reaction gave the two regioisomers **8c** and **9c** in 81% yield and 3:1 ratio (Scheme 6).

2.4. Ring opening of aziridine 2 with *S*-nucleophiles

There are several reports of such a reaction.[7a,18,19] One describes the opening of a *Z*-protected serine-derived aziridine with various thiols used in large excess.[18a] The reaction, catalyzed by boron trifluoride etherate, required severals days to reach completion and was very regioselective. Crotti et al.[18b] used thiophenol (3 equiv) under metal assisted ($LiClO_4$) or basic (Et_3N) conditions in aprotic (CH_3CN) or protic (MeOH) solvents to open activated bicyclic tosyl aziridines. They also observed very good regioselectivity as did Dauban et al.[18c] in their study of a Ac or *Z*-protected bicyclic aziridine.



Scheme 7. Opening of **2** with benzyl mercaptan.

Thus, **2** was treated with benzyl mercaptan under the conditions described by Maligres[7a] and Crotti.[18b] The best results were obtained under basic conditions with Et_3N (5 equiv) in methanol and benzylmercaptan (3 equiv) at room temperature or Et_3N (0.2 equiv) in THF and benzylmercaptan (1.05 equiv) at 30 °C. In both cases, the thioether **13** was obtained after 5 days in 65% yield as a single regioisomer (Scheme 7).

The present study shows that benzyloxycarbamate-protected aziridines, although less activated than tosylaziridines, are sufficiently reactive to be easily and regioselectively opened by *N*-nucleophiles giving 1, 2-diamino compounds suitably protected for further transformations. The opening of **2** with the methyl ester of H-Lys(Boc)-OMe (entry 10, Table 1) provided the methyleneaminopseudopeptide *Z*-Asp(OBut)Ψ[CH_2-NH]Lys(Boc)-OMe with a good yield and excellent regioselectivity thereby affording a new route to this kind of compound. Treatment of **2** with alcohol in presence of boron trifluoride etherate gave mixtures of regioisomers whereas the use of a thiol as nucleophile gave only the product of C-3 attack. The synthesized compounds are presently being explored as building blocks in pseudopeptide synthesis.

3. Experimental

3.1. General

Protected amino acids are from Novabiochem (VWR) and Senn Chemicals. L-Lysine was purchased from Sigma. Commercially available reagents were used as received. Solvents were dried on dry basic alumina prior to use. Analytical TLC was conducted on Merck 60F-254 silica gel on precoated aluminum sheets; compounds were visualized with UV-light or with ninhydrine.

Flash column chromatography was performed using Merck silica gel 60 (40–63 μ). Infrared spectra were recorded on a Perkin–Elmer Spectrum BX instrument. Optical rotations were measured on a Jasco polarimeter using a cell of 1 dm-length path. Mass spectra were obtained using LCT Micromass (low and high resolution ES^+) spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a AM300, AVANCE 300 Bruker 300 MHz. Chemical shifts are expressed in ppm referenced to the peak of $CDCl_3$, defined at $\delta=77.1$ (^{13}C). Microanalyses were performed by the analytical laboratory in Gif. HPLC analysis was performed on a Waters apparatus consisting of Alliance gradient controller, an automatic 717 injector, a multi-wavelength UV detector and a chromatogram analyser. Analyses were carried out on a *C*18-Symmetry column

(5 μ, 4.6×250 mm). The eluent was a mixture of H_2O and acetonitrile both containing 0.1% trifluoroacetic acid at a 1 mL/min flow rate. The mass spectrometer connected to the HPLC apparatus was a Waters Micromass ZQ with an ESI probe. The microwave oven was a Discover™ monomodal apparatus from CEM μWaves (Orsay, France). Experimental parameters were: power: 40 W, temperature: 100 °C.

3.1.1. (2*R*)-2-*tert*-Butoxycarbonylmethyl-aziridine-1-carboxylic acid benzyl ester 2. To a solution of triphenylphosphine (2.62 g, 10 mmol) in THF (25 mL) cooled in an ice-water bath was added DEAD (1.6 mL, 10 mmol) over 30 min. A solution of *Z*-Asp(OBu^t)-ol[9b] (1.55 g, 5 mmol) in THF (12.5 mL) was added dropwise over 1 h at the same temperature. After 1 h at 0 °C, the reaction mixture was stirred at room temperature for 19 h. After evaporation of the solvents, the residue was taken up in CH_2Cl_2 and separated by column chromatography on silica gel. Elution with CH_2Cl_2 gave 0.667 g of pure aziridine and further elution with CH_2Cl_2–MeOH (99/1) gave 0.468 g of a less pure fraction, which was further purified on a silica gel column with heptane–EtOAc (85/15) yielding 0.344 g of pure product as a clear oil. Overall yield: 69%. R_f 0.53 (heptane/EtOAc, 7:3); R_f 0.67 (CH_2Cl_2/ether, 95:5).

$[\alpha]_D$ +23.7 (*c* 0.76, MeOH). MS (EI): *m*/*z* 292 ($M^{+\cdot}$), 236 ($M^{+\cdot}-56$), 192 ($M^{+\cdot}-100$), 107, 91, 57. ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.08 (d, *J*=3.6 Hz, 1H), 2.27 (dd, *J*=6.6, 16 Hz, 1H), 2.43 (d, *J*=6 Hz, 1H), 2.58 (dd, *J*=6, 16 Hz, 1H), 2.80 (M, 1H), 5.14 (S, 2H), 7.35 (s, 5H); ^{13}C NMR (75 MHz): δ 28.14, 31.57, 34.16, 38.88, 68.32, 81.30, 128.29, 128.41, 128.63, 135.82, 163.06, 169.74. Anal. Calcd for $C_{16}H_{21}NO_4$ C, 65.96, H, 7.27, N, 4.81. Found: C, 66.09, H, 7.17, N, 4.69.

3.1.2. (3*S*)- *tert*-Butyl-3-benzyloxycarbonylamino-4-chloro-butyrate 7. *Z*-L-Asp(OBu^t)-ol **1**[9b] (3.21 g, 10 mmol) was dissolved in THF (20 mL), DMAP (25 mg, 0.2 mmol) and DIPEA (4 mL, 23 mmol) were added, the mixture was cooled to −20 °C and then CH_3SO_2Cl (1 mL, 12 mmol) was added dropwise. The resulting suspension was warmed gradually to room temperature and then refluxed at 90 °C for 20 h. The mixture was cooled to room temperature; EtOAc (30 mL) and NaCl solution (20 mL) were added; the organic phase was isolated, dried over Na_2SO_4 and evaporated under vacuum to leave a syrup, which was purified by chromatography (EtOAc/pentane, 1:8–1:4) to give 2.61 g (90%) of the chloride derivative R_f 0.51 (EtOAc/heptane, 1:2). $[\alpha]_D$ −2.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz): 1.38 (s, 9H), 2.28–2.37 (q, 1H), 2.63–2.69 (q, 1H), 4.05–4.10 (q, 1H), 4.26–4.36 (m, 1H), 4.47–4.53 (t, 1H), 5.15 (s, 2H), 7.25–7.33 (m, 5H); ^{13}C NMR (75 MHz): 28.1, 42.1, 60.2, 72.3, 73.8, 81.0, 128.1, 128.4, 135.2, 163.1, 170.4. IR (neat) 3325, 2977, 1697, 1529, 1367, 1246, 1149, 1043, 955, 840, 737. MS (ES): *m*/*z* 350 (MNa^+), 294 (MNa^+-56); HRMS $C_{16}H_{22}ClNO_4Na$. Found: 350. 1126; calcd: 350.1135.

3.2. General procedure for opening of 2 with *N*-nucleophiles

Method A. Aziridine **2** (0.3 mmol) was dissolved in acetonitrile (1.5 mL). $LiClO_4$ (31 mg, 0.3 mmol) followed by the nucleophile (0.45 mmol or as described in Table 1) were added to the solution. The reaction mixture was refluxed (except in the case of entry 4 where it was heated at 50 °C) and monitored by TLC. At the end of the reaction period, the mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography.

Method B. Aziridine **2** (0.2 mmol) was dissolved in acetonitrile (1 mL) in a heavy-walled tube. $LiClO_4$ (10 mg, 0.1 mmol) followed by the nucleophile (0.6 mmol) were added to the solution. The tube was sealed with a teflon cap. The reaction mixture was submitted to microwave irradiation at *T*=100 °C and *P*=40 W under magnetic stirring for at least 20 min in the Discover microwave apparatus. The reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was washed with brine and dried with Na_2SO_4. Alternatively, the reaction mixture was evaporated under vacuum. In both cases, the crude product was purified by silica gel column chromatography.

3.2.1. With benzylamine (Method A).

3.2.1.1. (3*S*)-*tert*-Butyl-4-benzylamino-3-benzyloxycarbonylamino-butyrate 3a. Yield: 55%, R_f 0.17 (EtOAc/heptane, 4:6). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 1.51 (br s, 1H), 2.50 (m, 2H), 2.75 (m, 2H), 3.79 (s, 2H), 4.10 (m, 1H), 5.12 (s, 2H), 5.48 (m, 1H), 7.31, 7.36 (s, 10H); ^{13}C NMR (75 MHz): 28.0, 38.4, 48.2, 51.8, 53.7, 66.6, 81.1, 127.0, 128.1, 128.4, 128.5, 136.5, 140.1, 155.9, 170.8. MS: MH^+: 399, MH^+-56: 243; HRMS Found: $C_{23}H_{31}N_2O_4$ 399.2272; calcd: 399. 2284; IR (neat): 3330, 2976, 1721, 1249, 1156, 741.

3.2.1.2. 3(*R*)-3-Benzylamino-4-benzyloxycarbonylamino-butyric acid-*tert*-butyl ester 4a. Yield: 5%, R_f 0.30 (EtOAc/heptane, 4:6). ^{1}H NMR (300 MHz): 1.45 (s, 9H), 1.75 (br s, 1H), 2.42 (d, 2H), 3.14 (m, 1H), 3.26 (m, 1H), 3.35 (m, 1H), 3.80 (s, 2H), 5.12 (s, 2H), 5.31 (m, 1H), 7.32, 7.38 (s, 10H); ^{13}C NMR: 28.1, 38.3, 43.4, 50.9, 53.9, 66.7, 67.0, 81.1, 127.1, 128.2, 128.5, 128.6, 136.4, 139.9, 156.3, 171.2. MS: MNa^+: 421, MH^+: 399, MH^+-56: 343; HRMS $C_{23}H_{31}N_2O_4Na$. Found: 421.2096; calcd: 421.2103.

3.2.2. With allylamine (Method B).

3.2.2.1. (3*S*)-*tert*-Butyl-4-allylamino-3-benzyloxycarbonylamino-butyrate 3b. Yield: 62%. $[\alpha]_D$ −5 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 1.67 (br s, 1H), 2.51 (m, 2H), 2.73 (m, 2H), 3.25 (br s, 2H), 4.06 (m, 1H), 5.10 (br s+m, 4H), 5.50 (m, 1H), 5.86 (m, 1H), 7.37 (s, 5H); ^{13}C NMR (75 MHz): 28.0, 38.4, 48.2, 51.6, 52.1, 66.6, 81.1, 116.1, 128.0, 128.3, 128.5, 128.6, 136.5, 155.8, 170.8. IR (neat): 3338, 2978, 1722, 1537, 1253, 1158, 1054, 919, 919, 738, 697. MS: MNa^+: 371, MH^+: 349, MH^+-56: 293; HRMS $C_{19}H_{29}N_2O_4$. Found: 349.2132; calcd: 349.2127.

3.2.2.2. (3*R*)-*tert*-Butyl-3-allylamino-4-benzyloxycarbonylamino-butyrate 4b. Yield: 8%, R_f 0.54 (EtOAc/heptane, 4:6). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.39 (d, 2H), 2.96–3.40 (m, 4H), 5.03–5.31 (br s+m, 5H), 5.85

(m, 1H), 7.37 (s, 5H); ^{13}C NMR (75 MHz): 28.1, 38.3, 41.3, 49.3, 53.7, 66.7, 81.1, 116.5, 128.1, 128.5, 136.5, 157, 171.2. MS: MNa^+: 371, MH^+: 349, MH^+-56:293; IR (neat): 3338, 1722.

3.2.3. With *O*-benzylhydroxylamine (Method A).

3.2.3.1. (3*S*)-*tert*-Butyl-4-benzyloxyamino-3-benzyloxycarbonylamino-butyrate 3c. Yield: 60%, R_f 0.25 (EtOAc/heptane, 3:7). $[\alpha]_D$ +18 (*c* 1.1, $CHCl_3$). ^{1}H NMR: 1.43 (s, 9H), 2.56 (d, 2H), 3.08 (m, 2H), 4.20 (m, 1H), 4.69 (s, 2H), 5.11 (s, 2H), 5.47 (m, 1H), 5.74 (br s, 1H), 7.34, 7.37 (s, 10H); ^{13}C NMR (75 MHz): 28.0, 38.1, 46.9, 54.3, 66.6, 76.1, 81.1, 128.0, 128.1, 128.4, 128.5, 136.5, 137.5, 155.8, 170.7. MS: MK^+: 453, MNa^+: 437, MH^+: 415, MNa^+-56: 381, MH^+-56: 359; HRMS (ES) $C_{23}H_{30}N_2O_5Na$. Found: 437.2028; calcd: 437.2052

3.2.3.2. (3*R*)-3-Benzyloxyamino-4-benzyloxycarbonylamino-butyric acid-*tert*-butyl ester 4c. Yield: 16%. ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.34 (m, 1H), 2.46 (m, 1H), 3.21 (m, 1H), 3.33 (m, 1H), 4.55 (s, 2H), 4.96 (br s, 1H), 5.10 (s, 2H), 6.04 (br s, 1H), 7.36, 7.37 (s, 10H); ^{13}C NMR (75 MHz): 28.1, 35.2, 42.2, 56.9, 66.7, 76.6, 81.1, 128.0, 128.1, 128.4, 128.5, 128.6, 136.5, 137.6, 155.8, 171.1. MS: MK^+: 453, MNa^+: 437, MH^+: 415, MNa^+-56: 381, MH^+-56: 359.

3.2.4. With *N*-benzyloxycarbonylhydrazine (Method A).

3.2.4.1. 3(*S*)-4-(*N*-Benzyloxycarbonyl-hydrazino)-3-benzyloxycarbonylamino-butyric acid-*tert*-butyl ester 3d. Yield: 63%, R_f 0.25 (EtOAc/heptane, 4:6). $[\alpha]_D$ +53 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz): 1.42 (s, 9H), 2.32–2.61 (dd, 2H), 2.75–3.06 (m, 2H), 4.12 (m, 2H), 5.13 (m, 5H), 5.52 (m, 1H), 6.83 (m, 1H), 7.37 (10H); ^{13}C NMR (75 MHz): 28.1, 38.0, 46.3, 54.1, 54.6, 66.8, 67.0, 81.3, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 136.1, 136.4, 156.6, 157.2, 170.7; HRMS (ES) $C_{24}H_{31}N_3O_6Na$. Found: 480.2134; calcd: 480.2111.

3.2.5. With 2,2-diethoxyethylamine (Method B).

3.2.5.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-(2,2-diethoxy-ethylamino)-butyrate 3e. Yield: 82%, R_f 0.22 (EtOAc/heptane, 3:1). $[\alpha]_D$ +2.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz): 1.22 (t, 6H, *J*=7.1 Hz), 1.43 (s, 9H), 2.49 (m, 2H), 2.76 (m, 4H), 3.53 (m, 2H), 3.68 (m, 2H), 4.08 (m, 1H), 4.54 (t, 1H), 5.10 (s, 2H), 5.45 (br, 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz): 15.4, 28.0, 38.3, 48.3, 52.1, 52.3, 62.3, 66.6, 81.01, 102.0, 128.0, 128.5, 136.6, 155.9, 170.7. MS (m/z): 425.2 (MH^+); IR (neat): 3332, 2976, 2930, 1725, 1530, 1455, 1368, 1250, 1157, 1061, 844, 738

3.2.6. With *p*-methoxybenzylamine (Method B).

3.2.6.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-(4-methoxy-benzylamino)-butyrate 3f. Yield: 88%, R_f 0.31 (EtOAc/heptane, 5:2). $[\alpha]_D$ −0.6 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.50 (m, 2H), 2.74 (m, 2H), 3.74 (s, 2H), 3.82 (s, 3H), 4.09 (m, 1H), 5.11 (s, 2H), 5.44 (br, 1H), 6.79 (d, 2H, *J*=8.6 Hz), 7.15 (d, 2H, *J*=8.6 Hz), 7.38 (m, 5H); ^{13}C NMR (75 MHz): 28.0, 38.4, 48.1, 51.7, 53.1, 55.2, 66.6, 81.0, 113.8, 128.0, 128.5, 129.2, 132.3, 136.6, 155.9, 158.7, 170.8. MS (m/z): 451 (MNa^+), 429 (MH^+), 373 (MH^+-56); HRMS $C_{24}H_{31}N_2O_5Na$. Found: 451.2217; calcd: 451.2209; IR (neat): 3335, 2977, 2836, 1723, 1611, 1513, 1247, 1157, 1037, 843, 739.

3.2.7. With glycine *tert*-butyl ester (Method B).

3.2.7.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-(*tert*-butoxycarbonylmethyl-amino)-butyrate 3g. Yield: 77%, R_f 0.23 (EtOAc/heptane, 3:1). $[\alpha]_D$ +5.7 (*c* 1.9, $CHCl_3$). ^{1}H NMR (300 MHz): 1.4 (s, 9H), 1.43 (s, 9H), 2.48 (m, 2H), 2.76 (m, 2H), 3.35 (AB s, 2H, *J*=17 Hz), 4.03 (m, 1H), 5.11 (s, 2H), 5.50 (br, 1H), 7.36 (m, 5H); ^{13}C NMR (75 MHz): 28.0, 28.1, 38.3, 48.3, 51.6, 52.0, 66.6, 81.0, 81.2, 128.0, 128.4, 136.6, 155.9, 170.7, 171.6. MS (m/z): 445 (MNa^+), 423 (MH^+), 389 (MNa^+-tBu), 367 (MH^+-tBu), 311 (MNa^+-Z); HRMS $C_{22}H_{34}N_2O_6Na$. Found: 445.2351; calcd: 445.2315; IR (neat): 3338, 2978, 1728, 1530, 1368, 1247, 1157, 1054, 846, 752.

3.2.8. With sodium azide (Method B).

3.2.8.1. (3*S*)-*tert*-Butyl-4-azido-3-benzyloxycarbonylamino-butyrate 3h. Yield: 47%, R_f 0.41 (EtOAc/heptane, 1:2). $[\alpha]_D$ −3.0 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz): 1.45 (s, 9H), 2.54 (d, 2H), 3.51 (m, 2H), 4.16 (m, 1H), 5.13 (s, 2H), 5.45 (m, 1H), 7.38 (br s, 5H); ^{13}C NMR (75 MHz): 28.0, 37.2, 47.9, 53.7, 66.9, 81.7, 128.1, 128.2, 128.5, 136.2, 155.6, 170.1. MS (m/z): 357 (MNa^+), 301 (MNa^+-56); HRMS $C_{16}H_{22}N_4O_4Na$. Found: 357.1549; calcd: 357.1539; IR (neat): 3328, 2979, 2103, 1727, 1532, 1454, 1368, 1255, 1157, 1055, 961, 843, 738.

3.2.9. With H-Lys(Boc)-OMe (Method B).

3.2.9.1. (2*S*)-Methyl-2-(2-benzyloxycarbonylamino-3-*tert*-butoxycarbonyl-propylamino)-6-*tert*-butoxycarbonylamino hexanoate 3i. Yield: 83%, R_f 0.23 (EtOAc/heptane, 4:6); R_f 0.28 (CH_2Cl_2/MeOH, 98:2). ^{1}H NMR (300 MHz): 1.46 (s, 9H), 1.47 (s, 9H), 2.37 (d, 2H, *J*=6.3 Hz), 3.08 (m, 1H), 3.25 (m, 2H), 3.33 (s, 2H), 5.12 (s, 2H), 5.49 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (75 MHz): 28.0, 38.8, 43.5, 49.1, 54.5, 66.6, 81.0, 81.4, 128.1, 128.5, 136.6, 156.6, 170.7, 171.6. IR (neat): 3342, 2975, 2928, 1728, 1530, 1366, 1236, 1145, 843, 751. MS (m/z): 574 (MNa^+), 552 (MH^+); HRMS $C_{28}H_{46}N_3O_8Na$. Found: 552.3286; calcd: 552.3285.

3.3. General procedure for opening of aziridine 2 with *O*-nucleophiles.

3.3.1. With benzyl alcohol. $BF_3\cdot OEt_2$ (6 μL, 0.1 equiv) was added to a solution of **2** (146 mg, 0.5 mmol) and benzyl alcohol (104 μL, 2 equiv) in dry $CHCl_3$ (6 mL) cooled to −30 °C. After 3 h 30 min stirring at this temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was then washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (217 mg) containing **8a**, **9a** and benzyl alcohol, which was separated on a silica gel column. Elution with heptane/EtOAc 8:2 gave pure **8a** (19 mg), a mixture of **8a** and **9a** (107 mg) and pure **9a** (27 mg). Overall yield: 74%.

3.3.1.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-benzyloxy-butyrate 8a. R_f 0.53 (heptane/EtOAc, 7:3). $[\alpha]_D$ −8 (*c* 1.1, MeOH).^{1}H NMR (300 MHz): 1.38 (s, 9H), 2.53 (d, 2H, *J*=6.3 Hz), 3.51 (m, 2H), 4.19 (m, 1H), 4.48 (s, 2H), 5.07 (s, 2H), 5.38 (br d, 1H), 7.32 (br s, 10H); ^{13}C NMR

(75 MHz): 28.1, 37.5, 48.1, 66.8, 71.1 73.3, 81.1, 127.8, 127.7, 128.5, 128.2, 128.6, 136.6, 138.0, 155.8, 170.7. MS (m/z): 438 (MK^+), 422 (MNa^+), 366 (MNa^+-56), 266 (MH^+-134); IR (neat): 3335, 2977, 1732, 1538, 738, 697.

3.3.1.2. (3*S*)-*tert*-Butyl-3-benzyloxy-4-benzyloxycarbonylamino-butyrate 9a. R_f 0.45 (heptane/EtOAc, 7:3). $[\alpha]_D$ +1 (*c* 1.1, MeOH). ^1H NMR (300 MHz): 1.41 (s, 9H), 2.50 (AB s, 2H, $J=6.3$ Hz), 3.25 (m, 1H), 3.39 (m, 1H), 3.94 (m, 1H), 4.58 (AB s, 2H, $J=11$ Hz), 5.05 (s, 3H), 7.31 (br s, 10H); ^{13}C NMR (75 MHz): 28.2, 39.0, 43.9, 66.8, 72.0 75.1, 81.1, 127.9, 128.2, 128.6, 136.6, 138.1, 156.6, 170.4. MS (m/z): 438 (MK^+), 422 (MNa^+), 400 (MH^+), 366 (MNa^+-56), 344 (MH^+-56), 266 (MH^+-134); IR (neat): 3343, 2976, 1718, 1540, 737, 697.

3.3.2. With (*S*)-methyl lactate. To a cold solution of $BF_3\cdot OEt_2$ (9 μL, 0.2 equiv) in $CHCl_3$ (0.4 mL) was added methyl lactate (72 μL, 2 equiv) followed by a solution of **2** (111 mg, 0.4 mmol) in $CHCl_3$ (1.2 mL). After 1 h stirring in the ice bath, the reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was then washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (157 mg) containing **8b** and **9b**. MS-HPLC analysis of the crude product indicated that the 2 regioisomers were present ($t_R=$ 11.79 and 12.35 min) in a 1.5–1 ratio. The analysis was performed on a Waters Symmetry column. The eluent was a gradient of H_2O and acetonitrile both containing 0.1% TFA starting from 35% acetonitrile to 100% over 20 min at a 1 mL/min flow rate.

3.3.3. With acetic acid. Acetic acid (86 μL, 5 equiv) was added to a solution of aziridine **2** (87 mg, 0.3 mmol) in CH_2Cl_2 (0.9 mL). The solution was stirred under argon during 24 h. The reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure afforded 102 mg of a yellow oil. The crude product was separated by flash chromatography. Elution with heptane/EtOAc 75/25 did not allow separation of the two regioisomers and gave 95 mg of a mixture of **8c** and **9c**. ^1H NMR analysis showed a of 3:1 ratio of **8c**:**9c**. A second flash chromatography using petroleum ether–acetone (9:1) gave pure **8c** (8 mg) and a mixture of **8c** and **9c**.

3.3.3.1. (3*S*)-4-Acetoxy-3-benzyloxycarbonylamino-butyric acid *tert*-butyl ester 8c. R_f 0.31 (EtOAc/heptane, 3:7). ^1H NMR (300 MHz): 1.43 (s, 9H), 2.05 (s, 3H), 2.52 (d, $J=5.9$ Hz, 2H), 4.15 (m, 2H), 4.28 (m, 1H), 5.11 (s, 2H), 5.41 (d, $J=9$ Hz, 1H), 7.35 (s, 5H); ^{13}C NMR (75 MHz): 20.7, 28.0, 37.1, 47.2, 65.1, 66.8, 81.5, 127.1, 128.1, 128.5, 136.3, 155.3, 155.6, 170.0, 170.7. MS (m/z): 390 (MK^+), 374 (MNa^+), 318 (MNa^+-56).

3.3.4. With benzyl (2*S*)-6-(*tert*-butyloxycarbonylamino)-2-hydroxy-hexanoate 10. $BF_3\cdot OEt_2$ (52 μL, 0.2 equiv) in dry $CHCl_3$ (0.2 mL) was added to a solution of **2** (65 mg, 0.22 mmol) and alcohol **10** (151 mg, 2 equiv) in dry $CHCl_3$ (0.6 mL) cooled to 0 °C. After 15 min stirring at this temperature and 4 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was then washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (207 mg). The residue was purified by flash chromatography with heptane–EtOAc (7/3) to remove excess **10**. Elution with methanol and evaporation of methanol fractions gave a mixture of **11** and **12** (79 mg) as a transparent oil, which could only be separated by HPLC. Analysis of the mixture showed a 7:3 ratio of **11** and **12**. Elution on a *C*18-symmetry column was isocratic with a mixture of H_2O and acetonitrile (1/1) both containing 0.1% trifluoroacetic acid at a 1 mL/min flow rate. t_R (**11**)= 23.0 min, t_R (**12**)=24.1 min.

Chromatography under the same conditions provided each compound as a pure sample (2 mg) allowing 2D NMR analysis. Both compounds had an identical ESI mass spectum corresponding to MNa^+-56: 595.

Compound **11**. ^{13}C NMR (100 MHz) in DMSO-d_6: 21.9, 28.0, 29.4, 33.7, 38.4, 40.7, 44.3, 66.8, 67.3, 70.2, 81.2, 128.1, 124.4, 128.5, 128.6, 128.7, 135.1, 136.4, 155.7, 156.5, 155.7, 169.2, 174.9.

3.4. Opening of 2 with benzyl mercaptan.

3.4.1. (2*S*)-*tert*-Butyl 3-(benzyloxycarbonylamino)-4-(benzylthio) butyrate propanoate 13. (a) Benzyl mercaptan (37 μL, 1.05 equiv) was added to a solution of aziridine **2** (87 mg, 0.3 mmol) and Et_3N (8 μL, 0.2 equiv) in THF (0.3 mL). The reaction was run under argon for 5 days at 30 °C. The reaction mixture was diluted with ether and the organic phase was washed with water, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (121 mg). The residue was purified by flash chromatography with heptane–EtOAc (8/2) to give **13** (81 mg) as an oil.

(b) Benzylmercaptan (105 μL, 3 equiv) was added to a solution of aziridine **2** (87 mg, 0.3 mmol) and Et_3N (208 μL, 5 equiv) in methanol (0.3 mL). The reaction was run under argon for 5 days at room temperature. The reaction mixture was diluted with ether and the organic phase was washed with water, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (176 mg). The residue was purified by flash chromatography with heptane–EtOAc (8/2) to give **13** (82 mg).

R_f 0.53 (EtOAc/heptane, 3:7). $[\alpha]_D$ +10.8 (*c* 1.6, $CHCl_3$). ^1H NMR (300 MHz): 1.43 (s, 9H), 2.49–2.69 (m, 4H), 4.74 (br s, 2H), 4.14 (m, 1H), 5.12 (s, 2H), 5.42 (1H), 7.36 (m, 10H); ^{13}C NMR (75 MHz): 28.0, 35.4, 36.5, 38.6, 47.6, 66.7, 81.3, 127.1, 128.0, 128.1, 128.5, 128.9, 136.5, 138.0, 155.6, 170.5. MS (m/z): 438 (MNa^+), 382 (MNa^+-56); HRMS $C_{23}H_{29}NO_4NaS$. Found: 438.1675; calcd: 438.1715.

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Star-like fluorene based polyamines: non-conjugated building blocks for light-harvesting materials

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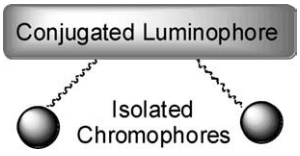
Abstract—We report herein a series of novel tetramines (**2**–**6**) built using the fluorene core. The design features a diamine conjugated by a fluorene core and two non-conjugated triarylamines dangling through the bridge methine moiety. These polyamines are amorphous in nature and display moderate emission properties that are either dependent on the nature of the arylamine segments or reminescent of the fluorene backbone. The phenyl, naphthyl, fluorenyl and carbazolyl amine based materials are blue emissive while the pyrenylamine based compound emits yellow-green color. We demonstrate a possibility of using blue-emitting fluorene derivatives (**2** and **4**) blended with poly(*N*-vinylcarbazole) (PVK) to fabricate organic light emitting diodes (OLEDs). Emissions in the EL devices purely originated from the fluorene derivatives alone (blue) are contaminated with those of complex species (electromer/electroplex) formed by intermolecular interactions.

1. Introduction

Triarylamines incorporating rigid and photoactive polyaromatics have recently attracted much attention in various research fields as advanced materials for electronic, photonic, and magnetic applications.[1] In particular, their use as hole transporting layers in organic light emitting diodes (LEDs) triggered the need of synthesizing thermally stable amorphous triarylamines with tunable luminescent characteristics.[2] We have earlier reported carbazole-,[2c–f] pyrene-,[3] and hexathienylbenzene-based[4] polyamines and they have been proved to be efficient hole transporting and/or emitting materials.

9,9-Dialkyl fluorene moieties have been used widely as building blocks in polymers and small molecules for photonic applications.[5] Incorporation of functional groups at 9 methine position and subsequent conversion into functional materials is rather rare. Fluorene containing crown ethers have been obtained exploiting the substitution at 9-position.[6] This also offers opportunity to design conjugated luminophores with non-conjugated functional units (shown as the following chart).



Such a site isolation technique has been recently demonstrated to be useful in obtaining advanced materials with both hole and electron-transporting capabilities besides emissive nature.[7] Also, suitably designed molecules could be useful systems for energy transfer studies.[8] It is interesting to note that a single blue-emitting phosphor[8] dopant in combination with its excimer emission can generate white light efficiently.

In this work, we report the synthesis and characterization of tetramines containing fluorene core. The four amines are positioned in such a way that two of them are interacting through the fluorene bridge while the remaining two triarylamines are dangling. We have fabricated devices containing PVK blended with these amines as host for carbazole based dopant emitter, 9-ethyl-*N*,*N*′-diphenyl-*N*,*N*′-dipyren-1-yl-9*H*-carbazole-3,6-diamine (carb9). The devices exhibited a mixed profile EL with a blue emission originating from the fluorene amine and a red electroplex (or electromer) emission. We also unravel that by varying the concentration of the fluorene amine, the ratio of the red electroplex (or electromer) emission to the blue emission

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from the fluorene amine can be tuned. This allows us a possibility to demonstrate a white light emitting diodes.

2. Experimental

2.1. Materials

Unless otherwise specified all the reactions were performed under nitrogen atmosphere using standard Schlenk techniques. Toluene was distilled from sodium and benzophenone under nitrogen atmosphere. All chromatographic separations were carried out on silica gel (60 M, 230–400 mesh) using hexane, dichloromethane mixtures.

The synthesis and characterization of 9-ethyl-*N*,*N*′-diphenyl-*N*,*N*′-dipyren-1-yl-9*H*-carbazole-3,6-diamine (carb9) has been published before.[9] The synthetic procedures of tris(8-quinolinolato)-aluminum(III) (Alq_3) as an electron-transporting layer and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (BCP) as a hole-blocking layer were reported in the literature.[11]

2.1.1. 2,7-Dibromo-9,9-bis-(4-bromo-benzyl)-9*H*-fluorene (1). A two-necked round bottom flask was charged with 2,7-dibromofluorene (3.24 g, 10 mmol), potassium *tert*-butoxide (3.36 g, 30 mmol) and dimethylsulfoxide (70 mL). After heating the contents to 50 °C, 4-bromobenzylbromide (6.0 g, 24 mmol) was added in small portions over 1 h. The reaction was continued for overnight at that temperature and quenched by pouring in ice. The solids formed were extracted with diethyl ether and purified by column chromatography (SiO_2, hexane–dichlormethane (8/2)) to yield 5.95 g (90%) of **1** as a colorless solid. ^{1}H NMR ($CDCl_3$): 3.26 (s, 4H, CH_2), 6.44–6.49 (m, 4H, ph), 7.02–7.07 (m, 4H, ph), 7.20 (d, J=8.1 Hz, 2H, flourene 4-CH), 7.35 (dd, J=8.1, 1.9 Hz, 2H, fluorene 3-CH), 7.52 (d, J=1.9 Hz, 2H, fluorene 2-CH). FAB MS (*m*/*z*): 662 (M^+). Anal. Calcd for $C_{27}H_{18}Br_4$: C, 48.98; H, 2.74. Found: C, 49.04; H, 2.67.

2.2. General amination procedure

A two-necked flask containing bromide (**1**), 4.4 equiv of diarylamine, $Pd(dba)_2$ (4 mol%), P(*t*-bu)$_3$ (4–8 mol%), sodium *tert*-butoxide (6 equiv) was added 20 mL toluene and heated at 80 °C for 12 h. After all the bromide was consumed, the reaction was quenched by the addition of ice water and extracted with diethyl ether. The organic extract was dried over anhydrous $MgSO_4$ and evaporated to dryness to yield the crude product. It was purified by column chromatography on silica gel using hexane and dichlomethane mixture as eluant. Typical yields range from 75 to 90%.

2.2.1. 9,9-Bis-(4-diphenylamino-benzyl)-*N*,*N*,*N*′,*N*′-tetraphenyl-9*H*-fluorene-2,7-diamine (2). Colorless solid. ^{1}H NMR (acetone-d_6): 3.34 (s, 4H, CH_2), 6.59–6.67 (m, 8H, ph), 6.85–6.88 (m, 8H), 6.91–6.99 (m, 10H), 7.03–7.06 (m, 8H), 7.15–7.24 (m, 16H), 7.41–7.45 (m, 4H). FAB MS (*m*/*z*): 1015 (M^+). Anal. Calcd for $C_{75}H_{58}N_4$: C, 88.72; H, 5.76; N, 5.52. Found: C, 88.65; H, 5.48; N, 5.49.

2.2.2. *N*,*N*′-Di-naphthalen-1-yl-9,9-bis-[4-(naphthalen-1-yl-phenyl-amino)-benzyl]-*N*,*N*′-diphenyl-9*H*-fluorene-2,7-diamine (3). Pale yellow solid. ^{1}H NMR (acetone-d_6): 3.81 (s, 4H, CH_2), 6.33–6.36 (m, 4H, ph), 6.47–6.50 (m, 4H, ph), 6.83–6.91 (m, 14H), 7.07–7.36 (m, 24H), 7.49 (q, J=7.9 Hz, 4H), 7.71–7.74 (m, 4H), 7.83 (t, J=8.2 Hz, 4H), 7.96 (dd, J=7.9, 3.1 Hz, 4H). FAB MS (*m*/*z*): 1216 (M^+). Anal. Calcd for $C_{91}H_{66}N_4$: C, 89.92; H, 5.47; N, 4.61. Found: C, 89.71; H, 5.59; N, 4.52.

2.2.3. *N*,*N*′-Bis-(9,9-diethyl-9*H*-fluoren-2-yl)-9,9-bis-{4-[(9,9-diethyl-9*H*-fluoren-2-yl)-phenyl-amino]-benzyl}-*N*,*N*′-diphenyl-9*H*-fluorene-2,7-diamine (4). Pale yellow solid. ^{1}H NMR (acetone-d_6): 0.22–0.31 (m, 24H, CH_3), 1.80–2.03 (m, 16H, CH_2), 3.38 (s, 4H, CH_2), 6.65 (d, J=8.4 Hz, 4H, ph), 6.77 (d, J=8.4 Hz, 4H, ph), 6.88–7.04 (m, 6H), 7.08–7.11 (m, 4H), 7.16–7.35 (m, 16H), 7.46 (d, J=8.2 Hz, 2H), 7.53–7.70 (m, 10H). FAB MS (*m*/*z*): 1592 (M^+). Anal. Calcd for $C_{119}H_{106}N_4$: C, 89.77; H, 6.71; N, 3.52. Found: C, 89.55; H, 6.73; N, 3.66.

2.2.4. *N*,*N*′-Diphenyl-9,9-bis-[4-(phenyl-pyren-1-yl-amino)-benzyl]-*N*,*N*′-di-pyren-1-yl-9*H*-fluorene-2,7-diamine (5). Yellow solid. ^{1}H NMR (acetone-d_6): 3.06 (s, 4H, CH_2), 6.36 (d, J=8.4 Hz, 4H, ph), 6.58 (d, J=8.4 Hz, 4H, ph), 6.73–6.76 (m, 2H), 6.83–6.88 (m, 8H), 6.95–7.00 (m, 8H), 7.19–7.25 (m, 4H), 7.34 (d, J=1.9 Hz, 2H), 7.41 (d, J=8.2 Hz, 2H), 7.47 (d, J=7.5 Hz, 2H), 7.59 (d, J=9.5 Hz, 2H), 7.65 (d, J=8.1 Hz, 3H), 7.68 (d, J=8.2 Hz, 2H), 7.88–8.08 (m, 14H), 8.14–8.20 (m, 8H), 8.27 (t, J=8.4 Hz, 4H). FAB MS (*m*/*z*): 1511.7 (M^+). Anal. Calcd for $C_{115}H_{74}N_4$: C, 91.36; H, 4.93; N, 3.71. Found: C, 91.23; H, 5.02; N, 3.54.

2.2.5. *N*,*N*′-Bis-(9-ethyl-9*H*-carbazol-3-yl)-9,9-bis-{4-[(9-ethyl-9*H*-carbazol-3-yl)-phenyl-amino]-benzyl}-*N*,*N*′-diphenyl-9*H*-fluorene-2,7-diamine (6). Pale yellow solid. ^{1}H NMR (acetone-d_6): 1.27 (t, J=7.2 Hz, 6H, CH_3), 1.38 (t, J=7.2 Hz, 6H, CH_3), 3.23 (s, 4H, CH_2), 4.28 (q, J=7.2 Hz, 4H, CH_2), 4.43 (q, J=7.2 Hz, 4H, CH_2), 6.57 (d, J=8.4 Hz, 4H, ph), 6.70–6.78 (m, 6H), 6.85–6.95 (m, 8H), 6.99 (d, J=-7.6 Hz, 4H), 7.03–7.19 (m, 14H), 7.23–7.32 (m, 6H), 7.35–7.44 (m, 8H), 7.48–7.55 (t, J=9.5 Hz, 4H), 7.76–7.79 (m, 4H), 7.92 (d, J=1.9 Hz, 2H), 7.98 (d, J=7.7 Hz, 2H). FAB MS (*m*/*z*): 1483.8 (M^+). Anal. Calcd for $C_{107}H_{86}N_8$: C, 86.61; H, 5.84; N, 7.55. Found: C, 86.56; H, 5.75; N, 7.41.

2.3. Preparation of devices

Glass slides precoated with indium tin oxide (ITO) with sheet resistances of ~20 Ω/sq and with an effective individual device area of 3.14 mm^2 were used for fabrication of devices. The ITO glasses were routinely cleaned by ultrasonic treatment in detergent solutions, followed by through rinsing in acetone and then ethanol, and dried in oxygen plasma for 3 min before being loaded into the vacuum chamber. Since the molecular weight of the amines **2–6** are too large to be sublimed by thermal vacuum deposition for OLED devices, the amines **2–6** are blended with PVK to fabricate PLED devices and their photophysical properties are studied. The carb9 dopant and the amine derivatives **2–6** blended

in PVK are dissolved in 1,2-dichloroethane with a concentration of 30 mg/mL and the spin coating rate was 3000 rpm for 40 s. The hole-blocking (BCP) and/or electron-transporting (Alq_3) layers were deposited thermally at a rate of 0.1–0.3 Å/s under a pressure of $\sim 2\times 10^{-5}$ Torr in an Ulvac Cryogenic deposition system. An alloy of magnesium and silver (ca. 10:1, 50 nm) was deposited as a cathode, which was then capped with 100 nm of silver.

2.4. Instrumentation

Dichloromethane for spectroscopic and voltammetric measurements were distilled from calcium hydride under nitrogen atmosphere. NMR spectra were recorded on Bruker 300 MHz spectrometer operating at 300.135 MHz. Electronic absorption spectra were obtained from a Cary 50 probe UV–visible spectrophotometer. Emission spectra were recorded on Perkin–Elmer spectrofluorometer. Differential scanning calorimetry (DSC) measurements were carried out on a Perkin–Elmer DSC-7 at a heating rate of 10 °C/min under nitrogen atmosphere. Electrochemical measurements were performed in a BAS 100B electrochemical analyzer using a conventional three-electrode cell assembly comprising of glassy carbon working electrode, platinum auxiliary electrode and Ag/$AgNO_3$ reference electrode. Tetrabutylammonium hexafluorophosphate was used as a supporting electrolyte. Potentials were calibrated by using ferrocene as an internal standard. The photoluminescence (PL) and electroluminescence (EL) spectra were recorded on a Hitachi spectrofluorimeter. Diphenylamine, $Pd(dba)_2$ and 4-bromobenzylbromide were procured from commercial sources and used as received.

3. Results and discussion

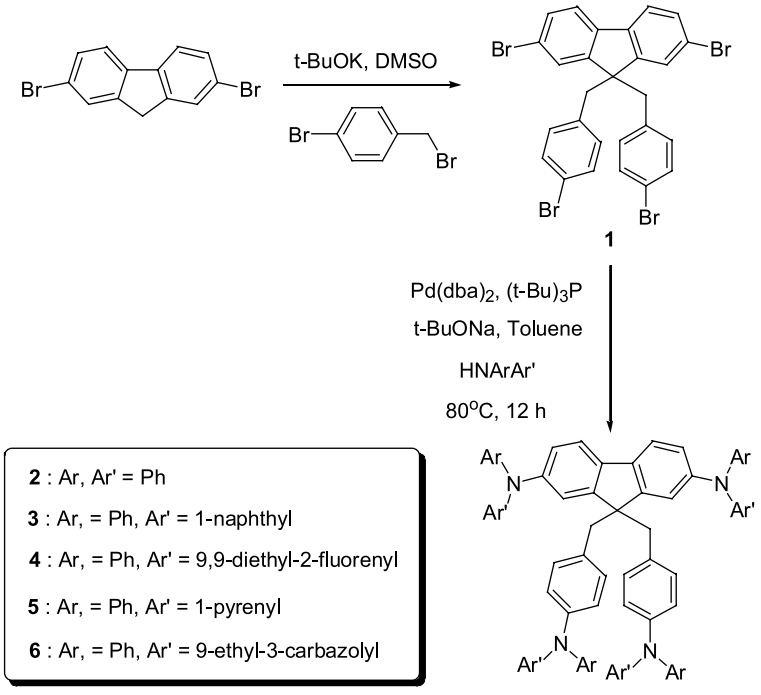
3.1. Synthesis

The synthetic procedure of fluorene based tetramines (**2–6**) is shown in Scheme 1. Tethering 4-bromobenzyl units on fluorene core is achieved by treating 2 equiv of 4-bromobenzyl bromide with 2,7-substituted fluorenes in the presence of potassium *t*-butoxide in dimethylsulfoxide. The resulting tetrabromide (**1**) undergoes facile cross coupling reactions with various diarylamines in the presence of $Pd(dba)_2$, (*tert*-$Bu)_3P$, and *tert*-BuONa to produce the target amines (**2–6**) in good yields.[10] The structures of the new compounds **1–6** have been confirmed by ^1H NMR spectroscopy, mass spectrometry, and elemental analysis. The All amines are stable towards air in the solid state and soluble in commonly used organic solvents.

3.2. Thermal, photophysical and electrochemical properties

In order to ensure that these materials are useful in organic light emitting diode fabrications, the thermal, photophysical and electrochemical properties in dichloromethane solutions are surveyed. The pertinent data are listed in Table 1.

3.2.1. Thermal properties. All amine derivatives **2–6** form glasses and possess high glass transition temperatures (T_g). According to the rigidity of the substituents, the glass transition temperatures of the fluorene derivatives **2–6** (shown in Table 1) are in the following order: **5** (pyrenyl substituents) > **6** (carbazolyl substituents) > **3** (naphthyl substituents) > **4** (diethyl-fluorenyl substituents) > **2** (phenyl



Scheme 1. The synthetic route of fluorene based tetramines (**2–6**).

Table 1. Thermal, photophyscial and electrochemical data of the amines (**2–6**)

Compound	λ_{max} (ε_{max}) (nm) ($\times 10^{-3}$ M^{-1} cm^{-1})[a]	$\lambda_{PL,\ sol}$ (nm)	$\Phi_{PL,\ sol}$[b]	E_{ox} (ΔE_p) (mV)[c]	T_g (°C)[d]	HOMO/LUMO (eV)
2	366 (45.0)	398	0.40	392 (69)	101	5.00/1.81
3	364 (49.9)	432	0.06	375 (65)	132	4.98/1.88
4	337 (117.7)	408	0.72	343 (74)	125	4.95/1.93
5	378 (65.4)	464	0.05	362 (72)	185	4.98/2.28
6	375 (44.4)	426	0.15	237 (68)	156	4.85/1.71

[a] Only the lowest energy absorption peak and extinction coefficient are listed.
[b] Quantum yield (PL) was measured in dichloromethane with reference to coumarin-1 (0.99 in ethyl acetate).
[c] First oxidation potential values are quoted against $Ag/AgNO^3$ non-aqueous reference electrode.
[d] Glass transition temperature was measured at the heating rate of 10 °C/min.

substituents). Therefore, the glass transition temperature of **5** is substantially increased to the highest value (T_g= 185 °C) due to the highest rigidity of the pyrene units. We have reported the enhancement of T_g due to the presence of pyrene for carbazole derivatives earlier.[2c,3]

3.2.2. Photophysical properties. Absorption and PL emission spectra of the fluorene derivatives **2–6** are shown in Figure 1a and b. All the amines (**2–6**) display two prominent transitions in the absorption spectra. The red shifted absorption in each amine is attributed to the π–π* transition of the fluorene backbone end-capped with terminal amines. The higher energy absorption with larger optical density probably originates from the *n*–π* transition of the triarylamine segments. All the compounds emit in the blue region except **5**, which displays green color in photoluminescence (PL) and electroluminescence (EL) spectra (Fig. 1). The amines containing naphthalenyl and pyrenyl units (**3** and **5**) exhibit broad and structureless emissions with relatively large Stokes shifts and low quantum yields in PL. This is clearly indicative of excimer formation at the excited state.[12] This intramolecular excimer formation has been also realized earlier for certain non-conjugative molecules possessing multiple pyrene segments.[13] Moreover, careful examination of emission maxima and pattern reveals that the emission in tetramines (**2–6**) originates from the main fluorene backbones. Hence, due to the additional contribution from the star-branched diethyl-fluorenyl substituents in **4**, it possesses the highest quantum yield ($\Phi_{PL,\ sol}$=0.72) among all amine derivatives.

3.2.3. Electrochemical properties. Two reversible oxidations corresponding to one and three electrons, respectively, were located in the cyclic voltammograms of the amines **2–6**. The electron count is by analogy with the intensity of the redox wave of the internal standard ferrocene. In the amines **2–6**, the first one electron oxidation must stem from one of the diarylamine units attached directly to the fluorene cores. This suggestion is also in agreement with the oxidation potential values. Diphenylamino and 1-naphthyl phenylamino segments generally possess high oxidation potentials if they are connected to phenyl or related aromatics.[2,12] It is also interesting to note that the first oxidation potentials in these fluorene derivatives (**2–6**) are reminiscent of the electron richness of the capping diarylamine units and they are cathodically shifted in the following order: diphenylamine > 1-naphthylphenylamine > 1-pyrenylphenylamine > 9,9-diethyl-2-fluorenylphenylamine > 9-ethyl-3-carbazolylphenylamine.

3.3. Electro-optical properties

The EL devices were made by blending the newly synthesized amines with the polymer PVK in appropriate ratios. For a device structure of ITO/PVK:**X** (**X**=**2**) (100:50 by weight)/BCP (5 nm)/Alq_3 (15 nm)/MgAg (50 nm)/Ag (100 nm) the EL spectra displayed features due to the amine and a distinct band at ca. 600 nm. However, this red shifted profile is not present in the PL spectra for the blends (see for instance Fig. 2a). This strongly implies that the EL emission peak at ~600 nm is owing to the formation of electromers[14] from **2** or electroplexes[15] from the interface of **2** and PVK. We also observe that the addition of carb9 to the PVK:**2** blend, completely suppresses the intrinsic emission of **2**

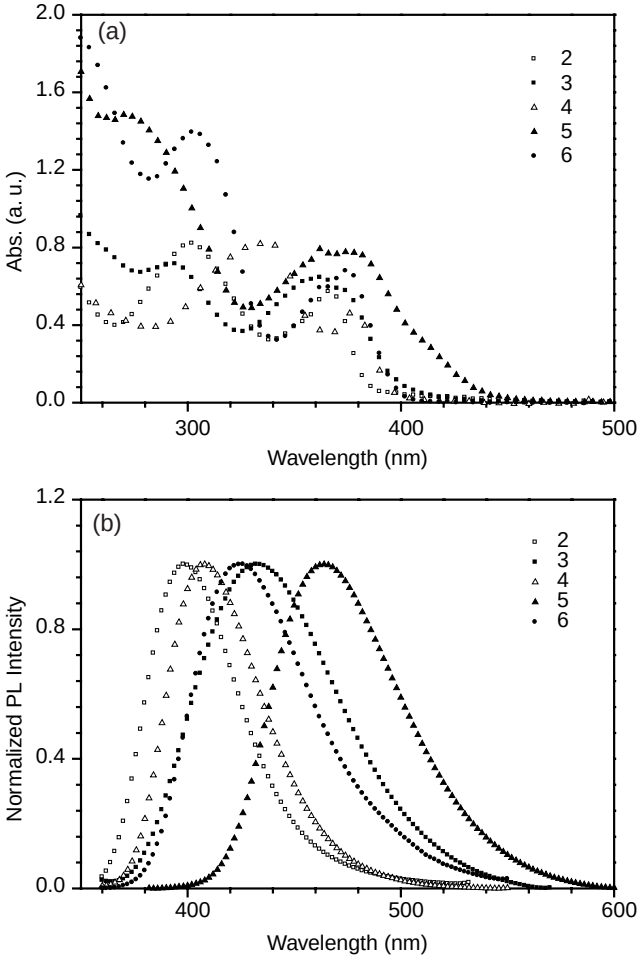


Figure 1. Absorption (a), PL emission (excitation at 350 nm) (b) spectra of **2–6** recorded in dichloromethane solutions.

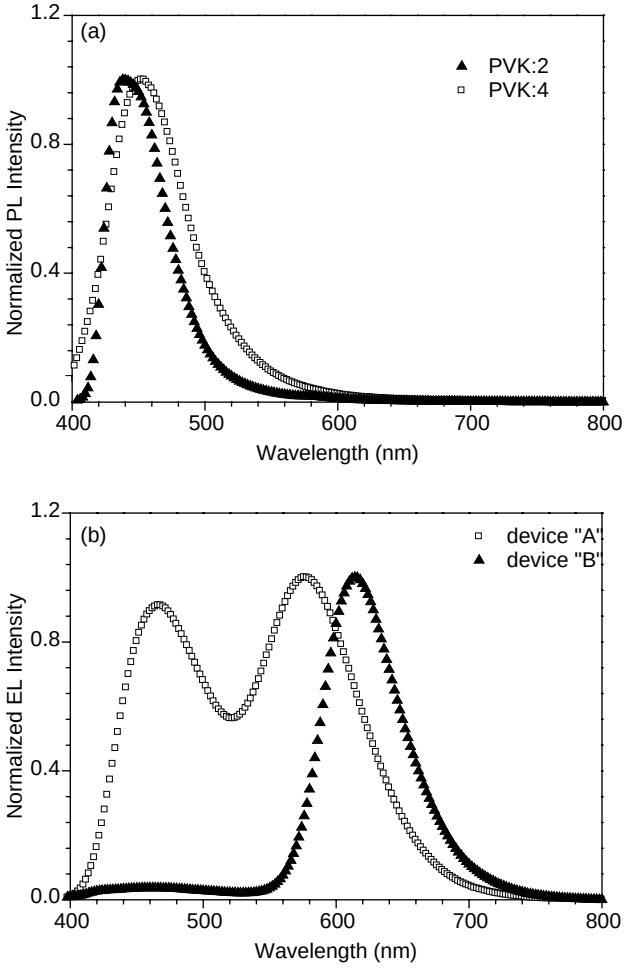


Figure 2. (a) PL spectra of PVK:**2** (or **4**) blend films and (b) EL spectra of the devices A (ITO/PVK:**2**:carb9 (100:200:20 by weight)/BCP (5 nm)/Alq_3 (15 nm)/MgAg (50 nm)/Ag (100 nm)) and B (ITO/PVK:**4**:carb9 (100:300:5 by weight)/BCP (10 nm)/Alq_3 (20 nm)/MgAg (50 nm)/Ag (100 nm)).

(ca. 420 nm). This is possibly due to the efficient energy transfer from **2** and/or PVK to carb9, which emits at ~460 nm. So the EL spectra of the devices that contained the matrix composition PVK:**X** (**2** or **6**):carb9 exhibit features due to carb 9 and electroplex/electromer emission. Subsequently we have tested two devices with the following configurations: the device 'A' of ITO/PVK:**2**:carb9 (100:200:20 by weight)/BCP (5 nm)/Alq_3 (15 nm)/MgAg (50 nm)/Ag (100 nm) and the device 'B' of ITO/PVK:**4**:carb9 (100:300:5 by weight)/BCP (10 nm)/Alq_3 (20 nm)/MgAg (50 nm)/Ag (100 nm). In fact, these two example devices were taken from a series of engineering work done by altering the composition of blend. The EL spectra obtained from these devices are displayed in Figure 2b. From that it is clearly evident that by adjusting the composition of the PVK:**X**:carb9 blend it is possible to realize either the white or red emission. In general, lesser concentration of carb9 leads to red electroplex/electromer emission while higher dopant ratio enhances the emission contribution from carb9 thus leading to white emission. The optimum performance of these devices has a brightness reaching 17368 cd/m^2 (maximum external quantum efficiency: 1.84%, CIE coordinate=0.33, 0.35) for white light emission and 3440 cd/m^2 for orange-red-light emission (maximum external quantum efficiency: 0.42%, CIE coordinate=0.60, 0.29). Full details on the EL characteristics will be published elsewhere.

4. Conclusions

In conclusion, we have synthesized a series of star-like fluorene based polyamines possessing novel photophysical properties. This strategy may be extended further to obtain discrete macromolecules and polymers with insulated functional chromophores (site isolation) or multi-functional moieties. We observed that by altering the aromatic substituents on the amine functionality the emission wavelength and glass transition temperature of the compounds can be tuned. The EL devices fabricated using the blends of these amines with PVK were investigated. They exhibited intense electroplex/electromer emission and by doping carb9 in those blends we demonstrate an unique way of fabricating white light emitting devices with good performance characteristics.

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Pentamethylcyclopentadienide in organic synthesis: nucleophilic addition of lithium pentamethylcyclopentadienide to carbonyl compounds and carbon–carbon bond cleavage of the adducts yielding the parent carbonyl compounds

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Abstract—Lithium pentamethylcyclopentadienide (C_5Me_5Li, Cp*Li) reacted with aromatic aldehyde to provide the corresponding carbinol in excellent yield. The carbinol returns to the parent aldehyde and pentamethylcyclopentadiene upon exposure to acid or due to heating. Chlorodimethylaluminum is essential as an additive to attain the nucleophilic addition of Cp*Li to aliphatic aldehyde. The carbinol derived from aliphatic aldehyde returns to the parent aldehyde and pentamethylcyclopentadiene by the action of a catalytic amount of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). The reversible addition/elimination of the Cp* group can represent a protection of aldehyde. Mechanistic details of the carbon–carbon bond cleavage are also disclosed.

1. Introduction

Pentamethylcyclopentadienide ($Me_5C_5^-$, Cp^{*-}) is an extremely important ligand in transition metal chemistry because of its unique structure and electronic property.[1,2] Cp^{*-} serves as a ligand of transition metal catalysts in organic synthesis. However, there are few reports to use Cp^{*-} by itself as a reagent in organic synthesis.[3] We have been exploring the utility of Cp^{*-} as a reagent in organic synthesis,[4] and here we report the full details of reversible addition/elimination of the Cp* group to carbonyl, which can represent a protection of a carbonyl group.

2. Results and discussions

2.1. Addition of Cp^{*-} to aromatic aldehydes and its reverse process

Treatment of *p*-bromobenzaldehyde (**1a**, 2.0 mmol) with Cp*Li (2.4 mmol, derived from ^{n}BuLi and pentamethylcyclopentadiene, Cp*H) in THF at −20 °C for 1 h provided the corresponding adduct **2a** in 95% isolated yield (Table 1, entry 1, from **1** to **2**).[5] Reactions at higher temperatures such as 0 °C resulted in the concurrence of a side reaction, that is, Meerwein–Ponndrof–Verley

Table 1. Formally reversible addition of Cp*Li to aromatic aldehydes

Entry	Ar	From **1** to **2** (%)[a]	From **2** to **1** (%)[b]
1	*p*-BrC_6H_4 (**a**)	95	92
2	2-$C_{10}H_7$ (**b**)	88	87
3	*p*-PhC(=O)C_6H_4 (**c**)	85	87
4	*p*-MeOC(=O)C_6H_4 (**d**)	87	91
5	*p*-NCC_6H_4 (**e**)	95	79
6	*p*-$BuOC_6H_4$ (**f**)	98	87
7	*p*-^{i}PrC(=O)C_6H_4 (**g**)	84	93
8	*o*-$MeOC_6H_4$ (**h**)	97	69

[a] Conditions: 1.2 equiv CpLi, THF, −20 °C, 1 h; then quenching with water.
[b] Conditions: 0.10 equiv trichloroacetic acid, dichloromethane, 25–30 °C, 0.25–1.5 h.

Keywords: Pentamethylcyclopentadiene; Nucleophilic addition; Carbon–carbon bond cleavage; Protection; Carbonyl compounds.
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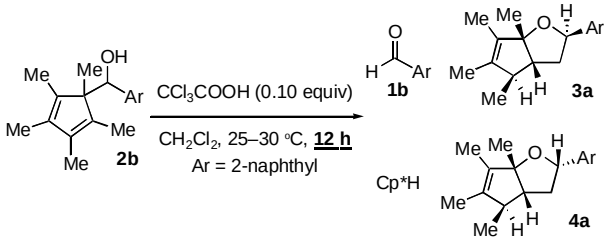
reduction/Oppenauer oxidation, to yield *p*-bromobenzyl alcohol and *p*-Br–$C_6H_4C(=O)Cp^*$. Use of methylmagnesium bromide instead of ^{n}BuLi also enhanced the reduction/oxidation side reaction. The attempted nucleophilic addition reaction led to no or little conversion under Cs_2CO_3/DMSO, $KN(SiMe_3)_2$/THF, or $NaN(SiMe_3)_2$/THF deprotonation conditions. Replacement of LiCp* with lithium cyclopentadienide led to the formation of the corresponding fulvene by facile dehydration.[6]

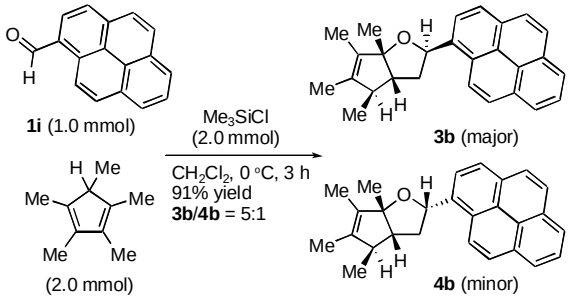
A variety of aromatic aldehydes were subjected to the nucleophilic addition of Cp*Li (Table 1, from **1** to **2**). The reaction was so chemoselective that keto (entries 3 and 7), ester (entry 4), and cyano (entry 5) moieties survived during the reaction. Sterically demanding *ortho*-substitution did not interfere with the reaction (entry 8). In contrast to the reactions with **1c** and **1g**, enolization of *p*-formylacetophenone was inevitable, furnishing the expected adduct in less than 30% yield.

Carbinols **2** were sensitive to acids. Specifically, acid-induced carbon–carbon bond cleavage took place to afford the parent aldehydes and Cp*H.[7,8] Carbinol **2a** was exposed to 10 mol% of trichloroacetic acid in dichloromethane at 25–30 °C for 1.5 h to provide **1a** in 92% isolated yield (entry 1, from **2** to **1**). It is worth noting that quantitative recovery of Cp*H upon the cleavage is advantageous since Cp*H is expensive. Other acids such as trifluoroacetic acid, camphorsulfonic acid monohydrate, *p*-toluenesulfonic acid monohydrate also promoted the carbon–carbon bond cleavage under the otherwise same reaction conditions, although the yields of **1a** were lower by ca. 20% because of several unidentified byproducts (vide infra). Acetic acid is too weak to cleave the carbon–carbon bond at a satisfactory rate. Silica gel in dichloromethane did not work at all. In polar coordinating solvents such as THF and methanol, acid-catalyzed cleavage was not observed. Under the standard reaction conditions, all the carbinols **2** returned to the parent aldehydes (Table 1, from **2** to **1**).

The progress of the acid-induced cleavage should be monitored by thin-layer chromatography. When the reaction was performed for an unnecessarily long time or with a too strong acid, the reactions yielded more complex mixtures. For instance, the reaction of **2b** with trichloroacetic acid overnight gave not only **1b** and Cp*H but also **3a** and **4a** (Eq. 1, yields undetermined). The formations of **3a** and **4a** are unusual, and the exact structures of **3a** and **4a** were not determined even with the aid of two-dimensional NMR technique. Alternatively, compounds **3b** and **4b**, the analogues of **3a** and **4a**, could be prepared by the reaction of **1i** and Cp*H in the presence of chlorotrimethylsilane (Eq. 2). Luckily the structures of **3b** and **4b** were fully determined by X-ray crystallographic analysis (Fig. 1)[9] as well as by ^{1}H, ^{13}C NMR, DEPT, and COSY spectra. The products **3b** and **4b** are epimers, with respect to the location of the pyrenyl ring. Other acids such as trichloroacetic acid also mediated the same transformation, while the yields of **3b** and **4b** were low. The mechanism for the formation of **3b** and **4b** is unclear.

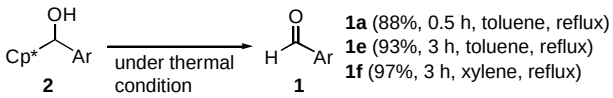


(1)



(2)

A similar carbon–carbon bond cleavage was observed in the absence of acid, which can avoid the careful monitoring. Boiling **2a** and **2e** in toluene furnished aldehydes **1a** and **1e** in 88 and 93% yields, respectively (Eq. 3). Electron-rich carbinol **2f** required a higher temperature to return efficiently to **1f** in boiling xylene. Complete conversion of **2f** in refluxing toluene took more than 20 h, albeit the yield was quantitative.



(3)

The lithium alkoxides of **2** can be trapped with *N*-trimethylsilylimidazole (Scheme 1). Trimethylsilylimidazole is the best reagent for the trapping. Chlorotrimethylsilane, trimethylsilyl triflate, and other *N*-silylimidazoles were less effective. Interestingly, the silyl ethers **2-Si** could return to **1** with the aid of tetrabutylammonium fluoride. The generation of **1** did not go to completion in some cases. However, treatment of the crude mixture of **1** and **2** with trichloroacetic acid afforded **1** in reasonable overall yield.

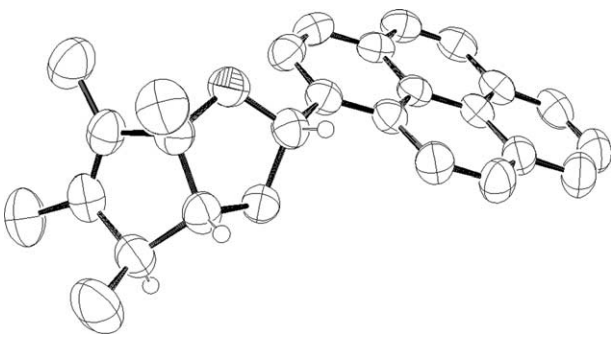
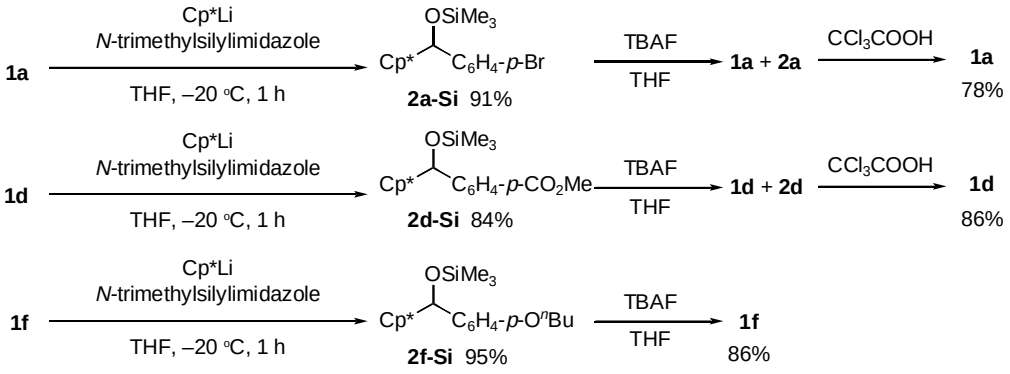
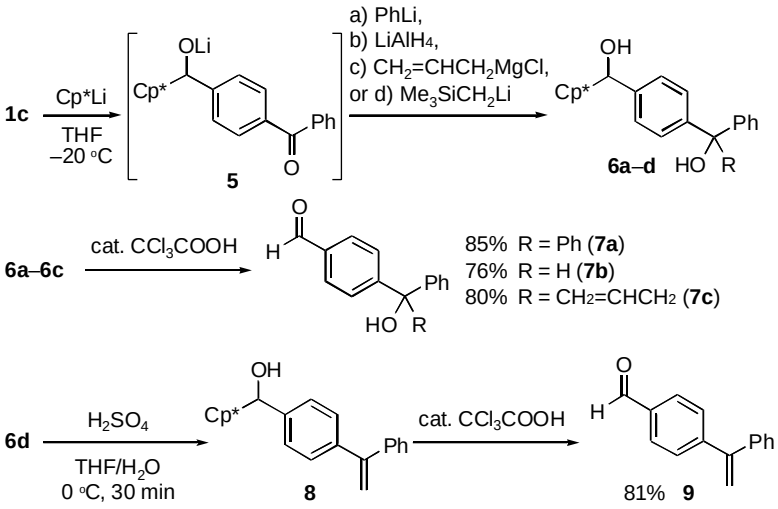


Figure 1. ORTEP drawing of **4b**. Thermal ellipsoids are 50% probability level. Three hydrogen atoms are shown for convenience.



Scheme 1.



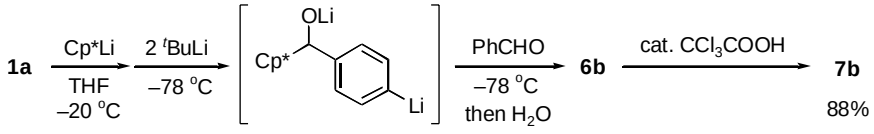
Scheme 2.

The utility of the Cp* group as a protective group is outlined in Scheme 2. After Cp* had masked the aldehyde moiety of **1c** in situ, the keto group was subjected to nucleophilic addition reaction with phenyllithium to afford diol **6a**. The crude oil was exposed to the acidic conditions to produce hydroxy aldehyde **7a** in 85% overall yield. Chemoselective reduction and allylation provided **7b** and **7c**, respectively.[10,11] Attempted Wittig reaction of **5** with $CH_2{=}PPh_3$ failed, and the methylenation of the aldehyde moiety that must be masked was partly observed. Alternatively, addition of trimethylsilylmethyllithium to **5** followed by acid-catalyzed olefination in aqueous THF yielded carbinol **8**. Treatment of **8** under the deprotection conditions afforded **9** in 81% overall yield. All the procedures proceeded so cleanly that no purification of the intermediates such as **6** and **8** was necessary.

The protective method allowed for preparation of a formyl-substituted phenyllithium equivalent (Scheme 3). Nucleophilic addition of Cp*Li to **1a** followed by bromine–lithium exchange furnished the corresponding aryllithium. The lithium reagent could be trapped with benzaldehyde to yield crude diol **6b**. Subsequent removal of Cp*H afforded **7b** in 88% overall yield.

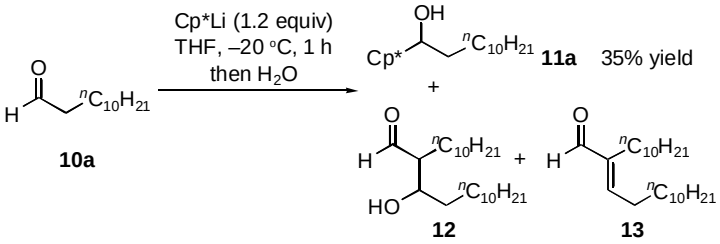
2.2. Addition of Cp^{*-} to aliphatic aldehyde and ketone with the aid of chlorodimethylaluminum and its reverse process

The reaction of Cp*Li with aliphatic aldehyde failed to yield a satisfactory amount of the corresponding adduct. For instance, treatment of dodecanal (**10a**) with Cp*Li afforded the corresponding adduct **11a** in only 35% yield (Eq. 4). The byproducts mainly comprised β-hydroxy aldehyde **12** and



Scheme 3.

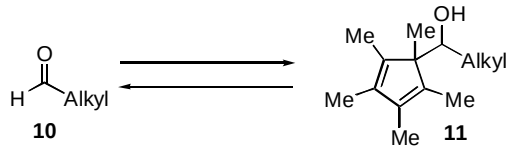
α,β-unsaturated aldehyde **13**, which means that Cp*Li served as a base to generate the lithium enolate of **10a**. Many additives were thus screened, and we found that chlorodimethylaluminum promotes the addition of Cp^{*-} to aliphatic aldehydes.



(4)

Chlorodimethylaluminum (6.0 mmol) was added to a suspension of Cp*Li (6.0 mmol) in THF at −20 °C. Aldehyde **10a** (5.0 mmol) was then added, and the mixture was stirred at −20 °C for 1 h. Extractive workup followed by silica gel column purification provided alcohol **11a** in 92% yield (Table 2, entry 1, from **10** to **11**). Trace amounts of **12** and **13** were detected in the crude oil. The role of chlorodimethylaluminum is unclear. No visible or spectroscopic changes of significance were observed. Chlorodimethylaluminum can activate the carbonyl group as a Lewis acid. Alternatively, Me_2Cp^*Al reagent may be formed via transmetallation and can effect the selective nucleophilic attack. Other Lewis acids including chlorotrimethylsilane, triethylaluminum, and magnesium dibromide were much less effective than chlorodimethylaluminum. Titanium tetraisopropoxide similarly assisted the addition reaction (81% yield).

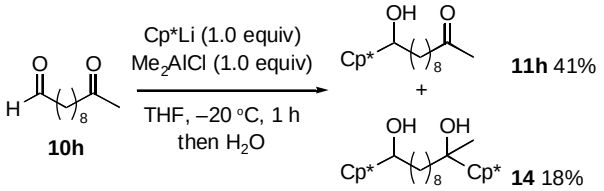
Table 2. Formally reversible addition of Cp*Li to aliphatic aldehydes



Entry	Alkyl	From **10** to **11** (%)[a]	From **11** to **10** (%)[b]
1	$CH_3(CH_2)_{10}$ (**a**)	92	92 (12 h)
2	$PhCH_2CH_2$ (**b**)	94	80 (12 h)
3[c]	$^cC_6H_{11}$ (**c**)	97	82 (24 h)[d]
4	$^tC_4H_9$ (**d**)	<10	—
5	$NC(CH_2)_5$ (**e**)	89	75 (24 h)
6	$Cl(CH_2)_9$ (**f**)	93	95 (12 h)
7	$CH_3OC(=O)(CH_2)_4$ (**g**)	82	81 (36 h)

[a] Conditions: 1.2 equiv Cp*Li, 1.2 equiv Me_2AlCl, THF, −20 °C, 1 h; then quenching with water.
[b] Conditions: 0.01 equiv DDQ, toluene, reflux. The reaction time of each run is in parentheses.
[c] To complete the reaction, 1.5 equiv of Cp*Li and Me_2AlCl were used.
[d] Isolated as 1-cyclohexylpentanol after treatment of the crude oil with *n*-butyllithium because cyclohexanecarbaldehyde is volatile.

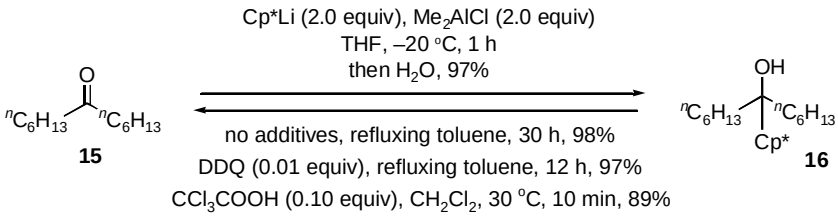
The nucleophilic addition is applicable to a wide range of aliphatic aldehydes (Table 1, from **10** to **11**). Whereas the reaction of cyclohexanecarbaldehyde (**10c**) cleanly provided **11c**, sterically congested pivalaldehyde (**10d**) resisted the reaction. The reaction was chemoselective enough to leave cyano, chloro, and ester moieties untouched (entries 5–7). The reactions with catalytic amounts of chlorodimethylaluminum did not go to completion and gave rise to ca. 80% conversion. Unfortunately, the reaction with keto aldehyde **10h** exhibited unsatisfactory chemoselectivity (Eq. 5).



(5)

Removal of the Cp* group of **11**, which corresponds to regeneration of **10**, can represent a protective method of aliphatic aldehydes. Contrary to the instability of aromatic carbinols **2** under the acidic or thermal conditions, carbinols **11** were stable toward acids or at high temperature. By extensive screening of reaction conditions, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), proved to induce smooth carbon–carbon bond cleavage to produce the parent aldehyde **10** and Cp*H. Treatment of **11a** with 1 mol% of DDQ in boiling toluene for 12 h furnished **10a** in 92% isolated yield (entry 1, from **11** to **10**), with quantitative generation of Cp*H. With the aid of DDQ, all the carbinols **11** returned to the original aldehydes (Table 1, from **11** to **10**). Carbinols **11e** and **11g** with polar cyano and ester moieties were transformed more slowly to **10e** and **10g**, respectively. The bulkier cyclohexyl group of **11c** also retarded the reaction. Other organic oxidants such as chloranil, 2,3-dichlorobenzoquinone, trityl tetrafluoroborate ($Ph_3C^+BF_4^-$) also facilitated the removal albeit the efficiency was much lower.

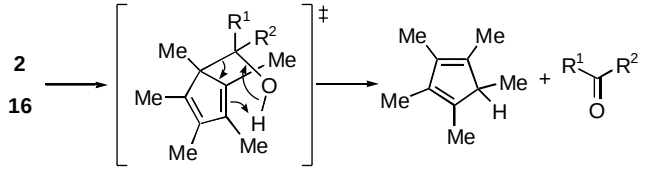
Chlorodimethylaluminum also promoted the addition onto dihexyl ketone (**15**) (Eq. 6). Without the additive, enolization of **15** predominated and none of **16** was obtained. Interestingly, boiling **16** in toluene for 30 h yielded **15** and Cp*H quantitatively. It is worth noting that DDQ accelerated the transformation (reflux, 12 h). A catalytic amount of trichloroacetic acid also effected the degradation of **16** into **15** and Cp*H.



(6)

2.3. Mechanisms of the carbon–carbon bond cleavage

A concerted retro-carbonyl-ene mechanism can rationalize the fragmentation reaction under the thermal cleavage conditions (Scheme 4).[12] Generally, thermal retro-carbonyl-ene reactions require higher temperature, most of which were performed in a gas phase.[12e] The reaction temperatures used herein are low as being temperatures for retro-carbonyl-ene reactions.



Scheme 4.

To clarify the origin of the facile retro-carbonyl-ene process, we set up five simplified models, Eqs. A–E, and performed ab initio calculations. The energy profile of the model reactions is shown in Figure 2. The activation barrier of the retro-carbonyl-ene reaction from **Adduct A** to **Products A** was calculated to be 29.25 kcal/mol. The higher barrier of 33.18 kcal/mol in Eq. B suggests that the methyl group at the 1 position of Cp* plays an important role to enhance the carbon–carbon bond cleavage. The removal of the cyclopentadienyl group, without any methyl groups on the cyclopentadiene ring, should go over the higher barrier (35.97 kcal/mol) from **Adduct C** to **Products C** (Eq. C). The steric hindrance of the Cp* group thus contributes to the facile retro-carbonyl-ene reaction. In addition, the conjugated diene system of Cp* proved to be much more important than the steric factor, by comparison of the activation barriers of Eqs. A, D, and E. The activation barriers of Eqs. D and E, wherein pentamethylcyclopentenes liberate, are calculated to be higher than that of Eq. A by ca. 10 kcal/mol. The characteristic features of the Cp* group, that is, its steric bulkiness and conjugated diene system, allows for the retro-carbonyl-ene reaction at a low temperature. It is worth noting that the activation barrier of the retro-carbonyl-ene reaction of 2-methyl-4-penten-2-ol was calculated to be 35.40 kcal/mol at the B3LYP/6-311+G**//RHF/6-311+G** levels of theory.[13]

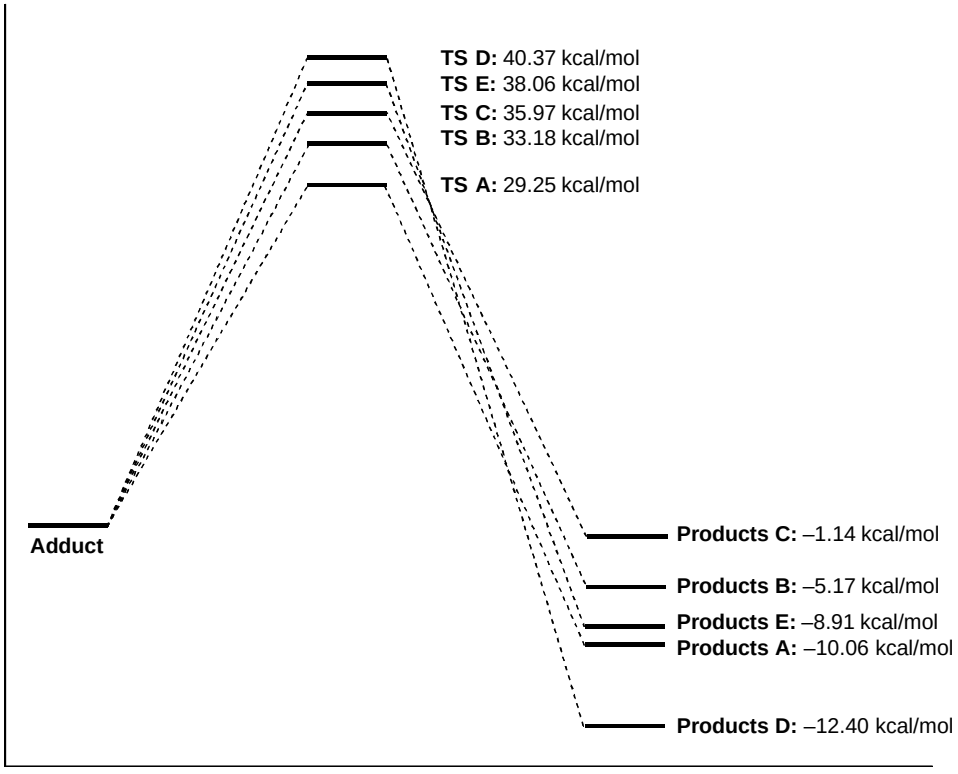
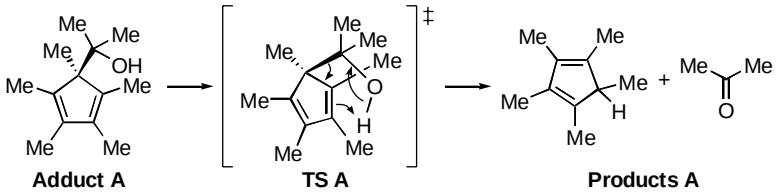
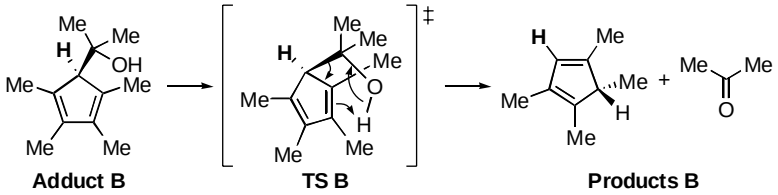


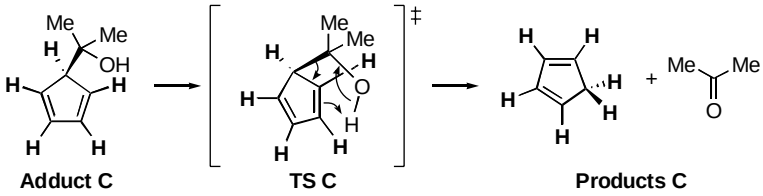
Figure 2. Calculated energy profile for Eqs. A–E at the B3LYP/6-311+G**//RHF/6-311+G** levels of theory.



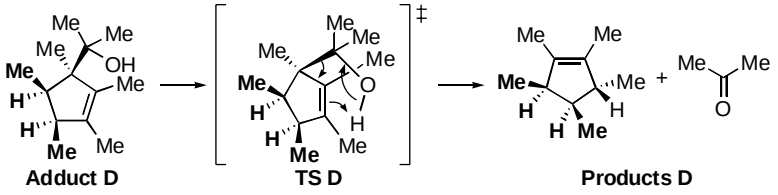
(A)



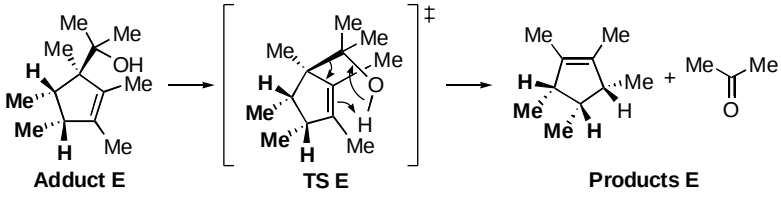
(B)



(C)

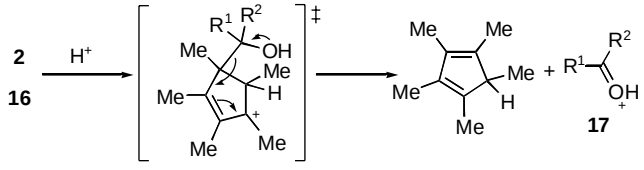


(D)



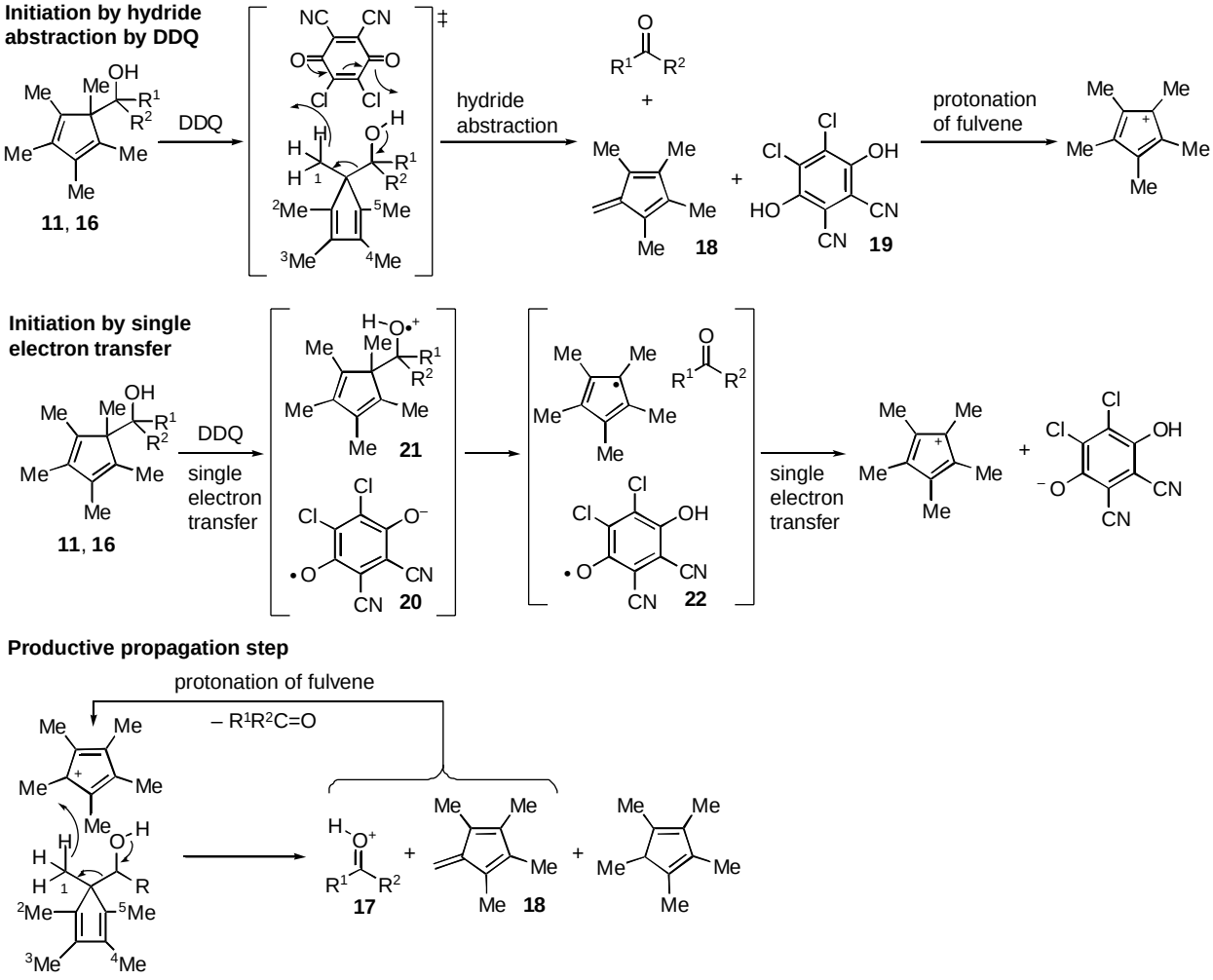
(E)

Under the acid-catalyzed conditions, protonation at the Cp* group would facilitate the carbon–carbon bond cleavage (Scheme 5). The Cp* group would be more easily protonated than the hydroxy group.[14] As described, the acid-catalyzed cleavage did not take place in a coordinating solvent. A coordinating solvent would interfere with the protonation of the Cp* group. Solvents of less coordinating nature such as dichloromethane facilitated the protonation. The protonation would promote release of the steric hindrance and recovery of a stabilized conjugated diene and result in carbon–carbon bond cleavage to form Cp*H and oxonium cation **17**.



Scheme 5.

While the mechanism of the DDQ-promoted cleavage is not clear, we are tempted to propose the two possible mechanisms (Scheme 6). One mechanism begins with hydride abstraction by DDQ, a strong hydride acceptor.[15] DDQ would abstract the hydride at the 1-methyl group of the Cp* group,[16] which generates the original carbonyl compound, tetramethylfulvene (**18**), and **19**. Protonation of **18** with **19** would yield unstable pentamethylcyclopentadienyl cation (Cp^{*+}).[17] The cyclic 4π-electronic cation Cp^{*+} would be a hydride acceptor efficient enough to abstract hydride from $Cp^*R^1R^2COH$ to produce oxonium cation **17**, **18**, and Cp*H. Protonation of the fulvene **18** with the oxonium cation **17** again generates Cp^{*+} to complete the catalytic cycle. An alternative scenario involves single electron transfer.[18] Single electron transfer from $Cp^*R^1R^2COH$ to DDQ generates radical anion **20** and radical cation **21**. The cation **21** undergoes fragmentation into pentamethylcyclopentadienyl radical (Cp*·) and the original carbonyl compound. Cp*· would be oxidized by **22** to form Cp^{*+}. The cation Cp^{*+} takes part in the same catalytic cycle in the hydride abstraction mechanism. It is noteworthy that no deuterium incorporation was observed in the cleavage reaction in toluene-d_8, which eliminates the possibility of hydrogen abstraction of the possible radical intermediates from solvent.



Scheme 6.

The hydroxy group of **11** plays a key role in the carbon–carbon bond cleavage process. Additional polar groups such as cyano and ester groups in **11e** and **11g** would prevent the weak interaction between the hydroxy group and electron deficient species such as DDQ and Cp^{*+}. The bulkier cyclohexyl group of **11c** hampered the access of the electron deficient species to the hydroxy group of **11c**. Namely, rate-determining hydride abstraction or single electron transfer would be retarded. It is worth noting that the silyl ether of **11b** completely resisted the cleavage upon treatment with DDQ in boiling toluene.

3. Conclusion

Pentamethylcyclopentadienide has now participated in organic synthesis as a new 'reagent'. The protection of an aldehyde moiety with Cp* emerges by utilizing the facile cleavage of the Cp^{*}–CR^1R^2OH bond. The cleavage is due to the unique nature of Cp* group.

4. Experimental

4.1. Instrumental

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken on Varian Mercury 300 spectrometers and were recorded in C_6D_6. Chemical shifts (δ) are in parts per million relative to benzene at 7.16 ppm for ^1H and at 128.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

4.2. Material

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Aldehydes were purified by distillation or recrystallization prior to use. 1,2,3,4,5-Pentamethyl-1,3-cyclopentadiene

was purchased from TCI. THF (dehydrated, stabilizer free) was purchased from Kanto Chemical Co., stored under nitrogen, and used without distillation. Dichloromethane was dried over molecular sieves 3 Å. Trichloroacetic acid was diluted with dichloromethane to prepare a 0.1 M solution. *n*-Butyllithium, *t*-butyllithium, trimethylsilylmethyllithium were purchased from Nacalai Tesque, Kanto Chemical, and Aldrich, respectively. DDQ was purchased from Wako Pure Chemical Co. Chlorodimethylaluminum was purchased from Kanto Chemical. All reactions were carried out under argon atmosphere.

4.3. Theoretical calculations

All the calculations were performed by using Spartan'04.[19] All the structures were optimized at the HF/6-311+G** level of theory. Single point calculations of the total energies were performed at the B3LYP/6-311+G** at the HF/6-311+G** optimized geometries. The transition states obtained gave proper single imaginary frequencies.

5. Experimental

5.1. General procedure for nucleophilic addition of Cp*Li to aromatic aldehydes (Table 1)

A solution of ^{n}BuLi in hexane (1.6 M, 1.57 mL, 2.4 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (0.42 mL, 2.6 mmol) in THF (20 mL) at −78 °C. The mixture was stirred for 30 min at room temperature to provide a white suspension of pentamethylcyclopentadienyllithium. To the resulting mixture, a solution of 4-bromobenzaldehyde (**1a**, 370 mg, 2.0 mmol) in THF (3.0 mmol) was added at −20 °C, and the reaction mixture was stirred for 1 h at −20 °C. After quenching the reaction with water, the mixture was extracted with hexane–ethyl acetate (10/1, 20 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel afforded **2a** (609.1 mg, 1.90 mmol) in 95% yield.

5.2. Acid-induced cleavage reaction (Table 1)

A solution of trichloroacetic acid in CH_2Cl_2 (0.1 M, 0.50 mL, 0.05 mmol) was added to a solution of **2a** (160.4 mg, 0.50 mmol) in CH_2Cl_2 (3.0 mL) at room temperature. The mixture was stirred for 90 min at 28 °C. After quenching the reaction with saturated aqueous $NaHCO_3$, the mixture was extracted with hexane–ethyl acetate (10/1, 20 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. Silica gel column purification provided 4-bromobenzaldehyde (**1a** 84.8 mg, 0.458 mmol) in 92% yield.

5.3. Acid-mediated coupling of pyrenecarbaldehyde with Cp*H (Eq. 2)

A mixture of 1-pyrenecarbaldehyde (**1i**, 230 mg, 1.0 mmol) and Cp*H (0.31 mL, 2.0 mmol) was dissolved in dichloromethane (1.0 mL). Chlorotrimethylsilane (0.26 mL, 2.0 mmol) was added dropwise at 0 °C. After the mixture was stirred for 4 h at 0 °C, the reaction was quenched with sodium hydrogencarbonate solution. Work-up followed by silica gel column purification provided **3b** and **4b** in 91% combined yield (330 mg, 0.91 mmol) in a ratio of 5:1.

5.4. Thermal cleavage reaction (Eq. 3)

Carbinol **2a** (643.7 mg, 2.0 mmol) was dissolved in toluene (10 mL). After the solution was stirred at 110 °C for 0.5 h, the solvent was removed under reduced pressure. Purification of the residue by chromatography on silica gel gave 4-bromobenzaldehyde (**1a**, 324.1 mg, 1.75 mmol) in 88% yield.

5.5. Synthesis of 2-Si (Scheme 1)

Butyllithium in hexane (1.6 M, 7.4 mL, 12 mmol) was added dropwise to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (2.0 mL, 13 mmol) in THF (100 mL) at −20 °C. The resulting suspension was stirred for 30 min. A solution of 4-bromobenzaldehyde (1.85 g, 10 mmol) in THF (10 mL) was added to the suspension. The reaction mixture was stirred at −20 °C for 1 h. *N*-Trimethylsilylimidazole (1.9 mL, 13 mmol) was then added at −20 °C, and the resulting mixture was stirred for 1 h at the same temperature. After the reaction was terminated by an addition of water, the organic layer was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by column chromatography (Wakogel C-200, pretreated with Et_3N in hexane and eluted with hexane) to afford **2a-Si** (3.60 g, 9.1 mmol, 91%).

5.6. Regeneration of 1f from 2f-Si

A solution of tetrabutylammonium fluoride in THF (1.0 M, 0.60 mL, 0.60 mmol) was added to a solution of **2f-Si** (193 mg, 0.50 mmol) in THF (3.3 mL) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. Chromatographic purification on silica gel (Wakogel C-200, hexane/ethyl acetate=20:1) furnished **1f** (76.5 mg, 0.43 mmol, 86%).

5.7. From 2a-Si to 1a

Tetrabutylammonium fluoride (1.0 M THF solution, 0.60 mL, 0.60 mmol) was added to a solution of **2a-Si** (197 mg, 0.50 mmol) in THF (1.7 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic parts were washed with brine, dried, and concentrated in vacuo to give a crude oil. Trichloroacetic acid in dichloromethane (0.1 M, 0.5 mL, 0.05 mmol) was added to the crude oil in dichloromethane (3.3 mL) at 30 °C. After 1 h, the reaction was quenched with saturated $NaHCO_3$ solution, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel column

chromatography (Wakogel C-200, hexane/ethyl acetate = 20:1) yielded 72.1 mg of **1a** (0.39 mmol, 78%).

5.8. From 2d-Si to 1d

Tetrabutylammonium fluoride (1.0 M THF solution, 0.60 mL, 0.60 mmol) was added to a solution of **2d-Si** (186 mg, 0.50 mmol) in THF (1.7 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Trichloroacetic acid (0.1 M in dichloromethane, 0.5 mL, 0.05 mmol) was added to the crude oil in dichloromethane (3.3 mL) at 30 °C and the mixture was stirred for 1 h. Additional trichloroacetic acid in dichloromethane (0.1 M, 0.5 mL, 0.05 mmol) was added to the reaction mixture, and the reaction mixture was stirred for another 30 min. After being quenched with saturated $NaHCO_3$ solution, the mixture was extracted with ethyl acetate. Usual workup followed by purification on silica gel (Wakogel C-200, hexane/ethyl acetate = 10:1) provided **1d** (70.7 mg, 0.43 mmol, 86%).

5.9. Synthesis of 7a from 1c (Scheme 2)

Butyllithium (1.6 M hexane solution, 0.39 mL, 0.60 mmol) was added to a solution of Cp^*H (0.11 mL, 0.65 mmol) in THF (5 mL) at −78 °C under argon. By removing a dry ice/acetone bath, the resulting mixture was allowed to warm to room temperature. After being stirred at room temperature for 30 min, the mixture was cooled to −20 °C. Keto aldehyde **1c** (105 mg, 0.50 mmol in 1.5 mL of THF) was then added. The mixture was stirred for 1 h at the same temperature. The reaction mixture was then cooled to −78 °C. Phenyllithium (0.77 mL, 0.75 mmol, 0.98 M in cyclohexane/ether, Kanto Chemical Co.) was added and the whole mixture was stirred for 20 min. Water (10 mL) was added at −78 °C to quench the reaction. Extractive workup afforded a crude oil of **6a**. Trichloroacetic acid in dichloromethane (0.1 M, 0.5 mL, 0.05 mmol) was added to the crude oil in dichloromethane (3 mL) under argon at 25–30 °C, and the resulting solution was stirred for 1 h. After being quenched with saturated $NaHCO_3$ solution, the mixture was extracted with ethyl acetate (20 mL×3). The combined organic layer was dried over anhydrous sodium sulfate. Evaporation followed by silica gel column purification (hexane/ethyl acetate = 3:1) yielded 123 mg of **7a** (0.427 mmol, 85% overall yield).

5.10. Synthesis of 7b from 1c (Scheme 2)

Butyllithium (1.6 M hexane solution, 0.75 mL, 1.2 mmol) was added to a solution of Cp^*H (0.21 mL, 1.3 mmol) in THF (10 mL) at −20 °C. After being stirred for 30 min, keto aldehyde **1c** (210 mg, 1.0 mmol in 3.0 mL of THF) was then added. The mixture was stirred for 1 h at the same temperature. The reaction mixture was then cooled to −78 °C. Lithium aluminum hydride (57 mg, 1.5 mmol) was added in one portion. The whole mixture was stirred for 1 h at 0 °C. Water (10 mL) was added to quench the reaction. Extractive workup gave a crude oil of **6b**. Trichloroacetic acid in dichloromethane (0.1 M, 1.0 mL, 0.1 mmol) was added to a solution of **6b** in dichloromethane (6.7 mL) under argon at 25–30 °C, and the resulting solution was stirred for 1 h. After being quenched with saturated $NaHCO_3$ solution, the mixture was extracted with ethyl acetate (20 mL×3). Removal of volatiles followed by silica gel column purification (hexane/ethyl acetate = 2:1) yielded 136 mg of **7b** (0.76 mmol, 76% overall yield).

5.11. Synthesis of 7c from 1c (Scheme 2)

After similar treatment of **1c** (0.50 mmol-scale) with Cp^*Li at −20 °C, allylmagnesium chloride (0.92 M ethereal solution, 1.1 mL, 1.0 mmol) was added to the reaction flask at −20 °C. The whole mixture was stirred for 1 h. Quenching with water (10 mL) followed by extractive workup gave a crude oil of **6c**. Trichloroacetic acid in dichloromethane (0.1 M, 1.0 mL, 0.1 mmol) was added to a solution of **6c** in dichloromethane (5 mL) under argon at 25–30 °C, and the resulting solution was stirred for 45 min. After the reaction was quenched with saturated $NaHCO_3$ solution, extraction, evaporation, and purification on silica gel (hexane/ethyl acetate = 5:1) furnished 101 mg of **7c** (0.402 mmol, 80% overall yield).

5.12. Synthesis of 9 from 1c (Scheme 2)

The reaction started from 0.50 mmol of **1c**. Trimethylsilylmethyllithium (0.66 M pentane solution, 1.5 mL, 1.0 mmol) was added at −78 °C to **5** prepared in the method described above. The resulting mixture was stirred for 30 min. Quenching with water (10 mL) followed by extraction with ethyl acetate gave **6d**. Under air, 2.0 M aqueous sulfuric acid (1.0 mL) was added to a solution of crude **6d** in THF–H_2O (4.0 mL/1.0 mL) at 0 °C. The mixture was stirred for 30 min at the same temperature. After addition of aqueous $NaHCO_3$, extraction with ethyl acetate and evaporation under reduced pressure afforded crude **8**, clean formation of which NMR analysis revealed. Trichloroacetic acid in dichloromethane (0.1 M, 0.5 mL, 0.05 mmol) was added to a solution of **8** in dichloromethane (3 mL) under argon at 25–30 °C, and the resulting solution was stirred for 30 min. After the reaction was quenched with saturated $NaHCO_3$ solution, extraction, evaporation, and purification on silica gel (hexane/ethyl acetate = 10:1) furnished 84.3 mg of **9** (0.405 mmol, 81% overall yield).

5.13. Synthesis of 7b from 1a (Scheme 3)

Butyllithium (1.6 M hexane solution, 0.75 mL, 1.2 mmol) was added to a solution of Cp^*H (0.21 mL, 1.3 mmol) in THF (10 mL) at −78 °C, and the resulting mixture was allowed to warm to room temperature. After being stirred for 30 min, the mixture was cooled to −20 °C. Bromo aldehyde **1a** (186 mg, 1.0 mmol in 1.5 mL of THF) was then added and the mixture was stirred for 1 h at the same temperature. The reaction mixture was then cooled to −78 °C and *t*-butyllithium in pentane (1.56 M, 1.4 mL, 2.2 mmol) was added. After 40 min, benzaldehyde (0.16 mL, 1.6 mL) was added and the whole mixture was stirred for an additional 40 min at −78 °C. Water (10 mL) was added to quench the reaction. Extractive workup gave a crude oil of **6b**. Trichloroacetic acid in dichloromethane (0.1 M, 1.0 mL, 0.1 mmol) was added to a solution of **6b** in

dichloromethane (4 mL) under argon at 25–30 °C, and the resulting solution was stirred for 30 min. Workup as above followed by silica gel column purification (hexane/ethyl acetate=2:1) yielded 187 mg of **7b** (0.88 mmol, 88% overall yield).

5.14. General procedure for nucleophilic addition of Cp*Li to aliphatic aldehydes (Table 2)

A solution of ^{n}BuLi in hexane (1.6 M, 3.8 mL, 6.0 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (0.95 mL, 6.5 mmol) in THF (50 mL) at −20 °C. The mixture was stirred for 30 min at the same temperature to provide a white suspension of pentamethylcyclopentadienyllithium. Chlorodimethylaluminum in hexane (1.0 M, 6.0 mL, 6.0 mmol) was added to the resulting mixture, and the reaction mixture was stirred for 30 min at −20 °C. After an addition of dodecanal (**10a**, 1.1 mL, 5.0 mmol), the mixture was stirred for an additional 1 h at −20 °C. After being stirred for 1 h, the reaction was quenched with water, and the mixture was extracted with ethyl acetate three times. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by chromatography on silica gel (Wakogel C-200, hexane/ethyl acetate=10:1) to afford **11a** (1.47 g, 92%).

5.15. General procedure of DDQ-induced cleavage (Table 2)

A solution of **11a** (321 mg, 1.0 mmol) in toluene (1.0 mL) was added to a solution of DDQ (2 mg, 0.01 mmol) in toluene (19 mL). The mixture was warmed up to 110 °C and stirred for 12 h. After the reaction was terminated by an addition of water, the organic layer was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude oil obtained was subjected to silica gel column purification (Wakogel C-200, hexane/ethyl acetate=10:1) to afford **10a** (170 mg, 0.92 mmol, 92%).

5.16. Preparation of 10-chlorodecanal

To a solution of pyridinium chlorochromate (3.9 g, 18 mmol) and silica gel (Silica Gel 60, spherical, neutrality, Nacalai Tesque, 3.9 g) in CH_2Cl_2 (60 mL) was added a solution of 10-chloro-1-decanol (2.4 mL, 12 mmol) for 12 h at room temperature. The resulting mixture was filtered through a pad of Celite 545 and the organic layer was concentrated in vacuo to give a crude oil. The crude product was chromatographed on silica gel (Wakogel C-200, hexane/ethyl acetate=30:1) to afford the title compound (1.7 g, 74%). *10-Chlorodecanal* (**10f**). IR (neat) 650, 723, 1356, 1466, 1726, 2719, 2930, 3429 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24–1.82 (m, 14H), 2.92 (td, J=7.2, 1.8 Hz, 2H), 3.53 (t, J=6.6 Hz, 2H), 9.76 (t, J=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.00, 26.79, 28.76, 29.07, 29.20 (×2), 32.56, 43.87, 45.15, 202.95. HRMS CI [M+H$^+$] 191.1203. Calcd for $C_{10}H_{20}ClO$: 191.1202.

5.17. Characterization data

5.17.1. (4-Bromophenyl)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methanol (2a). IR (neat) 3458, 2856, 1657, 1591, 1487, 1445, 1379, 1072, 1009, 812, 773, 719, 659, 607 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.08 (s, 3H), 1.35–1.42 (m, 1H), 1.43 (s, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 1.95 (s, 3H), 4.31 (d, J=3.0 Hz, 1H), 6.87 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H); ^{13}C NMR (C_6D_6) δ 10.77, 10.82, 11.27, 12.07, 18.09, 61.34, 77.78, 121.02, 128.59, 130.08, 136.40, 136.54, 137.66, 139.28, 140.89. Found: C, 63.58; H, 6.86%. Calcd for $C_{17}H_{21}BrO$: C, 63.56; H, 6.59%.

5.17.2. (2-Naphthyl)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methanol (2b). IR (neat) 3444, 3057, 2856, 1654, 1600, 1508, 1444, 1379, 1033, 858, 815, 748, 686, 478 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.22 (s, 3H), 1.42 (d, J=1.0 Hz, 3H), 1.50 (d, J=1.0 Hz, 3H), 1.59–1.61 (m, 1H), 1.62 (s, 3H), 2.07 (s, 3H), 4.68 (d, J=3.0 Hz, 1H), 7.20–7.28 (m, 2H), 7.37 (dd, J=1.5, 8.5 Hz, 1H), 7.57 (d, J=8.5 Hz, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.67–7.70 (m, 2H); ^{13}C NMR (C_6D_6) δ 10.83, 10.85, 11.50, 12.09, 18.44, 61.50, 78.50, 125.68, 125.81, 125.87, 126.47, 127.86, 127.91, 128.29, 133.21, 133.36, 136.28, 136.40, 138.19, 139.65, 139.68. Found: C, 85.98; H, 8.34%. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27%.

5.17.3. {4-[(Hydroxy)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methyl]phenyl}(phenyl)methanone (2c). IR (Nujol) 3438, 1639, 1604, 1317, 1280, 1147, 1035, 943, 704 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.14 (s, 3H), 1.47 (s, 3H), 1.51 (s, 3H), 1.58 (s, 3H), 1.40–1.80 (br s, 1H), 2.00 (s, 3H), 4.47 (s, 1H), 7.05–7.20 (m, 5H), 7.68–7.74 (m, 4H); ^{13}C NMR (C_6D_6) δ 10.79, 10.86, 11.34, 12.11, 18.15, 61.26, 78.05, 126.70, 128.26, 128.99, 130.08, 131.83, 136.38, 136.64, 136.70, 137.70, 138.61, 139.45, 146.49, 195.63. Found: C, 82.97; H, 7.58%. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56%. Mp 89–90 °C.

5.17.4. Methyl 4-[(hydroxy)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methyl]benzoate (2d). IR (Nujol) 3521, 1706, 1608, 1438, 1282, 1109, 1049, 1018, 763, 711 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.26 (d, J=4.0 Hz, 3H), 1.35–1.55 (br s, 1H), 1.43 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 1.99 (s, 3H), 3.46 (s, 3H), 4.41–4.45 (m, 1H), 7.15–7.18 (m, 2H), 8.04–8.09 (m, 2H); ^{13}C NMR (C_6D_6) δ 10.73, 10.79, 11.26, 12.12, 18.07, 51.41, 61.18, 78.07, 126.79, 128.42, 129.46, 136.35, 136.61, 137.59, 139.39, 147.09, 166.72. Found: C, 75.82; H, 8.16%. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05%. Mp 91–92 °C.

5.17.5. 4-[(Hydroxy)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methyl]benzonitrile (2e). IR (Nujol) 3488, 2220, 1606, 1313, 1201, 1037, 819, 775, 875, 609 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.03 (s, 3H), 1.27 (s, 1H), 1.40 (d, J=1.5 Hz, 3H), 1.42 (d, J=1.5 Hz, 3H), 1.46 (s, 3H), 1.90 (s, 3H), 4.21 (d, J=8.5 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H); ^{13}C NMR (C_6D_6) δ 10.64, 10.73, 11.14, 12.01, 17.79, 60.99, 77.63, 111.20, 119.07, 117.08, 130.40, 136.53, 136.88, 137.17, 139.09, 146.56. Found: C, 80.79; H, 8.16%. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92%. Mp 99–100 °C.

5.17.6. (4-Buthoxyphenyl)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methanol (2f). IR (neat) 3469, 2931, 1612, 1512, 1446, 1244, 1174, 1029, 821, 603 cm^{-1}; ^1H NMR (C_6D_6) δ 0.80 (t, J=7.5 Hz, 3H), 1.22 (s, 3H), 1.20–1.30 (m, 1H), 1.30 (dq, J=7.5, 7.5 Hz, 2H), 1.51 (s, 3H), 1.54 (dd, J=7.5, 7.5 Hz, 2H), 1.59 (s, 3H), 1.67 (s, 3H), 2.07 (s, 3H), 3.59 (t, J=7.5 Hz, 2H), 4.56 (d, J=3.0 Hz, 1H), 6.77 (d, J=3.5 Hz, 2H), 7.15 (d, J=3.5 Hz, 2H); ^{13}C NMR (C_6D_6) δ 10.94 (C×2), 11.41, 12.24, 13.95, 18.58, 19.49, 31.64, 61.45, 67.35, 78.35, 113.18, 128.29, 134.08, 135.98, 136.07, 138.46, 139.74, 158.78. Found: C, 79.91; H, 9.68%. Calcd for $C_{21}H_{30}$: C, 80.21; H, 9.62%.

5.17.7. 1-{4-[(Hydroxy)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methyl]phenyl}-2-methyl-1-propanone (2g). IR (neat) 3492, 2872, 1682, 1606, 1382, 1228, 981, 823, 759, 704 cm^{-1}; ^1H NMR (C_6D_6) δ 1.06 (d, J=7.0 Hz, 6H), 1.14 (s, 3H), 1.43 (d, J=3.0 Hz, 1H), 1.46 (s, 3H), 1.50 (s, 3H), 1.60 (s, 3H), 2.02 (s, 3H), 3.11 (septet, J=7.0 Hz, 1H), 4.46 (d, J=3.0 Hz, 1H), 7.18 (d, J=8.5 Hz, 2H), 7.81 (d, J=8.5 Hz, 2H); ^{13}C NMR (C_6D_6) δ 10.78, 10.85, 11.27, 12.39, 18.31, 19.21, 19.28, 35.26, 61.29, 78.14, 126.94, 127.10, 134.98, 136.10, 136.41, 137.72, 139.64, 147.46, 203.68. Found: C, 80.71; H, 8.94%. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 8.78%.

5.17.8. (2-Methoxyphenyl)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methanol (2h). IR (neat) 3469, 2925, 1600, 1587, 1490, 1400, 1240, 1033, 752, 607 cm^{-1}; ^1H NMR (C_6D_6) δ 1.30 (s, 3H), 1.57 (d, J=1.0 Hz, 3H), 1.67 (d, J=1.0 Hz, 3H), 1.74 (s, 3H), 1.84 (d, J=4.5 Hz, 1H), 2.08 (s, 3H), 3.26 (s, 3H), 5.39 (d, J=4.5 Hz, 1H), 6.47 (d, J=7.5 Hz, 1H), 6.85 (dd, J=7.5, 7.5 Hz, 1H), 7.03 (dd, J=7.5, 7.5 Hz, 1H), 7.46 (d, J=7.5 Hz, 1H); ^{13}C NMR (C_6D_6) δ 11.04 (C×2), 11.54, 12.08, 18.82, 54.55, 61.89, 71.90, 109.88, 120.02, 128.13, 128.87, 130.65, 135.56, 135.77, 139.49, 140.40, 157.03. Found: C, 79.16; H, 9.02%. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88%.

5.17.9. (4-Bromophenyl)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)(trimethylsiloxy)methane (2a-Si). IR (neat) 841, 889, 1076, 1250, 1377, 1458, 1655, 2924 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 (s, 9H), 1.11 (s, 3H), 1.44 (br s, 3H), 1.48 (br s, 3H), 1.79 (s, 3H), 1.93 (s, 3H), 4.56 (s, 1H), 6.83–6.88 (m, 2H), 7.15–7.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −0.08, 10.52, 10.64, 10.91, 12.60, 18.07, 60.74, 79.40, 120.02, 127.72, 129.08, 135.77, 136.05, 136.83, 139.29, 140.76. Found: C, 60.84; H, 7.33%. Calcd for $C_{20}H_{29}BrOSi$: C, 61.06; H, 7.43%.

5.17.10. Methyl 4-[(trimethylsiloxy)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methyl]benzoate (2d-Si). IR (neat) 619, 710, 764, 841, 1076, 1279, 1437, 1611, 1728, 1931, 2957 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 (s, 9H), 1.13 (s, 3H), 1.40 (br s, 3H), 1.43 (br s, 3H), 1.81 (s, 3H), 1.94 (s, 3H), 3.87 (s, 3H), 4.65 (s, 1H), 7.02–7.07 (m, 2H), 7.72–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −0.11, 10.46, 10.60, 10.94, 12.59, 18.03, 51.87, 60.83, 79.62, 125.96, 127.47, 128.16, 135.75, 136.16, 136.70, 139.30, 147.14, 167.40. Found: C, 70.97; H, 8.49%. Calcd for $C_{22}H_{32}O_3Si$: C, 70.92; H, 8.66%.

5.17.11. (4-Butoxyphenyl)(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)(trimethylsiloxy)methane (2f-Si). IR (neat) 619, 750, 841, 891, 1070, 1173, 1250, 1512, 1612, 2959 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (s, 9H), 0.96 (t, J=7.2 Hz, 3H), 1.11 (s, 3H), 1.40–1.52 (m, 8H), 1.67–1.78 (m, 5H), 1.94 (s, 3H), 3.88 (t, J=6.6 Hz, 2H), 4.56 (s, 1H), 6.56–6.62 (m, 2H), 6.83–6.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −0.02, 10.59, 10.66, 10.90, 12.67, 13.92, 18.24, 19.26, 31.42, 60.96, 67.44, 79.84, 112.03, 127.11, 133.92, 135.39, 135.41, 137.40, 139.59, 157.58. Found: C, 74.30; H, 9.83%. Calcd for $C_{24}H_{38}O_2Si$: C, 74.55; H, 9.91%.

Compound **3b**: IR (neat) 839, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, J=7.0 Hz, 3H), 1.61 (s, 3H), 1.72 (br s, 3H), 1.74 (br s, 3H), 2.20–2.31 (m, 3H), 2.51 (distorted q, 1H), 5.97 (dd, J=5.5, 10.0 Hz, 1H), 7.96–8.09 (m, 4H), 8.14–8.17 (m, 3H), 8.26–8.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 9.73, 12.46, 20.35, 25.07, 43.45, 50.54, 54.79, 75.93, 95.96, 122.93, 123.21, 124.71, 124.75, 124.84, 124.92, 125.09, 125.66, 126.80, 127.10, 127.51, 127.83, 130.39, 130.65, 131.30, 132.51, 135.62, 138.74. Found: C, 88.18; H, 7.21%. Calcd for $C_{27}H_{26}O$: C, 88.48; H, 7.15%. Mp 131.2–132.4 °C.

Compound **4b**: IR (Nujol) 852, 1076 cm^{-1}; ^1H NMR (500 MHz, ppm, $CDCl_3$) δ 1.11 (d, J=7.0 Hz, 3H), 1.56 (s, 3H), 1.63 (br s, 3H), 1.67–1.74 (m, 1H), 1.87 (br s, 3H), 2.24 (distorted q, 1H), 2.36 (m, 1H), 2.90 (m, 1H), 5.97 (dd, J=5.5, 10.5 Hz, 1H), 7.96–8.09 (m, 4H), 8.14–8.17 (m, 3H), 8.21 (d, J=7.5 Hz, 1H), 8.29 (d, J=9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.79, 12.53, 19.63, 25.45, 44.55, 47.99, 56.03, 77.65, 96.41, 122.82, 123.11, 124.69, 124.75, 124.92, 124.95, 125.10, 125.72, 126.75, 127.06, 127.51, 127.60, 130.33, 130.67, 131.37, 134.56, 135.19, 136.51. Found: C, 88.49; H, 7.14%. Calcd for $C_{27}H_{26}O$: C, 88.48; H, 7.15%. Mp 159.4–160.8 °C.

5.17.12. 4-[(Hydroxy)(diphenyl)methyl]benzaldehyde (7a)[20] and 4-[(hydroxy)(phenyl)methyl]benzaldehyde (7b) .[21] The title compounds are found in the literature.

5.17.13. 4-(1-Hydroxy-1-phenyl-3-butenyl)benzaldehyde (7c). IR (neat) 3477, 3060, 2839, 1699, 1606, 1573, 1446, 1213, 1174, 1062, 991, 825, 731, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.69 (s, 1H), 3.07 (dd, J=7.2, 14.1 Hz, 1H), 3.15 (dd, J=7.2, 14.1 Hz, 1H), 5.19–5.30 (m, 2H), 5.58–5.73 (m, 1H), 7.22–7.28 (m, 2H), 7.31–7.36 (m, 2H), 7.44–7.49 (m, 2H), 7.62–7.66 (m, 2H), 7.81–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 46.34, 76.81, 121.18, 125.88, 126.56, 127.32, 128.44, 129.68, 132.62, 134.94, 145.53, 153.28, 191.92. Found: C, 80.69; H, 6.55%. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39%.

5.17.14. 4-(1-Phenylethenyl)benzaldehyde (9). IR (neat) 3028, 2829, 2734, 1697, 1604, 1566, 1211, 1168, 840, 779, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.58 (d, J=1.0 Hz, 1H), 5.59 (d, J=1.0 Hz, 1H), 7.30–7.38 (m, 5H), 7.51 (d, J=8.0 Hz, 2H), 7.86 (d, J=8.0 Hz, 2H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 116.48, 128.08, 128.16, 128.35, 128.79, 129.66, 135.59, 140.53, 147.59, 149.12, 191.80. Found: C, 86.28; H, 5.81%. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81%.

5.17.15. 1-(1,2,3,4,5-Pentamethyl-2,4-cyclopentadienyl)-1-dodecanol (11a). IR (neat) 1013, 1379, 1445, 1657, 2924, 3483 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.02 (s, 3H), 1.05–1.53 (m, 21H), 1.70 (s, 3H), 1.76 (br s, 6H), 1.79 (s, 3H), 3.54 (dt, $J=7.2$, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.93 (×2), 11.05, 11.40, 14.12, 18.21, 22.69, 27.25, 29.34, 29.63 (×2), 29.65, 29.69, 29.71, 31.56, 31.91, 60.34, 75.96, 135.12, 135.33, 138.69, 139.87. Found: C, 82.05; H, 12.67%. Calcd for $C_{22}H_{40}O$: C, 82.43; H, 12.58%.

5.17.16. 1-(1,2,3,4,5-Pentamethyl-2,4-cyclopentadienyl)-3-phenyl-1-propanol (11b). IR (neat) 700, 1030, 1454, 2920, 3483 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3H), 1.34–1.47 (m, 3H), 1.59 (s, 3H), 1.74 (br s, 6H), 1.80 (s, 3H), 2.54 (dt, $J=13.8$, 7.8 Hz, 1H), 2.82 (dt, $J=13.8$, 7.8 Hz, 1H), 3.48–3.62 (m, 1H), 7.10–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.84, 11.07, 11.20, 11.62, 18.30, 33.44, 33.50, 60.27, 75.21, 125.57, 128.16 (×2), 128.41 (×2), 135.12, 135.28, 138.44, 139.59, 142.32. Found: C, 84.59; H, 9.97%. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69%.

5.17.17. 1-Cyclohexyl-1-(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)methanol (11c). IR (neat) 974, 1379, 1448, 1655, 2922, 3504 cm^{-1}; ^1H NMR (C_6D_6) δ 0.99–1.58 (m, 15H), 1.66 (s, 3H), 1.71 (br s, 6H), 2.04 (s, 3H), 3.35 (d, $J=5.1$ Hz, 1H); ^{13}C NMR (C_6D_6) δ 10.87, 11.35, 11.51, 13.41, 21.32, 27.14, 27.18, 27.61, 27.87, 33.37, 40.86, 61.04, 81.52, 134.81, 134.90, 140.13, 142.13. Found: C, 82.10; H, 11.53%. Calcd for $C_{17}H_{28}O$: C, 82.10; H, 11.36%.

5.17.18. 7-Hydroxy-7-(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)heptanenitrile (11e). IR (neat) 1059, 1379, 1445, 1657, 2247, 2932, 3520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3H), 1.10–1.67 (m, 9H), 1.70 (s, 3H), 1.76 (br s, 6H), 1.79 (s, 3H), 2.32 (t, $J=7.2$ Hz, 2H), 3.53 (dt, $J=7.5$, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.93, 10.94, 11.07, 11.37, 17.08, 18.14, 25.38, 26.43, 28.67, 31.14, 60.27, 75.77, 119.85, 135.33, 135.58, 138.46, 139.69. HRMS FAB [$M+H^+$] 261.2094. Calcd for $C_{17}H_{28}NO$: 261.2093.

5.17.19. 10-Chloro-1-(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)-1-decanol (11f). IR (neat) 1036, 1379, 1447, 2926, 3449 cm^{-1}; ^1H NMR (C_6D_6) δ 0.97–1.66 (m, 20H), 1.70 (s, 3H), 1.71 (s, 3H), 1.73 (s, 3H), 1.97 (s, 3H), 3.11 (t, $J=6.9$ Hz, 2H), 3.45–3.55 (m, 1H); ^{13}C NMR (C_6D_6) δ 10.62, 10.97, 11.13, 12.14, 18.75, 27.04, 27.51, 29.08, 29.74, 29.98, 30.03, 31.88, 32.81, 44.93, 60.80, 75.99, 134.97, 135.07, 139.21, 140.91. HRMS FAB [$M+H^+$] Found: 326.2376. Calcd for $C_{20}H_{36}ClO$: 326.2376.

5.17.20. Methyl 6-hydroxy-6-(1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl)hexanoate (11g). IR (Nujol) 1377, 1462, 1724, 2361, 2853, 3520 cm^{-1}; ^1H NMR (C_6D_6) δ 1.05 (s, 3H), 1.07–1.60 (m, 7H), 1.64 (s, 3H), 1.69 (s, 3H), 1.71 (s, 3H), 1.94 (s, 3H), 2.07 (t, $J=7.2$ Hz, 2H), 3.33 (s, 3H), 3.37–3.45 (m, 1H); ^{13}C NMR (C_6D_6) δ 10.55, 10.94, 11.10, 12.10, 18.70, 25.05, 26.75, 31.29, 34.09, 50.88, 60.71, 75.53, 134.93, 135.04, 139.14, 140.87, 173.41. Found: C, 72.52; H, 10.11%. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%. Mp 63–65 °C.

5.17.21. 7-(1,2,3,4,5-Pentamethyl-2,4-cyclopentadienyl)-7-tridecanol (16). IR (neat) 523, 621, 725, 935, 1036, 1136, 1379, 1456, 1653, 1715, 2926, 3508 cm^{-1}; ^1H NMR (C_6D_6) δ 0.91 (t, $J=6.3$ Hz, 6H), 0.97 (s, 1H), 1.18 (s, 3H), 1.20–1.64 (m, 20H), 1.74 (s, 6H), 1.98 (s, 6H); ^{13}C NMR (C_6D_6) δ 11.23 (×2), 13.94 (×2), 14.30 (×2), 17.03, 23.02 (×2), 24.63 (×2), 30.61 (×2), 32.23 (×2), 37.12 (×2), 64.38, 77.62, 135.51 (×2), 141.69 (×2). HRMS FAB [M−OH] Found: 317.3203. Calcd for $C_{23}H_{41}$: 317.3210.

5.17.22. 1-(1,2,3,4,5-Pentamethyl-2,4-cyclopentadienyl)-3-phenyl-1-(trimethylsilyloxy)propane (the trimethylsilyl ether of 11b). IR (neat) 511, 698, 748, 866, 1059, 1250, 1447, 1605, 1657, 1938, 2957 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.24 (s, 9H), 1.12 (s, 3H), 1.43–1.51 (m, 1H), 1.54–1.62 (m, 4H), 1.67 (s, 3H), 1.70 (s, 3H), 2.06 (s, 3H), 2.49 (ddd, $J=13.5$, 10.0, 7.0 Hz, 1H), 2.80 (ddd, $J=13.5$, 10.5, 5.0 Hz, 1H), 3.80 (dd, $J=8.0$, 2.5 Hz, 1H), 6.99–7.03 (m, 1H), 7.07–7.13 (m, 4H); ^{13}C NMR (C_6D_6, 126 MHz) δ 0.96 (×3), 10.16, 10.92, 11.07, 12.49, 20.25, 33.78, 34.98, 60.90, 77.39, 125.96, 128.62 (×2), 128.70 (×2), 134.88, 134.93, 139.19, 141.50, 142.93. Found: C, 77.38; H, 10.18%. Calcd for $C_{22}H_{34}Si$: C, 77.13; H, 10.00%.

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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.2006.01.097. Supplementary data including the coordinates of the atoms obtained by the ab initio calculations can be found online alongside the electronic version of the manuscript.

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Seragamides A–F, new actin-targeting depsipeptides from the sponge *Suberites japonicus* Thiele

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Abstract—Six new depsipeptides, seragamides A–F (**1**–**6**), and a known geodiamolide I (**7**) have been isolated as cytotoxic metabolites from the Okinawan sponge *Suberites japonicus*. Their structures were elucidated by means of spectroscopic analysis and chemical transformations. Seragamide A (**1**) promotes the polymerization of G-actin and stabilizes F-actin filaments.

1. Introduction

The eukaryotic cytoskeleton is composed of three groups of protein polymers: microtubules, intermediate filaments and microfilaments. Among these, the microtubule apparatus is critical for mitosis and is the target of anticancer agents that include vinca alkaloids and paclitaxel. The microfilament apparatus on the other hand is rarely considered as a target for chemical therapy. Recent studies, however, suggest that actin and the actin filament system of tumor cells, like microtubules, may serve as a critical target for small molecule drugs.[1]

Microfilaments are composed of F-actin and associated proteins; these filamentous assemblies play essential roles in cytokinesis, cell motility, and cell adhesion.[2] Actin filament dynamics in eukaryotic cells is regulated by a large number of actin-binding proteins (ABP) such as cofilin, gelsolin, thymosin β4 and profilin. Given the complexity of the cell cytoskeleton, studies that aim to understand the regulation of actin filament dynamics usually employ small molecule drugs such as fluorescent phalloidin, a marker of F-actin, and cytochalasin D, which inhibits actin polymerization. Recently, several highly specific actin-targeting drugs have been identified from marine natural products. The first, and most frequently used marine-derived drugs are latrunculins A and B, which block polymerization by plugging the ATP site of G-actin.[3] Other actin-targeting marine drugs include jaspamide/jasplakinolide, which stabilizes F-actin,[4,5] trisoxazole macrolides,[6–8] swinholide A,[9] hectochlorin,[10] and amphidinolide H.[11]

During a functional screen for cytotoxic drugs that inhibit the actin-driven processes of cytokinesis, we found that a lipophilic extract of the yellow sponge *Suberites japonicus* killed cells at 2 μg/mL with the formation of characteristic morphological changes similar to that found for trisoxazole macrolides, swinholide A, and misakinolide A. At a lower concentration range of 0.2–0.02 μg/mL, the extract led to the formation of multiple nuclei, which suggests that the active drug might target the actin cytoskeleton. We isolated and chemically characterized the bioactive products and determined their mode of action. The seragamides A–F identified from these studies represent new and novel molecular tools to study the regulation of the actin cytoskeleton and may prove useful as anti-cancer drugs.

2. Results and discussion

2.1. Structures of 1–7

A small amount of the sponge *S. japonicus* Thiele was initially collected at Seragaki, Okinawa. Its lipophilic extract gave rise to two new cytotoxic depsipeptides named seragamides A (**1**) and B (**2**). A larger amount of the sponge collected off Manza yielded seragamides C–F (**3**–**6**) in addition to **1**, **2**, and the known geodiamolide I (**7**).

Keywords: Geodiamolide; Actin polymerization; Cytokinesis; Jaspamide; Jasplakinolide.
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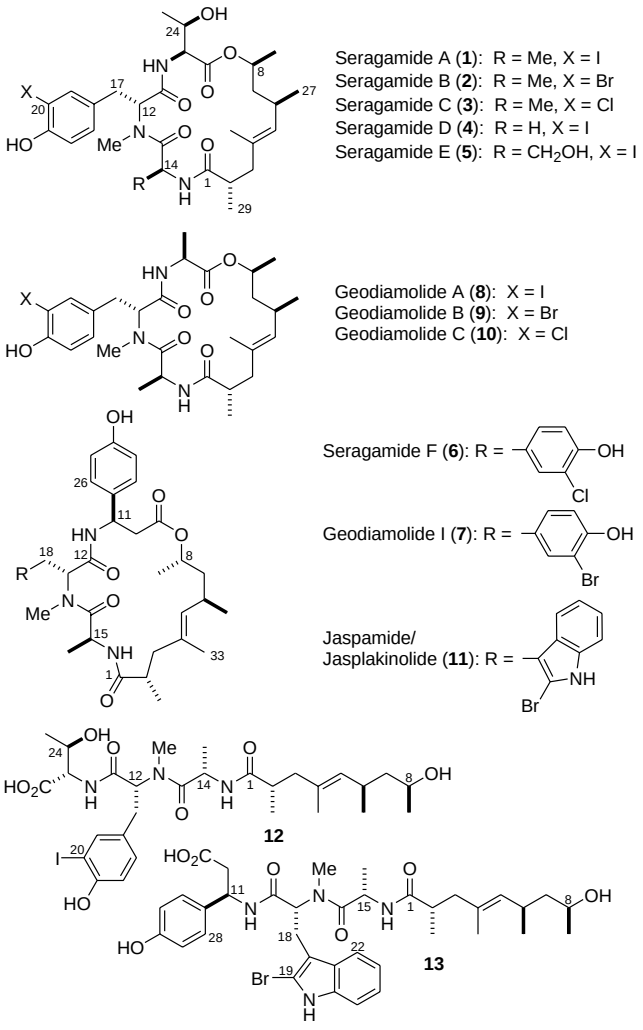

Seragamide A (**1**) obtained as an amorphous solid was analyzed for $C_{29}H_{42}N_3O_7I$ by HRFABMS. It showed IR absorption bands due to hydroxyl (3320 cm^{-1}), ester (1732 cm^{-1}), and amide (1635 cm^{-1}) functionalities. The peptidic nature of compound **1** was suggested by two amide signals (δ 6.49 and 6.71; δ 170–176) in NMR in addition to the IR absorption. The ^{1}H NMR data exhibited the presence of an *N*-methyl (δ 3.00) and aromatic protons (δ 6.90, 7.09, and 7.50). NMR analysis indicated the presence of three amino acid residues: Thr, iodo-*N*-methyl-tyrosine (I-*N*-Me-Tyr), and Ala.

A downfield signal (δ 6.71) for an amide proton showed a COSY correlation with a methine proton signal at δ 4.42 (δ 58.1), which in turn coupled to an oxymethine proton resonance at δ 4.29 (δ 67.7). This signal further coupled to a methyl signal at δ 1.09 (δ 18.7). Thus, this unit was deduced to Thr. The amide proton signal showed HMBC correlation to a carbonyl carbon signal (δ 170.0), while a resonance (δ 4.42) for an alpha proton showed cross peaks with δ 170.0 and another carbonyl at δ 169.4.

Second amino acid residue was assigned as I-*N*-Me-Tyr as follows. An *N*-methyl resonance (δ 3.00) showed an HMBC cross peak to an alpha carbon signal at δ 56.7. A signal (δ 5.32) for the alpha proton showed COSY cross peaks with downfield shifted β-methylene signals (δ 2.93 and 3.20). The presence of a 1,2,4-trisubstituted benzene ring was shown by observing three aromatic protons at δ 6.90 (d, J= 8.5 Hz), 7.09 (dd, J=8.5, 2.1 Hz), and δ 7.50 (d, J= 2.1 Hz). The chemical shifts of the proton at δ 6.90 and the carbon at δ 154.0 suggested the ring to be phenolic. The β-methylene protons showed HMBC correlation with three aromatic carbons at δ 130.3, 138.2 and 130.6, whereas aromatic protons at δ 7.50 and 7.09 showed correlation to the beta carbon at δ 32.8 indicating the residue as a tyrosine derivative. The aromatic signal (δ 7.50) showed correlation to a characteristic high-field carbon signal at δ 85.5, suggesting the presence of iodine atom on this carbon. The ^{1}H and ^{13}C NMR data for the iodo-tyrosine residue were comparable with those of the same moiety of geodiamolide A (**8**).[12]

The last amino acid unit was assigned as Ala by observing ^{1}H NMR signals for a methine at δ 4.77, a methyl at δ 1.13, and an amide proton at δ 6.49. Both the methyl and the methine protons showed HMBC correlation to a carbonyl carbon at δ 174.5, while the amide proton exhibited HMBC cross peak to another carbonyl at δ 175.3.

The remaining portion of the molecule $C_{12}H_{20}O_2$ was elucidated as a polyketide composed of four units of propionates by the following NMR data. Four methyl groups were separated into three aliphatic doublets (δ 0.87, 1.15, 1.25) and one vinyl methyl (δ 1.52). HMBC correlations from these four methyl groups to the rest of the residue allowed us to construct a fatty acid residue as 2,4,6-trimethyl-non-4-enoyl, the same moiety observed in geodiamolides and jaspamides. The *E* configuration of the 4,5-double bond was determined by the NOE signals between the vinyl methyl (δ 1.52) and the methine proton (δ 2.22) at C-6, and between the olefinic proton (δ 4.91br d) and one of the methylene protons (δ 2.02) at C-3.

The cyclic nature of seragamide A (**1**) was evident from its ten degrees of unsaturation, nine of which were accounted for four carbonyls, one aromatic, and one double bond. Connection of the amino acid residues and the alkanoate unit was obtained by HMBC correlations: the amide proton at δ 6.71 and a carbonyl of I-*N*-Me-Tyr at δ 170.0s, *N*-methyl group of I-*N*-Me-Tyr at δ 3.00 and a carbonyl of Ala at δ 174.5s, the amide proton at δ 6.49 and a carbonyl of the alkanoate at δ 175.3s, and the oxymethine proton at δ 4.87 and the ester carbonyl at δ 169.4s. Therefore, the structure of seragamide A was assembled as shown in **1**.

Absolute configurations of the amino acid residues were determined by applying Marfey's method on its acid hydrolysate (see Section 3). The result revealed the amino acids to be L-Ala, L-Thr, and D-*N*-Me-Tyr. All of the three amide bonds are in trans geometry as shown by NOEs between NH-Ala (δ 6.49) and H-2 (δ 2.36), NH-Thr (δ 6.71) and alpha proton (δ 5.32) of I-*N*-Me-Tyr, and *N*-Me-Tyr (δ 3.00) and alpha proton (δ 4.77) of Ala. When ^{1}H and ^{13}C NMR data of **1** were compared with those of **8** as shown in Table 1, most of the coupling constants and chemical shifts for the fatty acid portion were nearly identical suggesting that the three chiral centers were the same as those of geodiamolide A (**8**) and its congeners. For further

Table 1. NMR data for seragamide A (**1**) and for geodiamolide A (**8**)

	Seragamide A (**1**)				**8**[12]	
C#	^{13}C	^{1}H (*J* in Hz)	HMBC	COSY	^{13}C	^{1}H
1	175.3s				170.9s	
2	42.0d	2.36ddq (4.0, 11.0, 7.0)		H-3ab,29	42.4d	2.32m
3	42.9t	a2.02dd (4.0, 14.0)	C-4	H-2,3b,5	43.3t	a2.04dd
		b2.16m	C-4	H-2,3a		b2.16d
4	133.2s				129.6s	
5	131.2d	4.91br d (9.0)	C-27	H-3a,6,28	131.6d	4.93d
6	29.0d	2.22m		H-5,7ab,27	29.0d	2.16m
7	43.4t	a1.38ddd (5.8, 8.0, 13.7)	C-5,6,26,27	H-6,7b,8	43.7t	a1.34m
		b1.63m	C-5,6,26,27	H-6,7a,8		b1.59m
8	71.8d	4.87ddq (6.0, 7.0, 6.5)	C-7,9	H-7ab,26	71.0d	4.91m
9	169.4s				168.8s	
10	58.1d	4.42dd (3.0, 8.5)	C-9,11	H-10NH	49.0d	4.75dq
11	170.0s				175.1s	
12	56.7d	5.32dd (7.6, 9.2)	C-11,13,16,17	H-17ab	56.7d	5.21dd
13	174.5s				174.4s	
14	45.8d	4.77dq (6.7, 6.7)	C-13,15	H-14NH,15	45.9d	4.46dq
15	19.7q	1.13d (6.7)	C-13,14	H-14	18.8q	1.34q
16	30.6q	3.00s	C-12,13		30.7q	2.97s
17	32.8t	a2.93dd (9.2, 14.6)	C-11,12,19,23	H-12,17b	32.7t	a2.95dd
		b3.20dd (7.6, 14.6)	C-12,18,19	H-12,17a		b3.15dd
18	130.3s				133.0s	
19	138.2d	7.50d (2.1)	C-17,18,20,21	H-23	132.2d	7.29d
20	85.5s				85.1s	
21	154.0s				154.5s	
22	115.1d	6.90d (8.5)	C-18,20,21,23	H-23	116.1d	6.87d
23	130.6d	7.09dd (2.1, 8.5)	C-17,19,21	H-19,22	129.4d	7.05dd
24	67.7d	4.29dq (3.0, 6.5)		H-25	18.7q	1.02d
25	18.7q	1.09d (6.5)	C-10,24	H-24		
26	20.6q	1.25d (6.5)	C-7,8	H-8	20.6q	1.24d
27	20.5q	0.87d (6.5)	C-5,6,7	H-6	18.2q	0.86d
28	17.8q	1.52d (1.2)	C-3,4,5	H-5	17.7q	1.49s
29	18.9q	1.15d (7.0)	C-1,3	H-2	20.4q	1.14d
10NH		6.71d (8.5)	C-11	H-10		6.52d
14NH		6.49d (6.7)	C-1	H-14		6.59d
TyrOH		5.55br s				6.27s
ThrOH		3.49s				

confirmation, ring-opened derivatives **12** and **13** were prepared by saponification of **1** and **11**, respectively, and their NMR data were compared. Except for the H-2 chemical shifts ($\Delta\delta$ 0.09), all other chemical shifts and coupling constants for the polyketide portion were in good agreement as shown in Table 2, indicating the same stereochemistry for the portion in **1** and **11**. Thus, we concluded the stereochemistry of seragamide A (**1**) as shown.

The molecular formula of seragamide B (**2**), $C_{29}H_{42}N_3O_7Br$, suggested that it had a bromine atom instead of an iodine atom in **1**. The IR spectrum showed similar absorptions (3320, 1733, 1650 cm^{-1}) to those of **1**. Inspection of NMR spectra of **2** indicated that almost all signals in **2** are the same with those of **1** except for the aromatic portion of Tyr residue (Tables 1 and 3). Further comparison of the data with those of geodiamolide B (**9**),[12] which retains Br-*N*-Me-Tyr residue, confirmed that **2** contained a bromine atom in the place of iodine in **1**. Marfey analysis of the acid hydrolysate of **2** determined the residues as L-Ala and L-Thr. As in the discussion of seragamide A (**1**), the remaining chiralities of **2** are regarded to be the same.

Table 2. Comparison of the ^{1}H NMR data for the polyketide portion of **12** and **13** (*J* in Hz)

H#	12	13
2	2.47ddq (7.1, 8.1, 6.8)	2.38ddq (7.3, 8.0, 6.8)
2-Me	1.04d (6.8)	1.02d (6.8)
3a	1.96dd (8.1, 13.9)	1.94dd (8.0, 13.7)
3b	2.26dd (7.1, 13.9)	2.25dd (7.3, 13.7)
4-Me	1.57s	1.56s
5	4.95d (9.3)	4.91d (9.8)
6	2.43dddq (5.9, 8.8, 9.3, 6.6)	2.39dddq (5.9, 9.8, 9.3, 6.6)
6-Me	0.89d (6.6)	0.87d (6.6)
7a	1.34ddd (5.9, 13.4, 6.1)	1.31ddd (5.9, 13.4, 6.1)
7b	1.43ddd (8.8, 13.4, 6.1)	1.41ddd (9.3, 13.4, 6.1)
8	3.69ddq (6.1, 6.1, 6.1)	3.68ddq (6.1, 6.1, 6.1)
8-Me	1.12d (6.1)	1.12d (6.1)

Seragamide C (**3**) was found to have a molecular formula $C_{29}H_{42}N_3O_7Cl$ by HRFABMS. Except for aromatic portions of Tyr residue in **3**, most NMR signals are similar to those of **1** and **2**. The aromatic protons (δ 6.94, 7.03, 7.17) are virtually identical to those (δ 6.93, 7.01, 7.15) of geodiamolide C (**10**),[13] which has Cl-*N*-Me-Tyr residue. The structure of **3** was elucidated as shown.

The molecular formula of seragamide D (**4**), $C_{28}H_{40}N_3O_7I$, suggested that it is a demethyl analogue of seragamide A (**1**). The methyl group (δ 19.7) of Ala residue in **1** disappeared in **4**, and two characteristic downfield shifted methylene protons (δ 3.80, 4.17) appeared instead. As most other portions showed similar NMR data (Tables 3 and 4) as **1**, seragamide D (**4**) was elucidated as a congener having Gly in the place of Ala in seragamide A (**1**). The linkage of

Table 3. ^{1}H NMR data for seragamides B–E (**2**–**5**) (*J* in Hz)

	B (**2**)	C (**3**)	D (**4**)	E (**5**)
2	2.36m	2.36m	2.47tq (7.9, 6.7)	2.42ddq (4.0, 11.0, 6.7)
3a	2.02dd (3.0, 14.0)	2.02dd (3.0, 14.0)	2.12d (7.9, 2H)	2.08dd (4.0, 14.0)
3b	2.17dd (11.5, 14.0)	2.17dd (11.3, 14.0)		2.16m
5	4.91d (10.0)	4.91d (8.8)	4.98d (7.9)	4.93d (9.2)
6	2.22m	2.20m	2.23m	2.20m
7a	1.39m	1.39ddd (6.1, 7.9, 13.7)	1.44ddd (6.8, 8.2, 13.7)	1.39ddd (5.2, 7.9, 13.7)
7b	1.64m	1.63ddd (6.7, 7.1, 13.7)	1.70ddd (6.1, 6.1, 13.7)	1.60m
8	4.87ddq (5.2, 7.2, 6.5)	4.87ddq (6.1, 7.1, 6.4)	4.80ddq (6.1, 6.8, 6.1)	4.92m
10	4.42dd (3.1, 8.8)	4.42dd (3.0, 8.8)	4.46dd (2.4, 9.2)	4.41dd (2.7, 8.8)
12	5.33dd (7.3, 9.2)	5.34dd (7.6, 8.8)	5.18dd (6.4, 9.5)	5.31dd (7.6, 8.8)
14	4.77dq (6.5, 6.5)	4.77dq (6.7, 6.7)	a3.80dd (3.0, 17.7) b4.17dd (4.3, 17.7)	4.83m
15	1.12d (6.5)	1.12d (6.7)		3.59m (2H)
16	3.00s	3.00s	2.96s	3.08s
17a	2.94dd (9.2, 14.6)	2.93dd (8.8, 14.6)	2.83dd (6.4, 13.7)	2.93dd (8.8, 14.6)
17b	3.21dd (7.3, 14.6)	3.21dd (7.6, 14.6)	3.26dd (9.5, 13.7)	3.23dd (7.6, 14.6)
19	7.31d (2.1)	7.17d (2.1)	7.53d (1.8)	7.50d (2.1)
22	6.94d (8.3)	6.94d (8.2)	6.91d (8.5)	6.91d (8.5)
23	7.07dd (2.1, 8.3)	7.03dd (2.1, 8.2)	7.10dd (1.8, 8.5)	7.09dd (2.1, 8.5)
24	4.29m	4.30m	4.22m	4.33m
25	1.09d (6.5)	1.09d (6.4)	0.99d (6.7)	1.08d (6.4)
26	1.25d (6.5)	1.25d (6.4)	1.27d (6.1)	1.25d (6.1)
27	0.88d (6.5)	0.87d (6.7)	0.90d (6.7)	0.89d (6.7)
28	1.52d (1.2)	1.52d (1.2)	1.56s	1.52d (1.2)
29	1.15d (7.0)	1.15d (7.0)	1.17d (6.7)	1.18d (6.7)
10NH	6.72d (8.8)	6.69d (8.8)	6.64d (9.2)	6.66d (8.8)
14NH	6.48d (6.5)	6.47d (6.7)	6.48br s	6.70d (6.4)
15OH				3.55m
21OH	5.55br s	5.52br s	5.35s	5.47br s
24OH	3.49br s	3.49br s	3.49br s	3.50d (4.9)

the residues was confirmed by HMBC correlations (H-10/C-11, NH-Thr/C-11, *N*-Me/C-12,13, H-14/C-1).

Seragamide E (**5**), $C_{29}H_{42}N_3O_8I$, was analyzed to have an additional oxygen atom on the formula of seragamide A (**1**). In the NMR spectra of **5**, it lacked methyl signals corresponding to Ala residue in **1**, while it exhibited signals for a primary alcohol (δ 65.1; δ 3.59), suggesting the presence of Ser residue instead of Ala in **1**. This disposition was also supported by HMBC correlations (*N*-Me/C-12,13, H-14/C-13). The remaining portions showed nearly the same NMR data with other seragamides (Tables 3 and 4). The absolute stereochemistry of Ser was determined to be L by Marfey's method.

Table 4. ^{13}C NMR data for seragamides B–E (**2**–**5**)

	B (**2**)	C (**3**)	D (**4**)	E (**5**)
1	175.2s	175.2s	175.8s	177.4s
2	41.9d	41.9d	41.8d	42.0d
3	42.8t	42.8t	42.9t	42.9t
4	133.2s	133.3s	133.5s	132.9s
5	131.1d	131.0d	131.0d	131.6d
6	29.0d	29.1d	29.2d	29.1d
7	43.4t	43.5t	43.4t	43.8t
8	71.8d	71.8d	72.6d	71.5d
9	169.4s	169.4s	169.2s	169.5s
10	58.0d	58.0d	57.8d	58.0d
11	169.9s	170.0s	169.2s	169.8s
12	56.6d	56.7s	57.7d	57.0d
13	174.5s	174.5s	169.9s	171.8s
14	45.8d	45.8d	42.1t	52.5d
15	19.7q	18.6q		65.1t
16	30.6q	30.6q	29.8q	31.0s
17	32.9t	33.0q	32.5t	32.8t
18	129.8s	129.5s	130.4s	130.2s
19	132.0d	129.0d	138.6d	138.2d
20	110.1s	119.8s	85.7s	85.6s
21	151.2s	150.3s	154.0s	154.0s
22	116.2d	116.4d	115.2d	115.2d
23	129.6d	128.8d	130.8d	130.6d
24	67.7d	67.7d	68.1d	67.6d
25	18.6q	19.7q	19.5q	19.8q
26	20.5q	20.5q	20.6q	20.7q
27	20.5q	20.6q	20.6q	20.5q
28	17.8q	17.9q	18.2q	18.0q
29	18.9q	19.0q	18.4q	18.9q

Seragamide F (**6**), $C_{34}H_{44}N_3O_7Cl$, showed the presence of two aromatic rings as observed for geodiamolide I (**7**).[14] Of the two aromatic rings in **6**, a *p*-disubstitued one is virtually the same as in **7**, while 1,2,4-trisubstituted one (δ 7.13d, 6.90d, 6.99dd) is similar to the one found for seragamide C (**3**) (δ 7.17d, 6.94d, 7.03dd). Therefore, the structural difference between **6** and **7** lies at the halogen substitution on the latter aromatic ring. Close similarities of NMR data of **6** to **7** indicate that they have the same stereochemistry.

2.2. Biological activity

The IC_{50} values of seragamides A–E (**1**–**5**) were determined as 0.064, 0.12, 0.10, 0.18 and 0.58 μM, respectively. Seragamides A–E (**1**–**5**) caused multinuclei formation in cells at 0.01, 0.02, 0.01, 0.01, and 0.04 μg/mL, respectively. Seragamide F (**6**) was not tested.

Using a Prodan-actin polymerization assay[15] we found that seragamide A (**1**) in the range of 20–200 nM facilitated the polymerization of 1 μM G-actin, as shown in Figure 1. In the Prodan-actin depolymerization assay, 1 nM seragamide A (**1**) inhibited the depolymerization of F-actin at 100 nM (Fig. 2). Since these activities are similar to those observed for jaspamide/jasplakinolide (**11**), we suggest that

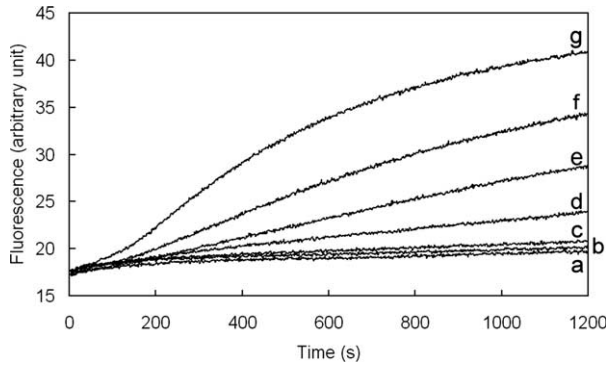

Figure 1. The effect of seragamide A (**1**) on polymerization of G-actin. Prodan-labeled G-actin (1 μM) is mixed with seragamide A (**1**) at the concentration of 0 nM (a), 1 nM (b), 10 nM (c), 20 nM (d), 50 nM (e), 100 nM (f), and 200 nM (g).

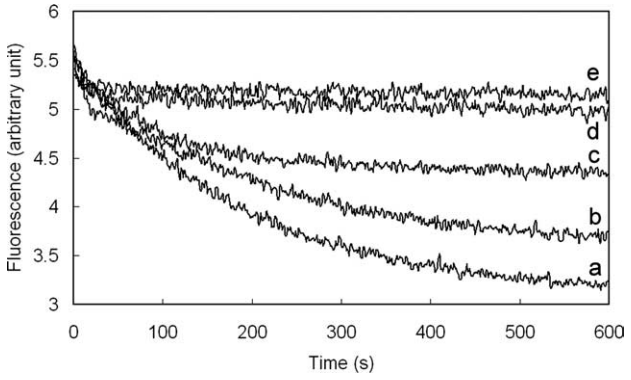

Figure 2. The effect of seragamide A (**1**) on depolymerization of F-actin. Prodan-labeled F-actin (28 μM) is mixed to a final concentration at 100 nM with seragamide A (**1**) at 0 nM (a), 0.05 nM (b), 0.1 nM (c), 1 nM (d), and 10 nM (e).

seragamides also function as cell permeable, F-actin stabilizing drugs.

3. Experimental

3.1. General experimental procedures

^{1}H and ^{13}C NMR spectra were recorded on a Jeol α-500 spectrometer. Mass spectra were measured on Jeol JMS-D300. IR, UV spectra and the optical rotations were measured using a Shimadzu FTIR-8300A instrument, a Hitachi U-2001 spectrophotometer, and a Jasco DIP-1000 polarimeter, respectively. Fluorescence spectra were taken on a Jasco FP6500 fluorometer. A microplate reader TECAN GENios was used for cytotoxicity. High-performance liquid chromatography (HPLC) was performed on a Hitachi L-6000 pump equipped with a Hitachi RI monitor (655A-30) and a Hitachi L-4000 UV detector, using Cosmosil packed ODS HPLC column (5C18-AR-II, 10× 250 mm). Merck silica gel was used for vacuum flash chromatography. Nacalai Cosmosil was used for reversed phase column chromatography. All solvents used were reagent grade.

3.2. Animal material

The yellow round sponge was identified as *S. japonicus* Thiele (Order Hadromerida, Family Suberitidae) by Dr. John N.A. Hooper, Queensland Museum, Brisbane. The specimen is deposited at the museum (QMG317382).

3.3. Extraction and isolation

The first collection (40 g, wet) of the sponge *S. japonicus* was made in 2001 by R.F.B. at a depth of 60 m by hand using SCUBA at Seragaki, Okinawa. The fresh sample was soaked and kept in MeOH until extraction. The MeOH solution was concentrated and the residual material was partitioned between EtOAc and H_2O. The residue of the EtOAc extract (33 mg) was chromatographed on a column packed with Cosmosil using MeOH–H_2O to give six fractions. These fractions were submitted for a cell-based high content imaging assay; fractions 1 and 2 were found to be active (fraction 1: 0.2 μg/mL and fraction 2: 2 μg/mL), showing vacuoles, blebs, arborization similar to that observed for misakinolide A.[16] Each fraction was separated by reversed phase HPLC using MeOH–H_2O (60/40) to give compounds **1** (4.1 mg) and **2** (1.6 mg).

The second specimen (0.5 kg, wet), collected at a depth of 50 m off Manza, was repeatedly extracted with MeOH and then with acetone. After concentration the combined extracts were partitioned between EtOAc and H_2O. The residue (6.4 g) of the organic extract was subjected to vacuum flash column chromatography (VFC) on silica gel (hexane, hexane–EtOAc, EtOAc, and EtOAc–MeOH) to afford four fractions. ^{1}H NMR spectrum of each fraction was compared with those of **1** and **2**. The spectrum of fraction **3** clearly indicated the presence of **1**. The fraction was roughly separated by MPLC (Lobar column) using 60% aqueous MeOH to give three subfractions. Each of these fractions was purified on reversed phase HPLC using the same solvent (60% aqueous MeOH) to afford compounds **1–7** in the amount of 145.8, 23.0, 2.0, 1.5, 1.8, 0.4, and 0.9 mg, respectively.

3.3.1. Seragamide A (1). White amorphous solid, $[\alpha]_D^{27}$ +45.6 (*c* 0.215, $CHCl_3$); IR (neat) ν_{max}: 3320, 1732, 1635 cm^{-1}; UV λ_{max} (MeOH): 207 (ε 3.4×10^4) and 286 nm (2.8×10^3); FABMS: *m/z* 672 ([M+H]$^+$), 546, 423; HRFABMS: *m/z* 672.2133, calcd for $C_{29}H_{43}N_3O_7I$ 672.2146; ^{1}H and ^{13}C NMR ($CDCl_3$): Table 1.

3.3.2. Seragamide B (2). White amorphous solid, $[\alpha]_D^{27}$ +39 (*c* 0.090, $CHCl_3$); IR (neat) ν_{max}: 3320, 1733, 1650 cm^{-1}; UV λ_{max} (MeOH): 205 (ε 3.1×10^4) and 283 nm (2.3×10^3); FABMS: *m/z* 626, 624 ([M+H]$^+$); HRFABMS: 624.2240, calcd for $C_{29}H_{43}N_3O_7{}^{79}Br$ 624.2284; ^{1}H and ^{13}C NMR ($CDCl_3$): Tables 3 and 4.

3.3.3. Seragamide C (3). Colorless glass, $[\alpha]_D^{23}$ +53 (*c* 0.10, $CHCl_3$); IR (neat) ν_{max}: 3330, 1738, 1651 cm^{-1}; UV λ_{max} (MeOH): 217 (ε 1.2×10^4) and 281 nm (2.3×10^3); FABMS: *m/z* 580, 582 ([M+H]$^+$); HRFABMS: *m/z* 580.2790, calcd for $C_{29}H_{43}N_3O_7{}^{35}Cl$ 580.2787; ^{1}H and ^{13}C NMR ($CDCl_3$): Tables 3 and 4.

3.3.4. Seragamide D (4). Colorless glass, $[\alpha]_D^{23}$ +46 (*c* 0.075, $CHCl_3$); IR (neat) ν_{max}: 2290, 1734, 1665 cm^{-1}; UV λ_{max} (MeOH): 217 (ε 1.2×10^4) and 285 nm (2.6×10^3); FABMS: *m/z* 658 ($[M+H]^+$); HRFABMS: *m/z* 658.1989, calcd for $C_{28}H_{41}N_3O_7I$ 658.1975; ^1H and ^{13}C NMR ($CDCl_3$): Tables 3 and 4.

3.3.5. Seragamide E (5). Colorless glass, $[\alpha]_D^{24}$ +33 (*c* 0.090, $CHCl_3$); IR (neat) ν_{max}: 3340, 1732, 1653 cm^{-1}; UV λ_{max} (MeOH): 218 (ε 1.1×10^4) and 285 nm (2.5×10^3); FABMS: *m/z* 688 ($[M+H]^+$); HRFABMS: *m/z* 688.2095, calcd for $C_{29}H_{43}N_3O_8I$ 688.2103; ^1H and ^{13}C NMR: Tables 3 and 4.

3.3.6. Seragamide F (6). Colorless glass, $[\alpha]_D^{24}$ +10 (*c* 0.02, $CHCl_3$); IR (neat) ν_{max}: 3350, 1716, 1684 cm^{-1}; UV λ_{max} (MeOH): 229 (ε 4.7×10^3) and 279 nm (1.4×10^3); FABMS: *m/z* 642 ($[M+H]^+$); HRFABMS: *m/z* 642.2946, calcd for $C_{34}H_{45}N_3O_7^{35}Cl$ 642.2906; ^1H NMR ($CDCl_3$): δ 0.85 (d, 3H, J=6.7 Hz; H-32), 1.06 (d, 3H, J=6.7 Hz; H-16), 1.08 (d, 3H, J=6.4 Hz; H-31), 1.17 (d, 3H, J=7.0 Hz; H-34), 1.17 (m, 1H; H-7), 1.33 (m, 1H; H-7), 1.58 (d, 3H, J=4.0 Hz; H-33), 1.92 (br d, 1H, J=15.6 Hz; H-3), 2.27 (m, 1H; H-6), 2.39 (dd, 1H, J=11.7, 15.6 Hz; H-3), 2.55 (m, 1H; H-2), 2.61 (dd, 1H, J=6.0, 15.3 Hz; H-10), 2.69 (dd, 1H, J=4.6, 15.3 Hz; H-10), 2.91 (dd, 1H, J=10.6, 14.7 Hz; H-18), 2.92 (s, 3H; H-17), 3.25 (dd, 1H, J=6.4, 14.7 Hz; H-18), 4.63 (m, 1H; H-8), 4.78 (m, 1H; H-5), 4.79 (m, 1H; H-15), 5.26 (m, 1H; H-11), 5.45 (dd, 1H, J=6.4, 10.6 Hz; H-13), 6.66 (d, 1H, J=7.0 Hz; 15-NH), 6.76 (d, 2H, J=8.8 Hz; H-27, 29), 6.90 (d, 1H, J=8.2 Hz; H-23), 6.99 (dd, 1H, J=1.8, 8.2 Hz; H-24), 7.06 (d, 2H, J=8.2 Hz; H-26, 30), 7.13 (d, 1H, J=1.8 Hz; H-20), 7.43 (br d, 1H, J=9.2 Hz; 11-NH).

3.3.7. Geodiamolide I (7). Colorless glass, $[\alpha]_D^{24}$ +37 (*c* 0.045, $CHCl_3$; lit.[14] +39.3); IR (neat) ν_{max}: 3330, 1734, 1684 cm^{-1}; UV λ_{max} (MeOH): 227 (ε 1.0×10^4) and 282 nm (2.5×10^3); ^1H and ^{13}C NMR ($CDCl_3$) data were identical with those reported.[14]

3.4. Acid hydrolysis of 1, 2 and 5

To a sample (0.3 mg) of **1** in a small glass tube was added 6 M HCl (0.5 mL). After sealing, it was heated at 110 °C for over night in an oven. The reaction mixture was cooled to ambient temperature and partitioned between EtOAc and H_2O. Each layer was concentrated to dryness under N_2 stream. The H_2O layer was used for making FDAA derivatives. The same procedure was applied for the hydrolysis of **2** and **5**.

3.5. Derivatization of amino acid with Marfey's reagent and HPLC analysis

To a 2 mL reaction vial containing 0.3 mg standard D-Ala in 10 μL of water was added 50 μL of *N*,α-(2,4-dinitro-5-fluorophenyl)-L-alaninamide (FDAA, Marfey's reagent) acetone solution (10 μg/mL) followed by 20 μL of 1 M $NaHCO_3$. The mixture was heated at 40 °C for 1 h. After cooling at room temperature it was neutralized by adding 10 μL of 2 M HCl solution. The resulting solution was filtered and concentrated by N_2 stream, and the resulting residue was stored in a freezer until HPLC analysis. The FDAA derivatives of L-Ala, D- and L-Thr, D- and L-*allo*-Thr, and D- and L-*N*-Me-Tyr were prepared in the same manner.

HPLC analyses of FDAA derivatives were carried out by using a reverse phase column (RP-18, Mightysil 250×10 mm) eluting with buffer–MeOH–MeCN (65/15/20) (flow rate: 0.8 mL/min) and detecting UV absorption at 340 nm. The buffer was prepared by adjusting 20 mM potassium hydroxide to pH 2–3 with 85 wt% phosphoric acid. Individual amino acid was identified by comparing retention times with those of FDAA derivatives of standard amino acids. The retention times were: L-Thr (24.5 min), D-Thr (40.6 min), L-*allo*-Thr (25.6 min), D-*allo*-Thr (29.9 min), L-Ala (39.2 min), D-Ala (42.8 min), L-*N*-Me-Tyr (43.0 min), and D-*N*-Me-Tyr (44.8 min). Derivatives of seragamide E (**5**) and standards were analyzed on a different column using the same solvents as above to give retention of L-Ser (14.6 min) and D-Ser (16.0 min).

3.6. Saponification of 1 and 11

Seragamide A (**1**, 10.8 mg) was dissolved in 1 mL of MeOH and 75 μL of 1 M KOH, and the mixture was kept stirring at room temperature for 4 h. The resulting solution was neutralized by adding 0.1 M HCl and partitioned between EtOAc and water. The organic layer was purified by preparative TLC (hexane/EtOAc, 1–6) on silica to give 3.0 mg (27%) of **12**.

Pure jaspamide (**11**) was isolated from a lipophilic extract of a yellow sponge *Jaspis* sp. collected off Makassar, Indonesia.[17] Its authentic nature was confirmed by NMR.[4,5] Jaspamide (**11**, 1.6 mg) was dissolved in 500 μL of MeOH and 100 μL of 1 M KOH, and the mixture was stirred at 40–50 °C for 5 h. Similar work-up as for **12** furnished 1.3 mg (79%) of **13**.

3.6.1. Compound 12. ^1H NMR ($CDCl_3$–CD_3OD, 9–1) δ 1.00 (d, 3H, J=6.8 Hz; H-15), 1.09 (d, 3H, J=6.1 Hz; H-25), 2.84 (dd, J=11.0, 14.6 Hz; H-17a), 2.98 (s, 3H; H-16), 3.25 (dd, J=5.6, 14.6 Hz; H-17b), 4.22 (m, 2H; H-10, 24), 4.61 (q, J=7.1 Hz; H-14), 5.33 (m; H-12), 6.76 (d, J=8.3 Hz; H-22), 7.00 (dd, J=1.9, 8.3 Hz; H-23), 7.46 (br s; H-19). For H-2 to 8-Me, see Table 2. ESIMS *m/z* 688 $[M-H]^-$, *m/z* 690 $[M+H]^+$, 712 $[M+Na]^+$.

3.6.2. Compound 13. ^1H NMR ($CDCl_3$–CD_3OD, 9–1) δ 0.78 (d, 3H, J=7.1 Hz; H-16), 2.60 (d, 2H, J=6.8 Hz; H-10), 2.94 (s, 3H; H-17), 3.18 (dd, J=10.7, 14.9 Hz; H-18a), 3.40 (m; H-18b), 4.59 (q, J=7.1 Hz; H-15), 5.22 (br; H-13), 5.26 (t, J=6.2 Hz; H-11), 6.60 (d, 2H, J=8.5 Hz; H-29, 31), 6.99 (d, 2H, J=8.5 Hz; H-28, 32), 7.04 (t, J=7.8 Hz; H-24), 7.11 (t, J=7.8 Hz; H-23), 7.27 (d, J=7.8 Hz; H-22), 7.48 (d, J=7.8 Hz; H-25). For H-2 to 8-Me, see Table 2. ESIMS *m/z* 725, 727 $[M-H]^-$, *m/z* 749, 751 $[M+Na]^+$, 771, 773 $[M+2Na-H]^+$.

3.7. Cell assay

NBT-T2 cells (BRC-1370) were purchased from Riken and cultured under a standard protocol using DMEM. Aliquots of test compounds in MeOH were added to culture wells

plated cells 1 day before. After incubating the sample wells for 1 or 2 days, the toxic effect of a drug was observed under a microscope. The IC_{50} values were measured by MTT colorimetric method. Cultured cells were inoculated into each well (24-well plate) with 1 mL of the medium. After preincubation (24 h, 37 °C, 5% CO_2), the sample solution was added to each well and it was incubated for 48 h. And then, MTT solution (100 μL, 5 mg/mL in PBS) was added to each well and incubated for 3 h. The medium was removed by aspiration. The residual formazan was dissolved in 1 mL of dimethylsulfoxide (DMSO). The resulting solution was diluted with DMSO (four times) and the absorbance was measured at 540 nm.

3.8. Actin polymerization/depolymerization assay

Prodan-labeled actin was prepared by the method described by G.M.[15] Polymerization of G-actin was carried out by making a Prodan-G-actin solution at 1 μM in F-buffer (100 mM KCl, 2 mM $MgCl_2$, 0.2 mM $CaCl_2$, 1 mM DTT, 0.1 mM ATP, 5 mM Tris, pH 8.0) in a cuvette. The time course of F-actin polymerization was recorded for 200 s using an excitation wavelength of 385 nm and emission at 490 nm in the presence of 1, 10, 20, 50, 100, and 200 nM of seragamide A (**1**), or without **1** as control. The depolymerization assay of Prodan-F-actin was performed by diluting a preformed 28 μM solution of Prodan-F-actin to 100 nM in G-buffer (0.2 mM $CaCl_2$, 1 mM DTT, 0.1 mM ATP, 5 mM Tris, pH 8.0). Time course experiments were similarly carried out as for polymerization in the presence of 0.05, 0.1, 1, and 10 nM of seragamide A (**1**) or without **1** as control.

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Synthesis of tetrathiafulvalene-annulated phthalocyanines

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Abstract—The synthesis of three new TTF-annulated phthalocyanine (Pc) derivatives **5a–c** are described. All of them have been characterized by elemental analysis, IR and UV–vis spectroscopy. In all cases, the incorporation of long and flexible aliphatic side-chains into the rigid TTF-annulated Pc core did not promote the formation of a discotic mesophase.

1. Introduction

Being a versatile class of functional dyes and pigments, phthalocyanines (Pcs) have been studied extensively over the last few decades.[1–2] Since they exhibit high thermal and chemical stability, well-defined optical absorption, semiconducting and photoconducting properties, and self-organizing abilities to form columnar mesophases, Langmuir–Blodgett (LB) multilayers, or aggregates in solution,[3–5] Pcs have been employed as subunits for the construction of functional materials. In particular, a great and growing interest in liquid crystalline Pc systems aroused because a columnar arrangement of Pc cores gives rise to a low dimensional conduction pathway and therefore can be considered as molecular wires, which can transport charge or excitons.[6–10] As a consequence, the mesophase structures of a number of Pcs with variations in the number, length, type and position of flexible side-chains, including linear alkyl, alkoxymethyl and alkoxy chains, have been investigated.[1,11] It has been demonstrated that in contrast to crystalline phases, liquid-crystalline phases are more suitable for applications in electronic devices due to their improved processing characteristics and self-healing of structural defects.[12]

Tetrathiafulvalene (TTF) and its derivatives can sequentially and reversibly be oxidized to the stable cation radicals and dications and therefore, they act as π-electron donor molecules.[13] Moreover, liquid crystalline TTF derivatives have been reported, in which nematic, smectic A and columnar phases were observed.[14]

Within this context, several Pcs linked with appended TTF moieties by various spacers have been reported in the last 10 years.[15–20] Interestingly, it has been found that covalent linkage of TTF units to a Pc system can lead to fluorescence quenching due to intramolecular charge transfer between TTF units and Pc*.[15] Noteworthy, so far only one example of a TTF-appended Pc shows a liquid crystalline behavior.[19] Based on an efficient synthetic approach to TTF-annulated Pc derivatives developed in our group,[21] much effort will be devoted to characterize new systems with peripheral substitutions.

In the present work, we describe the synthesis and properties of three new TTF-annulated Pc derivatives **5a–c**, substituted with four or eight long and flexible aliphatic chains at the periphery (Scheme 1). Such systems are of prime interest because the suitably functionalized derivatives could show a discotic liquid crystalline phase due to the increase in the aromatic core size and overall planarity of the molecules.

2. Result and discussion

The synthesis of **5a–c** required the preparation of the key phthalonitrile precursors **4a–c** (Scheme 2). The latter were obtained from the cross-coupling reaction of **3** with the corresponding 1,3-dithiole-2-thione derivatives **2**, bearing

Keywords: Synthesis; Tetrathiafulvalene-annulated phthalocyanines; Phthalonitrile derivatives; Liquid crystal.
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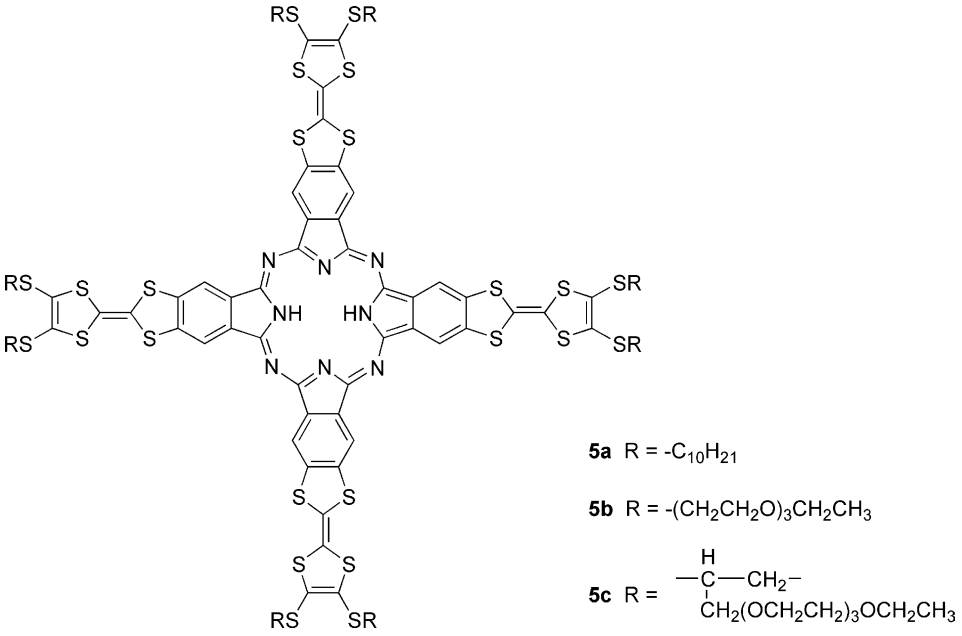
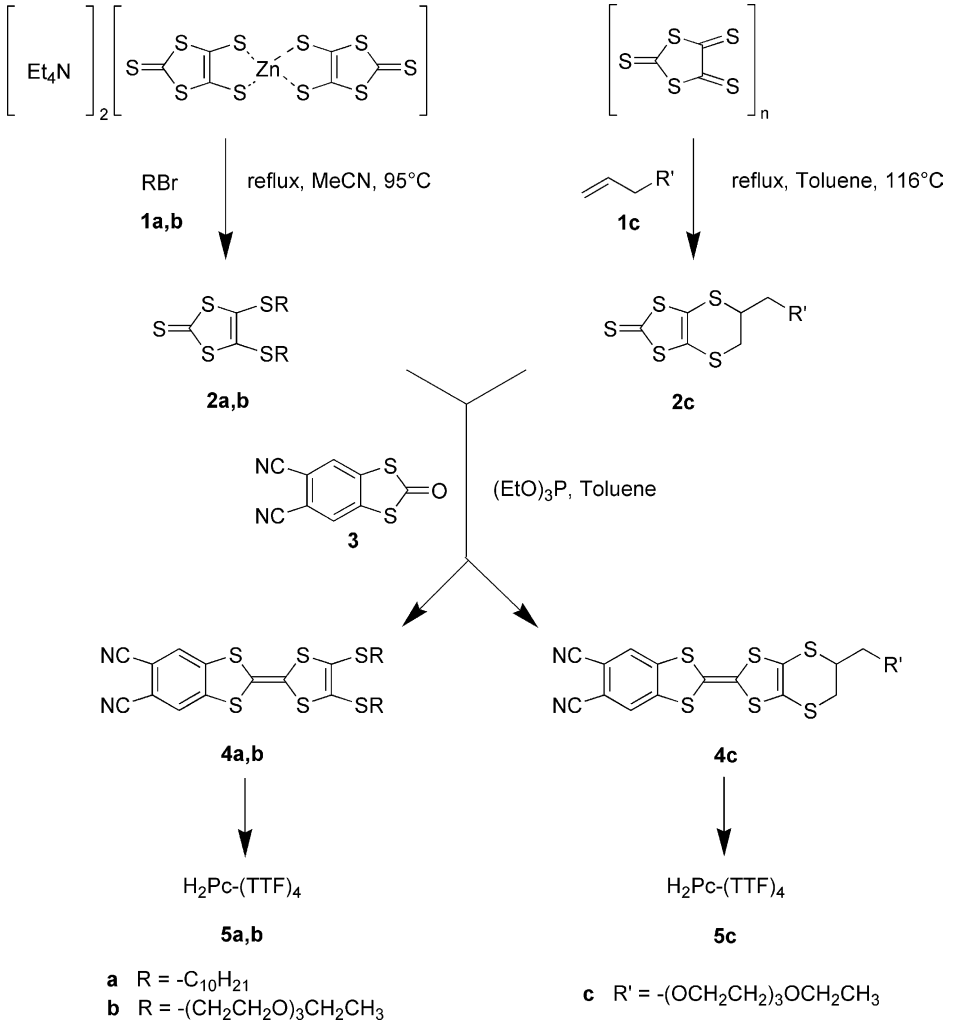


Scheme 1. Molecular structure of the TTF-annulated Pc derivatives.



Scheme 2. Synthesis of the tetrakis-TTF-annulated Pc derivatives.

the different flexible aliphatic chains. The thione intermediates **2a–c** were prepared by using two different strategies. The well-established substitution reaction of bis(tetraethylammonium)bis(1,3-dithiole-2-thione-4,5-dithiolate)zincate with the suitable bromide gave compounds **2a** and **2b** in high yields, while the Diels–Alder reaction of oligo(1,3-dithiole-2,4,5-trithione) with **1c** in toluene at 116 °C afforded compound **2c** in a good yield. The phosphite-mediated cross-coupling reaction of **3** with **2a–c** produced phthalonitrile intermediates **4a–c** in reasonable yields, and their tetramerization in the presence of lithium pentoxide at 120 °C under nitrogen resulted in the formation of the corresponding metal-free Pc derivatives **5a–c**.

All new precursors have been purified by column chromatography and fully characterized by elemental analysis, NMR, IR and MS as listed in the Section 4. Compound **4a** is soluble in THF and slightly soluble in $CHCl_3$, CH_2Cl_2 and ether, **4b** soluble in $CHCl_3$, CH_2Cl_2, THF, CH_3CN, acetone, DMSO, EtOAc and ether, and **4c** soluble in $CHCl_3$, CH_2Cl_2, THF, DMSO, EtOAc and slightly soluble in CH_3CN.

It has been noted that the order of the melting point values for the compounds **4** of similar side-chain length is as follows: alkyl > oxyethylene. Quite probably, the difference is related to the greater rigidity of the alkyl chains.

Suitable crystals of compound **4a** for a X-ray diffraction study could be obtained by recrystallization from acetonitrile. This compound crystallizes in a triclinic space group (*P*-1) and an ORTEP[22] plot of the molecule with the atomic numbering scheme is shown in Figure 1. As expected, the TTF-fused phthalonitrile moiety is essentially planar with a rms deviation of 0.05 Å from the least-squares plane through all atoms comprising the unit. This moiety is nearly perpendicular to the mean plane consisting of the aliphatic side-chains with a dihedral angle of 83°.

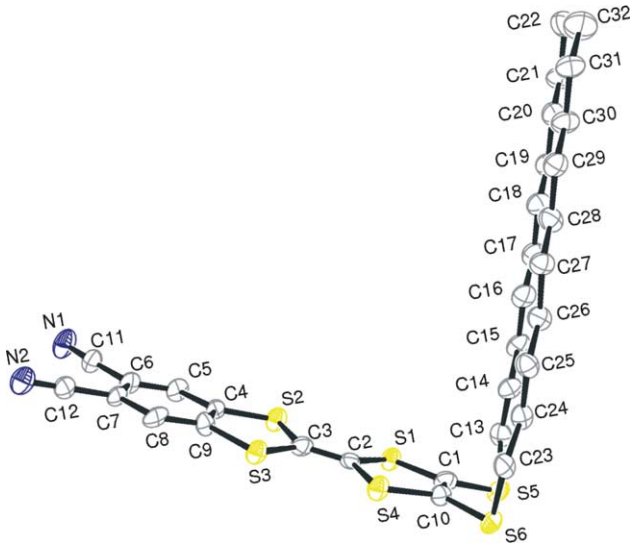


Figure 1. Molecular structure of compound **4a** (50% probability ellipsoids). Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: C1–S5 1.730; C1–S1 1.765; C2–C3 1.328; C2–S1 1.740; C2–S4 1.764; C3–S3 1.756; C3–S2 1.773; C4–C9 1.400; C4–S2 1.739; C9–S3 1.736; C10–S6 1.756; C10–S4 1.761. Selected bond angles [°]: S3–C3–S2 114.24; S1–C2–S4 114.16; C9–C8–C7 119.40; C8–C7–C6 119.76; C5–C6–C7 120.10; C6–C5–C4 120.78; C5–C4–C9 119.29; C8–C9–C4 120.60.

In the crystal lattice of **4a**, along the *a*-axis, the molecules are arranged in layers exhibiting C8-H···N1 type of hydrogen bonds [C···N 3.222 Å]. Along the *b* direction, molecules related by a center of symmetry are mutually shifted and form dimers via a C–H···N hydrogen bond, C14-H14B···N2 [C···N 3.593 Å], with an interplanar separation of 3.46 Å (in the dimer) and 3.39 Å (between adjacent dimers), respectively (Fig. 2). Obviously, the resulting peculiar stacks are dominated by H-bonds and van der Waals forces between the side-chains.

The Pc derivative **5a** is soluble in $CHCl_3$, CH_2Cl_2, THF and ethers, and **5b** is soluble in $CHCl_3$, CH_2Cl_2, THF, acetone, DMSO, EtOAc, ethers and slightly soluble in CH_3CN. In contrast, **5c** is very insoluble in most common organic solvents. In the mass spectrum of **5a**, the monoisotopic mass was observed at *m/z* 2594. An additional peak was found at *m/z* 2312, corresponding to the fragment of **5a** with two missing side-chains. The mass spectrum of **5b** displays the monoisotopic molecular peak at *m/z* 2754. The TGA measurements reveal that the compounds contain solvent molecules in agreement with the elemental analysis results.

For the octasubstituted TTF-annulated Pcs **5a** and **5b**, ^1H NMR spectra are not available due to the high aggregation of the Pcs, a fact which is frequently encountered at the concentrations used for NMR measurements.[23] Their UV–vis spectra in CH_2Cl_2 exhibit characteristic, rather broad Q-band absorptions of $\pi \rightarrow \pi^*$ transitions at 616 and 627 nm, respectively. For the tetra-substituted compound **5c**, solution properties are impossible to be investigated owing to its extreme insolubility.

In order to address the electrochemical properties, **5a** was studied by cyclic voltammetry. A variety of experiments under different conditions have been carried out and the discrepancies of cyclic voltammograms are observed due to strong aggregation phenomena in solutions, which was reported in the literature.[24] The best cyclic voltammogram obtained is shown in Figure 3. Two reversible oxidation processes were observed at 0.16 and 0.57 V (vs Fc^+/Fc), which correspond to the formation of the radical tetracation and octacation species of the TTF moieties and are comparable to those of its analogue with propyl groups at the periphery.[21] However, a redox wave in the negative direction, presumably arising from the reduction of the Pc macrocycle, is hardly to be assigned. Unfortunately, more detailed information can not be provided by differential-pulse voltammetry (DPV), thin-layer cyclic voltammetry, and spectroelectrochemical measurements because of a high degree of aggregation.

Finally, the Pc derivatives **5a–c** as well as the precursors **4a–c** were investigated by DSC measurements. In all cases, the attachment of long and flexible aliphatic side-chains to the TTF moieties and also to the TTF-annulated Pc cores did not promote the formation of a discotic liquid crystalline phase. Noteworthy, **4b** exhibits two peaks at 86 and 119 °C, but no mesophase could be observed by the polarized optical microscope.

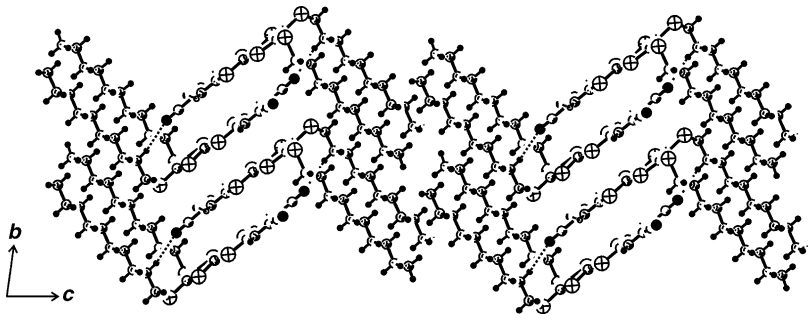


Figure 2. *bc* Projection of the crystal structure of **4a**, showing the formation of hydrogen bonded (dashed lines) dimers.

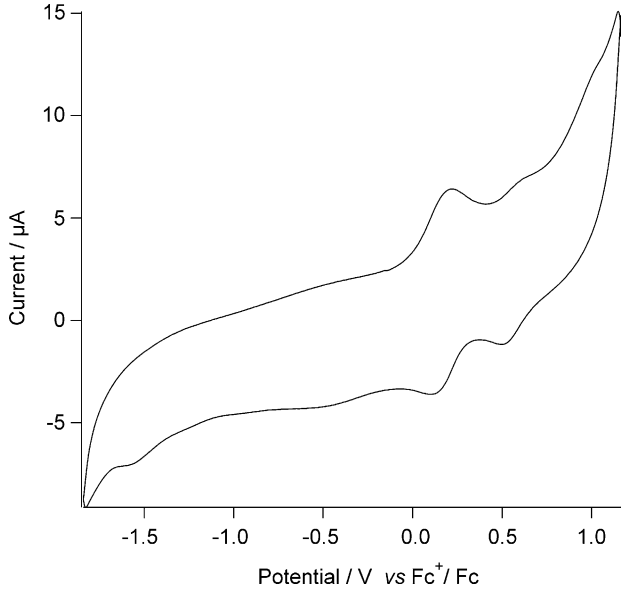


Figure 3. Cyclic voltammogram for **5a**.

3. Conclusion

We achieved the syntheses of new tetra- and octa-substituted TTF-annulated Pc derivatives with long and flexible alkyl or oxyethylene chains at the periphery. However, in all cases, no mesophases were observed. Probably, branching of the side-chain could introduce disorder and hence a decrease in the transition temperature. Therefore, studies are underway to prepare TTF-annulated Pc derivatives appropriately functionalized with branched hydrocarbon substituents to further investigate their liquid crystalline behavior.

4. Experimental

4.1. Equipment

^{1}H NMR spectra were obtained on a Bruker AC 300 and AC 400 spectrometer operating at 300.18 MHz: chemical shifts reported in parts per million relative to TMS. The following abbreviations were used s, singlet; d, doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were performed on a Bruker AC 500 spectrometer operating at 100.61 MHz. UV–vis absorption spectra were recorded on a Perkin–Elmer Lambda 10 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1110 CHN apparatus. Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer using KBr pellets or with a JACSO FT/IR-460Plus spectrometer in the case of oily substances. EI spectra were recorded using an Auto SpecQ spectrometer. MALDI-MS was carried out with a FTMS 4.7 TBioAPEX II TOF apparatus. Cyclic voltammetric measurements were conducted on a Metrohm VA-Stand 663 electrochemical analyser. All oxidation potentials were determined under N_2 in CH_2Cl_2 versus Ag/AgCl at room temperature. Measurements have been done at a scan rate of 100 mV s^{-1} using 0.1 M Bu_4NPF_6 as electrolyte and Pt as working electrode. Solid state measurements for thermogravimetry were performed with a Mettler TG 50 system and differential scanning calorimetry with a Mettler DSC 25 apparatus.

4.2. Crystallography

An orange plate-like crystal of compound **4a** was mounted on a Stoe Mark II-Imaging Plate Diffractometer System[25] equipped with a graphite-monochromator. Data collection was performed at −100 °C using Mo Kα radiation (λ= 0.71073 Å). 128 Exposures (10 min per exposure) were obtained at an image plate distance of 135 mm, 128 frames with ϕ=0° and 0<ω<180° with the crystal oscillating through 1.4° in ω. The resolution was D_{min}–D_{max} 23.99–0.82 Å. The structure was solved by direct methods using the program SHELXS-97[26] and refined by full matrix least squares on F^2 with SHELXL-97.[27] The hydrogen atoms were included in calculated positions and treated as riding atoms using SHELXL-97 default parameters. All non-hydrogen atoms were refined anisotropically. No absorption correction was applied. Crystal data has been deposited at the Cambridge Crystallographic Data Centre, reference CCDC 290264. Copy 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).

4.3. Materials

All reagents and solvents were of commercial quality and distilled or dried when necessary using standard procedures. All reactions were carried out under inert atmosphere unless otherwise stated. Bis(tetraethylammonium)bis(1,3-dithiole-2-thione-4,5-dithiolate)-zincate,[28] oligo(1,3-dithiole-2,4,5-trithione),[28] 5,6-dicyanobenzene-1,3-dithiole-2-one **3**[21] and 1-bromo-3,6,9-trioxaundecane **1b**[29] were prepared according to literature procedures.

4.3.1. 4,7,10,13-Tetraoxapentadecene (1c). A mixture of triethylenglycolmonoethylether (2.96 ml, 16.9 mmol), NaOH aqueous solution (6 N, 14.6 ml) and tetrabutylammoniumhydrogensulfat (0.57, 1.68 mmol) was stirred for 30 min at 30 °C under nitrogen. Allylchloride (4.15 ml, 51 mmol) was then added dropwise and stirred for an additional 1 h. The resulting solution was heated up to 45 °C and stirred overnight. The product was extracted with ethyl acetate and washed with water. The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2) with a gradient of 100–0% hexane in EtOAc. Yield: 3.19 g (88%), colorless oil. MS (EI): *m/z* 218 (M^+, 13%). ^{1}H NMR ($CDCl_3$) δ: 5.75–5.63 (m, 1H), 5.02–4.92 (m, 2H), 3.82–3.79 (m, 2H), 3.49–3.27 (m, 14H), 1.01 (t, $J=7.05$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 134.73, 116.94, 72.15, 70.60, 70.57, 70.54, 69.76, 69.37, 66.54, 15.07. IR (thin film, cm^{-1}): 2862, 1454, 1348, 1293, 1247, 1105, 995, 921, 847.

4.3.2. 4,5-Bis(decylthio)-1,3-dithiole-2-thione (2a). Bis-(tetraethylammonium)bis(1,3-dithiole-2-thione-4,5-dithiolate)zincate (2.5 g, 3.48 mmol) was dissolved in 45 ml acetonitrile and degassed under N_2 for 20 min. Then, 1-bromodecane (3.5 ml, 14.84 mmol) was carefully added to the dark red solution. This mixture was refluxed for at least 4 h at 95 °C. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2) eluting initially with hexane and then with dichloromethane, to afford **2a** as a yellow solid. Yield: 2.83 g (85%), mp 41 °C. Anal. Calcd for $C_{23}H_{42}S_5$: C 57.68, H 8.84; found C 57.98, H 9.00. MS (EI): *m/z* 478 (M^+, 59%). ^{1}H NMR ($CDCl_3$) δ: 2.88 (t, $J=7.34$ Hz, 4H), 1.69–1.63 (m, 4H), 1.42–1.25 (m, 28H), 0.89 (t, $J=6.69$ Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 211.48, 136.34, 36.75, 31.85, 29.64, 29.50, 29.45, 29.26, 29.05, 28.48, 22.65, 14.08. IR (KBr, cm^{-1}): 2919, 2849, 1471, 1059, 1029, 889, 719.

4.3.3. 4,5-Bis(3,6,9-trioxaundecylthio)-1,3-dithiole-2-thione (2b). Bis(tetraethylammonium)bis(1,3-dithiole-2-thione-4,5-dithiolate)zincate (0.6 g 0.84 mmol) was dissolved in 10 ml acetonitrile and degassed for 15 min. Then, 1-bromo-3,6,9-trioxaundecane (0.86 g, 3.6 mmol) was carefully added to the dark red solution. This mixture was refluxed for at least 4 h at 95 °C. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, initially with pure hexane and then with ethyl acetate as eluting solvent), to afford **2b** as a yellow oil. Yield: 0.727 g (83%). Anal. Calcd for $C_{19}H_{34}O_6S_5$: C 43.99, H 6.61; found C 44.60, H 6.87. MS (EI): *m/z* 518 (M^+, 19%). ^{1}H NMR ($CDCl_3$) δ: 3.65 (t, $J=$ 6.39 Hz, 4H), 3.59–3.48 (m, 20H), 3.08 (t, $J=6.40$ Hz, 4H), 1.22 (t, $J=6.96$ Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 211.41, 136.95, 71.17, 71.05, 70.97, 70.26, 70.22, 67.04, 36.54, 15.57. IR (thin film, cm^{-1}): 2970, 2862, 1459, 1348, 1285, 1244, 1102, 1060, 941, 887, 847.

4.3.4. 4,5-(2,5,8,11-Tetraoxatridecylethylenedithio)-1,3-dithiole-2-thione (2c). 4,7,10,13-Tetraoxapentadecene (2.5 g 11.4 mmol) was dissolved in 25 ml toluene and stirred for 20 min at 30 °C. Then, 4.4 g of oligo(1,3-dithiole-2,4,5-trithione) was added. The orange suspension was stirred for another 20 min at 30 °C, and then heated up to 116 °C and refluxed for at least 4 h. A dark brown solution was formed, cooled down to room temperature, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, EtOAc/hexane 2:1). Yield: 2.54 g (54%), a yellow oil. Anal. Calcd for $C_{14}H_{22}O_4S_5$: C 40.55, H 5.35; found C 40.66, H 5.34. MS (EI): *m/z* 414 (M^+, 17%). ^{1}H NMR ($CDCl_3$) δ: 3.91–3.81 (m, 2H), 3.67–3.48 (m, 15H), 3.41–2.28 (m, 2H), 1.22 (t, $J=7.06$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 207.79, 123.38, 122.11, 71.89, 70.95, 70.63, 70.57, 70.42, 69.75, 66.56, 42.43, 31.29, 15.10. IR (thin film, cm^{-1}): 2861, 1736, 1486, 1348, 1295, 1237, 1105, 1055, 924, 887, 867, 847, 787.

4.3.5. 5,6-Dicyano-2-(4,5-bis(decylthio)-1,3-dithio-2-ylidene)-benzo[*d*]-1,3-dithiole (4a). Compounds **3** (50 mg, 0.23 mmol) and **2a** (218 mg, 0.46 mmol) were dissolved in a mixture of triethyl phosphite (0.41 ml) and toluene (2.5 ml). This solution was heated to 120 °C and refluxed for 4 h. After cooling to room temperature, a red precipitate was formed and filtered off. The crude product was purified by column chromatography on silica gel eluting with a gradient of 100–0% hexane in CH_2Cl_2 to afford compound **4a** as an orange solid. Yield: 60.2 mg (40%), mp 178 °C. Anal. Calcd for $C_{32}H_{44}N_2S_6$: C 59.21, H 6.83, N 4.32; found C 59.25, H 6.90, N 4.06. MS (EI): *m/z* 648 (M^+, 44%). ^{1}H NMR ($CDCl_3$) δ: 7.51 (s, 2H), 2.84 (t, $J=7.25$ Hz, 4H), 1.67–1.57 (m, 4H), 1.41–1.25 (m, 28H), 0.89 (t, $J=6.69$ Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 145.05, 128.41, 125.35, 118.01, 115.14, 113.38, 104.49, 36.85, 32.3, 30.12, 29.95, 29.90, 29.71, 29.50, 28.88, 23.08, 14.51. IR (KBr, cm^{-1}): 2923, 2849, 2235, 1567, 1465, 1128, 873, 773, 726.

4.3.6. 5,6-Dicyano-2-(4,5-bis(3,6,9-trioxaundecylthio)-1,3-dithio-2-ylidene)-benzo[*d*]-1,3-dithiole (4b). Compounds **3** (230 mg, 1.05 mmol) and **2b** (1.1 g, 2.12 mmol) were dissolved in a mixture of triethyl phosphite (1.88 ml) and toluene (7.5 ml). The resulting solution was refluxed at 120 °C for 4 h. After cooling to room temperature, hexane was added to the brownish solution. A red solid was formed immediately, filtered off and washed with hexane. The crude product was purified by column chromatography on silica gel, initially with hexane and then with EtOAc as eluent. Compound **4b** was obtained as a red solid. Yield: 185.2 mg (26%), mp 119 °C. Anal. Calcd for $C_{28}H_{36}N_2O_6S_6$: C 48.81, H 5.27, N 4.07; found C 48.98, H 5.27, N 3.82. MS (EI): *m/z* 688 (M^+, 79%). ^{1}H NMR ($CDCl_3$) δ: 7.53 (s, 2H), 3.64–3.48 (m, 24H), 3.04 (t, $J=6.68$ Hz, 4H), 1.22 (t, $J=6.9$ Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 144.88, 128.52, 125.42, 117.27, 115.12, 113.43, 105.54, 71.17, 70.97, 70.38, 70.22, 67.07, 36.01, 15.57. IR (KBr, cm^{-1}): 2864, 2232, 1565, 1456, 1354, 1246, 1115, 1037, 875, 859, 774, 725.

4.3.7. 5,6-Dicyano-2-(4,5-(2,5,8,11-tetraoxatridecylethylenedithio)-1,3-dithio-2-ylidene)-benzo[*d*]-1,3-dithiole (4c). Compound **2c** (0.514 g 1.23 mmol) was dissolved in a mixture of toluene (5.5 ml) and triethyl phosphite (1.14 ml) and stirred for 5 min at 30 °C. 5,6-Dicyanobenzene-1,3-dithiole-2-one was added. The mixture was heated up to 115 °C and refluxed for 3 h. After cooling down to room temperature, a red solid was formed upon the addition of hexane. After filtration, the red solid was washed thoroughly with hexane and purified by column chromatography on

silica gel, initially with hexane and then with EtOAc. Yield: 223 mg (55%), mp 117 °C. Anal. Calcd for $C_{23}H_{24}N_2O_4S_6$: C 47.24, H 4.14, N 4.79; found C 47.40, H 4.12, N 4.51. MS (EI): *m/z* 584 (M^+, 39%). ^{1}H NMR ($CDCl_3$) δ: 7.53 (s, 2H), 3.89–3.76 (m, 2H) 3.68–3.48 (m, 15H), 3.33–3.19 (m, 2H), 1.22 (t, J=7.07 Hz, 3H). IR (KBr, cm^{-1}): 2905, 2873, 2229, 1565, 1458, 1348, 1244, 1128, 1102, 964, 885, 773.

4.3.8. 2,3,9,10,16,17,23,24-Tetrakis[4′,5′-bis(decylthio)-tetrathiafulvalene]phthalocyanine (5a). Lithium metal (33.4 mg, 4.81 mmol) was dissolved in 1-pentanol (2.6 ml) at 60–80 °C. To this lithium pentoxide solution was added compound **4a** (30 mg, 0.046 mmol). The mixture was heated up to 120 °C and refluxed for 5 h. The color of the solution turned within 15 min from red to an intensive green. The green solution was allowed to cool down to room temperature. A mixture of ethanol (10 ml) and glacial acetic acid (10 ml) was added. The resulting suspension was kept overnight. A dark green solid was obtained by decantation and centrifugation. The crude product was purified by washing with a combination of water, ethanol and acetone. The solid was dried at 45 °C and also in vacuo. Yield: 20.8 mg (66%). It decomposes at 300 °C. Anal. Calcd for $C_{128}H_{178}N_8S_{24}\cdot 5H_2O$: C 57.18, H 7.04, N 4.17; found C 56.73, H 6.62, N 3.68. MS (MALDI, dithranol as matrix): *m/z* 2594 (M^+). UV–vis λ_{max} (dichloromethane, $\varepsilon\times 10^{-3}$ M^{-1} cm^{-1}): 615.7 (51.9), 356.79 (76.3), 305.79 (71.2). IR (KBr, cm^{-1}): 2923, 2853, 1458, 1429, 1407, 1376, 1324, 1071, 1022, 870, 776, 742, 720.

4.3.9. 2,3,9,10,16,17,23,24-Tetrakis[4′,5′-bis(3,6,9-trioxaundecylthio)tetrathiafulvalene]phthalocyanine (5b). Lithium metal (39.44 g, 5.68 mol) was dissolved in 1-pentanol (3.2 ml) at 60–80 °C. To this lithium pentoxide solution was added compound **4b** (40 mg, 0.058 mmol). The mixture was heated to 120 °C and stirred for 5 h. After cooling to room temperature, a mixture of ethanol (10 ml) and glacial acetic acid (10 ml) was added to the green solution. The solution was allowed to stand overnight and neutralized with aqueous NaOH solution. After extraction with CH_2Cl_2 (50 ml), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was washed with a mixture of hexane and ethyl acetate (15/1). The green sticky compound was dried at 45 °C and also in vacuo. Yield: 42.07 mg (26%). It decomposes at 285 °C. Anal. Calcd for $C_{112}H_{146}N_8O_{24}S_{24}\cdot 5H_2O$: C 47.23, H 5.52, N 3.93; found C 46.82, H 4.98, N 3.53. MS (MALDI, dithranol as matrix): *m/z* 2754 (M^+). UV–vis λ_{max} (dichloromethane, $\varepsilon\times 10^{-3}$ M^{-1} cm^{-1}): 627.0 (56.1), 358.64 (79.2), 308.70 (68.3). IR (KBr, cm^{-1}): 3438, 2863, 1565, 1409, 1377, 1349, 1112, 1072, 1023, 776, 740, 680.

4.3.10. 2,3,9,10,16,17,23,24-Tetrakis[4′,5′-(2,5,8,11-tetraoxatridecylethylenedithio)tetrathiafulvalene]phthalocyanine (5c). Lithium metal (23.3 mg, 3.35 mmol) was dissolved in 1-pentanol (1.90 ml) at 60–80 °C. To this lithium pentoxide solution was added compound **4c** (20 mg, 0.034 mmol). The mixture was heated up to 120 °C and stirred for 5 h. The color of the resulting solution changed from red over brownish to green. Then, the solution was allowed to cool down to room temperature and a mixture of hexane (10 ml) and glacial acetic acid (10 ml) was added. The mixture was kept overnight. A dark green solid was obtained by centrifugation. The crude product was purified by washing with a combination of hexane and ethylacetate. The solid was dried at 45 °C and also in vacuo. Yield: 9 mg (45%). It decomposes at 150 °C. Anal. Calcd for $C_{92}H_{98}N_8O_{16}S_{24}\cdot C_6H_{14}$: C 48.48, H 4.65, N 4.62; found C 47.98, H 4.36, N 4.36. IR (KBr, cm^{-1}): 2861, 1728, 1452, 1406, 1372, 1106, 1071, 1021, 934, 875, 771, 678.

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Synthesis of 5,8-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one

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Abstract—The synthesis of the title compound, which shares its skeleton with a number of biologically active natural products, is described. The key steps are construction of a 3,4-disubstituted furan by a tandem Diels–Alder-retro-Diels–Alder reaction of an alkyne with 4-phenyloxazole, and an intramolecular Friedel–Crafts acylation.

1. Introduction

The naphtho[2,3-*c*]furan-4(9*H*)-ones, represented by the parent compound **1** (Fig. 1), comprise a small group of natural and synthetic products displaying diverse biological activity. The chemistry of this class of compounds and their more common congeners, the naphtho[2,3-*c*]furan-4,9-diones (**2**), has recently been comprehensively reviewed.[1]

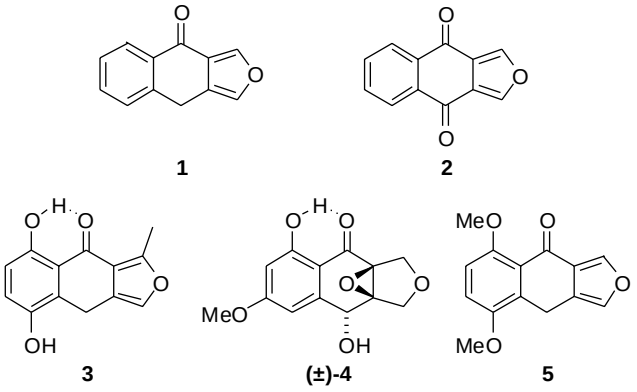

Figure 1.

Previous syntheses of natural products containing the naphtho[2,3-*c*]furan-4(9*H*)-one moiety include that of MS-444 (**3**), which involved a key Michael–Dieckmann annulation,[2] and racemic arthrinone [(±)-**4**] and co-occuring metabolites, which made use of a Dieckmann condensation (Fig. 1).[3] Herein, we detail studies of alternative synthetic approaches to the naphtho[2,3-*c*]furan-4(9*H*)-one ring system, culminating in the synthesis of 5,8-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one (**5**).

2. Results and discussion

The *o*-quinonedimethide **7**, generated thermally from the protected benzocyclobutenol **6**,[†] reacts regiospecifically with α,β-unsaturated ketones **8** (R = sugar residues) to give Diels–Alder adducts **9** as mixtures of stereoisomers (Scheme 1).[17] We proposed that a similar reaction of **7** with an appropriate acetylenic dienophile (**10**) would afford the adduct **11**, which could, in principle, be elaborated to give the natural product 5-hydroxynaphtho[2,3-*c*]furan-4(9*H*)-one (**12**)[18] (Scheme 1).

As a model system for the route depicted above, and as a means to access the unknown parent naphtho[2,3-*c*]furan-4(9*H*)-one (**1**), we decided to examine the reaction of the acetylenic dienophile **15** with the TBS-protected benzocyclobutenol **17**.[17] The dienophile **15** was conveniently prepared by quenching the dilithium salt **14** of propargyl alcohol **13** with methyl chloroformate (Scheme 2). The methyl ketone **16** required for the synthesis of the natural product **12** was similarly obtained when **14** was quenched with acetic anhydride.

Thermal generation of the *o*-quinonedimethide **18** in the presence of the acetylenic dienophile **15** gave the expected adduct **19**, along with the naphthalene **20** resulting from transannular elimination of *t*-butyldimethylsilanol

Keywords: Naphtho[2,3-*c*]furan-4(9*H*)-ones; Tandem Diels–Alder–retro-Diels–Alder; Intramolecular Friedel–Crafts acylation; *o*-Quinonedimethide.
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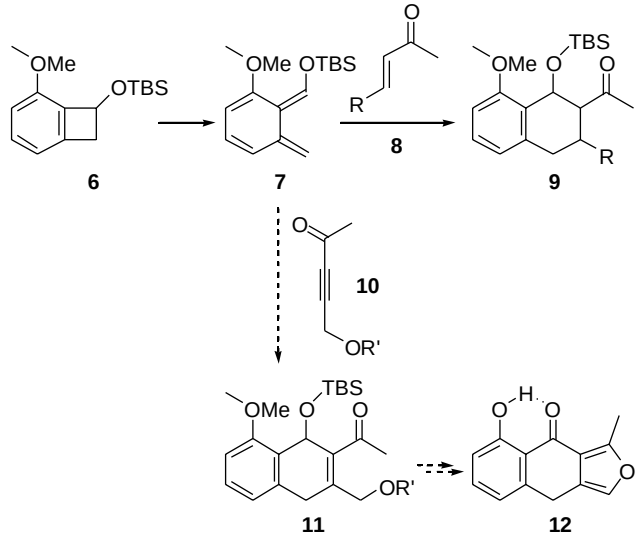
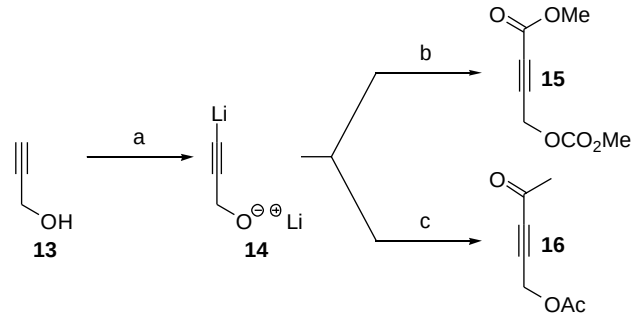
[†] The chemistry of benzocyclobutenes[4–10] and *o*-quinonedimethides[11–16] has been extensively reviewed.

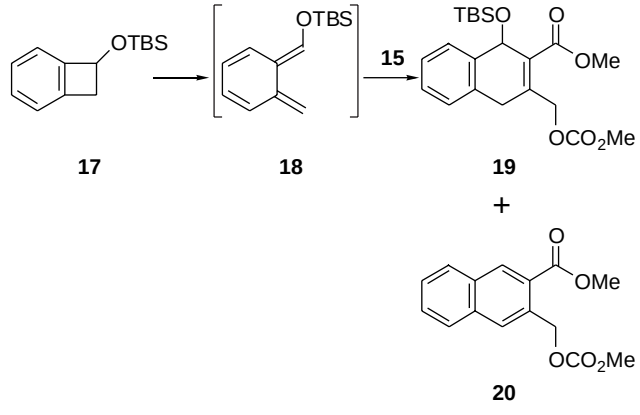


Scheme 1.



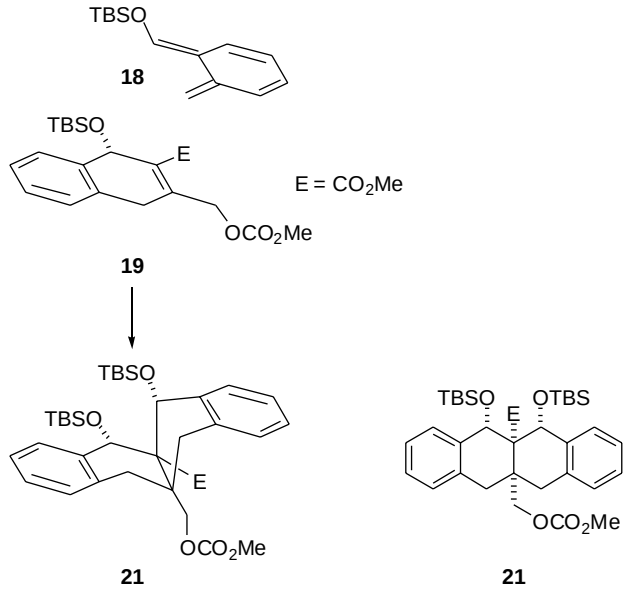
Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, −78°; (b) methyl chloroformate, 44%; (c) Ac_2O, 47%.

(Scheme 3). The ^{1}H NMR spectrum of **19** was obtained, but further characterisation was impossible due to the facile aromatisation. A similar elimination of methanol from the adducts of the methoxy substituted *o*-quinonedimethides with variously substituted acetylenes has been used intentionally for the regiospecific construction of substituted naphthalenes.[19]



Scheme 3. Reagents and conditions: PhMe, steam bath, 32 h, 54% (**19**), 26% (**20**).

On a separate occasion, the reaction of the *o*-quinonedimethide **18** with the dienophile **15** produced a small quantity of the product **21** arising from capture of a second molecule of **18** by the initial adduct **19** (Scheme 4). The ^{1}H NMR spectrum of **21** showed only one set of TBS signals implying a *cis* relationship of these groups. Given the preference for *endo* addition in Diels–Alder reactions, and the probable approach of the diene **18** *anti* to the bulky silyl group of the initial product **19**, the all *cis* configuration **21** is most likely for this product.

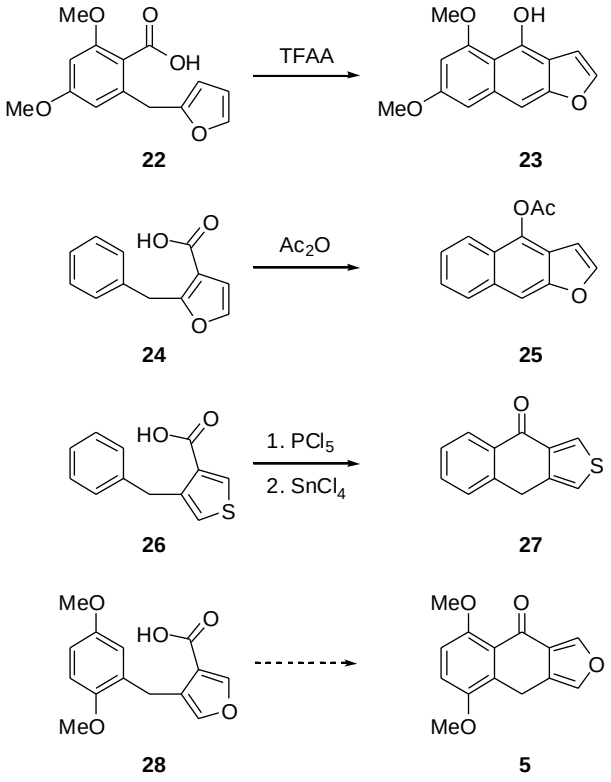


Scheme 4.

Unfortunately, attempts to elaborate **19** also resulted in aromatisation. For example, reduction with diisobutylaluminium hydride (DIBAL) gave only naphthalene-2,3-dimethanol[20] in 82% yield. Accordingly, the route was abandoned.

Several published routes to naphtho[2,3-*b*]furans have involved an intramolecular Friedel–Crafts acylation step late in the synthesis (Scheme 5). Both benzoic acids (**22**→**23**)[21] and furoic acids (**24**→**25**)[22,23] have been used. Although the intramolecular acylation concept has not been adapted to the synthesis of naphtho[2,3-*c*]furan-4(9*H*)-ones, it has been applied to the synthesis of naphtho[2,3-*c*]thiophene **27**.[24] Given these precedents, we were confident that the naphtho[2,3-*c*]furan-4(9*H*)-one skeleton would be accessible via an intramolecular Friedel–Crafts acylation. The furoic acid **28** was chosen to test this hypothesis.

We envisaged that the furoic acid **28** necessary for the intramolecular Friedel–Crafts acylation could be obtained via a tandem Diels–Alder-retro-Diels–Alder reaction[25,26] of the alkyne **31** and 4-phenyloxazole **34** (Scheme 6). However, lithiated ethyl propiolate (**29**)[27] failed to react with the benzyl bromide **30**,[28] even in the presence of HMPA,[29] presumably due to competing auto-condensation

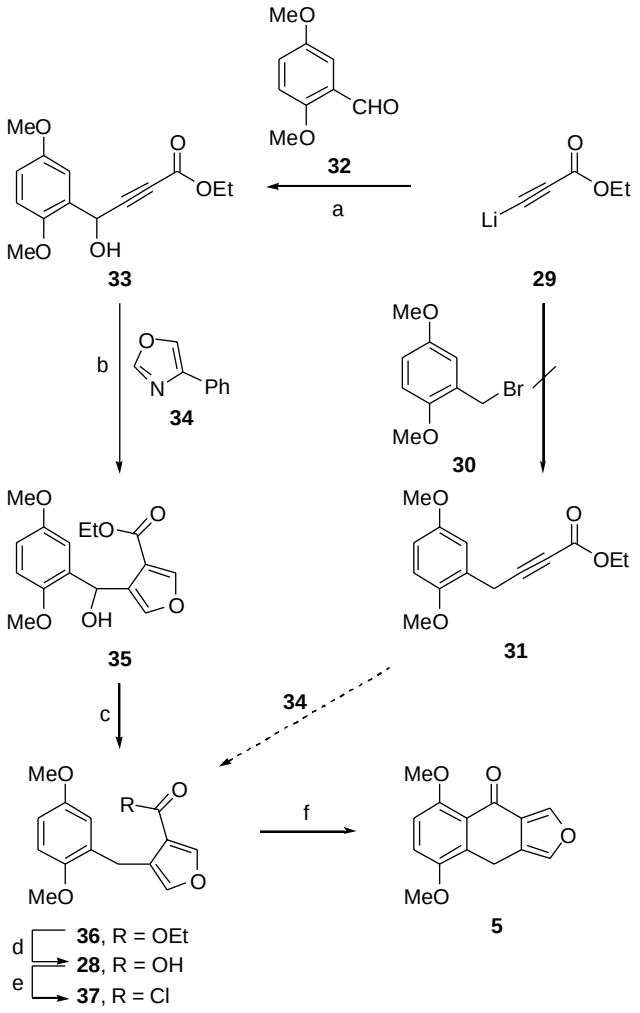


Scheme 5.

of **29**. The lithium acetylide did react smoothly with 2,5-dimethoxybenzaldehyde (**32**) and the resulting alcohol **33** underwent the expected cycloaddition–cycloreversion with 4-phenyloxazole (**34**) to give the furan **35**.

Hydrogenolysis of the benzylic alcohol **35** was complicated by concomitant reduction of the furan ring, while **35** failed to react with lithium in liquid ammonia[30] and decomposed with sodium borohydride/TFA.[31] Fortunately, with TMSI[22] the deoxygenation was complete within 10 min, giving a quantitative yield of the diarylmethane **36**. Hydrolysis of the ethyl ester then gave the target acid **28**.

Attempts to effect the cyclisation of **28** with TFAA, alone[23] or in conjunction with TFA,[32] were unsuccessful. Oxalyl chloride has been used to bring about the cyclisation of an activated aromatic acid,[33] but attempts with this reagent were also unsuccessful in the present case. The acid chloride **37** was resistant to cyclisation with graphite catalysis[33] in refluxing chlorobenzene and decomposed with aluminium chloride in 1,2-dichloroethane.[1] Stannic chloride is a milder reagent than aluminium chloride[34] and has been used with success in intramolecular Friedel–Crafts acylations involving furans.[35] An advantage of this Lewis acid is that when the acid chlorides are prepared with phosphorus pentachloride, it may be added directly to the reaction mixture, obviating the need for a purification step.[34] Accordingly, the acid **28** was converted into the acid chloride **37** with phosphorus pentachloride and the reaction mixture was transferred to a solution of stannic chloride in cold benzene. Obligingly, after workup, the



Scheme 6. Reagents and conditions: (a) 1. THF, −78°; 2. AcOH, −78°–rt, 71% (82% based on recovered **32**); (b) 200°, 72%; (c) NaI, TMSCl, MeCN, quant.; (d) 1. NaOH, MeOH, 2. H_3O^+, 97%; (e) PCl_5, PhH, Δ, (or $SOCl_2$, PhMe, Δ); (f) $SnCl_4$, 5°–rt, 89% from **28**.

cyclised product 5,8-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one **5** was isolated in excellent yield.

3. Conclusion

5,8-Dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one **5**, which shares its skeleton with a number of biologically active natural products, was prepared in six steps and 44% overall yield. The synthesis includes construction of a 3,4-disubstituted furan by a tandem Diels–Alder-retro-Diels–Alder reaction of an alkyne with 4-phenyloxazole, and an intramolecular Friedel–Crafts acylation.

4. Experimental

4.1. General

All solvents were distilled prior to use; anhydrous solvents and reagents were distilled under N_2. MeCN, benzene, DCM, 1,2-dichloroethane and toluene were dried by

refluxing with calcium hydride. DMF, was dried over 4 Å molecular sieves. THF was distilled from potassium benzophenone ketyl. Propargyl alcohol and methyl chloroformate were dried over anhydrous K_2CO_3. Petrol denotes the hydrocarbon fraction distilling from 64–67 °C.

All reaction temperatures refer to bath temperatures. Kugelrohr distillation temperatures refer to the oven temperature. Organic extracts were dried over anhydrous $MgSO_4$ and then filtered. The concentrations of hexane solutions of *n*-BuLi were determined by titration against diphenylacetic acid in anhydrous THF.

Rapid silica filtration refers to chromatography on a short column of silica (BDH, for flash chromatography, 40–63 μm) in a sintered glass funnel, in which the eluent is sucked through the column under vacuum. Elutions were generally performed with increasing percentages of EtOAc in petrol up to the values shown in parentheses. Analytical TLC was performed on Whatman flexible plates (250 μL layer, Al Sil G/UV254). Spots were visualised under UV light and by staining with a 6% (w/v) solution of ceric sulfate in 2 M sulfuric acid followed by heating.

Melting points were measured on a Kofler hot stage melting point apparatus and are uncorrected. Microanalyses were performed by MHW laboratories (Arizona). Mass spectra were recorded on a VG Autospec instrument using a direct insertion probe and electron impact ionisation (EI) or fast atom bombardment (FAB) where indicated. Nuclear magnetic resonance (NMR) spectra were acquired on Gemini 200 (200 MHz, ^{1}H), Bruker AM300 (300 MHz, ^{1}H; 75.5 MHz, ^{13}C) and Bruker 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C) instruments. Spectra were recorded in $CDCl_3$ unless otherwise indicated. Chemical shift values are expressed in ppm, relative to $CHCl_3$ (^{1}H, 7.26 ppm), $CDCl_3$ (^{13}C, 77.0 ppm), C_6D_5H (^{1}H, 7.15 ppm), C_6D_6 (^{13}C, 128.0 ppm), D_3CSOCD_2H (^{1}H, 2.49 ppm) or D_3CSOCD_3 (^{13}C, 39.5 ppm) as appropriate. Routine assignments of ^{13}C NMR spectra were made with the assistance of DEPT 135 and DEPT 90 experiments.

4.1.1. Methyl 4-[(methoxycarbonyl)oxy]but-2-ynoate (15). A 0.91 M hexane solution of *n*-BuLi (49 mL, 45 mmol) was added to a stirred solution of anhydrous propargyl alcohol (**13**) (1.3 mL, 22 mmol) in anhydrous THF (25 mL) at −78 °C under argon, whereupon a white precipitate formed. After 90 min the suspension was treated dropwise with a solution of methyl chloroformate (5.1 mL, 66 mmol) in anhydrous THF (25 mL). The reaction mixture was allowed to slowly warm to room temperature before being poured onto ice (500 mL), then extracted with ether (3×200 mL). The extract was washed with water (200 mL), dried and evaporated and the residue was subjected to rapid silica filtration. Elution with petrol gave **15** as pale yellow liquid (1.67 g, 44%); ^{1}H NMR (300 MHz) δ 4.81 (s, 2H, CH_2O), 3.79 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O). The spectrum was identical to that reported.[36]

4.1.2. 5-Acetoxy-3-pentyn-2-one (16). A 1.3 M hexane solution of *n*-BuLi (59.5 mL, 77.4 mmol) was added to a stirred solution of anhydrous propargyl alcohol (**13**) (2.2 mL, 39 mmol) in anhydrous THF (100 mL) at −78 °C under argon, whereupon a white precipitate formed. The suspension was diluted with anhydrous THF (100 mL) and then stirred for 1 h before being transferred via cannula to a dropping funnel. The cold suspension was added dropwise to a stirred solution of acetic anhydride (15 mL, 159 mmol) in anhydrous THF (10 mL) at −78 °C under argon. The reaction mixture was allowed to slowly warm to room temperature and stirring was continued overnight. The orange solution was poured into ice-cold saturated aqueous sodium bicarbonate (400 mL), then extracted with ether (3×200 mL). The extract was washed with brine (200 mL), dried and evaporated and the residue was subjected to rapid silica filtration. Elution with petrol gave several fractions, which were combined and distilled (Kugelrohr, 180 °C, 25 mmHg) to give **16** as a colourless liquid (2.486 g, 47%); ^{1}H NMR (300 MHz) δ 4.81 (s, 2H, CH_2O), 2.36 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). This compound is known.[37]

4.1.3. 7-(*t*-Butyldimethylsilyloxy)bicyclo[4.2.0]octa-1,3,5-triene (17). A solution of bicyclo[4.2.0]octa-1,3,5-trien-7-ol[38] (0.75 g, 6.2 mmol), TBSCl (1.62 g, 10.7 mmol) and imidazole (1.12 g, 16.4 mmol) in anhydrous DMF (1.5 mL) was stirred for 6 h. The reaction mixture was diluted with water (50 mL) and extracted with ether (3× 20 mL). The extract was washed with 1 M HCl (20 mL) and water (2×20 mL), dried and evaporated to give a pale yellow liquid, which was subjected to rapid silica filtration. Elution with petrol gave **17** as a pale yellow liquid (1.21 g, 84%); ^{1}H NMR (500 MHz)[‡] δ 7.30–7.27 (m, 1H, Ar), 7.26–7.23 (m, 1H, Ar), 7.20–7.19 (m, 1H, Ar), 7.15–7.14 (m, 1H, Ar), 5.33 (br dd, $J_{7,8\text{-}trans}$=4.5 Hz, $J_{7,8\text{-}cis}$=2.0 Hz, 1H, H7), 3.57 (ddd [apparent br dd], J_{gem}=13.9 Hz, $J_{8\text{-}trans,7}$= 4.5 Hz, $J_{8\text{-}trans,6}$=0.4 Hz, 1H, H8-*trans*), 3.10 (ddd [apparent dt], J_{gem}=13.9 Hz, $J_{8\text{-}cis,7}$=2.0 Hz, $J_{8\text{-}cis,3}$= 0.6 Hz, 1H, H8-*cis*), 0.98 (s, 9H, *t*-Bu), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$); ^{13}C NMR (125.8 MHz) δ 148.5 (Ar), 142.0 (Ar), 129.0 (ArH), 126.9 (ArH), 123.4 (ArH), 122.2 (ArH), 70.6 (C7), 42.3 (C8), 25.9 ($C[CH_3]_3$), 18.2 (SiC), −4.57 ($SiCH_3$), −4.64 ($SiCH_3$). This ether has been reported previously but no NMR data were published.[39]

4.1.4. Diels–Alder reaction of the *o*-quinonedimethide 18 and 15. A solution of **15** (0.26 g, 1.51 mmol) and **17** (0.34 g, 1.45 mmol) in anhydrous toluene (2 mL) under argon, was heated on a steam bath for 32 h. The toluene was evaporated and the residue was subjected to rapid silica filtration. Elution with EtOAc/petrol (1:99) gave the slightly impure methyl 1-(*t*-butyldimethylsilyloxy)-3-[(methoxycarbonyloxy)methyl]-1,4-dihydronaphthalene-2-carboxylate (**19**) as an unstable white solid (0.32 g, 54%), which crystallised from petrol, mp 63–64 °C; ^{1}H NMR (200 MHz) δ 7.35 (m, 1H, Ar), 7.23 (m, 3H, Ar), 5.77 (br s, 1H, H1), 5.33 (d, J_{gem}=14.4 Hz, 1H, OC*Ha*Hb), 5.19 (d, J_{gem}=14.4 Hz, 1H, OCHa*Hb*), 3.82 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.63 (br s, 2H, H4a/H4b), 0.74 (s, 9H, *t*-Bu), −0.04 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$). Further characterisation was impossible due to the facile elimination of *t*-butyldimethylsilanol.

[‡] The analysis of the spectrum was aided by a homonuclear decoupling experiment.

Further elution gave methyl 3-[(methoxycarbonyloxy)-methyl]naphthalene-2-carboxylate (**20**) as a white crystalline solid (0.10 g, 25%), which crystallised from petrol as colourless needles, mp 66–68 °C; (Found: C, 65.90, H, 5.08. $C_{15}H_{14}O_5$ requires C, 65.69, H, 5.15%); MS *m/z* 274 (M, 12%), 183 (100), 127 (16), 57 (23); ^{1}H NMR (300 MHz) δ 8.59 (s, 1H, H1), 7.95 (br s, 1H, H4), 7.93–7.85 (m, AB part of ABXY, 2H, Ar), 7.63–7.51 (m, XY part of ABXY, 2H, Ar), 5.73 (d, $J_{4,CH2}$=0.8 Hz, 2H, CH_2), 3.96 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O); ^{13}C NMR (75.5 MHz) δ 167.1 (CO_2), 155.6 (OCO_2), 134.7 (Ar), 132.8 (ArH), 132.6 (Ar), 131.9 (Ar), 128.8 (ArH), 128.6 (ArH), 127.8 (ArH), 127.7 (ArH), 127.0 (ArH), 125.9 (Ar), 68.2 (CH_2O), 54.9 (CH_3O), 52.2 (CH_3O).

On another occasion, a small amount of the double adduct, methyl 5α,5aα,6α,11aα-5,6-bis[(*t*-butyldimethylsilyl)oxy]-11a-[(methoxycarbonyl)methoxy]-5,5a,6,11,11a,12-hexahydronaphthacene-5a-carboxylate (**21**), was isolated by rapid silica filtration as a colourless oil (27 mg, 3%); ^{1}H NMR (300 MHz)[§] δ 7.01 (ddd, $J_{B,C}=J_{B,A}$=7.4 Hz, $J_{B,D}$=1.4 Hz, 2H, Ar [B]), 6.94 (ddd, $J_{C,B}$=7.4 Hz, $J_{C,D}$=7.4 Hz, $J_{C,A}$=1.0 Hz, 2H, Ar [C]), 6.85 (dd, $J_{A,B}$=7.4 Hz, $J_{A,C}$=1.0 Hz, 2H, Ar [A]), 6.82 (d, $J_{D,C}$=7.4 Hz, 2H, Ar [D]), 4.92 (s, 2H, H5/H6 or CH_2O), 4.77 (s, 2H, H5/H6 or CH_2O), 3.80 (s, 3H, CH_3O), 3.66 (s, 3H, CH_3O), 3.33 (d, J_{gem}=15.4 Hz, 2H, H11a/H12a), 2.59 (d, J_{gem}=15.4 Hz, 2H, H11b/H12b), 0.79 (s, 18H, *t*-Bu), 0.00 (s, 6H, $SiCH_3$), −0.31 (s, 6H, $SiCH_3$); ^{13}C NMR (75.5 MHz) δ 170.9 (CO_2), 155.8 (OCO_2), 136.6 (Ar), 136.2 (Ar), 127.9 (ArH), 127.8 (ArH), 127.3 (ArH), 125.4 (ArH), 75.6 (CH_2O), 74.7 (C5/C6), 62.1 (C5a), 54.6 (CH_3O), 51.4 (CH_3O), 41.2 (C11a), 38.3 (C11/C12), 25.8, (C[CH_3]$_3$), 18.1 (SiC), −4.3 ($SiCH_3$), −4.6 ($SiCH_3$).

4.1.5. Attempted reduction–deprotection of the Diels–Alder adduct (19). A stirred solution of **19** (100 mg, 0.25 mmol) in anhydrous DCM (15 mL) in an ice/salt bath under argon, was treated dropwise with a 1.2 M toluene solution of DIBAL (1.25 mL, 1.5 mmol). After 2 h the solution was allowed to warm to room temperature and the excess DIBAL was quenched with methanol (5 mL). Ice-cold 1 M HCl (50 mL) was added and the phases were separated. The aqueous layer was extracted with DCM (3×20 mL) and the combined organic solution was dried and evaporated to give naphthalene-2,3-dimethanol as a white solid (38 mg, 82%), which crystallised from DCM/petrol as colourless rhomboids, mp 160 °C (lit.[20] 160 °C); ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.47 (s, 2H, H1/H4), 7.43 (m, AA′ part of AA′BB′, 2H, Ar), 7.08 (m, BB′ part of AA′BB′, 2H, Ar), 4.77 (br t, J=5.0 Hz, 2H, OH), 4.45 (d, J=5.0 Hz, 4H, CH_2); ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 137.0 (Ar), 131.8 (Ar), 126.6 (ArH), 126.2 (ArH), 125.0 (ArH), 62.0 (CH_2). The ^{1}H NMR spectrum is somewhat different to that published at lower field.[20]

4.1.6. 2,5-Dimethoxybenzaldehyde (32). The methodology of Scarpatie et al. was used.[40] A solution of titanium tetrachloride (26 mL, 0.24 mol) in anhydrous DCM (45 mL) was added to a stirred solution of 1,4-dimethoxybenzene (13.82 g, 0.10 mol) in anhydrous DCM (200 mL) at 0 °C under argon, whereupon the colourless solution turned deep red. The reaction mixture was treated dropwise with a solution of dichloromethoxymethane (12.36, 0.14 mol) in anhydrous DCM (90 mL) over 1.5 h. The ice bath was removed and stirring was continued for 30 min before the reaction mixture was poured onto a mixture of ice (300 g) and concentrated HCl (8 mL). The biphasic mixture was stirred for 2 h, during which time the dark red organic layer turned green. The phases were separated and the aqueous layer was extracted with ether (2×200 mL). The combined organic solutions were washed with water (3×200 mL) and brine (200 mL), dried and evaporated to give essentially pure **32** as a green oil, which solidified on standing (16.57 g, 100%), and crystallised from ether as pale green microneedles, mp 48–50 °C (lit.[41] 53 °C); ^{1}H NMR (200 MHz) δ 10.37 (s, 1H, CHO), 7.25 (d, $J_{6,4}$=3.3 Hz, 1H, H6), 7.06 (m, 1H, H4), 6.87 (d, $J_{3,4}$=9.0 Hz, 1H, H3), 3.82 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O). The spectrum was similar to that reported.[42]

4.1.7. Ethyl 4-(2,5-dimethoxyphenyl)-4-hydroxy-2-butynoate (33). A 1.18 M solution of *n*-BuLi in hexane (8.5 mL, 10 mmol) was added dropwise to a stirred solution of ethyl propiolate (981 mg, 10 mmol) in anhydrous THF (20 mL) at −78 °C under argon. After 10 min a solution of **32** (1.662 g, 10.0 mmol) in anhydrous THF (20 mL) was added dropwise. Stirring was continued for 10 min and then for a further 10 min with the cryogenic bath removed. Acetic acid (2 mL, 35 mmol) was added and the reaction mixture was allowed to warm to room temperature before being partitioned between ether (100 mL) and saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the aqueous phase was extracted with ether (2×50 mL). The combined ether solution was washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL), dried and evaporated to give a red-brown oil, which was subjected to rapid silica filtration. Elution with EtOAc/petrol (1:19) gave unreacted **32** (233 mg). Further elution with EtOAc/petrol (1:4) gave **33** as a honey coloured oil (1.870 g, 71%, 82% based on recovered **32**); MS (FAB) *m/z* 264 (M, 80%), 247 (100), 175 (20), 165 (39); HRMS found: 247.0986. $[C_{14}H_{16}O_5–H_2O]^+$ requires 247.0970; ^{1}H NMR (300 MHz, C_6D_6)[¶] δ 7.07 (d, $J_{6',4'}$=3.1 Hz, 1H, H6′), 6.66 (dd, $J_{4',3'}$=8.9 Hz, $J_{4',6'}$=3.1 Hz, 1H, H4′), 6.34 (d, $J_{3',4'}$=8.9 Hz, 1H, H3′), 5.63 (br d, $J_{4,OH}$=7.1 Hz, 1H, H4), 3.81 (q, J=7.1 Hz, 2H, CH_2O), 3.29 (s, 3H, CH_3O), 3.19 (s, 3H, CH_3O), 2.92 (br d, $J_{OH,4}$=7.1 Hz, 1H, OH), 0.78 (t, J=7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, C_6D_6) δ 154.4 (C), 153.5 (C), 150.9 (C), 128.8 (C1′), 115.0 (ArH), 113.4 (ArH), 112.5 (ArH), 87.1 (C3), 77.3 (C2), 61.7 (CH_2O), 61.0 (C4), 55.6 (CH_3O), 55.2 (CH_3O), 13.7 (CH_3); IR ν_{max} br 3446 (OH), 2233 (C≡C), 1709 cm^{-1} (CO).

4.1.8. Ethyl 4-[(2,5-dimethoxyphenyl)(hydroxy)methyl]-3-furoate (35). A mixture of **33** (1.016 g, 3.8 mmol), 4-phenyloxazole (**34**)[41] (2.72 g, 18.7 mmol) and hydroquinone (5 mg) under argon, was stirred at 200 °C for 1.5 h,

[§] The designations A,B,C,D are meant only to represent the relationship of the Ar protons to each other as determined by the coupling constants. Thus, A and D correspond to H1/H10 and H4/H7; B and C correspond to H2/H9 and H3/H8, but not necessarily, respectively, as shown.

[¶] The ^{1}H NMR. spectrum in $CDCl_3$ was not first order.

after which time TLC showed the reaction to be complete. The reaction mixture was cooled and the crude product was subjected to rapid silica filtration. Elution with EtOA/petrol (1:19) gave excess **34**. Further elution with EtOAc/petrol (1:9) gave **35** as a yellow oil (844 mg, 72%); MS (FAB) *m/z* 306 (M, 83%), 290 (20), 289 (100), 229 (20), 153 (22); EI-HRMS ($M^{+\cdot}$) found: 306.1090. $C_{16}H_{18}O_6$ requires 306.1103; ^{1}H NMR (300 MHz) δ 7.97 (d, $J_{2,5}=1.7$ Hz, 1H, H2), 7.14 (m, 1H, H5, 6.88, dd, $J_{6',4'}=1.7$ Hz, $J_{6',3'}=1.0$ Hz, 1H, H6′), 6.80 (m [apparent d], 2H, H3′/H4′), 6.23 (s, 1H, CHOH), 4.92 (br s, 1H, OH), 4.32 (q, $J=7.1$ Hz, 2H, CH_2O), 3.76 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 1.33 (t, $J=7.1$ Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz) δ 164.8 (CO), 153.8 (ArO), 150.3 (ArO), 149.4 (C2), 142.0 (C5), 130.9 (Ar), 128.4 (Ar), 117.9 (Ar), 113.5 (ArH), 112.8 (ArH), 111.5 (ArH), 62.0 (CHOH), 61.0 (CH_2O), 56.0 (CH_3O), 55.7 (CH_3O), 14.1 (CH_3); IR ν_{max} br 3437 (OH), 1696 cm^{-1} (CO).

4.1.9. Ethyl 4-(2,5-dimethoxybenzyl)-3-furoate (36). TMSCl (4.2 mL, 33 mmol) was added to a stirred solution of NaI (5.00 g, 33 mmol) in anhydrous MeCN (40 mL) under argon, whereupon NaCl precipitated. A solution of **35** (1.702 g, mmol) in anhydrous MeCN (100 mL) was added dropwise to the suspension, whereupon iodine colour developed immediately. After 10 min the reaction mixture was diluted with water (500 mL) then extracted with ether (4×100 mL). The extract was washed with aqueous sodium thiosulfate solution (2×100 mL) and brine (100 mL), dried and evaporated to give essentially pure **36** as a yellow oil (1.61 g, 100%). Distillation under vacuum gave the analytical sample as a colourless oil; (Found: C, 66.45, H, 6.32. $C_{16}H_{18}O_5$ requires C, 66.20, H, 6.25%); MS *m/z* 167 (68%), 97 (100), 95 (26), 84 (26); ^{1}H NMR (300 MHz) δ 7.97 (d, $J_{2,5}=1.7$ Hz, 1H, H2), 7.01 (m, 1H, H5), 6.80 (d, $J_{3',4'}=8.6$ Hz, 1H, H3′), 6.76–6.70 (m, 2H, H4′/H6′), 4.27 (q, $J=7.1$ Hz, 2H, CH_2O), 3.97 (br s, 2H, CH_2), 3.78 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 1.29 (t, $J=7.1$ Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz) δ 163.6 (CO), 153.4 (ArO), 151.6 (ArO), 148.7 (C2), 142.1 (C5), 129.6 (Ar), 124.0 (Ar), 118.5 (Ar), 116.4 (ArH), 111.4 (ArH), 111.2 (ArH), 60.0 (CH_2O), 55.9 (CH_3O), 55.6 (CH_3O), 24.5 (CH_2), 14.1 (CH_3); IR ν_{max} 1720 cm^{-1} (CO).

4.1.10. 4-(2,5-Dimethoxybenzyl)-3-furoic acid (28). Aqueous sodium hydroxide (20% (w/v), 5 mL) was added to a solution of **36** (166 mg, 0.57 mmol) in methanol (5 mL), whereupon a white precipitate formed. The suspension was heated under reflux for 1 h and the solution, which formed was cooled and poured onto ice-cold 1 M HCl (50 mL), whereupon a white precipitate formed. The suspension was extracted with EtOAc (3×25 mL) and the extract was washed with water (25 mL) and brine (25 mL), dried and evaporated to give **28** as a white crystalline solid (146 mg, 97%), which crystallised from ether/petrol as colourless needles, mp 138–140 °C; (Found: C, 64.34, H, 5.49. $C_{14}H_{14}O_5$ requires C, 64.12, H, 5.38%); MS (FAB) *m/z* 263 (M+H, 24%), 262 (M, 20), 245 (14); ^{1}H NMR (300 MHz) δ 11.05 (br s, 1H, CO_2H), 8.09 (d, $J_{2,5}=1.7$ Hz, 1H, H2), 7.05 (m, 1H, H5), 6.83–6.80 (m, 2H, Ar), 6.75 (dd, $J_{4',3'}=8.9$ Hz, $J_{4',6'}=2.9$ Hz, 1H, H4′), 4.00 (br s, 2H, CH_2), 3.79 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O); ^{13}C NMR (75.5 MHz) δ 169.4 (CO), 153.4 (ArO), 151.6 (ArO), 150.2 (C2), 142.4 (C5), 129.3 (Ar), 124.4 (Ar), 117.7 (Ar), 116.4 (ArH), 111.7 (ArH), 111.4 (ArH), 55.9 (CH_3O), 55.5 (CH_3O), 24.4 (CH_2); IR ν_{max} v br 2400–3300 (OH), 1689 cm^{-1} (CO).

4.1.11. 5,8-Dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one (5). PCl_5 (0.86 g, 4.1 mmol) was added to a stirred suspension of **28** (0.899 g, 3.4 mmol) in partially frozen, anhydrous benzene (15 mL), in an ice bath under argon. The reaction mixture was allowed to warm to room temperature, and then heated under reflux for 1 h. The solution of 4-(2,5-dimethoxybenzyl)-3-furoyl chloride (**37**) was cooled to room temperature then added dropwise to a stirred solution of stannic chloride (0.5 mL, 4.25 mmol) in partially frozen, anhydrous benzene (15 mL), whereupon a red precipitate formed. The reaction mixture was allowed to slowly warm to room temperature and stirring in the dark was continued overnight. The benzene was evaporated and the residue was partitioned between 1 M HCl (300 mL) and EtOAc (80 mL). Oxalic acid was added to help break down the tin complex. The layers were separated and the aqueous phase was extracted with EtOAc (4×80 mL). The combined organic solution was washed with saturated aqueous sodium bicarbonate solution (2×80 mL), water (80 mL) and brine (2×80 mL), dried and evaporated to give **5** as a yellow solid (752 mg, 89%), which crystallised from EtOAc/petrol as an amorphous yellow solid, mp 140–143 °C; (Found: C, 68.61, H, 4.84. $C_{14}H_{12}O_4$ requires C, 68.85, H, 4.95%); MS (FAB) *m/z* 245 (M+H, 100), 244 (M, 38); ^{1}H NMR (300 MHz) δ 8.12 (d, $J_{3,1}=1.6$ Hz, 1H, H3), 7.45 (dt, $J_{1,3}=J_{1,9}=1.6$ Hz, 1H, H1), 7.04 (d, $J_{7,6}=9.1$ Hz, 1H, H7), 6.89 (d, $J_{6,7}=9.1$ Hz, 1H, H6), 3.96 (m [apparent br d], 2H, CH_2), 3.91 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O); ^{13}C NMR (75.5 MHz) δ 181.5 (CO), 155.3 (ArO), 150.5 (ArO), 144.1 (C3), 138.2 (C1), 132.0 (Ar), 124.5 (Ar), 123.0 (Ar), 120.5 (Ar), 115.0 (ArH), 110.7 (ArH), 56.6 (CH_3O), 55.8 (CH_3O), 19.6 (CH_2); IR ν_{max} 1667 cm^{-1} (CO).

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Haval–Argade contrathermodynamic rearrangement of alkylidenesuccinimides to alkylmaleimides via the corresponding isoimides: a general approach to alkyl and dialkyl substituted maleimides☆

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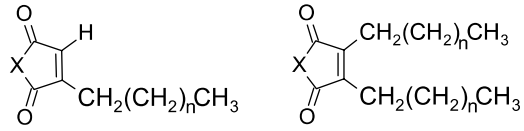
Abstract—A simple and efficient access to alkyl and dialkyl substituted maleimides has been demonstrated via the new contrathermodynamic rearrangement of (*E*)-alkylidenesuccinimides to alkylmaleimides. The (*E*)-alkylidenesuccinimides obtained from the Wittig-condensation of *N*-arylmaleimide with aliphatic aldehydes on regioselective hydrolysis furnished the corresponding (*E*)-alkylidenesuccinanilic acids in 95–98% yields. The β-alkylidenesuccinanilic acids on treatment with cyanuric chloride in the presence of triethylamine gave the corresponding β-alkylisomaleimides in 78–80% yields via the β-alkylideneisosuccinimides with the exocyclic to endocyclic carbon–carbon double bond migration. The kinetically controlled products alkylisomaleimides in refluxing acetic acid furnished the thermodynamically controlled alkylmaleimides in 98% yield. The Wittig condensation of alkyl substituted isomaleimides/maleimides with aliphatic aldehydes gave the desired dialkyl substituted maleimides in high yields. A conversion of α-methylenesuccinanilic acids to α-methylisomaleimides has also been described, with 90% yield.

1. Introduction

The cyclic anhydrides and imides are the compounds of choice for all chemists from both the basic and applied point of view for multiple purposes. The vast array of nucleophilic reactions undergone by symmetrical and unsymmetrical maleic anhydrides and maleimides confer on them a high synthetic potential. As such, a large number of maleic anhydrides and maleimides have been extensively used in the synthesis of natural and unnatural bioactive heterocyclic compounds,[1] structurally interesting compounds highlighting regiochemical dichotomy[2] and several types of polymers with tailored material characteristics.[3] Maleic anhydrides and maleimides bearing both hydrophilic groups and hydrophobic parts are very important for their bioactivities and material properties[4] (Fig. 1). Several alkylmethyl substituted maleic anhydrides such as chaetomellic acids A and B, aspergillus acids A–D, maleic anhydride segment of tautomycin and tyromycin A are known in the literature[5,6] as bioactive natural products and one can surmise that nature might be designing them by employing the condensation of pyruvic acid with the other respective carboxylic acids. Several elegant routes to alkylmethylmaleic anhydrides have been reported in the past decade.[6] To the best of our knowledge, to date no natural product with a simple monoalkyl or dialkyl substituted maleic anhydride moiety is known in the literature. Only one method for the synthesis of monoalkyl substituted maleic anhydrides is known—by the Heck reaction using palladium-catalyzed dicarbonylation of terminal acetylenes.[7] The use of poisonous carbon monoxide is a drawback of this simple one-step approach. The dialkyl substituted maleic anhydrides have been designed using the Grignard coupling reactions with dimethyl acetylenedicarboxylate at −78 °C followed by



X = O, NAr, n = 0 - 12

Figure 1. Alkyl and dialkyl substituted maleic anhydrides and imides.

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Keywords: Maleimides; Wittig coupling; Isomaleimides; Contrathermodynamic rearrangement; Alkyl and dialkylmaleimides.
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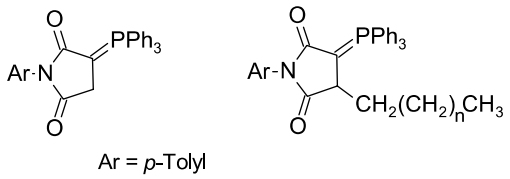


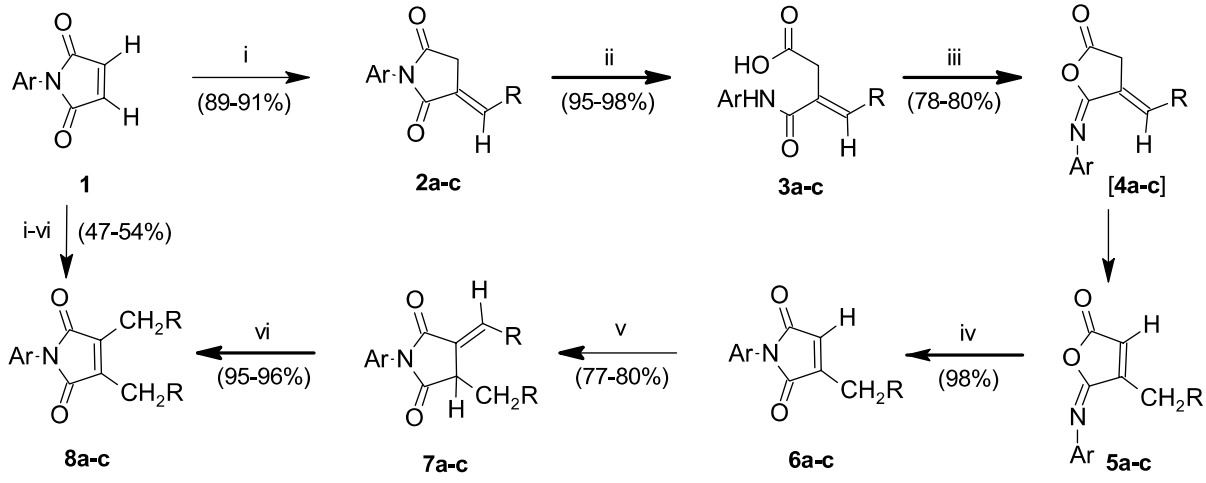
Figure 2. Triphenylphosphine and maleimide adducts (Wittig adducts).

trapping the *cis*-enolate with alkyl halides.[8] The low temperature reactions, lower reactivities of *cis*-enolates at that temperature and contamination of *trans*-enolates are the limitations of this approach. Hence, development of a new practical approach to the alkyl and dialkyl substituted maleic anhydrides and maleimides is still a useful and challenging task of current interest. In continuation of our studies on cyclic anhydrides chemistry,[9] now we herein report an easy approach to monoalkyl and dialkyl substituted maleimides via the contrathermodynamic (*E*)-alkylidenesuccinimides to alkylmaleimides rearrangement as a key reaction.

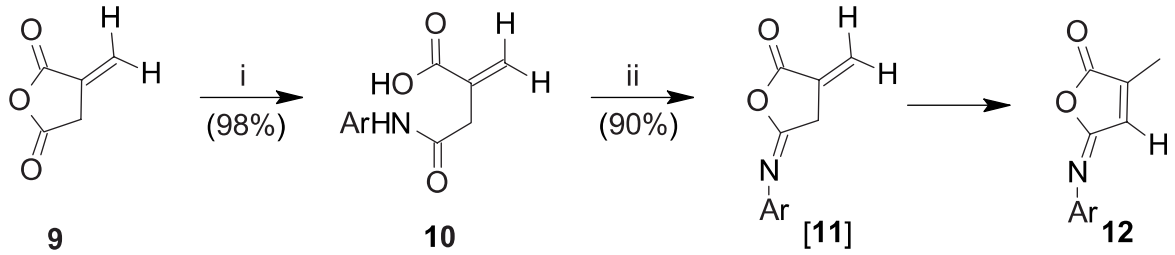
2. Results and discussion

The formation of maleimide–triphenylphosphine adduct is well known[10] (Fig. 2) and we felt that the stepwise activation of two vinylic protons in maleimide as Wittig adducts would provide an efficient approach to alkylmaleimides and dialkylmaleimides. In this context, starting from *N*-*p*-tolylmaleimide (**1**), we prepared the (*E*)-alkylidenesuccinimides **2a–c** in 89–91% yield[11] (Scheme 1). We thought that trisubstituted exocyclic carbon–carbon double bond in compounds **2** will migrate easily to form the trisubstituted endocyclic compounds **6** for the two reasons, viz. (i) exocyclic to endocyclic carbon–carbon double bond migrations are generally more easy and (ii) the endocyclic trisubstituted carbon–carbon double bond will be in conjugation with two imide carbonyls.[12] We tried several reagents and reaction conditions for the conversion of **2–6**, but all our attempts met with failure. The conversion of **2–6** under basic conditions (Et_3N, Pyridine, DBU, NaH, *t*-BuO^-K^+, *t*-BuLi), under the thermal conditions (heat 150–200 °C, tetralin reflux) and under the transition metal catalyzed isomerization conditions [$RuCl_3$, $HRuCl(PPh_3)_3$, $RhCl_3$, $HRhCl(PPh_3)_3$] were fruitless. We learnt from these experiments that such type of (*E*)-alkylidenesuccinimides **2** to alkylmaleimides **6** conversion is a difficult process. The compounds **2a–c** could be thermodynamically more stable due to the extra stability of carbon–carbon double bond with (*E*)-geometry, than the corresponding compounds **6a–c**. We planned with reason and decided to alter the imide dicarbonyl symmetry of **2** for such type of double bond migrations. The amic/anilic acids under kinetically controlled dehydration conditions are known to furnish the corresponding isoimides.[13] We felt that preparation of isoimides would be helpful for such a carbon–carbon double bond migration as the isomaleimides are expected to be more stable than the corresponding alkylidineisosuccinimides due to the extension of π-cloud conjugation from the aryl ring to the butyroiminolide carbonyl group. The highly regioselective aqueous lithium hydroxide induced hydrolysis of **2** exclusively furnished the β-alkylidenesuccinanilic acids **3** in 95–98% yields.

Cyanuric chloride is a decent dehydrating agent for such type of kinetic dehydrations[13] and the treatment of acids **3** with cyanuric chloride in the presence of triethyl amine as a base at room temperature directly furnished the expected *anti*-β-alkylisomaleimides **5** in 78–80% yields. Both the dehydrative cyclizations of acids **3** to form the intermediates β-alkylideneisosuccinimides **4** (which could not be isolated) and the abstraction of the α-methylene proton on intermediate **4** to form the β-alkyl isomaleimides **5** took place in one-pot. Our hypothesis turned out to be correct and to the best of our knowledge this is the first example of carbanion generation on an isoimide skeleton, though in situ, and its application for the facile carbon framework rearrangement. The structures of isomaleimides **5a–c** were unambiguously established on the basis of lactone carbonyl (1794–1798 cm^{-1}) and imine (1676–1678 cm^{-1}) stretching frequencies in IR-spectra, appropriate ^1H NMR data and the presence of imine carbon atom (δ 140.9–141.0) in ^{13}C NMR spectra. We could very easily convert these kinetically controlled alkylisomaleimides **5a–c** to the



Scheme 1. Reagents, conditions and yields: (i) PPh_3, THF, RCHO, reflux, 10 h (89–91%); (ii) aq 2 N LiOH, THF, 0 °C to rt, 5 h, (95–98%); (iii) cyanuric chloride, NEt_3, DCM, 0 °C to rt, 8 h (78–80%); (iv) AcOH, reflux, 5 h (98%); (v) PPh_3, AcOH, RCHO, reflux, 18 h (77–80%); (vi) NEt_3 + THF (1:1), reflux, 48 h (95–96%).



Scheme 2. Reagents, conditions and yields: (i) Et_2O, $ArNH_2$, rt, 1 h (98%); (ii) cyanuric chloride, NEt_3, DCM, 0 °C to rt, 8 h (90%).

desired corresponding thermodynamically more stable alkylmaleimides **6a–c** in 98% yield, by just refluxing them in glacial acetic acid for five hours. Both the opening of iminobutenolides **5** with acetic acid to form the mix anhydride intermediates and the intramolecular cyclization via the amide nitrogen lone pair to form the compounds **6** took place in one-pot. We feel that these monoalkyl substituted maleimides **6** will be potential precursors for several bioactive natural products containing butenolide/butyrolactone and butyrolactam core with fatty alkyl chain substituents.[14] Both the alkylisomaleimides **5** and alkylmaleimides **6** on treatment with refluxing acetic acid–sodium acetate mixture or on treatment with triethylamine in THF reverted to the more stable (*E*)-alkylidenesuccinimides **2** in quantitative yield, proving that in these systems the endocyclic to exocyclic carbon–carbon double bond migrations are more facile. These observations revealed and confirmed that the order of thermodynamic stability for these imides and isoimides is **2**>**6**>**5**>**4** and what we have accomplished was the contrathermodynamic rearrangement of exoimides **2** to endoimides **6** via the isoimides **4** and **5**. Finally, with the application of our earlier developed synthetic protocol[6f] for the synthesis of chaetomellic acid A, we could very easily transform the alkyl substituted maleimides to the symmetrically dialkyl substituted maleimides **8** via the intermediates **7** in very good yields. As expected the alkylisomaleimides on triphenylphosphine induced Wittig condensation with aliphatic aldehydes in refluxing acetic acid also furnished the imides **8** via the intermediates **6** and **7** in 77–80% yield. In the present 4-step approach the alkylmaleimides were obtained in 65–70% overall yields, while in the 5-step approach, the dialkylsubstituted maleimides were obtained in 48–55% overall yields. In the present synthetic sequence, the stepwise use of two different aliphatic aldehydes would provide a way to the unsymmetrically dialkylsubstituted maleimides. The hydrolysis of alkylsubstituted maleimides **6** under acidic conditions followed by the dehydration to the corresponding alkylmaleic anhydrides and the hydrolysis of dialkylmaleimides to the corresponding dialkylmaleic anhydrides is well known in the literature.[6f,7,9i]

In the above mentioned strategy, we have proved that the α-protons on the inisolable intermediate alkylideneisosuccinimides **4** are accessible for such type of rearrangements. We planned to verify the accessibility of the corresponding β-protons in α-alkylideneisosuccinimides. In this context, we performed the regioselective ring opening of itaconic anhydride (**9**) with *p*-toluidine and obtained the α-methylenesuccinanilic acid **10** in 98% yield (Scheme 2). The treatment of acid **10** with cyanuric chloride in the presence of triethylamine also gave α-methylisomaleimide **12** in 90% yield via the intermediate α-methyleneisosuccinimide **11**, proving that β-methylene protons can also be abstracted in a similar fashion for such type of *exo–endo* framework rearrangements.

3. Conclusion

In summary, we have demonstrated a simple and efficient approach to alkylmaleimides and dialkylmaleimides via the two Wittig coupling reactions, taking advantage for the first time of kinetically controlled isoimides as intermediates to enforce the difficult migration of exocyclic carbon–carbon double bonds to the endocyclic position (**2a–c** to **6a–c**). We have also demonstrated that in the present strategy, both the α- and β-methylene protons on isosuccinimide skeleton are accessible for such type of exocyclic to endocyclic carbon–carbon double bond migrations. The present Haval–Argade contrathermodynamic rearrangement is noteworthy and lots of new chemistry will be possible from this important isoimide functionality. The present practical approach with scale up potential is general in nature and it will be useful to design a large number of analogs and congeners of alkylmaleimides and dialkylmaleimides of interest, to a large section of the chemists' community. We also feel that the present approach will be useful to design carbocyclic compounds like byssochlamic acid and its analogs. The present results will also be of interest to chemists studying such type of *exo–endo* carbon–carbon double bond isomerization reactions.

4. Experimental

4.1. General

Commercially available cyclic anhydrides, aromatic amines, aliphatic aldehydes and triphenylphosphine were used. Freshly recrystallized cyanuric chloride (CCl_4) was used. Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as internal standard and in DMSO-d_6 on a Bruker AC 200, MSL 300 and Bruker DRX 500 NMR spectrometers (200, 300 and 500 MHz, respectively). ^{13}C NMR spectra were recorded on a Bruker AC 200, MSL 300 and Bruker DRX 500 NMR spectrometers (50, 75 and 125 MHz, respectively).

4.2. General procedure for *N*-*p*-tolyl-3(*E*)-alkylidene-succinimides 2a–c

A solution of *N*-*p*-tolylmaleimide (**1**, 50 mmol) and triphenylphosphine (50 mmol) in THF (125 mL) was stirred at room temperature for 30 min. To the reaction mixture was added aliphatic aldehyde (75 mmol) and it was refluxed for 10 h. The THF was distilled off in vacuo at 50 °C and the residue was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to obtain the alkylidenesuccinimides **2a/b/c** in 89–91% yields.

4.2.1. 3-Hexylidene-1-*p*-tolyl-pyrrolidine-2,5-dione (2a). White solid (12.34 g, 91%), mp 112–113 °C (petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J=6 Hz, 3H), 1.22–1.45 (m, 4H), 1.53 (quintet, J=6 Hz, 2H), 2.23 (q, J=6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, J=2 Hz, 2H), 6.93 (tt, J=8, 2 Hz, 1H), 7.18 (d, J=8 Hz, 2H), 7.27 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7, 20.9, 22.2, 27.5, 29.6, 31.2, 31.8, 125.1, 126.0, 129.2, 129.4, 138.1, 139.6, 168.7, 173.0; MS (*m*/*e*) 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53; IR (Nujol) ν_{max} 1771, 1749, 1712, 1691, 1676 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.92; N, 5.07.

4.2.2. 3-Decylidene-1-*p*-tolyl-pyrrolidine-2,5-dione (2b). White solid (14.54 g, 89%), mp 106–108 °C (petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J=6 Hz, 3H), 1.27 (bs, 12H), 1.52 (quintet, J=6 Hz, 2H), 2.23 (q, J=6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, J=2 Hz, 2H), 6.93 (tt, J=8, 2 Hz, 1H), 7.18 (d, J=8 Hz, 2H), 7.27 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.6, 28.0, 29.18, 29.24, 29.31, 29.37, 29.9, 31.8, 32.0, 125.2, 126.2, 129.3, 129.7, 138.4, 140.0, 169.0, 173.2; IR (Nujol) ν_{max} 1771, 1709, 1676, 1466 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.89; H, 9.02; N, 4.16.

4.2.3. 3-Tetradecylidene-1-*p*-tolyl-pyrrolidine-2,5-dione (2c). White solid (17.06 g, 89%), mp 58–60 °C (petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J=6 Hz, 3H), 1.25 (bs, 20H), 1.55 (quintet, J=6 Hz, 2H), 2.25 (q, J=6 Hz, 2H), 2.39 (s, 3H), 3.38 (d, J=2 Hz, 2H), 6.95 (tt, J=8, 2 Hz, 1H), 7.20 (d, J=8 Hz, 2H), 7.28 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 20.8, 22.3, 27.9, 29.1, 29.2, 29.3 (7×CH_2), 29.5, 31.8, 125.4, 125.9, 129.2, 129.5, 137.8, 139.1, 168.5, 172.6; MS (*m*/*e*) 383, 355, 257, 228, 215, 202, 189, 172, 108, 95, 81; IR (Nujol) ν_{max} 1785, 1720, 1695, 1470 cm^{-1}. Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.19; H, 9.64; N, 3.60.

4.3. General procedure for *N*-*p*-tolyl-3(*E*)-alkylidene-succinanilic acids 3a–c

To a solution of alkylidenesuccinimides (**2a**–**c**, 40 mmol) in THF (50 mL) was added 2 N aqueous LiOH (50 mL) in a dropwise fashion at 0 °C and the reaction mixture was stirred for 5 h at room temperature. THF was distilled off in vacuo and the aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave the desired alkylidenesuccinanilic acids **3a**–**c** in 95–98% yields.

4.3.1. 3-*p*-Tolylcarbamoyl-non-3-enoic acid (3a). White solid (11.33 g, 98%), mp 143–145 °C (petroleum ether+ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J=6 Hz, 3H), 1.20–1.40 (m, 4H), 1.47 (quintet, J=6 Hz, 2H), 2.27 (s, 3H), 2.37 (q, J=6 Hz, 2H), 3.38 (s, 2H), 7.06 (d, J=8 Hz, 2H), 7.16 (t, J=6 Hz, 1H), 7.33 (d, J=8 Hz, 2H), 8.01 (bs, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.0, 20.6, 22.1, 28.0, 28.5, 31.1, 34.1, 119.0, 119.1, 129.2, 131.9, 137.0, 137.1, 168.3, 168.4; IR (Nujol) ν_{max} 2383, 2700–2500, 1682, 1657, 1597 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.43; H, 7.96; N, 4.85.

4.3.2. 3-*p*-Tolylcarbamoyl-tridec-3-enoic acid (3b). White solid (13.24 g, 96%), mp 138–140 °C (petroleum ether+ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J=6 Hz, 3H), 1.24 (bs, 12H), 1.47 (quintet, J=6 Hz, 2H), 2.28 (s, 3H), 2.39 (q, J=6 Hz, 2H), 3.38 (s, 2H), 7.07 (d, J=8 Hz, 2H), 7.18 (t, J=6 Hz, 1H), 7.34 (d, J=8 Hz, 2H), 7.96 (bs, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.2, 20.6, 22.3, 28.3, 28.5, 28.6, 28.7, 28.9, 29.1, 29.2, 31.5, 119.0, 119.1, 129.2, 131.9, 137.0, 137.1, 168.4, 168.5; IR (Nujol) ν_{max} 3420, 2700–2500, 1682, 1661, 1597 cm^{-1}. Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.04; N, 4.05. Found: C, 73.12; H, 9.13; N, 4.16.

4.3.3. 3-*p*-Tolylcarbamoyl-heptadec-3-enoic acid (3c). White solid (15.21 g, 95%), mp 126–128 °C (petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J=6 Hz, 3H), 1.24 (bs, 20H), 1.47 (quintet, J=6 Hz, 2H), 2.28 (s, 3H), 2.38 (q, J=6 Hz, 2H), 3.38 (s, 2H), 7.07 (d, J=8 Hz, 2H), 7.17 (t, J=6 Hz, 1H), 7.33 (d, J=8 Hz, 2H), 7.94 (bs, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz) δ 12.6, 19.2, 20.9, 27.0, 27.3, 27.5, 27.6, 27.7, 27.9 (5×CH_2), 30.2, 33.1, 117.8, 125.4, 127.5, 130.7, 135.2, 143.6, 167.0, 167.4; IR (Nujol) ν_{max} 3411, 2700–2500, 1688, 1660, 1599 cm^{-1}. Anal. Calcd for $C_{25}H_{39}NO_3$: C, 74.77; H, 9.79; N, 3.49. Found: C, 74.69; H, 9.82; N, 3.51.

4.4. General procedure for *N*-*p*-tolylalkylisomaleimides 5a–c

To a slurry of alkylidenesuccinanilic acids (**3a**–**c**, 30 mmol) in DCM (50 mL) was added triethylamine (90 mmol) in a dropwise fashion with constant stirring at 0 °C. To the resulting reaction mixture was added a solution of cyanuric chloride (33 mmol) in DCM (50 mL) and the reaction mixture was further stirred under argon atmosphere for 8 h at room temperature. The reaction mixture was concentrated in vacuo and residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, 5% aqueous sodium bicarbonate, brine and dried over Na_2SO_4. The ethyl acetate layer was concentrated in vacuo and the crude product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to obtain pure *N*-*p*-tolylalkylisomaleimides **5a**–**c** in 78–80% yields.

4.4.1. 4-Hexyl-5-*p*-tolylimino-5*H*-furan-2-one (5a). Thick oil (6.50 g, 80%), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J=6 Hz, 3H), 1.35 (bs, 6H), 1.69 (quintet, J=6 Hz, 2H), 2.35 (s, 3H), 2.64 (t, J=6 Hz, 2H), 6.29 (s, 1H), 7.17 (d, J=8 Hz, 2H), 7.33 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$,

50 MHz) δ 13.9, 21.0, 22.4, 26.2, 27.3, 28.8, 31.3, 121.0, 125.3, 129.4, 137.1, 140.9, 150.1, 159.7, 167.1; IR (neat) ν_{max} 1798, 1678, 1622, 1506 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.12; H, 7.93; N, 5.02.

4.4.2. 4-Decyl-5-*p*-tolylimino-5*H*-furan-2-one (5b). White solid (7.67 g, 78%), mp 53–55 °C (petroleum ether); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 3H), 1.25 (bs, 14H), 1.68 (quintet, $J=6$ Hz, 2H), 2.35 (s, 3H), 2.64 (t, $J=6$ Hz, 2H), 6.29 (s, 1H), 7.17 (d, $J=8$ Hz, 2H), 7.33 (d, $J=8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 26.3, 27.4, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 121.1, 125.4, 129.5, 137.1, 141.0, 150.2, 159.8, 167.2; IR ($CHCl_3$) ν_{max} 1798, 1678, 1622, 1506 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.11; H, 9.04; N, 4.33.

4.4.3. 4-Tetradecyl-5-*p*-tolylimino-5*H*-furan-2-one (5c). White solid (8.96 g, 78%), mp 58–60 °C (petroleum ether); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 3H), 1.25 (bs, 22H), 1.68 (quintet, $J=6$ Hz, 2H), 2.35 (s, 3H), 2.64 (t, $J=6$ Hz, 2H), 6.29 (s, 1H), 7.17 (d, $J=8$ Hz, 2H), 7.33 (d, $J=8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 26.3, 27.4, 29.1, 29.2, 29.3, 29.4, 29.6 ($5\times CH_2$), 31.9, 121.1, 125.4, 129.5, 137.1, 141.0, 150.2, 159.8, 167.2; IR ($CHCl_3$) ν_{max} 1794, 1676, 1620, 1506 cm^{-1}. Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.33; H, 9.59; N, 3.60.

4.4.4. 3-Methyl-5-*p*-tolylimino-5*H*-furan-2-one (12). This compound was obtained in 90% yield by using the same procedure as used for the synthesis of compounds **5a–c**; off white solid; mp 115–116 °C (petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 2.36 (s, 3H), 7.02 (s, 1H), 7.19 (d, $J=9$ Hz, 2H), 7.32 (d, $J=9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7, 21.0, 125.0, 129.4, 136.5, 136.9, 138.7, 141.2, 148.9, 168.7; IR (Nujol) ν_{max} 1778, 1674, 1599, 1462 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.77; H, 5.48; N, 6.93.

4.5. General procedure for *N*-*p*-tolylalkylmaleimides 6a–c

A solution of *N*-*p*-tolylalkylisomaleimides (**5a–c**, 20 mmol) in glacial acetic acid (50 mL) was refluxed for 5 h. Acetic acid was distilled off in vacuo at 50 °C and the residue was dissolved in ethyl acetate. The organic layer was washed with water, aqueous sodium bicarbonate, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained residue, on silica gel column chromatographic purification using petroleum ether and ethyl acetate (9.5:0.5), gave *N*-*p*-tolylalkylmaleimides **6a–c** in 98% yields.

4.5.1. 3-Hexyl-1-*p*-tolyl-pyrrole-2,5-dione (6a). White solid (5.31 g, 98%), mp 70–72 °C (petroleum ether+ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, $J=6$ Hz, 3H), 1.15–1.50 (m, 6H), 1.64 (quintet, $J=6$ Hz, 2H), 2.36 (s, 3H), 2.50 (dt, $J=6$, 2 Hz, 2H), 6.40 (t, $J=2$ Hz, 1H), 7.10–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.4, 25.4, 27.0, 28.8, 31.4, 125.8, 126.2, 128.9, 129.6, 137.6, 150.3, 169.9, 170.5; IR ($CHCl_3$) ν_{max} 1773, 1713, 1638, 1516 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.20; H, 7.73; N, 5.11.

4.5.2. 3-Decyl-1-*p*-tolyl-pyrrole-2,5-dione (6b). White solid (6.40 g, 98%), mp 58–60 °C (petroleum ether+ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 3H), 1.26 (bs, 14H), 1.64 (quintet, $J=6$ Hz, 2H), 2.36 (s, 3H), 2.50 (dt, $J=6$, 2 Hz, 2H), 6.40 (t, $J=2$ Hz, 1H), 7.10–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.6, 25.5, 27.0, 29.2, 29.3, 29.4, 29.5, 30.1, 31.9, 125.8, 126.2, 128.9, 129.7, 137.6, 150.3, 170.0, 170.6; IR ($CHCl_3$) ν_{max} 1773, 1713, 1638, 1516 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.95; H, 8.88; N, 4.21.

4.5.3. 3-Tetradecyl-1-*p*-tolyl-pyrrole-2,5-dione (6c). White solid (7.52 g, 98%), mp 72–74 °C (petroleum ether+ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 3H), 1.25 (bs, 22H), 1.64 (quintet, $J=6$ Hz, 2H), 2.36 (s, 3H), 2.50 (dt, $J=6$, 2 Hz, 2H), 6.40 (t, $J=2$ Hz, 1H), 7.10–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 25.5, 27.1, 29.2, 29.3, 29.5, 29.6 ($6\times CH_2$), 31.9, 125.9, 126.2, 128.9, 129.7, 137.7, 150.3, 169.9, 170.6; IR ($CHCl_3$) ν_{max} 1773, 1713, 1638, 1516 cm^{-1}. Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.22; H, 9.81; N, 3.54.

4.6. General procedure for *N*-*p*-tolyl-2-alkylidene-3-alkylsuccinimides 7a–c

A solution of *N*-*p*-tolylalkylmaleimides (**6a–c**, 10 mmol), triphenylphosphine (10 mmol) and aliphatic aldehyde (15 mmol) in glacial acetic acid (30 mL) was refluxed for 18 h with constant stirring. Acetic acid was distilled off in vacuo at 50 °C and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (9:1) gave *N*-*p*-tolyl-2-alkylidene-3-alkylsuccinimides **7a–c** in 77–80% yields.

The above compounds were also obtained from *N*-*p*-tolylalkylisomaleimides **5a–c** using the same procedure.

4.6.1. 3-Hexyl-4-hexylidene-1-*p*-tolyl-pyrrolidine-2,5-dione (7a). Off white solid (2.85 g, 80%), mp 69–70 °C (petroleum ether+ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, $J=6$ Hz, 3H), 0.91 (t, $J=6$ Hz, 3H), 1.15–1.45 (m, 12H), 1.53 (quintet, $J=6$ Hz, 2H), 1.75–1.98 (m, 1H), 1.98–2.15 (m, 1H), 2.28 (q, $J=8$ Hz, 2H), 2.38 (s, 3H), 3.51 (unresolved multiplet, 1H), 6.93 (dt, $J=8$, 2 Hz, 1H), 7.17 (d, $J=8$ Hz, 2H), 7.27 (d, $J=8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 14.0, 21.2, 22.4, 22.5, 24.6, 28.1, 29.2, 29.3, 30.7, 31.5, 31.6, 42.5, 126.2, 129.0, 129.3, 129.7, 138.4, 140.3, 169.3, 176.9; IR ($CHCl_3$) ν_{max} 1767, 1709, 1670, 1516 cm^{-1}. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.79; H, 9.43; N, 3.72.

4.6.2. 3-Decyl-4-decylidene-1-*p*-tolyl-pyrrolidine-2,5-dione (7b). Off white solid (3.62 g, 78%), mp 71–73 °C (petroleum ether+ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 6H), 1.25 (bs, 28H),

1.40–1.60 (m, 2H), 1.75–2.15 (m, 2H), 2.27 (q, $J=8$ Hz, 2H), 2.37 (s, 3H), 3.50 (unresolved multiplet, 1H), 6.92 (dt, $J=8$, 2 Hz, 1H), 7.17 (d, $J=8$ Hz, 2H), 7.27 (d, $J=8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.2, 22.6, 24.7, 28.5, 29.3, 29.4, 29.5 (11×CH_2), 30.7, 31.9, 42.5, 126.2, 129.0, 129.4, 129.7, 138.4, 140.3, 169.2, 176.8; IR (Nujol) ν_{max} 1769, 1719, 1670, 1516 cm^{-1}. Anal. Calcd for $C_{31}H_{49}NO_2$: C, 79.60; H, 10.56; N, 2.99. Found: C, 79.52; H, 10.44; N, 3.07.

4.6.3. 3-Tetradecyl-4-tetradecylidene-1-*p*-tolyl-pyrrolidine-2,5-dione (7c). Off white solid (4.48 g, 77%), mp 73–75 °C (petroleum ether+ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80–0.90 (m, 6H), 1.10–1.40 (m, 44H), 1.45–1.55 (m, 2H), 1.80–1.95 (m, 1H), 1.95–2.10 (m, 1H), 2.20–2.33 (m, 2H), 2.37 (s, 3H), 3.50 (unresolved multiplet, 1H), 6.91 (dt, $J=8$, 2 Hz, 1H), 7.17 (d, $J=10$ Hz, 2H), 7.26 (d, $J=10$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 21.2, 22.7, 24.7, 28.5, 29.3–29.6 (21×CH_2), 30.8, 31.9, 42.5, 126.2, 129.1, 129.4, 129.7, 138.5, 140.4, 169.3, 176.9; IR ($CHCl_3$) ν_{max} 1769, 1705, 1670, 1518 cm^{-1}. Anal. Calcd for $C_{39}H_{65}NO_2$: C, 80.77; H, 11.30; N, 2.42. Found: C, 80.67; H, 11.16; N, 2.53.

4.7. General procedure for *N*-*p*-tolyldialkylmaleimides 8a–c

To a stirred solution of *N*-*p*-tolyl-2-alkylidene-3-alkyl-succinimides (**7a–c**, 5 mmol) in THF (20 mL) was added triethylamine (20 mL) and the reaction mixture was refluxed for 48 h and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (9.5:0.5) gave *N*-*p*-tolyldialkylmaleimides **8a–c** in 95–96% yields.

4.7.1. 3,4-Dihexyl-1-*p*-tolyl-pyrrole-2,5-dione (8a). Thick oil (1.70 g, 96%), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, $J=6$ Hz, 6H), 1.15–1.45 (m, 12H), 1.57 (quintet, $J=6$ Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J=8$ Hz, 4H), 7.22 (s, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.5, 23.9, 28.6, 29.3, 31.4, 125.7, 129.3, 129.5, 137.2, 141.1, 170.9; IR ($CHCl_3$) ν_{max} 1707, 1516, 1395 cm^{-1}. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.79; H, 9.45; N, 3.99.

4.7.2. 3,4-Bis-decyl-1-*p*-tolyl-pyrrole-2,5-dione (8b). Thick oil (2.22 g, 95%), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 6H), 1.25 (bs, 28H), 1.57 (quintet, $J=6$ Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J=6$ Hz, 4H), 7.22 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 21.0, 22.6, 23.9, 28.6, 29.3, 29.5, 29.6 (3×CH_2), 31.9, 125.7, 129.3, 129.5, 137.1, 141.1, 170.9; IR (neat) ν_{max} 1711, 1516, 1389 cm^{-1}. Anal. Calcd for $C_{31}H_{49}NO_2$: C, 79.60; H, 10.56; N, 2.99. Found: C, 79.66; H, 10.47; N, 3.03.

4.7.3. 3,4-Ditetradecyl-1-*p*-tolyl-pyrrole-2,5-dione (8c). Thick oil (2.76 g, 95%), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, $J=6$ Hz, 6H), 1.25 (bs, 44H), 1.57 (quintet, $J=6$ Hz, 4H), 2.36 (s, 3H), 2.44 (t, $J=6$ Hz, 4H), 7.22 (s, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 23.9, 28.6, 29.3, 29.5, 29.6 (7×CH_2), 31.9, 125.7, 129.3, 129.5, 137.2, 141.1, 170.9; IR ($CHCl_3$) ν_{max} 1707, 1516, 1394 cm^{-1}. Anal. Calcd for $C_{39}H_{65}NO_2$: C, 80.77; H, 11.30; N, 2.42. Found: C, 80.81; H, 11.42; N, 2.37.

4.8. 2-Methylene-*N*-*p*-tolyl-succinamic acid (10)

To a stirred solution of itaconic anhydride (2.00 g, 17.8 mmol) in ether (10 mL) at room temperature was added a solution of *p*-toluidine (1.90 g, 17.8 mmol) in ether (10 mL) in a dropwise fashion over a period of 10 min. The reaction mixture was stirred at room temperature for 50 min. and the precipitated product was filtered, washed with ether (2×10 mL) and dried under vacuum to obtain 2-methylene-*N*-*p*-tolyl-succinamic acid **10** (4.00 g, 98% yield); White solid; mp 188–190 °C (ethyl acetate+ethanol); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz) δ 2.20 (s, 3H), 3.28 (s, 2H), 5.69 (s, 1H) 6.21 (s, 1H), 6.98 (d, $J=8$ Hz, 2H), 7.39 (d, $J=8$ Hz, 2H), 9.48 (bs, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 20.7, 39.8, 119.3, 127.8, 129.4, 132.2, 136.2, 137.1, 168.0, 168.6; IR (Nujol) ν_{max} 3292, 2700–2500, 1676, 1655, 1630, 1462 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.62; H, 6.05; N, 6.24.

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Polybrominated diphenyl ethers (BDEs); preparation of reference standards and fluorinated internal analytical standards

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Abstract—Four new difluorinated tetra- and pentabromo BDE internal standards for GC–MS/GC–ECD analysis, **2F-BDE 47**, **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119**, have been prepared in 98–99.0% purity, mainly by coupling of the new tribromodifluorophenols (**19**–**21**) and symmetrical bromodiphenyliodonium salts (**8**, **22**). The four difluorinated BDEs showed promising properties as internal standards for quantitative BDE analysis. Tetra-, penta-, hexa- and hepta-brominated BDE reference standards, **BDE 75**, **BDE 85**, **BDE 138** and **BDE 183**, were also prepared in 98.4–99.8% purity and characterised.

1. Introduction

Polybrominated diphenyl ethers (BDEs)[1–8] are industrial chemicals used as flame-retardants in electronics, plastics, furnishing foam, textiles, automobile components etc. Three crude technical mixtures of penta-, octa- and deca-brominated BDEs, respectively, are commercially available. They are released into the environment at industrial sites or from household trash. The presence of BDEs in air and biological samples even from remote areas indicates a world-wide pollution problem.

The structurally similarity of BDEs and PCBs has given rise to environmental concern. Like PCBs, BDEs resist degradation in the environment and are thus persistent organic pollutants that remain in the environment for years. BDEs appear to share some toxicological properties with PCBs. In particular, the less brominated isomers such as the tetra-, penta- and hexa-BDEs are potential toxins and accumulate in the bodies of animals and humans due to their high affinity for lipids. Octa- and deca-brominated congeners have lower bioaccumulative and biological activity, but a potential degradation of these BDEs into the less brominated and more toxic BDEs has been suggested. Compared with PCBs, the effects of human exposure to BDEs are not well known and little information is available of human toxicity, carcinogenicity and behavioural effects. The effect of these widespread pollutants on human health and the environment is still under investigation. There are 209 theoretically possible congeners divided into 10 congener groups from mono- to deca-BDE. They are numbered according to IUPAC's PCB based system.[9,10]

Methods for detection and quantification of BDEs are mostly based on extraction and clean-up followed by GC–MS or GC–ECD analysis. However, individual BDEs are not commercially readily available. Due to the lack of pure reference standards for most BDE congeners, quantitative analyses have been carried out using technical BDE product mixtures as standards.

Internal standards are used for quantitative analysis. Some ^{13}C incorporated compounds have been used as internal standard for quantification of BDEs. The preparation of ^{13}C products[11] is, however, inconvenient and laborious since the carbon skeleton of these compounds have to be built up from small ^{13}C isotope labelled building blocks. A small change in the physical and chemical properties of a compound is, however, obtained by the introduction of a fluoro substituent. The slightly more volatile character of such fluoro derivatives make them as suitable internal standards for GC–MS (-ECD). Monofluorinated PAHs have been used as standards for environmental analysis due to their suitable chemical and physical properties. We wanted to prepare fluorinated BDE analogues (F-BDE) and investigate whether these derivatives correspondingly would have suitable physical and chemical properties to be used as internal standards in BDE analysis. Different *o*, *m* and *p* mono- or difluoro isomers were expected to give different degree of chromatographic resolution relative to the parent compounds. This will be discussed.

Keywords: Polybrominated diphenyl ethers; BDE; Flame retardants; Fluorinated BDE; 2F-BDE; Internal standard; Analytical standard; Synthesis.
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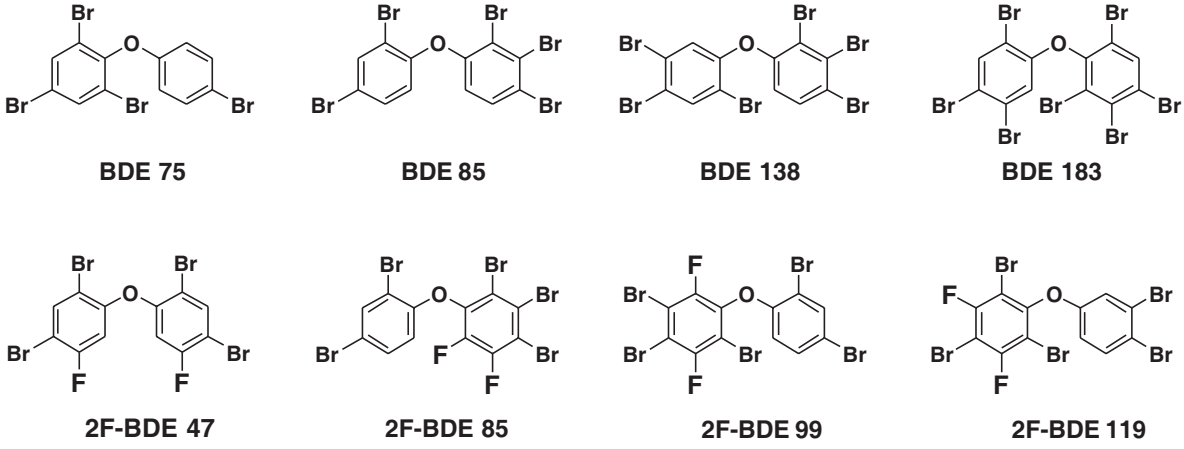
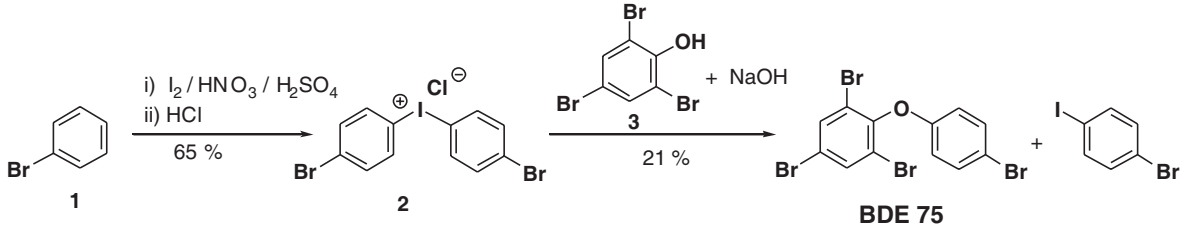


Scheme 1.

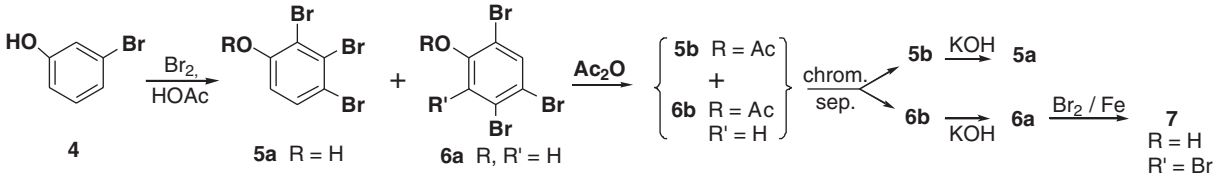
Since there is a need for analytical BDE standards for qualitative and quantitative BDE analysis, we hereby present the synthesis of high purity reference standards and fluorinated internal standards. The four new internal standards **2F-BDE 47**, **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119** (see Scheme 1) and their respective tribromodifluorophenolic precursors (**19**–**21**) have not previously been prepared, while the four reference standards **BDE 75**, **BDE 85**, **BDE 138** and **BDE 183** have not been spectroscopically fully characterised earlier.

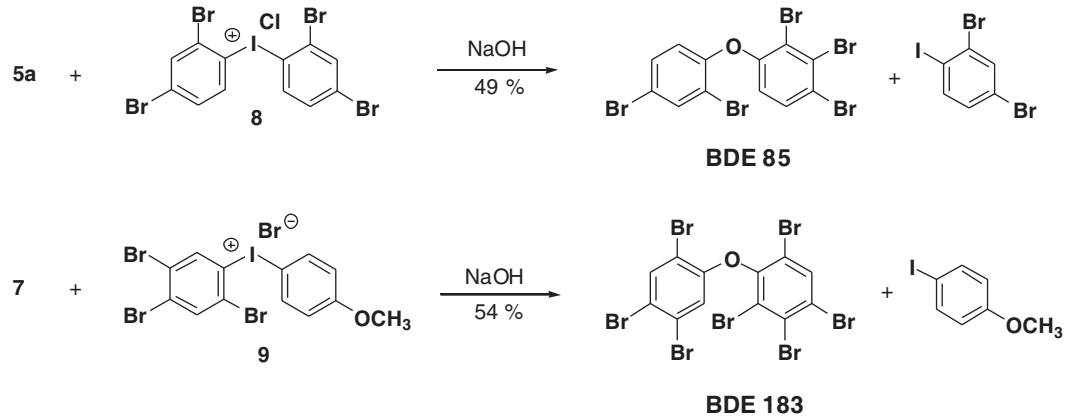
2. Results and discussion

The BDE analytical standards were prepared as described below (Schemes 2–6), mainly from the appropriate

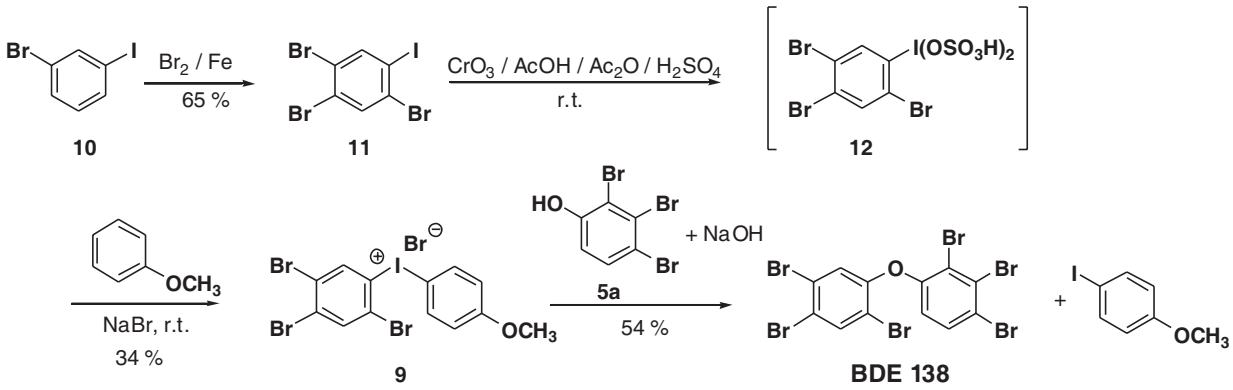


Scheme 2.

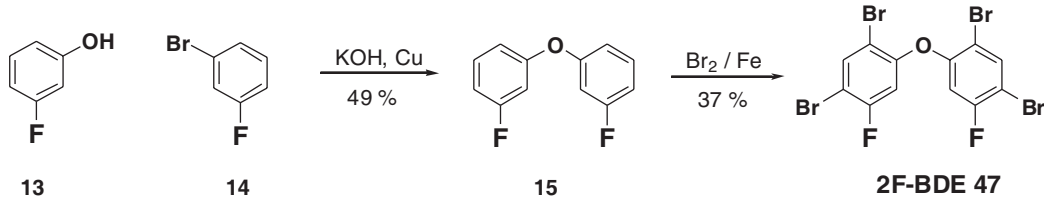




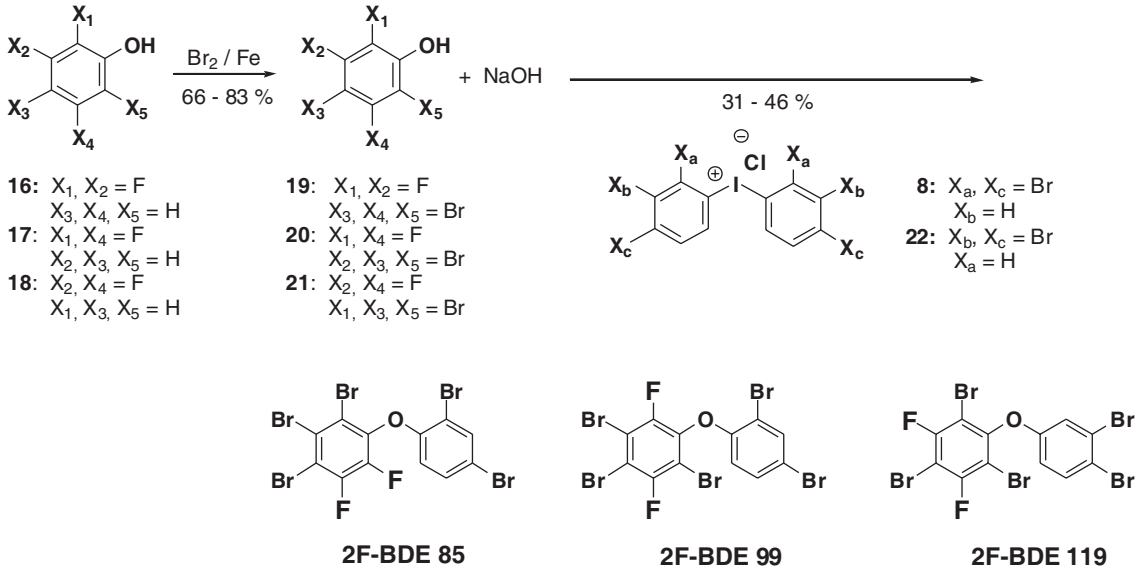
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

brominated diphenyliodonium salts and bromo(fluoro) phenols. Since the purpose of the work was the preparation of reference compounds and internal standards, we focused more on the purity of the products and intermediates than the respective yields.

2.1. Reference standards

Compound **BDE 75**[12,16] was prepared in 98.4% purity from bromobenzene (**1**) and 2,4,6-tribromophenol (**3**) via 4,4′-dibromodiphenyliodium chloride (**2**) as shown in Scheme 2.[13–15] The diphenyliodonium salt (**2**)[16] was prepared by $(IO_2)SO_4$ oxidation of bromobenzene (**1**) followed by coupling with **1** by electrophilic aromatic substitution.[17–20] The coupling is reported always to give only the *para* product, due to steric reasons. Compound **2** was precipitated as the hydrochloride salt by the addition of HCl. Nucleophilic substitution by phenol **3** afforded **BDE 75**. The 4-bromoiodobenzene leaving group was removed by chromatography.

Compounds **BDE 85**[21] (99.0% purity) and **BDE 183**[22] (99.4% purity) were prepared as shown in Scheme 3 from the tri- and tetrabromophenols (**5a**, **7**) and 2,2′,4,4′-tetrabromodiphenyliodonium chloride (**8**) and 4-methoxyphenyl-2′,4′,5′-tribromophenyliodonium bromide (**9**), respectively.[23] The bromophenol nucleophiles **5a** and **7** were prepared by bromination of **4**. As expected, the activated 3-bromophenol

4 gave a mixture of the two *ortho* and *para* substituted product isomers (**5a**, **6a**), with the less sterically hindered **6a** as the dominating isomer. The isomers could not be separated and the bromination product mixture **5a/6a** was therefore acetylated directly to give a mixture of the acetates **5b/6b**. Chromatographic separation of **5b** and **6b** and individual hydrolysis of the respective isomers afforded the pure phenols **5a** and **6a** in 98.2 and 99.4% purity. Due to a modified preparation method, much higher yields of the acetates (**5b**/9% and **6b**/24%) and phenols (**5a**/82% and **6a**/98%) were obtained compared to previous reports (**5b**/1% and **6b**/3%; **5a**/33% and **6a**/88%).[23] Compound **7** was obtained in 98% purity and 71% yield after a final *ortho* bromination[16] of the major isomer **6a**. The symmetrical tetrabrominated diphenyliodonium chloride **8** was prepared from 1,3-dibromobenzene as described in Scheme 2 for the preparation of **2**. The unsymmetrical diphenyliodonium bromide **9** was prepared from 3-bromoiodobenzene (**10**) as shown in Scheme 4 for the preparation of **BDE 138**. As a consequence of the geometry of the transition state, it has been shown that nucleophiles preferentially attack unsymmetrical diphenyliodonium salts, such as **9**, at the aryl group with a large *ortho* substituent.[24] Nucleophilic substitution by tetrabromophenol **7** therefore afforded the coupling product **BDE 183**[25] by nucleophilic attack on the tribromophenyl group of **9**.

Compound **BDE 138**[21] was prepared in 99.8% purity from 3-bromoiodobenzene (**10**) and 2,3,4-tribromophenol (**5a**) as shown in Scheme 4. Bromination[16] of **10** afforded the *ortho* and *para* brominated product **11** in 98% purity after recrystallization. Compound **9** has previously been prepared via the dihydrogensulfate **12** by H_2O_2 oxidation of **11**.[25] However, we obtained a higher yield by CrO_3 oxidation[26] of **11** to **12**, which was not isolated before the *para* coupling with anisole to afford the unsymmetrical appropriately brominated diphenyliodonium bromide (**9**). The tribromophenol **5** was obtained as discussed above for the preparation of **BDE 85** (Scheme 3).

2.2. Internal standards

Internal standards for chromatography are supposed to elute close together with the parent compounds with baseline resolution. There are indications[27] that the *ortho* monofluorinated F-BDEs give larger chromatographic separation from the parent compounds than the corresponding *meta* substituted isomers, while the *para* monofluorinated BDEs give hardly any separation. As expected, difluorinated 2F-BDEs give a larger separation than mono F-BDEs. Based on this experience the four *m*,*m*- and *o*,*m*-difluorinated 2F-BDEs discussed below were supposed to be promising as internal standards and hence they were selected for synthesis.

Compound **2F-BDE 47** was prepared in 98.0% purity by bromination of bis(*m*-fluorophenyl) ether (**15**). Intermediate **15** was synthesised[21] in 98.8% purity from 3-fluorophenol (**13**) and 3-bromofluorobenzene (**14**), see Scheme 5. As expected, the desired and less sterically hindered *ortho* and *para* tetrabrominated isomer was formed on bromination of **15**. The identity of the product was established by ^{1}H and ^{13}C NMR studies. Only two proton signals were observed by ^{1}H NMR, indicating the symmetry of the molecule. Both signals were doublets, and the coupling constants were as expected from *o* or *m* F–H coupling (J_{FH}=7.1, 8.7 Hz). The particular low frequency (*d* 6.68) of the H6 and H6′ signal is caused by the characteristic shielding effect of the fluoro substituent. The ^{13}C NMR data also supported the structure of **2F-BDE47**, and the most characteristic observations were the large C–F coupling constants, $^1J_{CF}$= 250 Hz (J_{F-C1}) and $^2J_{CF}$=26.6 Hz (J_{F-C6}), and the high frequency of the C5 signal at *d* 158.7.

Compounds **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119** were obtained in 99.0, 98.8 and 99.0% purity, respectively, by coupling of the appropriate tribromodifluorophenols (**19–21**) and the iodonium salts **8** and **22** as shown in Scheme 6. The nucleophilic substitution reactions were corresponding to the reactions discussed above for the preparation of the external standards in Schemes 2–4. The new phenols (**19–21**) were prepared in 98.4–99.2% purity by complete bromination of the difluorophenol substrates (**16–18**). Bromination in tetrachloromethane as solvent was unsuccessful since a series of chloro-substituted products were isolated. However, the fully brominated phenolic precursors (**19–21**) were obtained in good yields using 1,2-dibromoethane as a solvent. ^{1}H, ^{13}C, and ^{19}F NMR spectra of the new phenols (**19–21**) and the fluorinated **2F-BDE** products showed the characteristic features of fluorinated aryl compounds. Only one single phenolic signal was observed in ^{1}H NMR for the fully substituted phenols (**19–21**) while the 2F-BDEs had the expected ^{1}H NMR coupling patterns to be assigned with the various dibromophenyl groups, similar to **8** and **22**. ^{13}C NMR confirmed the expected tribromodifluoro phenolic and 2F-BDE structures, especially based on the large C–F coupling constants ($^1J_{CF}$ approx.=245–260 Hz, $^2J_{CF}$ approx.=20–26 Hz) and the high frequency of the fluoro connected carbons (approx. d_{C-F} 140–160). The number of signals, the shift values and the coupling patterns in the respective ^{19}F NMR spectra supported the proposed tribromodifluorophenolic (**19–21**) and **2F-BDE** structures.

2.3. GC–MS analysis

All the four internal fluorinated standards prepared in this work separated from the non-fluorinated analogues by GC–MS. The analyses showed that a higher resolution was obtained in the **BDE 47/2F-BDE 47** system and the **2F-BDE 85/BDE 85** system (see Fig. 1) compared to the **2F-BDE 99/BDE 99** and **2F-BDE 119/BDE 119** systems, correspondingly. Since we have experienced[27] that *ortho* fluorinated F-BDEs give larger chromatographic separation from the parent compounds than the corresponding *meta* substituted isomers, the higher net dipole effect obtained by the introduction of two neighbouring *o*-/*m*- fluoro substituents in **2F-BDE 85** could explain the greater separation compared to the *m*-/*m*- difluoro compound **2F-BDE 119**. In **2F-BDE 99** the fluoro substituents are *para* to each other and this may neutralize the effect of the introduction of two fluorines.

All the analytical standards are now available from Chiron AS, Norway, and further work on the syntheses of (2F-)BDEs and the development of analytical methods based on BDE analytical standards are in progress.

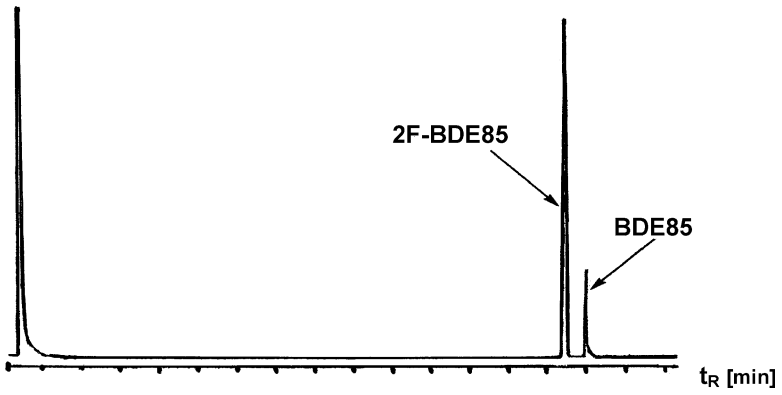


Figure 1. GLC of **2F-BDE 85** and **BDE 85**.

3. Conclusion

Four new difluorinated tetra- and pentabromo BDE internal standards for GC–MS/GC–ECD analysis, **2F-BDE 47**, **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119**, have been prepared in 98–99.0% purity. **2F-BDE 47** was prepared by bromination of the bis(fluorophenyl) ether (**15**). **2F-BDE 85**, **2F-BDE 99** and **2F-BDE 119** were synthesised by coupling of the new tribromodifluorophenols (**19–21**) and the symmetrical iodonium salt (**22**, **23**) precursors. All four difluorinated BDEs showed promising properties as internal standards for quantitative BDE analysis. Four tetra-, penta-, hexa- and hepta-brominated reference standards of BDE (**BDE 75**, **BDE 85**, **BDE 138**, **BDE 183**) were prepared in 98.4–99.8% purity from the appropriate brominated diphenyliodonium salts (**2**, **8**, **9**) and phenols (**3**, **5a**, **7**) and characterised.

4. Experimental

4.1. General

Chemicals. Compounds **1**, **3**, **4**, **10**, **13**, **14**, **16**, **17** and **18** were purchased from Acros. Solvents. Analytical quality. $^{1}H/^{13}C$ NMR. Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in ppm downfield from TMS. Hexafluorobenzene was used as reference for ^{19}F NMR. MS: Finnigan MAT 95 XL Mass Spectrometer (EI/70 eV). All the multiple MS molecular ions for polybrominated compounds, due to the presence of the $^{79}Br/^{81}Br$ isotopes, are assigned as M. IR. Thermo Nicolet Nexus FT-IR spectrophotometer. All melting points are uncorrected, measured by Sanyo Gallenkamp apparatus. Flash chromatography. Silica (sds, 60 A, 40–63 μm).

Method A. General method[13–16] for the preparation of symmetrical diphenyliodonium chlorides (**2**, **8**, **22**). To a mixture of sulfuric acid (concd, 1.9 ml) and fuming sulfuric acid (30%, 3.75 ml) was added I_2 (1.62 g, 6.37 mmol) with stirring. An additional mixture of sulfuric acid (concd, 0.5 ml), fuming sulfuric acid (65%, 0.25 ml) and fuming HNO_3 (100, 0.8 ml) was added slowly. Yellow crystals precipitated after stirring at 75 °C for 1.5 h. The reaction mixture was cooled to 0 °C and the appropriate bromobenzene substrate (32 mmol) was added slowly. After stirring at 45 °C for 2 h and cooling to 0 °C, water (15 ml) was slowly added and nitrogen oxides were removed by N_2 flushing while stirring for 1 h. Water was removed and the brown oily product was dissolved in methanol (150 ml). White crystalline product was obtained by addition of hydrochloric acid (concd, 60 ml), filtering and washing by methanol.

Method B. General method[16–20] for the coupling of diphenyliodonium salts and phenols for the preparation of **BDE 75**, **BDE 85**, **BDE 138**, **BDE 183**, **2F-BDE 85**, **2F-BDE 99**, **2F-BDE 119**. A solution of the phenol (1 equiv) in aqueous NaOH (approx. 1.1 equiv) was refluxed before the addition of the diphenyliodonium chloride (1 equiv). A brown oily product was obtained after 2 h reflux. If necessary, the pH was adjusted by the addition of aqueous NaOH before the crude product was isolated by extraction at pH 11 and dried. The pure diphenyl ether was obtained by flash chromatography (10% dichloromethane in hexane). The product was recrystallised from methanol.

Method C. General method[16] for the Br_2/Fe bromination for the preparation of **7**, **11**, **19**, **20**, **21**. A solution of the substituted phenol or benzene substrate (1 equiv) and Fe powder (0.5–1 equiv) in dichloromethane or 1,2-dibromoethane was refluxed and a solution of bromine (1–6 equiv) in dichloromethane or dibromoethane was added dropwise. (The amount of Fe and Br_2 depended on the number of bromo substituents to be introduced and is given specifically for each experiment below). After 2–5 h reflux $NaHSO_3$ (5%) was added and the product was extracted, dried and recrystallized from hexane.

4.1.1. 4,4′-Dibromodiphenyliodonium chloride (2).[16,17] The title compound was prepared from bromobenzene (**1**) by Method A; 65% yield, pure by ^{1}H NMR (lit.[16] 23%); mp 211–212 °C (lit.[17] 212 °C).

4.1.2. 2,3,4-Tribromophenyl acetate (5b) and 2,4,5-tribromophenyl acetate (6b). The title compound was prepared from 3-bromophenol (**4**).[23] 3-Bromophenol (**4**) (1 equiv) in acetic acid (80 ml) was added dropwise to bromine (2.2 equiv) in acetic acid (125 ml) and stirred at room temperature for 1.5 h. The reaction mixture was added to $NaHSO_3$ (5%, 100 ml) and the 3,4-dibromophenol intermediate was extracted, dried and purified by flash chromatography (CH_2Cl_2/hexane; 3:2). Bromination was

repeated as described above, using 3,4 dibromophenol (1 equiv) in acetic acid (40 ml) and bromine (1 equiv) in acetic acid (18 ml). The product mixture (45% yield) of 2,3,4 tribromophenol (**5a**) and 2,4,5 tribromophenol (**6a**) (1 equiv), pyridine (1 equiv) and acetic acid anhydride (3 equiv) in dichloromethane (100 ml) was stirred vigorously at room temperature for 2 h. The individual acetate products (**5b**) and (**6b**) were isolated by flash chromatography (CH_2Cl_2/hexane; 1:1).

4.1.3. 2,3,4-Tribromophenyl acetate (5b). White crystals; 8.81% yield; 96.9% purity (GLC); mp 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J=8.7 Hz, 1H, H5), 7.00 (d, J=8.7 Hz, 1H, H6), 2.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5 (carbonyl), 148.8 (C1), 132.8 (C5), 129.2 (C3), 123.6 (C6), 123.4 (C4), 121.8 (C2), 21.2 (CH_3); MS: *m*/*z* 376 (M, 2%), 374 (M, 6), 372 (M, 6), 370 (M, 2), 334 (28), 332 88 (100), 330 (99), 328 (28). IR (KBr) ν_{max}: 3070 (w), 1758 (s), 1561 (w), 1458 (w), 1432 (s), 1369 (s), 1353 (s), 1239 (m), 1202 (s), 1052 (m), 1013 (m), 946 (w), 923 (s), 861 (m), 807 (m), 732 (m) cm^{-1}.

4.1.4. 2,4,5-Tribromophenyl acetate (6b).[28] White crystals; 24.2% yield; 99.0% purity (GLC); mp 98.5–99.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H, H3), 7.43 (s, 1H, H6), 2.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9 (s, 1C, carbonyl), 147.8 (C1), 136.8 (C3), 128.4 (C6), 123.9 (C5 or C4), 122.5 (C4 or C5), 115.9 (C2), 20.7 (CH_3); MS: *m*/*z* 376 (M, 3%), 374 (M, 8), 372 (M, 8), 370 (M, 3), 334 (28), 332 (100), 330 (99), 328 (30). IR (KBr) ν_{max}: 3501 (w, br), 3080 (m), 1762 (s), 1452 (m), 1363 (m), 1331 (m), 1244 (w), 1221 (m), 1198 (s), 1108 (m), 1052 (s), 1009 (w), 928 (m), 887 (m) cm^{-1}.

4.1.5. 2,3,4-Tribromophenol (5a).[25,29] The title compound was prepared from **5b**; 2,3,4-tribromophenyl acetate (**5b**) (5.94 g, 15.28 mmol) and KOH (2 M, 10 ml) in methanol (100 ml) were refluxed for 24 h. Methanol was distilled off and the remaining oil was extracted at pH 2–3 after addition of HCl (10%). The product was recrystallised from hexane to give white crystals; 81.7% yield; 98.2% purity (GLC); mp 93–94 °C (lit.[25] 95 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=8.8 Hz, 1H, H5), 6.90 (d, J=8.8 Hz, 1H, H6), 5.63 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6 (C1), 132.9 (C5), 126.8 (C3), 115.9 (C4), 115.8 (C6), 114.6 (C2); MS: *m*/*z* 334 (M, 30%), 332 (M, 98), 330 (M, 100), 328 (M, 32), 252 (12$^+$), 250 (22), 248 (11), 143 (17), 141 (17); IR (KBr) ν_{max}: 3478 (m, br), 3060 (w), 2360 (w), 1886 (w), 1701 (w), 1635 (w), 1575 (m), 1557 (m), 1439 (s), 1381 (m), 1279 (s), 1197 (s), 1181 (m), 1157 (m), 1129 (w), 881 (m), 816 (s) cm^{-1}.

4.1.6. 2,4,5-Tribromophenol (6a).[25,29] The title compound was prepared by hydrolysis of **6b** as described for **5a** above, to give white crystals; 98.4% yield; 99.4% purity (GLC); mp 85–86 °C (lit.[25] 87 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (s, 1H, H3), 7.31 (s, 1H, H6), 5.48 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 152.5 (C1), 135.6 (C3), 125.1 (C5), 121.2 (C6), 116.0 (C4), 110.0 (C2); MS: *m*/*z* 334 (M, 29%), 332 (M, 99), 330 (M, 100), 328 (M, 30),143 (17), 141 (7), 63 (5), 62 (8), 61 (5) IR (KBr) ν_{max}: 3363 (m, br), 3074 (w), 1726 (w), 1574 (w), 1552 (m), 1465 (m), 1446 (s), 1383 (w), 1362 (m), 1281 (m), 1246 (w), 1195 (m), 1106 (w), 1044 (m), 874 (s) cm^{-1}.

4.1.7. 2,3,4,6-Tetrabromophenol (7).[25,30] The title compound was prepared from **6a** by Method C (Fe 1.0 equiv; Br_2 1.1 equiv). The crude product was recrystallised from hexane to give 70.7% yield; 98.0% purity (GLC); mp 113–114 °C (lit.[25] 112 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H, H5), 6.03 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9 (C1), 134.9 (C5), 127.0 (C3), 116.0 (C4), 114.3 (C2), 108.7 (C6); MS: *m*/*z* 414 (M, 13%), 412 (M, 60), 410 (M, 100), 408 (M, 64), 406 (M, 3), 330 (9), 328 (9), 221 (11); IR (KBr) ν_{max}: 3418 (m, br), 3057 (w), 1708 (w), 1540 (w), 1465 (w), 1429 (s), 1348 (s), 1294 (m), 1274 (w), 1251 (w), 1178 (m), 1150 (m), 1076 (m), 895 (w), 868 (m) cm^{-1}.

4.1.8. 2,2′,4,4′-Tetrabromodiphenyliodonium chloride (8).[12,16,25] The title compound was prepared from **5a** by Method A and characterised according to literature.[12]

4.1.9. 2,4,5-Tribromoiodobenzene (11).[25] The title compound was prepared from 3-bromoiodobenzene **10** by Method C (Fe 0.9 equiv; Br_2 2 equiv). The product was recrystallised from hexane to give beige crystals; 64.9% yield; 97.7% purity (GLC); mp 164–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, H6), 7.84 (s, 1H, H3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (C6), 136.2 (C3), 129.3 (C2), 125.5 (C4), 124.3 (C5), 100.0 (C1); MS: *m*/*z* 444 (M, 27%), 442 (M, 99), 440 (M, 100), 438 (M, 28), 317 (6$^+$), 315 (19), 313 (19), 310 (8), 236 (7), 234 (14), 232 (7), 74 (28). IR (KBr) ν_{max}: 3062 (w), 1737 (w), 1458 (w), 1438 (m), 1414 (m), 1288 (m), 1110 (m), 1100 (m), 1037 (w), 1010 (s), 878 (s) cm^{-1}.

4.1.10. 4-Methoxyphenyl-2′,4′,5′-tribromophenyliodonium bromide (9).[16,25] The title compound was prepared[26] from **11**; CrO_3 (1.5 g, 15 mmol) was dissolved in acetic acid (600 ml) and acetic acid anhydride (275 ml), cooled to 0 °C and added **11** (4.5 g, 11.4 mmol). Sulfuric acid (concd 1.9 ml, 34.9 mmol) was added drop-wise to keep the temperature below 25 °C and the reaction was left stirring for 22 h. Anisole (1.365 ml, 12.5 mmol) was added slowly at 0 °C before stirring at room temperature for 96 h. The reaction mixture was poured over an aqueous methanol solution (30%, 1200 ml), stirred for 1 h. and filtered. Aqueous NaBr (2.5 g, 24.3 mmol in 30 ml H_2O) was added slowly and the solution was stirred for 3 h. The beige crystals were filtered off, washed with water and acetone and dried; 34.1% yield; mp 179–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.92 (s, 1H, H6′), 8.34 (s, 1H, H3′), 8.10 (d, 2H, H3, H5), 7.07 (d, 2H, H2, H6), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$: δ 162.3 (C4), 141.8 (C6′), 137.6 (C3′), 137.5 (C2, C6), 129.8 (C2′, C4′, C5′), 129.2 (C2′, C4′, C5′), 127.0 (C2′, C4′, C5′), 125.9 (C1′), 118.1 (C3, C5), 110.7 (C1), 56.5 (OCH_3).

4.1.11. Bis(*m*-fluorophenyl) ether (15).[31] The title compound was prepared from 3-fluorophenol (**13**) and 3-bromofluorophenol (**14**);[21] **13** (3.11 g, 27.8 mmol) and KOH (1.56 g, 27.8 mmol) was stirred at 50 °C for 30 min before the addition of **14** (5.0 g, 28.7 mmol) and Cu powder (1.72 g, 27.1 mmol). The reaction was heated to 170 °C for 2 h. The product was isolated as an oil by flash

chromatography (10% CH_2Cl_2 in hexane). 49.1% yield; 98.8% purity (GLC); ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.29 (dd, J=8.3, 1.6 Hz, 2H, H5 and H5′), 6.83 (ddt, J=8.3, 2–7, 0.8 Hz, 2H, H6, H6′), 6.81 (dd, J=8.3, 2.2 Hz, 2H, H4, H4′), 6.73 (dt, J=10.0, 2.3 Hz, 2H, H2, H2′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (d, $^1J_{CF}$=247.1 Hz, C3, C3′), 158.3 (d, $^3J_{CF}$=11.0 Hz, C1, C1′) 131.1 (d, $^3J_{CF}$=9.4 Hz, C5, C5′), 115.0 (d, $^4J_{CF}$=2.8 Hz, C6, C6′), 111.1 (d, $^2J_{CF}$=21.0 Hz, C4, C4′), 107.2 (d, $^2J_{CF}$=24.3 Hz, C2, C2′); MS: *m/z* 206 (M, 100%), 178 (40), 177 (57), 112 (38), 95 (28); IR (KBr) ν_{max}: 3076 (m), 1606 (s), 1480 (s), 1450 (s), 1309 (s), 1276 (s), 1164 (s), 1135 (s), 1071 (m), 975 (s), 853 (s), 773 (s), 679 (s) cm^{-1}.

4.1.12. 2,3,4-Tribromo-5,6-difluorophenol (19). The title compound was prepared from 2,3-difluorophenol (**16**) by Method C (Fe 0.6 equiv, Br_2 5.8 equiv) to afford beige crystals; 78.8% yield; 99.2% purity (GLC); mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4 (dd, $^1J_{CF}$=249.9 Hz, $^2J_{CF}$=13 Hz, C5), 142.8 (dd, $^2J_{CF}$=11.0 Hz, $^3J_{CF}$=3.3 Hz, C1), 139.1 (dd, $^1J_{CF}$=252.6 Hz, $^2J_{CF}$=16.5 Hz, C6), 121.9 (d, $^3J_{CF}$=4.8 Hz, C3), 109.8 (dd, $^3J_{CF}$=3.7 Hz, $^4J_{CF}$=1.1 Hz, C2), 104.9 (d, $^2J_{CF}$=20.5 Hz, C4); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −120.4 (d, J=21.1 Hz, F5), −153.4 (d, J=21.1 Hz, F6); MS: *m/z* 370 (M, 29%), 368 (M, 100), 366 (M, 100), 364 (M, 30), 288 (6), 286 (11), 284 (5), 259 (8), 257 (8), 179 (12), 177 (12). IR (KBr ν_{max}): 3673 (w), 3528 (m, br), 1605 (m), 1575 (m), 1480 (s), 1405 (m), 1332 (w), 1299 (m), 1240 (m), 1199 (m), 1072 (m), 926 (m), 804 (s) cm^{-1}. HRMS calcd for $C_6Br_3F_2HO$ (M^+): 363.7546. Found: 363.7545.

4.1.13. 2,4,5-Tribromo-3,6-difluorophenol (20). The title compound was prepared from 3,6-difluorophenol (**17**) by Method C (Fe 0.5 equiv; Br_2 5.5 equiv) to afford beige crystals; 66.3% yield; 99.0% purity (GLC); mp 78–79.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1 (dd, $^1J_{CF}$=244.3 Hz, $^4J_{CF}$=3.9 Hz, C3), 145.4 (dd, $^1J_{CF}$=242.6 Hz, $^4J_{CF}$=4.5 Hz, C6), 142.1 (dd, $^2J_{CF}$=17.1 Hz, $^3J_{CF}$=3.8 Hz, C1), 112.6 (dd, $^2J_{CF}$=21.5 Hz, $^3J_{CF}$=1.6 Hz, C5), 103.6 (d, $^2J_{CF}$=26.0 Hz, C4), 98.6 (dd, $^2J_{CF}$=27.1 Hz, $^3J_{CF}$=2.4 Hz, C2); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −96.5 (d, J=9.8 Hz, F3), −125.2 (d/J=9.8 Hz, F6), MS: *m/z* 370 (M, 28%), 368 (M, 99), 366 (M, 100), 364 (M, 29), 98 (15); IR (KBr) ν_{max}: 3506 (m, br), 3403 (w, br), 3126 (m, br), 1583 (w), 1439 (s), 1350 (m), 1325 (m), 1247 (w), 1175 (w), 1078 (m), 1070 (m), 912 (m), 838 (s) cm^{-1}. Anal. Calcd for $C_6Br_3F_2HO$: C, 19.65; H, 0.27. Found: C, 19.45; H, 0.18.

4.1.14. 2,4,6-Tribromo-3,5-difluorophenol (21). The title compound was prepared from 3,5-difluorophenol (**18**) by Method C (Fe 0.5 equiv; Br_2 5 equiv) to afford beige crystals; 83.0% yield; 98.4% purity (GLC); mp 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4 (dd, $^1J_{CF}$=246.5 Hz, $^3J_{CF}$=5.8 Hz, C3,C5), 150.9 (t, $^3J_{CF}$=4.8 Hz, C1), 94.1 (dd, $^2J_{CF}$=26.5 Hz, $^4J_{CF}$=4.4 Hz, 2C, C2, C6), 90.2 (t, $^2J_{CF}$=27.0 Hz, 1C, C4); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −96.7 (s, 2F); MS: *m/z* 370 (M, 33%), 368 (M, 97), 366 (M, 100), 364 (M, 35), 290 (6), 288 (12), 286 (10). IR (KBr) ν_{max}: 3482 (m, br), 1762 (w), 1685 (w), 1591 (m), 1578 (m), 1451 (s), 1428 (s), 1346 (w), 1297 (m), 1214 (m), 1113 (w), 1078 (m), 1060 (m), 710 (s), 701 (s), 684 (s) cm^{-1}. Anal. Calcd for $C_6HOBr_3F_2$ C: C, 19.65; H, 0.27. Found: C, 19.50; H, 0.26.

4.1.15. 3,3′,4,4′-Tetrabromodiphenyliodonium chloride (22).[12,16,25] The title compound was prepared from 1,2-dibromobenzene by Method A and characterised according to literature.[25]

4.1.16. 2,4,4′,6-Tetrabromodiphenyl ether (BDE 75).[12,16] The title compound was prepared from (**2**) and 2,4,6-tribromophenol (**3**) by Method B; 21% yield, 98.4% purity (GLC) (lit.[16] 23% yield); mp 149–150 °C (lit.[16] 134–135 °C); ^{1}H and ^{13}C NMR was in accordance with literature data;[16] MS: *m/z* 490 (M, 14%), 488 (M, 61), 486 (M, 100), 484 (M, 64), 482 (M,15), 328 (34) 326 (75), 324 (34); IR (KBr) ν_{max}: 2063 (w), 1879 (w), 1730 (w), 1580 (w), 1547 (m), 1483 (s), 1440 (s), 1399 (w), 1372 (m), 1354 (w), 1282 (m), 1253 (s), 1202 (s), 1163 (m), 1070 (m), 1006 (m), 860 (s), 822 (s), 809 (m), 748 (m), 739 (m) cm^{-1}.

4.1.17. 2,2′,3,4,4′-Pentabromodiphenyl ether (BDE 85).[21,25] The title compound was prepared from **5a** and **8** by Method B to give white crystals; 49.2% yield; 99.3% purity (GLC); mp 123–124 °C; ^{1}H NMR were in accordance with literature data;[21] ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8 (C1), 152.3 (C1′), 136.8 (C3′), 132.8 (C5), 132.3 (C5′), 129.9 (C3), 121.5 (C6′, C6 or C4), 120.7 (C6′, C6 or C4), 119.3 (C6′, C6′ or C4), 118.5 (C4′or C2), 118.1 (C4′ or C2), 115.9 (C2′); MS: *m/z* 570 (M, 9%), 568 (M, 46), 566 (M, 95), 564 (M, 100), 562 (M, 49), 560 (M, 10), 408 (26), 406 (81), 404 (83), 402 (27), 203 (19), 202 (19). IR (KBr) ν_{max}: ca 3100 (w), 1573 (w), 1556 (m), 1463 (s), 1427 (s), 1374 (m), 1356 (m), 1256 (s), 1247 (s), 1215 (m), 1076 (w), 1049 (m), 953 (w), 906 (m), 842 (m), 803 (m), 721 (m) cm^{-1}.

4.1.18. 2,2′,3,4,4′,5′-Hexabromodiphenyl ether (BDE 138).[21] The title compound was prepared from **5a** and **9** by Method B; white crystals; 54.0% yield; 99.8% purity (GLC); mp 135–136 °C; (lit.[21] 134.2 °C); ^{1}H NMR were in accordance with literature data;[21] ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7 (C1 or C1′), 152.4 (C1 or C1′), 137.5 (C3′), 132.7 (C5), 129.8 (C3), 124.3 (C5′), 123.4 (C6′), 121.2 (C4 or C4′) 120.3 (C4 or C4′), 119.4 (C6), 119.0 (C2), 113.4 (C2′); MS: *m/z* 649 (M, 4%), 647 (M, 25), 645 (M, 70), 643 (M, 100), 641 (M, 74), 639 (M, 28), 637 (M, 5), 488 (14), 486 (63), 484 (100), 482 (64), 480 (15), 242 (19), 74 (23). IR (KBr) ν_{max}: 3076 (w), 1572 (w), 1552 (m), 1454 (m), 1426 (s), 1358 (w), 1332 (m), 1265 (m), 1248 (m), 1208 (w), 1107 (m), 1049 (m), 931 (m), 884 (m), 842 (w), 798 (m) cm^{-1}.

4.1.19. 2,2′,3,4,4′,5′,6-Heptabromodiphenyl ether (BDE 183).[22,25] The title compound was prepared from **9** and **7** by Method B to afford white crystals; 54.0% yield; 99.4% purity (GLC); mp 174–174.5 °C; ^{1}H NMR were in accordance with literature data;[25] ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.7 (s, C1), 148.6 (s, C1′) 137.5 (s, C3′), 136.1 (s, C3), 128.8 (s, C5), 124.0 (s, C5′), 123.6 (s, C4), 123.0 (s, C6′), 118.7 (s, C4′or C2) 118.4 (s, C4′ or C2), 117.0 (s, C6), 111.4 (s, C2′); MS: *m/z* 729 (M, 3%), 727 (M, 17), 725 (M, 55), 723 (M, 98), 721 (M, 100), 719 (M, 58), 717 (M, 18), 715 (M, 3), 567 (8), 565 (40), 563 (91), 561 (92), 559 (43),

557 (9), 281 (18), 74 (15). IR (KBr) ν_{max}: 3078 (w), 1716 (w), 1568 (m), 1530 (w), 1456 (s), 1435 (m), 1405 (s), 1328 (s), 1250 (m), 1236 (m), 1208 (m), 1151 (m), 1115 (m), 1079 (m), 1048 (s), 921 (m), 874 (m), 864 (m), 842 (w), 762 (m), 755 (m), 719 (m) cm^{-1}.

4.1.20. 2,2′,4,4′-Tetrabromo-5,5′-difluorodiphenyl ether (2F-BDE 47). The title compound was prepared from bis(*m*-fluorophenyl) ether (**15**). To refluxing **15** (0.3 g, 1.46 mmol) in CCl_4 (9 ml) was slowly added Br_2 (1.28 g, 0.41 ml, 8.0 mmol, 6.5 equiv) in CCl_4 (5 ml). After 24 h reflux, $NaHSO_3$ (5%, 25 ml) was added and the product isolated by extraction. The crude product was recrystallised twice to obtain 282 mg white crystals; 37.3% yield; 98.0% purity (GLC); mp 137.5–138.5 °C; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.85 (d, J_{FH}=7.1 Hz, 2H, H3, H3′), 6.68 (d, J_{FH}=8.7 Hz, 2H, H6, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7 (d, $^1J_{CF}$=250 Hz, C5, C5′), 152.5 (d, $^3J_{CF}$=8.7 Hz, C1, C1′) 137.2 (d, $^3J_{CF}$=1.6 Hz, C3, C3′), 109.3 (d, $^4J_{CF}$=4.4 Hz, C2, C2′), 108.1 (d, $^2J_{CF}$=26.6 Hz, C6, C6′), 105.0 (d, $^2J_{CF}$=22.1 Hz, C4, C4′); MS: *m/z* 526 (M, 13%), 524 (M, 60), 522 (M, 100), 520 (M, 64), 518 (M, 14), 364 (39), 362 (88), 360 (39); IR (KBr) ν_{max}: 3026 (w), 1720 (w), 1680 (w), 1579 (m), 1460 (s), 1376 (s), 1280 (m), 1263 (m), 1163 (s), 1142 (m), 1070 (m), 1007 (m), 881 (m), 843 (m).

4.1.21. 2,2′,3,4,4′-Pentabromo-5,6-difluorodiphenyl ether (2F-BDE 85). The title compound was prepared from **19** and **8** by Method B; to afford white crystals; 45.7% yield; 99.0% purity (GLC); mp 129.5–130.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J=2.3 Hz, 1H, H3′), 7.31 (dd, J=8.7, 2.3 Hz, 1H, H5′), 6.45 (dd, J=8.8, 1.1 Hz, 1H, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3 (s, C1′), 148.5 (dd, $^1J_{CF}$=253.2 Hz, $^2J_{CF}$=12.7 Hz, C5), 143.7 (dd, $^1J_{CF}$=260.3 Hz, $^2J_{CF}$=16.0 Hz, C6), 141.3 (dd, $^2J_{CF}$=11.0 Hz, $^3J_{CF}$=2.2 Hz, C1), 136.4 (s, C3′), 131.4 (s, C5′), 123.8 (d, $^3J_{CF}$=5.0 Hz, C3), 117.1 (d, $^3J_{CF}$=4.4 Hz, C2), 116.5 (s, C4′), 115.8 (s, C6′), 112.8 (s, C2′), 111.9 (d, $^2J_{CF}$=20.0 Hz, C4);^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −118.1 (d, J=21.1 Hz, F5), −144.8 (dd, J=21.1, 1.0 Hz, F6); MS: *m/z* 605 (M, 8%), 603 (M, 45), 601 (M, 98), 599 (M, 100), 597 (M, 47), 595 (M, 9), 444 (25), 442 (82), 440 (83), 438 (26), 333 (9), 221 (18), 220 (15). IR (KBr) ν_{max}: 3442 (w), 3072 (w), 1733 (w), 1571 (m), 1461 (s), 1396 (s), 1380 (m), 1281 (w), 1259 (w), 1221 (m), 1147 (w), 1069 (m), 1041 (m), 940 (w), 868 (m), 846 (m), 808 (m) cm^{-1}. Anal. Calcd for $C_{12}Br_5F_2H_3O$: C, 23.99; H, 0.50. Found: C, 23.65; H, 0.39.

4.1.22. 2,2′,4,4′,5-Pentabromo-3,6-difluorodiphenyl ether (2F-BDE 99). The title compound was prepared from **20** and **8** by Method B to afford white crystals; 36.70% yield; 98.8% purity (GLC); mp 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J=2.3 Hz, 1H, H3′), 7.31 (dd, J=8.8, 2.3 Hz, 1H, H5′), 6.46 (dd, J=8.7, 1.1 Hz, 1H, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153. 7 (dd, $^1J_{CF}$=246.8 Hz, $^4J_{CF}$=3.9 Hz, C3), 152.4 (s, C1′), 149.9 (dd, $^1J_{CF}$=252.6 Hz, $^4J_{CF}$=4.4 Hz, C6), 140.6 (dd, $^2J_{CF}$=16.0 Hz, $^3J_{CF}$=3.4 Hz, C1), 136.4 (s, C3′), 131.4 (s, C5′), 116.5 (s, C4′), 116.11 (s, C6′), 113.8 (dd, $^2J_{CF}$=22.2 Hz, $^3J_{CF}$=1.1 Hz, C5), 112.9 (s, C2′), 110.8 (d, $^2J_{CF}$=25.9 Hz, C4), 105.8 (dd, $^2J_{CF}$=26.1 Hz, $^3J_{CF}$=1.6 Hz, C2); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −93.9 (d, J=10.9 Hz, F3), −115.6 (dd, J=10.1, 1.0 Hz, F6); MS: *m/z* 605 (M, 8%), 603 (M, 44), 601 (M, 94), 599 (M, 100), 597 (M, 46), 595 (M, 9), 444 (22), 442 (74), 440 (76), 438 (23), 333 (9), 221 (16), 220 (13); IR (KBr) ν_{max}: 3069 (w), 1741 (w), 1630 (w), 1569 (m), 1467 (s), 1434 (s), 1408 (s), 1377 (m), 1260 (m), 1224 (m), 1066 (m), 1039 (m), 923 (m), 872 (m), 840 (m), 802 (m), 759 (m), 720 (m) cm^{-1}. Anal. Calcd for $C_{12}Br_5F_2H_3O$: C, 23.99; H, 0.50. Found: C, 23.68; H, 0.52.

4.1.23. 2,3′,4,4′,6-Pentabromo-3,5-difluorodiphenyl ether (2F-BDE 119). The title compound was prepared from **21** and **22** by Method B to afford white crystals; 30, 7% yield; 99, 0% purity (GLC); mp 136.5–137.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J=8.8 Hz, 1H, H5′), 7.11 (d, J=3.0 Hz, 1H, H2′), 6.67 (dd, J=8.9, 3.0 Hz, 1H, H6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0 (dd, $^1J_{CF}$=248.8 Hz, $^4J_{CF}$=5.5 Hz, C3,C5), 155.5 (s, C1′), 149.6 (t, $^3J_{CF}$=3.8 Hz, C1), 134.7 (s, C5′), 126.0 (s, C3′), 120.9 (s, C2′), 119.0 (s, C4′), 116.0 (s, C6′), 102.8 (dd, $^2J_{CF}$=24.8 Hz, $^4J_{CF}$=4.4 Hz, C2, C6), 97.4 (t, $^2J_{CF}$=27.1 Hz, C4); ^{19}F NMR (376 MHz, $CDCl_3$/hexafluorobenzene): δ −94.2 (s); MS: *m/z* 605 (M, 8%), 603 (M, 36), 601 (M, 77), 599 (M, 78), 597 (M, 39), 595 (M, 8), 444 (31), 442 (99), 440 (100), 438 (33), 333 (12), 221 (23), 220 (22); IR (KBr) n_{max}: 3447 (w), 3094 (w), 1570 (m), 1455 (m), 1421 (s), 1369 (m), 1270 (w), 1254 (m), 1200 (m), 1099 (m), 1066 (m), 1010 (w), 864 (w), 857 (m), 798 (m), 757 (w), 703 (m) cm^{-1}. Anal. Calcd for $C_{12}Br_5F_2H_3O$: C, 23.99; H, 0.50. Found: C, 23.84; H, 0.43.

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Enantioselective oxidation of olefins catalyzed by chiral copper bis(oxazolinyl)pyridine complexes: a reassessment

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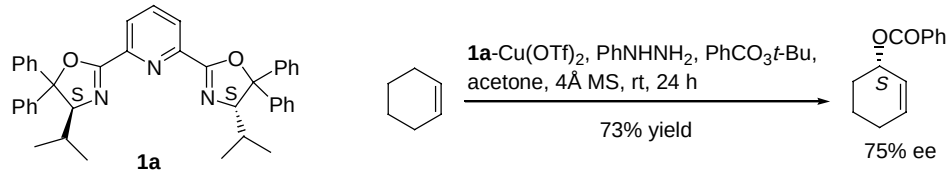
Abstract—Copper complexes of chiral tridentate pybox ligands synthesized using a modified procedure have been studied as catalysts for the enantioselective allylic oxidation of olefins. A variety of olefins have been used in this reaction. Using 5 mol% of a Cu(II) complex of the tridentate pybox ligand, phenylhydrazine, and *tert*-butyl perbenzoate as oxidant in acetone, optically active allylic benzoates were obtained up to 94% ee in few hours. It was also observed that the use of molecular sieves in the reaction did not alter the enantioselectivity. Temperature was found to be very crucial in rate of the enantioselective allylic oxidation of olefins. Using EPR spectra, it has been shown that the Cu(II) species is reduced to Cu(I) by phenylhydrazine and phenylhydrazone, but the reduction with the former is faster in comparison to the latter. It was concluded that the rate enhancement was not specific to the presence of phenylhydrazine or phenylhydrazone, but both were equally responsible provided acetone was used as a solvent.

1. Introduction

Enantioselective allylic oxidation of olefins catalyzed by chiral copper complexes continues to be an important area in asymmetric synthesis.[1,2] Early attempts with this reaction using copper complexes of (+)-α-ethyl camphorate,[3a] chiral Schiff bases,[3b] and L-amino acids[4] gave poor asymmetric induction (5–63% ee). Although important contributions were made in this area by Pfaltz,[5] Andrus,[6] Katsuki,[7] and Singh[8] using peresters and *t*-butyl peroxide[9] as oxidant with copper complexes of chiral bis and trisoxazoline ligands,[10] the longer reaction time was a universal problem with all these reports. The enantioselectivity using the oxazoline ligands had been reasonably good (60–93% ee), but the longer reaction time (up to a month) precluded broader use of these methods in applied synthesis. We later discovered that the use of phenylhydrazine with copper(II) complex of pyridine 2,6-bis(4′-isopropyl-5′,5′-diphenyloxazoline) **1a** (hence forth this is referred to as 'ip-pybox-diph' ligand) in acetone reduced reaction time to a great extent without affecting the enantioselectivity (Scheme 1).

The concept of using phenylhydrazine in the allylic oxidation of olefins catalyzed by chiral bipyridine–copper complexes has also been used by other researchers in this field.[11] The reaction was complete in few hours, but the asymmetric induction was moderate (55% ee in the case of cyclohexene and 75% ee in the case of cycloheptene).[11a] While working on this and related asymmetric reactions using the **1a**, we discovered some discrepancy in the physical data of this ligand. After some time, we could detect and solve the problem (vide infra). It was also discovered that the use of the 'ip-pybox-diph' ligand (**1a**)



Scheme 1.

Keywords: Enantioselective allylic oxidation; Olefins; Phenylhydrazine; Phenylhydrazone.
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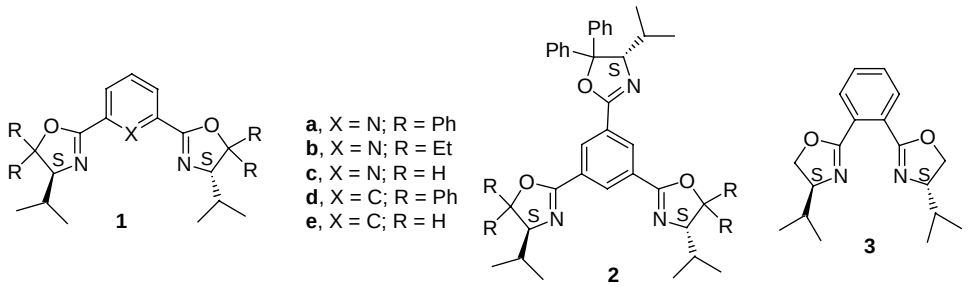
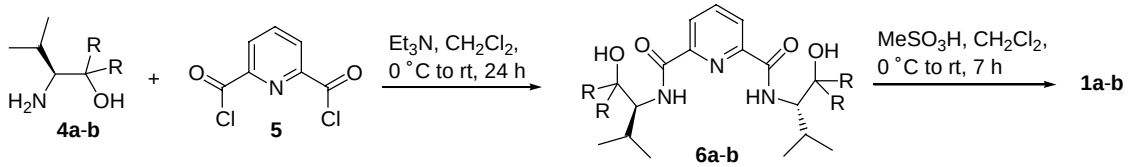
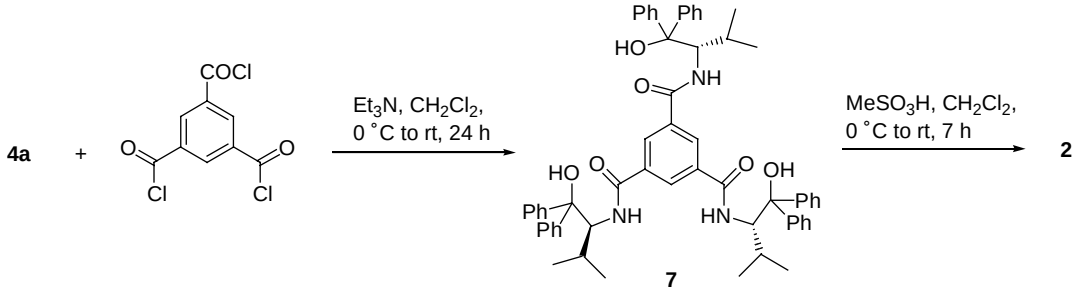


Figure 1.



Scheme 2.



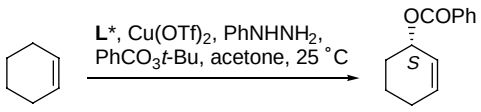
Scheme 3.

from a new procedure gave 93% ee as opposed to a 75% ee reported earlier in the enantioselective allylic oxidation of cyclohexene.[8b] To our delight, the reaction was complete in 1 h (67% yield, 91% ee) not 24 h (73% yield, 75% ee;). In view of this remarkable result, we extended our study further and report our full results in this paper.

It was planned to study the general role of phenylhydrazine in the enantioselective oxidation of olefins using the ligand **1a** (Fig. 1), which was prepared using a procedure previously reported.[12] During the synthesis of **1a**, it was observed that there is an overlapping spot with higher R_f seen on a silica gel tlc plate as an impurity. In a normal way, these were seen as a single spot under UV light, but the impurity becomes clear only when the tlc plate was seen under UV light after exposure to iodine vapour. The impurity could be removed only when the compound was recrystallized from ether. It was observed that the impurity could be minimized if the cyclization of **6a** with methanesulfonic acid was done at rt (Scheme 2). Ligand **1b** was prepared in the same fashion (Scheme 2). A new chiral ligand **2** was also prepared using the above procedure from (*S*)-diphenylvalinol **4a** and the corresponding acid chloride (Scheme 3).

In our initial study, 5 mol% complex of the newly prepared ligand (*S*)-**1a** and $Cu(OTf)_2$, in conjunction with phenylhydrazine, was found to be effective for the allylic oxidation of cyclohexene with *tert*-butyl perbenzoate in acetone. The reaction was complete in 1 h and the (*S*)-allylic benzoate was obtained in 67% yield and 91% ee (Table 1, entry 1). The ip-pybox-dieth ligand **1b** was equally efficient, but the enantioselectivity was slightly lower (85% ee). Under the identical condition, ligand **1c**[13] gave 65% ee (Table 1, entry 3). We could also reproduce Pfaltz's result where 71% ee was reported with this ligand in MeCN.[5] As reported earlier, ligand **1d**[8b] gave racemic product. Along the same line, it was expected that **1e** would not give any enantioselection

Table 1. Enantioselective allylic oxidation of cyclohexene with different ligands



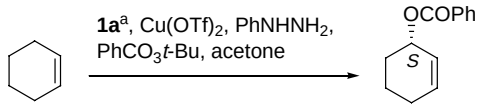
Entry	Ligand (**L***)[a]	Time (h)	Yield (%)	ee (%)
1	**1a**	01	67	91
2	**1b**	07	66	85
3	**1c**	18	85	65[b]
4	**1d**	02	50	00
5	**1e**	15	59	00
6	**2**	05	42	00
7	**3**	37	58	00

[a] 5 mol% of the chiral ligand was used.
[b] The **1c** is known (Ref. 5) to give 71% ee under other condition (**1c**–CuOTf, MeCN, 3 days).

and this was indeed the case (Table 1, entry 5). These results indicated that the pyridine nitrogen is important in chelation with copper in these systems. The results (Table 1, entries 6 and 7) from the ligands **2** and **3** support this hypothesis.

Having achieved good results in the above reaction at rt with ligand **1a**, the reaction at different temperature was studied with the hope to increase the enantioselectivity. The reaction was very sluggish at −20 °C and we could isolate only 3% of the product with the same level of enantioselectivity in 33 days (Table 2, entry 1). Although the reaction took a little longer time (11–29 h) for completion at 0 and 10 °C, the optical yield of the product was slightly better (up to 93% ee), although the chemical yield was similar (Table 2, entries 2 and 3). It was also observed that if the reaction was initiated at 0 °C and then warmed to rt, the optical activity of the product was similar (92% ee) but the reaction time was 20 h (Table 2, entry 4). Thus, it was concluded that 20–25 °C was the optimal temperature for this reaction. In order to see whether the reaction was moisture sensitive, the reaction was carried out in the presence of water (6 mol%) at 25 °C. To our delight, there was no erosion in chemical nor optical yield, however, the reaction time increased from 1 h (67% yield, 91% ee) to 11 h (74% yield, 90% ee) (Table 2, entry 6). In view of our earlier observation that 4 Å molecular sieves are beneficial to this reaction, its effect was also studied. To our surprise, it was found out that as such there was no effect of molecular sieves on chemical and optical yield of this reaction (Table 2, entry 7).

Table 2. Effect of temperature and additive on allylic oxidation



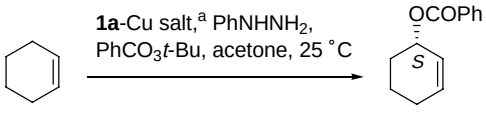
Entry	Additive	Temperature (°C)	Time	Yield (%)	ee (%)
1	Nil	−20	33 days	03	90
2	Nil	0	29 h	67	93
3	Nil	10	11 h	62	91
4	Nil	0 to 25	20 h	75	92
5	Nil	25	01 h	67	91
6	H_2O[b]	25	11 h	79	90
7	4 Å MS	25	04 h	74	91

[a] 5 mol% of the complex was used.
[b] 6 mol% of water added.

As established earlier by us, phenylhydrazine plays an important role in increasing the rate of the allylic oxidation of olefins with *tert*-butyl perbenzoate catalyzed by copper triflate in acetone.[8a] In order to ascertain its role with various Cu salt, the reaction was investigated in different solvents and the results are summarized in Table 3. We already know that the high enantioselectivity is obtained by a complex of **1a** with Cu(I) species and not by Cu(II). Thus, **1a**–CuOTf complex gave 91% ee and the reaction took 39 h for completion in acetone (Table 3, entry 2). In the presence of phenylhydrazine, the same reaction was complete in only 9 h without affecting the enantioselectivity (Table 3, entry 1). If the Cu(I) species was prepared in situ by reduction of **1a**–$Cu(OTf)_2$ with phenylhydrazine in acetone, the reaction was complete in 1 h with 91% ee (Table 3, entry 12). On changing the solvent to acetonitrile using Cu(I) complex and phenylhydrazine, the reaction time was not affected as it took 11–13 days to reach completion with slightly lower optical yield (Table 3, entries 7 and 8). As observed above, if a complex of **1a**–$Cu(OTf)_2$ and phenylhydrazine were used in acetonitrile, where Cu(I) species were prepared in situ by reduction, the reaction time was reduced to 3–4 days without affecting the ee (Table 3, entry 9). A similar trend was observed in benzene, except the enantioselectivity was poor (Table 3, entries 10 and 11). Invariably, lower enantioselectivity (47–60% ee) was obtained when benzene was used as a solvent in this reaction. From the results listed in Table 3, it was concluded that the Cu(I) species prepared by reduction of **1a**–$Cu(OTf)_2$ with phenylhydrazine in acetone is more efficient than use of Cu(I) salt directly in allylic oxidation of olefins.

In order to determine the optimal amount of catalyst in the allylic oxidation of cyclohexene, the reaction was tried with varying amounts of the copper complex (Table 4). Initially, the reaction was tried with 10 mol% of the complex using 10 equiv of cyclohexene (Table 4, entry 1). The reaction was complete in 1 h with high yield (86%) and

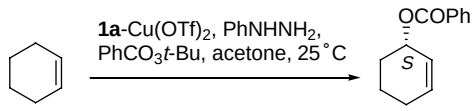
Table 3. Effect of solvent, $PhNHNH_2$, and Cu salt on the reaction



Entry	Solvent	$PhNHNH_2$	Cu salt	Time	Yield (%)	ee (%)
1	Acetone	Yes	CuOTf·PhH	09 h	73	91
2	Acetone	No	CuOTf·PhH	39 h	67	91
3	Acetone	Yes	$[Cu(MeCN)_4]PF_6$	11 h	62	92
4	Acetone	No	$[Cu(MeCN)_4]PF_6$	43 h	90	91
5	MeCN	Yes	CuOTf·PhH	11 days	79	89
6	MeCN	No	CuOTf·PhH	13 days	88	88
7	MeCN	Yes	$[Cu(MeCN)_4]PF_6$	10 days	75	86
8	MeCN	No	$[Cu(MeCN)_4]PF_6$	10 days	88	88
9	MeCN	Yes	$Cu(OTf)_2$	88 h	50	86
10	Benzene	Yes	$[Cu(MeCN)_4]PF_6$	22 h	59	60
11	Benzene	No	$[Cu(MeCN)_4]PF_6$	06 days	61	48
12	Acetone	Yes	$Cu(OTf)_2$	01 h	67	91

[a]5 mol% of the complex was used in the reaction.

Table 4. Effect of amount of the catalyst on the reaction[a]



Entry	**1a**–Cu(OTf)$_2$ (mol%)	Time (h)	Yield (%)	ee (%)
1	10	01	86	91
2	10	03	79	91[b]
3	05	01	67	91
4	05	11	56	91[c]
5	05	14	66	92[d]
6	2.5	08	82	91
7	01	39	91	91

[a] Usually 10 equiv of cyclohexene was used in all the reactions unless stated otherwise.
[b] 5 equiv of cyclohexene was used.
[c] 2 equiv of cyclohexene used.
[d] After disappearance of PhCO$_3$*t*-Bu, 1 equiv of this was added again.

enantioselectivity (91% ee). By reducing the amount of the catalyst to 5 mol%, there was no change in the reaction rate (Table 4, entry 3). On further reduction of the amount of the catalyst to 2.5 and 1 mol%, the similar chemical and optical yields were obtained, but the reaction time was 8 and 39 h, respectively (Table 4, entries 6 and 7). Normally, in all the above reactions, 10 equiv of olefins with respect to *tert*-butyl perbenzoate were used. By reducing the amount of olefin to 5 and 2 equiv, the reaction time was little increased slightly (3 and 11 h), but there was no change in the enantioselectivity (Table 4, entries 2 and 4). Since the reaction was monitored by the disappearance of the perester, an extra equivalent of the perester was added after a tlc indicated disappearance of the 1st equivalent of the perester, but there was no affect on the reaction (Table 4, entry 5).

Initially, phenylhydrazine was used in the reaction for reducing the Cu(II) complex of the ligand to Cu(I).[14] Since the rate enhancement was much higher when acetone was used as a solvent, it was assumed that phenylhydrazone might be responsible for enhancing the rate. It was further found that phenylhydrazine and phenylhydrazone were both reducing Cu(II) to Cu(I) species (green to dark brown), but the rate enhancement in the reaction could be mainly due to phenylhydrazone formed in situ from phenylhydrazine and acetone. In order to confirm and determine the extent of reduction, EPR spectra were run. EPR study of the complex **1a**–Cu(OTf)$_2$ with phenylhydrazine in acetone indicated that the reduction required 15 min (Fig. 2). For the same reduction, phenylhydrazone took 3 h (Fig. 3). So, it was concluded that phenylhydrazone also reduced Cu(II) to a Cu(I) species, but the reduction process was slower. This is also clear from the results shown in Table 5. The reaction was catalyzed by a Cu(II) complex containing chiral ligand **1a**, but the enantioselectivity was not good (Table 5, entry 1). By addition of phenylhydrazine, the reaction time was reduced from 7 days to 1 h and the enantioselectivity was enhanced from 62 to 91% (Table 5, entry 2).

Assuming that phenylhydrazone formed in situ in the above reaction was responsible for the rate enhancement in the reaction, it was used in place of phenylhydrazine. Thus, an equivalent amount (5–6 mol%)

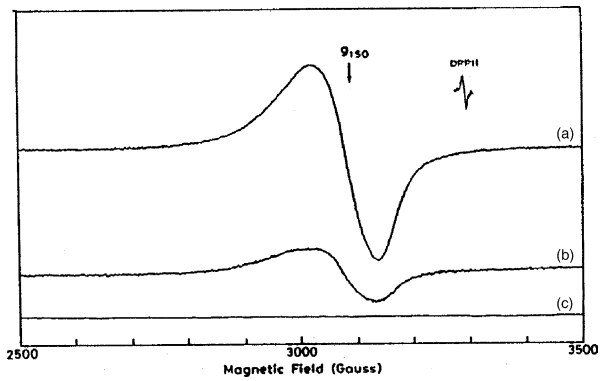


Figure 2. EPR spectrum study with phenylhydrazine in acetone. (a) EPR spectrum of **1a**–Cu(OTf)$_2$ in acetone at rt. (b) PhNHNH$_2$ was added immediately and EPR spectrum was run. (c) EPR spectrum was run after 15 min.

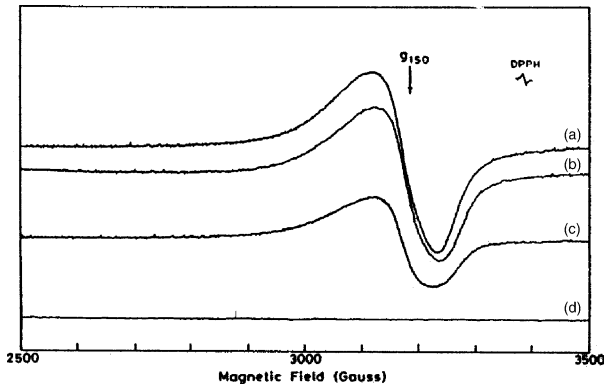
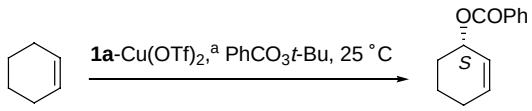
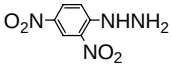
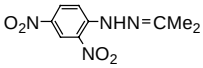


Figure 3. EPR spectrum study with phenylhydrazone in acetone. (a) EPR spectrum of **1a**–Cu(OTf)$_2$ in acetone at rt. (b) PhNHN=CMe$_2$ was added and EPR spectrum was run after 30 min. (c) EPR spectrum was run after 1.5 h. (d) EPR was run after 3 h.

of phenylhydrazone was added to **1a**–Cu(OTf)$_2$ and stirred for 0.5, 1, 2 and 3.5 h before adding cyclohexene and perester. As the reduction time of the Cu(II) complex was increased from 0.5 to 1 h, the time for completion of the reaction was reduced from 24 to 8 h and there was very little improvement in the enantioselectivity (Table 5, entries 3 and 4). However, there was not much difference on increasing the reduction time to 2–3.5 h (Table 5, entries 5 and 6). This was in accord with the above fact from EPR spectra that the reduction of the Cu(II) complex with phenylhydrazone was slower. Reaction in acetone indicated that phenylhydrazine and phenylhydrazone both were increasing the rate of the allylic oxidation reaction, but the former was more efficient (Table 5, entry 2; 1 h reaction time) than the latter (Table 5, entry 6; 3 h reaction time). However, on changing the solvent to acetonitrile, the reaction was slower in both cases (Table 5, entries 9 and 10) and there was no difference in the rate (reaction time 88 and 74 h). Thus, it was concluded that the rate enhancement was not specific to the presence of phenylhydrazine or phenylhydrazone, but both were equally responsible provided acetone was used as a solvent. 2,4-Dinitrophenylhydrazine and its corresponding hydrazone had no effect on the reaction rate (35 days). This observation is more obvious as the electron transfer rate will be much more slower due to the nitro-substitution.

Table 5. Effect of reducing agents on the reaction[a]

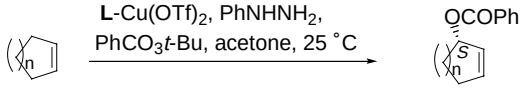


Entry	Reducing agent	Solvent	Time	yield (%)	ee (%)
1	Nil	Acetone	07 days	35	62
2	$PhNHNH_2$	Acetone	01 h	67	91
3	$PhNHN{=}CMe_2$	Acetone	24 h	64	89
4	$PhNHN{=}CMe_2$	Acetone	08 h	67	90[b]
5	$PhNHN{=}CMe_2$	Acetone	08 h	69	90[c]
6	$PhNHN{=}CMe_2$	Acetone	03 h	62	90[d]
7	$PhNHN{=}CMe_2$	CH_2Cl_2	18 h	75	66
8	$PhNHN{=}CMe_2$	Benzene	76 h	65	40
9	$PhNHNH_2$	Acetonitrile	88 h	50	86
10	$PhNHN{=}CMe_2$	Acetonitrile	74 h	51	89
11		Acetone	35 days	40	78
12		Acetone	35 days	41	66

[a] Normally the reaction mixture (RM) was stirred for 30 min after the addition of a reducing agent unless stated otherwise (viz. b,c, and d).
[b] The RM was stirred for 1 h.
[c] The RM was stirred for 2 h.
[d] The RM was stirred for 3.5 h.

Having established optimal conditions for enantioselective allylic oxidation of cyclohexene, the reaction was extended to other olefins with *tert*-butyl perbenzoate using chiral ligands **1a** and **1b**. The results are summarized in Table 6. Cyclopentene and cycloheptene gave a maximum of 70 and 86% ee, respectively. Although cyclooctene gave the highest enantioselectivity (94% ee), cyclooctadiene gave only 80% ee.

Table 6. Enantioselective allylic oxidation of different olefins with *tert*-butyl perbenzoate[a]

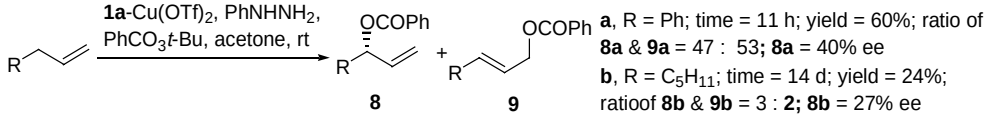


Entry	Olefin	L	Time	Yield (%)	ee (%)
1		**1a**	01 h	67	91
2		**1b**	07 h	66	85
3		**1a**	03 h	76	70
4		**1b**	24 h	58	65
5		**1a**	06 h	47	86
6		**1b**	48 h	37	60
7		**1a**	06 h	34	94
8		**1b**	06 d	46	71
9		**1a**	05 d	31	80
10		**1b**	05 d	40	71

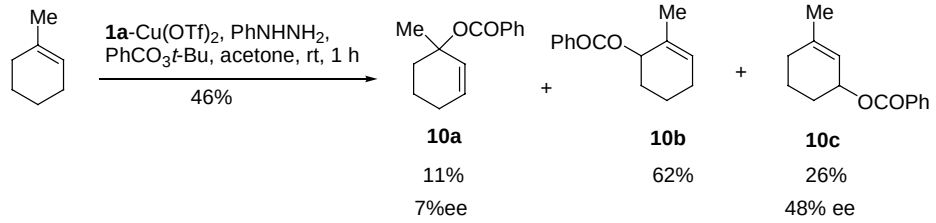
[a] The ee was determined by HPLC on chiral columns as mentioned in Section 2.

Although a high ee was obtained for cyclic olefins, acyclic olefins gave poor selectivity (Scheme 4). During the oxidation of allylic benzene, 60% yield of a mixture of benzoates (**8a** and **9a**) with a ratio of 47:53 were obtained. The optical purity of **8a** was 40%. 1-Octene gave a poor yield of products (**8b** and **9b**) in a ratio of 3:2. Enantioselectivity in this case was very poor (27% ee). The allylic oxidation was also attempted on 1-methylcyclohexene (Scheme 5). Under optimal conditions, 46% yield of a mixture of three products (**10a**, **10b**, and **10c**) was obtained. Among these, we could determine the enantioselectivity only in case of **10a** (7% ee) and **10c** (48% ee). Although **10b** was a major product, its enantiomeric excess could not be determined.

The transition state model based on π-stacking with the ligand **1a** has been proposed earlier for this reaction.[8b] The results detailed in this paper also support the transition state model proposed earlier. There is an enhancement of enantioselectivity from 65 to 91% from the ligand ip-pybox **1c** to ip-pybox-diph **1a** (Table 1, entries 1 and 3). This does suggest that the *gem*-diphenyl groups play an important role in stabilizing the transition state, and we feel that it is primarily due to π-stacking.[15] *gem*-Diethyl groups also enhanced the ee to 85% (Table 1, entry 2), but its effect is less than that of *gem*-diphenyl groups. The effect from



Scheme 4. Enantioselective allylic oxidation of acyclic olefins.



Scheme 5. Enantioselective oxidation of 1-methylcyclohexene.

diphenyl to diethyl groups in the chiral ligand is quite consistent in all the olefins studied (Table 6).

In conclusion, we have investigated enantioselective allylic oxidation of olefins with a copper complex of pybox ligands with *tert*-butyl perbenzoate. We have shown that the reaction time is reduced drastically by using phenylhydrazine in acetone as a solvent. It was also confirmed that phenylhydrazone formed in situ is also responsible for the same effect. It was concluded that the shorted reaction time was not specific to the presence of phenylhydrazine or phenylhydrazone, but both were equally responsible, provided acetone was used as a solvent. Under the optimal conditions using 'ip-pybox-diph' ligand (*S*,*S*)-**1a**, we were able to convert olefins into (*S*)-allylic benzoate in up to 94% ee.

2. Experimental

2.1. General methods

^{1}H NMR spectra were recorded on 400 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in Hz. Routine monitoring of reactions were performed by TLC, using precoated silica gel TLC plates obtained by E-Merck. All the column chromatographic separations were done by using silica gel (Acme's, 60–120 mesh). Petroleum ether used was of boiling range 60–80 °C. Reactions that needed anhydrous conditions were run under the atmosphere of nitrogen or argon using flame-dried glassware. The organic extracts were dried over anhydrous sodium sulfate. Evaporations of solvents was performed at reduced pressure. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Benzene, dichloromethane, acetonitrile and acetone were distilled from CaH_2.

2.1.1. *N*,*N*′-Bis[1′-(*S*)-isopropyl-2′2′-diphenyl-2′-hydroxyethyl]-2,6-pyridine-dicarboxamide (6a).[8b] This was prepared as per our procedure. But, the purification was done by column chromatography over silica gel followed by recrystallization from CH_2Cl_2/*n*-hexane. Yield 95%; mp 220–221 °C (lit.[8b] mp 110–111 °C); R_f 0.27 (1:2, EtOAc in petroleum ether); $[\alpha]_D^{25}$ −50.3 (*c* 1, $CHCl_3$) [lit.[8b] $[\alpha]_D^{25}$ −46.2 (*c* 1, $CHCl_3$)]. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.83 (d, J=6.8 Hz, 6H), 1.08 (d, J=6.6 Hz, 6H), 1.81 (m, 2H), 2.49 (s, 2H, OH), 5.02 (d, J=10.7 Hz, 2H), 6.07(s, 2H, NH) 7.02 (t, J=7.3 Hz, 2H), 7.11–7.19 (m, 6H), 7.32 (t, J=7.6 Hz, 4H), 7.52–7.55 (m, 8H), 7.99–8.08 (m, 1H), 8.26 (d, J=10.7 Hz, 2H); MS (FAB, *m*/*z*) 642 (M^++1).

2.1.2. *N*,*N*′-Bis[1′-(*S*)-isopropyl-2′2′-diethyl-2′-hydroxyethyl]-2,6-pyridine-dicarboxamide (6b). This was prepared as per our procedure. But, the purification was done by column chromatography over silica gel followed by recrystallization from CH_2Cl_2/*n*-hexane. Yield 50%; mp 141–142 °C; R_f 0.37 (1:1, EtOAc in petroleum ether); $[\alpha]_D^{25}$ −8.2 (*c* 1, $CHCl_3$); [lit.[8a] $[\alpha]_D^{25}$ −3.6 (*c* 0.6, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, J=7.6 Hz, 6H), 0.90 (d, J=7.6 Hz, 6H), 0.96 (d, J=6.8 Hz, 6H), 0.99 (d, J=6.8 Hz, 6H), 1.45–1.70 (m, 8H), 2.21 (m, 2H), 4.02 (dd, J=10.3, 1.9 Hz, 2H), 8.03 (t, J=7.8 Hz, 1H), 8.27 (d, J=10.0 Hz, 2H), 8.32 (d, J=7.8 Hz, 2H).

2.2. General procedure for cyclization of amido alcohols (6) to ip-Pybox-diph (1a) and ip-Pybox-dieth (1b)

Methanesulfonic acid (30 mmol) was added dropwise to a solution of amido alcohol **6** (5 mmol) in CH_2Cl_2 (120 mL) at 0 °C over a period of approximately 10 min and the reaction mixture was stirred for 7 h in the case of **1a** and 18 h in the case of **1b** and during the process the cooling bath warmed to rt (0 to 25 °C). It was diluted with CH_2Cl_2 (100 mL) and washed with aqueous $NaHCO_3$, water and brine. The organic layer was dried over anhydrous $NaSO_4$ and the solvent was evaporated in vacuo to afford **1** as off-white solid, which was purified by column chromatography and recrystallization.

2.2.1. 2,6-Bis[5′,5′-diphenyl-4′-(*S*)-isopropyloxazolin-2′-yl]pyridine (1a).[8] This was prepared from **6a** using a general procedure mentioned above and then recrystallized with Et_2O to afford the product **1a** as a white crystal: yield 65%; mp 161–163 °C (lit.[8b] mp 65–66 °C); R_f 0.37 (1:2, EtOAc in petroleum ether); $[\alpha]_D^{25}$ −386.2 (*c* 1.1, $CHCl_3$) [lit.[8b] $[\alpha]_D^{25}$ −233.0 (*c* 2.7, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (d, J=6.6 Hz, 6H), 1.06 (d, J=6.8 Hz, 6H), 1.93 (m, 2H), 4.87 (d, J=4.6 Hz, 2H), 7.21–7.30 (m, 9H), 7.34–7.42 (m, 7H), 7.66 (d, J=6.1 Hz, 4H), 7.89 (t, J=6.0 Hz, 1H), 8.22 (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 17.3, 21.9, 30.3, 80.5, 93.5, 125.6, 126.3, 127.0, 127.3, 127.7, 127.8, 128.3, 137.4, 140.5, 145.2, 147.2, 160.6; MS (FAB, *m*/*z*) 606 (M^++1).

2.2.2. 2,6-Bis[5′,5′-diethyl-4′-(*S*)-isopropyloxazolin-2′-yl]pyridine (1b).[8a] This was prepared from **6b** using the above general procedure: yield 85%; mp 82–84 °C; R_f 0.4 (2:3, EtOAc in petroleum ether); $[\alpha]_D^{25}$ −36.4 (*c* 1.1, $CHCl_3$) [lit.[8b] $[\alpha]_D^{25}$ −37.1 (*c* 1.4, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J=7.6 Hz, 6H), 1.02–1.06 (m, 12H), 1.16 (d, J=6.6 Hz, 6H) 1.70 (m, 4H), 1.86–2.0 (m, 6H), 3.74 (d, J=7.8 Hz, 2H), 7.82 (t, J=7.8 Hz, 1H), 8.03 (d, J=7.8 Hz, 2H).

2.2.3. *N*,*N*′,*N*″-Tris[1′-(*S*)-isopropyl-2′2′-diphenyl-2′-hydroxyethyl]-1,3,5-benzene-tricarboxamide (7). A solution of 1,3,5-benzenetricarboxylic chloride (4.8 mL, 1.0 M solution in CH_2Cl_2) was added slowly to a mixture of (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol **4a**[8] (3.63 g, 14.2 mmol), Et_3N (5 mL, 36 mmol) and CH_2Cl_2 (50 mL) at 0 °C over a period of 15 min and the mixture was stirred for 24 h (0 °C to rt). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with aqueous $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous $NaSO_4$, and the solvent was evaporated in vacuo to afford white solid, which was purified by column chromatography over silica gel and recrystallised from CH_2Cl_2/hexane to get pure product **7** (3.10 g, yield 80%): mp 178–180 °C; R_f 0.22 (1:4, EtOAc in petroleum ether); $[\alpha]_D^{25}$ −82.0 (*c* 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, J=6.8 Hz, 9H), 0.97 (d, J=6.8 Hz, 9H), 1.96 (m, 3H), 6.74 (d, J=10 Hz, 3H), 7.09 (t, J=7.6 Hz, 3H), 7.19–7.26 (m, 11H), 7.35 (t, J=7.6 Hz, 6H), 7.51 (t, J=7.6 Hz, 13H), 7.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 18.0, 22.9, 29.1, 58.9, 76.7, 77.0, 77.3, 82.2, 125.2, 125.3, 126.9, 127.8, 128.3, 128.4, 135.4, 145.2, 146.0, 166.3. Anal. Calcd for $C_{60}H_{63}N_3O_6$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.0; H, 6.97; N, 4.48.

2.2.4. 1,3,5-Tris[5′,5′-diphenyl-4′-(*S*)-isopropyloxazolin-2′-yl]benzene (2). Methane sulfonic acid (571 μL, 8.8 mmol) was added dropwise to a solution of amido alcohol **7** (900 mg, 0.98 mmol) in CH_2Cl_2 (40 mL) at 0 °C over a period of 10 min and the mixture was stirred for 18 h (0 °C to rt). The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with aqueous $NaHCO_3$, water and brine. The organic layer was dried over anhydrous $NaSO_4$ and the solvent was evaporated in vacuo to afford **2** as a off-white solid, which was purified by column chromatography (650 mg, yield 77%): mp 121–124 °C; R_f 0.56 (1:4, EtOAc in petroleum ether); $[\alpha]_D^{25}$ −376.3 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (d, J=6.6 Hz, 9H), 1.06 (d, J=6.6 Hz, 9H), 1.87 (m, 3H), 4.85 (d, J=4.6 Hz, 3H), 7.23–7.38 (m, 24H), 7.59 (d, J=7.6 Hz, 6H), 8.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 17.1, 21.9, 30.5, 80.2, 93.2, 126.3, 127.0, 127.3, 127.7, 127.8, 128.3, 128.9, 130.6, 140.5, 145.2, 160.4. Anal. Calcd for $C_{60}H_{57}N_3O_3$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.90; H, 6.71; N, 4.76.

2.3. General procedure for enantioselective allylic oxidation of olefins with *tert*-butyl perbenzoate in the presence of $PhNHNH_2$ using a complex of chiral ligands and $Cu(OTf)_2$

A solution of a chiral ligand (0.06 mmol) and $Cu(OTf)_2$ (0.05 mmol) in appropriate solvent (4 mL) was stirred at appropriate temperature (see Tables) for 1 h. To this colored (green for **1a**; blue for **1b**, **1c**, **1d**, **1e**, and 3; colorless for **2**,) solution was added phenylhydrazine (6 μL, 0.06 mmol), and the mixture was stirred for 30 min. During this time, the color of the solution changed (dark brown for **1a** and **1b**; light brown for **1c**; yellow for **1d**, **1e**, and **3**; fluorescent orange for **2**) giving an indication for reduction of Cu(II) to Cu(I) species. Then, an olefin (2 mmol to 10 mmol depending upon the experiment) was added followed by a dropwise addition of a *tert*-butylperbenzoate (1 mmol) under N_2 atmosphere. After few minutes, the color of the solution changed (green for **1a**, **1b**, **1c**, **1d**, **1e**, and **3**; fluorescent reddish brown for **2**). The reaction mixture was left at rt until the reaction was complete (disappearance of perester by TLC) during which time the color of the reaction mixture again changed (dark brown for **1a** and **1b**; light brown for **1c**; green for **1d**; yellow for **1e** and **3**; fluorescent reddish brown for **2**). After the reaction was over, the solvent was removed in vacuo and the crude product was purified by column chromatography using silica gel.

2.4. General procedure for enantioselective allylic oxidation of cyclohexene with *tert*-butyl perbenzoate using a complex of chiral ligand (1a) and $(CuOTf)_2\cdot PhH$ or $[Cu(CH_3CN)_4]PF_6$

A solution of **1a** (0.06 mmol) and Cu(I) salt (0.05 mmol) in appropriate solvent (4 mL) was stirred at rt for 1 h. To this brown solution was added cyclohexene (10 mmol), and the mixture was stirred for 5 min. Then, *tert*-butyl perbenzoate (1 mmol) was added dropwise under N_2 atmosphere. After few minutes, the color of the solution turned green. The reaction mixture was left at rt until the reaction was complete (disappearance of perester by TLC) during which time the color of the reaction mixture turned dark brown again. After the reaction was over, the solvent was removed in vacuo and the crude product was purified by column chromatography using silica gel.

2.5. General procedure for enantioselective allylic oxidation of cyclohexene with *tert*-butyl perbenzoate using a complex of chiral ligand (1a) and $(CuOTf)_2\cdot PhH$ or $[Cu(CH_3CN)_4]PF_6$ in the presence of $PhNHNH_2$

A solution of a chiral ligand (0.06 mmol) and Cu(I) salt (0.05 mmol) in appropriate solvent (4 mL) was stirred at rt for 1 h. To this brown solution was added phenylhydrazine (6 μL, 0.06 mmol), and the mixture was stirred for 30 min. Then, an olefin (10 mmol) was added followed by a dropwise addition of a perester (1 mmol) under N_2 atmosphere. After few minutes, the color of the solution started changing towards green. The reaction mixture was left at rt until the reaction was complete (disappearance of perester by TLC) during which time the color of the reaction mixture turned dark brown again. After the reaction was over, the solvent was removed in vacuo and the crude product was purified by column chromatography using silica gel.

2.6. General procedure for enantioselective allylic oxidation of cyclohexene with *tert*-butyl perbenzoate using (1a)–$Cu(OTf)_2$ in the presence of hydrazones

A solution of a **1a** (0.06 mmol) and $Cu(OTf)_2$ (0.05 mmol) in appropriate solvent (4 mL) was stirred at rt for 1 h. To this green solution was added appropriate arylhydrazone (0.06 mmol), and the mixture was stirred for appropriate time (Table 5). During this time, the color of the solution changed (brown for phenylhydrazone and yellow for 2,4-dinitrophenylhydrazone) giving an indication for reduction of Cu(II) to Cu(I) species. Then, an olefin (10 mmol) was added followed by a dropwise addition of a perester (1 mmol) under N_2 atmosphere. After few minutes, the color of the solution turned green in the case of phenylhydrazone. The reaction mixture was left at rt until the reaction was complete (disappearance of perester by

TLC) during which time the color of the reaction mixture again changed to dark brown in the case of phenylhydrazone. After the reaction was over, the solvent was removed in vacuo and the crude product was purified by column chromatography using silica gel.

2.6.1. (*S*)-2-Cyclohexenyl-1-benzoate (Table 2, entry 2).[8b] It was obtained in a maximum of 93% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 99.7:0.3]; flow rate 0.5 mL/min; t_R=11.52 min (*R*), 12.63 min (*S*); $[\alpha]_D^{25}$ −167.2 (*c* 4.4, $CHCl_3$) [lit.[8b] (86% ee); $[\alpha]_D^{25}$ −157.0 (*c* 0.45, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68–2.17 (m, 6H), 5.51 (m, 1H), 5.81–5.85 (m, 1H), 5.99–6.03 (m, 1H), 7.43 (t, *J*=7.8 Hz, 2H), 7.54 (t, *J*=7.3 Hz, 1H), 8.06 (dd, *J*=6.8, 1.3 Hz, 2H).

2.6.2. (*S*)-2-Cyclopentenyl-1-benzoate (Table 6, entry 11).[7b] It was obtained in a maximum of 70% ee. The optical purity was determined by HPLC on chiralcel OD column [hexane/2-propanol 99.9:0.1]; flow rate 0.5 mL/min; t_R=26.82 min (*S*), 32.35 min (*R*). $[\alpha]_D^{25}$ −136.2 (*c* 0.9, $CHCl_3$) [lit.[7b] (93% ee); $[\alpha]_D^{25}$ −179.0 (*c* 0.37, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93–2.01 (m, 1H), 2.34–2.45 (m, 2H), 2.55–2.64 (m, 1H), 5.92–5.97 (m, 2H), 6.16 (p, 1H), 7.25–7.44 (m, 2H), 7.53 (tt, *J*=7.6, 1.2 Hz, 1H), 8.03 (m, 2H).

2.6.3. (*S*)-2-Cycloheptenyl-1-benzoate (Table 6, entry 14).[8b] It was obtained in a maximum of 86% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 99.7:0.3]; flow rate 0.5 mL/min; t_R=15.70 min (*R*), 16.37 min (*S*); $[\alpha]_D^{25}$ −57.8 (*c* 0.6, $CHCl_3$) [lit.[8b] (82% ee) $[\alpha]_D^{25}$ −38.2 (*c* 1, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43–2.30 (m, 8H), 5.65 (d, *J*=9.8 Hz, 1H), 5.81–5.92 (m, 2H), 7.44 (t, *J*=7.8 Hz, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 8.06 (d, *J*=7.3 Hz, 2H).

2.6.4. (*S*)-2-Cyclooctenyl-1-benzoate (Table 6, entry 17).[8b] It was obtained in a maximum of 94% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 99.7:0.3]; flow rate 0.5 mL/min; t_R=21.79 min (*S*), 12.63 min (*R*); $[\alpha]_D^{25}$ +86.5 (*c* 1.2, $CHCl_3$) [lit.[8b] (82% ee) $[\alpha]_D^{25}$ +72.6° (*c* 1.25, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43–1.75 (m, 7H), 2.04–2.40 (m, 3H), 5.60–5.75 (m, 2H), 5.87–5.92 (m, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 7.54 (t, *J*=7.3 Hz, 1H), 8.05 (d, *J*=7.3 Hz, 2H).

2.6.5. (*S*)-2-Cyclooctadienyl benzoate (Table 6, entry 20).[16] It was obtained in a maximum of 80% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 99.7:0.3]; flow rate 0.5 mL/min; t_R=17.71 min (*S*), 19.01 min (*R*): $[\alpha]_D^{25}$ −132.0 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47–1.54 (m, 1H), 1.64–1.72 (m, 1H), 1.85–1.96 (m, 2H), 2.07 (m, 1H), 2.37 (m, 1H), 5.65 (m, 2H), 5.75–5.81 (m, 1H), 5.93–6.00 (m, 2H), 7.43 (t, *J*=7.8 Hz, 2H), 7.55 (t, *J*=7.6 Hz, 1H), 8.05 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 21.6, 28.3, 30.0, 74.4, 125.8, 126.1, 128.2, 129.5, 130.7, 130.9, 132.8, 133.1, 165.8. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: 78.78; H, 7.21.

2.6.6. (*R*)-1-Phenyl-2-propenylbenzoate (8a).[6a] It was obtained in a maximum of 40% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 99.7:0.3]; flow rate 0.5 mL/min; t_R=13.28 min (*R*), 14.01 min (*S*). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.30 (td, *J*=10.5, 1.2 Hz, 1H), 5.40(td, *J*=17.3, 1.2 Hz, 1H), 6.13 (s, *J*=5.8 Hz, 1H), 6.52 (d, *J*=5.8 Hz, 1H), 7.29–7.47 (m, 8H), 8.10 (dd, *J*=8.3, 1.2 Hz, 2H).

2.6.7. (*S*)-1-Octenyl-3-benzoate (8b).[6a] It was obtained in a maximum of 27% ee. The optical purity was determined by HPLC on chiralcel OD column [hexane/2-propanol 99.9:0.1]; flow rate 0.5 mL/min; t_R=20.91 min (*R*), 22.78 min (*S*). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88–1.84 (m, 11H), 5.20 (d, *J*=6.5 Hz, 1H), 5.32(d, *J*=17.0 Hz, 1H), 5.46–5.51 (m, 1H), 5.85–5.93 (m, 1H), 7.44 (t, *J*=7.3 Hz, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 8.06 (d, *J*=8.3 Hz, 2H).

2.6.8. 1-Methyl-1-cyclohexen-3-yl benzoate (10c).[5,9] It was obtained in a maximum of 47.6% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 99.7:0.3]; flow rate 0.5 mL/min; t_R=11.71 min (minor), 12.19 min (major) δ 1.77 (s, 3H), 1.46–2.06 (m, 6H), 5.50 (bs, 1H), 5.60 (bs, 1H), 7.42 (t, *J*=7.6 Hz, 2H), 7.54 (t, *J*=7.3 Hz, 1H), 8.05 (d, *J*=7.3 Hz, 2H).

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13. The ligand was first introduced by Nishiyama and later used by others. For the original reference, see: Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846–848.
14. (a) We have confirmed by UV–vis and EPR methods that **1a**–Cu(II) triflate complex gets reduced to Cu(I) species in the presence of phenylhydrazine. For details, see Ref. 10. (b) For reduction of Cu(II) species to Cu(I) with phenylhydrazine, also see: Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193–198. (c) For use of the same reduction method in the cyclopropanation reaction, see: Kanemasa, S.; Hamura, S.; Harada, E.; Yamamoto, H. *Tetrahedron Lett.* **1994**, *35*, 7985–7988.
15. (a) For a review on π-stacking in asymmetric synthesis, see: Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–497. (b) Also, see: Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.
16. The absolute stereochemistry is unknown, but it was temporarily assigned (*S*) based on a similar case.

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New indium-mediated cyclisation reactions of tethered haloenynes in aqueous solvent systems

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Dedicated with great respect to Professor Steven V. Ley on the occasion of his 60th birthday

Abstract—The intramolecular cyclisation of tethered allyl bromides onto terminal alkynes mediated by metallic indium proceeds smoothly and cleanly in mixtures of THF and H_2O to give unsaturated carbocycles and heterocycles in good yield. Alternatively, the cyclisation may be carried out in anhydrous THF with the aid of acid catalysis. The reaction is also mediated by a range of indium salts and proceeds with substoichiometric quantities of indium in the presence of a co-reductant. Deuteration studies show that the reaction proceeds via a concerted *syn* carboindination of the carbon–carbon triple bond to give an intermediate, which is protonated in situ.

1. Introduction

In recent years there has been a great deal of interest in the application of indium to organic synthesis.[1] Indium-mediated Barbier[2] and Reformatsky-type[3] reactivity of organoindium reagents derived from allylic and propargylic precursors with a wide range of C=O and C=NR derived functional groups[4] are well-documented, and the synthetic utility of these methods has been demonstrated in the synthesis of a number of pharmaceutical and natural products.[5] The addition reactions of allylic indium reagents to carbonyl-derived electrophiles proceed with high diasteroselectivity via predominantly γ-addition of the organometallic, although the ratio of α:γ-addition has been found to be dependent on solvent.[6] Additionally, indium-mediated methodology has also been extended to take in a wide range of transformations including Michael additions,[7] indium hydride[8] and dissolving metal reductions,[9] and Pd(0) catalysed cross-coupling reactions of organoindium reagents.[10] Additionally, indium reagents have been used to facilitate radical cyclisation[11] and atom transfer cyclisation reactions.[12]

In view of the obvious importance of indium-mediated reactions, it is therefore surprising that the reactions of organoindium reagents with carbon–carbon and carbo-heteroatom triple bonds have received comparatively little attention. In early work, Araki et al. reported the addition reactions of allylic indium sesquihalides with alkynols[13] and allenols[14] to give (*E*)-2,5-hexadien-1-ols and (*E*)-2,6-heptadien-1-ols, respectively. They showed that the addition of the organoindium reagent occurs regioselectively in the anti-Markovnikov mode, which it was proposed arose as a result of coordination of the intermediate organometallic species by the hydroxyl group, which directs addition to the terminal carbon of the alkyne. Subsequently the carboindination of unactivated terminal alkynes,[15] which do not bear an adjacent hydroxyl group, to give 1,4-dienes via Markovnikov addition and the carboindination of nitriles to give enamines[16] was reported. Thus, while the synthetic scope and mechanistic aspects of the intermolecular carboindination of alkynes and nitriles have received attention, the corresponding intramolecular carboindination of alkynes with allyl halides remains is much less well understood.

In the intramolecular reaction manifold, a number of potential reaction pathways may be considered. For example, it may be reasoned that exposure of tethered haloenynes **1** (X=O, NR, CR^1R^2) to indium metal would give the corresponding allylindium species **2a** which could exist in equilibrium with the *endo* isomer **2b**. Furthermore,

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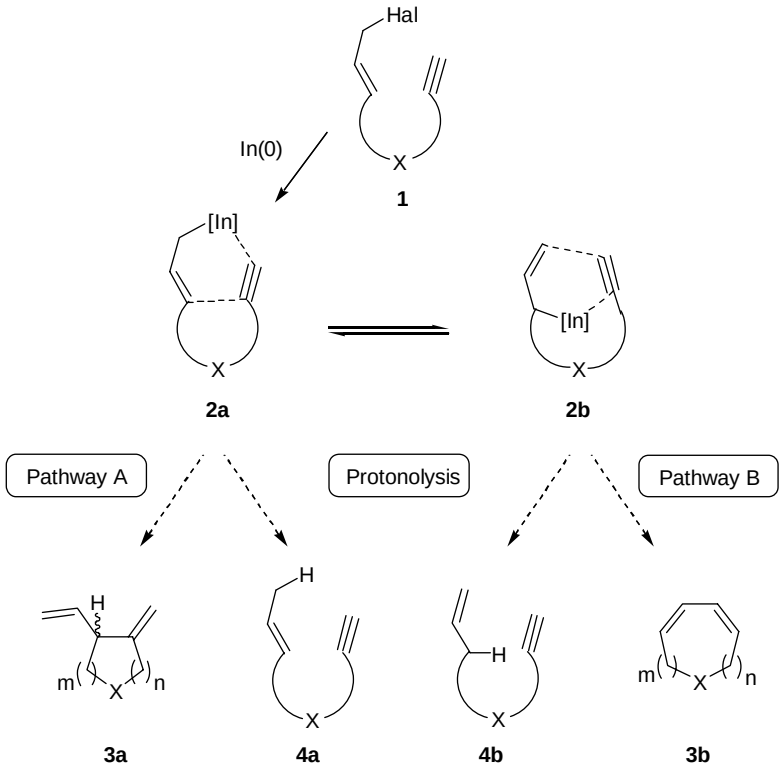
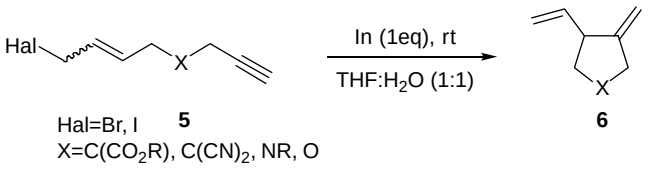


Scheme 1. Possible pathways for the reaction between indium and haloallylalkynes.

such intermediates could be expected to react by (i) a process of carboindation of the alkyne triple bond by either a Markovnikov (pathway A) or *anti*-Markovnikov (pathway B) route to give the corresponding *exo* 1,4-dienes **3a** or *endo* 1,3-dienes **3b**, respectively[17] or (ii) proteodebromination of the organometallic (for example, on workup) to give either the crotyl **4a** or allylic species **4b**. At the outset of our work, it was not clear whether the cyclisation reaction was possible or whether the pathway of proteodebromination would predominate (Scheme 1).

We herein report[18] that a broad range of bromooct-6-en-1-ynes **5** undergo smooth cyclisation at room temperature in the presence of indium metal via pathway A to give *exo*-1,4 carbocyclic and heterocyclic dienes **6** cleanly (Scheme 2). Whilst the cyclisation of enynes to five-membered carbocycles and heterocycles under the influence of a range of transition metals has been previously demonstrated[19] these procedures often necessitate the use of expensive catalysts and/or ligands, which are often moisture and air sensitive or must be prepared in situ immediately prior to use. In contrast, not only is the method discussed in the current submission robust, operationally simple and relatively inexpensive, in fact the efficiency of the reaction



Scheme 2. Indium-mediated cyclisation of tethered terminal haloallylalkynes.

is greatly enhanced by the addition of water to the reaction solvent.

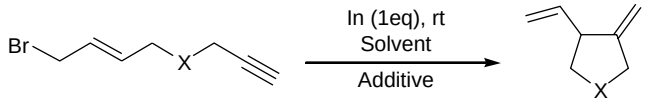
2. Results and discussion

2.1. Initial approaches to the indium-mediated cyclisation reaction

The first substrate chosen for investigation was the parent bromoenyne, (*E*)-1-bromobut-2-ene-4-ol propargyl ether **7a**, which may be readily synthesized from propargyl alcohol and *trans*-1,4-dibromobut-2-ene. In a typical procedure **7a** and indium powder (1 equiv) were suspended in the appropriate solvent and stirred at room temperature or reflux for 12–21 h, before being subjected to standard aqueous acidic workup (Table 1).

Initial results using these conditions were not encouraging. Neither stirring an equimolar mixture of **7a** and indium powder in dry THF (entry 1) or dry DMF (entry 2) under an N_2 atmosphere at room temperature led to the formation of the desired cyclised product but only to recovery of unchanged starting material. Heating the reaction to reflux in dry THF in line with the protocol reported for the corresponding intermolecular reaction[15] also failed to yield any of the cyclised product **8a** (entry 3). However, to our delight when the reaction was carried out in a 1:1 mixture of THF/H_2O overnight, followed by mild protolytic workup, the desired 3-vinyl-4-methylenetetrahydrofuran **8a** was obtained in 62% yield (entry 4) as a single product. This result represents the first example of an intramolecular carboindination of alkynes, and is testament to the profound effect that the addition of water is known to have on

Table 1. Initial approaches to the In-mediated cyclisation



7 or 9 **8 or 10**

Entry	Haloenyne	X	Solvent	Additive	*t*/h	Product	Conversion/%[a]
1	**7a**	O	THF (dry)	—	14	—	0
2	**7a**	O	DMF (dry)	—	12	—	0
3	**7a**	O	THF (dry)[b]	—	14	—	0
4	**7a**	O	THF/H_2O[c]	—	16	**8a**	>95 (62)
5	**9a**	$C(CO_2Me)_2$	THF (dry)[b]	—	21	—	Trace
6	**9a**	$C(CO_2Me)_2$	THF/H_2O[c]	—	17	**10a**	>95 (74)
7	**9a**	$C(CO_2Me)_2$	THF (dry)	TFA (0.1 equiv)	4.5	**10a**	>95 (80)
8	**9a**	$C(CO_2Me)_2$	THF (dry)	AcOH[d] (0.2 equiv)	16	**10a**	72 (35)
9	**9a**	$C(CO_2Me)_2$	THF (dry)	$PhCO_2H$ (0.15 equiv)	20	**10a**	65 (–)[e]
10	**9a**	$C(CO_2Me)_2$	THF (dry)	10-CSA[f] (0.15 equiv)	17	**10**	15 (–)

[a] Conversion estimated from ^{1}H NMR. Isolated yields given in parentheses.
[b] Reaction heated at reflux.
[c] 1:1 ratio.
[d] GPR glacial acetic acid.
[e] Product not isolated.
[f] Dried by azeotroping from toluene.

the rate,[20] as well as the stereo-[21] and regioselectivity[22] of indium-mediated reactions.[23]

Encouraged by this result we decided to examine the possibility of using a substrate bearing a geminal diester group in the hope of utilising the Thorpe–Ingold effect[24] to promote the cyclisation. To this end we prepared dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(prop-2-ynyl)malonate **9a** in one step from commercially available dimethyl-2-(propynyl)malonate. Unsurprisingly, heating this new substrate with indium metal in dry THF at reflux gave only a trace of the desired heterocycle (entry 5). Gratifyingly however, exposure of **9a** to indium metal in THF/H_2O (1:1) at room temperature afforded the corresponding carbocyclic *exo*-1,4 diene **10a** with >95% conversion and in 74% isolated yield (entry 6). Interestingly, it was found that the cyclisation could be effected in dry THF by the addition of a catalytic amount of an anhydrous organic acid to the reaction mixture (entries 7–10). Although most common laboratory acids promoted the reaction to some degree, the efficiency of the cyclisation was related to the strength of the acid added, best results being obtained with TFA (80% yield, 4.5 h). The exact function of the acid in the reaction is still unclear although it is possible that, at the very least, the acid acts to remove any oxide on the surface of the indium thus rendering it more reactive.

The cyclisation reactions in THF/H_2O were extremely clean. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture shows only peaks corresponding to the desired cyclic compound along with those of small amounts of residual starting material. The success or failure of the reactions in THF/H_2O can be conveniently assessed by observing the state of the crude reaction mixture prior to work-up. Appearance of a thick white precipitate of $In(OH)_3$ is normally indicative that the transformation has proceeded smoothly. Typically the reaction mixture also contains a metallic residue, which is approximately 25–30% of the weight of the indium added to the reaction.

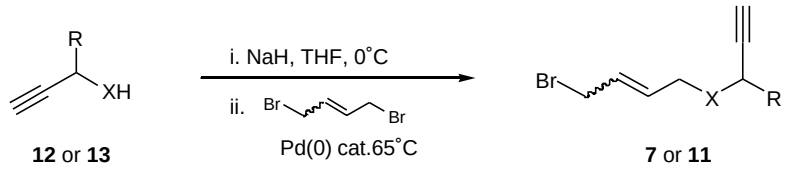
We also screened a number of aqueous and non-aqueous solvent systems for the cyclisation of **9a** to the carbocycle **10a** and the conversion of the reaction was established by inspection of the ^{1}H NMR spectra of the crude reaction mixture. These studies showed that the cyclisation reaction proceeds to some extent in most common laboratory solvents ($THF > DMF > H_2O \approx MeOH \gg Et_2O \approx EtOAc$,) but that in all cases the conversion was improved by conducting the reaction in a 1:1 mixture of the organic solvent and H_2O. The best conversions and yields of the carbocycle were obtained in THF/H_2O (1:1), although it was possible to reduce the amount of THF to approximately 9% (THF/H_2O 1:10) without serious detrimental effect on the conversion of **9a** to **10a**. The reaction was also found to proceed in pure H_2O although the conversion dropped to 75–80%, which may in part be due to the insolubility of the substrate in a completely aqueous environment.

2.2. Synthesis of other haloallyl alkyne cyclisation precursors

The initial results described above prompted us to probe further the scope of the indium-mediated cyclisation of terminal haloenynes. To this end, we prepared three groups of substrates in which the allylic halide and alkyne were linked by an oxygen, nitrogen or carbon atom. The heteroatom-tethered substrates **7a–d** (Table 2, X=O) and **11a–e** (Table 2, X=NR) were prepared as shown below from common starting materials in moderate yields by allylation of the sodium salt of propargyl alcohols **12a–d** or *N*-protected propargyl amines **13a–e** with (*E*)- or (*Z*)-1,4-dibromo-2-butene in moderate yields (Table 2). In some cases, the reaction was promoted using a Pd(0) catalyst in accordance with literature protocols.[25]

The carbon-tethered cyclisation substrates **9a–h** were synthesised in a similar manner, either from commercially available active methylene compounds **14a–e** (Table 3) or,

Table 2. Synthesis of heteroatom-centered cyclisation precursors



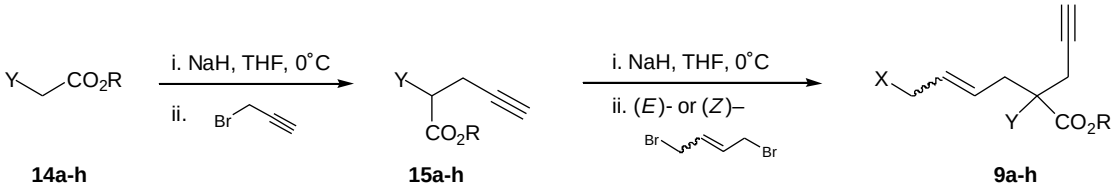
12 or **13** **7** or **11**

Entry	**12/13**[a]	X	R	Product/(% yield)
1	**12a**	O	H	**7a** (34)
2	**12b**	O	Ph	**7b** (30)
3	**12c**	O	^{n}Pr	**7c** (38)
4	**12d** (*E*)	O	^{n}Pen	**7d** (*E*) (37)
5	**12d** (*Z*)	O	^{n}Pen	**7d** (*Z*) (33)[b]
6	**13a**	NTs	H	**11a** (34)[c]
7	**13b**	NTs	^{n}Pen	**11b** (35)[c]
8	**13c**	NBoc	H	**11c** (46)
9	**13e**	NCbz	H	**11d** (63)
10	**13g**	NBn	H	**11e** (37)

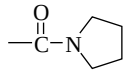
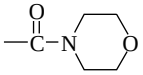
[a] (*E*)-geometry unless otherwise stated.
[b] >97% (*Z*).
[c] Reaction carried out in the presence of 5 mol% $Pd^{2}(dba)_3$ + 5 equiv (wrt Pd) PPh_3 prepared by stirring in degassed reaction solvent for 1 h at rt then added via cannular to the reaction mixture.

in the case of mixed ester/amide substrates **14f–h**, from the corresponding amide, which was in turn prepared in good yield by treatment of commercially available ethyl malonyl chloride with the appropriate amine in CH_2Cl_2–H_2O. *gem* Dinitrile substrate **9i** which was synthesised from propargyl malononitrile **16** which itself was prepared by dehydration of diamide **17**, prepared from commercial dimethylpropargyl malonate **15a** (Scheme 3).[26]

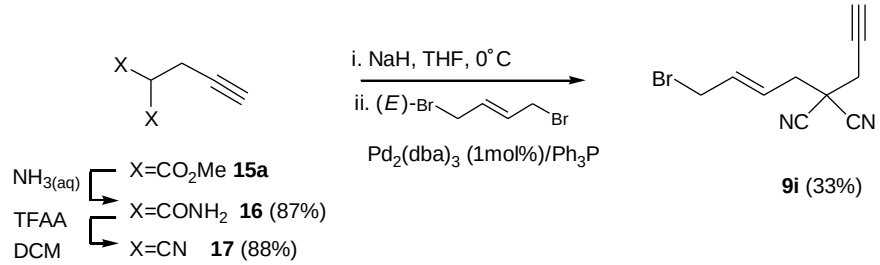
Table 3. Synthesis of carbon-centred terminal haloallylalkynes



14a-h **15a-h** **9a-h**

Entry	**14**[a]	R	Y	**15**/(%)	**9**/%[a]
1	**14a**	Me	CO_2Me	**15a**[b]	**9a** (*E*) (53)
2	**14a**	Me	CO_2Me	**15a**[b]	**9a** (*Z*) (47)[c]
3	**14b**	Et	CO_2Et	**15b** (–)	**9b** (18)[d]
4	**14c**	^{t}Bu	CO_2Me	**15c** (–)	**9c** (17)[d]
5	**14d**	^{t}Bu	^{t}Bu	**15d** (–)	**9d** (27)[d]
6	**14e**	Me	SO_2Ph	**15e** (–)	**9e** (49)[d]
7	**14f**	Et	$CONMe_2$	**15f** (32)	**9f** (37)
8	**14g**	Et		**15g** (52)	**9g** (38)
9	**14h**	Et		**15h** (48)	**9h** (32)

[a] (*E*)-isomer unless otherwise stated.
[b] Purchased from commercial sources.
[c] (*Z*)/(*E*) ratio 94:6.
[d] Yield from **14** over 2 steps.



9i (33%)

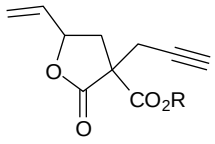
Scheme 3. Synthesis of 2-(4-bromobut-2-enyl)-2-(prop-2-ynyl)malononitrile **9i**.

2.3. Investigation of the scope of the indium-mediated cyclisation reaction

Having synthesised the desired substrates, our attention turned to establishing the scope of the intramolecular carboindination reaction. To this end the heteroatom-tethered haloallylalkynes **7a–d** and **13a–e** were stirred with indium powder (1 equiv) in THF/H_2O (1:1) at room temperature for 15–18 h before being submitted to mild acidic work up and purification. As shown in Table 4, the oxygen-tethered substrates **7a–d** underwent smooth cyclisation to give the corresponding *exo*-diene tetrahydrofurans **8a–d** in moderate to acceptable yield and with a small preference for the *syn* diastereomer[27] in the case of substrates bearing a substituent in the α-position (entries 2–5). The (*E*)/(*Z*) geometry of the allylic fragment exerts little influence on the stereochemical course of the reaction, as both the (*E*)- and (*Z*)-allyl bromide of **7d** undergo smooth cyclisation to give *exo* diene tetrahydrofuran **8d** (entries 4 and 5). It is noteworthy that although the diastereoselectivity of this reaction was modest, the degree of selectivity and the sense of selectivity (i.e., *syn* rather than *anti*) was the same regardless of the geometry of the allylic group in the starting material.

Nitrogen-tethered substrates **13a–e** bearing common protecting groups the such as 4-toluenesulfonyl (**13a–b**, X=NTs, entries 6 and 7), *tert*-butoxycarbonyl (**13c**, X=NBoc, entry 8) and benzyloxycarbonyl (**13d**, X=NCbz, entry 9) also underwent smooth, clean cyclisation to afford the corresponding pyrrolidines in relatively good yield. One exception was the *N*-benzyl derivative (**13e**, X=NBn, entry 10), which decomposed under the reaction conditions, possibly by intramolecular S_N2' attack of the nucleophilic nitrogen at the allylic position assisted by Lewis acidic nature of the allylindium intermediate.

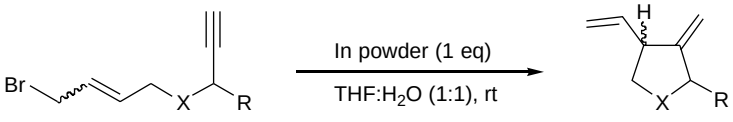
The cyclisation reaction of the carbon-centred substrates was also investigated using the precursors described above (Table 5). Gratifyingly it was found that in nearly all cases the substrates **9a–9i** also underwent smooth indium-mediated cyclisation in aqueous THF to give the corresponding cyclopentyl dienes **10a–10i** in moderate to good yield. The only exception was the geminal di-*tert*-butyl enyne **9d** which did not give the expected carbocycle on treatment with indium. In this case, a complex reaction mixture was obtained from which two compounds, tentatively assigned as the lactones **19** and **20**, were isolated in low yield.[28] In all other cases the cyclisation of the substrates proceeded very cleanly without the need for any additives to give the corresponding hetero- or carbocycle as essentially the only organic product.[29] As with the oxygen and nitrogen-tethered series, the cyclisation reaction proceeded equally efficiently starting with either **9a**(*E*)- (entry 1) or **9a**(*Z*)- (entry 2), or a mixture of both isomers of **9a** (entry 3).



19 (R=^{t}Bu)
20 (R=H)

In contrast to the heterocyclic series, the stereoselectivity of the cyclisation of substrates that gave diastereomeric products was poor (entries 5, 7–11) and it was generally not possible to separate the individual diastereomers or assign their *syn* or *anti* character with certainty by NOESY spectroscopy. However, unambiguous confirmation of the structure of the carbocyclic products was obtained by single-crystal X-ray analysis of **9h** (Fig. 1)[30] which was one of of the few cyclic products obtained as a microcrystalline solid, the remainder being isolated as clear, viscous oils.

Table 4. Cyclisation of heteroatom-tethered haloenynes

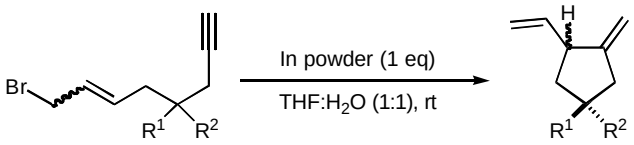


7 or **11** **8** or **18**

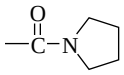
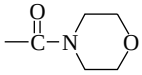
Entry	Haloenyne[a]	X	R	*t*/h	Product/(%)[b]	*syn*/*anti*[c]
1	**7a**	O	H	16	**8a** (62)	—
2	**7b**	O	Ph	16	**8b** (50)	2:1[d]
3	**7c**	O	^{n}Pr	17	**8c** (56)	3.5:1[d]
4	**7d** (*E*)	O	^{n}Pen	17	**8d** (52)	3:1[d]
5	**7d** (*Z*)[e]	O	^{n}Pen	17	**8d** (45)	3.6:1
6	**13a**	NTs	H	16	**18a** (62)	—
7	**13b**	NTs	^{n}Pen	17	**18b** (83)[c]	dr 14:1[f]
8	**13c**	NBoc	H	16	**18c** (69)	—
9	**13d**	NCbz	H	15	**18d** (66)	—
10	**13e**	NBn	H	17	**18e** (0)[g]	—

[a] (*E*)-isomer unless otherwise stated.
[b] Isolated yields after chromatography.
[c] Isomers assigned by analogy to **8d**.
[d] *syn*/*anti* ratios provisionally assigned by ^{1}H NOESY spectral analysis of mixture of diastereomers.
[e] 95:5 (*Z*)/(*E*) ratio of isomers.
[f] *syn*/*anti* isomers could not be identified.
[g] Decomposition/polymerisation only observed.

Table 5. Cyclisation of carbon-tethered haloenynes



9a-h **10a-h**

Entry	Haloenyne[a]	R^1	R^2	*t*/h	Product/(%)[b]	dr[c]
1	**9a**	CO_2Me	CO_2Me	17	**10a** (74)	—
2	**9a** (*Z*)[d]	CO_2Me	CO_2Me	16	**10a** (75)	—
3	**9a** (*E*)/(*Z*)[e]	CO_2Me	CO_2Me	17	**10a** (74)	—
4	**9b**	CO_2Et	CO_2Et	18	**10b** (71)	—
5	**9c**	CO_2Me	CO_2^tBu	16	**10c** (56)	1:1
6	**9d**	CO_2^tBu	CO_2^tBu	17	**10d** (0)	—
7	**9e**	SO_2Ph	CO_2Me	16	**10e** (44)	4.5:1
8	**9f**	$CONMe_2$	CO_2Et	18	**10f** (84)	1.3:1
9	**9g**		CO_2Et	17	**10g** (77)	1:1
10	**9h**		CO_2Et	17	**10h** (63)	1.3:1
11	**9i**	CN	CN	17	**10i** (49)	—

[a] (*E*)-isomers (>99%) unless otherwise stated.
[b] Isolated yields after chromatography.
[c] *syn* and *anti* diastereomers could not been conclusively distinguished by NOESY NMR.
[d] 94:6 (*Z*)/(*E*) mixture of alkene isomers.
[e] 67:33 (*E*)/(*Z*) mixture of alkene isomers.

2.4. Effect of the allylic precursor on the cyclisation reaction

We also investigated the influence of the nature of the allylic precursor on the course of the reaction. Although the (*E*)-allyl bromides were used as the precursors of choice due to their ready availability we found that the (*E*)-iodo analogue **21**, which could be prepared in 79% yield from dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(prop-2-ynyl)malonate **9a** by treating it with NaI (5 equiv) in acetone, also underwent efficient indium-mediated cyclisation under standard conditions to give carbocycle **10a** in >95% conversion and 73% isolated yield (Table 6, entry 1). By contrast, the (*E*)-chloro analogue **22** was almost completely inert to the reaction conditions[31] (entry 2) even in the presence of NaBr (entry 3), although NaI (entry 4) or KI (entry 5) were more effective in promoting the reaction. The corresponding allyl mesylate **23** (3:2 *cis*/*trans* mixture) was similarly inert (entry 6) but could also be made to undergo smooth cyclisation in aqueous THF by the addition of KI (entry 7).

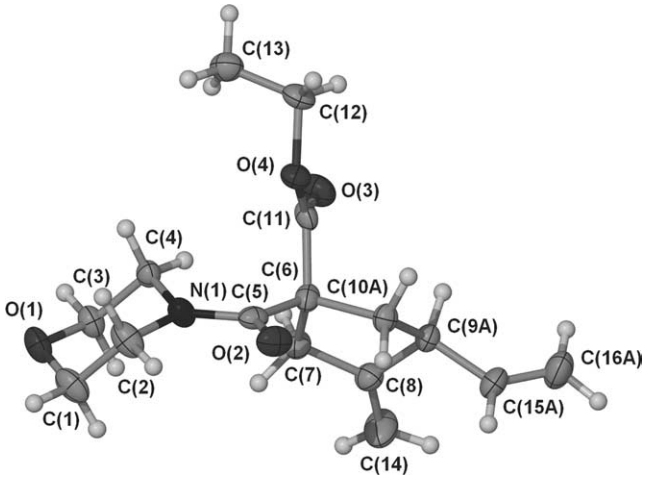


Figure 1. X-ray structural analysis of carbocycle **9h**.

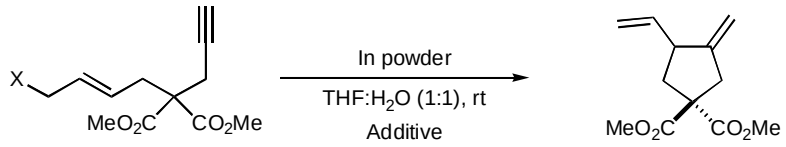
2.5. Influence of the nature of the indium reagent on the cyclisation reaction

Having demonstrated the viability of the indium mediated cyclisation of terminal haloallylalkynes we wished to investigate the scope of the reaction with respect to the indium reagent. Accordingly a number of indium reagents were screened for their efficiency in promoting the cyclisation of **9a**.

In a typical procedure the indium was added as In(0) powder (1 equiv, 99.99 atom% In) (Table 7, entry 1), a procedure which afforded the carbocyclic product in 75%. We found that the amount of indium could be reduced to 0.67 equiv without compromising yield (entry 2) but that the use of smaller amounts (entries 3 and 4) led to a reduction in the efficiency of reaction, giving lower conversions in direct proportion to the amount of indium added. A combination of sub-stoichiometric indium metal and excess manganese failed to turn the reaction over (entry 5).[32]

It was found that presenting the indium as wire (entry 6), 2–5 mm shot (entry 7) or 0.5 mm foil (entry 8) had a marginally detrimental effect on yield presumably due to the greatly reduced surface area of these forms relative to

Table 6. Scope of the allylic precursor

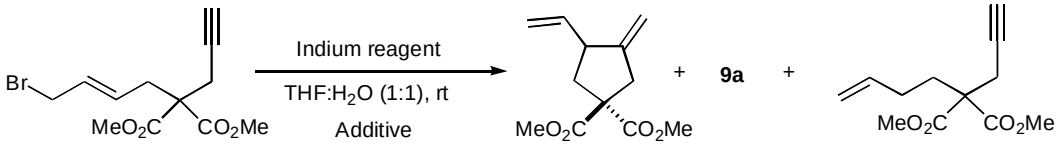


21-23 **10a**

Entry	Haloenyne	X	Additive	Conversion **10a**/(%)[a]
1	**21**	I	—	>95 (75)
2	**22**	Cl	—	17 (–)[b]
3	**22**	Cl	NaBr (2 equiv)	12 (–)[b]
4	**22**	Cl	NaI (5 equiv)	80 (–)[b]
5	**22**	Cl	KI (5 equiv)	50 (14)
6	**23**	OMs	—	0[c]
7	**23**	OMs	KI (5 equiv)	97 (71)

[a] Isolated yield in parentheses.
[b] Product not isolated.
[c] Approx. 8% of the corresponding allyl alcohols arising from hydrolysis of the starting mesylate was observed.

Table 7. Use of different indium sources for the cyclisation reaction



9a **10a** **24**

Entry	In source	Mol% In	Additive	*t*/h	Yield **10a**/%	Ratio **10a**:**9a**:**24**[a]
1	In(0) powder	100	—	17	75	95:5:0
2	In(0) powder	67	—	16	73	75:25:0
3	In(0) powder	50	—	18	—[b]	51:49:0
4	In(0) powder	10		18	—[b]	10:90:0
5	In(0) powder	10	Mn (5 equiv)	18	—[b]	<5:95:0
6	In(0) wire[c]	100	—	15	50	64:36 (21)[d]:0
7	In(0) shot[e]	100	—	17	71	94:6:0
8	In(0) foil[f]	100		17	63	80:20:0
9	None	—	Ga (1 equiv)	18	0	0:100 (90)[g]:0
10	InBr[h]	100	—	17	53	69:21(18)[i]:0
11	InI[h]	100	—	18	34	66:34 (15)[i]:0
12	$InBr_3$	100	—	17	0	0:100 (95)[g]:0
13	$InCl_3$	100	—	16	0	0:100 (80)[g]:0
14	$In(OH)_3$	100	—	17[j]	0	0:100:0
15	$InBr_3$	100	Zn (5 equiv)	17	72	87:0:13
16	$InBr_3$	10	Zn (5 equiv)	17	44	13:77:0
17	$InBr_3$	10	Zn (2 equiv)	18	17	24:0:76 (79)[k]
18	$InBr_3$	10	Zn (1 equiv)	16	—[b]	50:0:50
19	$InBr_3$	10	Mn (5 equiv)	16	0	0:100:0
20	$InBr_3$	10	Mg (5 equiv)	17	0	0:100:0
21	$InBr_3$	10	Ga (3 equiv)	17	0	0:10 0:0[l]
22	$InBr_3$	10	Al (3 equiv)	18	0	0:100:0
23	$InBr_3$	10	Fe (3 equiv)	18	0	0:100:0
24	$InCl_3$	100	Zn (5 equiv)	16	62	64:0:36

[a] Estimated from ^{1}H NMR.
[b] Not isolated.
[c] 99.99% In cut into approx. 1 mm lengths.
[d] Isolated yield in parentheses.
[e] 2–5 mm shot (99.99+% In).
[f] 99.99% In cut into 1–2 mm squares.
[g] Recovered starting material yield in parentheses.
[h] 99.99% InX beads crushed to powder.
[i] Starting material recovered as 2:1 mixture of iodo- and bromo isomers (16% total recovery).
[j] Dry THF only used as solvent.
[k] Isolated yield in parentheses.
[l] Some hydrolytic decomposition observed.

indium powder. In addition, the comparative softness of indium metal also meant that adding it in any form other than a fine powder (which is light enough to be suspended in the solvent) often resulted in it being flattened into a 'mirror' on the inside of the flask. The same problem was experienced with gallium metal, which did not promote the reaction at all (entry 9).

In addition to elemental indium, the reaction was found to proceed in the presence of indium salts. Use of InBr (entry 10) and InI (entry 11) in aqueous THF promoted the cyclisation but under these conditions the reaction was more capricious than with In(0) and proceeded with lower conversions and in poorer chemical yield. Additionally in the case of InI the product mixture also contained 2-((*E*)-4-iodobut-2-enyl)-2-(prop-2-ynyl)malonate **19** as well as the carbocyclic product and unreacted allyl bromide starting material. It should be noted that when using indium(I) salts, it was essential to crush the reagent to a powder before addition due to the poor solubility of In(I) in the reaction medium.

More highly oxidised In(III) salts such as $InBr_3$ (entry 12), $InCl_3$ (entry 13) or $In(OH)_3$ (entry 14) did not promote cyclisation; the unreacted starting bromide being the only species present in the crude reaction mixture as determined by ^1H NMR spectroscopy. Whilst InX_3 salts alone were not effective reagents for the transformation, the use of a co-reductant such as zinc (entry 15) with $InBr_3$ (1 equiv) to generate a reduced indium species in situ afforded the carbocyclic product smoothly and cleanly in essentially the same yield as that obtained with In(0) powder. Significantly, it was found that under these conditions the reaction could be made to turn over even in the presence of substoichiometric quantities of $InBr_3$ (0.1 equiv)[33] (entries 16–18) although both the conversion and isolated yield of the carbocycle was dramatically reduced. In all cases where $InBr_3$ was used to mediate the reaction, proteodebrominated product **24** was also generated in varying amounts. A number of co-reductants in addition to zinc were screened (entries 20–23) but none were found to be effective in promoting the reaction. Use of the cheaper $InCl_3$ as the In(III) source in the presence of zinc dust (5 equiv) did facilitate the cyclisation reaction, however, whilst conversion of the starting allylbromoalkyne was in line with other methods much higher quantities of the proteodebrominated by-product **24** was generated.

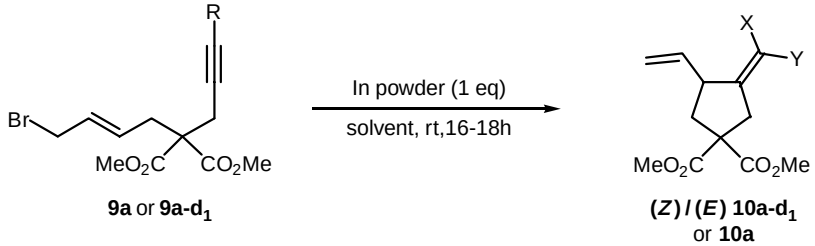
The failure of more highly oxidised salts alone to facilitate the cyclisation is unsurprising in view of the likely sesquihalide nature of the organoindium intermediate which may be assumed to develop in this type of reaction.[34] The generation of such an intermediate from the allyl halide would require formal oxidative addition of the indium reagent to the substrate, which would be possible for both In(0) and In(I) but would not be possible for In(III) species.

2.6. Deuteration studies aimed at elucidating the mechanism of the cyclisation reaction

Whilst the synthetic scope of the indium-mediated cyclisation had been established, a number of the mechanistic aspects of the reaction remained unexplored. For example, it was still not known whether the addition of the allyl bromide fragment to the alkyne proceeded by regioselective *syn* or *anti* carboindination of the carbon–carbon triple bond or by another, non-regioselective, pathway. Furthermore, it was also unclear whether the protonation of the organindium intermediate generated on cyclisation of the precursor takes place during the reaction, or occurs on acidic work-up. In order to investigate the protonation process a deuteration study of the indium-mediated cyclisation reaction of (*E*)-**9a** was carried out (Table 8).

Firstly, **9a** was allowed to react with indium in a mixture of dry THF/H_2O (1:1) under a N_2 atmosphere for 16 h whereupon the reaction mixture was evaporated to dryness in vacuo. The resulting milky-white solid was suspended in diethyl ether and treated with 18% DCl in D_2O (99.99 atom% D), stirred at room temperature for 5 min and then the mixture was partitioned between diethyl ether and water, and the organic layer was washed with brine and then dried ($MgSO_4$). The ^1H NMR spectrum of the residue obtained on

Table 8. Deuterium labling studies



9a or **9a-d$_1$** → **(*Z*) / (*E*) 10a-d$_1$** or **10a**

Entry	R	Solvent[a]	Work-up	Conversion (%)[b]	X	Y
1	H	THF/H_2O	18% DCl/D_2O	>95 (65)	H	H
2	H	THF/D_2O	15% $HCl_{(aq)}$	>95 (50)	D[c]	H
3	D[d]	THF/H_2O	15% $HCl_{(aq)}$	>97 (86)	H	D[d]
4	H	d_8-THF/H_2O	15% $HCl_{(aq)}$	>95 (73)	H	H

[a] (1:1) mixture of solvents.
[b] Estimated from ^1H NMR. Isolated yield in parentheses.
[c] 90% incorporation.
[d] 50% incorporation.

filtration and removal of solvent showed that cyclisation had occurred as expected but that no deuterium had been incorporated into the product (Table 8, entry 1). The procedure was repeated using dry THF/D_2O (1:1) as solvent and the reaction was worked up according to the method described above except that 15% HCl in H_2O was used to quench the reaction. Significantly, the cyclised product generated under these conditions contained an atom of deuterium at the terminal end of the 1,1-disubstituted exocyclic alkene generated by carboindination of the alkyne moiety (entry 2). The geometry of the newly-formed double bond in (*Z*)-**10a–d$_1$** was established by NOESY spectroscopy. No incorporation into the (*E*) position was observed. Interestingly, deuterated haloallylalkyne **9a–d$_1$** in which the acetylinic proton has been replaced with deuterium (50%) also underwent smooth reaction with In(0) in THF/H_2O to give the cyclised product (*E*)-**10a–d$_1$** with essentially quantitative conversion and in 86% isolated yield with no loss of deuterium (entry 3). No scrambling of the deuterium into the (*Z*)-position was observed. Unsurprisingly, the use of d_8-THF/H_2O as the solvent followed by $HCl_{(aq)}$ work-up did not lead to the incorporation of deuterium into the product (entry 4).

These results indicate that the protonation (deuteration) event in the cyclisation occurs as the reaction cycle is turning over and not at the time of the protolytic (deuterolytic) work-up. It follows therefore that an organic and/or inorganic indium hydroxide (deuteroxide) species is present in the mixture during the reaction cycle. Furthermore, the exclusive (*Z*)-geometry of the newly-formed exocyclic alkene strongly suggests that the reaction proceeds via a *syn*-selective concerted carboindination of the alkyne, a postulate that is reinforced by the observation that the d_1-alkyne substrate undergoes cyclisation to give exclusively the (*E*)-deuterated carbocylic product. The fact that this latter transformation proceeds without the integrity of the alkynic deuterium atom being compromised rules out the possibility that the reaction proceeds via an acetylinic indium species, an observation that is consistent with the mechanism for the intermolecular addition of organoindium reagents to aliphatic terminal alkynes.[16b]

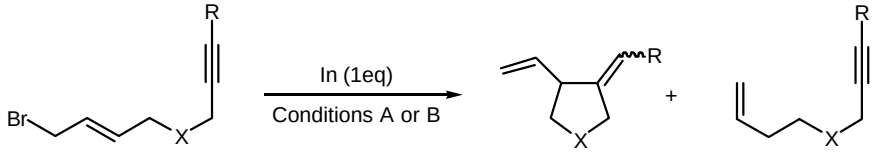
2.7. Cyclisation of non-terminal haloallyl alkynes in THF/H_2O (1:1)

Whilst terminal haloenynes undergo indium-mediated cyclisation under mild conditions in aqueous solvent systems without the need for additives, attempts to extend this methodology to the cyclisation of non-terminal haloallyl alkynes were largely unsuccessful. Exposure of non-terminal *gem*-diester haloallylalkyne **25** or **26** to indium metal in THF/H_2O (1:1) at room temperature did not lead to the generation of either of the desired carbocyclic products **30** or **31** but instead gave the corresponding proteodebrominated materials (Table 9, entries 1 and 2) as the major product of the reaction. Attempts to effect the cyclisation of **25** by generation of a more active indium species by in situ reduction of $InBr_3$ (1 equiv) with Zn (5 equiv) also met with failure (entry 3). Addition of KI either in THF/H_2O (1:1) or DMF/H_2O (1:1) did not improve matters. Indeed, it was necessary to move to much more forcing conditions (DMF, 100 °C, entry 5) to effect the cyclisation of non-terminal alkyne systems **25**, **26** (entries 4 and 5).[35]

2.8. Intramolecular carboindination of non-terminal haloenynes

Although unactivated non-terminal alkynes proved inert to cyclisation using the aqueous protocol, electron-poor haloallyl alkyne **27** underwent smooth and clean cyclisation to give the corresponding carbocycle **32** in good yield (Table 9, entry 6). It is reasonable to suggest that the greatly altered electronic nature of **27** compared with that of **25** or **26** in which the alkyne triple bond is essentially unpolarised, shifts the mechanism of the reaction from an

Table 9. Cyclisation of non-terminal bromoenynes



25-29 **30-34** Cyclic product Alkene product

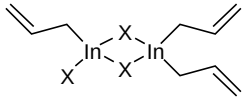
Entry	Enyne	X	R	In source	Conditions[a]	Product	Cyclic/alkene[b]
1	**25**	$C(CO_2Me)_2$	Me	In(0)	A	**30**	0:88(59)[c]
2	**26**	$C(CO_2Me)_2$	Ph	In(0)	A	**31**	0:100(66)
3	**25**	$C(CO_2Me)_2$	Me	$InBr_3$/Zn	A	**30**	0:100(84)
4	**26**	$C(CO_2Me)_2$	Ph	In(0)	B	**31**	91(85):9[d]
5	**25**	$C(CO_2Me)_2$	Me	In(0)	B	**30**	89(65):11
6	**27**	$C(CO_2Me)_2$	CO_2Me	In(0)	A	**32**	95(65)[e]:5
7	**28**	O	Ph	In(0)	A	**33**	40(30):60
8	**29**	O	^{n}Pr	In(0)	A	**34**	—[f]

[a] Conversion estimated from ^{1}H NMR. Isolated yields in parentheses.
[b] Condition A: THF/H^{2}O (1:1), rt. Condition B: DMF (anhydrous), 100 °C.
[c] Ref. 36
[d] Starting material also recovered.
[e] 92:8 (*E*)/(*Z*) mixture of diastereomers.
[f] Decomposition of starting material observed.

alkyne carbometalation pathway to an intramolecular Michael addition-type pathway. Intriguingly however, the oxygen-centred haloallyl alkyne **28** did undergo indium-mediated cyclisation in THF/H_2O (1:1) at room temperature to a certain extent (entry 7) to give **33** although the major product was still the proteodebrominated material. The contrast in reactivity of the **28** the carbon-centred non-terminal haloenynes may be partially due to the C–O bond in **28** being slightly shorter than the analogous C–C bond in the carbon-centred substrates. However, the failure of propyl-substituted oxygen-centred substrate **29** to undergo cyclisation indicates that the reaction is finely balanced and is governed by both steric and electronic factors.

2.9. Nature of the allyindium intermediate

The difference in the reactivity of non-terminal haloallyl alkynes towards indium in aqueous THF and anhydrous DMF is striking especially in view of the fact that it has been established that the cyclisation does not proceed via a route involving insertion into a C≡C–H bond (vide supra). The explanation of this observation lies in the likely nature of the organoindium intermediate present in each reaction. It is known that reactions of allyindium reagents in highly polar solvents such as DMF or THF proceed via an indium sesquihalide intermediate ($R_3In_2X_3$) **35** but that this structure can be transformed into the corresponding dialkylindium species by the addition of KBr or KI. However under aqueous conditions, the monomeric allylindium species **36** has been shown to be present in the reaction mixture.[37]



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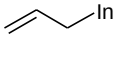
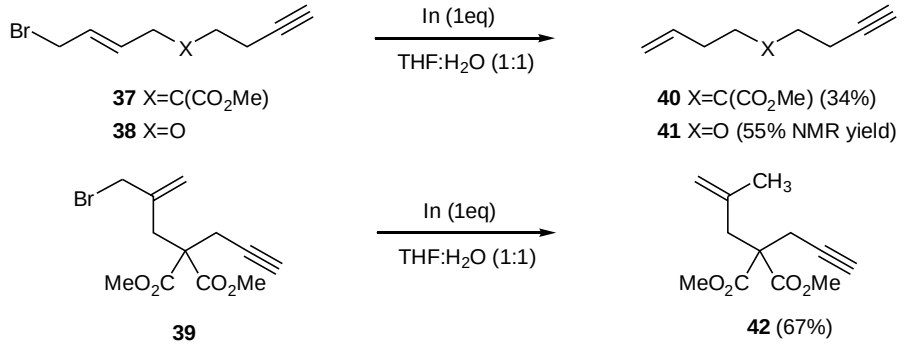


36

In the analogous intermolecular carboindinations of alkynes it has been demonstrated that the two of the three allyl groups are added across the alkyne carbon–carbon triple bond, and the third acts as a ligand for the indium complex in the reaction.[33] Accordingly in the intermolecular case, 0.6 equiv of indium with respect to the alkyne substrate (representing an effective 1.2 fold excess of allylindium reagent over the alkyne) are typically used and one allyl group per molecule of the organoindium complex is sacrificed. However, in the case of intramolecular carboindination the ratio of allyl group to alkyne is necessarily fixed at 1:1. Thus if the organoindium species generated during the cyclisation of tethered terminal haloallyl alkynes in THF/H_2O is an indium sesquihalide, the maximum possible yield for the reaction would be 66% with the remaining 33% of the organic reagent being lost as a ligand for the indium complex generated in the reaction. The fact that the cyclisation in THF/H_2O proceeds without loss of yield with only 0.67 equiv of indium with respect to the substrate (Table 6, entry 2) would appear to support a sesquihalide intermediate. However, this is offset by the observation that the yield of the reaction can exceed 66%, and that the reaction does not proceed in dry THF (which would be expected to lead to the formation of an indium sesquihalide) but only turns over in aqueous solvent systems (which would promote a dimeric or monomeric allylic indium species). Therefore, whilst it is still not possible to identify the exact nature of the intermediate in THF/H_2O, these data suggest that it is most likely composed of a mixture of mono- and dimeric organoindium species which are Lewis acidic enough to undergo addition to a terminal alkyne but not sufficiently reactive to add to more sterically congested non-terminal alkynes, in contrast to the indium sesquihalide intermediate which would likely be present in more polar DMF. Furthermore, the fact that the (*E*)/(*Z*) geometry of the allylic precursor has no effect on the yield or stereoselectivity of the reaction indicates that the cyclisation to a five-membered ring proceeds from a common intermediate.[38]

Something of the constraints placed upon on the cyclisation of this intermediate can be understood by contrasting the smooth cyclisation of the substrates described above with indium in THF/H_2O to give five-membered carbo- and heterocycles with the failure of 1-bromo-2-nonene-8-ynes **37–38** and bromomethallylalkyne **39** to cyclise to the corresponding six-membered analogues (Scheme 4) under them same conditions. These observations indicate that in the presence of a protic solvent mixture,[33] the rate of proteodebromination of substrates **37–39** to give alkenes **40–42** is faster than that of cyclisation, and therefore it seems likely that the reaction proceeds by a cyclic rather than open transition state.

Therefore, whilst the exact structure of this intermediate is still unclear, the deuterium labelling results and consideration of the geometries involved in the cyclisation suggests that the reaction most likely proceeds through the (*E*)-form



37 X=C(CO_2Me)
38 X=O

40 X=C(CO_2Me) (34%)
41 X=O (55% NMR yield)

39

42 (67%)

Scheme 4. Attempted extension of the cyclisation reaction to six-membered systems.

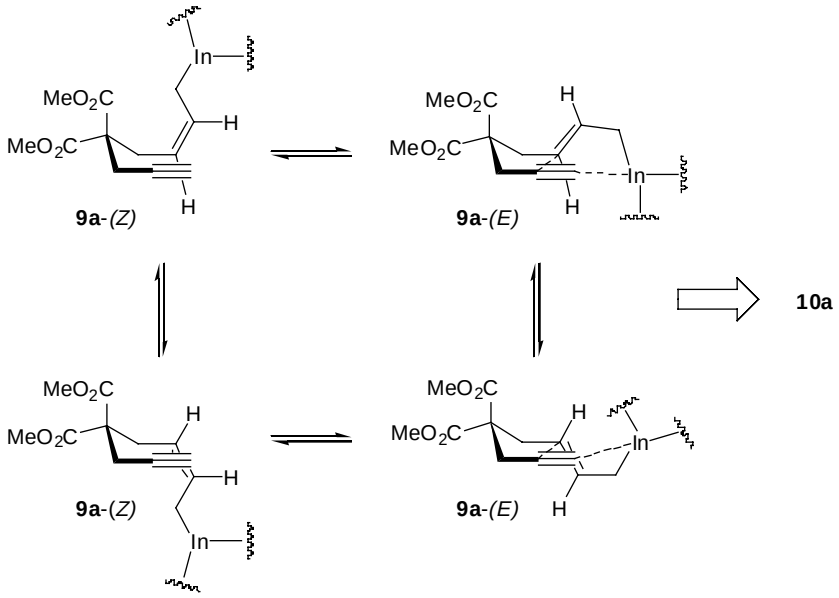


Figure 2. Suggested structures for the cyclisation intermediate.

of the allylindium intermediate, generated either from the action of indium on the (*E*)-allylic halide or from isomerisation of the (*Z*)-allylindium. This then adds across the alkyne in *syn* fashion with complete specificity, a reaction mode which would be accommodated only by a concerted carboindination of the triple bond and would not be consistent with a radical mechanism (Fig. 2).

3. Conclusion

In summary, we have demonstrated a novel indium-mediated cyclisation reaction of terminal haloallyl alkynes which proceeds in THF/H_2O via intramolecular allylindination of the unactivated alkyne C–C triple bond. The reactions, which occur smoothly under extremely mild conditions without the need for the addition of NaI or KI, are operationally simple and provide a quick and convenient route to the synthesis of a variety of five-membered heterocycles and carbocycles.

The reaction was facilitated by both In(0) and In(I) species although not by the addition of either In(III) salts or Ga(0). Generation of indium reagent by in situ reduction of In(III) species with zinc allowed the use of catalytic quantities (10 mol%) of indium. The presence of water in the reaction medium was found to be essential for smooth and efficient cyclization, and although a 1:1 mixture of THF/H_2O was established as the solvent system of choice, the reaction still proceeds in $>90\%$ water without any serious detrimental effect on the reaction.

Deuteration studies demonstrated that alkynylindium intermediate is not involved in the reaction, but that the intramolecular addition of the allylindium reagent to the alkyne occurs via concerted *syn* specific carboindination of the triple bond to generate a putative vinylindium species which is protonated in situ by the aqueous component of the solvent system.

Not only is this protocol very attractive from a synthetic standpoint due to operational simplicity, convenience and cleanliness of the reactions, but is also provides a practical contribution to the field of Green Chemistry. The use of aqueous media for organic synthesis is a field of growing importance[22] and the development of environmentally benign protocols by the minimisation of the use of organic solvents is of considerable interest from both an economic and environmental standpoint. We believe that the current method represents a valuable addition to this important field.

4. Experimental

4.1. General experimental procedure

^1H and ^{13}C NMR data were recorded on a Brucker AM400 or AM360 spectrometer in deuterochloroform, referenced to either TMS or residual $CHCl_3$ as an internal standard. Chemical shifts were measured in ppm and coupling constants (*J*) were measured in Hz. Mass spectra were obtained on a Jeol AX505W spectrometer using EI or CI. IR spectra were recorded neat or from solution, as stated, on a Perkin–Elmer paragon 1000 Fourier transform IR spectrometer. Analytical tlc was carried out on Merck 60 F_{245} plastic backed silica gel plates. Short wave UV (245 nm) or $KMnO_4$, were used to visualise components. Compounds were purified by column chromatography using Merck silica gel 60 (0.040–0.063 mm. Diethyl ether was dried over sodium wire in a septum sealed Winchester under argon. THF was distilled under N_2 from sodium benzophenone ketal NaH was freed of mineral oil by triturating three times with 60–80 °C petroleum ether. Other chemicals were used as obtained from commercial sources. All reactions were carried out in oven dried glassware.

4.2. Representative procedure for the synthesis of carbon-centred haloenynes

4.2.1. Dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(prop-2-ynyl)malonate 9a. Sodium hydride (60% in oil, 2.40 g, 60 mmol) was washed with dry hexane (3×30 mL) and dried in vacuo. The NaH was suspended in dry THF (50 mL) and cooled to 0 °C. To this was added dimethyl-(2-propynyl)malonate dropwise via syringe and after the addition was complete the mixture was stirred and allowed to come to room temperature over 30 min. This was then added via a wide-bore cannula to a solution of (*E*)-1,4-diromo-2-butene (15.67 g, 75 mmol) in THF (75 mL) at 0 °C over 5 min. The mixture was allowed to come to room temperature and stirred for a further 2 h during which time a white precipitate formed. The mixture was quenched with a mixture of diethyl ether and water and then partitioned between diethyl ether and 2 M $HCl_{(aq)}$. The aqueous layer was extracted with diethyl ether (2×50 mL) and the combined organics washed with water (1×50 mL), brine and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography (SiO_2, hexane/EtOAc 5:1) to give the required allyl bromide as a clear, colourless oil (8.10 g, 53%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.05 (1H, brs), 2.81 (2H, m), 2.83 (2H, d, J=7.7 Hz), 3.77 (6H, s), 3.91 (2H, d, J=7.5 Hz), 5.63 (1H, dt, J=7.5, 15.1 Hz), 5.86 (1H, dt, J=7.5, 15.1 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 23.4, 32.5, 35.3, 53.3, 57.3, 72.2, 78.9, 129.3, 131.9, 170.3; IR (thin film): 3291, 2954, 2122, 1736, 1661 cm^{-1}; MS (EI): m/z (%)=320 [MNH_4^+] (100.0), 223 (16.0), 162 (6.0).

4.3. Representative procedure for the synthesis of heteroatom-centred haloenynes

4.3.1. (*E*)-1-Bromo-4-(prop-2-ynyloxy)but-2-ene 8a. Propargyl alcohol, (1.40 g, 1.45 mL, 25 mmol) was added dropwise via syringe to a suspension of NaH (60% in oil which had been removed by washing with dry hexane, 1.00 g, 1 equiv) in dry THF (25 mL) at 0 °C. The mixture was stirred at ice point for 30 min and then (*E*)-1,4-dibromo-2-butene (5.59 g, 1.1 equiv) in dry THF (25 mL) was added via a cannula and the reaction was heated at 50 °C for 15 h. The mixture was allowed to cool and then quenched with a mixture of diethyl ether and water and then poured onto diethyl ether and 2 M $HCl_{(aq)}$. The aqueous layer was extracted with diethyl ether (2×50 mL) and the combined organics washed with water (1×50 mL), brine and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography (SiO_2, hexane/EtOAc 5:1) to give the required propargylic ether as a clear, colourless oil (1.6 g, 34%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.47 (1H, br s), 4.03 (2H, d, J=8.2 Hz), 4.16 (2H, br s), 4.21 (2H, dd, J=1.5, 6.5 Hz), 5.85 (1H, dt, J=5.6, 15.3 Hz), 5.96 (1H, 6.5, 15.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 26.3, 57.4, 64.2, 74.9, 17.4, 129.3, 130.1; IR (thin film): 3293, 2853, 2116, 1667 cm^{-1}; MS (CI): m/z (%)=168 (27.0), 151 (100.0).

4.4. Representative procedure for the cyclisation of bromoallyl alkynes

4.4.1. Tetrahydro-3-methylene-4-vinylfuran 8a. To a well-stirred solution of (*E*)-1-bromo-4-(prop-2-ynyloxy)-but-2-ene **7a** (1.89 g, 10 mmol) in dry THF (10 mL) and distilled water (10 mL) at room temperature, was added indium (Aldrich, 99.99%, 1.41 g, 10 mmol, 1 equiv). The mixture was stirred for a further 16 h and then the reaction mixture was poured onto a mixture of Et_2O and 2 M HCl. The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organics were washed with water (2×25 mL), saturated aqueous NaCl (1×25 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography on silica (hexane/Et_2O, 10:1) to give the cyclised product **8a** (680 mg, 62%) as a clear colourless oil: ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.24 (1H, m), 3.48 (1H, dd, J=8.5, 8.6 Hz), 4.03 (1H, dd, J=8.0, 8.1 Hz), 4.23 (1H, d, J=13.3 Hz), 4.34 (1H, br d, J=13.1 Hz), 4.85 (1H, br s), 4.94 (1H, br s), 5.58 (1H, ddd, J=8.3, 10.1, 16.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 49.5, 71.8, 73.8, 105.6, 117.6, 136.8, 151.0; IR (thin film): 3447, 3079, 2979, 2847, 1665, 1637 cm^{-1}; MS (EI): m/z (%)=110 (20.5) [M^+], 80 (100.0).

4.4.2. Tetrahydro-3-methylene-2-phenyl-4-vinylfuran 8b. 1-(1-((*E*)-4-Bromobut-2-enyloxy)prop-2-ynyl)benzene **7b** (226 mg, 1 mmol), indium powder (114 mg, 1 mmol) in 1:1 THF/H_2O (2 mL) were reacted and worked up according to the general procedure. Chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as 2:1 mixture of diastereomers as a clear colourless oil (82 mg, 50%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.52 (1H, m, two diastereomers), 3.64 (1H, dd, J=8.3, 10.2 Hz, major), 3.88 (1H, dd, J=6.7, 8.6 Hz, minor), 4.12 (1H, m, two diastereomers), 4.15 (1H, dd, J=8.6, 15.2 Hz, minor), 4.31 (1H, dd, J=8.1, 16.1 Hz, major), 4.75 (1H, s, minor), 4.85 (1H, s, major), 4.97 (1H, s, major), 5.03 (1H, s, minor), 5.1–5.3 (2H, m, two diastereomers), 5.68 (1H, ddd, J=8.3, 10.4, 16.1 Hz, major), 5.79 (1H, ddd, J=8.2, 10.4, 16.2 Hz, minor); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 49.5 (minor), 49.9 (major), 72.6 (minor), 72.9 (major), 83.9 (minor), 84.1 (major), 106 (major), 109.2 (minor), 117.2 (minor), 118.2 (major), 127.3, 127.7, 128.2, 128.3, 128.7, 128.8, 136.4, 137.6, 141.6 (minor), 141.9 (major), 154.3 (minor), 154.7 (major); IR (thin film): 3079, 2929, 2851, 1718, 1663, 1637 cm^{-1}; MS (CI): m/z (%)=204 [MNH_4^+] (100.0), 190 (6.8), 187 [MH^+] (5.5), 173 (6.3).

4.4.3. Tetrahydro-3-methylene-2-propyl-4-vinylfuran 8c. 3-((*E*)-4-Bromobut-2-enyloxy)hex-1-yne **7c** (345 mg, 1.5 mmol), indium powder (180 mg, 1.57 mmol) in 1:1 THF/H_2O (1.5 mL) were reacted and worked up according to the general procedure. Chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as 3.5:1 mixture of diastereomers as a clear colourless oil (128 mg, 56%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 0.94 (3H, m, two diastereomers), 1.40–1.70 (4H, m), 3.31 (1H, m), 3.44 (1H, dd, J=8.5, 8.6 Hz, major), 3.63 (1H, dd, J=8.6, 8.7 Hz, minor), 3.97 (1H, dd, J=7.6, 8.6 Hz, minor), 4.12 (1H, dd, J=8.0, 8.1 Hz, major), 4.31 (1H, m, major), 4.35 (1H, m, minor), 4.88 (1H, br s, two diastereomers), 4.91 (1H, br s, two diastereomers), 5.12 (2H, m, two diastereomers), 5.61

(1H, ddd, J=8.3, 9.7, 16.3 Hz, major), 5.65 (1H, m, minor); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.1, 19.6 (major), 19.1 (minor), 37.1 (minor), 37.8 (major), 49.5 (minor), 49.7 (major), 71.1 (minor), 71.9 (major), 80.7 (minor), 81.2 (major), 105.2 (major), 105.6 (minor), 116.4 (minor), 117.5 (major), 136.3 (major), 137.6 (minor), 154.4 (major), 154.5 (minor); IR (thin film): 3309, 2958, 2871, 1663, 1640 cm^{-1}; MS (CI): m/z (%)=151 (40.1) [MH$^+$], 137 (20.1), 123 (23.0), 111 (35.0), 97 (62.0), 83 (63.0), 69 (67.0), 57 (100.0).

4.4.4. Tetrahydro-3-methylene-2-pentyl-4-vinylfuran 8d. 3-((*E*)-4-Bromobut-2-enyloxy)oct-1-yne **7d** (213 mg, 0.83 mmol), indium powder (94 mg, 0.83 mmol) in 1:1 THF/H_2O (2 mL) were allowed to react and then worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 5:1) gave the desired carbocycle **8b** as 3.6:1 mixture of diastereomers as a clear colourless oil (77 mg, 52%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 0.88 (3H, m, two diastereomers), 1.26–1.66 (8H, m), 3.30 (1H, m, two diastereomers), 3.42 (1H, dd, J=8.5, 9.8 Hz, major), 3.61 (1H, dd, J=6.9, 8.7 Hz, minor), 3.96 (1H, dd, J=7.5, 7.6 Hz, minor), 4.10 (1H, dd, J=8.0, 8.1 Hz, major), 4.30 (1H, m, two diastereomers), 4.86 (1H, br s, two diastereomers), 4.90 (1H, s, two diastereomers), 5.16 (2H, m, two diastereomers), 5.58 (1H, ddd, J=8.6, 10.5, 16.2 Hz, major), 5.78 (1H, ddd, J=8.2, 10.3, 16.1 Hz, minor); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.0, 21.5 (minor), 21.6 (major), 24.0 (major), 24.58 (minor), 30.8 (minor), 30.9 (major), 33.9 (minor), 34.5 (major), 48.5 (minor), 48.7 (major), 70.1 (minor), 70.9 (major), 79.9 (minor), 80.4 (major), 104.1 (minor), 104.6 (major), 115.4 (minor), 116.5 (major), 135.3 (major), 136.6 (minor), 153.3 (minor), 153.5 (minor); IR (thin film): 3079, 2932, 2859, 1663, 1641 cm^{-1}; MS (EI): m/z (%)=180 (10.0) [M$^+$], 150 (19.0), 124 (45.0), 109 (100.0).

4.4.5. 3-Methylene-1-tosyl-4-vinylpyrrolidine 18a. (*E*)-4-Bromo-*N*-(prop-2-ynyl)-*N*-tosylbut-2-en-1-amine **13a** (105 mg, 0.31 mmol), indium powder (35 mg, 0.31 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and then worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 5:1) gave the pyrrolidine **18a** as a clear colourless oil (50 mg, 62%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.44 (3H, s), 2.86 (1H, dd, J=8.9, 9.2 Hz), 3.25 (1H, m), 3.62 (1H, dd, J=8.0, 9.3 Hz), 3.72 (1H, br d, J=14.2 Hz), 3.99 (1H, br d, J=14.2 Hz), 4.86 (1H, br s), 4.97 (1H, br d), 5.07–5.13 (2H, m), 5.50 (1H, ddd, J=8.2, 10.4, 16.5 Hz), 7.33 (2H, d, J=8.0 Hz), 7.71 (2H, d, J=8.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.9, 48.1, 52.3, 53.6, 108.7, 118.5, 128.2, 130.1, 133.1, 135.9, 144.1, 147.0; IR (thin film): 3272, 3081, 2984, 2923, 2851, 1736, 1667, 1597, 1348, 1163 cm^{-1}; MS (EI): m/z (%)=263 (27.9), 222 (15.5), 155 (28.0), 108 (100.0).

4.4.6. 3-Methylene-2-pentyl-1-tosyl-4-vinylpyrrolidine 18b. *N*-((*E*)-4-Bromobut-2-enyl)-*N*-tosyloct-1-yn-3-amine **13b** (206 mg, 0.5 mmol), indium powder (57 mg, 0.5 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and then worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 4:1) gave the desired pyrrolidine **18b** as a 14:1 mixture of diastereomers as a clear colourless oil (139 mg, 83%). *Data for major isomer*. ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 0.86 (3H, t, J=6.8 Hz), 1.16–1.80 (8H, m), 2.42 (3H, s), 2.63 (1H, br dd, J=6.5, 10.1 Hz), 3.05 (1H, dd, J=10.3, 12.2 Hz), 3.74 (1H, dd, J=8.4, 12.2 Hz), 4.25 (1H, br m), 4.80 (1H, s), 4.88 (1H, s), 4.93 (1H, d, J=17.3 Hz), 5.07 (1H, d, J=10.2 Hz), 5.45 (1H, ddd, J=8.1, 10.2, 17.3 Hz), 7.28 (2H, d, J=8.2 Hz), 7.71 (2H, d, J=8.2 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.5, 21.9, 22.9, 24.7, 32.2, 36.0, 47.9, 52.6, 63.8, 108.4, 118.3, 127.7, 130.1, 136.3, 136.5, 143.8, 152.1; IR (thin film): 3080, 2953, 2929, 1653, 1640 cm^{-1}; MS (CI): m/z (%)=351 (32.5) [MNH$_4^+$], 334 [MH$^+$] (100.0).

4.4.7. *N*-*tert*-Butoxycarbonyl(3-methylene-4-vinylpyrrolidine) 18c. *N*-(*tert*-Butoxycarbonyl)-(*E*)-4-bromobut-2-enylprop-2-ynylamine **13c** (864 mg, 3 mmol), indium powder (342 mg, 3 mmol) in 1:1 THF/H_2O (6 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 10:1) gave the *N*-protected pyrrolidine **18c** as a clear colourless oil (430 mg, 69%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.45 (9H, s), 3.13 (1H, m), 3.30 (1H, br m), 3.75 (1H, m), 4.01 (1H, br d, J=18.7 Hz), 4.08 (1H, br d, J=18.3 Hz), 4.90 (1H, s), 5.00 (1H, br s), 5.14 (2H, m), 5.65 (1H, ddd, J=8.6, 10.3, 16.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.7 (rotamer), 47.5 (rotamer), 48.2 (rotamer), 50.6 (rotamer), 50.9 (rotamer), 51.2 (rotamer), 51.7 (rotamer), 79.8, 107.6 (rotamer), 107.8 (rotamer), 117.9, 136.8, 147.9 (rotamer), 148.8 (rotamer), 154.8; IR (thin film): 3466, 3081, 2977, 2868, 1701, 1644 cm^{-1}; MS (EI): m/z (%)=209 (2.2) [M$^+$], 154 (22.1), 108 (43.5), 79 (30.2), 57 (100.0).

4.4.8. *N*-(Benzyloxycarbonyl(3-methylene-4-vinylpyrrolidine)) 18d. *N*-(Benzyloxycarbonyl)-(*E*)-4-bromobut-2-enylprop-2-ynylamine **13d** (626 mg, 1.94 mmol), indium powder (221 mg, 1.94 mmol) in 1:1 THF/H_2O (3 mL) were reacted together and worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 5:1) gave the *N*-protected pyrrolidine **18d** as a clear colourless oil (310 mg, 66%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.24 (1H, bs dd, J=8.6, 10.2 Hz), 3.34 (1H, m), 3.85 (1H, br dd, J=8.7, 9.7 Hz), 4.08 (2H, m), 4.95 (1H, br s), 5.06 (1H, br d, J=14.9 Hz), 5.16 (4H, m), 5.68 (1H, br m),7.35 (5H, br m); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 47.4 (rotamer), 48.2 (rotamer), 50.7 (rotamer), 51.1 (rotamer), 51.5 (rotamer), 51.7 (rotamer), 67.2 (rotamer), 67.5 (rotamer), 108.2, 118.2 (rotamer), 119.1 (rotamer), 128.3 (rotamer), 123.4 (rotamer), 128.8 (rotamer), 128.9 (rotamer), 136.5 (rotamer), 137.2 (rotamer), 155.1; IR (thin film): 3080, 2979, 2948, 2867, 1953, 1704, 1542 cm^{-1}; MS (EI): m/z (%)=242 (14.8), 230 (6.5), 198 (8.6), 152 (48.7), 91 (100.0).

4.4.9. Dimethyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate 10a. (*E*)-2-(4-Bromobut-2-enyl)-(2-prop-2-ynyl)-malonic acid dimethyl ester **9a** (451 mg, 1.5 mmol), indium powder (171 mg, 1.5 mmol) in 1:1 THF/H_2O (1.5 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 3:1) gave the cyclised product **10a** as a clear colourless oil (249 mg, 74%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.01 (1H, dd, J=11.0, 13.0 Hz), 2.57 (1H, dd, J=8.0, 13.0 Hz), 2.95

(1H, ddd, J=3.0, 6.0, 18.0 Hz), 3.08 (1H, br d, J=18.0 Hz), 3.17 (1H, m), 3.73 (3H, s), 3.75 (3H, s), 4.82 (1H, s), 4.98 (1H, s), 5.05 (1H, br s), 5.08 (1H, m), 5.64 (1H, ddd, J=8.0, 10.5, 13.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 40.7, 48.1, 53.2, 53.2, 58.9, 108.6, 116.5, 139.4, 150.8, 172.4, 172.6; IR (thin film): 3660, 3471, 3078, 2953, 1731, 1714, 1659, 1642 cm^{-1}; MS (FAB): m/z (%)=225 (73.2) [MH$^+$], 193 (36.5), 165 (65.1), 154 (74.3), 137 (68.1), 136 (61.7), 105 (100), 91 (49.7), 77 (49.1).

4.4.10. Diethyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate 10b. (*E*)-2-(4-Bromobut-2-enyl)-(2-prop-2-ynyl)-malonic acid diethyl ester **9b** (660 mg, 2 mmol), indium powder (228 mg, 2 mmol) in 1:1 THF/H_2O (2 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as a clear colourless oil (360 mg, 71%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.25 (3H, m), 2.05 (1H, dd, J=10.8, 12.9 Hz), 2.58 (1H, dd, J=8.0, 12.9 Hz), 2.93 (1H, ddd, J=2.9, 6.0, 17.8 Hz), 3.09 (1H, br d, J=17.8 Hz), 3.18 (1H, m), 4.19 (2H, m), 4.83 (1H, s), 4.99 (1H, s), 5.06 (1H, br s), 5.11 (1H, m), 5.64 (1H, ddd, J=8.0, 10.3, 12.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.4, 40.6, 48.1, 58.9, 61.9, 108.4, 116.4, 139.6, 151.0, 171.9, 172.2; IR (thin film): 3079, 2982, 1732, 1658, 1640 cm^{-1}. MS (FAB): m/z (%)=253 (2.3) [MH$^+$], 252 (4.5), 207 (10.1), 178 (57.8), 105 (100.0).

4.4.11. Ethyl-*tert*-butyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate 10c. (*E*)-Ethyl-*tert*-butyl-2-(4-bromobut-2-enyl)-(2-prop-2-ynyl)-malonate diethyl ester **9c** (344 mg, 1 mmol), indium powder (114 mg, 1 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as a 1:1 mixture of diastereomers in the form of a clear colourless oil (150 mg, 56%). ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.45 (4.5H, s, diastereotopic), 1.46 (4.5H, s, diastereotopic), 1.98 (1H, m, two diastereomers), 2.53 (1H, m, two diastereomers), 2.96 (1H, ddd, J=3.0, 5.9, 17.8 Hz, two diastereomers), 3.11 (1H, br d, J=17.8 Hz, two diastereomers), 3.16 (1H, br m, two diastereomers), 3.73 (1.5H, s, diastereotopic), 3.75 (1.5H, s, diastereotopic), 4.81 (1H, s, two diastereomers), 4.98 (1H, s, two diastereomers), 5.06 (1H, br s, two diastereomers), 5.09 (1H, m, two diastereomers), 5.66 (1H, ddd, J=7.9, 8.2, 13 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.17, 28.19, 40.51, 40.55, 48.03, 48.15, 52.88, 52.93, 59.58, 59.76, 82.14, 108.22, 116.25, 116.33, 139.65, 151.15, 151.19, 170.84, 171.08, 172.76, 173.00; IR (thin film): 3079, 2980, 1731, 1658, 1640 cm^{-1}. MS (FAB): m/z (%)= 284 (52.7) [MNH$_4^+$], 267 (14.4), 228 (100.0), 211 (12.1).

4.4.12. Methyl 3-methylene-1-(phenylsulfonyl)-4-vinylcyclopentanecarboxylate 10e. (*E*)-Methyl 6-bromo-2-(phenylsulfonyl)-2-(prop-2-ynyl)hex-4-enoate **9e** (258 mg, 0.67 mmol), indium powder (100 mg, 0.87 mmol) in 1:1 THF/H_2O (1.5 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 3:1) gave the cyclised product **10b** as a 4.5:1 mixture of diastereomers in the form of a clear colourless oil (91 mg, 44%):^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.23 (1H, m, minor), 2.29 (1H, dd, J=12.2, 12.3 Hz, major), 2.59 (1H, ddd, J=1.6, 7.2, 12.5 Hz, major), 2.80 (1H, dd, J=8.6, 14.4 Hz, minor), 2.99 (1H, br m, major), 3.08 (1H, br d, J=18.7 Hz, minor), 3.14 (1H, br d, J=18.2 Hz, major), 3.21 (1H, d, J=18.7 Hz, major), 3.23 (1H, br d, J=18.2 Hz, minor), 3.39 (1H, m, minor), 3.62 (3H, s, minor), 3.66 (3H, s, major), 4.84 (1H, br s two diastereomers), 5.00 (1H, br s, two diastereomers), 5.04 (1H, br s, two diastereomers), 5.07 (1H, m, two diastereomers), 5.54 (1H, ddd, J=8.2, 9.9, 15.9 Hz, minor), 5.64 (1H, ddd, J=8.1, 10.2, 13.0 Hz, major), 7.54 (2H, dd, J=7.5, 8.0 Hz, two diastereomers), 7.67 (1H, dd, J=7.4, 7.6 Hz, two diastereomers), 7.82 (2H, dd, J=7.2, 7.5 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 38.1 (major), 38.3 (two diastereomers), 38.5 (minor), 47.6 (minor), 48.1 (major), 53.6 (minor), 53.8 (major), 77.3 (major), 77.7 (minor), 109.3 (minor), 109.8 (major), 129.3 (major), 130.0 (major), 130.3 (minor), 134.6 (major), 134.7 (minor), 136.6 (minor), 137.2 (major), 138.5 (major), 138.8 (minor), 148.5 (major), 149.3 (minor), 168.8 (major), 169.1 (minor); IR (thin film): 3077, 2952, 1977, 1910, 1737, 1658, 1639 cm^{-1}; MS (FAB): m/z (%)=324 (100.0) [MNH$_4^+$].

4.4.13. Ethyl 1-(dimethylcarbamoyl)-3-methylene-4-vinylcyclopentanecarboxylate 10f. (*E*)-Ethyl 2-(dimethylcarbamoyl)-6-bromo-2-(prop-2-ynyl)hex-4-enoate **9f** (330 mg, 1 mmol), indium powder (114 mg, 2 mmol) in 1:1 THF/H_2O (1.5 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/Et_2O 3:1 gradient to 1:1) gave the cyclised product **10e** as a 1.3:1 mixture of diastereomers as a clear colourless oil (210 mg, 84%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7.2 Hz, diastereotopic), 1.92 (1H, dd, J=11.3, 12.6 Hz, major), 2.23 (1H, dd, J=11.5, 13.2 Hz, minor), 2.40 (1H, dd, 7.7, 13.2 Hz, minor), 2.58 (1H, dd, J=7.8, 12.6 Hz, major), 2.80 (3H, br s, two diastereomers), 2.85 (1H, m), 2.94 (3H, br s, two diastereomers), 3.20 (1H, m, two diastereomers), 4.19 (2H, q, J=7.0 Hz, two diastereomers), 4.77 (1H, br s, two diastereomers), 4.92 (1H, br s, two diastereomers), 5.06 (1H, br s, two diastereomers), 5.09 (1H, m, two diastereomers), 5.66 (1H, ddd, J=8.5, 10.5, 13.3 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.6 (minor), 15.6 (major), 37.2 (broad, two diastereomers), 41.1 (minor), 41.5 (minor), 41.6 (major), 41.8 (major), 47.7 (minor), 48.6 (major), 57.7 (major), 58.0 (minor), 60.8 (major), 61.9 (minor), 107.4 (major), 107.6 (minor), 116.4 (minor), 116.6 (major), 139.4 (major), 139.6 (minor), 151.4 (minor), 151.6 (major), 170.6 (minor), 172.2 (major), 173.9 (major), 174.3 (minor); IR (thin film): 3501, 3077, 2980, 2934, 1729, 1650 cm^{-1}. MS (FAB): m/z (%)=269 (3.2) [MNH$_4^+$], 252 (100.0) [MH$^+$].

4.4.14. Ethyl 1-(pyrrolidinylcarbamoyl)-3-methylene-4-vinylcyclopentanecarboxylate 10g. (*E*)-Ethyl 2-(pyrrolidinylcarbamoyl)-6-bromo-2-(prop-2-ynyl)hex-4-enoate **9g** (355 mg, 1 mmol), indium powder (114 mg, 2 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 3:2) gave the cyclised product **10f** as a 1:1 mixture of diastereomers as a clear colourless oil (212 mg, 77%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.26 (3H, m, diastereotopic), 1.88 (4.5H, m, two

diastereomers), 1.96 (1H, dd, $J=11.0$, 12.9 Hz, diastereomer), 2.21 (1H, dd, $J=11.6$, 13.1 Hz, diastereomer), 2.47 (1H, dd, $J=7.3$, 12.9 Hz, diastereomer), 2.62 (1H, dd, $J=8.0$, 13.0 Hz, diastereomer), 3.00 (1H, dd, $J=2.2$, 16.8 Hz, diastereomer), 3.25 (3H, m, diasteromers), 4.21 (2H, m, two diastereomers), 4.79 (1H, br s, two diastereomers), 4.95 (1H, br s, two diastereomers), 5.06 (1H, br s, two diastereomers), 5.12 (1H, m, two diastereomers), 5.66 (1H, ddd, $J=8.5$, 10.5, 13.1 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.6 (two diastereomers), 26.0 (rotamer), 28.93 (rotamer), 42.6 (diastereomer), 42.9 (diastereomer), 43.2 (diastereomer), 43.3 (diastereomer), 48.5 (diastereomer and rotamer), 48.6 (diastereomer and rotamer), 49.5 (diastereomer and rotamer), 49.6 (diastereomer and rotamer), 49.9 (diastereomer), 50.6 (diastereomer), 60.6 (diastereomer), 61.0 (diastereomer), 63.9, 109.4 (diastereomer), 109.7 (diastereomer), 118.3 (diastereomer), 118.6 (diastereomer), 141.6 (diastereomer), 141.8 (diastereomer), 153.6 (diastereomer), 153.9 (diastereomer), 171.1 (diastereomer), 171.5 (diastereomer), 176.1 (diastereomer); IR (thin film): 3076, 2977, 2877, 1730, 1637 cm^{-1}; MS (FAB): m/z (%)=278 (100.0) [MH$^+$], 179 (5.6).

4.4.15. Ethyl 1-(morpholinocarbamoyl)-3-methylene-4-vinylcyclopentanecarboxylate 10h. (*E*)-Ethyl 2-(morpholinocarbamoyl)-6-bromo-2-(prop-2-ynyl)hex-4-enoate **9h** (323 mg, 0.868 mmol), indium powder (100 mg, 0.877 mmol) in 1:1 THF/H_2O (0.8 mL) reacted and worked up following the general procedure. Purification by on silica (hexane/EtOAc 2:1) gave the carbocyclic product **10g** as a 1:1 mixture of diastereomers as a clear colourless oil (159 mg, 63%) which crystallised on standing (mp 87.7–89.4 °C): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.28 (3H, m, diastereotopic), 1.95 (1H, dd, $J=11.4$, 12.4 Hz, major), 2.27 (1H, dd, $J=11.4$, 13.2 Hz, minor), 2.42 (1H, dd, $J=7.6$, 13.2 Hz, minor), 2.62 (1H, dd, $J=7.8$, 12.6 Hz, diastereomer), 3.00 (1H, dd, $J=2.2$, 16.8 Hz, diastereomer), 3.21 (1H, br m, diastereomers, 3.30 (3H, br m, diastereomers), 3.66 (6H, br s, diasteromers), 4.23 (2H, m, two diastereomers), 4.81 (1H, br s, two diastereomers), 4.96 (1H, br s, two diastereomers), 5.08 (1H, br s, two diastereomers), 5.13 (1H, m, two diastereomers), 5.66 (1H, ddd, $J=8.3$, 10.7, 15.0 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.6 (two diastereomers), 41.1 (diastereomer), 41.4 (diastereomer), 41.6 (diastereomer), 41.8 (diastereomer), 47.6 (diastereomer), 48.6 (diastereomer), 57.6 (diastereomer), 57.9 (diastereomer), 62.2 (two diastereomers), 66.0–68.0 (broad peak, diasteromers and rotamers), 107.8 (diastereomer), 107.9 (diastereomer), 116.6 (diastereomer), 116.8 (diastereomer), 139.2 (diastereomer), 139.4 (diastereomer), 151.0 (diastereomer), 151.2 (diastereomer), 169.6 (diastereomer), 169.9 (diastereomer), 173.8 (diastereomer), 174.2 (diastereomer); IR (thin film): 3076, 2978, 2919, 2856, 1730, 1653 cm^{-1}; MS (EI): m/z (%)=293 (47.8) [M$^+$], 239 (64.2), 220 (100.0, 205 (25.1), 179 (13.8), 133 (28.4).

4.4.16. 3-Methylene-4-vinylcyclopentane-1,1-dicarbonitrile 10i. 2-((*E*)-4-Bromobut-2-enyl)-2-(prop-2-ynyl)-malononitrile **9i** (236 mg, 1 mmol), indium powder (114 mg, 1 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react according to the general procedure. Mild acidic work-up and purification by chromatography on silica (hexane/EtOAc 10:1) gave the carbocyclic product **10i** as a light yellow oil (78 mg, 49%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.25 (3H, m), 2.22 (1H, dd, $J=10.7$, 13.1 Hz), 2.76 (1H, dd, $J=7.7$, 13.1 Hz), 3.11 (1H, d $J=17.9$ Hz), 3.25 (1H, br d, $J=17.9$ Hz), 3.42 (1H, m), 5.08 (1H, br s), 5.23 (1H, m), 5.67 (1H, ddd, $J=8.2$, 9.3, 16.5 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 32.6, 44.2, 44.7, 47.0, 112.7, 116.1, 116.3, 118.7, 136.8, 145.2; IR (thin film): 3084, 2985, 2252, 1849, 1660, 1640 cm^{-1}; MS (FAB): m/z (%)=158 (100) [M$^+$], 143 (30.4), 130 (56.9), 116 (66.0), 104 (21.5), 79 (85.5).

4.4.17. (*E*)-Dimethyl 3-ethylidene-4-vinylcyclopentane-1,1-dicarboxylate 30. Dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(but-2-ynyl)malonate **25** (316 mg, 1 mmol) and indium powder (114 mg, 1mmol) were placed in a round-bottomed flask under N_2 and dry DMF (1 mmol) was added. The mixture was heated at 100 °C for 1.25 h and then allowed to cool. The mixture was partitioned between 2 M HCl and diethyl ether and the aqueous layer was extracted with Et_2O (2×10 mL) and the combined organics were washed with water (2×10 mL), saturated aqueous NaCl (10 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography on silica (hexane/EtOAc, 6:1) to give the carbocyclic product **30** (154 mg, 65%) as a clear colourless oil as essentially a single diastereomer: ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.60 (3H, d, $J=6.7$ Hz), 1.95 (1H, dd, $J=11.5$, 12.8 Hz), 2.53 (1H, ddd, $J=1.6$, 8.7, 12.9 Hz), 2.84 (1H, d, $J=17.2$ Hz), 3.02 (1H, d, $J=17.3$ Hz), 3.09 (1H, m), 3.73 (3H, s), 3.75 (3H, s), 5.01 (2H, m), 5.2 (1H, m), 5.56 (1H, ddd, $J=8.3$, 11.2, 15.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.0, 37.2, 40.9, 48.2, 53.2, 53.2, 59.0, 116.3, 118.4, 140.0, 141.6, 172.6, 172.7; IR (thin film): 2954, 1716, 1661, 1644 cm^{-1}; MS (CI): m/z (%)=256 (100.0) [MNH$_4^+$], 239 [MH$^+$] (48.0).

4.4.18. (*E*)-Dimethyl 3-benzylidene-4-vinylcyclopentane-1,1-dicarboxylate 31. Dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(3-phenylprop-2-ynyl)malonate **26** (379 mg, 1 mmol) and indium powder (114 mg, 1 mmol) were placed in a round-bottomed flask and placed under a nitrogen atmosphere, Dry DMF (1 mmol) was added and the mixture was heated at 100 °C for 70 min and then allowed to cool. The mixture was partitioned between 2 M HCl and diethyl ether and the aqueous layer was extracted with Et_2O (2× 10 mL) and the combined organics were washed with water (10 mL), saturated aqueous NaCl (10 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography on silica (hexane/EtOAc, 5:1) to give the carbocyclic product **31** (258 mg, 85%) as a clear colourless oil as a 3.6:1 mixture of diastereomers: ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.94 (1H, d, $J=11.6$, 12.7 Hz, major), 2.15 (1H, dd, $J=4.4$, 8.7 Hz, minor), 2.54 (1H, ddd, $J=1.5$, 10.4, 12.8 Hz, major), 2.65 (1H, dd, $J=8.7$, 13.2 Hz, minor), 3.14 (1H, br d, $J=2.7$, 17.8 Hz, two diastereomer), 3.26 (1H, m, two diastereomers), 3.33 (1H, br d, $J=17.8$ Hz, major), 3.65 (3H, s, minor), 3.66 (6H, s, two diastereomers), 3.68 (3H, s, major), 4.92–5.10 (3H, m, two diastereomers), 5.62 (1H, ddd, $J=8.3$, 9.4, 17.6 Hz, major), 5.74 (1H, m, minor), 6.13 (1H, br s, major), 6.41 (1H, br s, minor), 7.18–7.28 (5H, m, two

diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 39.1 (major), 40.0 (minor), 41.3 (minor), 43.2 (major), 44.4 (minor), 50.0 (major), 53.1 (minor), 53.2 (two diastereomers), 53.3 (major), 58.2 (minor), 60.0 (major), 115.4 (diastereomer), 15.6 (diastereomer), 117.1 (diastereomer), 124.3 (diastereomer), 125.1 (diastereomer), 126.7 (diastereomer), 126.8 (diastereomer), 128.4 (diastereomer), 128.5 (diastereomer), 128.6 (diastereomer), 128.8 (diastereomer), 132.0 (diastereomer), 138.0 (major), 138.8 (minor), 139.5 (major), 142.3 (minor), 143.5 (major), 172.2 (diastereomers), 172.3 (diastereomer); IR (thin film): 2952, 2843, 1732, 1635 cm^{-1}; MS (EI): *m/z* (%)=300 (30.6) [M^+], 240 (100.0), 181 (93.7).

4.4.19. (*E*)-Dimethyl 3-((methoxycarbonyl)methylene)-4-vinylcyclopentane-1,1-dicarboxylate 32. (*E*)-Trimethyl 8-bromooct-6-en-1-yne-1,4,4-tricarboxylate **27** (114 mg, 0.32 mmol) and indium powder (36 mg, 0.32 mmol) in THF/H_2O (1:1) were allowed to react together and worked up in accordance with the general procedure. Purification of the crude reaction mixture on silica (hexane/EtOAc 2:1) gave the desired cyclic triester **32** as a clear, colourless oil (58 mg, 65%) as essentially a single diastereomer. *Data for major diastereomer*. ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.01 (1H, dd, J=12.6, 12.7 Hz),2.59 (1H, dd, J=7.3, 12.9 Hz), 3.34 (2H, m), 3.69 (3H, s), 3.74 (3H, s), 3.75 (3H, s), 5.16 (2H, m), 5.57 (1H, ddd, J=8.2, 10.1, 16.9 Hz), 5.67 (1H, s); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 39.7, 40.6, 50.1, 51.5, 53.3, 53.4, 59.1, 114.4, 118.7, 137.5, 165.0, 167.2, 172.0, 172.3; IR (thin film): 2998, 2953, 1737, 1659, 1640 cm^{-1}; MS (EI): *m/z* (%)=282 (8.9) [M^+], 250 (98.7), 223 (47.5), 188 (100.0), 162 (47.9), 131 (22.7), 102 (36.5).

4.4.20. 3-Benzylidene-tetrahydro-4-vinylfuran 33. 1-(3-((*E*)-4-Bromobut-2-enyloxy)prop-1-ynyl)benzene (264 mg, 1 mmol) and indium powder (114 mg) in THF/H_2O (1:1) were reacted together and worked up in accordance with the general method. Purification of the crude reaction mixture on silica (hexane/EtOAc 10:1) gave the desired vinylic furan **33** as essentially a single diastereomer as a yellowish oil (56 mg, 30%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.32 (1H, m), 3.93 (1H, dd, J=1.9, 11.2 Hz), 4.00 (1H, dd, J=1.9, 11.2 Hz), 4.32 (1H, dd, J=2.3, 16.1 Hz), 4.42 (1H, dd, J=2.1, 16.1 Hz), 4.94 (1H, d, J=17.2 Hz), 5.01 (1H, d, J=10.3 Hz), 5.79 (1H, ddd, J=7.8, 10.3, 17.2 Hz), 7.30 (5H, m); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 47.7, 59.6, 71.3, 117.8, 118.9, 127.9, 128.5, 128.8, 128.9, 132.2, 136.6, 137.7, 139.9; IR (thin film): 3400, 3057, 2851, 1954, 1883, 1725, 1693, 1659 cm^{-1}; MS (CI): *m/z* (%)=228 (100.0) [$MNaNH_4^+$], 193 (26.3), 165 (54.1).

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Supplementary data

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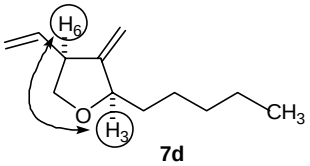

7d

28. It is postulated that these products occur from attack of one of the esters at the S_N2' site of the bromoallyl fragment followed by $A_{AL}1$-type, and/or similar loss of the *tert*-butyl group mediated by Lewis acidic indium salts generated in the reaction.
29. The crude reaction mixtures from the carbocyclisation reactions typically contained 5–10% of the corresponding proteodebrominated product.
30. Full crystallographic data is presented in the Supporting Information supplied with the present paper. Alernatively, 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 279213. 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 deposit@ccdc.cam.ac.uk].
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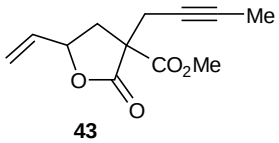

43

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Peracid dependent stereoselectivity and functional group contribution to the stereocontrol of epoxidation of (*E*)-alkene dipeptide isosteres

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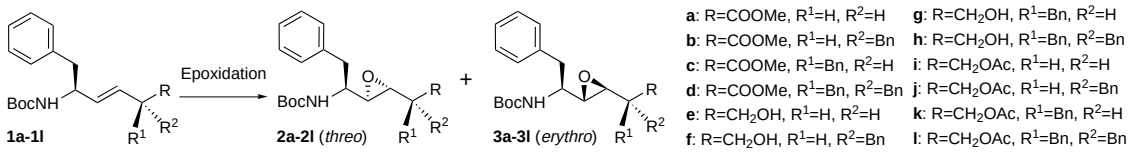
Abstract—Twelve *Boc*-protected phenylalanyl-phenylalanine and phenylalanyl-glycine *trans*-vinyl isosteres were epoxidised with magnesium monoperoxyphtalate hexahydrate (MMPP) and trifluoroperacetic acid, and the results have been compared with those from earlier studies on epoxidations with *m*-CPBA. The alkenes were synthesised in high yields with high *E*/*Z*-selectivities using either the Julia or Schlosser reactions. The formation of *threo* isomers was favoured in all epoxidation reactions except with CF_3CO_3H on substrates containing two allylic/homoallylic functional groups directing the peracid to opposite faces of the alkene. The switch to *erythro* selectivity observed with CF_3CO_3H is suggested to emanate from coordination to the allylic ester functionalities via hydrogen bond donation from the peracid. The other peracid reagents seem to be preferentially coordinated to the allylic carbamate function. The contribution of individual functional groups to the stereopreference was also investigated.

1. Introduction

Stereoselective epoxidation reactions have been studied experimentally[1,2] and theoretically[3] to a great extent over the years. Peracids are still commonly used, although several novel epoxidation reagents have been developed.[4] However, these new, usually metal-based reagents, have mainly been studied using simpler mono- or non-functionalised alkenes. In a project aimed at the synthesis and use of functionalised dipeptidomimetics we have for some time studied the stereoselective epoxidation of structurally more complex alkenes. In these studies, *Boc*-protected phenylalanyl-phenylalanine (Phe-Phe) and phenylalanyl-glycine (Phe-Gly) derived epoxides (**2a–l**, **3a–l**) were synthesised by *m*-CPBA treatment of the Phe-Phe and Phe-Gly vinyl isosteres **1a–l**, possessing two stereogenic centres and different oxygen containing functional groups at the C-terminus of the pseudo-dipeptide (Scheme 1).[5] The reactions are highly stereoselective with the formation of *threo* isomers being favoured.



Scheme 1.

Keywords: Epoxidation; Peracid; Dipeptidomimetics; Stereoselectivity; Allylic functional group; Coordination.
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The stereoselectivity has been suggested to originate from cooperative coordination of *m*-CPBA to the allylic carbamate and a suitably positioned ester or alcohol group.[6–8]

In a preliminary study on epoxidation of six Phe-Phe vinyl isosteres, we used trifluoroperacetic acid (generated from urea hydrogen peroxide (UHP) and trifluoroacetic anhydride) as oxidant in addition to *m*-CPBA.[9] It was found that the stereoselectivity was strongly dependent on the choice of peracid and the functionalities flanking the alkene, presumably by formation of different hydrogen bonding patterns between the peracid and the alkenes. Differences in stereoselectivity between the two peracids have been reported with cyclic alkenes containing one directing functional group.[10] To gain further understanding of these phenomena, we have made a more extensive study including more alkene substrates, and also added monoperoxyphthalate hexahydrate (MMPP), a peracid presumed to possess different hydrogen bonding properties compared to *m*-CPBA and trifluoroperacetic acid. A new method for the synthesis of β,γ-unsaturated esters based on the Schlosser reaction is also disclosed.

2. Results and discussion

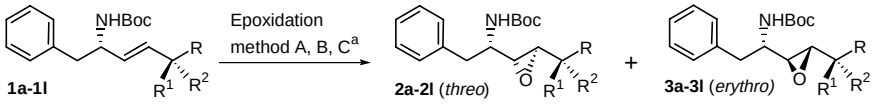
2.1. Peracid epoxidation

2.1.1. Epoxidation of 1a–h and 1k with MMPP. MMPP has been suggested as a replacement for *m*-CPBA in epoxidations and other oxidation reactions. MMPP has similar chemical properties to *m*-CPBA but it is considered safer to use in both small- and large-scale reactions.[11] We expected that MMPP might exhibit different hydrogen bonding properties to *m*-CPBA due to the additional *ortho*-positioned carboxylate. Compounds **1a–h** and **1k** were treated with MMPP in a two-phase system consisting of chloroform and water at room temperature in the presence of methyltrioctylammonium chloride as phase-transfer catalyst. Throughout, the epoxidation reactions with MMPP were much slower than those using *m*-CPBA, the alcohol derivatives **1e–h** being the most reactive (Table 1, entries 5–8). Epoxidation of methyl ester **1a** with MMPP proceeded in only ca. 50% yield even after extensively prolonged reaction times (17 days). No products were observed in epoxidation of **1b–d** and acetate **1k** after 7 days. The rate of MMPP epoxidations has been proposed to increase after addition of pyridine to the reaction medium.[11] However, in our hands, the reactions became more sluggish in the presence of catalytic amounts (0.1 equiv) of either pyridine or 4-dimethylaminopyridine or when using pyridine as the solvent. Due to the low rates of reaction of the ester derivatives, we did not consider it practical to perform the epoxidations on any other acetate derivative in the series.

The *threo*/*erythro* ratios of products in the MMPP epoxidations were about the same as those in reactions using *m*-CPBA (Table 1). Thus, the results indicate that the phthalic acid motif itself does not contribute to a change in the reagent–substrate hydrogen bonding interaction compared to *m*-CPBA. Consequently, the diastereoselectivity of the MMPP epoxidations may be rationalised by assuming the same influence of cooperative coordination as in the reactions with *m*-CPBA. This coordination may also explain the increased reactivity of the alcohols (**1e–h**) compared to the esters since additional hydrogen bonding between the substrate and the peracid should lead to an increased stability of the transition state.

2.1.2. Epoxidation of 1a–l with trifluoroperacetic acid. Trifluoroperacetic acid[11] can be generated in situ from urea-hydrogen peroxide (UHP) and trifluoroacetic anhydride. Substrates **1a–l** were epoxidised at 0 °C using a mixture of UHP, trifluoroacetic anhydride, and Na_2HPO_4 in CH_2Cl_2. Throughout, the trifluoroperacetic acid epoxidations were faster than the reactions with *m*-CPBA.

Table 1. Reaction conditions, yields and stereochemical results from epoxidations of the olefinic substrates **1a–l**[a]



Entry	Substrate	R	R_1	R_2	Ratio **2**:**3** (*threo*:*erythro*)[b]			Isolated yield (%)			Reaction time (h)		
					A	B[c]	C	A	B[c]	C	A	B[c]	C
1	**1a**	COOMe	H	H	88:12	89:11	84:16	46[d]	81	79	408	48	0.5
2	**1b**	COOMe	H	Bn	[e]	62:38	37:63	0[e]	80	75	168	44	0.5
3	**1c**	COOMe	Bn	H	[e]	91:9	87:13	0[e]	77	81	168	40	0.5
4	**1d**	COOMe	Bn	Bn	[e]	88:12	87:13	0[e]	90	86	168	24	0.5
5	**1e**	CH_2OH	H	H	79:21	88:12	85:15	57	68	78	24	12	0.5
6	**1f**	CH_2OH	H	Bn	63:37	60:40	48:52	71	89	63	26	6	0.5
7	**1g**	CH_2OH	Bn	H	88:12	87:13	88:12	76	89	82	30	5	0.5
8	**1h**	CH_2OH	Bn	Bn	64:36	76:24	78:22	70	94	76	24	5	0.5
9	**1i**	CH_2OAc	H	H		83:17	82:18		87	53		12	0.5
10	**1j**	CH_2OAc	H	Bn		68:32	36:64		84	71		45	0.5
11	**1k**	CH_2OAc	Bn	H	[e]	86:14	76:24	0[e]	80	81	168	24	0.5
12	**1l**	CH_2OAc	Bn	Bn		79:21	61:39		84	67		48	0.5

[a] A: MMPP, $(C_8H_{17})_3NMeCl$, $CHCl_3/H_2O$, rt; B: *m*-CPBA, CH_2Cl_2, rt; C: CF_3CO_3H, CH_2Cl_2, 0 °C.
[b] The relative ratios of epoxide isomers were determined by HPLC and NMR spectroscopy of the crude reaction product.
[c] Data on *m*-CPBA epoxidations are taken from Ref. 5c.
[d] 54% starting material was recovered after 408 h.
[e] No products were obtained even after long reaction times.

Most substrates followed the general trend affording mainly *threo* epoxide isomers in yields comparable to those obtained with *m*-CPBA, but a somewhat lower diastereoselectivity was obtained (Table 1). Interestingly, two substrates (methyl ester **1b** and acetate **1j**) afforded preferentially *erythro* products with *threo*/*erythro* diastereomeric ratios of 37:63, and 36:64, respectively. In contrast, *m*-CPBA epoxidation of **1b** and **1j** produced epoxides in a diastereomeric ratio of 62:38, and 68:32, respectively (Table 1, entries 2 and 10). In the trifluoroperacetic acid epoxidation reaction of the alcohol derivative **1f**, which has the same absolute configuration at the stereogenic centres as the ester derivatives **1b** and **1j**, stereoselectivity was essentially lost; however, the difference in *threo*/*erythro* ratio from that obtained with *m*-CPBA was small (Table 1, entry 6).

By-products were formed if the reaction time was prolonged. An isomeric mixture of by-products from the epoxidation reaction of **1b** with trifluoroperacetic acid was separated by column chromatography and the structures of the isomers were determined by NMR spectroscopy to be oxazolidinone derivatives **4a** and **4b**,[12] probably formed via an intramolecular ring opening of the corresponding epoxides by the carbamate carbonyl oxygen. The epoxide ring opening is probably catalysed by trifluoroacetic acid generated in the epoxidation reaction. The minor oxazolidinone isomer (**4b**) was analysed by X-ray crystallography,[13] which established the stereochemistry at C-4 and C-5 (Fig. 1). The 4*S*,5*S* stereochemistry also established that **4b** was formed from the *threo* epoxide isomer **1b**. Both the *threo* and *erythro* epoxides can undergo the cyclisation/ring opening reaction to form oxazolidinones, but the reaction rate of the *erythro* isomer seems to be considerably higher than that of the *threo* isomer since a change in the *threo*/*erythro* ratio of epoxides was observed over time. Epoxidation of **1b** gave after 30 min a *threo*/*erythro* ratio of 2:3, which changed to 2:1 after 120 min. This is probably due to formation of by-products preferentially from the *erythro* isomer. A decrease of the temperature in the trifluoroperacetic acid epoxidation suppressed the by-product formation, that is, epoxidation of **1f** produced 10–20% of by-products at 0 °C but no by-products were observed when the reaction was run at −78 °C.

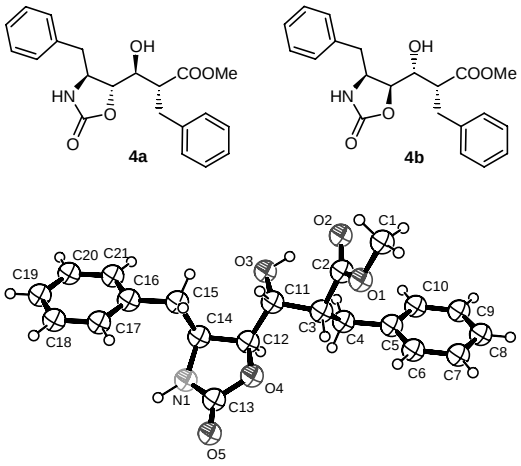


Figure 1. Perspective ORTEP view of the crystal structure of **4b** (CCDC no. 102769),[13] showing 50% probability displacement ellipsoids. Hydrogens are included to clarify the absolute configuration of chiral atoms.

The observed change of stereoselectivity for **1b** and **1j** indicates that the *threo* directing effect of the allylic carbamate is weaker with trifluoroperacetic acid and that the directing effect from the ester group is dominating. To gain further information on the directing role of each functionality, compounds **8a–e** having only one directing functional group, were synthesised and epoxidised.

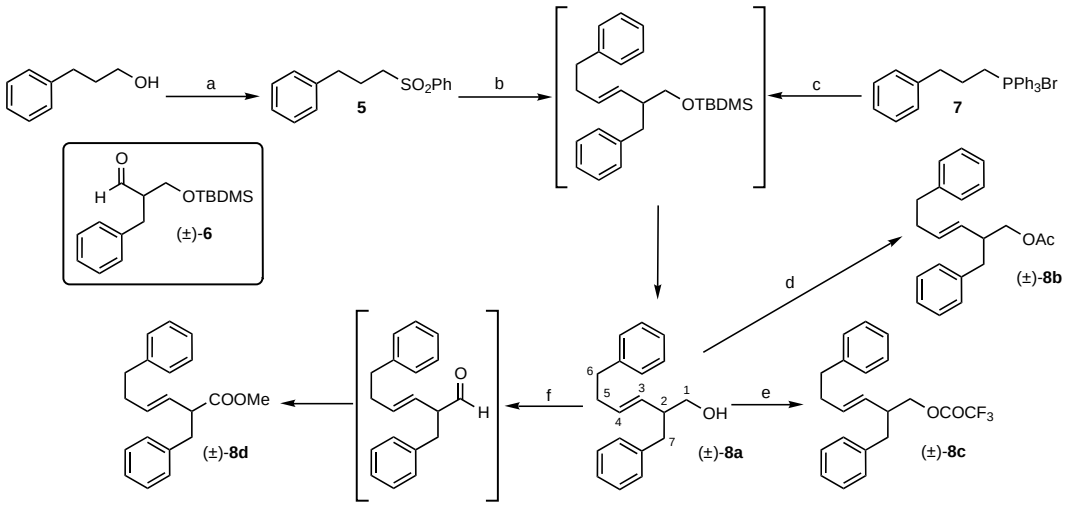
2.2. Directing effect contribution of allylic functional groups to the stereoselectivity of *m*-CPBA and trifluoroperacetic acid in epoxidation reactions

2.2.1. Synthesis of the alkenes 8a–e. To investigate the relative influence of the different functional groups on the stereoselectivity, analogues of **1** with only one functionality were synthesised and epoxidised. In previous studies,[5a,b] we have relied on the Julia olefination reaction[14] as a reliable method for the construction of (*E*)-alkene peptide isosteres (i.e., **1**). The reaction has good *E*-selectivity, whilst preserving the stereochemistry at C-5. The method was suitable also for the synthesis of the alkenes **8a–d** (Scheme 2) and the allylic carbamate **8e** (Table 2) as described previously.[5c] The anion of sulfone **5** and DIBAL·OMe-activated aldehyde **6**[5b] were reacted followed by desulfonylation and deprotection to give the *E*/*Z*-isomers of allylic alcohol **8a** in a ratio of 88:12 and 33% total yield.

The Julia reaction has some disadvantages as the procedure is laborious, and desulfonylation is accomplished using sodium amalgam. To avoid the hazardous handling of molten sodium and mercury, an alternative phosphorous ylide based strategy for forming the double bond from similar components was investigated. A standard Wittig reaction between the ylide generated from deprotonation of phosphonium salt **7**[15] with *n*-butyllithium and aldehyde **6** (Scheme 2) was expected[16] to give predominantly the *Z*-isomer of **8a** which was indeed found to be the case, the resulting *E*/*Z*-ratio was 12:88. An increased reaction temperature may sometimes give higher *E*-selectivity in the Wittig reaction;[16] performing the reaction at 0 °C resulted in a slightly higher yield of (*E*)-**8a** (*E*/*Z* 22:78).

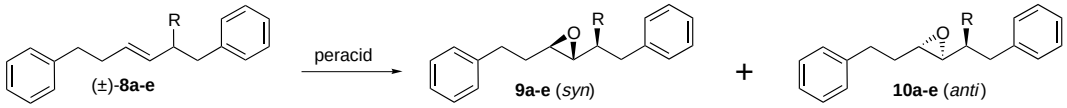
To gain further *E*-selectivity, the Schlosser modification[16] of the Wittig reaction was tried (Scheme 2). Deprotonation of **7** with *n*-butyllithium at −78 °C and addition of aldehyde **6**, was followed by a second equivalent of *n*-butyllithium at −41 °C and the β-oxido ylide was protonated with *tert*-butanol. No improvement of the *E*-selectivity was found, the *E*/*Z*-ratio was 19:81. Attempts to further optimise the reaction by trying different temperatures were made, but it was not until the base was changed to phenyllithium that any change in selectivity was found, the *E*/*Z*-ratio was essentially reversed to 87:13 and the alcohol **8a** was obtained in 61% total yield (Scheme 2). An explanation of the dependence of *E*-selectivity on the choice of alkyllithium was presented by Schlosser and co-workers during the course of this study.[17]

Alcohol **8a** was further transformed into acetate **8b** and trifluoroacetate **8c** by treatment with acetic anhydride and trifluoroacetic anhydride, respectively (Scheme 2). Methyl ester **8d** was prepared by oxidation of **8a** in two steps, first with the Dess–Martin periodinane to the corresponding



Scheme 2. Reagents, reaction conditions and yields: (a) (1) MsCl, Et_3N, CH_2Cl_2, 0 °C; (2) PhSH, NaOMe, THF/MeOH, rt; (3) *m*-CPBA, CH_2Cl_2, 0 °C–rt (73% over three steps). (b) (1) (i) *n*-BuLi, THF, −78 °C; (ii) **6**·DIBAL·OMe; (2) Na(Hg), Na_2HPO_4, MeOH, 0 °C; (3) HF, ACN, rt (33% over three steps, *E*/*Z* 88:12). (c) (1) (i) PhLi, THF, −60 °C; (ii) **6**, −60 to −41 °C; (iii) PhLi; (iv) MeOH; (v) *t*-BuOK −41 °C–rt; (2) TBAF, THF, rt (61% over two steps, *E*/*Z* 87:13). (d) Ac_2O, DMAP, Et_3N, rt (94%). (e) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt (81%). (f) (1) Dess–Martin periodinane, ACN/CH_2Cl_2, 0 °C–rt; (2) PDC, MeOH, DMF, rt (40% over two steps).

Table 2. Reaction conditions[a] and results of epoxidation of alkenes **8a–e** with *m*-CPBA and CF_3CO_3H



Entry	Substrate	R	Ratio **9**:**10** (*syn*/*anti*)[b]		Isolated yield (%)		Reaction time (h)	
			m-CPBA	CF_3CO_3H	*m*-CPBA	CF_3CO_3H	*m*-CPBA	CF_3CO_3H
1	(±)-**8a**	CH_2OH	71:29	72:28	93	74	2	0.5
2	(±)-**8b**	CH_2OAc	60:40	69:31	82	68	5	2
3	(±)-**8c**	CH_2OCOCF_3	63:37	64:36	82[c]	88[c]	15	5
4	(±)-**8d**	COOMe	67:33	79:21	86	80	24	4
5	(±)-**8e**	NHBoc	76:24[d]	66:33[e]	80	79	29	0.5

[a] Reactions with *m*-CPBA were performed at room temperature and reactions with CF_3CO_3H at 0 °C.
[b] Determined by HPLC and NMR of the crude reaction product.
[c] The yields refer to the crude product.
[d] Data taken from Ref. 5c.
[e] The reaction was run at −78 °C since the *anti* isomer was unstable at 0 °C.

aldehyde (oxidation with PCC gave substantial decomposition of the product), which was reacted with PDC and methanol[18] to form the unstable β,γ-unsaturated ester **8d**. Formation of the corresponding carboxylic acid had to be avoided since it was found to decompose immediately by decarboxylation.

2.2.2. Epoxidation of the alkenes 10a–e. The alkenes **8a–e** were reacted with trifluoroperacetic acid and *m*-CPBA to give diastereomeric mixtures of epoxides **9a–e** (*syn*) and **10a–e** (*anti*). The results are listed in Table 2. The stereochemical assignment of epoxides **9** and **10** was based on NMR-data. Consistent chemical shift differences between signals of the epoxide isomers observed in earlier studies[5b,c] was used also in the assignments of **9** and **10**. Diagnostic NMR spectral data of epoxide **9a–b** and **10a–b** are given in Table 3 and NMR data used for identification of epoxides **9d** and **10d** are given in Table 4. Epoxides **9c** and **10c** were identified by chemical correlation with **9a** and **10a** via methanolysis.

We observed that the epoxidations of **8b–d** using trifluoroperacetic acid were more *syn*-stereoselective than when using *m*-CPBA (Table 2, entries 2–4), which is in accord with an earlier report.[10] However, the *syn*-directing effect of the allylic carbamate group in **8e** was significantly decreased in the trifluoroperacetic acid epoxidation (Table 2, entry 5). No significant difference in stereoselectivity between the peracid in epoxidation of alcohol **8a** was found (Table 2, entry 1). These results again suggest that the two peracids have different preferences of coordination to different functional groups. Apparently, trifluoroperacetic acid coordinates more favourably to the methyl ester than to the allylic carbamate, alcohol, and acetate moieties. In contrast, *m*-CPBA coordinates better to the allylic carbamate than to the alcohol or ester functions. This is in line with the results found in our previous study of epoxidations of derivatives of **1f** in which the functional groups direct the peracid to different faces of the alkene.[9]

Table 3. Selected ^{1}H and ^{13}C NMR shifts (in ppm) for assignment of the relative stereochemistry of epoxides **9a**, **10a**, **9b** and **10b**[a,b]

Compound	Rel. stereochem.	H-1	H-4	C-1	C-7
2f	*syn*	3.67	2.63	63.06	32.94
3f	*anti*	3.46	2.98	62.43	34.92
2g	*syn*	3.67	2.56	63.50	34.22
3g	*anti*	3.54	3.07	62.66	35.34
9a	*syn*	3.71	2.56	64.11	31.73
10a	*anti*	3.45	2.96	62.50	34.69
2j	*syn*	4.11	2.48	64.49	34.52
3j	*anti*	3.90	2.85	63.56	34.92
2k	*syn*	4.12	2.72	64.78	34.81
3k	*anti*	3.95	2.77	63.83	35.13
9b	*syn*	4.15	2.45	64.82	34.89
10b	*anti*	3.97	2.85	63.78	34.99

[a] Data for compounds **2f**,**g**,**j**,**k** and **3f**,**g**,**j**,**k** are from Ref. 5b and c.
[b] See Scheme 2 for atom numbering. For compounds **2f**, **g**,**j**,**k** and **3f**,**g**,**j**,**k** this implies the corresponding atoms.

Table 4. Selected ^{1}H NMR shifts (in ppm) for assignment of the relative stereochemistry of epoxides **9d** and **10d**[a,b]

Compound	Rel. stereochem.	H-5
9a	*syn*	1.63–1.76
10a	*anti*	1.78–1.99
9b	*syn*	1.60–1.71
10b	*anti*	1.77–1.89
9d	*syn*	1.63–1.72
10d	*anti*	1.82–1.90
9e	*syn*	1.67–1.75
10e	*anti*	1.68–1.83

[a] Data for compounds **9e** and **10e** are from Ref. 5c
[b] See Scheme 2 for atom numbering.

Obviously, there are several factors that control the face selectivity in peracid epoxidation of acyclic alkenes with directing groups, of which the most important are; (i) the conformational preferences in the transition state, (ii) the directing effect, which is due to hydrogen bonding between the coordinating functionality and the peracid. The steric preferences in the transition state have been a matter of discussion. Extensive theoretical work on 1,2 asymmetric induction[19] and empirical studies on epoxidation of cyclic allylic alcohols[8c,20] support a staggered model (Fig. 2), but a model where the hydrogen is eclipsed with the double bond (Fig. 2) has also been used, and possibly there are different transition states depending on the substitution pattern of the alkene.[6c,21] The interpretation of our results is not affected by choice of model. Regarding the directing effect, the hydrogen bond donor–acceptor capability of the reactants, and the distance between the alkene and the coordinating group should influence the stereoselectivity.

The mode of hydrogen bonding between the peracid and the coordinating group can influence the stereoselectivity in the peracid epoxidations. For allylic alcohols it is believed that the face selectivity is due to hydrogen bonding from OH to O-3 in the peracid (A, Fig. 2).[22] Similarly, allylic carbamates can direct the peracid via hydrogen bonding from NH to O-3 in the peracid (B, Fig. 2).[5b,8d] However, there is also evidence for a directing effect via reverse hydrogen bonding, that is, the peracid is donating a hydrogen bond to the carbonyl oxygen of the carbamate group. This was proposed by Kočovský and Starý who showed that an allylic carbamate group with a disubstituted

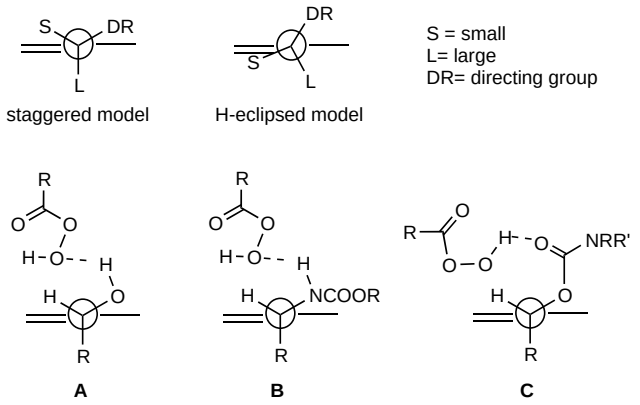
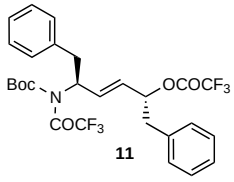


Figure 2. Top: proposed transition state models for epoxidation of alkenes by peracids. Bottom: different modes of hydrogen bonding interactions of peracids with allylic functional groups.

nitrogen atom also gives a strong *syn* direction (C, Fig. 2).[8d] Analogously, de Sousa et al. found evidence that homoallylic silyl ethers are moderate *syn*-directors by reverse hydrogen bonding.[23] A similar observation has been made by us when alkene **11** was treated with trifluoroperacetic acid.[9] The trifluoroacetylated carbamate is a hydrogen bond acceptor, and the directing carbonyl group appears to be more basic than that of the trifluoroacetate, resulting in epoxide products with a *threo*/*erythro* ratio of 81:19. Hence, reverse hydrogen bonding may well explain the directing effects of the acetate and methyl ester functions in the present study.



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The acidity of the peracid should influence the direction of the hydrogen bonding; the more acidic the peracid the stronger the hydrogen bond donating capability. Thus, trifluoroperacetic acid ($pK_a = 3.7$) is more prone to coordinate to different functional groups through hydrogen bond donation than *m*-CPBA ($pK_a = 7.57$). This hypothesis is supported by the current study in that the acetate function in **8b** directs trifluoroperacetic acid more strongly than *m*-CPBA to the *syn* face of the alkene (Table 2), and that the acetate is a better hydrogen bond acceptor than the trifluoroacetate of **8c**, for which no significant difference between the peracids was found.

3. Conclusions

Suitable reaction conditions for efficient synthesis of β,γ-unsaturated esters using the *E*-selective Schlosser reaction were identified. Careful monitoring of the temperature and the use of phenyllithium as the base allowed the production of *E*-alkenes in high yield and high *E*/*Z*-selectivity. The peracid epoxidation of the synthesised *E*-alkene dipeptidomimetics was highly stereoselective, and the formation of the *threo*-isomers was favoured in most reactions. The results strongly suggest a powerful directing effect from the

carbamate function, which is difficult to overcome by changing the peracid or the reaction conditions. However, the second functional group also exhibited strong directing effects. Employing trifluoroperacetic acid as the epoxidation reagent we obtained a reversed stereoselectivity in the epoxidation of two vinylic dipeptide isosteres (**1b** and **1j**). This change in stereodirection probably emanates from a stronger coordination of the peracid to the ester function than to the carbamate moiety. The ester functionality in **1b** and **1j** would direct the epoxidation to the *erythro* face of the alkene. This change of directing properties is supposed to be due to differences in peracid acidity and thereby differences in hydrogen bond donating capacity.

4. Experimental

4.1. General methods

Melting points were determined with a Tomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at ambient temperature. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 spectrometer at 270 and 68 MHz, respectively, or a JEOL Eclipse 400 spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$. Chemical shifts are reported in ppm with the solvent residual peak as internal standard ($CHCl_3$ δ^{H} 7.26, $CDCl_3$ δ^{C} 77.0). 2D COSY, HMQC and HMBC NMR spectroscopy was used to validate structural assignment of the signals. Analytical thin-layer chromatography was performed on Merck silica gel, grade 60 F_{254} and the spots were visualised by UV light (254 nm) and treatment with 5% phosphomolybdic acid in ethanol and heating. Flash chromatography was performed on Merck silica gel SI-60 Å. For analytical HPLC a Hitachi system (L-4000 UV detector at 254 nm and L-6200 pump with flow rate 1.5 mL/min) fitted with a LiChroCART 4× 250 mm 5 μm LiChrospher Si 60 column was used. Infrared spectra were recorded on a Perkin-Elmer 298 or 16PC FT-IR spectrometer and only the major peaks are listed. Elemental analyses were conducted by MikroKemi AB, Uppsala, Sweden. High-resolution mass analysis was performed by Stenhagen analyslab AB, Mölndal, Sweden. The synthesis of the olefins **1a–l**, data for epoxides **2a–l** and **3a–l**, and the analysis procedure of isomeric ratios of epoxides using NMR-spectroscopy and HPLC are described in Ref. 5b and 5c The synthesis and the epoxidation of olefin **8e** are described in Ref. 5c, and the preparation of aldehyde **6** in Ref. 5b. Phosphonium salt **7** was prepared according to literature procedures.[15]

4.2. General procedures for epoxidation reactions

4.2.1. Epoxidation with MMPP (method A). MMPP (2 equiv) was added to a solution of the substrate (0.13 M) and trioctylmethylammonium chloride (0.05 equiv) in a two-phase system consisting of $CHCl_3$ and H_2O (1:1). After stirring at room temperature for the reaction time specified in Table 1, the mixture was poured into satd aq $Na_2S_2O_3$ and the phases were separated. The organic phase was further washed with 1 M aq HCl, satd aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude products were purified by column chromatography as described earlier.[5b,c]

4.2.2. Epoxidation with *m*-CPBA (method B). *m*-CPBA (1.5 equiv) was added to a solution of the substrate (0.2 M) in CH_2Cl_2. After stirring at room temperature for the reaction time specified in Table 1, the reaction was worked up as described above for method A.

4.2.3. Epoxidation with trifluoroperacetic acid (method C). Trifluoroacetic acid anhydride (4 equiv) was added to a solution of urea–hydrogen peroxide (15 equiv, 3 M) and Na_2HPO_4 (10 equiv) in CH_2Cl_2. After stirring at 0 °C for 30 min, substrate was added. Stirring was continued (see Table 1 for reaction times) at the same temperature after which the reaction was quenched immediately by addition of satd aq $NaHCO_3$ and the phases were separated. The organic phase was further washed with satd aq $Na_2S_2O_3$, 1 M aq HCl and brine. The organic layers were dried ($MgSO_4$), filtered and the solvent was removed. The crude products were purified by column chromatography as described earlier.[5b,c]

4.3. Data for the oxazolidinones (4). (4*S*,5*R*)-4-Benzyl-5-[(1*S*)-hydroxy-(2*R*)-methoxycarbonyl-3-phenylpropyl]-1,3-oxazolidin-2-one (4a) and (4*S*,5*S*)-4-benzyl-5-[(1*R*)-hydroxy-(2*R*)-methoxycarbonyl-3-phenylpropyl]-1,3-oxazolidin-2-one (4b)

The compounds were isolated from the trifluoroperacetic acid-mediated epoxidation reaction of **1b** after chromatography using ether/pentane 1:3 as eluent (see method C).

4.3.1. Compound 4a. Mp 115–117 °C; $[\alpha]_D^{20}$ −46.3 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz) δ 7.35–7.16 (m, 10H), 4.94 (bs, 1H), 4.11 (dd, 1H, J=8.5, 4.6 Hz), 3.98 (dt, 1H, J=9.3, 4.8 Hz), 3.66 (s, 3H), 3.58 (m, 2H), 3.15–2.94 (m, 4H), 2.74 (t, 1H, J=13.6 Hz); ^{13}C NMR (68 MHz) δ 175.8, 157.4, 137.4, 136.1, 129.1 (2C), 129.0 (4C, s), 128.7 (2C), 127.3, 126.9, 81.3, 71.8, 57.0, 52.1, 46.8, 42.3, 35.4; IR (KBr) 3343, 1748 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.28; H, 6.17; N, 3.87.

4.3.2. Compound 4b. Mp 188–190 °C. $[\alpha]_D^{20}$ −40.5 (*c* 0.74, $CHCl_3$); ^{1}H NMR (270 MHz) δ 7.38–7.18 (m, 10H), 4.92 (bs, 1H), 4.64 (dd, 1H, J=10.1, 7.3 Hz), 4.35 (dd, 1H, J=10.0, 2.2 Hz), 4.07 (ddd, 1H, J=12.0, 7.2, 3.2 Hz), 3.65 (bs, 1H), 3.52 (s, 3H), 3.33–3.08 (m, 4H), 2.64 (t, 1H, J=13.0 Hz); ^{13}C NMR (68 MHz) δ 176.1, 157.6, 138.1, 136.7, 129.1 (4C), 129.0 (2C), 128.5 (2C), 127.2, 126.6, 76.7, 68.0, 56.3, 51.9, 48.4, 35.9, 31.2; IR (KBr) 3373, 1744 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_5\times0.5H_2O$: C, 66.65; H, 6.39; N, 3.70. Found: C, 66.74; H, 6.31; N, 3.59. The stereochemistry of this compound was established by X-ray crystallography.[13]

4.4. Synthesis of the alkenes 8a–d

4.4.1. Phenyl-(3-phenylpropyl)sulfone (5). 3-Phenylpropanol (15.0 g, 110 mmol) and Et_3N (6.0 mL, 330 mmol) were dissolved in CH_2Cl_2 (450 mL). Methanesulfonyl chloride (21.5 g, 275 mmol) was added drop wise at 0 °C. After 2 h H_2O was added and the mixture was extracted three times with CH_2Cl_2. The combined organic phases

were dried ($MgSO_4$) and concentrated in vacuo without heating to afford a crude oil, which was used in next step without further purification.

Thiophenol (73.0 mL, 716 mmol) was added to a solution of $NaOCH_3$ (38.65 g, 716 mmol) in THF/MeOH (5:1, 300 mL). The mixture was stirred for 30 min at room temperature and the mesylate from the previous step was added as an oil. The reaction mixture was stirred at room temperature overnight. The day after, satd aq $NaHCO_3$ was added and the organic solvent was evaporated. The mixture was partitioned between H_2O and ether, and the aqueous phase was extracted three times with ether. The combined ether layers were dried ($MgSO_4$) and concentrated to afford a yellow-brown oil. Purification by column chromatography (petroleum ether) gave phenyl-(3-phenylpropyl)sulfide (24.37 g, 97% over two steps): ^1H NMR data were in agreement with those reported;[24] ^{13}C NMR (68 MHz) δ 141.2, 136.5, 129.0 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 125.9, 125.7, 34.6, 32.8, 30.5.

The sulfide (1.50 g, 6.57 mmol) was dissolved in CH_2Cl_2 (75 mL) and *m*-CPBA (5.18 g, 21.0 mmol) was added at 0 °C. The mixture was allowed to reach room temperature while stirring overnight. The reaction was quenched by slow addition of aq NaOH (10%, 25 mL) saturated with $NaHSO_3$. After filtration and dilution, the aqueous phase was extracted four times with CH_2Cl_2. The combined organic layers were extracted once with 1 M NaOH, dried ($MgSO_4$) and concentrated. The crude product was recrystallised (CH_2Cl_2/hexane) to afford sulfone **5** (1.24 g, 72%). ^1H NMR data and melting point were in agreement with those reported;[25] ^{13}C NMR (68 MHz) δ 139.7, 138.9, 133.6 (2C), 129.2 (2C), 128.5 (2C), 128.3 (2C), 127.9, 126.3, 55.3, 33.9, 24.1.

4.4.2. 2-Benzyl-6-phenyl-(*E*)-3-hexen-1-ol (8a). *By Julia olefination with* **5**. Sulfone **5** (0.64 g, 2.46 mmol) was dissolved in dry THF (20 mL) under N_2 atmosphere. The solution was cooled to −78 °C and *n*-butyllithium (1.6 M in hexane, 1.84 mL, 2.95 mmol) was added. The solution was stirred for 30 min at −78 °C. In a separate flask, aldehyde **6** (1.03 g, 3.69 mmol) was treated with DIBAL-methoxide (1.16 M, 3.18 mL) at −78 °C in THF (10 mL). The solution of the activated aldehyde was added immediately to the solution of the sulfone anion, and the mixture was stirred for 30 min at −78 °C. The reaction was quenched by addition of satd aq NH_4Cl and allowed to reach room temperature. After removal of THF by evaporation, the mixture was extracted five times with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to afford a colourless oil.

The crude oil was dissolved in MeOH (75 mL) and Na_2HPO_4 (3.49 g, 24.6 mmol) and 6% Na(Hg) (9.43 g) were added at 0 °C. After 4 h, H_2O and 1 M HCl were added and the insoluble material was filtered off. MeOH was removed by evaporation and the mixture was extracted with CH_2Cl_2 four times. The organic phase was dried ($MgSO_4$) and concentrated. Purification by column chromatography (ether/petroleum ether 1:19) gave an *E*/*Z* mixture of 2-benzyl-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-3-hexene.

The crude product (500 mg, 1.31 mmol) was dissolved in acetonitrile (40 mL) containing 2% HF (2 mL of a 40% aqueous HF solution) at room temperature. After 1 h H_2O was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to afford 470 mg of a crude oil. The *E*/*Z* ratio was 88:12 according to GC and NMR (33% combined yield over two steps). The isomers were separated by repeated column chromatography (CH_2Cl_2/MeOH/hexane 4:1:25) to afford **8a** as a colourless oil: HPLC (0.5% EtOH in hexane), t_R 13.2 min; ^1H NMR (270 MHz) δ 7.30–7.11 (m, 10H), 5.48 (app dt, 10H, J=6.6, 15.4 Hz), 5.21 (ddt, 1H, J=1.1, 8.1, 15.4 Hz), 3.51 (ddd, 1H, J=4.7, 8.1, 10.7 Hz), 3.33 (ddd, 1H, J=4.3, 7.7, 10.7 Hz), 2.74–2.51 (m, 4H), 2.50–2.40 (m, 1H), 2.38–2.26 (m, 2H), 1.22 (app ddd, 1H, J=1.1, 4.3, 8.1 Hz); ^{13}C NMR (68 MHz) δ 141.6, 139.8, 132.8, 131.3, 129.1 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 125.9, 125.8, 65.0, 47.1, 37.7, 35.7, 34.3; IR (neat) 3370, 3020, 2920, 1600, 1490, 1450 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.6; H, 8.5.

By Schlosser olefination with **7**. Phosphonium salt **7** (1.19 g, 2.58 mmol) was suspended by magnetic stirring in dry THF (5 mL) under N_2. The vessel was cooled to −60 °C and phenyllithium (2.0 M in dibutyl ether, 1.36 mL, 2.72 mmol) was added. The reaction was allowed to warm to room temperature and was stirred for 30 min during which an orange colour solution developed. The reaction was again cooled to −60 °C and a solution of **6** (0.72 g, 2.59 mmol) in THF (2 mL) was added drop wise at which the colour faded. The reaction was allowed to warm to −41 °C and was left with stirring for 30 min. Another equivalent of phenyllithium was added to yield a dark violet solution which was stirred for 30 min. Addition of MeOH (0.105 mL, 2.29 mmol) gave a slight yellow solution, which was stirred for 30 min at −41 °C. *t*-BuOK (0.29 g, 2.59 mmol) was added in one portion and the reaction was stirred for 30 min and was then allowed to reach room temperature. The reaction was quenched by addition of diethyl ether (15 mL) and satd aq NH_4Cl (25 mL). The mixture was stirred briefly and the phases were separated. The aqueous phase was extracted with diethyl ether (25 mL) and the combined organic phases were washed with H_2O and brine, dried over $MgSO_4$ and evaporated. The product, 2-benzyl-1-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-3-hexene (mixture of *E*/*Z*-isomers), was purified by column chromatography as described above.

The crude product was dissolved in THF (4 mL) and TBAF (1 M in THF, 6.9 mL, 6.9 mmol) was added and the resulting mixture was stirred for 26 h. The mixture was diluted with diethyl ether (60 mL) and washed with 10% aq citric acid solution (60 mL), satd aq $NaHCO_3$ (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by gradient column chromatography (EtOAc/hexanes 1:20–1:10) to yield the title compound with an *E*/*Z*-ratio of 87:13 (0.42 g, 61% combined yield over two steps). The *E*/*Z*-isomers were separated as indicated above.

4.4.3. 2-Benzyl-6-phenyl-(*E*)-3-hexenylacetate (8b). Alcohol **8a** (50 mg, 0.188 mmol) and Et_3N 131 μL, 0.938 mmol) were dissolved in CH_2Cl_2 (5 mL). Acetic

anhydride (89 μL, 0.938 mmol) and a catalytic amount of DMAP were added. The reaction was stirred at room temperature overnight. The mixture was extracted with 1 M HCl and satd aq $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification of the crude oil by column chromatography (ether/pentane 1:12) afforded the title compound (54.6 mg, 94%): HPLC (10% EtOAc in hexane), t_R 4.6 min, ^{1}H NMR (270 MHz) δ 7.29–7.09 (m, 10H), 5.42 (app dt, 1H, J=6.4, 15.4 Hz), 5.28 (app dd, 1H, J=7.5, 15.4 Hz), 4.02–3.91 (m, 2H), 2.78–2.51 (m, 5H), 2.31–2.23 (m, 2H), 2.02 (s, 3H); ^{13}C NMR (68 MHz) δ 171.0, 141.7, 139.4, 131.7, 130.3, 129.2 (2C), 128.4 (2C), 128.2 (4C), 126.0, 125.7, 66.8, 43.3, 38.2, 35.8, 34.3, 20.9; IR (neat) 3020, 2930, 1740, 1490, 1450, 1240 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.8; H, 7.8. Found: C, 81.7; H, 7.9.

4.4.4. 2-Benzyl-6-phenyl-(*E*)-3-hexenyltrifluoroacetate (8c). Alcohol **8a** (150 mg, 0.563 mmol) and Et_3N (235 μL, 1.69 mmol) were dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic anhydride (86 μL, 0.619 mmol) was added. The reaction was stirred at room temperature. More Et_3N and trifluoroacetic anhydride were added twice since there was starting material left after 2 and 4 h, respectively. After 5 h, the reaction mixture was extracted with 1 M aqueous HCl and saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated. Purification of the crude oil by column chromatography (ether/pentane 1:4) afforded the title compound (166 mg, 81%) as a colourless oil: HPLC (2% EtOAc in hexane), t_R 4.8 min; ^{1}H NMR (270 MHz) δ 7.31–7.08 (m, 10H), 5.49 (dt, 1H, J=6.5, 15.4 Hz), 5.32–5.23 (m, 1H), 4.26–4.15 (m, 2H), 2.74–2.58 (m, 5H), 2.33–2.25 (m, 2H); ^{13}C NMR (68 MHz) δ 157.4 (q, J_{CCF}= 42 Hz), 141.6, 138.5, 133.0, 129.1, 128.9 (2C), 128.4 (4C), 128.2 (2C), 126.4, 125.8, 114.5 (q, J_{CF}=285 Hz), 69.8, 43.1, 37.7, 35.6, 34.3; IR (neat) 3020, 2930, 1780, 1490, 1450, 1220, 1160 cm^{-1}. Anal. Calcd for $C_{21}H_{21}F_3O_2$: C, 69.60; H, 5.84. Found: C, 69.57; H, 5.90.

4.4.5. Methyl 2-benzyl-6-phenyl-(*E*)-3-hexenoate (8d). Alcohol **8a** (110 mg, 0.413 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and acetonitrile (2 mL) under a N_2 atmosphere and cooled to 0 °C. Dess–Martin periodinane (15 wt% solution in CH_2Cl_2, 1.46 g solution, 0.516 mmol) was added drop wise to the stirred solution. The reaction was stirred for 30 min at 0 °C and another 3 h at rt. The solvent volume was reduced to half by rotary evaporation without heating, and the remaining solution was cooled to 0 °C, and cold satd aq $Na_2S_2O_3$ solution was added and stirring was continued for 20 min. The mixture was extracted three times with diethyl ether, and the combined organic layers were washed with cold satd aq $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. The product was purified by rapid chromatography on a short column (EtOAc/hexanes 1:20) to yield the unstable compound *E*-2-benzyl-6-phenyl-3-hexenal as a crude oil (95 mg), which was used immediately in the next step. ^{1}H NMR (400 MHz) δ 9.57 (d, 1H, J=1.8 Hz), 7.32–7.10 (m, 10H), 5.61–5.54 (m, 1H), 5.32 (dd, 1H, J=8.4, 15.8 Hz), 3.25 (q, 1H, J=7.4 Hz), 3.11 (dd, 1H, J=6.2, 13.9 Hz), 2.74 (dd, 1H, J=7.7, 13.9 Hz), 2.68–2.62 (m, 2H), 2.38–2.32 (m, 2H).

The crude aldehyde (approx 0.36 mmol) was dissolved in dry DMF (2 mL) under a N_2 atmosphere and MeOH (106 μL, 2.6 mmol) was added. The mixture was stirred for 10 min and subsequently PDC (0.982 g, 2.20 mmol) was added. The reaction was quenched after 19 h by adding the reaction solution in small portions to a vigorously stirred mixture of H_2O (25 mL) and diethyl ether (75 mL). The resulting suspension was filtered through Celite and the filtrate was washed with H_2O. The aqueous layer was washed extracted twice with ether and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification of the unstable product was done by rapid chromatography on a short column (EtOAc/hexanes 1:100) to yield the title compound (49 mg, 40% over two steps, repeated attempts gave comparable yields). ^{1}H NMR (400 MHz) 7.30–7.09 (m, 10H), 5.52–5.48 (m, 2H), 3.63 (s, 3H), 3.31–3.23 (m, 1H), 3.06 (dd, 1H, J=7.7, 13.6 Hz), 2.79 (dd, 1H, J=7.3, 13.6 Hz), 2.63 (dt, 2H, J= 3.3, 7.7 Hz), 2.33–2.27 (m, 2H); ^{13}C NMR (100 MHz) 174.2, 141.6, 138.8, 133.0, 129.0 (2C), 128.4 (2C), 128.2 (4C), 127.6, 126.3, 125.8, 51.7, 51.0, 38.8, 35.5, 34.2; IR (neat) 3027, 2928, 1735, 1449, 1160 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{23}O_2$ (MH^+) 295.170, found 295.167.

4.5. Epoxidation of the alkenes 8a–d

Epoxidations were performed as described above (method B and C). Data on isomeric ratios, yields and reaction times are given in Table 2.

4.5.1. (2*R,3*S**,4*R**)-2-Benzyl-3,4-epoxy-6-phenyl-hexan-1-ol (9a) and (2*R**,3*R**,4*S**)-2-benzyl-3,4-epoxy-6-phenyl-hexan-1-ol (10a).** Purification by column chromatography (CH_2Cl_2/MeOH/hexane 4:1:12) afforded **9a** and **10a**.

Compound **9a**. HPLC (3% EtOH in hexane), t_R 9.9 min; ^{1}H NMR (270 MHz) δ 7.32–7.09 (m, 10H), 3.75–3.68 (m, 2H), 2.82 (dd, 1H, J=6.8, 13.7 Hz), 2.70 (dd, 1H, J=2.4, 7.7 Hz), 2.66–2.43 (m, 4H), 2.07 (br s, 1H), 1.76–1.63 (m, 3H); ^{13}C NMR (68 MHz) δ 141.1, 139.2, 129.1 (2C), 128.9 (2C), 128.4 (2C), 128.2 (2C), 126.3, 126.0, 64.1, 60.9, 57.8, 45.0, 34.9, 33.5, 31.7; IR (neat) 3440, 3020, 2920, 1600, 1490, 1450 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_2 \times 0.1H_2O$: C, 80.3; H, 7.8. Found: C, 80.3; H, 8.0.

Compound **10a**. HPLC (3% EtOH in hexane, t_R 8.6 min; ^{1}H NMR (270 MHz) δ 7.33–7.15 (m, 10H), 3.53–3.37 (m, 2H), 2.96 (app dt, 1H, J=2.3, 5.8 Hz), 2.88–2.69 (m, 4H), 2.61 (dd, 1H, J=8.6, 13.7 Hz), 1.99–1.78 (m, 3H), 1.67–1.63 (m, 1H); ^{13}C NMR (68 MHz) δ 141.1, 139.0, 129.0 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 126.2, 126.1, 62.5, 61.1, 56.9, 43.9, 34.7, 33.6, 32.1; IR (neat) 3440, 3020, 2920, 1600, 1490, 1450 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.7; H, 7.7.

4.5.2. (2*R,3*S**,4*R**)-2-Benzyl-3,4-epoxy-6-phenyl-hexanyl acetate (9b) and (2*R**,3*R**,4*S**)-2-benzyl-3,4-epoxy-6-phenyl-hexanyl acetate (10b).** Purification by column chromatography (diethyl ether/pentane 1:9) afforded **9b** and **10b**.

Compound **9b**. HPLC (10% EtOAc in hexane), t_R 18.1 min; ^{1}H NMR (270 MHz) δ 7.32–7.10 (m, 10H), 4.22–4.09

(m, 2H), 2.77 (dd, 1H, J=6.5, 13.5 Hz), 2.68–2.64 (m, 1H), 2.61–2.48 (m, 3H), 2.47–2.43 (m, 1H), 2.09 (s, 3H), 1.86–1.73 (m, 1H), 1.71–1.60 (m, 2H); ^{13}C NMR (68 MHz) δ 171.0, 141.1, 138.8, 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.2 (2C), 126.4, 126.0, 64.8, 59.2, 58.0, 42.9, 34.9, 33.5, 31.8, 20.9; IR (neat) 3020, 2930, 1740, 1490, 1450, 1240 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.8; H, 7.5. Found: C, 77.6; H, 7.6.

Compound **10b**. HPLC (10% EtOAc in hexane), t_R 12.7 min; ^{1}H NMR (270 MHz) δ 7.32–7.15 (m, 10H), 4.00–3.94 (m, 2H), 2.93 (dd, 1H, J=5.0, 13.7 Hz), 2.85 (app dt, 1H, J=2.3, 5.8 Hz), 2.83–2.63 (m, 4H), 2.01 (s, 3H), 1.89–1.77 (m, 3H); ^{13}C NMR (68 MHz) δ 170.8, 141.0, 138.4, 129.1 (2C), 128.5 (4C), 128.3 (2C), 126.4, 126.0, 63.8, 59.9, 58.0, 42.5, 35.0, 33.8, 32.1, 20.8; IR (neat) 3020, 2930, 1740, 1490, 1450, 1240 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.8; H, 7.5. Found: C, 77.7; H, 7.5.

4.5.3. (2*R,3*S**,4*R**)-2-Benzyl-3,4-epoxy-6-phenyl-hexanyl trifluoroacetate (9c) and (2*R**,3*R**,4*S**)-2-benzyl-3,4-epoxy-6-phenyl-hexanyl trifluoroacetate (10c).** The epoxides **9c** and **10c** were not isolated, instead the crude mixture was treated with K_2CO_3 in MeOH to produce a mixture with unchanged ratio of the corresponding alcohol epoxides **9a** and **10a**.

4.5.4. Methyl (2*R,3*S**,4*R**)-2-benzyl-3,4-epoxy-6-phenyl-hexanoate (9d) and methyl (2*R**,3*R**,4*S**)-2-benzyl-3,4-epoxy-6-phenyl-hexanoate (10d).** Purification by gradient column chromatography (EtOAc/hexanes 1:33–1:20) afforded **9d** and **10d**.

Compound **9d**. HPLC (5% EtOH in hexane), 1.5 mL/min, t_R 14.4 min; ^{1}H NMR (400 MHz) δ 7.31–7.08 (m, 10H), 3.71 (s, 3H), 3.06 (dd, 1H, J=7.0, 13.9 Hz), 2.94 (dd, 1H, J=2.2, 8.4 Hz), 2.80 (dd, 1H, J=8.8, 13.9 Hz), 2.67–2.58 (m, 1H), 2.56–2.48 (m, 1H), 2.48–2.41 (m, 2H), 1.72–1.63 (m, 2H); ^{13}C NMR (100 MHz) δ 173.2, 141.0, 138.0, 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.2 (2C), 126.7, 126.0, 58.5, 58.1, 52.0, 50.3, 35.3, 33.3, 31.7; IR (neat) 3027, 2949, 1732, 1604, 1495, 1454, 1200, 1165. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.4; H, 7.1. Found: C, 77.5; H, 7.3.

Compound **10d**. HPLC (5% EtOAc in hexane), 1.5 mL/min, t_R 8.4 min; ^{1}H NMR (400 MHz) δ 7.34–7.20 (m, 10H), 3.61 (s, 3H), 3.06 (app d, 2H, J=7.0 Hz), 2.94–2.89 (m, 2H), 2.82–2.68 (m, 2H), 2.53 (app q, 1H, J=7.3 Hz), 1.89–1.84 (m, 2H); ^{13}C NMR (100 MHz) δ 172.4, 141.0, 138.0, 128.9 (2C), 128.4 (4C), 128.3 (2C), 126.6, 126.0, 58.4, 57.9, 51.8, 50.2, 35.7, 33.5, 32.1; IR (neat) 3027, 2949, 1738, 1604, 1496, 1454, 1201, 1164 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{23}O_3$ (MH^+) 311.165, found 311.167

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Supplementary data

NMR spectral assignments of characterised compounds. ^{1}H and ^{13}C NMR spectra of **8d** and **10d**. Experimental details, selected details of the final structure refinement and crystal data of **4b**.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.095

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Tetrahedron

The methoxycarbonylcarbene insertion into 1,3-dithiolane and 1,3-oxathiolane rings

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Abstract—Treatment of substituted 1,3-dithiolanes and 1,3-oxathiolanes with methyl diazoacetate in the presence of $Rh_2(OAc)_4$ effects ring expansion to the corresponding substituted 1,4-dithiane-2-carboxylates and 1,4-oxathiane-3-carboxylates. The sulfur ylides initially generated in these reactions undergo Stevens rearrangement in competition with both [2,3]-C–C-sigmatropic rearrangement and intramolecular fragmentation. In the case of 2-styryl-substituted 1,3-oxathiolane and 1,3-dithiolane, ring expansion on one-, three- and four-carbons subsequently takes place.

1. Introduction

The formation of ylides by intermolecular or intramolecular reactions of carbenes or metal carbenoids with heteroatom-bearing molecules such as sulfides,[1] ethers,[2] or amines,[3] has been widely investigated. Sulfur ylides have become increasingly useful intermediates in synthetic organic chemistry. Their chemistry has been thoroughly discussed in a number reviews.[4] These ylides can undergo three types of reaction: (a) intramolecular fragmentation, (b) [1,2]-C–C-shift (Stevens rearrangement), (c) [2,3]-C–C-sigmatropic rearrangement. With simple allyl sulfides the [2,3]-C–C-sigmatropic rearrangement is the major reaction pathway,[5] and the advantage of using this method has recently been demonstrated in the synthesis of penicillins and 3-piperidinol alkaloids.[6,7] Previous studies of the metal-catalysed reactions of diazo compounds have shown that ylides derived from *O*,*O*-,[8] *O*,*N*-[9] and *S*,*S*-cyclic acetals[10] undergo the [1,2]-C–C-shift to form new carbon–carbon bonds with the expansion of the heterocycle.

2. Results and discussion

In this work, the interaction of methoxycabonylcarbene with 2-phenyl- and 2-styryl-1,3-dithiolanes, with 2-phenyl- and 2-styryl-1,3-oxathiolanes has been studied. It was established that the reaction of methyl diazoacetate with 2-phenyl-1,3-dithiolane **1** in the presence of 0.5 mol% $Rh_2(OAc)_4$ resulted in the formation of ring expansion products, *cis*-**2** and *trans*-**3** dithianes, in a ratio 5:1 with a combined yield of 42% with the diester **4** in 6% yield (Scheme 1). Separation of the reaction mixture by column chromatography on silica afforded *cis*-dithiane **2** (31%), diester **4** (6%) and a fraction, which contained a 1:2 mixture of **2** and **3**. The composition and structures of esters **2** and **4** were confirmed by elemental and spectral analysis. The ^{1}H NMR spectra of compounds **2** and **3** have doublet signals at δ 3.73 and 4.57 (J=3.5 Hz) and δ 4.19 and 4.39 (J=10.2 Hz), respectively, belonging to the methine protons at the C(2) and C(3) atoms of ester **2** and **3**, respectively. From X-ray diffraction analysis data it was determined that, in ester **2**, the phenyl group occupies the equatorial position, and the ethyl ester occupies the axial position (Fig. 1). The olefinic proton of the diester **4** is seen at δ 5.9. Hydrolysis of diester **4** afforded diacid **7**.

Treatment of 2,2-disubstituted 1,3-dithiolanes **8a**,**b** with methyldiazoacetate (1.2-fold excess of diazo ester) in the presence of rhodium(II) acetate leads to 1,4-dithianes **9a**,**b** (yields of 37 and 44%, respectively) and 1,4-dithiepanes

Keywords: Carbenes; Diazocompounds; Ylides; Dithiolanes; Oxathiolanes; Stevens rearrangement; Sigmatropic rearrangement; Ring expansion.
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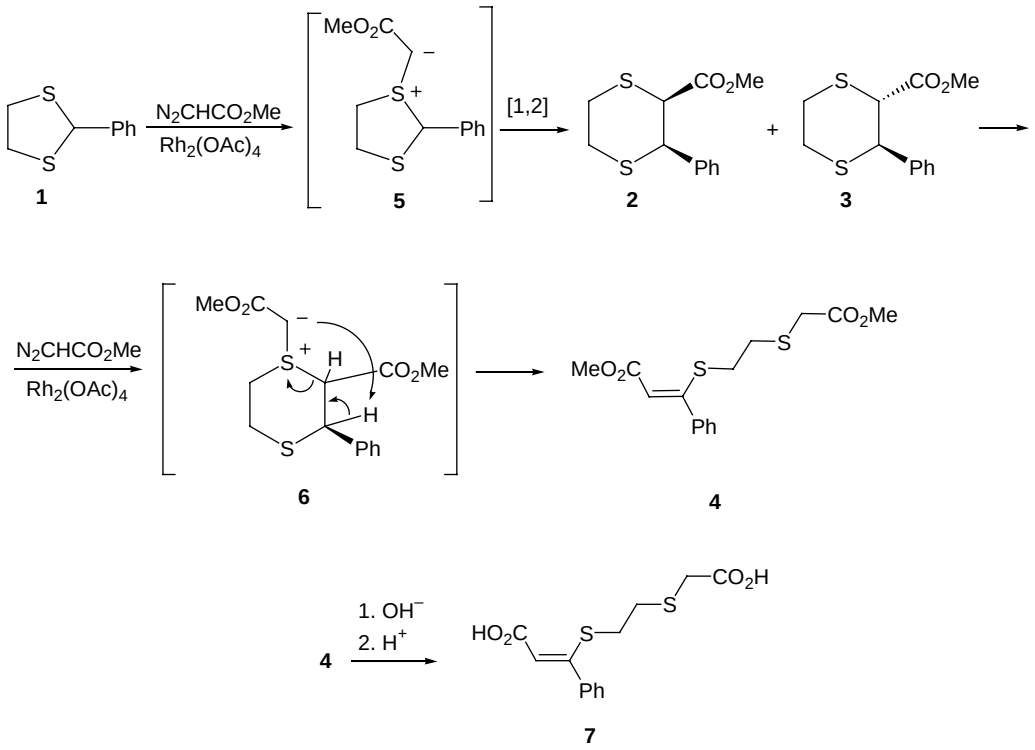


Scheme 1.

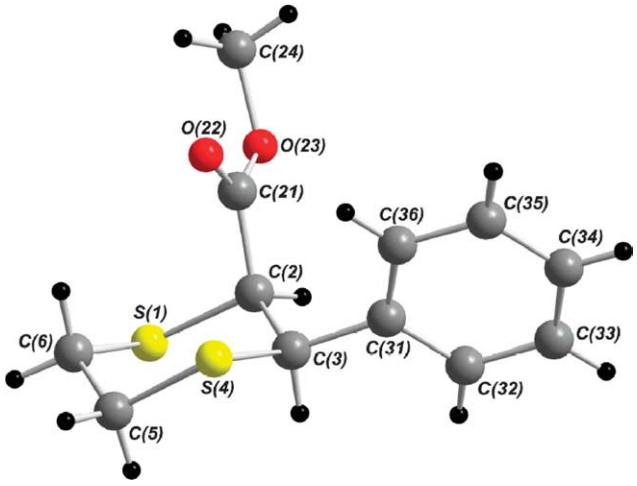


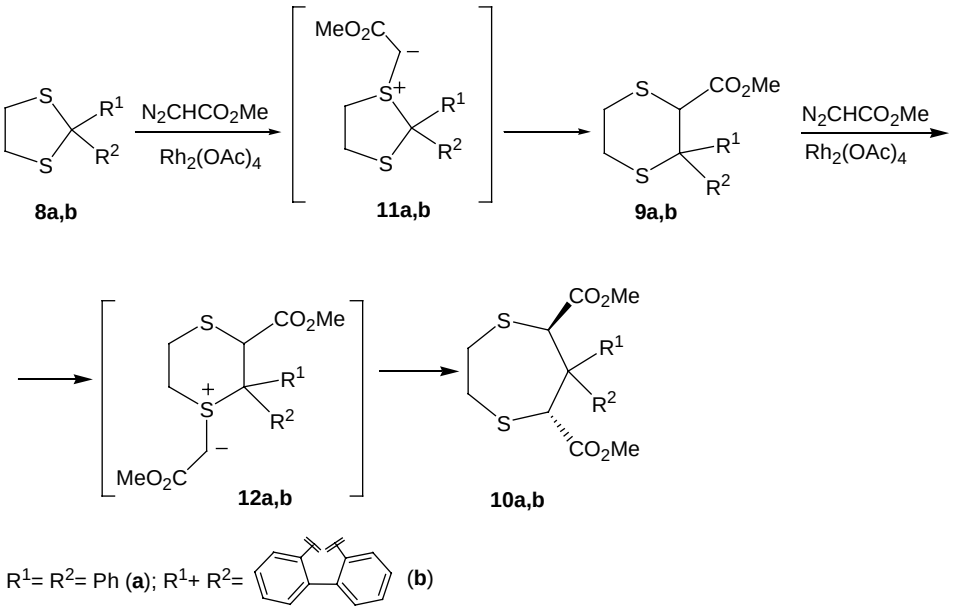
Figure 1. The X-ray crystal structure of compound **2**.

10a,**b** (in 11 and 8% yield, respectively) (Scheme 2). The composition and the structures of compounds **9a**,**b** and **10a**,**b** were confirmed by elemental and spectral analysis. The ^{1}H NMR spectra of compounds **9a**,**b** exhibit signals for the methine proton at the C(2) atom at δ 4.36 and 4.68, respectively. The shift of the signal of the ester groups to a higher field [δ 3.39 (**9a**) and 3.25 (**9a**)] is due to the shielding effect induced by the benzene rings. The ^{1}H NMR spectra of compounds **10a**,**b** show singlet signals for the methine protons at the C(2) and C(4) atoms at δ 5.24 (2H) and 5.08 (2H), respectively. The trans-arrangement of the esters groups in compound **10a** was confirmed by X-ray diffraction studies (Fig. 2).

Recently, it has been noted that the treatment of 2-phenyl-1,3-oxathiolane **13** with ethyl diazoacetate in the presence of copper(II) acetylacetonate leads to a ring expansion, giving a mixture of cis- and trans-isomers of ethyl 2-phenyl-1,4-oxathiane-3-carboxylate in 19% yield.[11] In the present study, it has been established that the reaction of 1,3-oxathiolane **13** with methyl diazoacetate in the presence of $Rh_2(OAc)_4$ affords a mixture of *cis*-**14** and *trans*-**15** isomers of methyl 2-phenyl-1,4-oxathiane with 48% yield, in a ratio of 1:1.8, respectively (Scheme 3). The diester **16** was produced in 5% yield after column chromatography on silica. The pure trans-isomer **15** was obtained by recrystallisation at low temperatures of the isomeric mixture.

^{1}H NMR spectra of 1,4-oxathianes **14** and **15** exhibit doublet signals at δ 3.39 and 4.95 (J=3.1 Hz) and δ 3.85 and 4.78 (J=9.3 Hz), respectively, belonging to the methine protons at the C(2) and C(3) atoms of ester **14** and **15**, respectively. The olefinic proton of the diester **16** is observed at δ 5.3. The reaction of 2,2-diphenyl-1,3-oxathiolane **19** with methoxycarbonylcarbene, which was generated under the same conditions, resulted in the formation of methyl 3,3-diphenyl-1,3-oxathiane-2-carboxylate **20** in 51% yield (Scheme 4).

The results obtained in the present study provide evidence that methoxycarbonylcarbene reacts with dithiolanes **1**, **8a**,**b** and oxathiolanes **13**, **19** to form *S*-ylides **5**, **11a**,**b**, **17** and **21**, which undergo the Stevens rearrangement with ring expansion to produce dithiane and oxathiane derivatives. In the reactions of methoxycarbonylcarbene with oxathiolanes **13** and **19**, the formation of isomeric oxathianes, which should be obtained as a result of the rearrangement of the corresponding *O*-ylides, was not observed. Therefore, it



Scheme 2.

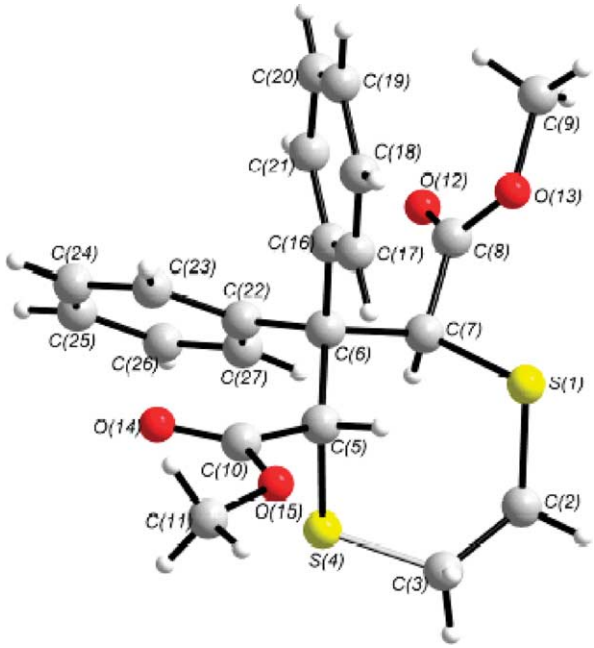


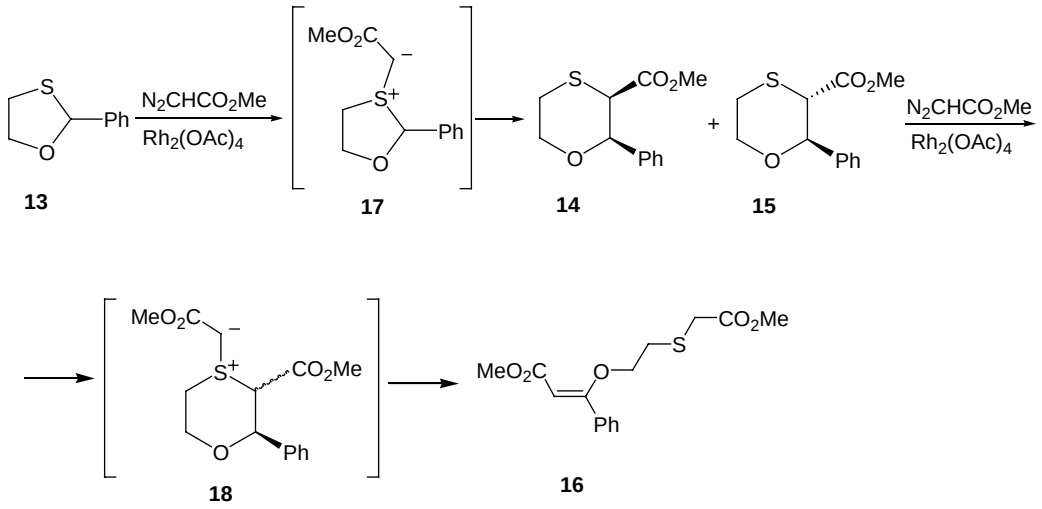
Figure 2. The X-ray crystal structure of compound **10a**.

can be proposed that this reaction occurs only through the formation of *S*-ylides. The subsequent reactions of esters **9a**,**b** with methoxycarbonylcarbene also gave *S*-ylides **12a**,**b**, which rearranged into diesters **10a**,**b**. The esters **2**, **3**, **14**, **15** also react with methoxycarbonylcarbene to give sulfur ylides **6** and **18**. In these cases it appears that intermediate ylides suffer a fragmentation process rather than undergoing ring expansion. It should be noted that such fragmentation products have been found earlier in the reaction of ethyl diazoacetate with substituted 1,3-dithianes.[10] It seems that intramolecular fragmentation in both cases results in the formation of olefins **4** and **16**.

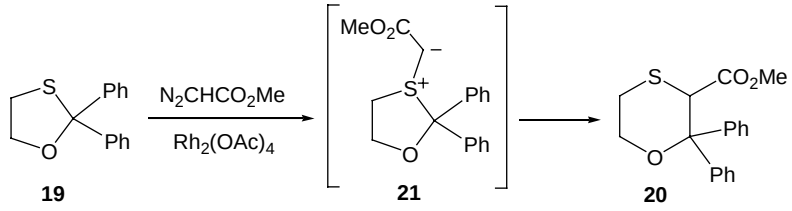
The treatment of 2-styryl-1,3-dithiolane **22** with methyl diazoacetate in the presence of 0.5 mol% $Rh_2(OAc)_4$ afforded a complex mixture of products. Column chromatography of this mixture made it possible to isolate methyl *cis*-6-phenyl-2,3,5,6-tetrahydro-1,4-dithiocine-5-carboxylate **23** in 34% yield and also *cis*-**24** and *trans*-**25** dimethyl 6-phenyl-2,3,6,9-tetrahydro-5*H*-1,4-dithionine-5,9-dicarboxylates in yields of, 7 and 3%, respectively (Scheme 5).

The ^{1}H NMR spectrum of ester **23** exhibit signals for the methine protons at the C(8) and C(7) atoms at δ 3.76 (d, J=2.2 Hz) and 5.05 (dd, J=8.7, 2.2 Hz), respectively, and signals for the olefinic protons at the C(5) and C(6) atoms at δ 6.26 (d, J=8.7 Hz) and 7.01 (t, J=8.7 Hz), respectively. The coupling constants are indicative of a cis-arrangement of the substituents at the C(8) and C(7) atoms. The coupling constant for the olefinic protons is 8.7 Hz, indicating that there is a cis-double bond in compound **23**.[12] The ^{1}H NMR spectra of the diesters **24** and **25** exhibit signals of δ 6.14, 6.65 and δ 5.95, 6.25, respectively, belonging to the olefinic protons. The coupling constant for the olefinic protons is both 16.1 Hz, indicating that there is a trans-double bond in compounds **24** and **25**. The structures of compounds **24** and **25** were confirmed by X-ray diffraction studies (Figs. 3 and 4).

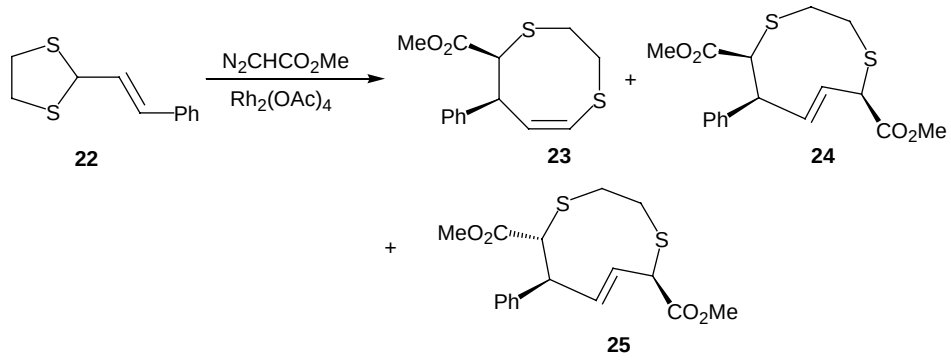
The results above provide evidence that methoxycarbonylcarbene reacts with dithiolane **22** to form the *S*-ylide **26**, which undergoes the [2,3]-C–C-sigmatropic rearrangement with the ring expansion to produce dithiocine **23** (path A). Alternatively conversion of the *S*-ylide **26** by the Stevens rearrangement may form the styryl-dithiane **27** (path B). Compound **27** then reacts with methoxycarbonylcarbene to form the *S*-ylide **28**, and as a result of [2,3]-C–C-sigmatropic rearrangement of *S*-ylide **28**, the isomeric diesters **24** and **25** are formed (Scheme 6). It is important to note that signals corresponding to dithiane **27** were not observed in the ^{1}H NMR spectra of reaction mixtures.



Scheme 3.



Scheme 4.



Scheme 5.

The interaction of 2-styryl-1,3-oxathiolane **29** with methoxycarbonylcarbene afforded a complex mixture of products. The esters **30** and **31** were produced in 13 and 24% yield, respectively, after column chromatography on silica (Scheme 7). The ^{1}H NMR spectra of esters **30** and **31** exhibit signals for the olefinic protons at δ 5.65 (dd, J=5.8, 4.9 Hz) and 6.19 (d, J=5.8 Hz) for compound **30** and δ 6.22 (dd, J=16.2, 6.2 Hz) and 6.70 (dd, J=16.2, 1.5 Hz) for compound **31**, and signals for the methine protons at δ 3.67 (d, J=2.3 Hz) and 4.55 (dd, J=4.9, 2.3 Hz) for compound **30** and δ 3.32 (d, J=2.3 Hz) and 4.57 (ddd, J=6.2, 2.3, 1.5 Hz) for compound **31**. The coupling constants (2.3 Hz in both cases) are indicative of a cis-arrangement of the substituents at the C(2) and C(3) atoms in ester **31** and also at the C(7) and C(8) atoms in ester **30**. On the basis of this data, it can be proposed that transformation of ylide **32**, which is formed by the reaction of oxathiolane **29** with methoxycarbonylcarbene, may occur by two different

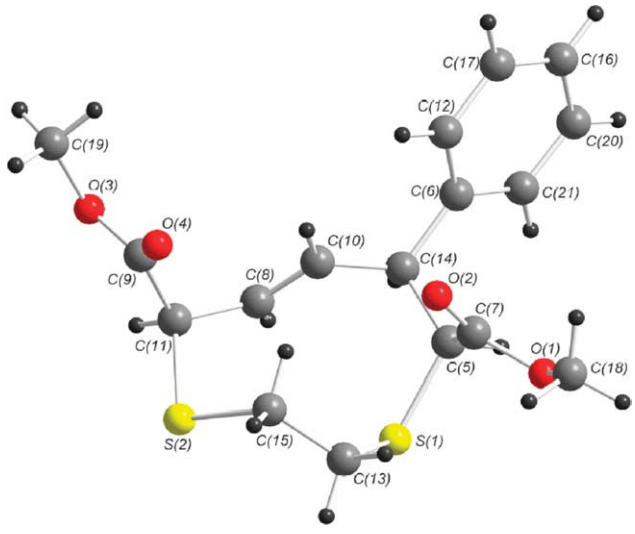


Figure 3. The X-ray crystal structure of compound **24**.

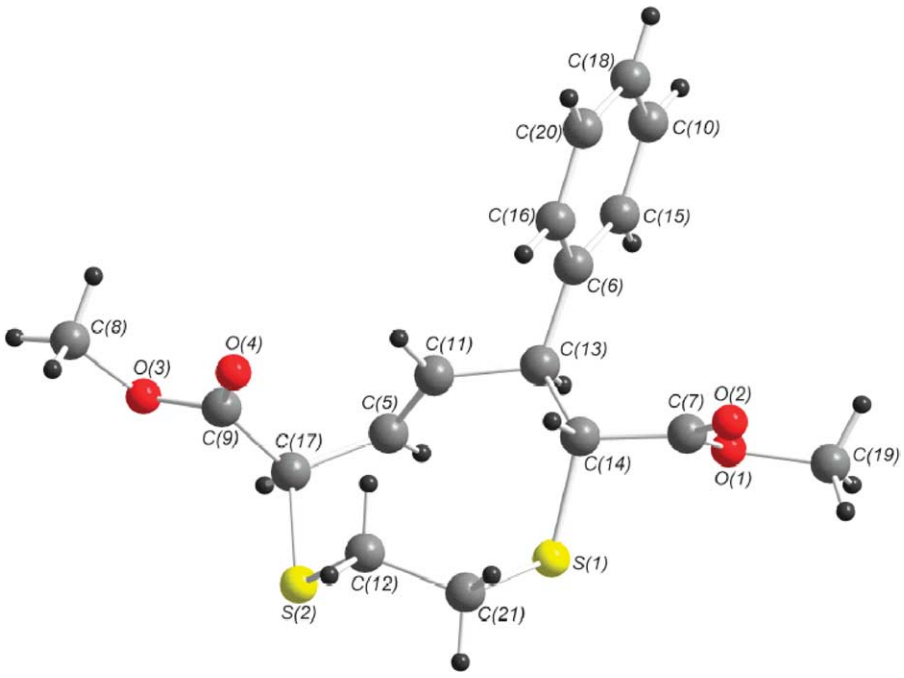
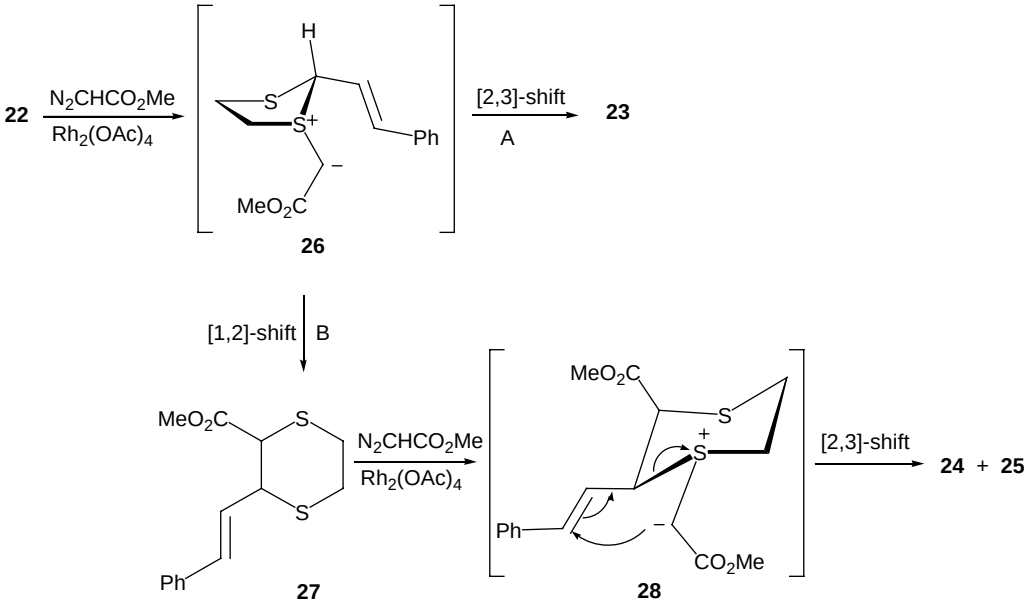


Figure 4. The X-ray crystal structure of compound **25**.

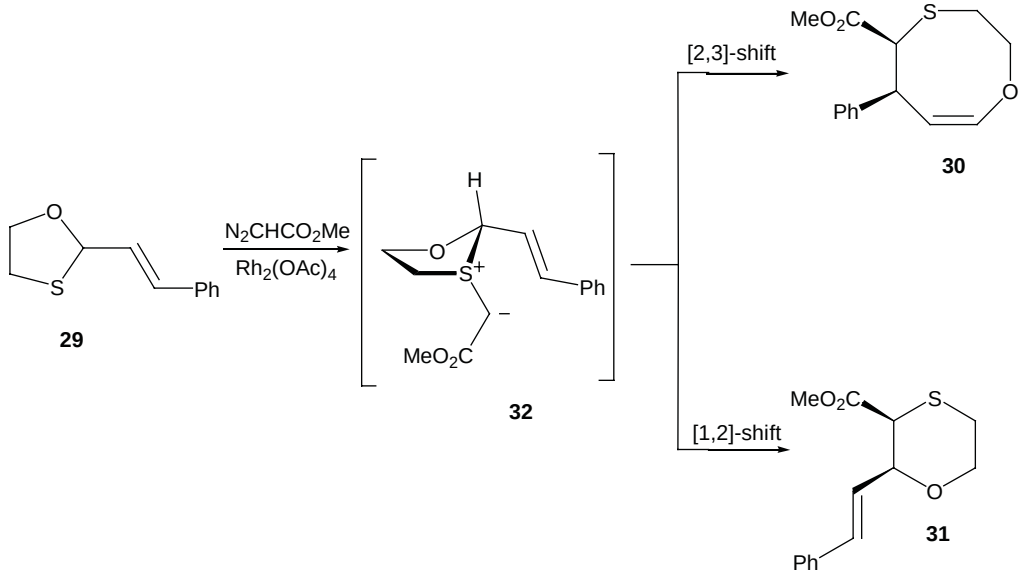
paths: both [2,3]-C–C-sigmatropic rearrangement, with formation of ester **30**, and Stevens rearrangement, with formation of ester **31**.

3. Conclusion

In summary, we have established that ring expansion of 2-substituted 1,3-dithiolanes and 1,3-oxathiolanes may be carried out by treatment with methyl diazoacetate in the presence of $Rh_2(OAc)_4$ in a moderate yield. It has been shown that the initially generated *S*-ylides in the reaction of methoxycarbonylcarbene with these compounds can undergo [1,2]-C–C-shift with the expansion of the five membered rings. *S*-Ylides, which are formed in the reaction of methoxycarbonylcarbene with 2-styryl-1,3-dithiolane and 2-styryl-1,3-oxathiolane undergo [1,2]- and [2,3]-C–C-sigmatropic rearrangement. The *S*-ylides generated from $Rh_2(OAc)_4$ catalyzed reactions of methyl diazoacetate with substituted 1,4-dithianes and 1,4-oxathianes undergo [1,2]-C–C-shift in competition with intramolecular fragmentation.



Scheme 6. A plausible mechanism of formation products **23**–**25**.



Scheme 7.

4. Experimental

4.1. General

Melting points are uncorrected and were determined with a Boetius hot stage. Elemental analyses were performed on a Hewlet–Packard 185B CHN analyzer. IR spectra were recorded on a UR-20 spectrophotometer as a 2% solution in $CHCl_3$. ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX-300 spectrometer (300 and 75 MHz, respectively). Purity checking of products and analysis of reaction mixtures were carried out by TLC on Silufol UV-254 plates. Column chromatography was performed on silica gel 30–70 and 40–100 mesh eluted with hexane/ethyl acetate mixtures. Methyl diazoacetate,[13] 1,3-dithiolane[14] **1**, **5a**,**b**, **17** and 1,3-oxathiolane[15] **10**, **14**, **24** were synthesized according to known procedures.

4.2. Experimental procedures

4.2.1. Methyl *cis*-3-phenyl-1,4-dithiane-2-carboxylate (2), methyl *trans*-3-phenyl-1,4-dithiane-2-carboxylate (3) and (*Z*)-methyl 3-(2-methoxycarbonylmethylsulfanyl-ethylsulfanyl)-3-phenyl-acrylate (4). Methyl diazoacetate (0.24 g, 2.4 mmol) was added with rapid stirring to a mixture of dithiolane **1** (0.4 g, 2.2 mmol) and $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol) in benzene (2 ml) at 80 °C during 2 h. The reaction mixture was stirred at this temperature for 45 min and then cooled. The solvent was distilled off in vacuo. Separation of the reaction mixture on a column with silica gel using a 6:1 hexane/ethyl acetate mixture as the eluent afforded **2** (0.17 g, 31%), **4** (43 mg, 6%) and a fraction, which contained a 1:2 mixture of **2** and **3**.

Compound **2**. Colorless crystals; mp 111–112 °C (recryst. from MeOH); IR ($CHCl_3$) 3040, 1730, 1490, 1450, 1350, 1240, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.68–2.75 (1H, m, CH_2), 3.03–3.09 (1H, m, CH_2), 3.16–3.28 (1H, m, CH_2), 3.49–3.56 (1H, m, CH_2), 3.59 (3H, s, OCH_3), 3.73 (1H, d, J=3.5 Hz, $CHCO_2Me$), 4.57 (1H, d, J=3.5 Hz, *CH*Ph), 7.28–7.34 (5H, m, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (CH_2), 31.0 (CH_2), 44.2 (C-2), 47.6 (C-3), 52.3 (OMe), 128.0, 128.4, 129.0, 140.5 (aromatic), 170.4 (CO). MS (EI): *m*/*z* (%) 254 (35) [M^+], 194 (33), 134 (19), 122 (100), 121 (34), 103 (17), 92 (23). Anal. Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.55. Found: C, 56.61; H, 5.54.

Compound **3**. ^1H NMR (300 MHz, $CDCl_3$) δ 2.89–2.98 (2H, m, CH_2), 3.31–3.39 (2H, m, CH_2), 3.44 (3H, s, OCH_3), 4.19 (1H, d, J=10.2 Hz, $CHCO_2Me$), 4.39 (1H, d, J=10.2 Hz, *CH*Ph), 7.27–7.41 (5H, m, Ar-*H*).

Compound **4**. Pale yellow oil; IR ($CHCl_3$) 3050, 2960, 1730, 1590, 1440, 1350, 1290, 1160, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (2H, t, J=6.3 Hz, SCH_2CH_2-SCH_2), 2.97 (2H, t, J=6.3 Hz, $SCH_2CH_2SCH_2$), 3.20 (2H, s, SCH_2CO_2Me), 3.54 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 5.87 (1H, s, *CH*=C), 7.28–7.36 (5H, m, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5 (CH_2), 32.2 (CH_2), 33.7 (CH_2), 51.5 (OMe), 52.9 (OMe), 111.8 (MeO_2C–*C*H=C), 128.4, 128.7, 129.5, 137.1 (aromatic), 159.1 (CH=*C*-Ph), 164.9 (CO), 170.9 (CO). Anal. Calcd for $C_{15}H_{18}O_4S_2$: C, 55.19; H, 5.56. Found: C, 55.22; H, 5.51.

4.2.2. (*Z*)-3-(2-Carboxymethylsulfanyl-ethylsulfanyl)-3-phenyl-acrylic acid (7). A solution of **4** (40 mg, 0.12 mmol) and KOH (27 mg, 0.48 mmol) in MeOH (1 ml) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. The crystalline precipitate was filtered off, washed with water and air dried to give **7** (31 mg, 87%) as colorless crystals; mp 124–125 °C; IR ($CHCl_3$) 3430, 3050, 2960, 1720, 1620, 1450, 1300, 1190, 1120, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/$(CD_3)_2CO$) δ 2.44 (2H, t, J=6.3 Hz, $SCH_2CH_2SCH_2$), 2.56 (2H, t, J=6.3 Hz, $SCH_2CH_2SCH_2$), 2.77 (2H, s, CH_2CO_2H), 5.38 (1H, s, *CH*=C), 6.77–6.89 (7H, m, Ar-*H*, $2CO_2H$); ^{13}C NMR (75 MHz, $CDCl_3$/$(CD_3)_2CO$) δ 30.6 (CH_2), 31.7 (CH_2), 32.9 (CH_2), 111.5 (MeO_2C–*C*H=C), 127.7, 128.3, 128.7, 137.0 (aromatic), 158.4 (CH=*C*-Ph), 165.2 (CO), 171.2 (CO). Anal. Calcd

for $C_{13}H_{14}O_4S_2$: C, 52.33; H, 4.73. Found: C, 52.33; H, 4.69.

4.2.3. Methyl 3,3-diphenyl-1,4-dithiane-2-carboxylate (9a) and dimethyl (5*R,7*R**)-6,6-diphenyl-1,4-dithiepane-5,7-dicarboxylate (10a).** Methyl diazoacetate (0.17 g, 1.7 mmol) was added under rapid stirring to a mixture of dithiolane **8a** (0.4 g, 1.5 mmol) and rhodium(II) acetate (4.4 mg, 0.01 mmol) in benzene (2 ml) at 80 °C for 2 h. The reaction mixture was stirred at this temperature for 1.5 h and then cooled. After removal of the solvent, the oily residue was purified by column chromatography (6:1 hexane/ethyl acetate) to afford **9a** (0.18 g, 37%) and **10a** (66 mg, 11%).

Compound **9a**. Colorless crystals; mp 142–143 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 1740, 1460, 1420, 1390, 1310, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.60–2.67 (1H, m, CH_2), 2.83–2.88 (2H, m, CH_2), 3.39 (3H, s, OCH_3), 3.50–3.59 (1H, m, CH_2), 4.36 (1H, s, $CHCO_2Me$), 7.19–7.36 (8H, m, Ar-*H*), 7.72 (2H, d, $J=7.2$ Hz, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6 (CH_2), 28.2 (CH_2), 47.1 (C-2), 52.3 (OMe), 54.3 (C-3), 127.4, 127.7, 128.3, 128.4, 128.5, 129.8, 144.0, 144.5 (aromatic), 170.7 (CO). MS (EI): *m*/*z* (%) 330 (69) [M^+], 269 (50), 207 (17), 198 (100), 178 (25), 165 (52), 121 (31), 92 (87). Anal. Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.51; H, 5.47.

Compound **10a**. Colorless crystals; mp 153–155 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 2960, 1730, 1610, 1510, 1440, 1420, 1290, 1170, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.11–3.21 (4H, m, CH_2CH_2), 3.36 (6H, s, $2OCH_3$), 5.24 (2H, s, 2*CH*), 7.23–7.36 (8H, m, Ar-*H*), 7.51 (2H, d, $J=7.1$ Hz, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.0 ($2CH_2$), 52.4 (C-5 and C-7), 58.9 (2OMe), 60.5 (C-6), 127.3, 128.5, 130.6, 139.9 (aromatic), 170.9 (2CO). MS (EI): *m*/*z* (%) 402 (2) [M^+], 238 (98), 237 (36), 207 (59), 179 (45), 178 (41), 165 (20), 105 (100), 92 (25). Anal. Calcd for $C_{21}H_{22}O_4S_2$: C, 62.66; H, 5.51. Found: C, 62.73; H, 5.46.

4.2.4. Methyl spiro[fluorene-9′,2-[1,4]dithiane-2-carboxylate] (9b) and dimethyl spiro[fluorene-9′,6-[1,4]dithiepane-5,7-dicarboxylate] (10b). Methyl diazoacetate (0.23 g, 2.3 mmol) was added with intense stirring to a mixture of dithiolane **8b** (0.5 g, 1.9 mmol) and rhodium(II) acetate (6 mg, 0.014 mmol) in benzene (4 ml) at 80 °C for 2.5 h. The reaction mixture was stirred at this temperature for 2 h and then cooled. After removal of the solvent, the oily residue was purified by column chromatography (6:1 hexane/ethyl acetate) to afford **9b** (0.21 g, 44%) and **10b** (61 mg, 8%).

Compound **9b**. Colorless crystals; mp 131–133 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 1740, 1470, 1450, 1330, 1290, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98–3.03 (1H, m, CH_2), 3.25 (3H, s, OCH_3), 3.30–3.44 (2H, m, CH_2), 3.53–3.62 (1H, m, CH_2), 4.68 (1H, s, *CH*), 7.35–7.48 (4H, m, Ar-*H*), 7.76 (3H, br t, $J=8.0$ Hz, Ar-*H*), 8.51 (1H, d, $J=7.3$ Hz, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5 (CH_2), 30.4 (CH_2), 50.7 (C-3), 52.4 (C-2), 52.6 (OMe), 120.5, 120.6, 124.8, 126.6, 127.6, 127.9, 128.7, 129.4, 139.7, 140.0, 146.6, 148.0 (aromatic), 168.8 (CO). MS (EI): *m*/*z* (%) 328 (54) [M^+], 236 (100), 205 (27), 196 (72), 176 (15), 165 (21), 92 (23). Anal. Calcd for $C_{18}H_{16}O_2S_2$: C, 65.83; H, 4.91. Found: C, 65.78; H, 4.92.

Compound **10b**. Colorless crystals; mp 193–195 °C (recryst. from EtOH); IR ($CHCl_3$) 3050, 2950, 1730, 1600, 1450, 1410, 1300, 1160, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (6H, s, $2OCH_3$), 3.24–3.35 (4H, m, CH_2CH_2), 5.08 (2H, s, 2*CH*), 7.35 (2H, t, $J=6.9$ Hz, Ar-*H*), 7.40 (2H, t, $J=6.9$ Hz, Ar-*H*), 7.63 (2H, d, $J=6.9$ Hz, Ar-*H*), 7.98 (2H, d, $J=6.9$ Hz, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.6 ($2CH_2$), 49.7 (C-5 and C-7), 57.1 (2OMe), 62.8 (C-6), 119.4, 120.2, 124.1, 134.9, 147.5, 149.1 (aromatic), 169.6 (2CO). MS (EI): *m*/*z* (%) 400 (2) [M^+], 236 (100), 205 (37), 178 (17), 165 (23), 105 (24). Anal. Calcd for $C_{21}H_{20}O_4S_2$: C, 62.98; H, 5.03. Found: C, 62.94; H, 5.09.

4.2.5. Methyl *cis*-2-phenyl-1,4-oxathiane-3-carboxylate (14), methyl *trans*-2-phenyl-1,4-oxathiane-3-carboxylate (15) and (*Z*)-methyl 3-(2-methoxycarbonylmethylsulfanyl-ethoxy)-3-phenyl-acrylate (16). Methyl diazoacetate (0.4 g, 4 mmol) was added with intense stirring to a mixture of oxathiolane **13** (0.55 g, 3.3 mmol) and rhodium(II) acetate (5 mg, 0.011 mmol) in benzene (5 ml) at 80 °C during 2 h. The reaction mixture was stirred at this temperature for 1 h and then was cooled. The solvent was distilled off in vacuo. Separation of the reaction mixture on a silica gel column, using a 6:1 hexane/ethyl acetate mixture as the eluent, afforded fractions, which contained a 1:1.8 mixture of **14** and **15** (0.38 g, 48%) and **16** (51.2 mg, 5%). Pure trans-isomer **15** was obtained by means of cooling the mixture of isomers in mixture of liquid nitrogen–isooctane and then filtration and recrystallisation of the crystalline product from methanol.

Compound **14**. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25–2.29 (1H, m, SCH_2), 3.39 (1H, d, $J=3.1$ Hz, S*CH*), 3.50 (3H, s, OCH_3), 3.58–3.68 (1H, m, SCH_2), 3.97–4.05 (1H, m, OCH_2), 4.53–4.57 (1H, m, OCH_2), 4.95 (1H, d, $J=3.1$ Hz, O*CH*), 7.29–7.40 (5H, m, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (C-5), 42.4 (C-3), 52.1 (OMe), 70.1 (C-6), 80.0 (C-2), 125.8, 127.3, 128.3, 140.1 (aromatic), 170.8 (CO). Anal. Calcd for $C_{12}H_{14}O_3S_2$: C, 60.48; H, 5.92. Found: C, 60.47; H, 5.88.

Compound **15**. Colorless crystals; mp 51–52 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 1720, 1450, 1310, 1160, 1090, 1030, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52–2.56 (1H, m, SCH_2), 3.11–3.20 (1H, m, SCH_2), 3.48 (3H, s, OCH_3), 3.85 (1H, d, $J=9.3$ Hz, S*CH*), 3.96–4.03 (1H, m, OCH_2), 4.37–4.41 (1H, m, OCH_2), 4.78 (1H, d, $J=9.3$ Hz, O*CH*), 7.25–7.37 (5H, m, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5 (C-5), 48.9 (C-3), 52.7 (OMe), 69.7 (C-6), 82.6 (C-2), 127.3, 128.9, 129.1, 139.5 (aromatic), 169.8 (CO). MS (EI): *m*/*z* (%) 238 (12) [M^+], 132 (100), 107 (35), 105 (48), 104 (53), 91 (10). Anal. calcd for $C_{12}H_{14}O_3S_2$: C, 60.48; H, 5.92. Found: C, 60.51; H, 5.87.

Compound **16**. Pale yellow oil; IR ($CHCl_3$) 3050, 2970, 1720, 1590, 1450, 1280, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (2H, t, $J=6.3$ Hz, CH_2CH_2S), 3.30 (2H, s, CH_2CO_2Me), 3.59 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 4.15

(2H, t, J=6.3 Hz, OCH_2), 5.27 (1H, s, CH=C), 7.36–7.47 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8 (CH_2), 35.3 (CH_2), 50.6 (OMe), 51.7 (OMe), 58.4 (CH_2), 114.6 (MeO_2C–CH=C), 127.5, 128.1, 128.9, 135.3 (aromatic), 163.6 (CH=C-Ph), 165.7 (CO), 171.2 (CO). Anal. Calcd for $C_{15}H_{18}O_5S_2$: C, 58.05; H, 5.85. Found: C, 57.94; H, 5.92.

4.2.6. Methyl 2,2-diphenyl-1,4-oxathiane-3-carboxylate (20). Methyl diazoacetate (0.5 g, 4.8 mmol) was added with intense stirring to a mixture of oxathiolane **19** (1.0 g, 4 mmol) and rhodium(II) acetate (6 mg, 0.014 mmol) in benzene (5 ml) at 80 °C for 2.5 h. The reaction mixture was stirred at this temperature for 2 h and then cooled. The crystalline precipitate was filtered off, washed with hexane and recrystallised from ethanol to afford pure **20** (0.71 g, 51%) as colorless crystals; mp 169–170 °C; IR ($CHCl_3$) 3050, 1730, 1510, 1480, 1340, 1250, 1170, 1080, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14–2.18 (1H, m, SCH_2), 3.38 (3H, s, OCH_3), 3.65–3.73 (1H, m, SCH_2), 3.86–3.94 (1H, m, OCH_2), 4.14–4.20 (1H, m, OCH_2), 4.21 (1H, s, SCH), 7.16–7.49 (10H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 (C-5), 42.5 (C-3), 52.2 (OMe), 62.6 (C-6), 78.1 (C-2), 126.1, 127.3, 127.8, 128.2, 128.3, 128.4, 128.9, 141.9, 145.3 (aromatic), 170.9 (CO). MS (EI): m/z (%) 314 (8) [M^+], 183 (49), 132 (100), 105 (86), 104 (27). Anal. Calcd for $C_{18}H_{18}O_3S_2$: C, 68.77; H, 5.77. Found: C, 68.70; H, 5.74.

4.2.7. Methyl (5R^*,6R^*)-6-phenyl-2,3,5,6-tetrahydro-1,4-dithiocine-5-carboxylate (23), dimethyl (5R^*,6R^*,9S^*)-6-phenyl-2,3,6,9-tetrahydro-5H-1,4-dithionine-5,9-dicarboxylate (24), dimethyl (5R^*,6S^*,9R^*)-6-phenyl-2,3,6,9-tetrahydro-5H-1,4-dithionine-5,9-dicarboxylate (25). Methyl diazoacetate (0.45 g, 4.5 mmol) was added with intense stirring to a mixture of dithiolane **22** (0.63 g, 3 mmol) and rhodium(II) acetate (6 mg, 0.015 mmol) in benzene (6 ml) at 80 °C over the period of 2 h. The reaction mixture was stirred at this temperature for a further 1 h and then cooled. The solvent was distilled in vacuo. Separation of the reaction mixture on a silica gel column, using a 7:1 hexane/ethyl acetate mixture as the eluent, afforded **23** (0.29 g, 34%), **24** (74 mg, 7%) and **25** (32 mg, 3%).

Compound **23**. Colorless crystals; mp 82–83 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 1730, 1520, 1490, 1460, 1250, 1210, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63–2.76 (1H, m, CH_2), 2.91–2.97 (1H, m, CH_2), 3.27–3.35 (2H, m, CH_2), 3.71 (3H, s, OCH_3), 3.76 (1H, d, J=2.2 Hz, S$CH$$CO_2$Me), 5.05 (1H, dd, J=8.7, 2.2 Hz, CHPh), 6.26 (1H, d, J=8.7 Hz, SCH=CH), 7.01 (1H, t, J=8.7 Hz, SCH=CH), 7.23–7.36 (5H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4 (C-3), 39.9 (C-2), 49.7 (C-6), 50.2 (C-5), 52.6 (OMe), 119.4 (S–CH=CH), 127.7, 127.8, 129.5, 142.0 (aromatic), 149.2 (S–CH=CH), 171.7 (CO). MS (EI): m/z (%) 280 (25) [M^+], 220 (34), 219 (58), 187 (75), 161 (18), 147 (100), 128 (15), 115 (20), 92 (11). Anal. Calcd for $C_{14}H_{16}O_2S_2$: C, 59.97; H, 5.75. Found: C, 59.88; H, 5.81.

Compound **24**. Colorless crystals; mp 125–126.5 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 2960, 1730, 1610, 1440, 1350, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38–2.50 (1H, m, CH_2), 2.92–3.23 (2H, m, CH_2), 3.26–3.36 (1H, m, CH_2), 3.57–3.64 (4H, m, OCH_3 and SCHCHPh), 3.77 (3H, s, OCH_3), 4.12–4.21 (2H, CHPh and SCHCH=CH), 6.14 (1H, dd, J=16.0, 6.5 Hz, SCHCH=CH), 6.65 (1H, br s, SCHCH=CH), 7.25–7.34 (5H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1 (C-3), 32.6 (C-2), 48.4 (C-6), 50.3 (C-5), 51.4 (C-9), 52.2 (OMe), 52.7 (OMe), 120.3 (Ph-CH–CH=CH), 124.4 (Ph-CH–CH=CH), 125.8, 127.9, 128.7, 140.6 (aromatic), 169.1 (CO), 171.9 (CO). Anal. Calcd for $C_{17}H_{20}O_4S_2$: C, 57.93; H, 5.72. Found: C, 58.01; H, 5.84.

Compound **25**. Colorless crystals; mp 170–171.5 °C (recryst. from MeOH); IR ($CHCl_3$) 3050, 2970, 1730, 1600, 1440, 1350, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39–2.51 (1H, m, CH_2), 2.99–3.31 (4H, CH_2 and SCHCHPh), 3.46–3.52 (4H, m, OCH_3 and CHPh), 3.70 (3H, s, OCH_3), 4.15 (1H, d, J=5.8 Hz, SCHCH=CH), 5.95 (1H, dd, J=16.1, 10.2 Hz, SCHCH=CH), 6.25 (1H, dd, J=16.1, 5.8 Hz, SCHCH=CH), 7.24–7.33 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (C-3), 31.5 (C-2), 47.8 (C-6), 50.9 (C-5), 51.2 (C-9), 51.8 (OMe), 52.5 (OMe), 118.6 (Ph-CH–CH=CH), 123.7 (Ph-CH–CH=CH), 126.7, 128.9, 129.4, 141.5 (aromatic), 168.8 (CO), 172.6 (CO). Anal. Calcd for $C_{17}H_{20}O_4S_2$: C, 57.93; H, 5.72. Found: C, 58.89; H, 5.77.

4.2.8. Methyl (5R^*,6R^*)-6-phenyl-2,3,5,6-tetrahydro-1,4-oxathiocine-5-carboxylate (30) and methyl *cis*-2-styryl-1,4-oxathiane-3-carboxylate (31). Methyl diazoacetate (0.22 g, 2.2 mmol) was added with intense stirring to a mixture of oxathiolane **29** (0.35 g, 1.8 mmol) and rhodium-(II) acetate (4 mg, 0.01 mmol) in benzene (4 ml) at 80 °C for 1.5 h. The reaction mixture was stirred at this temperature for 1.5 h and then cooled. After removal of the solvent, the oily residue was purified by column chromatography (8:1 hexane/ethyl acetate) to afford **30** (62 mg, 13%) and **31** (0.11 g, 24%).

Compound **30**. Pale yellow oil; IR ($CHCl_3$) 3050, 2940, 1730, 1610, 1510, 1480, 1360, 1180, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52–2.57 (1H, m, SCH_2), 3.53–3.60 (1H, m, SCH_2), 3.66 (3H, s, OCH_3), 3.67 (1H, d, J=2.3 Hz, SCH), 3.99–4.09 (2H, m, OCH_2), 4.55 (1H, dd, J=4.9, 2.3 Hz, CHPh), 5.65 (1H, dd, J=5.8, 4.9 Hz, O–CH=CH–), 6.19 (1H, d, J=5.8 Hz, O–CH=CH–), 7.23–7.35 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8 (C-3), 39.5 (C-5), 45.7 (C-6), 51.7 (OMe), 66.8 (C-2), 96.4 (CH=CH–O), 124.3, 128.5, 129.9, 136.5 (aromatic), 141.6 (CH=CH–O), 171.2 (CO). Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. Found: C, 63.70; H, 6.03.

Compound **31**. Pale yellow oil; IR ($CHCl_3$) 3050, 1730, 1510, 1480, 1360, 1320, 1160, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (1H, dt, J=11.6, 2.3 Hz, SCH_2), 3.32 (1H, d, J=2.3 Hz, SCH), 3.39–3.50 (1H, m, SCH_2), 3.72 (3H, s, OCH_3), 3.92 (1H, dt, J=11.6, 2.3 Hz, OCH_2), 4.44 (1H, dt, J=11.6, 2.3 Hz, OCH_2), 4.57 (1H, ddd, J=6.2, 2.3, 1.5 Hz, OCH–CH=CH-Ph), 6.22 (1H, dd, J=16.2, 6.2 Hz, –CH=CH-Ph), 6.70 (1H, dd, J=16.2, 1.5 Hz, –CH=CH-Ph), 7.26–7.40 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0 (C-5), 41.8 (C-3), 52.5 (OMe), 69.0 (C-6), 78.2 (C-2), 127.0 (Ph-CH=CH), 127.1 (aromatic), 128.4 (Ph-CH=CH), 129.0, 132.3, 136.8

(aromatic), 170.9 (CO). Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. Found: C, 63.67; H, 6.14.

4.3. X-ray diffraction study

Crystallographic data for the structures **2**, **10a**, **24** and **25** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 269652 (**2**), CCDC 268293 (**10a**), CCDC 270097 (**24**) and CCDC 270098 (**25**). Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).

References and notes

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Homohelicity induction of propylene-linked zinc bilinone dimers by complexation with chiral amine and α-amino esters. Preorganization of structurally coupled homohelical subunits

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Abstract—Homohelicity induction of a series of propylene-linked zinc bilinone (ZnBL; linear tetrapyrrople-zinc(II) complex) dimers upon complexation with chiral amine and α-amino esters was investigated. Introduction of substituents such as dimethyl and diisobutyl to the central carbon of the propylene spacer gave rise to stabilization of the homohelical (*PP* and *MM*) conformers rather than the heterohelical (*PM*) conformer. As bulkiness of the substituent increased, stability of the homohelical conformers was raised. The preorganization of the homohelical structures led to significantly amplified homohelicity induction upon complexation with chiral amine and α-amino esters.

1. Introduction

Construction of multitopic receptors possessing structurally coupled subunits is a key matter to obtain amplified functions induced by chemical stimuli. In biological systems, allosteric proteins enhance or suppress their activities via cooperative motion of coupled subunits.[1] Hemoglobin, which consists of four subunits, is one of typical examples, where the first binding of an O_2 molecule to one of four subunits gives rise to its conformational change to induce the increasing O_2-affinity of the other subunits.[2] In artificial systems, a set of cooperatively operating guest-binding subunits is one of good candidates for construction of signal transmission/amplification systems for external stimuli, and therefore, is potentially applicable to molecular sensory systems and other signal transmitting devices.[3] Great efforts have so far been poured to investigation of allosteric host molecules possessing structurally coupled heterotopic and homotopic binding-sites.[4,5] However, few examples of host molecules that amplify structural information of chiral guests to provide integrated spectroscopic signals have been reported.[6–9] In order to develop a signal transmission/amplification system for chiral molecules, here we report homohelicity induction of zinc bilinone (ZnBL) dimers triggered by complexation with chiral amine and α-amino esters.

As shown in Figure 1, ZnBL is a linear tetrapyrrole zinc(II) complex and possesses a helical structure due to steric

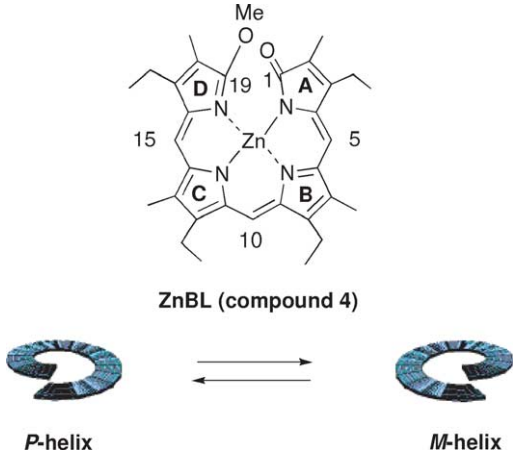

Figure 1. The helical structure and equilibria of zinc bilinone (ZnBL, compound **4**). The labels of A–D represent the custom naming for pyrrole rings.

Keywords: Zinc bilinone; Substituent effect; Homohelicity induction; Preorganization.
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repulsion between 1- and 19-oxygen atoms as well as a template effect of the central zinc ion. The helix inversion between the right-handed (*P*) and left-handed (*M*) helical conformers easily occurs due to the low energetic barrier. We previously reported that coordination of a chiral amine or a chiral α-amino ester to the zinc center induced preferred helicity of ZnBL (e.g., the compound **4** in Fig. 1).[10] Especially, the induced helicity showed good correspondence with chirality of the amino esters; *P*-helix for D-amino esters and *M*-helix for the L-isomers. The helicity excess (h.e.), that is, the diastereomeric excess of the ZnBL–guest complex with preferred helicity, depended on the structures of the chiral guests. The helicity induction process was conveniently monitored by ^{1}H NMR as well as circular dichroism (CD) spectroscopy.

In the case of ZnBL dimers, equilibria among the *PP*-, *PM*-, and *MM*-conformers exist as shown in Figure 2. If the two ZnBL subunits do not affect each other, each ZnBL subunit should behave just as a monomer upon complexation with a chiral guest. On the other hand, structural perturbation by steric interaction between the ZnBL subunits should break the statistical balance of the equilibria among three conformers, and the thermodynamically preferred conformer should be predominantly formed. Indeed, in the ethylene-linked ZnBL dimer previously reported, homohelicity induction efficiently occurred upon complexation with chiral α-amino esters, and the complexation-induced CD signal normalized by a molar concentration of the ZnBL subunit was enhanced compared with that in the ZnBL monomer.[8] On the other hand, the propylene-linked ZnBL dimer exhibited negative cooperativity, that is, heterohelicity enrichment, upon complexation with the chiral guests, indicating that the increase in flexibility of the spacer is unfavorable for cooperative motion of the ZnBL subunits.

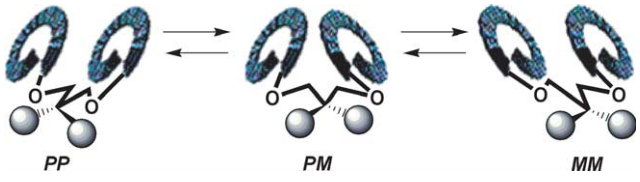


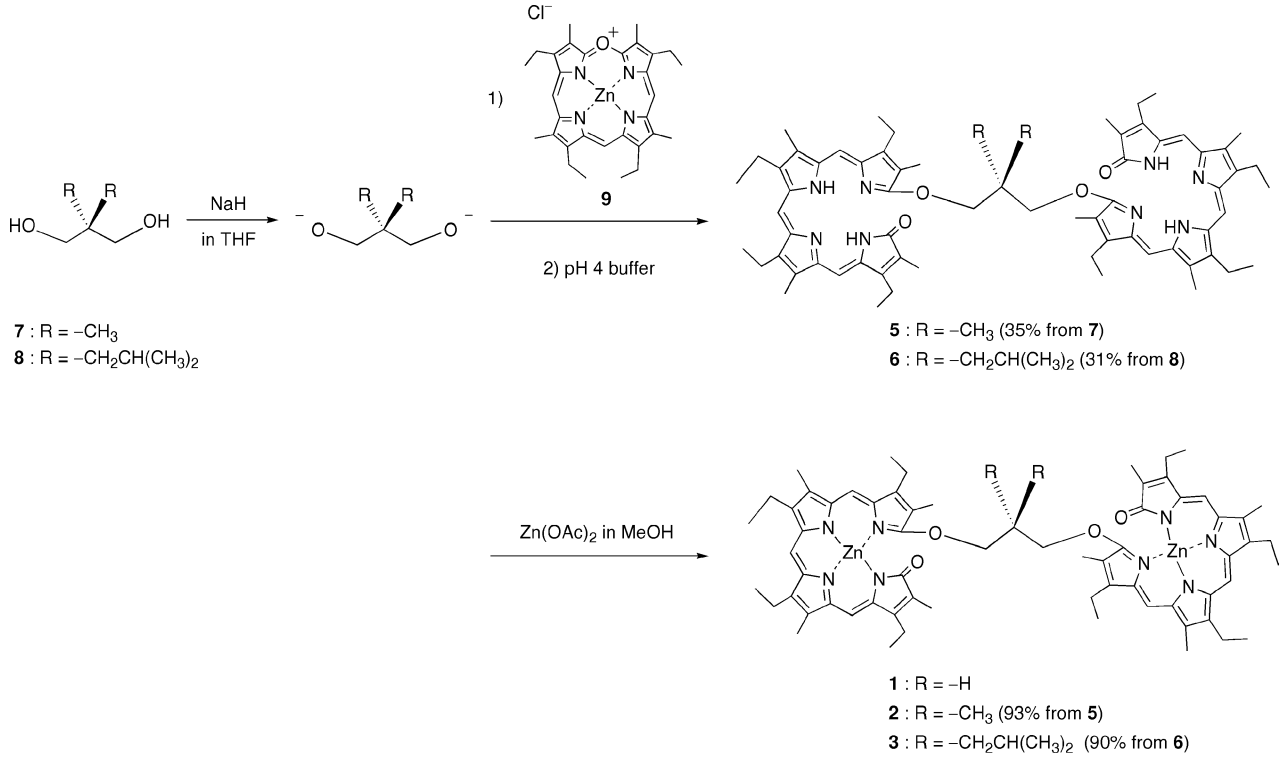
Figure 2. Illustration of equilibria in the ZnBL dimer system. Here the propylene-linked dimer is illustrated.

In the present study, we show preorganization of the *PP* and *MM* homohelicity conformers of the propylene-linked ZnBL dimer, where introduction of bulky substituents onto the central carbon of the spacer leads to stabilization of the homohelical (*PP* and *MM*) conformers rather than the heterohelical one (*PM*). We also report that the preorganization of the homohelical conformers leads to significantly enhanced homohelicity induction upon complexation with the chiral guests.

2. Results and discussion

2.1. Preparation of the propylene-linked ZnBL dimers

ZnBL dimers **1**–**3** were employed in this study. In **1**, two ZnBL moieties are linked by a propylene spacer. On the other hand, in **2** and **3**, dimethyl and diisobutyl substituents are introduced onto the central carbon atom in the propylene spacer, respectively. Preparation of **1** was reported previously.[8] Preparation of the dimers **2** and **3** was carried out in a modified way of preparation of **1**, as shown in Scheme 1. The ring-opening reaction of 2 equiv of



Scheme 1. Synthesis of ZnBL dimers.

(5-oxoniaporphyrinato)zinc(II) chloride **9** with 1 equiv of the dialkoxides of **7** and **8** followed by treatment with a buffer solution (pH 4) yielded the free-base bilinone dimers **5** and **6** in 35 and 31% yields, respectively.[11,12] Insertion of zinc(II) ions to **5** and **6** afforded the ZnBL dimers **2** and **3** in 93 and 90% yields, respectively. The ZnBL dimers were so sensitive to usual ways of purification such as silica or alumina column chromatography and recrystallization in a hot solvent as to give rise to demetallation of zinc(II) ions. Thus, the corresponding free-base bilinone dimers were thoroughly purified by silica gel column chromatography followed by gel permeation chromatography and reprecipitation, and then the ZnBL dimers were obtained just by zinc insertion to the free-base dimers. These dimers were characterized by ^{1}H NMR, IR and FAB MS spectra as well as elemental analyses. The assignment of the ^{1}H NMR signals of **2** and **3** was achieved using ROESY and HMBC techniques.

2.2. Stabilization of the homohelical conformers by introduction of bulky substituents on the spacer

In Figure 3 are shown the expanded region of the ^{1}H NMR spectra of **1**–**3** in $CDCl_3$ at 223 K. For each dimer, two sets of signals were observed with different integral ratios, which were assigned to the homohelical (*PP* and *MM*) and heterohelical (*PM*) conformers. As discussed later, the three conformers are distinguishable from one another upon complexation with chiral guests. In the complexed homohelical conformers ($PP\cdot 2G^*$ and $MM\cdot 2G^*$; G^*, chiral guest), two ZnBL subunits are magnetically equivalent. In addition, the $PP\cdot 2G^*$ and $MM\cdot 2G^*$ complexes are diasteromeric to each other, and their ^{1}H signals are observed independently with different integral ratios. On the other hand, in the complexed heterohelical conformer ($PM\cdot 2G^*$), the two subunits are magnetically unequivalent. Thus, the distribution of the three conformers can be determined. The ratio of *PP*:*PM*:*MM* for **1** was 22:56:22, showing approximation to statistical distribution (25:50:25). This indicated that two ZnBL subunits were likely to behave independently. On the other hand, the ratios of *PP*:*PM*:*MM* for **2** and **3** are 33:35:33 and 46:8:46, respectively. Obviously, the increase in steric hindrance on the spacer led to stabilization of the homohelical conformers. Therefore, the bulkiness of the substituents on the propylene spacer plays an essential role in positive cooperativity of formation of the homohelical conformers.

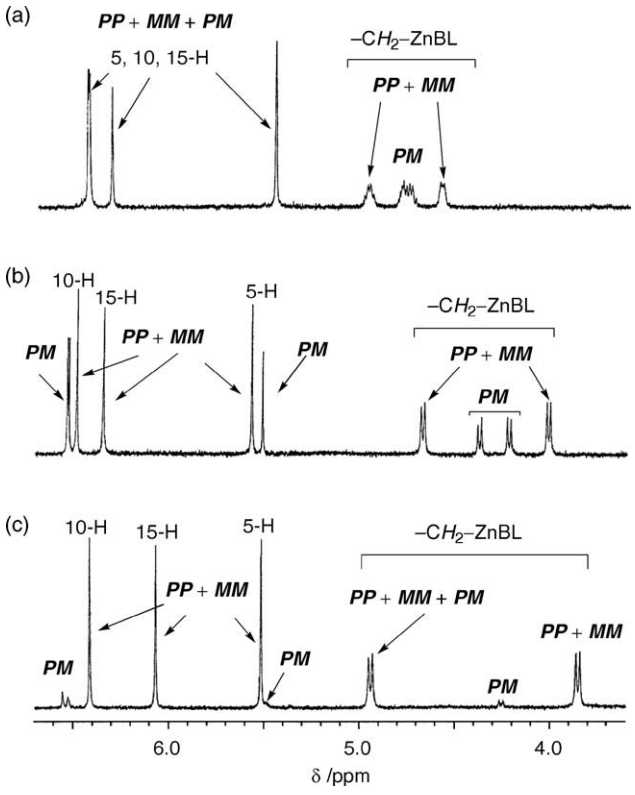


Figure 3. The expanded region of the ^{1}H NMR spectra of (a) **1**, (b) **2**, and (c) **3** in $CDCl_3$ at 223 K. The concentration of each dimer is 1.07–1.09 mM.

Interesting is that the cooperativity was enhanced by complexation of an achiral amine with each ZnBL subunit in the dimers. Upon addition of increasing amounts of benzylamine to solutions of **1**–**3**, all signals exhibited chemical shift changes accompanied by saturation behaviors (Fig. 4), and finally, the ratios of *PP*:*PM*:*MM* for **1**, **2** and **3** reached 15:70:15, 39:22:39 and 49:2:49, respectively. Upon complexation with benzylamine, the formation of the heterohelical conformer was facilitated in **1**, whereas the homohelical conformers were enriched in **2** and **3**. That is, coordination of the ligand to each zinc center enhanced the cooperativity between the two ZnBL subunits.

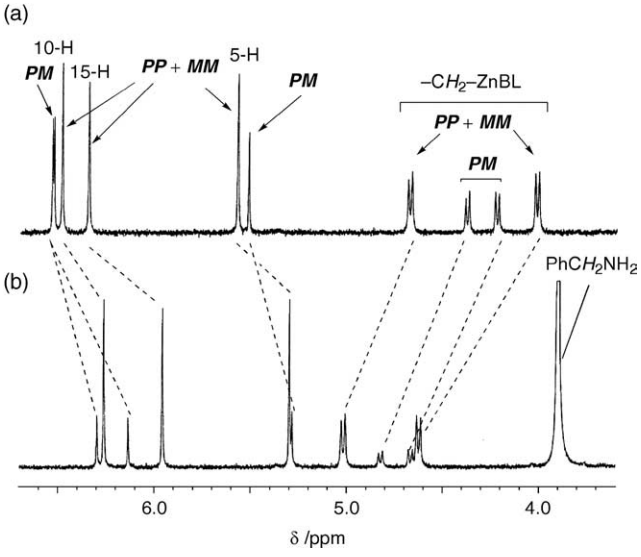


Figure 4. The expanded region of the ^{1}H NMR spectra of **2** in $CDCl_3$ at 223 K; (a) **2** (1.09 mM), (b) **2** (1.09 mM) and benzylamine (6.53 mM).

2.3. Molecular modeling study on stability of the homohelical conformers

Molecular modeling studies based on molecular mechanics and molecular orbital calculations afford valuable information on the geometries and energetics of supramolecules.[13] Most of the molecular orbital studies, however, are concerned with hydrogen bonding,[14–15] and less attention has been paid to the non-polar interactions such as attractive van der Waals forces. This is due to the fact that much more elaborate calculations, for instance the MP2 theory, are

needed to evaluate London's dispersion forces, and such calculations are limited to small molecular systems, such as a N_2–CO_2 complex[16] and a fucose–benzene complex.[17] We performed semi-empirical calculations of our ZnBL dimers in order to evaluate the importance of steric repulsive forces in the conformational equilibria. In the previous study, an important role of steric bulk of the guest molecules was revealed in binding energetics to zinc porphyrins.[18]

In order to obtain structural details about stability of the homohelical conformers, molecular modeling studies using grid search calculations were examined for the *PP* conformers of **1**–**3**. Particular attention was paid to the role of the steric bulk introduced to the spacer in the restriction of conformation of the dimers. As shown in Figure 5a, the bond rotation around O19–C1 defined by the dihedral angle θ of the C1–C2 and O19–C19 bonds were examined, where θ_0 represents the value of θ of the initial structure.[19] The grid search calculations were carried out for the 12 angles at 30° intervals, and the geometry was fully optimized except for θ by molecular orbital calculations at the MOPAC PM3 level.[20] In Figure 5b are shown plots of the changes in the enthalpy of formation ΔH_{PP} for **1**–**3** against the angle $\theta-\theta_0$. Obviously, no significant differences in ΔH_{PP} at any $\theta-\theta_0$ were observed in **1**. On the other hand, introduction of dimethyl or diisobutyl groups to the spacer brought about restriction of the preferred $\theta-\theta_0$ affording stable conformers, and the tendency was more remarkable in **3** than in **2**.

Comparison of the conformational energies of homohelical conformers of **1**–**3** with those of the heterohelical conformers indicated that the steric bulkiness restricted the conformations of both homohelical and heterohelical isomers (Fig. 5b and c). The restriction of conformations can be the prerequisite for the cooperative helicity induction, since the interactions between the two ZnBL units occurs with defined relative orientations of two helices. The more favorable conformational energy of homohelical **3** than heterohelical **3** cannot be reproduced by the modeling studies since the origin of the energy difference could be dispersion forces and more elaborate calculations such as those with the MP2 theory may be needed.

More detailed molecular modeling was carried out for **3**. The grid search for two bond rotations around O19–C1 and

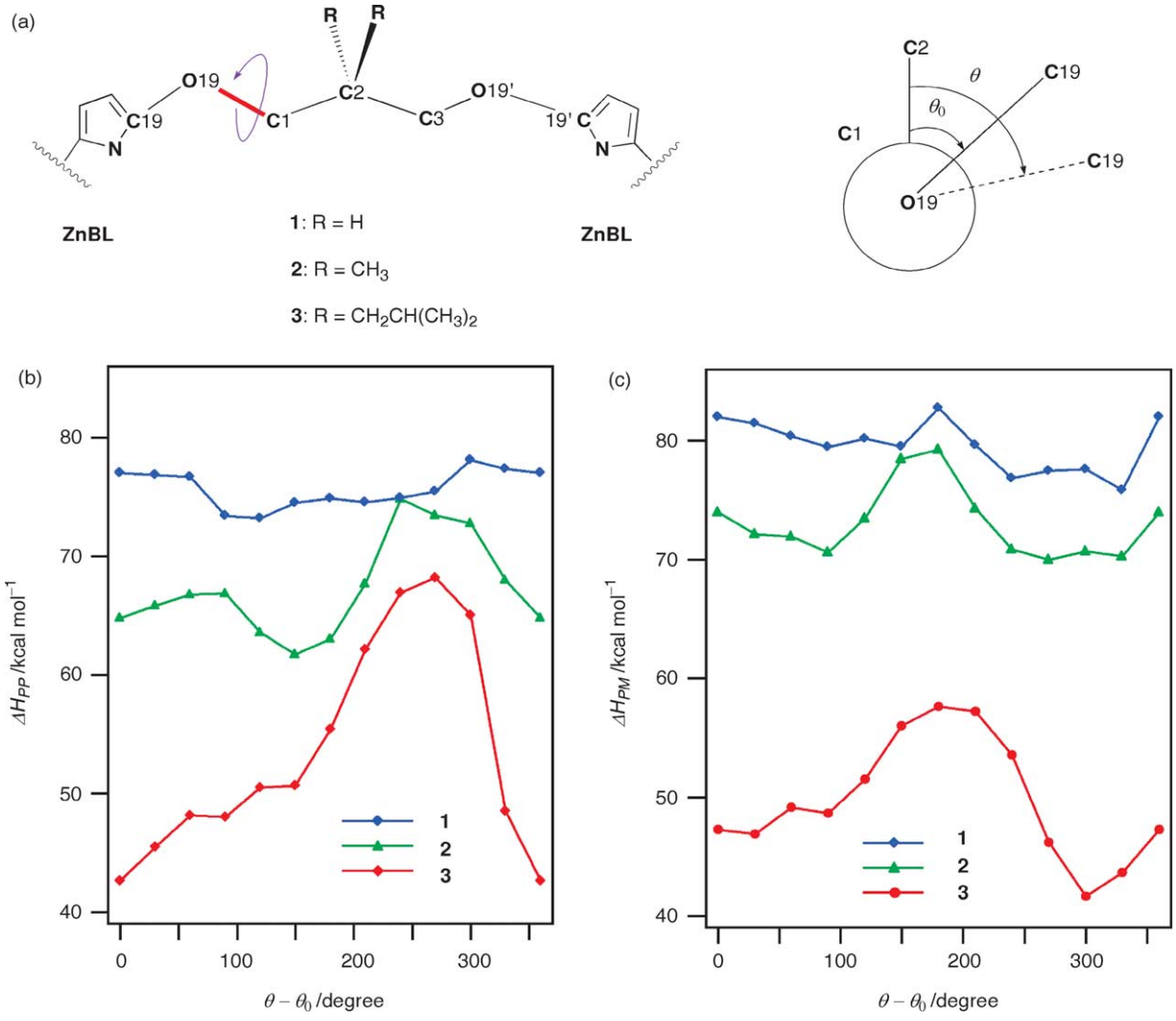


Figure 5. (a) A conceptual representation of the grid search for the ZnBL dimers, (b) potential energies of homohelical (*PP*) conformers and (c) those of heterohelical (*PM*) conformers of **1**–**3** obtained by the grid search calculations (MOPAC PM3).

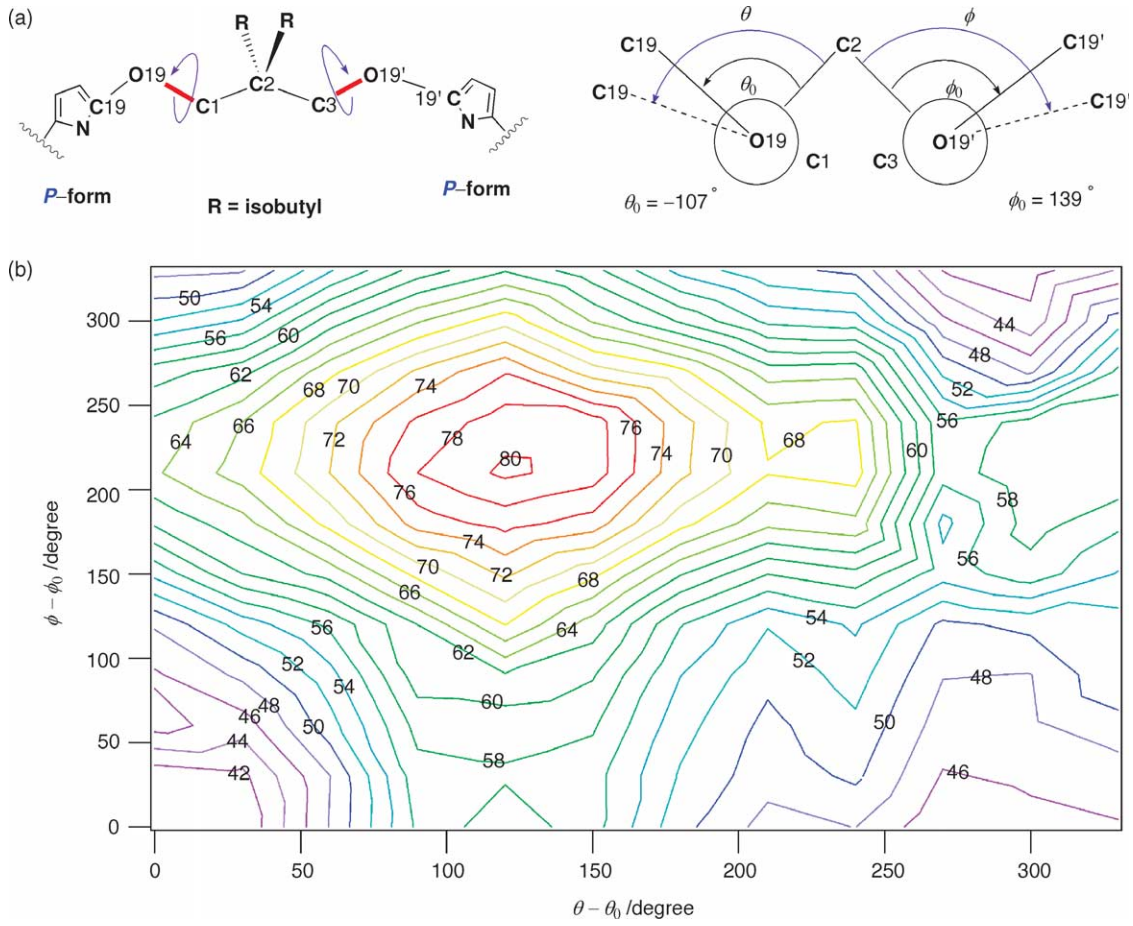


Figure 6. (a) A definition of two degrees of rotation, (b) the contour map of ΔH_{PP} (kcal/mol) for ZnBL dimer **3** as a function of dihedral angles $\theta-\theta_0$ and $\phi-\phi_0$.

C3–O19′ represented by $\theta-\theta_0$ and $\phi-\phi_0$, respectively, was examined as shown in Figure 6a. The conformational optimization for the *PP* form was performed using the MOPAC PM3 method for 144 pairs of $\theta-\theta_0$ and $\phi-\phi_0$ at 30° intervals. The contour map for ΔH_{PP} is shown in Figure 6b, where the contour lines are drawn at 2 kcal/mol intervals. Two most stable conformers were obtained in two sets of ($\theta-\theta_0$, $\phi-\phi_0$): (0, 0) and (300, 330) yielded $\Delta H_{PP}=39.00$ kcal/mol (structure in Fig. 7a) and 41.19 kcal/mol (structure in Fig. 7b), respectively. In both of the structures, proximity between the 18-methyl group in one ZnBL subunit and the A-ring in the other ZnBL was found, indicating that van der Waals interaction between the two ZnBL subunits contributed to the stabilization of the homohelical conformers.

In ^{1}H NMR spectra, upfield shifts of the 18-Me signals of the ZnBL subunits in the homohelical conformers of **2** and **3** were observed in comparison with the 18-Me signal of the monomer **4** (Fig. 8, $\Delta\delta$; −0.185 and −0.365 ppm for **2** and

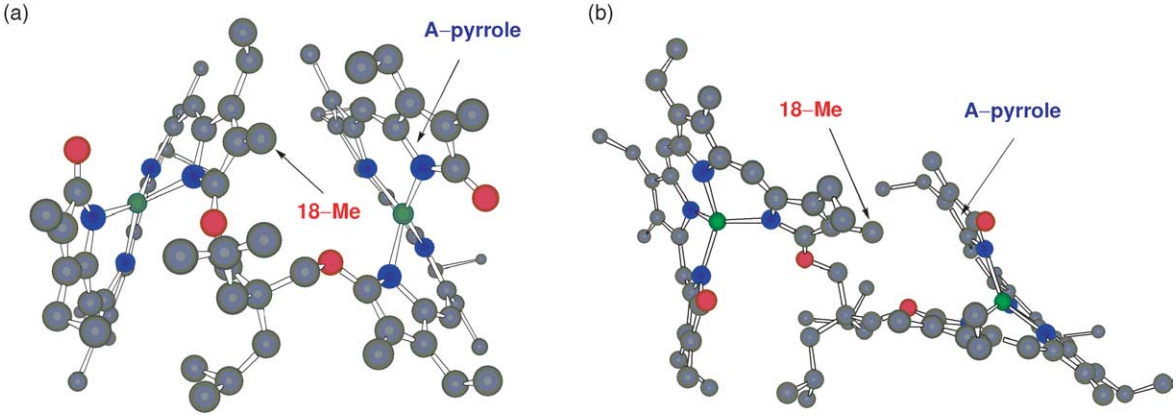


Figure 7. The most stable homohelical structures for **3** obtained from the contour map in Figure 6b. Hydrogen atoms are omitted for clarify; (a) ($\theta-\theta_0$, $\phi-\phi_0$)=(0, 0), (b) ($\theta-\theta_0$, $\phi-\phi_0$)=(300, 330).

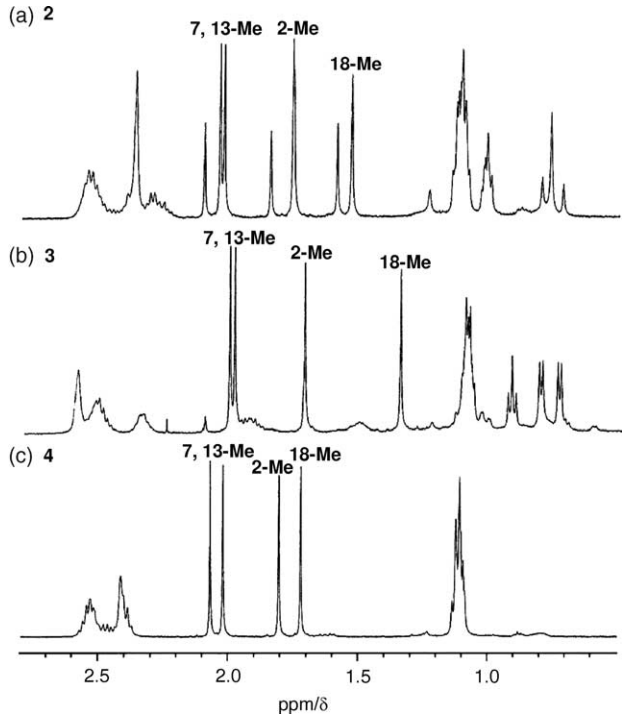


Figure 8. The expanded region of ^{1}H NMR spectra of (a) **2** (1.09 mM), (b) **3** (1.09 mM), and (c) **4** (2.17 mM). These spectra were obtained in $CDCl_3$ at 223 K. The 2-, 7-, 13-, and 18-methyls of the homohelical conformers are noted in the spectra.

3, respectively) showing that the 18-methyl groups in the homohelical conformers of **2** and **3** were magnetically affected by the ZnBL's π-conjugation system. That is, the upfield shifts of the 18-Me signals in the homohelical conformers agreed with the proximity of the 18-Me to the A-pyrrole ring of the neighboring subunit. According to the modeling study, the shortest distances between the 18-methyl hydrogen (18-H) and the A-ring pyrrole carbon (2-C or 4-C) in the homohelical conformer of **3** were 3.54 Å (18-H–4-C in the most stable conformer) and 3.37 Å (18-H–2-C in the next most stable conformer), while those in the heterohelical conformer were 4.51 Å (18-H–4-C in the most stable conformer) and 7.45 Å (18-H–2-C in the next most stable conformer). Thus, the homohelical conformer takes a folded conformation, where the methyl group is in van der Waals contact with the pyrrole ring. The NMR and modeling study revealed that introduction of the bulky substituents on the spacer should lead to conformational restriction in **2** and **3** to facilitate effective interactions between the ZnBL subunits stabilizing the homohelical structures.[21] The upfield shift was more remarkable in **3** than in **2**, and thus, the inter-subunit interaction stabilizing the homohelical structures should be more effective in **3**.

2.4. Homohelicity induction in ZnBL dimers upon complexation with chiral guests

Homohelicity induction in **1**–**3** upon complexation with chiral amine and α-amino esters was examined using CD spectroscopy. As reported previously,[10] complexation of chiral amines and α-amino esters to ZnBL gives rise to generation of alternative Cotton effects in the high (ca. 400 nm) and low energy (ca. 800 nm) regions, and the CD intensity in the high energy region is linearly proportional to the helicity excess (h.e.) of ZnBL. In the case of ZnBL dimer systems, h.e. is represented by Eq. 1

$$\text{h.e. } (\%) = \frac{[MM]-[PP]}{[MM]+[PP]+[PM]} \times 100 \qquad (1)$$

where [*PP*], [*MM*], and [*PM*] are concentrations of *PP*, *MM*, and *PM* conformers, respectively. According to this equation, the high h.e. value in the ZnBL dimer–guest complex system refers to effective homohelicity induction, and thus, the CD intensity induced by complexation with chiral guests is a good index for homohelicity induction. In Fig. 9 are shown CD spectra in the high-energy region for the ZnBL dimers **1**–**3** and the monomer **4** in $CHCl_3$ at 223 K in the presence of (*R*)-1-(1-naphthyl)ethylamine ((*R*)-NEA). The values of Δε were normalized by a molar concentration of the ZnBL subunit. To achieve complexation of the amine to each ZnBL subunit, addition of an excess amount of the guest as well as low-temperature experiments were required. Although a positive sign indicating *M*-helicity induction[10,22] was observed for each dimer, the intensity varied in the spacer: compared to the monomer **4**, the dimers **2** and **3** showed larger CD intensities, indicating that the cooperative motion to adopt *MM* homohelicity was allowed between the ZnBL subunits. On the other hand, the dimer **1** exhibited less effective CD induction, indicating negative cooperativity of the ZnBL subunits in homohelicity induction. The CD data obtained for a series of chiral guests are summarized in Table 1. For each guest, the predominant helicity of ZnBL in **1**–**3** induced by the complexation was the same as that in **4**, and the CD intensity increased in the order of **1**<**4**<**2**<**3**. Thus, the preorganization of the *PP* and *MM* homohelical conformers plays a substantial role in helicity–helicity synchronization of the ZnBL subunits triggered by point chirality–helicity interaction between the ZnBL subunit and the chiral guest. As discussed above, the preorganization effect was more remarkable in **3** than in **2**, and the large cooperativity in homohelicity induction should owe to the inter-subunit interactions optimized by the preorganization.

^{1}H NMR experiments afforded further information about the complexation-induced homohelicity induction: the quantitative analyses were allowed by analyzing magnetically distinguishable ^{1}H NMR signals of the *PP*, *MM* and *PM*

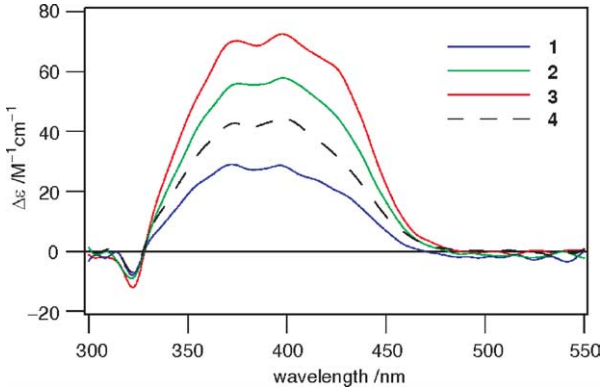


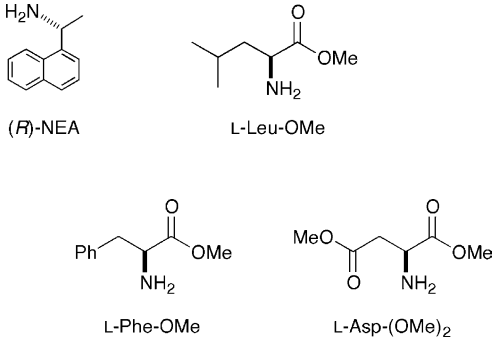
Figure 9. CD spectra in the high-energy region for **1**–**4** in the presence of (*R*)-NEA in $CHCl_3$ at 223 K: [ZnBL subunit]=40.4–43.1 μM, [(*R*)-NEA]=0.0530–0.0544 M.

Table 1. The differential dichroic absorption ($\Delta\varepsilon$)[a] and helicity excesses (h.e.s)[b] for the complexes of **1**–**4** with chiral amine and α-amino esters

Compound	$\Delta\varepsilon$ (M^{-1} cm^{-1}) (λ (nm), helicity[c]), h.e. (%)				
	(*R*)-NEA[d]	L-Leu-OMe[d]	D-PhGly-OMe[d]	L-Phe-OMe[d]	L-Asp-$(OMe)_2$[d]
1	26.6 (397, *M*), 34	33.2 (402, *M*), 40	−36.3 (399, *P*), 34	47.9 (398, *M*), 46	60.1 (404, *M*), 66
2	57.9 (398, *M*), 50	66.1 (398, *M*), 65	−69.9 (401, *P*), 68	85.8 (397, *M*), 74	97.7 (404, *M*), 85
3	72.5 (398, *M*), 68	90.4 (402, *M*), 76	−91.7 (403, *P*), 78	101.8 (398, *M*), 86	114.5 (402, *M*), 94
4	44.2 (397, *M*), 35	53.8 (401, *M*), 55	−61.2 (403, *P*), 54	75.2 (400, *M*), 67	89.2 (404, *M*), 84

[a] The values of $\Delta\varepsilon$ were corrected by a ZnBL unit. The spectral data were taken in $CHCl_3$ at 223 K.
[b] Determined by ^{1}H NMR spectra in $CDCl_3$ at 223 K.
[c] Helicity predominantly formed.
[d] Abbreviations: NEA, 1-(1-naphthyl)ethylamine; Leu-OMe, leucine methyl ester; PhGly-OMe, α-phenylglycine methyl ester; Phe-OMe, phenylalanine methyl ester; Asp-$(OMe)_2$, aspartic acid dimethyl ester.

conformers. In Figure 10 are shown ^{1}H NMR spectra of **2** in $CDCl_3$ at 223 K in the absence and presence of (*R*)-NEA. Upon addition of increasing amounts of (*R*)-NEA, each signal exhibited splitting, and the chemical shift change reached a plateau in the presence of an excess amount of (*R*)-NEA, indicating that full complexation of the ZnBL subunits with the guest molecules was achieved.[23] The major set of the signals split into two with the different integral ratios, whereas the minor into two with the same ratios. As complexation with chiral guests gives rise to identical and diastereomeric relationships of the ZnBL frameworks in the homohelical and heterohelical dimers, respectively, the former and latter splitting behaviors were due to formation of the homohelical and heterohelical **2**·2NEA, respectively. Thus, comparison of the integral ratios of the three conformers (complexed *PP*-, *MM*-, and *PM*-conformers) allowed us to determine the ratio of *PP*-**2**·2NEA: *PM*-**2**·2NEA: *MM*-**2**·2NEA as 16:18:66. In **1** and **3**, the distinguishable signal sets also afforded the distribution of the three conformers; 3:60:37 and 16:0:84 for **1** and **3**, respectively. For the other guests, the ratios of the conformers in **1**–**3** were similarly determined, and the h.e.s were obtained according to Eq. 1, as summarized in Table 1. Interesting is that no *PM*-conformer was observed for **3** on ^{1}H NMR upon complexation with any guests (see Table 3 in Section 4). Especially, in the case of the **3**·2Asp-$(OMe)_2$ complex, the homohelicity conformer was exclusively formed (h.e., 94%). In all dimers, the h.e.s increased in the order of NEA < Leu-OMe < PhGly-OMe < Phe-OMe < Asp-$(OMe)_2$. This tendency was similar to that of the monomer **4**. In addition, the helicity predominantly formed was determined by the point chirality of the chiral guests. That is, chiral molecular recognition between the ZnBL framework and the chiral guests was essential to determination of thermodynamic stability of each chiral helical ZnBL subunit complexed with the chiral guest. On the other hand, as indicated in the ^{1}H NMR as well as CD spectra, the h.e.s of **2** and **3** were larger than those of **4** for all guests employed in the present study, clearly showing positive cooperativity in homohelicity induction. Obviously, the h.e. increased with the increase in the bulkiness of the substituents on the spacer. Therefore, the inter-subunit interaction, afforded by the appropriate spacers, is essential to the helicity amplification, that is, the cooperative homohelicity induction.



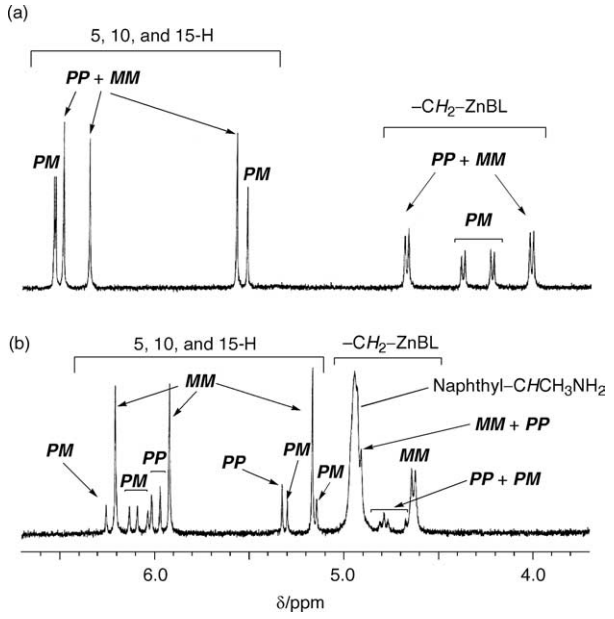


Figure 10. The expanded region of ^{1}H NMR spectra of **2** (1.09 mM) in $CDCl_3$ at 223 K; (a) **2** and (b) **2** and (*R*)-NEA (6.53 mM).

It is a common feature among **1**–**3** that the increase in the h.e. gives rise to the increase in the CD intensity, and as shown in Figure 11, these two are validly proportional to each other. The slopes for **1**–**4** are almost the same (Table 2). Thus, in each dimer, the CD signal and intensity reflect the absolute structures of the guest amine and α-amino esters. The structural information of the guests are amplified most effectively by **3**, compared to **4**, and such chiral signal amplification should not be achieved without steric interactions inducing the chiral homohelical framework.

3. Conclusions

We investigated homohelicity induction in the propylene-linked ZnBL dimers **1**–**3** in which the substituents

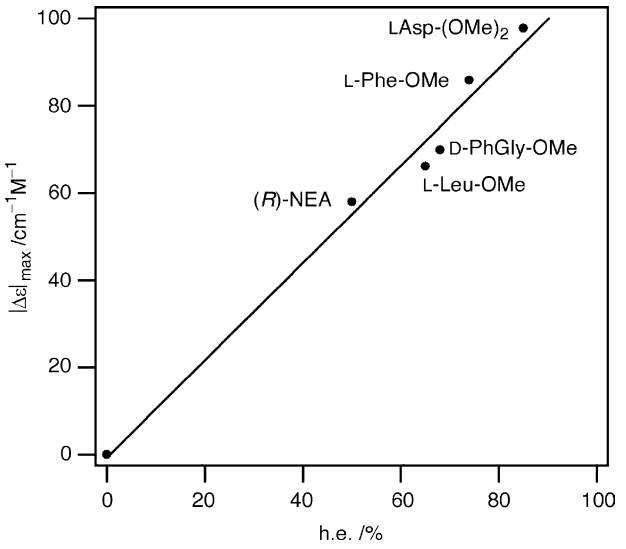


Figure 11. The linear correlation of h.e. and $\Delta\varepsilon$ in the complexes of **2** with various chiral guests. The h.e. and $\Delta\varepsilon$ were determined by ^{1}H NMR spectroscopy and CD spectra, respectively.

Table 2. The slopes (α) and correlation coefficients (R) of the plots of $\Delta\varepsilon$ versus h.e. for **1**–**4**

Compound	α	R
1	0.93	0.93
2	1.11	0.95
3	1.18	0.96
4	1.09	0.96

introduced onto the central carbon of the spacer varied in bulkiness. Introduction of methyls and isobutyls led to preorganization of the homohelical conformers *PP* and *MM*. Such a preorganization effect played an essential role in cooperative homohelicity induction triggered by chiral recognition of the ZnBL subunit for guests such as chiral amine and α-amino esters. The increase in bulkiness of the substituents on the spacer gave rise to enhancement of positive cooperativity in homohelicity induction of the ZnBL dimer by complexation with the chiral guests. Especially, the homohelicity induction in **3** was significantly enhanced, and the *MM*-homohelical conformer was exclusively formed upon complexation with L-Asp-(OMe)$_2$ (h.e., 94%). The results obtained in the present study show that this concept is potentially applicable to design of molecular sensors that can amplify signals for analytes.

4. Experimental

4.1. General

^{1}H NMR spectra were obtained on a Jeol JNM-LA400 (400 MHz) or a Jeol JNM GA500 (500 MHz) FT-NMR spectrometer, and the chemical shifts are reported in parts per million (ppm) downfield from TMS (0 ppm) as an internal standard. Elemental analyses were recorded on a Yanaco CHN-CORDER MT3 recorder. FAB MS spectra were obtained on a Finnigan Mat TSQ-70 spectrometer, using 3-nitrobenzyl alcohol as a matrix. Infrared absorption spectra were obtained on a Shimadzu FTIR-8400S spectrometer as KBr pellets. Melting points were determined with a Yanako MP-500D. Gel permeation chromatography was performed using SHODEX GPC K-2001 and K-2002 poly(styrene) gel column packages connected successively, where CH_2Cl_2 was used as eluent. UV–vis absorption spectra were obtained on a Shimadzu UV-3100 spectrometer. Circular dichroism (CD) spectra at 223 K were recorded on a Jasco J-600 spectrometer equipped with an Oxford DN1704 cryostat. The sample solutions for UV–vis and CD spectral analyses were prepared in a volumetric flask at 288 K, and the concentrations at 223 K were corrected on the basis of the thermal expansion coefficient of $CHCl_3$ (0.00126 K^{-1}).

4.2. Materials and solvents

Preparation of zinc bilinone **1** was reported previously.[8] α-Amino esters for the spectroscopic measurements were obtained by neutralization of the commercially available hydrochlorides followed by distillation just prior to use: L-Phe-OMe·HCl and L-Asp-(OMe)$_2$·HCl were purchased from Sigma Chemical Company, L-Leu-OMe·HCl was from Nakalai Tesque, Inc., and D-PhGly-OMe·HCl was from Wako Pure Chemicals Industries. (*R*)-NEA was purchased from Tokyo Chemical Industries and used after distillation. All solvents for the UV–vis, CD, and NMR measurements were of spectroscopic grade.

4.3. Experimental procedures

4.3.1. 19,19′-(2,2-Dimethyl-1,3-propylenedioxy)di-(3,8,12,17-tetraethyl-1,21-dihydro-2,7,13,18-tetramethyl-22*H*-bilin-1-one) (5). A mixture of 2,2-dimethyl-1,3-propanediol **7** (11.8 mg, 0.113 mmol) and sodium hydride (60% oil dispersion, 18.0 mg, 0.450 mmol) in dry THF (6 mL) was stirred at rt for 1 h under N_2. The (5-oxoniaporphynato)zinc(II) chloride **9** (131 mg, 0.226 mmol) was added, and the mixture was stirred at rt for 24 h. The solvent was removed on a rotary evaporator, and CH_2Cl_2 (50 mL) was added to the residue. The solution was washed with satd NH_4Cl (50 mL). The organic layer was vigorously shaken with a phthalate buffer solution (pH =4.0, 50 mL×3), washed with water (50 mL) and satd brine (50 mL), and then, dried over anhydrous Na_2SO_4. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (dichloromethane/benzene/acetone = 7.5:7.5:1, v/v/v, as eluent). Further purification by gel permeation chromatography on HPLC followed by reprecipitation from CH_2Cl_2–hexane afforded **5** as a dark blue solid (42.5 mg, 0.0399 mmol, 35%): mp>250 °C (dec) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 6H, $(CH_3)_2C(CH_2O–)_2$), 1.05–1.16 (m, 24H, $CH_3CH_2–$), 1.60 (s, 6H, $CH_3–$), 1.77 (s, 6H, $CH_3–$), 1.90 (s, 6H, $CH_3–$), 2.11 (s, 6H, $CH_3–$), 2.33–2.41 (m, 8H, $CH_3CH_2–$), 2.49–2.61 (m, 8H, $CH_3CH_2–$), 4.05 (br s, 4H, $–CH_2O–$), 5.69 (s, 2H, *meso*-H), 6.23 (s, 2H, *meso*-H), 6.62 (s, 2H, *meso*-H), 10.19 (br s, 2H, NH), 12.65 (br s, 2H, NH); IR (KBr) 2964, 2931, 2867, 1701, 1589, 1215 cm^{-1}; FAB MS *m*/*z* 1064 (M^+). Anal. Calcd for $C_{67}H_{84}N_8O_4\cdot0.5H_2O$: C 74.90, H 7.97, N 10.43. Found: C 74.62, H 8.17, N 10.11.

4.3.2. Zinc complex of 5 (2). To a solution of **5** (36.1 mg, 0.0339 mmol) in CH_2Cl_2 (6 mL) was added a solution of

Table 3. The ratios of the homohelical and heterohelical conformers (*PP*:*PM*:*MM*) for the complexes of ZnBL dimers **1–3** with amines and α-amino esters in $CDCl_3$ at 223 K: [ZnBL subunit] = 2.15–2.19 mM, [guest] = 6.53–10.9 mM

Compound	*PP*:*PM*:*MM*					
	Benzylamine	(*R*)-NEA	L-Leu-OMe	D-PhGly-OMe	L-Phe-OMe	L-Asp-$(OMe)_2$
1	15:70:15	3:60:37	3:54:43	38:57:5	6:42:52	4:26:70
2	39:22:39	16:18:66	9:27:74	75:18:7	6:14:80	5:5:90
3	49:2:49	16:0:84	12:0:88	89:0:11	7:0:93	3:0:97

zinc acetate (74.0 mg, 0.337 mmol) in methanol (3 mL), and then, the mixture was stirred at rt for 1 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in CH_2Cl_2 (25 mL) and washed with water (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed by evaporation to afford **2** as a dark green solid (37.4 mg, 0.0314 mmol, 93%). Further purification was not performed because demetallation of Zn(II) might occurred: mp 178–180 °C (dec) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (s, 3H for *PM*, $(CH_3)_2C(CH_2O–)_2$), 0.81 (s, 6H for *PP*+*MM*, $(CH_3)_2C(CH_2O–)_2$), 1.25 (s, 3H for *PM*, $(CH_3)_2C(CH_2O–)_2$), 1.00–1.18 (m, 24H for *PP*+*MM* and 24H for *PM*, $CH_3CH_2–$), 1.50 (s, 6H for *PP*+*MM*, $CH_3–$), 1.60 (s, 6H for *PM*, $CH_3–$), 1.73 (s, 6H for *PP*+*MM* and 6H for *PM*, $CH_3–$), 1.81 (s, 6H for *PM*, $CH_3–$), 1.98 (s, 6H for *PP*+*MM*, $CH_3–$), 2.02 (s, 6H for *PP*+*MM*, $CH_3–$), 2.08 (s, 6H for *PM*, $CH_3–$), 2.21–2.57 (m, 16H for *PP*+*MM* and 16H *PM*, $CH_3CH_2–$), 3.93–3.95 (d, *J*=10.0 Hz, 2H for *PP*+*MM*, $–CH_2O–$), 4.22–4.24 (d, *J*=10.0 Hz, 2H for *PM*, $–CH_2O–$), 4.36–4.38 (d, *J*=10.0 Hz, 2H for *PM*, $–CH_2O–$), 4.73–4.76 (d, *J*=10.0 Hz, 2H for *PP*+*MM*, $–CH_2O–$), 5.46 (s, 2H for *PP*+*MM*, *meso*-H), 5.50 (s, 2H for *PM*, *meso*-H), 6.30 (s, 2H for *PP*+*MM*, *meso*-H), 6.46 (s, 2H for *PP*+*MM*, *meso*-H), 6.52 (s, 2H for *PM*, *meso*-H), 6.53 (s, 2H for *PM*, *meso*-H); IR (KBr) 2964, 2929, 2869, 1652, 1573, 1207 cm^{-1}; FAB MS *m*/*z* 1188 (M^+). Anal. Calcd for $C_{67}H_{80}N_8O_4Zn_2\cdot H_2O$: C 66.50, H 6.83, N 9.26. Found: C 66.54, H 6.86, N 9.17.

4.3.3. 19,19′-(2,2-Diisobutyl-1,3-propylenedioxy)di-(3,8,12,17-tetraethyl-1,21-dihydro-2,7,13,18-tetramethyl-22*H*-bilin-1-one) (6). According to a similar procedure to the preparation of **5**, the reaction of a mixture of 2,2-diisobuthyl-1,3-propanediol **8** (22.8 mg, 0.121 mmol) and sodium hydride (60% oil dispersion, 27.8 mg, 0.695 mmol) in dry THF (6 mL) with **9** (141 mg, 0.243 mmol) afforded **6** as a dark blue solid (42.6 mg, 0.0371 mmol, 31%): mp 268–270 °C (dec) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72–0.74 (d, 12H, *J*=6.3 Hz, $(CH_3)_2CHCH_2–$), 0.98 (t, 6H, *J*=7.8 Hz, $CH_3CH_2–$), 1.03–1.04 (d, 4H, *J*=4.8 Hz, $(CH_3)_2CHCH_2–$), 1.09–1.16 (m, 18H, $CH_3CH_2–$), 1.41–1.54 (m, 6H for $CH_3–$ and 2H for $(CH_3)_2CHCH_2–$), 1.75 (s, 6H for $CH_3–$), 1.97 (s, 6H for $CH_3–$), 2.06–2.12 (m, 6H for $CH_3–$ and 4H for $CH_3CH_2–$), 2.36–2.42 (q, 4H, *J*=7.3 Hz, $CH_3CH_2–$), 2.49–2.59 (m, 8H, $CH_3CH_2–$), 3.58–4.81 (br, 4H, $–CH_2O–$), 5.69 (s, 2H, *meso*-H), 5.97 (s, 2H, *meso*-H), 6.57 (s, 2H, *meso*-H), 10.33 (br s, 2H, NH), 12.79 (br s, 2H, NH); IR (KBr) 2964, 2929, 2869, 1704, 1558, 1215 cm^{-1}; FAB MS *m*/*z* 1148 (M^+). Anal. Calcd for $C_{73}H_{96}N_8O_4\cdot 0.5H_2O$: C 75.68, H 8.44, N 9.67. Found: C 75.67, H 8.66, N 9.53.

4.3.4. Zinc complex of 6 (3). According to the procedure described for **2**, the reaction of **6** (47.2 mg, 0.0411 mmol) in CH_2Cl_2 (5 mL) with zinc acetate (230 mg, 1.05 mmol) in methanol (3 mL) afforded **3** as a dark green solid (47.4 mg, 0.0371 mmol, 90%): mp 272–274 °C (dec) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65–0.66 (d, *J*=6.4 Hz, 6H for *PM*, $(CH_3)_2CHCH_2–$), 0.73–0.75 (m, 6H for *PP*+*MM* and 6H for *PM*, $(CH_3)_2CHCH_2–$), 0.81–0.82 (d, *J*=6.4 Hz, 6H for *PP*+*MM*, $(CH_3)_2CHCH_2–$), 0.95 (t, *J*=7.6 Hz, 6H for *PP*+*MM*, $CH_3CH_2–$), 1.03 (t, *J*=7.6 Hz, 6H for *PM*, $CH_3CH_2–$), 1.06–1.21 (m, 18H for *PP*+*MM* and 24H for *PM*, $CH_3CH_2–$ and 4H for *PP*+*MM* and 4H for *PM*, $(CH_3)_2CHCH_2–$), 1.36 (s, 6H for *PP*+*MM*, $CH_3–$), 1.49–1.59 (m, 2H for *PP*+*MM* and 2H for *PM*, $(CH_3)_2CHCH_2–$ and 6H for *PM*, $CH_3–$), 1.71 (s, 6H for *PP*+*MM*, $CH_3–$), 1.82 (s, 6H for *PM*, $CH_3–$), 1.97 (s, 6H for *PP*+*MM*, $CH_3–$), 2.00 (m, 6H for *PP*+*MM* and 6H for *PM*, $CH_3–$), 2.09 (s, 6H for *PM*, $CH_3–$), 2.28–2.59 (m, 16H for *PP*+*MM* and 16H for *PM*, $CH_3CH_2–$), 3.85–3.87 (d, *J*=10.0 Hz, 2H for *PP*+*MM*, $–CH_2O–$), 4.22–4.24 (d, *J*=10.0 Hz, 2H for *PM*, $–CH_2O–$), 4.53–4.55 (d, *J*=10.0 Hz, 2H for *PM*, $–CH_2O–$), 4.95–4.97 (d, *J*=10.0 Hz, 2H for *PP*+*MM*, $–CH_2O–$), 5.43 (s, 2H for *PP*+*MM*, *meso*-H), 5.48 (s, 2H for *PM*, *meso*-H), 6.12 (s, 2H for *PP*+*MM*, *meso*-H), 6.43 (s, 2H for *PP*+*MM*, *meso*-H), 6.53 (s, 2H for *PM*, *meso*-H), 6.55 (s, 2H for *PM*, *meso*-H); IR (KBr) 2962, 2931, 2869, 1652, 1558, 1207 cm^{-1}; FAB MS *m*/*z* 1272 (M^+). Anal. Calcd for $C_{73}H_{92}N_8O_4Zn_2\cdot H_2O$: C 67.74, H 7.32, N 8.66. Found: C 67.68, H 7.37, N 8.65.

4.4. Determination of the distribution of the homohelical and heterohelical conformers

The distribution of the homohelical and heterohelical conformers was determined by comparison of the integral ratios of their ^{1}H NMR signals with one another. The signals assigned to 5-, 10-, 15-Hs or methylene's protons of the spacer ($–OCH_2–$) were monitored in $CDCl_3$ at 223 K. The ratios of the *PP*, *PM* and *MM* conformers for all guests are summarized in Table 3.

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19. The initial structures of **1**–**3** were generated by geometrical optimizaton performed by molecular mechanics calculations (MMFF94 force field) followed by semi-empirical molecular orbital calculations (MOPAC PM3 level), using a *Spartan '02* program package; Wavefunction, Inc., Irvine, California.
20. The molecular modelling was performed at the MOPAC PM3 level using the *winMOPAC 3.5 professional* program package; Fujitsu Co., Chiba, Japan.
21. Inter-subunit interactions to stabilize the homohelicity structure was also found in the homohelical ZnBL dimer with a chiral cyclohexane-1,2-dioxy spacer: see, Yagi, S.; Sakai, N.; Yamada, R.; Takahashi, H.; Mizutani, T.; Takagishi, T.; Kitagawa, S.; Ogoshi, H. *Chem. Commun.* **1999**, 911–912.
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23. Upon addition of the guest, an averaged spectrum of complexed and uncomplexed dimers was observed for each conformer, and the three conformers were independently observed even upon complexation with the guest. Thus, the complexation–dissociation between the dimer and the guest was faster than the ^{1}H NMR time scale under the present conditions, whereas the interconversion among the three conformers was slower.

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Efficient synthesis of indoles using [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines

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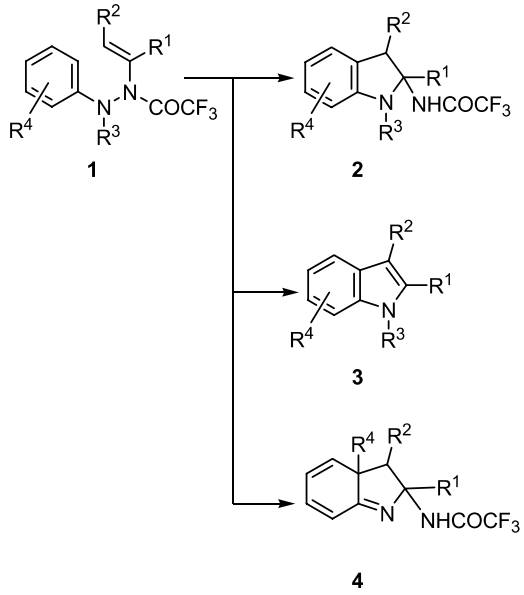
Abstract—[3,3]-Sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines provides a novel method for the construction of indoles. *N*-Trifluoroacetyl enehydrazine having a cyclopentene ring smoothly underwent [3,3]-sigmatropic rearrangement followed by cyclization to give indolines in excellent yield. On the other hand, both cyclohexenyl *N*-trifluoroacetyl enehydrazine and acyclic *N*-trifluoroacetyl enehydrazine gave indoles in good yield. Additionally, the substituent effect on the benzene ring was also studied. The rearrangement of *N*-trifluoroacetyl enehydrazines proceeded smoothly even under either aqueous or solvent-free conditions.

1. Introduction

Indole ring systems are the core structural elements in natural and synthetic organic compounds possessing a wide diversity of important biological activities. Therefore, there is continuously a need for developing concise and practical synthetic methods of indoles and the related compounds. Despite recently developed methodologies,[1] such as metal-catalyzed transformations and radical cyclization, the venerable Fischer indole synthesis has maintained its prominent role as a route to indoles. However, two major drawbacks to the Fischer indole synthesis are that yields are sometimes low[2–4] with numerous by products being formed. And the reactions involving unsymmetrical hydrazines or ketones often give products with low regioselectivity.[2,5–8] Particularly, the low yields are a persistent problem in the Fischer indole synthesis. Although the Fischer indolization is usually carried out in the presence of an acid catalyst, the acid may cause decomposition of the indole produced and, therefore, thermal cyclization in the absence of a catalyst appears to offer advantages over the acid-catalyzed procedure. However, high temperature (180–250 °C) is required for such cyclization.

Recently, we found that the [3,3]-sigmatropic rearrangement and subsequent cyclization of *N*-trifluoroacetyl enehydrazines **1** proceed smoothly under mild conditions (without acids and at below 90 °C) to give the indolines **2** and indoles **3**.[9,10a]

The [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines having either a methoxy or a methyl group on the benzene ring gave dienylimines **4** which correspond to the proposed intermediates of Fischer indolization.[10b]



Scheme 1.

Keywords: [3,3]-Sigmatropic rearrangement; *N*-Trifluoroacetyl enehydrazines; Indole; Indoline; Dienylimine.
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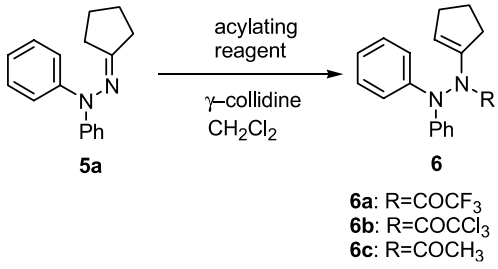
This reaction provides a new entry to the Fischer indole synthesis and was applied to not only one-pot synthesis of various types of indoles[11a] but also synthesis of natural indole products.[11b] We disclose herein the full details of the [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines which are indispensable in the synthesis of indoles (Scheme 1).[10]

2. Results and discussion

2.1. The substituent effects on the nitrogen atom in [3,3]-sigmatropic rearrangement of enehydrazines bearing a cyclopentene ring

At first, we investigated the substituent effects on the nitrogen atom. Three types of *N*-acyl enehydrazines **6a**, **6b**, and **6c** having a cyclopentene ring were employed as the substrate (Scheme 2, Table 1). The hydrazone **5a**,[12] prepared by condensation of cyclopentanone with *N*,*N*-diphenylhydrazine was subjected to acylation with trifluoroacetic anhydride (TFAA) in the presence of γ-collidine to give the corresponding *N*-trifluoroacetyl enehydrazines **6a** in excellent yield (entry 1). Similarly, *N*-trichloroacetyl enehydrazine **6b** and *N*-acetyl enehydrazine **6c** were prepared from **5a** (entries 2 and 3).

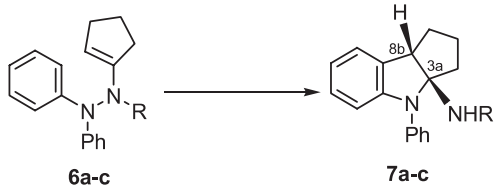


Scheme 2.

Table 1. The acylation of **5a** with various acylating agents

Entry	Acylating reagent	Temperature (°C)	Product	Yield (%)
1	TFAA	0	**6a**	99
2	$(CCl_3CO)_2O$	0	**6b**	99
3	AcCl, DMAP	25	**6c**	99

When a solution of **6a** in THF was heated at 65 °C for 5 h, indoline **7a** was obtained in 99% yield (Scheme 3, entry 1 in Table 2). Similarly, the reaction of *N*-trichloroacetyl enehydrazine **6b** at the same temperature gave indoline



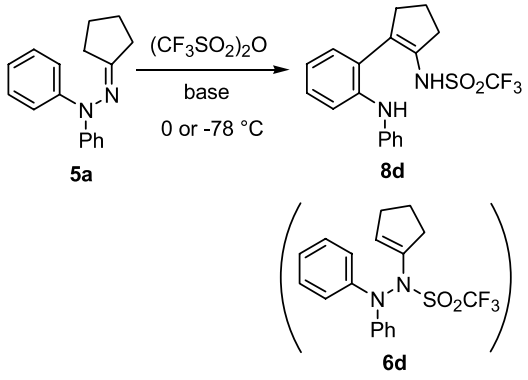
Scheme 3.

Table 2. The conversion of *N*-acyl enehydrazines **6a–c** into the indolines **7a–c**

Entry	Substrate	R	Conditions (°C)	Time (h)	Yield (%)
1	**6a**	$COCF_3$	THF (65)	5	99
2	**6b**	$COCCl_3$	THF (65)	5	56
3	**6c**	$COCH_3$	Xylene (140)	3	65

7b in 56% yield (entry 2). However, in the case of **6c**, higher reaction temperature (140 °C) was required for the successful rearrangement and cyclization (entry 3). These results suggest that strong electron-withdrawing group is suitable as the substituent on the nitrogen.

We next examined the rearrangement of the enehydrazine **6d** carrying a trifluoromethanesulfonyl group which has higher electron-withdrawing ability (Scheme 4, Table 3). The sulfonylation of hydrazone **5a** with trifluoromethanesulfonic anhydride was carefully carried out in the presence of γ-collidine at 0 °C. However, the reaction gave not the desired product **6d** but the rearranged product **8d** in low yield, along with the decomposition of **5a** (entry 1).



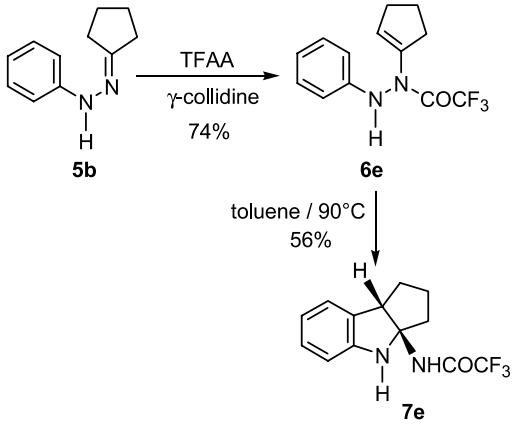
Scheme 4.

Table 3. The treatment of **5a** with $(CF_3SO_2)_2O$

Entry	Base	Temperature (°C)	Yield (%)
1	γ-Collidine	0	5
2	γ-Collidine	−78	25
3	Et_3N	−78	70

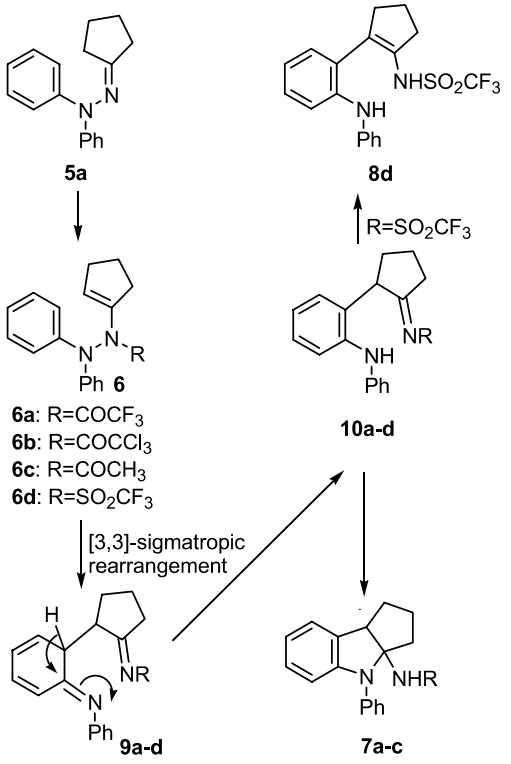
At lower reaction temperature of −78 °C, **8d** was obtained in 25% yield (entry 2). Replacement of γ-collidine to triethylamine as a base improved the yield to 70% (entry 3). Thus, this result suggests that the enehydrazine **6a** bearing a trifluoroacetyl group is the best substrate for our indole synthesis.

Similarly, the reaction of *N*-monophenylenehydrazine **6e**, prepared from **5b**,[13] proceeded smoothly in toluene at 90 °C to give the indoline **7e** along with the unreacted starting material **6e** (Scheme 5).



Scheme 5.

Considering our results obtained above and the related known Fischer indolization, we propose a plausible reaction pathway that is shown in Scheme 6. At first, [3,3]-sigmatropic rearrangement of the *N*-acyl enehydrazines **6a–c** followed by isomerization proceeds to form *N*-acylimines **10a–c** which then cyclized intramolecularly to give the indoline **7a–c**.

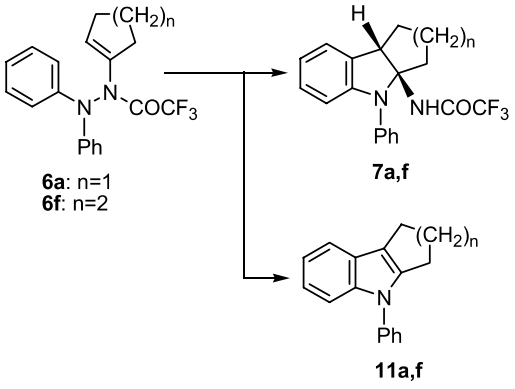


Scheme 6.

In sulfonylation of hydrazone **5a**, *N*-trifluoromethansulfonyl enehydrazine **6d** could not be isolated. Probably, the [3,3]-sigmatropic rearrangement of **6d** that would be transiently formed from hydrazone **5a** would take place easily even at −78 °C because a trifluoromethanesulfonyl group has a very strong electron-withdrawing property. The following cyclization of rearranged intermediate **10d** was prevented due to too low temperature (−78 °C). Therefore, **8d** was an isolable product in the reaction of **5a** with trifluoromethanesulfonic anhydride.

2.2. The substituent effect on the ene part in [3,3]-sigmatropic rearrangement of enehydrazines

We next investigated the substituent effects on the ene part. At first, *N*-trifluoroacetyl enehydrazines **6a** and **6f** having a cyclic enamine part was employed as substrate (Scheme 7, Table 4). As mentioned above, the reaction of enehydrazine **6a** having a cyclopentene ring gave the indoline **7a** in excellent yield (entry 1). Surprisingly, the reaction also proceeded at room temperature but required prolonged reaction time (entry 2). When the reaction of **6a** was carried out in toluene at 90 °C, a mixture of indoline **7a** and indole **11a**[14] was obtained (entry 3). The reaction of **6a** in xylene at 140 °C gave the indole **11a** as the sole product (entry 4). In the case of cyclohexenehydrazine **6f**,[15] the indole **11f**[16] was exclusively obtained without formation of the indoline **7f** (entry 5).



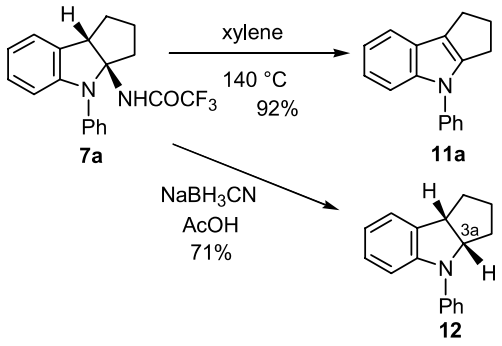
Scheme 7.

Table 4. The thermal reaction of enehydrazines **6a** and **6f** under various conditions

Entry	Substrate	Conditions (°C)	Time (h)	Yield (%)	
				7	**11**
1	**6a**	THF (65)	5	99	—
2	**6a**	$CDCl_3$ (25)	480	98	—
3	**6a**	Toluene (90)	3	61	30
4	**6a**	Xylene (140)	4	—	92
5	**6f**	THF (65)	11	—	53

Upon heating at 140 °C, the indoline **7a** was converted into the indole **11a** in quantitative yield as a result of the elimination of trifluoroacetamide (Scheme 8). Reductive deamination of **7a** with sodium cyanoborohydride proceeded smoothly to give the corresponding indoline **12**[17] in 71% yield that is unsubstituted at the 3a-position (Scheme 8).

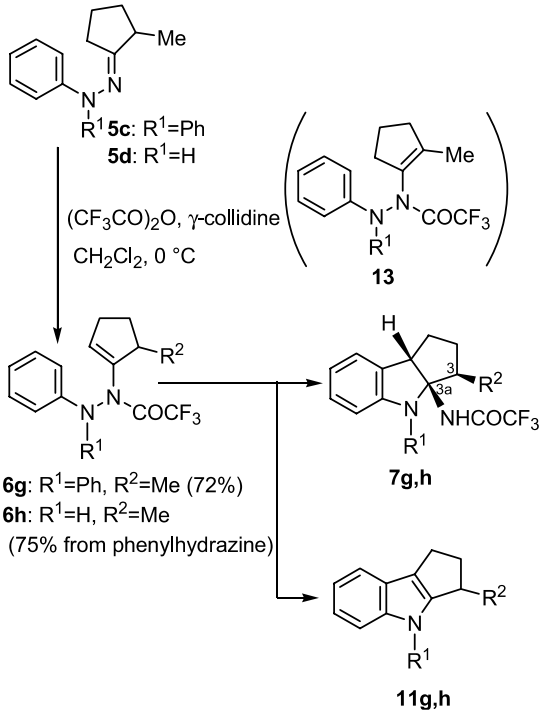
In general, it is difficult to isolate 2-aminoindolines which is proposed as an intermediate of Fischer indolization. To our knowledge, there has been only a few works[18–20] achieving the isolation of 2-aminoindoline derivatives.



Scheme 8.

The difference between the structures of products (indolines **7a** from cyclopentenehydrazine **6a** and indoles **11f** from cyclohexenehydrazines **6f**) could be explained as follows. The indole double bond is not readily accommodated in a fused system such as 1,2,3,3a,4,8b-hexahydrocyclopent-[*b*]indoles in which the two rings are five-membered and rather rigid. On the other hand, it is clear that no comparable difficulty exists in the elimination of trifluoroacetamide when the more flexible six-membered cyclohexane ring is present.

Next, the reaction of enehydrazines **6g** and **6h** having a methyl group on the cyclopentene ring was examined (Scheme 9, Table 5). The enehydrazines **6g** and **6h** were prepared by the treatment of hydrazones **5c** and **5d**[21] with TFAA without formation of the regioisomer **13**. The enehydrazine **6g** was subjected to the heating at 65 °C to give the indoline **7g** in 76% yield (entry 1) while the indoline **7h** could not be isolated from **6h** under the same conditions probably because of its instability. On the other hand, the reaction of **6h** in toluene at 90 °C gave the indole **11h**[22] in excellent yield (entry 2).



Scheme 9.

Table 5. The thermal reaction of enehydrazines **6g** and **6h**

Entry	Substrate	Conditions (°C)	Time (h)	Yield (%)	
				7	**11**
1	**6g**	THF (65)	5	76	—
2	**6h**	Toluene (90)	7	—	99

It is known[5] that the classical Fischer indolization of hydrazone prepared from unsymmetrical ketone gives a mixture of substituted indoles with no regioselectivity. Therefore, this regioselective formation of indolines and indoles from unsymmetrical hydrazones **5c**,**d** would be useful for the synthesis of variously substituted polycyclic indole alkaloids.

The stereostructures of indolines **7a**, **7g**, and **12** were established by NOESY of ^{1}H NMR spectra. The assignment of those configurations is based on the observed NOE correlations as shown in Figure 1. In the case of **7a**, NOE was observed between 8b-H and NH. NOE in **7g** was observed between 3-Me and 8b-H, 3-Me and NH, and NH and 8b-H. The stereostructures of **7b**,**c**,**e** were deduced from comparison of the ^{1}H NMR spectra with those of **7a**. In the case of **12**, NOE was observed between 8b-H and 3a-H.[23]

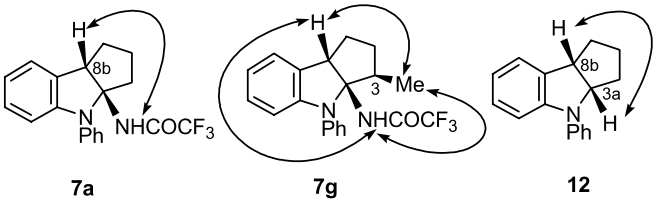
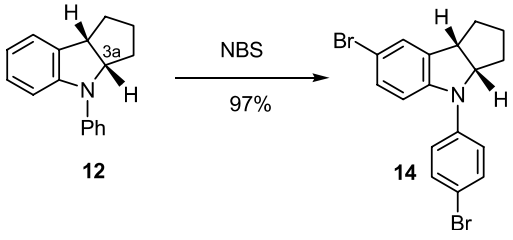


Figure 1. NOE correlations of compounds **7a**, **7g** and **12**.

Furthermore, the stereostructure of **12** was firmly established by the single-crystal X-ray analysis of the dibromide **14** which was prepared by bromination of **12** with NBS (Scheme 10, Fig. 2).



Scheme 10.

We propose the possible reaction pathway for the formation of **7g** as shown in Scheme 11. The rearrangement of **6g** would proceed via a stable conformation **A** of **6g** to give the intermediate **B** which was converted into the stable product **7g**.

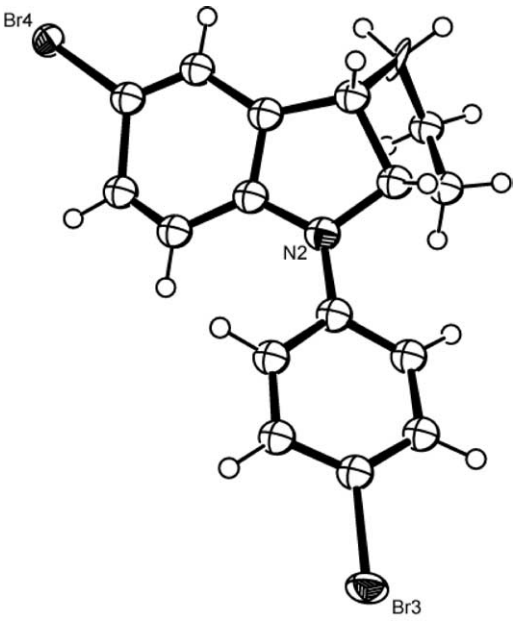
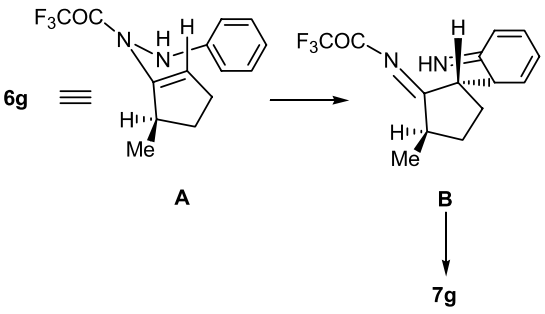
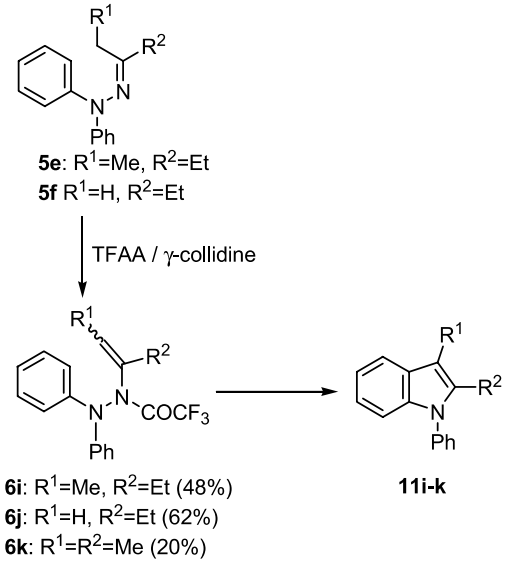


Figure 2. The single-crystal X-ray analysis of **14**.



Scheme 11.

We then investigated the reaction of enehydrazine with an acyclic chain on the ene part (Scheme 12, Table 6). The enehydrazine **6i** was prepared by the acylation of hydrazone **5e** with TFAA. The acylation of hydrazone **5f**[24] with TFAA



Scheme 12.

Table 6. The thermal reaction of enehydrazines **6i–k**

Entry	Substrate	Conditions (°C)	Time (h)	Yield (%)[a]
1	**6i**	THF (65)	4	69
2	**6i**	$CDCl_3$ (25)	480	50
3	**6j**	THF (65)	10	24 (38)
4	**6j**	Toluene (90)	6	77
5	**6k**	THF (65)	10	79

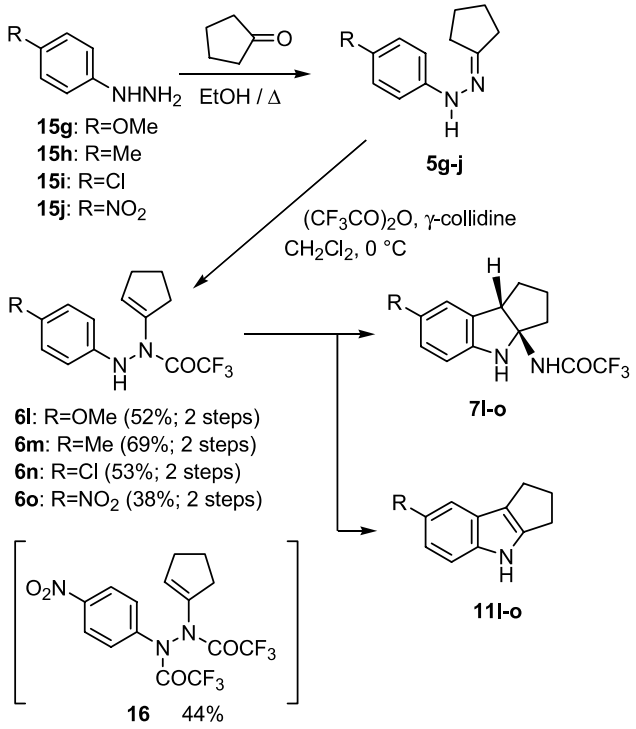
[a] Yield in parenthesis is for recovered starting material.

gave a 3:1 mixture of enehydrazines **6j** and **6k**. The stereostructures of **6i**,**k** have not been established. The enehydrazine **6i** was heated at 65 °C to afford the corresponding indoles **11i** as the sole product (entry 1).

The thermal reaction of **6j** at 90 °C gave indole **11j** in 77% yield (entry 4). Similarly, **11k**[25] was obtained from **6k** (entry 5). Since the rearrangement and cyclization of **6i–k** occurred with no isomerization of the olefin part under mild conditions, the substituted indoles such as 2-mono- and 2,3-disubstituted indoles would be selectively obtained as the sole product.

2.3. The substituent effects on benzene ring in [3,3]-sigmatropic rearrangement of enehydrazines bearing cycloalkene ring

To demonstrate the generality of the rearrangement and cyclization of *N*-trifluoroacetyl enehydrazines, we next investigated the substituent effects on the benzene ring. We chose methoxyl, methyl, nitro, and chloro groups as a substituent. At first, the reaction of enehydrazine having a substituent at the *p*-position on the benzene ring was examined (Scheme 13, Table 7).



Scheme 13.

Table 7. The thermal reaction of enehydrazines **6l–o**

Entry	Substrate	Conditions (°C)	Time (h)	Yield (%)	
				7	**11**
1	**6l**	THF (65)	5	99	—
2	**6m**	THF (65)	12	—	—
3	**6m**	Toluene (90)	8	68	—
4	**6n**	Toluene (90)	15	25	20
5	**6o**	Toluene (90)	15	—	—
6	**6o**	Toluene (110)	29	48	25
7	**6o**	Xylene (140)	6	54	19

The condensation of hydrazines **15g–i** with cyclopentanone gave the corresponding unstable hydrazones **5g–i**, which without isolation were acylated to give enehydrazines **6l–n** in 52–69% yield. On the other hand, in the case of **6o** having a nitro group, the hydrazone **5j**[26] could be isolated and then acylated to give the desired product **6o** and diacylated product **16** in 38 and 44% yields, respectively. The substrate **6l** having a methoxy group underwent cyclization at lower temperature (65 °C) than the reaction of unsubstituted enehydrazine **6e** at 90 °C (see Scheme 5). The indoline **7l** was produced in excellent yield (entry 1). Similarly, the substrate **6m** with a methyl group gave the indoline **7m** at 90 °C (entry 3). On the other hand, in the case of the enehydrazines **6n** and **6o** having an electron-withdrawing group, prolonged reaction time and high reaction temperature were required (entries 4–7). These substituent effects are almost in agreement with those obtained in the classical Fischer indolization.[2] The existence of an electron-donating group on a benzene ring makes the thermal reaction relatively easy to occur while in the case of an electron-withdrawing group, harsh conditions were required for successful reaction.

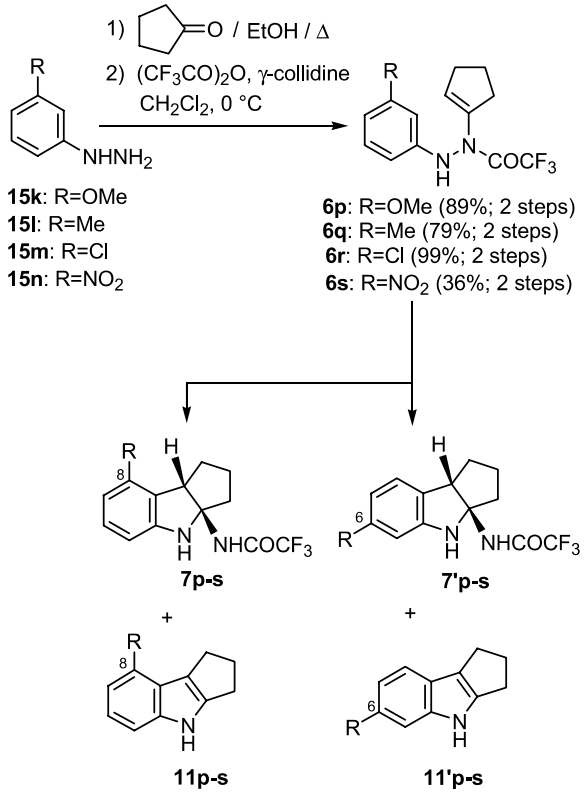
We next investigated the thermal reaction of *m*-substituted enehydrazines **6p–s**, prepared from *m*-substituted phenylhydrazines **15k–n** (Scheme 14, Table 8). The reaction of **6p** bearing an *m*-methoxy group proceeded in toluene at 90 °C to give the 8-substituted indoline **7p** and indole **11p**, and 6-substituted indoline **7′p** and indole **11′p** (entry 2).

Table 8. The thermal reaction of enehydrazines **6p–s**

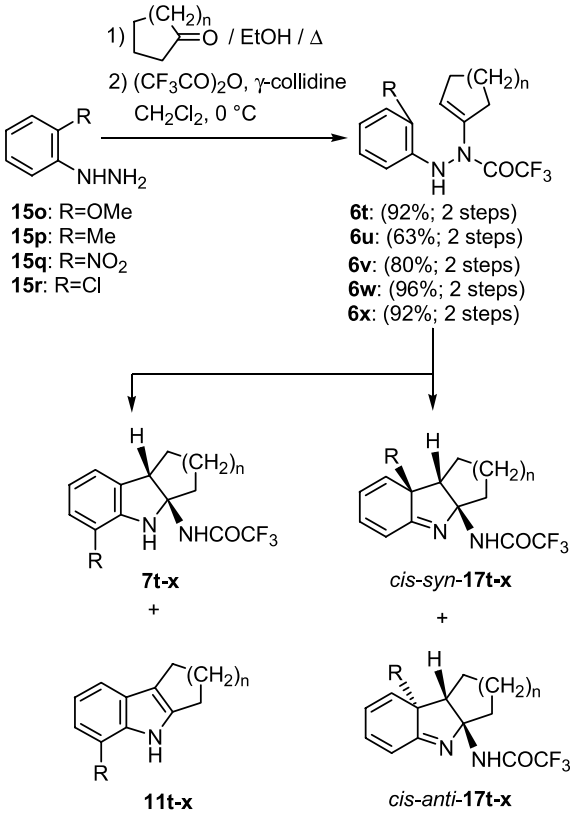
Entry	Substrate	Conditions (°C)	Time (h)	Yield (%)			
				7	**11**	**7′**	**11′**
1	**6p**	THF (65)	5	—	—	—	—
2	**6p**	Toluene (90)	11	11	24	6	20
3	**6q**	Toluene (90)	8	15	6	15	6
4	**6r**	Toluene (90)	15	17	8	12	—
5	**6s**	Toluene (90)	15	—	—	—	—
6	**6s**	Toluene (110)	29	14	66	14	5

Similarly, *m*-methyl enehydrazine **6q** gave the 8-substituted products **7q** and **11q**, and 6-substituted products **7′q** and **11′q** (entry 3). In the case of enehydrazine **6s** with a nitro group, four products **7s**, **11s**,[27] **7′s**, and **11′s**[27] were obtained after prolonged reaction time (entry 6). Thus, the [3,3]-sigmatropic rearrangement of *m*-substituted enehydrazines proceeded with low regioselectivity.

We next investigated the reaction of *o*-substituted enehydrazines (Scheme 15, Table 9). At first, [3,3]-sigmatropic rearrangement of **6t** having an *o*-methoxy group was



Scheme 14.



Scheme 15.

Table 9. The thermal reaction of enehydrazines **6t–x**

Entry	Substrate	R	*n*	Conditions (°C)	Time (h)	Yield (%)		
						7	**11**	**17** (*cis-syn*:*cis-anti*)
1	**6t**	OMe	1	THF (65)	10	63	—	36 (5:1)
2	**6t**	OMe	1	MeCN (80)	5	51	—	48 (5:1)
3	**6t**	OMe	1	Toluene (90)	7	69	—	29 (4:1)
4	**6t**	OMe	1	Hexane (70)	22	75	—	24 (4:1)
5	**6t**	OMe	1	MeOH (65)	6	—	24	15 (7:1)
6	**6u**	OMe	2	THF (65)	10	—	34	3 (2:1)
7	**6u**	OMe	2	MeCN (80)	10	—	52	17 (2:1)
8	**6u**	OMe	2	Toluene (90)	10	—	75	9 (2:1)
9	**6v**	Me	1	MeCN (80)	8	30	37	32 (7:1)
10	**6v**	Me	1	Toluene (90)	8	14	42	18 (14:1)
11	**6w**	Cl	1	Toluene (90)	15	66	—	—
12	**6x**	NO_2	1	Toluene (110)	29	31	—	—

examined. **6t** was heated in THF at 65 °C to give a mixture of indoline **7t** and two dienylimines **17t** in 63 and 36% yields, respectively (entry 1). The dienylimines **17t** were obtained as the result of the rearrangement at the root of a methoxy group. Furthermore, **17t** was easily separated into two diastereomers, *cis-syn*-**17t** and *cis-anti*-**17t**, in a 5:1 ratio. Interestingly, the polarity of the organic solvent used influences both the product ratio of the indoline and dienylimine and the reaction time. In MeCN, the reaction proceeded smoothly to give a 1:1 mixture of **7t** and **17t** in 99% yield (entry 2). On the other hand, in a less polar solvent, such as toluene and hexane, **7t** was obtained as a major product in 69–75% yield, although prolonged reaction time was required for complete consumption of **6t** (entries 3 and 4). In methanol, the indole **11t** and the dienylimines **17t** were obtained with no formation of indoline **7t** (entry 5). The reaction of cyclohexenyl hydrazine **6u** proceeded slowly under similar mild conditions to give 7-methoxyindole **11u**[28] and dienylimines **17u** (entries 6–8).

Next, we turned our attention to the corresponding *o*-methyl-*N*-trifluoroacetyl enehydrazine. The reaction of **6v** proceeded smoothly in MeCN and toluene at 80–90 °C to give the indoline **7v**, indole **11v**,[29] *cis-syn*-**17v**, and *cis-anti*-**17v** (entries 9 and 10). When an electron-withdrawing group such as a chlorine or nitro group was present in the *o*-position, the indolization occurred regioselectively at the unsubstituted position to give 5-substituted products (entries 11 and 12).

The stereostructures of *cis-syn*-**17t–v** and *cis-anti*-**17t–v** were firmly established by NOESY of the ^{1}H NMR spectra (Fig. 3). Taking *cis-syn*-**17t** and *cis-anti*-**17t** as a typical example, the assignment of those configurations is based on the observed NOE correlations as shown in Figure 3. In the case of *cis-syn*-**17t**, NOE was observed between MeO and 8b-H, 8b-H and NH, NH and MeO. On the other hand, NOE in *cis-anti*-**17t** was observed only between 8b-H and NH.

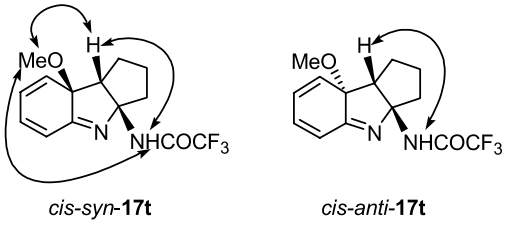
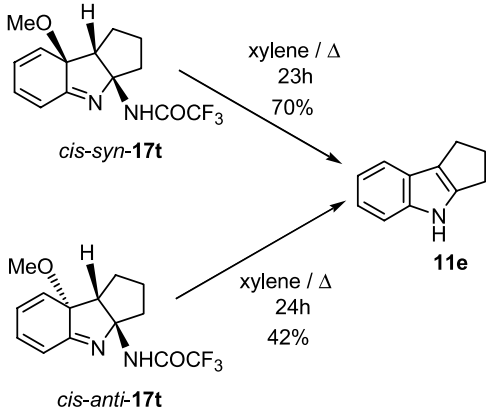


Figure 3. NOE correlations of compounds *cis-syn*-**17t** and *cis-anti*-**17t**.

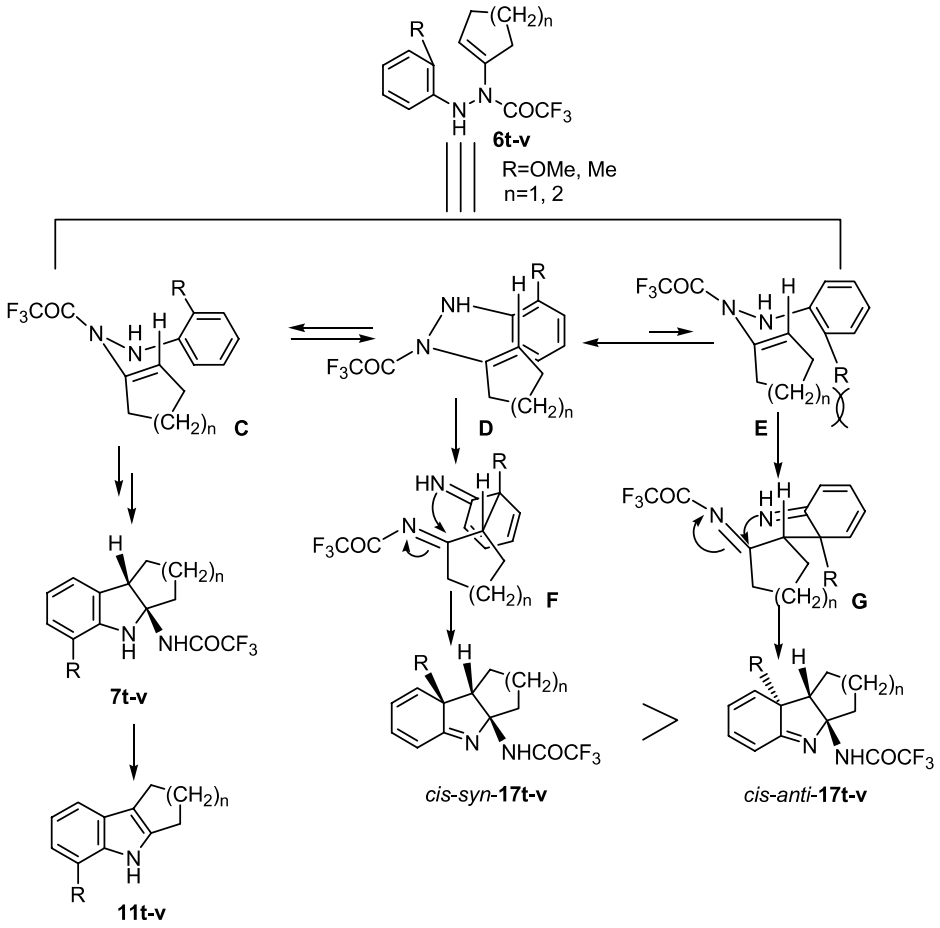
The stereostructure of *cis-syn*-**17t** was established unambiguously by single-crystal X-ray analysis.[30] Furthermore, heating the dienylimines, *cis-syn*-**17t** and *cis-anti*-**17t**, in xylene at 140 °C afforded exclusively indole **11e**[31] (Scheme 16). This reaction pathway is ambiguous at the moment.



Scheme 16.

We have now succeeded in the isolation and structure determination of the dienylimine intermediate in the thermal reaction of the *o*-methoxyenehydrazine. Additionally, the *cis-syn*-isomer was obtained as the major product among dienylimines.

It is well-known[2–4,32,33] that Fischer indolization of (2-methoxyphenyl)hydrazone gives 7-methoxyindole as a minor product and the abnormal 6-substituted indole as a major product without the isolation of dienylimine. The isolation and determination of the dienylimine intermediates in the Fischer indolization of *o*-methoxy and *o*-methyl enehydrazines provides good evidence for the postulated reaction mechanism, including a stereochemical rationalization, particularly for the [3,3]-sigmatropic rearrangement

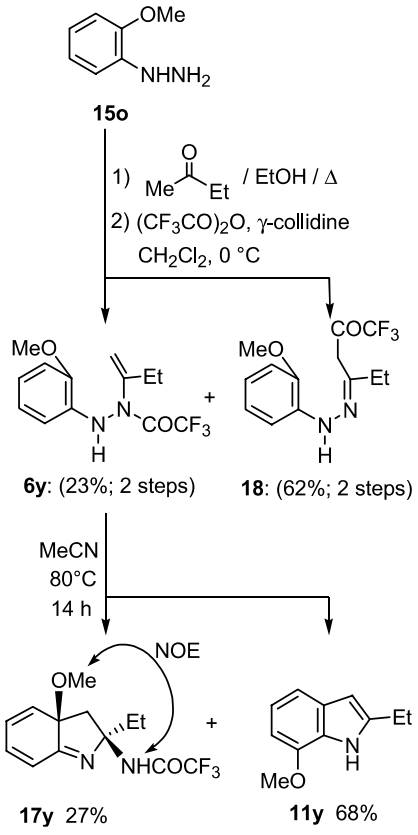


Scheme 17.

step. To the best of our knowledge, there has been only one paper[34] pertaining to the isolation of a pure dienylimine having a methyl group at the 3a-position in which the relative configurations at the 2-, 3- and 3a-position remain to be established. Additionally, Brown[35] has reported that attempts to isolate a tricyclic dienylimine having a methyl group were unsuccessful. Therefore, our result is the first example of isolation and structure determination of the tricyclic dienylimine with a methyl group.

The thermal reaction of *o*-substituted enehydrazine can be summarized as follows. The reaction of enehydrazines having an electron-donating group proceeded to give indolines, indoles, and dienylimines. The *cis-syn*-dienylimines were formed in preference to *cis-anti*-isomers. The degree of regioselectivity on [3,3]-sigmatropic rearrangement was shown to be dependent on the reaction solvent. Thus, in a polar solvent, ca. 1:1 mixture of indolines or indoles and dienylimines was obtained, while the reaction employing a less polar solvent gave the indole or indoline as a major product. In the case of enehydrazine bearing an electron-withdrawing group, prolonged reaction time and higher reaction temperature were required and no formation of dienylimines was observed.

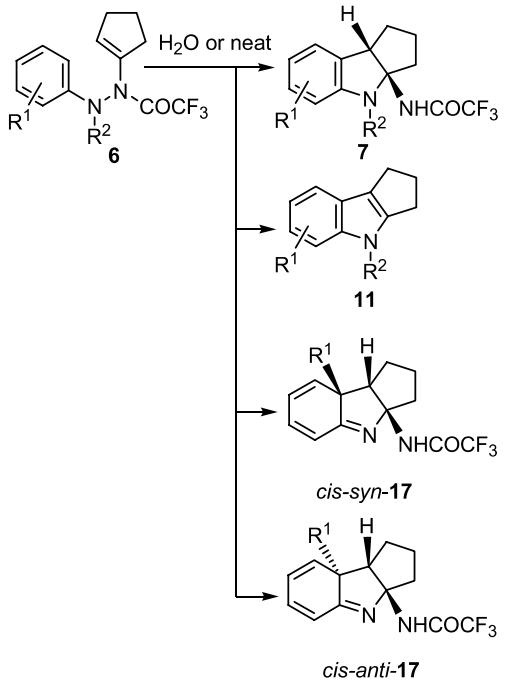
We next propose the possible reaction pathway for the formation of dienylimines **17t–v** (Scheme 17). The enehydrazines **6t–v** would exist in three different conformations **C**, **D**, and **E**. The indolines **7t–v** were obtained via



Scheme 18.

[3.3]-sigmatropic rearrangement of **C**. In the case of **7u**,**v**, they were converted into the indoles **11u**,**v** by the elimination of the trifluoroacetamido group. On the other hand, the rearrangement of **D** and **E** followed by the cyclization of the resulting imines **F** and **G** gave *cis-syn*-**17t–v** and *cis-anti*-**17t–v**, respectively. The conversion of **D** into *cis-syn*-**17t–v** proceeded more readily than that into *cis-anti*-**17t–v** because conformation **E** is less stable than conformation **D** due to the steric hindrance between a methoxy group and methylene on a cyclopentene or cyclohexene ring in **E**. The rearrangement of **6w**,**x** gave the indolines **7w**,**x** as the sole product. We are unable at this time to offer an explanation of the difference in regioselectivity between enehydrazine having an electron-donating group and enehydrazine having an electron-withdrawing group.

We next examined the reaction of acyclic enehydrazine **6y** having the *o*-methoxy group (Scheme 18). The condensation of **15o** with 2-butanone followed by acylation of the resulting hydrazone gave the enehydrazine **6y** and *C*-acylated product **18**. The isolated enehydrazine **6y** was heated at 80 °C to give *cis*-dienylimines **17y** and indole **11y**[36] in 27% and 68% yields, respectively.



Scheme 19.

2.4. [3,3]-Sigmatropic rearrangement of enehydrazines under both aqueous and solvent-free conditions

Due to the natural abundance of water as well as the inherent advantages of using water as a solvent, much interest has been recently growing in developing organic synthetic reactions in water.[37] We next investigated the [3,3]-sigmatropic rearrangement of enehydrazines **6a**,**l**,**o**,**t**,**x** in aqueous media (Scheme 19, Table 10). Suspension of enehydrazine **6a** in water was heated at 65 °C. Extraction and purification of the product by chromatography gave the indoline **7a** and indole **11a** in 61 and 33% yield, respectively (entry 1). The reaction of enehydrazine **6l** having a *p*-methoxy group gave the indole **11l** as the sole product. When a methoxy group exists at the *o*-position on the benzene ring, the dienylimines **17t** were obtained in addition to indoline **7t** and indole **11t**. The reaction of enehydrazines **6o** and **6x** bearing a nitro group on the benzene ring did not occur even at 100 °C.

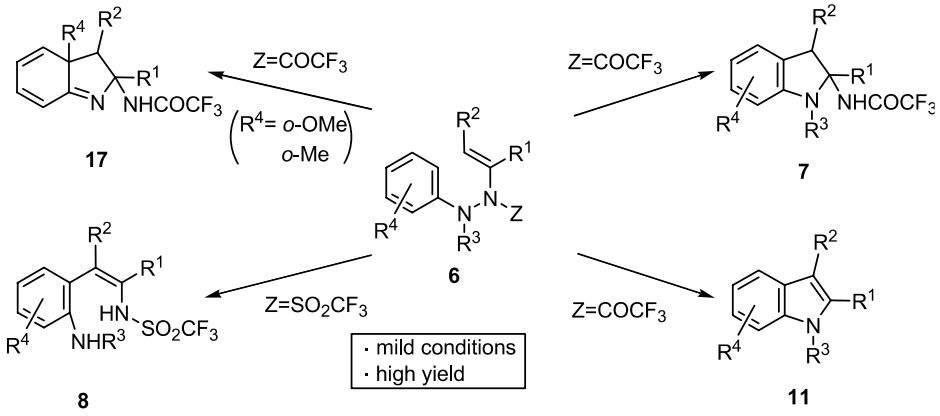
Finally, the rearrangement of enehydrazines was examined under solvent-free conditions (Scheme 19, Table 10). The reaction of enehydrazine **6a** at 65 °C afforded the indoline **7a** as a major product while the enehydrazine **6l** having a *p*-methoxy group gave the indole **11l** as the sole product (entries 6 and 7). In the case of enehydrazine **6o** and **6x** having a nitro group which did not undergo the reaction at 100 °C, heating at from 120 to 160 °C allowed the reaction to proceed but inefficiently (entries 8 and 10). The reaction of *o*-methoxy substituted enehydrazine **6t** gave **7t**, **11t**, and **17t** in favor of **7t** (entry 9). It is worth mentioning that the indoles **11** are predominantly obtained under both aqueous and solvent-free conditions except the case of *o*-methoxy substituted enehydrazine **6t**. Particularly, the enehydrazine **6l** having a *p*-methoxy group gave the indole **11l** even at 65 °C under these conditions while the reaction of **6l** proceeded at 65 °C in a solvent to give the indoline **7l** as the sole product (entry 1 in Table 7, Scheme 13).

3. Conclusion

We have established a novel [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydrazines for synthesis of indolines and indoles. At below 100 °C, *N*-trifluoroacetyl enehydrazine having a cyclopentene ring smoothly underwent [3,3]-sigmatropic rearrangement followed by cyclization to give indolines in excellent yield. On the other hand, both cyclohexenyl *N*-trifluoroacetyl enehydrazine and

Table 10. The thermal reaction of enehydrazines **6** under aqueous and solvent-free conditions

Entry	Substrate	R^1	R^2	Solvent	Temperature (°C)	Time (h)	Yield (%)		
							7	**11**	**17** (*cis-syn*:*cis-anti*)
1	**6a**	H	Ph	H_2O	65	5	61	33	—
2	**6l**	*p*-OMe	H	H_2O	65	0.5	—	60	—
3	**6o**	*p*-NO_2	H	H_2O	100	7	—	—	—
4	**6t**	*o*-OMe	H	H_2O	65	7	8	39	29 (14:1)
5	**6x**	*o*-NO_2	H	H_2O	100	7	—	—	—
6	**6a**	H	Ph	Neat	65	4	83	4	—
7	**6l**	*p*-OMe	H	Neat	65	5	—	89	—
8	**6o**	*p*-NO_2	H	Neat	160	5	—	41	—
9	**6t**	*o*-OMe	H	Neat	65	5	51	10	25 (4:1)
10	**6x**	*o*-NO_2	H	Neat	120	10	5	17	—



Scheme 20.

acyclic *N*-trifluoroacetyl enehydrazine gave indoles in good yield under the almost same conditions. The rearrangement of enehydrazine having an *o*-methoxy or an *o*-methyl group on the benzene ring gave dienylimines that were clearly characterized for the first time. The *N*-trifluoromethanesulfonyl enehydrazine was converted into the rearranged product at low temperature (Scheme 20).

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography (FCC) was preformed using E. Merck Kieselgel 60 (230–400 mesh). Medium-pressure column chromatography (MCC) was performed using Lober Größe B (E. Merck 310-25, Lichroprep Si60).

4.2. General procedure (A) for preparation of *N*-acyl enehydrazines 6

To a solution of hydrazone (10 mmol) in CH_2Cl_2 (100 mL) were added γ-collidine (30 mmol) and the corresponding acid anhydride (20 mmol) at 0 °C. After being stirred at the same temperature for 1.5–5.5 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by FCC (hexane/AcOEt 20:1–7:1) gave the *N*-acyl enehydrazine **6**.

4.2.1. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2,2-diphenylhydrazide (6a). According to the general procedure (A) given for preparation of *N*-acyl enehydrazine, the treatment of hydrazone **5a**[12] (2.5 g, 10 mmol) with TFAA (2.8 mL, 20 mmol) in the presence of γ-collidine (3.8 mL, 30 mmol) gave the enehydrazine **6a** (3.43 g, 99%) as a yellow oil; IR ($CHCl_3$) 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (2H, br quint, $J=8$ Hz), 2.28 and 2.58 (each 2H, m), 5.80 (1H, br s), 7.01–7.39 (10H, m); HRMS (EI, *m/z*) calcd for $C_{19}H_{17}F_3N_2O$ (M^+) 346.1292, found 346.1273.

4.2.2. Trichloroacetic acid 1-(1-cyclopenten-1-yl)-2,2-diphenylhydrazide (6b). According to the general procedure (A) given for preparation of *N*-acyl enehydrazine, the treatment of hydrazone **5a**[12] (2.5 g, 10 mmol) with trichloroacetic anhydride (4.1 mL, 20 mmol) in the presence of γ-collidine (3.8 mL, 30 mmol) gave the enehydrazine **6b** (3.90 g, 99%) as a yellow oil; IR ($CHCl_3$) 1699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (2H, br quint, $J=8$ Hz), 2.28 and 2.58 (each 2H, m), 5.81 (1H, br s), 7.01–7.39 (10H, m); HRMS (EI, *m/z*) calcd for $C_{19}H_{17}^{35}Cl_3N_2O$ (M^+) 394.0406, found 394.0406.

4.2.3. Acetic acid 1-(1-cyclopenten-1-yl)-2,2-diphenylhydrazide (6c). To a solution of hydrazone **5a**[12] (500 mg, 2.0 mmol) and γ-collidine (727 mg, 6.0 mmol) in CH_2Cl_2 (15 mL) was added acetyl chloride (314 mg, 4.0 mmol) and dimethylaminopyridine (DMAP) (12.2 mg, 0.1 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by FCC (*n*-hexane/ethyl acetate 10:1) gave the *N*-acetyl enehydrazine **6c** (548 mg, 99%) as a yellow oil; IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (2H, br quint, $J=7.5$ Hz), 2.04 (3H, s), 2.29 and 2.66 (each 2H, m), 5.70 (1H, br s), 6.99–7.33 (10H, m); HRMS (EI, *m/z*) calcd for $C_{19}H_{20}N_2O$ (M^+) 292.1575, found 292.1576.

4.3. General procedure for thermal reaction of *N*-acyl enehydrazines 6

A solution of enehydrazines **6** (0.12–0.50 mmol) in solvent (5–15 mL) was heated while monitoring the reaction by TLC. The reaction mixture was concentrated under reduced pressure. Purification of the residue by MCC (hexane/AcOEt 20:1–5:1) gave the products.

4.4. Thermal reaction of 6a–c (Table 2)

According to the general procedure given for the reaction of **6**, the enehydrazines **6a–c** were heated under the conditions shown in Table 2 to give the indoline **7a–c** in the yield shown in Table 2.

4.4.1. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-4-phenylcyclopent[*b*]indole (7a). Colorless crystals, mp 137–140 °C (hexane/AcOEt); IR ($CHCl_3$) 3425, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59–1.65 (1H, m), 1.79–1.86 (2H, m), 2.14–2.27 (2H, m), 2.35–2.42 (1H, m), 3.96 (1H, br dd, J=9.5, 3 Hz), 6.58 (1H, br d, J=8 Hz), 6.74 (1H, br s), 6.81 (1H, br t, J=8 Hz), 7.06 (1H, br t, J=8 Hz), 7.15 (1H, br d, J=8 Hz), 7.23 (1H, br t, J=8 Hz), 7.26 (2H, br d, J=8 Hz), 7.40 (2H, br t, J=8 Hz). NOE was observed between 8b-H (δ 3.96) and NH (δ 6.74) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 34.9, 36.4, 52.9, 90.9, 108.7, 115.4 (q, CF_3), 119.7, 124.5, 125.1, 125.8, 127.5, 129.7, 132.1, 140.2, 148.1, 155.7 (q, $COCF_3$); HRMS (EI, m/z) calcd for $C_{19}H_{17}F_3N_2O$ (M^+) 346.1292, found 346.1277. Anal. Calcd for $C_{19}H_{17}F_3N_2O$: C, 65.89; H, 4.95; N, 8.09, found: C, 65.93; H, 5.13; N, 8.14.

4.4.2. *cis*-3a-[(Trichloroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-4-phenylcyclopent[*b*]indole (7b). A yellow oil; IR ($CHCl_3$) 3424, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (1H, br s), 1.63 (2H, m), 1.83 (1H, m), 2.16–2.42 (3H, m), 4.00 (1H, dd, J=9.5, 3 Hz), 6.60 (1H, d, J=8 Hz), 6.80 (1H, br t, J=8 Hz), 6.93 (1H, br t, J=8 Hz), 7.06 (1H, m), 7.15–7.42 (5H, m); HRMS (EI, m/z) calcd for $C_{19}H_{17}^{35}Cl_3N_2O$ (M^+) 394.0406, found 394.0406.

4.4.3. *cis*-3a-Acetylamino-1,2,3,3a,4,8b-hexahydro-4-phenylcyclopent[*b*]indole (7c). Colorless crystals, mp 218–221 °C (AcOEt); IR ($CHCl_3$) 3436, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (1H, m), 1.70–1.81 (2H, m), 1.90 (3H, s), 2.08 (1H, m), 2.20–2.38 (2H, m), 3.96 (1H, dd, J=9.5, 3 Hz), 6.02 (1H, br s), 6.62 (1H, d, J=8 Hz), 6.76 (1H, br t, J=8 Hz), 7.02 (1H, br t, J=8 Hz), 7.13 (1H, m), 7.16–7.49 (5H, m); HRMS (EI, m/z) calcd for $C_{19}H_{20}N_2O$ (M^+) 292.1575, found 292.1576. Anal. Calcd for $C_{19}H_{20}N_2O\cdot 1/100H_2O$: C, 77.45; H, 6.77; N, 9.47, found: C, 77.28; H, 6.93; N, 9.49.

4.4.4. Reaction of hydrazone 5a with triflic anhydride (Table 3). (entry 1) According to the general procedure (A) given for the preparation of enehydrazine **6**, the hydrazone **5a** (2.50 g, 10 mmol) was treated with Tf_2O (5.64 g, 20 mmol) in the presence of γ-collidine (3.46 g, 30 mmol) at 0 °C. After being stirred at the same temperature for 3 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by FCC (hexane/ethyl acetate 20:1) gave *N*-[2-[2-(phenylamino)phenyl]cyclopenten-1-yl]trifluoromethanesulfonamide (**8d**) (191 mg, 5%) as a yellow oil; IR ($CHCl_3$) 3327, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (2H, br quint, J=8 Hz), 2.26 (1H, br s), 2.79 (4H, m), 7.05–7.38 (9H, m), 8.56 (1H, br s); HRMS (EI, m/z) calcd for $C_{18}H_{17}F_3N_2O_2S$ (M^+) 382.0962, found 382.0959.

(entry 2) To a solution of hydrazone **5a** (52.8 mg, 0.21 mmol) in CH_2Cl_2 (7 mL) was added γ-collidine (38.8 mg, 0.32 mmol) and Tf_2O (59.2 mg, 0.21 mmol) at −78 °C. The reaction mixture was stirred at the same temperature for 1.5 h, monitoring the reaction by TLC. The reaction mixture was purified without concentration by FCC (*n*-hexane/ethyl acetate 20:1) to give **8d** (20.1 mg, 25%) as a yellow oil.

(entry 3) To a solution of hydrazone **5a** (35.0 mg, 0.14 mmol) in CH_2Cl_2 (4 mL) was added triethylamine (14.2 mg, 0.14 mmol) and Tf_2O (39.5 mg, 0.14 mmol) at −78 °C. The reaction mixture was stirred at the same temperature for 1.5 h, monitoring the reaction by TLC. The reaction mixture was purified without concentration by FCC (*n*-hexane/ethyl acetate 20:1) to give **8d** (37.5 mg, 70%) as a yellow oil.

4.4.5. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-phenylhydrazide (6e). According to the general procedure (A) given for the preparation of enehydrazine **6**, the acylation of hydrazone **5b**[13] (348 mg, 2 mmol) with TFAA (0.6 mL, 4 mmol) gave enehydrazine **6e** (400 mg, 74%) as a yellow oil; IR ($CHCl_3$) 3421, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (2H, br quint, J=8 Hz), 2.36 and 2.69 (each 2H, m), 5.72 (1H, br s), 6.17 (1H, br s), 6.75 (2H, br d, J=8.5 Hz), 6.88 (1H, br t, J=8.5 Hz), 7.28 (2H, br d, J=8.5 Hz); HRMS (EI, m/z) calcd for $C_{13}H_{13}F_3N_2O$ (M^+) 270.0980, found 270.0994.

4.4.6. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (7e). According to the general procedure given for the thermal reaction of **6**, **6e** (30 mg, 0.11 mmol) was heated in toluene (15 mL) at 90 °C to give the indoline **7e** (17 mg, 56%) as a colorless oil; IR ($CHCl_3$) 3424, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, m), 1.74–1.88 (2H, m), 2.20 (1H, m), 2.31–2.42 (2H, m), 3.69 (1H, dd, J=8.5, 2 Hz), 4.67 (1H, br s), 6.57 (1H, dd, J=7, 1 Hz), 6.78 (1H, td, J=7, 1 Hz), 6.79 (1H, br s), 7.07 (2H, m); HRMS (EI, m/z) calcd for $C_{13}H_{13}F_3N_2O$ (M^+) 270.0980, found 270.0962.

4.4.7. Thermal reaction of 6a at 140 °C (entry 4, Table 4). According to the general procedure given for the thermal reaction of **6**, **6a** was heated in xylene at 140 °C to give 1,2,3,4-tetrahydro-4-phenylcyclopent[*b*]indole **11a**[14] (165 mg, 92%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.55 (2H, br quint, J=7 Hz), 2.91 (4H, t-like, J=7 Hz), 7.10–7.52 (9H, m); HRMS (EI, m/z) calcd for $C_{17}H_{15}N$ (M^+) 233.1203, found 233.1177.

4.4.8. Trifluoroacetic acid 1-(1-cyclohexen-1-yl)-2,2-diphenylhydrazide (6f). According to the general procedure (A) given for the preparation of enehydrazine **6**, the acylation of diphenylhydrazone[15] (2.64 g, 10 mmol) of cyclohexanone with TFAA (2.8 mL, 20 mmol) gave enehydrazine **6f** (3.38 g, 94%) as a yellow oil; IR ($CHCl_3$) 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44–1.80 (4H, m), 2.04 and 2.35 (each 2H, m), 5.55 (1H, br s), 7.00–7.24 (10H, m); HRMS (EI, m/z) calcd for $C_{20}H_{19}F_3N_2O$ (M^+) 360.1448, found 360.1423.

4.4.9. 1,2,3,4-Tetrahydro-9-phenyl-9*H*-carbazole (11f) (entry 5, Table 4). According to the general procedure given for the thermal reaction of **6**, **6f** (75 mg, 0.21 mmol) was heated in THF (10 mL) at 65 °C to give the indole **11f**[16] (27.5 mg, 53%) as a yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.89 (4H, br quint, J=3 Hz), 2.60 and 2.80 (each 2H, m), 7.02–7.54 (9H, m); HRMS (EI, m/z) calcd for $C_{18}H_{17}N$ (M^+) 247.1360, found 247.1357.

4.4.10. Conversion of indoline 7a into indole 11a. A solution of indoline **7a** (82.3 mg, 0.24 mmol) in xylene (4 mL) was refluxed, monitoring the reaction by TLC. After being refluxed at the same temperature for 4 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by MCC (hexane/ethyl acetate 9:1) gave **11a** (35.4 mg, 92%).

4.4.11. *cis*-1,2,3,3a,4,8b-Hexahydro-4-phenylcyclopent-[*b*]indole (12).[17] To a stirred solution of indoline **7a** (187 mg, 0.54 mmol) in AcOH (3 mL) was added $NaBH_3$-CN (67.9 mg, 1.08 mmol) at 0 °C. After being stirred at room temperature for 19 h, the reaction mixture was neutralized with 4 M-NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by MCC (hexane/AcOEt 9:1) afforded indoline **12** (129 mg, 71%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 and 1.64 (each 1H, m), 1.80–1.96 (3H, m), 2.03 (1H, dddd, J=12.5, 11, 8.5, 6.5 Hz), 3.83 (1H, td, J=8.5, 3 Hz), 4.73 (1H, ddd, J=8.5, 6.5, 3 Hz), 6.73–7.31 (9H, m); NOE was observed between 8b-H (δ 3.83) and 3a-H (δ 4.75) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 34.0, 34.8, 45.5, 68.7, 108.2, 118.7, 119.0, 121.1, 124.7, 127.1, 129.1, 135.0, 143.4, 147.3; HRMS (EI, *m*/*z*) calcd for $C_{17}H_{17}N$ (M^+) 235.1360, found 235.1361.

4.4.12. *cis*-7-Bromo-4-(4-bromophenyl)-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (14). To a solution of 1,2,3,3a,4,8b-hexahydro-4-phenylcyclopent[*b*]indole **12** (105.2 mg, 0.45 mmol) in acetone (4.5 mL) was added *N*-bromosuccinimide (NBS) (159.4 mg, 0.90 mmol) at 0 °C under a nitrogen atmosphere in the dark. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with H_2O and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated at reduced pressure. The crude solid obtained was recrystallized from *n*-hexane to afford **14** (169.8 mg, 97%) as colorless crystals, mp 151–153 °C (hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56–1.69 (2H, m), 1.81–1.88 (3H, m), 1.97–2.10 (1H, m), 3.80 (1H, br td, J=8.5, 3 Hz), 4.71 (1H, ddd, J=8.5, 6.5, 3 Hz), 6.80 (1H, d, J=8 Hz), 7.11 (2H, br d, J=8 Hz), 7.12 (1H, dd, J=8, 2.5 Hz), 7.19 (1H, dd, J=2.5, 1.5 Hz), 7.41 (2H, br d, J=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{15}Br_2N$ (M^+) 390.9574, found 390.9570. NOE was observed between 8b-H (δ 3.80) and 3a-H (δ 4.71) in NOESY spectroscopy.

Determination of single-crystal structures by X-ray crystallography: the dibromide **14** was recrystallized from acetone to give single crystals suitable for X-ray single crystallographic analysis. X-ray diffraction data was collected on a Rigaku RAPID imaging plate with two-dimensional area detector and graphite-monochromatized Cu Kα radiation (λ=1054186Å). The crystallographic calculation was performed with the TEXSAN software package from the Molecular Structure Corporation. The crystal structure was solved by direct methods (SIR-92), and refined by the full-matrix least-squares method. All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were located in idealized positions and were not subjected to further refinement. X-ray diffraction study was performed at 93 K. The independent four molecules are in a unit cell. Crystallographic data of: C_{68} H_{60} Br_8 N_4; space group *P*1; *a*=8.371(1) Å, *b*=12.564(2) Å, *c*=13.862(2) Å, α=86.99(1)°, β=81.07(1)°, γ=89.91(1)°; *V*=1438.2(4) Å^3 *Z*=1; *T*=93.2 K; μ=7.044 mm^{-1}; reflection total: 14240, unique: 4774, observed: 4774($I > -10.0\sigma(I)$); parameters refined:721; *R*1=0.067, *Rw*=0.181; GOF=1.81. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-292640. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.uk).

4.4.13. Trifluoroacetic acid 2,2-diphenyl-1-[1-(5-methylcyclopenten-1-yl)]hydrazide (6g). According to the general procedure (A) given for the preparation of enehydrazine **6**, the acylation of hydrazone **5c** (528 mg, 2 mmol) with TFAA (0.6 mL, 4 mmol) gave enehydrazine **6g** (520 mg, 72%) as a yellow oil; IR ($CHCl_3$) 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, d, J=8.5 Hz), 2.20 (4H, m), 3.56 (1H, m), 5.49 (1H, br s), 6.98–7.38 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{20}H_{19}F_3N_2O$ (M^+) 360.1448, found 360.1458.

4.5. General procedure (B) for preparation of *N*-acyl enehydrazines 6

To a solution of hydrazine (10 mmol) in EtOH (50 mL) was added ketone (20 mmol) at room temperature. After being stirred at the same temperature for 3–5 h, the reaction mixture was concentrated under reduced pressure to give the crude hydrazone. To a stirred solution of crude hydrazone in CH_2Cl_2 (100 mL) was added γ-collidine (30 mmol) and TFAA (20 mmol) at 0 °C. After being stirred at the same temperature for 1–5 h, the reaction mixture was concentrated under the reduced pressure. Purification of the residue by FCC (hexane/AcOEt 20:1–5:1) gave the enehydrazine **6**.

4.5.1. Trifluoroacetic acid 1-[1-(5-methylcyclopenten-1-yl)]-2-phenylhydrazide (6h). According to the general procedure (B) given for the preparation of **6**, the condensation of phenylhydrazine with 2-methylcyclopentanone (1.02 g, 10.4 mmol) followed by acylation of the resulting hydrazone with TFAA (2.9 mL, 20.8 mmol) gave enehydrazine **6h** (2.20 g, 75%) as a yellow oil; IR ($CHCl_3$) 3354, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, d, J=8.5 Hz), 2.19 (4H, m), 3.30 (1H, m), 5.53 (1H, br s), 6.05 (1H, br s), 6.71–7.32 (5H, m); HRMS (EI, *m*/*z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1136, found 284.1142.

4.5.2. (3α,3aα,8bα)-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-3-methyl-4-phenyl-cyclopent-[*b*]indole (7g). According to the general procedure given for the thermal reaction of **6**, **6g** (75.6 mg, 0.21 mmol) was heated in THF (10 mL) at 65 °C to give the indoline **7g** (57.5 mg, 76%) as colorless crystals, mp 92–94 °C (hexane/AcOEt); IR ($CHCl_3$) 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, d, J=7.5 Hz), 1.62–1.67 (2H, m), 1.91–1.96 (1H, m), 2.41–2.51 (2H, m), 4.13 (1H, br dd, J=9.5, 6 Hz), 6.40 (1H, br d, J=8 Hz), 6.71 (1H, br s), 6.78 (1H, br

t, J=8 Hz), 7.02 (1H, br t, J=8 Hz), 7.14 (1H, br d, J=8 Hz), 7.24 (2H, br d, J=8 Hz), 7.28 (1H, br t, J=8 Hz), 7.41 (2H, br t, J=8 Hz). NOE were observed between 3-Me (δ 0.95) and 8b-H (δ 4.13), 3-Me (δ 0.95) and NH (δ 6.71), NH (δ 6.71) and 8b-H (δ 4.13) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 32.6, 33.3, 43.9, 52.6, 91.3, 108.0, 115.7 (q, *C*F_3), 119.2, 123.8, 126.6, 127.1, 127.5, 129.8, 131.8, 140.3, 148.5, 156.1 (q, *C*OCF$_3$); HRMS (EI, *m*/*z*) calcd for $C_{20}H_{19}F_3N_2O$ (M^+) 360.1448, found 360.1455. Anal. Calcd for $C_{20}H_{19}F_3N_2O$: C, 66.66; H, 5.31; N, 7.77, found: C, 66.71; H, 5.42; N, 7.79.

4.5.3. 1,2,3,4-Tetrahydro-3-methylcyclopent[*b*]indole (11h). According to the general procedure given for the thermal reaction of **6**, **6h** (59.6 mg, 0.21 mmol) was heated in toluene(10 mL) at 90 °C to give the indole **11h** (35.5 mg, 99%) as a yellow oil; IR ($CHCl_3$) 3475 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, d, J=7 Hz), 2.05 (2H, m), 2.64–2.90 (3H, m), 6.95–7.48 (4H, m), 7.78 (1H, br s); HRMS (EI, *m*/*z*) calcd for $C_{12}H_{13}N$ (M^+) 171.1047, found 171.1065.

4.5.4. Trifluoroacetic acid 2,2-diphenyl-1-(1-ethyl-1-propenyl)hydrazide (6i). According to the general procedure (A) given for the preparation of **6**, the acylation of hydrazone **5e** (2.52 g, 10 mmol) with TFAA (2.8 mL, 20 mmol) gave the enehydrazine **6i** (1.67 g, 48%) as a yellow oil; IR ($CHCl_3$) 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, t, J=8 Hz), 1.64 (3H, d, J=6 Hz), 2.37 (2H, br q, J=8 Hz), 5.28 (1H, br q, J=6 Hz), 7.02 and 7.32 (each 5H, m); HRMS (EI, *m*/*z*) calcd for $C_{19}H_{19}F_3N_2O$ (M^+) 348.1449, found 348.1451.

4.5.5. Acylation of hydrazone 5f with TFAA. According to the general procedure given for the preparation of enehydrazine **6**, acylation of **5f**[24] (2.38 g, 10 mmol) with TFAA (2.8 mL, 20 mmol) gave **6j** (2.07 g, 62%) and **6k** (668 mg, 20%).

4.5.6. Trifluoroacetic acid 1-(1-methylenepropyl)-2,2-diphenylhydrazide (6j). A yellow oil; IR ($CHCl_3$) 1713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, m), 2.24 (2H, br q, J=8 Hz), 4.09 and 5.07 (each 1H, br s), 7.04 and 7.32 (each 5H, m); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{17}F_3N_2O$ (M^+) 334.1292, found 334.1285.

4.5.7. Trifluoroacetic acid 1-(1-methyl-2-propenyl)-2,2-diphenylhydrazide (6k). A yellow oil; IR ($CHCl_3$) 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (3H, br d, J=7 Hz), 1.98 (3H, s), 5.33 (1H, br q, J=7 Hz), 7.07 and 7.35 (each 5H, m); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{17}F_3N_2O$ (M^+) 334.1292, found 334.1291.

4.6. Thermal reaction of enehydrazines 6i–k

According to the general procedure for thermal reaction of enehydrazine **6**, **6i–k** was heated at temperature shown in Table 6 to afford **11i–k** in the yield shown in Table 6.

4.6.1. 2-Ethyl-3-methyl-1-phenyl-1*H*-indole (11i). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (3H, t, J=8 Hz), 2.34 (3H, s), 2.68 (2H, q, J=8 Hz), 7.07 (3H, m), 7.32 (2H, m), 7.49 (4H, m); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{17}N$ (M^+) 235.1360, found 235.1374.

4.6.2. 2-Ethyl-1-phenyl-1*H*-indole (11j). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (3H, t, J=8 Hz), 2.63 (2H, q, J=8 Hz), 6.42 (1H, br s), 7.08 (3H, m), 7.35 (2H, m), 7.43–7.61 (4H, m); HRMS (EI, *m*/*z*) calcd for $C_{16}H_{15}N$ (M^+) 221.1203, found 221.1226.

4.6.3. 2,3-Dimethyl-1-phenyl-1*H*-indole (11k).[25] A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 and 2.32 (each 3H, s), 7.10 (3H, m), 7.32 (2H, m), 7.41–7.59 (4H, m); HRMS (EI, *m*/*z*) calcd for $C_{16}H_{15}N$ (M^+) 221.1203, found 221.1208.

4.7. Preparation of *N*-trifluoroacetyl enehydrazines 6l–n

According to the general procedure (B) given for the preparation of enehydrazine **6**, the condensation of corresponding hydrazines **15g–i** with cyclopentanone followed by acylation of hydrazones **5g–i** gave **6l–n** in the yield shown in Table 7.

4.7.1. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(4-methoxyphenyl)hydrazide (6l). A yellow oil; IR ($CHCl_3$) 3478, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (2H, br q, J=8 Hz), 2.34 and 2.66 (each 2H, m), 3.77 (3H, s), 5.71 (1H, br s), 5.92 (1H, br s), 6.72 (2H, br d, J=8.5 Hz), 6.84 (2H, br d, J=8.5 Hz); HRMS (EI, *m*/*z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1101.

4.7.2. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(4-methylphenyl)hydrazide (6m). A yellow oil; IR ($CHCl_3$) 3354, 1717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (2H, br quint, J=7.5 Hz), 2.28 (3H, s), 2.34 and 2.68 (each 2H, m), 5.70 (1H, br s), 5.94 (1H, br s), 6.64 and 7.07 (each 2H, br d, J=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1113.

4.7.3. Trifluoroacetic acid 2-(4-chlorophenyl)-1-(1-cyclopenten-1-yl)hydrazide (6n). A yellow oil; IR ($CHCl_3$) 3353, 1721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (2H, br quint, J=7.5 Hz), 2.35 and 2.67 (each 2H, m), 5.64 (1H, br s), 6.13 (1H, br s), 6.69 (2H, br d, J=8.5 Hz), 7.24 (2H, br d, J=8.5 Hz); HRMS (EI, *m*/*z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0602.

4.7.4. Conversion of hydrazine 15j into 6o. According to the general procedure (B) given for the preparation of **6**, the condensation of hydrazine **15j** (3.06 g, 20 mmol) with cyclopentanone (1.68 g, 40 mmol) followed by acylation of the resulting hydrazone **5j** with TFAA (5.6 mL, 40 mmol) gave the enehydrazine **6o** (315 mg, 10%) and **5j** (3.9 g, 89%). According to the general procedure (A) given for preparation of **6**, the acylation of **5j** (3.9 g, 17.8 mmol) with TFAA (5 mL, 35.6 mmol) gave the enehydrazine **6o** (1.74 g, 31% from **15j**) and diacylated enehydrazine **16** (3.58 g, 49% from **15j**).

4.7.5. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(4-nitrophenyl)hydrazide (6o). A yellow oil; IR ($CHCl_3$) 3310, 1727, 1525, 1342 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (2H, br quint, J=7 Hz), 2.38 and 2.71 (each 2H, m),

5.71 (1H, br s), 6.62 (1H, br d, J=8.5 Hz), 6.82 (1H, d, J=8.5 Hz), 6.83 (1H, br s), 8.20 (2H, d, J=8.5 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0828.

4.7.6. Cyclopentanone 4-nitrophenylhydrazone (5j).[26] A yellow oil; IR ($CHCl_3$) 3602, 1521, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 and 1.93 (each 2H, quint, J=7 Hz), 2.31 and 2.51 (each 2H, br td, J=7, 2 Hz), 7.01 (2H, br d, J=9 Hz,), 7.30 (1H, br s), 8.13 (2H, br d, J=9 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}N_3O_2$ (M^+) 219.1007, found 219.1014.

4.7.7. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-trifluoroacetyl-2-(4-nitrophenyl) hydrazide (16). A yellow oil; IR ($CHCl_3$) 1725, 1752, 1535, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (2H, m), 2.46 (4H, m), 5.85 (1H, br s), 7.63 (2H, br d, J=8.5 Hz), 8.34 (2H, br d, J=8.5 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{11}F_6N_3O_4$ (M^+) 411.0652, found 411.0654.

4.8. Thermal reaction of *N*-trifluoroacetyl enehydrazines 6l–o

According to the general procedure given for the thermal reaction of **6**, enehydrazines **6l–o** were heated at the temperature shown in Table 7 to give indoline **7l–o** and indole **11l–o** in the yield shown in Table 7.

4.8.1. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-7-methoxycyclopent[*b*]indole (7l). A yellow oil; IR ($CHCl_3$) 3478, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, m), 1.82 (2H, m), 2.08 (1H, m), 2.40 (2H, m), 3.72 (1H, br d, J=8 Hz), 3.75 (3H, s), 4.31 (1H, br s), 6.52 (1H, br d, J=8 Hz), 6.65 (1H, dd, J=8, 2 Hz), 6.67 (1H, d, J=2 Hz), 6.78 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1095.

4.8.2. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-7-methylcyclopent[*b*]indole (7m). A yellow oil; IR ($CHCl_3$) 3423, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, m), 1.81 (2H, m), 2.13 (1H, m), 2.26 (3H, s), 2.38 (2H, m), 3.68 (1H, dd, J=10, 1 Hz), 4.49 (1H, br s), 6.49 (1H, br d, J=8.5 Hz), 6.74 (1H, br s), 6.86–6.91 (2H, m); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1153.

4.8.3. *cis*-7-Chloro-3a-[(trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (7n). A yellow oil; IR ($CHCl_3$) 3424, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, m), 1.72–1.90 (2H, m), 2.20 (1H, m), 2.28–2.38 (2H, m), 3.67 (1H, dd, J=10.5, 2.5 Hz), 4.66 (1H, br s), 6.47 (1H, br d, J=8.5 Hz), 6.81 (1H, br s), 7.00–7.04 (2H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0595.

4.8.4. 7-Chloro-1,2,3,4-tetrahydrocyclopent[*b*]indole (11n).[38] A yellow oil; IR ($CHCl_3$) 3475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (2H, br quint, J=8 Hz), 2.76–2.88 (4H, t-like, J=8 Hz), 7.03 (1H, dd, J=8.5, 2 Hz), 7.18 (1H, br d, J=8.5 Hz), 7.39 (1H, br d, J=2 Hz), 7.84 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{10}^{35}ClN$ (M^+) 191.0501, found 191.0516.

4.8.5. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-7-nitrocyclopent[*b*]indole (7o). A yellow oil; IR ($CHCl_3$) 3439, 1725, 1518, 1330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (1H, m), 1.78–1.94 (2H, m), 2.18 and 2.32 (each 1H, m), 2.44 (1H, m), 3.68 (1H, dd, J=9, 2 Hz), 5.59 (1H, br s,), 6.49 (1H, d, J=8.5 Hz), 6.99 (1H, br s), 7.95 (1H, br s), 8.19 (1H, dd, J=8.5, 2 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0848.

4.8.6. 1,2,3,4-Tetrahydro-7-nitrocyclopent[*b*]indole (11o). A yellow oil; IR ($CHCl_3$) 3468, 1519, 1334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (2H, br quint, J=8 Hz), 2.88 (4H, t-like, J=8 Hz), 7.31 (1H, dd, J=8.5, 1 Hz), 8.05 (1H, dd, J=8.5, 2.5 Hz), 8.28 (1H, br s), 8.39 (1H, br d, J=2.5 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{10}N_2O_2$ (M^+) 202.0742, found 202.0748.

4.9. Preparation of *N*-trifluoroacetyl enehydrazines 6p–s

According to the general procedure (B) given for the preparation of enehydrazine **6**, the condensation of corresponding hydrazines **15k–n** with cyclopentanone followed by acylation of the corresponding hydrazones gave **6p–s** in 36–99% yields.

4.9.1. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(3-methoxyphenyl)hydrazide (6p). A yellow oil; IR ($CHCl_3$) 3355, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (2H, br quint, J=7.5 Hz), 2.35 and 2.68 (each 2H, m), 3.77 (3H, s), 5.73 (1H, br s), 6.09 (1H, br s), 6.29 (1H, br s), 6.34 (1H, br d, J=8.5 Hz), 6.51 (1H, ddd, J=8.5, 2.5, 1 Hz), 7.17 (1H, t, J=8.5 Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1079.

4.9.2. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(3-methylphenyl)hydrazide (6q). A yellow oil; IR ($CHCl_3$) 3455, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (2H, br quint, J=7.5 Hz), 2.31 (3H, s), 2.35 and 2.68 (each 2H, m), 5.70 (1H, br s), 6.02 (1H, br s), 6.52 (1H, br d, J=8 Hz), 6.56 (1H, br s), 6.78 (1H, br d, J=8 Hz), 7.16 (1H, br t, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1154.

4.9.3. Trifluoroacetic acid 2-(3-chlorophenyl)-1-(1-cyclopenten-1-yl)hydrazide (6r). A yellow oil; IR ($CHCl_3$) 3408, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (2H, br quint, J=7.5 Hz), 2.36 and 2.69 (each 2H, m), 5.74 (1H, br s), 6.47 (1H, br s), 6.63 and 6.93 (each 1H, m), 6.76 (1H, br s), 7.19 (1H, br dd, J=8.5, 8 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0589.

4.9.4. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(3-nitrophenyl)hydrazide (6s). A yellow oil; IR ($CHCl_3$) 3315, 1725, 1515, 1340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.94 (2H, br quint, J=7.0 Hz), 2.37 and 2.72 (each 2H, m), 5.68 (1H, br s), 6.37 (1H, br s), 7.06 (1H, br dd, J=8, 2 Hz), 7.46 (1H, br t, J=8 Hz), 7.61 (1H, br s), 7.84 (1H, dd, J=8, 2 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0841.

4.10. Thermal reaction of *N*-trifluoroacetyl enehydrazines 6p–s

According to the general procedure given for the thermal reaction of **6**, enehydrazines **6p–s** were heated at the temperature shown in Table 8 to give indoline **7p–s**, **7′p–s** and indole **11p–s**, **11′p–s** in the yield shown in Table 8.

4.10.1. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-8-methoxycyclopent[*b*]indole (7p). A yellow oil; IR ($CHCl_3$) 3425, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (1H, m), 1.84 (2H, m), 2.14–2.35 (3H, m), 3.68 (1H, dd, $J=8$, 2 Hz), 3.81 (3H, s), 4.72 (1H, br s), 6.23 and 6.32 (each 1H, d, $J=8$ Hz), 6.76 (1H, br s), 7.05 (1H, t, $J=8$ Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1073.

4.10.2. 1,2,3,4-Tetrahydro-8-methoxycyclopent[*b*]indole (11p). A yellow oil; IR ($CHCl_3$) 3479 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (2H, m), 2.83 and 2.96 (each 2H, t-like, $J=7$ Hz), 3.90 (3H, s), 6.49 (1H, dd, $J=8$, 1 Hz), 6.92 (1H, dd, $J=8$, 1 Hz), 6.99 (1H, t, $J=8$ Hz), 7.81 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{12}H_{13}NO$ (M^+) 187.0996, found 187.1001.

4.10.3. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-6-methoxycyclopent[*b*]indole (7′p). A yellow oil; IR ($CHCl_3$) 3424, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60–1.88 (3H, m), 2.15–2.46 (3H, m), 3.61 (1H, br d, $J=8$ Hz), 3.75 (3H, s), 5.72 (1H, br s), 6.15 (1H, d, $J=3$ Hz), 6.31 (1H, dd, $J=8$, 3 Hz), 6.78 (1H, br s), 6.94 (1H, d, $J=8$ Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1094.

4.10.4. 1,2,3,4-Tetrahydro-6-methoxycyclopent[*b*]indole (11′p). A yellow oil; IR ($CHCl_3$) 3477 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (2H, m), 2.80 (4H, br m), 3.82 (3H, s), 6.74 (1H, dd, $J=8.5$, 2.5 Hz), 6.83 (1H, d, $J=2.5$ Hz), 7.30 (1H, d, $J=8.5$ Hz), 7.70 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{12}H_{13}NO$ (M^+) 187.0996, found 187.1011.

4.10.5. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-8-methylcyclopent[*b*]indole (7q) and *cis*-3a-[(trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-6-methylcyclopent[*b*]indole (7′q). The indolines **7q** and **7′q** are inseparable: a yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61–1.86 and 2.13–2.45 (6H, m), 2.23 and 2.27 (each 3/2H, s), 3.63 and 3.66 (each 1/2H, dd, $J=8$, 2 Hz), 4.63 and 4.66 (each 1/2H, br s), 6.41 (1/2H, br s), 6.43 (1/2H, br d, $J=8$ Hz), 6.59 (1H, br d, $J=8$ Hz), 6.94 (1/2H, br d, $J=8$ Hz), 6.99 (1/2H, t, $J=8$ Hz).

4.10.6. 1,2,3,4-Tetrahydro-8-methylcyclopent[*b*]indole (11q) and 1,2,3,4-tetrahydro-6-methylcyclopent[*b*]indole (11′q). The indoles **11q** and **11′q** are inseparable: a yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 and 2.57 (each 3/2H, s), 2.82 (4H, m), 3.04 (2H, m), 6.82, 6.89 and 7.09 (each 1/2H, br d, $J=8$ Hz), 6.97 (1/2H, t, $J=7.5$ Hz), 7.10 (1/2H, br s), 7.32 (1/2H, br d, $J=8$ Hz).

4.10.7. *cis*-8-Chloro-3a-[(trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (7r). A yellow oil; IR ($CHCl_3$) 3425, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (1H, m), 1.82–1.88 (2H, m), 2.27–2.40 (3H, m), 3.72 (1H, dd, $J=10$, 2.5 Hz), 4.81 (1H, br s), 6.44 and 6.71 (each 1H, br d, $J=8$ Hz), 6.82 (1H, br s, NH), 7.00 (1H, t, $J=8$ Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0569.

4.10.8. *cis*-6-Chloro-3a-[(trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (7′r). A yellow oil; IR ($CHCl_3$) 3426, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, m), 1.71–1.89 (2H, m), 2.23–2.36 (3H, m), 3.62 (1H, br dd, $J=9.5$, 2 Hz), 4.78 (1H, br s), 6.53 (1H, d, $J=2$ Hz), 6.72 (1H, dd, $J=8$, 2 Hz), 6.78 (1H, br s, NH), 6.95 (1H, dd, $J=8$, 1 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0604.

4.10.9. 8-Chloro-1,2,3,4-tetrahydrocyclopent[*b*]indole (11r).[39] A yellow oil; IR ($CHCl_3$) 3686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (2H, br quint, $J=7$ Hz), 2.85 and 3.04 (each 2H, t-like, $J=7$ Hz), 6.96 (1H, t, $J=8$ Hz), 7.03 and 7.17 (each 1H, dd, $J=8$, 1 Hz), 7.92 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{10}^{35}ClN$ (M^+) 191.0501, found 191.0504.

4.10.10. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-8-nitrocyclopent[*b*]indole (7s). A yellow oil; IR ($CHCl_3$) 3424, 1724, 1532, 1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76–1.89 (3H, m), 2.22 (1H, ddd, $J=13.5$, 10, 7.5 Hz), 2.48 (2H, m),4.21 (1H, dd, $J=12$, 2 Hz), 5.30 (1H, br s), 6.80 and 7.55 (each 1H, dd, $J=8.5$, 1 Hz), 6.91 (1H, br s), 7.22 (1H, t, $J=8.5$ Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0847.

4.10.11. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-6-nitrocyclopent[*b*]indole (7′s). A yellow oil; IR ($CHCl_3$) 3426, 1724, 1527, 1339 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (1H, m), 1.76–1.92 (2H, m), 2.30 (2H, m), 2.38 (1H, m), 3.74 (1H, dd, $J=9.5$, 2 Hz), 4.99 (1H, br s), 6.82 (1H, br s), 7.16 (1H, d, $J=8$ Hz), 7.32 (1H, d, $J=2$ Hz), 7.65 (1H, dd, $J=8$, 2 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0850.

4.10.12. 1,2,3,4-Tetrahydro-8-nitrocyclopent[*b*]indole (11s).[27] A yellow oil; IR ($CHCl_3$) 3471, 1514, 1327 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (2H, quint, $J=7$ Hz), 2.94 and 3.22 (each 2H, t-like, $J=7$ Hz), 7.11 (1H, t, $J=8$ Hz), 7.55 and 8.02 (each 1H, dd, $J=8$, 1 Hz), 8.28 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{10}N_2O_2$ (M^+) 202.0742, found 202.0768.

4.10.13. 1,2,3,4-Tetrahydro-6-nitrocyclopent[*b*]indole (11′s).[27] A yellow oil; IR ($CHCl_3$) 3468, 1513, 1323 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (2H, quint, $J=7$ Hz), 2.86 and 2.94 (each 2H, t-like, $J=7$ Hz), 7.43 (1H, d, $J=8.5$ Hz), 8.01 (1H, dd, $J=8.5$, 2 Hz), 8.26 (1H, d, $J=2$ Hz), 8.30 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{10}N_2O_2$ (M^+) 202.0742, found 202.0760.

4.11. Preparation of *N*-trifluoroacetyl enehydrazines 6t–x

According to the general procedure (B) given for the preparation of enehydrazine **6**, the condensation of

corresponding hydrazines **15o–r** with cyclopentanone or cyclohexanone followed by acylation of the corresponding hydrazones gave **6t–x** in 63–96% yields.

4.11.1. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(2-methoxyphenyl)hydrazide (6t). A yellow oil; IR ($CHCl_3$) 3418, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (2H, br quint, $J=7.5$ Hz), 2.32 and 2.64 (each 2H, m), 3.89 (3H, s), 5.67 (1H, br s), 6.65–6.94 (5H, m); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1101.

4.11.2. Trifluoroacetic acid 1-(1-cyclohexen-1-yl)-2-(2-methoxyphenyl)hydrazide (6u). A yellow oil; IR ($CHCl_3$) 3421, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50–1.63 (4H, m), 2.07–2.17 (4H, m), 3.81 (3H, s), 5.88 (1H, br s), 6.78 (1H, br s), 6.77–6.92 (4H, m); HRMS (EI, *m/z*) calcd for $C_{15}H_{17}F_3N_2O_2$ (M^+) 314.1241, found 314.1252.

4.11.3. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(2-methylphenyl)hydrazide (6v). A yellow oil; IR ($CHCl_3$) 3455, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (2H, br quint, $J=7.5$ Hz), 2.35 and 2.67 (each 2H, m), 2.23 (3H, s), 5.68 (1H, br s), 5.96 (1H, br s), 6.65 (1H, br d, $J=8$ Hz), 6.89 (1H, td, $J=7.5$, 1 Hz), 7.10–7.17 (2H, m); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1154.

4.11.4. Trifluoroacetic acid 2-(2-chlorophenyl)-1-(1-cyclopenten-1-yl)hydrazide (6w). A yellow oil; IR ($CHCl_3$) 3402, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (2H, br quint, $J=7.5$ Hz), 2.34 and 2.67 (each 2H, m), 5.68 (1H, br s), 6.71 (1H, br s), 6.75 (1H, br dd, $J=8$, 0.5 Hz), 6.91 (1H, ddd, $J=8$, 7.5, 1.5 Hz), 7.20 (1H, dddd, $J=8.5$, 8, 1.5, 0.5 Hz), 7.32 (1H, dd, $J=8$, 1.5 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0588.

4.11.5. Trifluoroacetic acid 1-(1-cyclopenten-1-yl)-2-(2-nitrophenyl)hydrazide (6x). A yellow oil; IR ($CHCl_3$) 3259, 1728, 1533, 1337 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (2H, br quint, $J=7.5$ Hz), 2.39 and 2.71 (each 2H, m), 5.78 (1H, br s), 6.93 (1H, br d, $J=8.5$ Hz), 7.03 and 7.58 (each 1H, td, $J=8.5$, 1 Hz), 8.25 (1H, dd, $J=8.5$, 1 Hz), 9.24 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0836.

4.12. Thermal reaction of *N*-trifluoroacetyl enehydrazines 6t–x

According to the general procedure given for the thermal reaction of **6**, enehydrazines **6t–x** were heated at the temperature shown in Table 9 to give indoline **7t–x**, indole **11t–x**, and dienylimine **17t–v** in the yield shown in Table 9.

4.12.1. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-5-methoxycyclopent[*b*]indole (7t). A yellow oil; IR ($CHCl_3$) 3490, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (1H, m), 1.83 (2H, m), 2.10 (1H, m), 2.33–2.53 (2H, m), 3.80 (1H, br d, $J=9.5$ Hz), 3.84 (3H, s), 4.48 (1H, br s), 6.69 (1H, br d, $J=8$ Hz), 6.72 (1H, br d, $J=8$ Hz), 6.79 (1H, br s), 6.80 (1H, t, $J=8$ Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1086.

4.12.2. (3aα,8aα,8bα)-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,8a,8b-hexahydro-8a-methoxycyclopent[*b*]-indole (*cis-syn*-17t). Colorless crystals, mp 140–141 °C (hexane); IR ($CHCl_3$) 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28–1.36 (2H, m), 1.75 (1H, m, 2-H), 1.90 (1H, m), 2.38 (1H, ddd, $J=17$, 9.5, 7.5 Hz), 2.47 (1H, m, 3-H), 2.82 (1H, dd, $J=10.5$, 5 Hz), 3.18 (3H, s), 6.12 (1H, dt, $J=9.5$, 1 Hz), 6.45 (1H, dt, $J=9.5$, 3.5 Hz), 6.53 (2H, dd, $J=3.5$, 1 Hz), 7.24 (1H, br s); NOE was observed between NH (δ 7.24) and 8a-OMe (δ 3.18), NH (δ 7.24) and 8b-H (δ 2.82), and 8a-OMe (δ 3.18) and 8b-H (δ 2.82) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1110. The crystal data of *cis-syn*-**17t** was shown in previous communication.[30]

4.12.3. (3aα,8aβ,8bα)-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,8a,8b-hexahydro-8a-methoxycyclopent[*b*]indole (*cis-anti*-17t). Colorless crystals, mp 140–141 °C (hexane); IR ($CHCl_3$) 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.94–2.21 (6H, m), 3.06 (1H, br dd, $J=9$, 2 Hz), 3.16 (3H, s), 6.03 (1H, dt, $J=9.5$, 1 Hz), 6.41 (1H, ddd, $J=9.5$, 5.5, 1 Hz), 6.52 (1H, ddd, $J=9.5$, 5.5, 1 Hz), 6.61 (1H, br dt, $J=9.5$, 1 Hz), 6.71 (1H, br s); NOE was observed between NH (δ 6.71) and 8b-H (δ 3.06) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O_2$ (M^+) 300.1085, found 300.1098.

4.12.4. 1,2,3,4-Tetrahydro-5-methoxycyclopent[*b*]indole (11t). A yellow oil; IR ($CHCl_3$) 3479 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (2H, br quint, $J=7.5$ Hz), 2.83 (4H, t-like, $J=7.5$ Hz), 3.94 (3H, s), 6.60 (1H, br dd, $J=9$, 1 Hz), 7.12 (2H, m), 8.05 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{12}H_{13}NO$ (M^+) 187.0996, found 187.0997.

4.12.5. 1,2,3,4-Tetrahydro-8-methoxy-9*H*-carbazole (11u).[28] A yellow oil; IR ($CHCl_3$) 3422 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (4H, m), 2.70 (4H, m), 3.93 (3H, s), 6.59 (1H, dd, $J=8$, 1 Hz, 7-H), 6.98 (1H, t, $J=8$ Hz), 7.07 (1H, dd, $J=8$, 1 Hz), 7.92 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{13}H_{15}NO$ (M^+) 201.1153, found 201.1160.

4.12.6. (4aα,4bα,9aα)-9a-[(Trifluoroacetyl)amino]-1,2,3,4,4a,9a-hexahydro-4b-methoxy-4b*H*-carbazole (*cis-syn*-17u). Colorless crystals, mp 139–140 °C (hexane/AcOEt); IR ($CHCl_3$) 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (1H, dtd, $J=13.5$, 12, 4 Hz), 1.12 (1H, qt, $J=13.5$, 3.5 Hz), 1.22–1.33 (1H, qt, $J=13.5$, 3.5 Hz), 1.57 (1H, m), 1.63–1.71 (2H, m), 2.16 (1H, td, $J=13.5$, 4.5 Hz), 2.63 (1H, dd, $J=12$, 7 Hz), 3.15 (1H, dtd, $J=13.5$, 3.5, 2 Hz), 3.17 (3H, s), 6.08 (1H, dt, $J=9.5$, 1 Hz), 6.43 (1H, ddd, $J=9.5$, 5.5, 1 Hz), 6.56 (1H, ddd, $J=9.5$, 5.5, 1 Hz), 6.63 (1H, br d, $J=9.5$ Hz), 7.41 (1H, br s); NOE was observed between NH (δ 7.41) and 4b-OMe (δ 3.17), and NH (δ 7.41) and 4a-H (δ 2.63) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{15}H_{17}F_3N_2O_2$ (M^+) 314.1241, found 314.1252.

4.12.7. (4aα,4bβ,9aα)-9a-[(Trifluoroacetyl)amino]-1,2,3,4,4a,9a-hexahydro-4b-methoxy-4b*H*-carbazole (*cis-anti*-17u). Colorless crystals, mp 138–140 °C (hexane/AcOEt); IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 1.44 (1H, qt, J=13.5, 3 Hz), 1.60 (1H, m), 1.65–1.87 (4H, m), 2.10 (1H, dm, J=13.5 Hz), 2.35 (1H, dm, J=13.5 Hz), 2.78 (1H, br dt, J=8, 1 Hz), 3.07 (3H, s), 6.11 (1H, dt, J=9.5, 1 Hz), 6.41 (1H, br s), 6.44 (1H, ddd, J=9.5, 5.5, 1 Hz), 6.54 (1H, ddd, J=9.5, 5.5, 1 Hz), 6.66 (1H, dt, J=9.5, 1 Hz); NOE was observed between NH (δ 6.41) and 4a-H (δ 2.78) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{15}H_{17}F_3N_2O_2$ (M^+) 314.1241, found 314.1260.

4.12.8. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-5-methylcyclopent[*b*]indole (7v). A yellow oil; IR ($CHCl_3$) 3423, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, m), 1.74–1.89 (2H, m), 2.13 (3H, s), 2.18 (1H, m), 2.30–2.48 (2H, m), 3.72 (1H, dd, J=10, 1 Hz), 4.43 (1H, br s), 6.73 (1H, t, J=8 Hz), 6.78 (1H, br s), 6.90–6.94 (2H, m); HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1142.

4.12.9. (3aα,8aα,8bα)-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,8a,8b-hexahydro-8a-methylcyclopent[*b*]indole (*cis-syn*-17v). Colorless crystals, mp 139–140 °C (hexane/AcOEt); IR ($CHCl_3$) 1721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.29 (1H, m), 1.51 (1H, m), 1.78 (1H, m), 1.99 (1H, br ddd, J=13, 7, 4 Hz), 2.07 (1H, dtd, J=13, 9.5, 6.5 Hz), 2.42 (1H, ddd, J=13, 9.5, 7 Hz), 2.90 (1H, dd, J=9.5, 5 Hz), 6.06 (1H, ddd, J=9.5, 5.5, 1 Hz), 6.23 (1H, br d, J=9.5 Hz), 6.27 (1H, dt, J=9.5, 1 Hz), 6.51 (1H, ddd, J=9.5, 5.5, 1 Hz), 8.11 (1H, br s); NOE was observed between NH (δ 8.11) and 8a-Me (δ 1.24), NH (δ 8.11) and 8b-H (δ 2.90), and 8a-Me (δ 1.24) and 8b-H (δ 2.90) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1125. Anal. Calcd for $C_{14}H_{15}F_3N_2O$: C, 59.15; H, 5.32; N, 9.85, found: C, 59.03; H, 5.31; N, 9.85.

4.12.10. (3aα,8aβ,8bα)-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,8a,8b-hexahydro-8a-methylcyclopent[*b*]indole (*cis-anti*-17v). Colorless crystals, mp 138–139 °C (hexane/AcOEt); IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.78 (1H, br dquint, J=13, 8 Hz), 1.89 (1H, m), 1.97 (1H, ddd, J=13, 8, 5.5 Hz), 2.05 (1H, m), 2.21–2.29 (2H, m), 3.04 (1H, br dd, J=9, 2 Hz), 5.99 (1H, ddd, J=9.5, 5.5, 1 Hz), 6.26 (1H, dt, J=9.5, 1 Hz), 6.41 (1H, br dt, J=9.5, 1 Hz), 6.48 (1H, ddd, J=9.5, 5.5, 1.5 Hz), 6.73 (1H, br s); NOE was observed between NH (δ 6.73) and 8b-H (δ 3.04) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{14}H_{15}F_3N_2O$ (M^+) 284.1135, found 284.1151. Anal. Calcd for $C_{14}H_{15}F_3N_2O$: C, 59.15; H, 5.32; N, 9.85, found: C, 59.13; H, 5.31; N, 9.83.

4.12.11. 1,2,3,4-Tetrahydro-5-methylcyclopent[*b*]indole (11v).[29] A yellow oil; IR ($CHCl_3$) 3480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (3H, s, Me), 2.55 (2H, br quint, J=7.5 Hz), 2.79–2.90 (4H, t-like, J=7.5 Hz), 6.90 (1H, br d, J=8 Hz), 7.00 (1H, t, J=8 Hz), 7.29 (1H, br d, J=8 Hz), 7.66 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{12}H_{13}N$ (M^+) 171.1048, found 171.1069.

4.12.12. *cis*-5-Chloro-3a-[(trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (7w). A yellow oil; IR ($CHCl_3$) 3424, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (1H, m), 1.73–1.90 (2H, m), 2.22 (1H, m), 2.29–2.43 (2H, m), 3.80 (1H, dd, J=8, 1 Hz), 4.83 (1H, br s), 6.70 (1H, t, J=8 Hz), 6.88 (1H, br s), 6.94 and 7.06 (each 1H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}^{35}ClF_3N_2O$ (M^+) 304.0590, found 304.0571.

4.12.13. *cis*-3a-[(Trifluoroacetyl)amino]-1,2,3,3a,4,8b-hexahydro-5-nitrocyclopent[*b*]indole (7x). A yellow oil; IR ($CHCl_3$) 3436, 1729, 1518, 1331 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (1H, m), 1.81–1.91 (2H, m), 2.24–2.44 (3H, m), 3.83 (1H, br d, J=9.5 Hz), 6.72 (1H, t, J=8 Hz), 6.86 (1H, br s), 7.16 (1H, br s), 7.25 and 7.87 (each 1H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{12}F_3N_3O_3$ (M^+) 315.0830, found 315.0842.

4.12.14. 1,2,3,4-Tetrahydrocyclopent[*b*]indole (11e) (conversion of dienylimines *cis-syn*-17t and *cis-anti*-17t into indole 11e). A solution of *cis-syn*-**17t** (27 mg, 0.09 mmol) in xylene (5 mL) was heated at 140 °C for 23 h. After the reaction mixture was concentrated under the reduced pressure, purification of the residue by MCC (*n*-hexane/ethyl acetate 2:1) gave the indole **11e**[31] (9.9 mg, 70%). Similarly, *cis-anti*-**17t** (27 mg, 0.09 mmol) was converted into indole **11e**[31] (5.9 mg, 42%) as a yellow oil, IR ($CHCl_3$) 3477 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (2H, br quint, J=8 Hz), 2.84 (4H, t-like, J=8 Hz), 7.07 (2H, m), 7.28 and 7.42 (1H, m,), 7.76 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{11}N$ (M^+) 157.0891, found 157.0891.

4.13. Condensation of hydrazine 15o followed by acylation

According to the general procedure (B) given for the preparation of enehydrazine **6**, the condensation of corresponding hydrazine **15o** (2.76 g, 20 mmol) with 2-butanone (1.79 mL, 20 mmol) followed by acylation of the corresponding hydrazone gave **6y** (1.29 g, 23%) and *C*-acylated product **18** (3.44 g, 62%).

4.13.1. Trifluoroacetic acid (*Z*)-2-(2-methoxyphenyl)-1-(1-ethyl-1-propenyl)hydrazide (6y). A yellow oil; IR ($CHCl_3$) 3357, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, t, J=7.5 Hz), 2.32 (2H, br q, J=7.5 Hz), 3.89 (3H, s), 5.09 (2H, br d, J=15 Hz), 6.68 (1H, br s), 6.77–6.95 (4H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{15}F_3N_2O_2$ (M^+) 288.1087, found 288.1079.

4.13.2. 1,1,1-Trifluoro-2,4-hexanedione 4-(2-methoxyphenyl)hydrazone (18). A yellow oil; IR ($CHCl_3$) 3372, 1711 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (3H, t, J=7.5 Hz), 2.04 (2H, br s), 2.41 (2H, br q, J=7.5 Hz), 3.85 (3H, s), 6.95–7.02 (2H, m), 7.29–7.42 (2H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{15}F_3N_2O_2$ (M^+) 288.1085, found 288.1079.

4.14. Thermal reaction of *N*-trifluoroacetyl enehydrazine 6y

According to the general procedure given for the thermal reaction of **6**, the enehydrazine **6y** (51.2 mg, 0.18 mmol) was heated at 80 °C in MeCN. After the reaction mixture was concentrated under reduced pressure, the residue was purified by MCC (hexane/AcOEt 10:1) to give the

dienylimine **17y** (13.7 mg, 27%) and indole **11y**[36] (21.2 mg, 68%).

4.14.1. *cis*-2-Ethyl-2-[(trifluoroacetyl)amino]-2,3-dihydro-3a-methoxy-3a*H*-indole (17y). Colorless crystals, mp 117–118 °C (hexane/Et_2O); IR ($CHCl_3$) 3416, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (3H, t, J=7.5 Hz), 1.98 (1H, dq, J=15, 7.5 Hz), 2.23 and 2.86 (each 1H, AB q, J=13.5 Hz), 2.47 (1H, dq, J=15, 7.5 Hz), 3.14 (3H, s), 6.19 (1H, br d, J=9.5 Hz), 6.41 (1H, br ddd, J=9.5, 5.5, 1 Hz), 6.57 (1H, br ddd, J=9.5, 5.5, 1 Hz), 6.61 (1H, br d, J=9.5 Hz), 6.96 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.0, 32.5, 49.9, 51.9, 82.3, 88.1, 115.6 (q, CF_3), 123.1, 126.5, 132.2, 134.5, 155.6 (q, $COCF_3$), 174.9; HRMS (EI, *m*/*z*) calcd for $C_{13}H_{15}F_3N_2O_2$ (M^+) 288.1084, found 288.1091. Anal. Calcd for $C_{13}H_{15}F_3N_2O_2$: C, 54.17; H, 5.24; N, 9.72, found: C, 54.37; H, 5.33; N, 9.68; NOE was observed between 3a-OMe (δ 3.14) and NH (δ 6.96) in NOESY spectroscopy.

4.14.2. 2-Ethyl-7-methoxyindole (11y). Colorless oil; IR ($CHCl_3$) 3372 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (3H, t, J=7.5 Hz), 2.76 (2H, q, J=7.5 Hz), 3.94 (3H, s), 6.21 (1H, br s), 6.58 (1H, br d, J=8 Hz), 6.97 (1H, br t, J=8 Hz), 7.14 (1H, br d, J=8 Hz), 8.11 (1H, br s); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{13}NO$ (M^+) 175.0997, found 175.0984.

4.15. Thermal reaction of *N*-trifluoroacetyl enehydrazines 6a,l,o,t,x in water

A suspended solution of enehydrazines **6a**,**l**,**o**,**t**,**x** (0.18–0.25 mmol) in H_2O (10–15 mL) was heated under the conditions shown in Table 10. The reaction mixture was extracted with $CHCl_3$ and the organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under the reduced pressure. Purification of the residue by MCC (hexane/AcOEt 20:1–5:1) afforded the indoline **7**, indole **11**, dienylimine **17** in the yield shown in Table 10.

4.16. Thermal reaction of *N*-trifluoroacetyl enehydrazines 6a,l,o,t,x under solvent-free conditions

The enehydrazines **6a**,**l**,**o**,**t**,**x** (0.18–0.25 mmol) was heated directly under the conditions shown in Table 10. Purification of the residue by MCC (hexane/AcOEt 20:1–5:1) afforded the indoline **7**, indole **11**, dienylimine **17** in the yield shown in Table 10.

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Regioselective functionalisation of nitrobenzene and benzonitrile derivatives via nucleophilic aromatic substitution of hydrogen by phosphorus-stabilized carbanions

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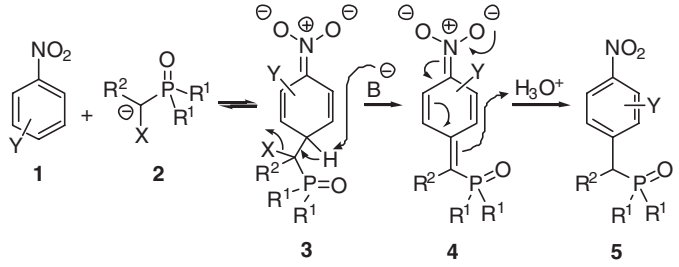
Abstract—The synthesis of *P*-benzylic products by reaction of anions stabilised by *N*-phosphorylphosphazenyl, *N*-methoxycarbonylphosphazenyl, phosphine borane complex, and phosphine oxide groups by displacement of hydrogen of a variety of electron-deficient benzene derivatives is described. Lithium phosphazenes were the most suitable nucleophiles for the substitution of hydrogen in nitrobenzene and some *ortho*-, *meta*-, and *para*- substituted nitrobenzenes. Lithiated phosphine borane complexes produced efficiently the substitution of the hydrogen at the *para* position of a cyano group in cyanobenzenes, whereas the anion of ethyldiphenylphosphine oxide lead to complex mixtures with all electrophiles assayed. The method reported here represents a convenient alternative to the vicarious nucleophilic substitution for the synthesis of benzylic phosphorus derivatives using phosphorus-stabilised anions that do not bear a leaving group at the carbanionic centre.

1. Introduction

The direct functionalisation of electron-deficient arenes via nucleophilic replacement of hydrogen is a process of great interest both in the academia and in the industry.[1] The introduction of a *P*-alkyl substituent into an aromatic system is particularly attractive owing to the possibility of using benzylic phosphorus derivatives into olefination reactions. The end products would be stilbenes, a compound class that have shown important biomedical properties.[2] Nucleophilic aromatic substitution of hydrogen, S_NAr^H, by phosphorus-stabilised carbanions has been achieved exclusively via vicarious nucleophilic substitution (VNS),[3] and only on nitrobenzenes. The VNS method requires that the nucleophile also contains a nucleofugal group (X) at the reactive centre. Attack of the carbanion **2** formed by deprotonation of the corresponding organophosphorus compound to the nitroarene **1** leads to a Meisenheimer complex **3**, which is in equilibrium with the starting reagents (Scheme 1). This σ-adduct undergoes β-elimination of HX promoted by a second equivalent of base. The resulting nitronate intermediate **4** provides the substituted arene **5** upon work-up.[4]

The organophosphorus reagents used in VNS reactions include chloromethyldiphenylphosphine oxide,[5] dimethyl



Scheme 1.

Keywords: Phosphazenes; Phosphine-boron complexes; Nucleophilic aromatic substitution; Carbanions; Cyano group.
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α-chlorobenzylphosphonate,[5a] and 2-(1,3-dithianyl)triphenylphosphonium chloride.[6] Phosphorus ylides derived from (halomethyl)triphenylphosphonium halides (halide = Cl, Br) failed to give VNS products in the reaction with nitrobenzene.[5c] Interestingly, Lawrence and co-workers showed that the vicarious nucleophilic substitution products formed in the reaction of the anion of chloromethyldiphenylphosphine oxide with a series of substituted nitrobenzenes can be transformed into stilbenes in a one-pot process.[5b,c]

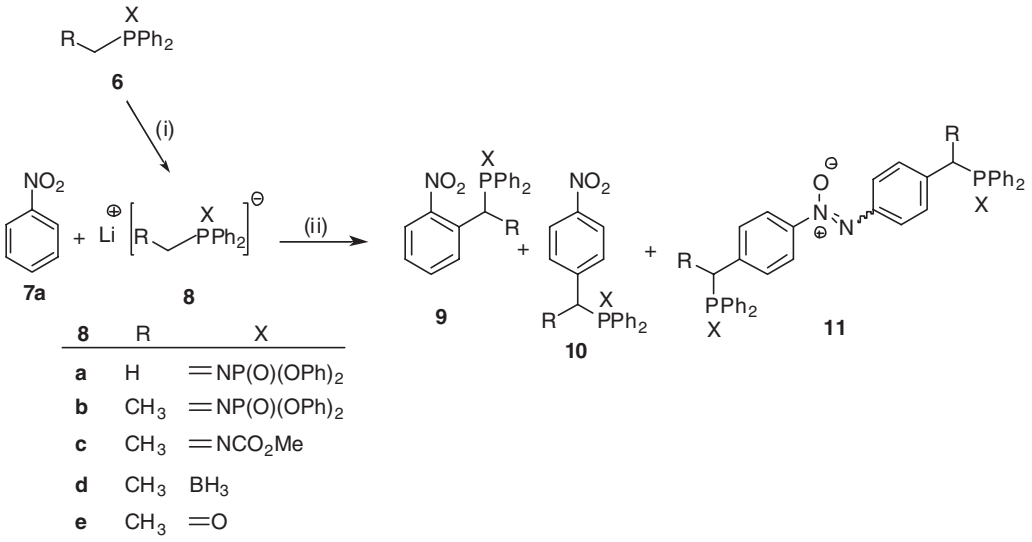
The introduction into an aromatic ring of alkyl side chains bearing phosphorus-containing functional groups through the VNS protocol shows two important limitations. On the one hand, the nucleophile must bear an auxiliary leaving group at the carbanionic centre. On the other, only nitrobenzenes have been used as electrophiles.

We have recently reported a new method for the direct introduction of alkylphosphorus substituents into nitro- and cyano-benzenes, with high yield and regioselectivity, through nucleophilic aromatic substitution of hydrogen without the requirement of a nucleofuge at the α position with respect to the phosphorus atom.[7] Generally, aromatization occurred spontaneously in the reaction medium or during work-up. In some cases the use of an external oxidant such as DDQ proved to be beneficial for increasing the yield of S_NAr^H products. Here we wish to report the full details of this investigation showing the scope of the methodology. We have evaluated the feasibility of α-lithiated *N*-phosphorylphosphazenes, *N*-methoxycarbonylphosphazenes, phosphine borane complexes, and phosphine oxides, as nucleophiles for the S_NAr^H reactions. The influence of the substituents for activating the aromatic nucleus and the different reactivity of primary and secondary carbanions are also discussed.

2. Results and discussion

2.1. Functionalisation of nitrobenzene and benzonitrile derivatives via S_NAr^H

We initially chose lithiated phosphazenes bearing electron-withdrawing groups at the nitrogen atom **8a–c** as nucleophiles for the reaction with nitrobenzene **7a** based on our experience on the synthetic applications of these anions,[8] which includes their utilisation in olefination reactions.[9] The carbanions **8a–c**, generated through metalation of phosphazenes **6a–c** with LiBu^n, were allowed to react with **7a** at low temperature in THF (Scheme 2). The results obtained are collected in Table 1 (entries 1–3). High conversions were observed for **8b–c**. The major products isolated consisted of compounds **9** and **10** resulting from the hydrogen substitution at the *ortho* and *para* position to the nitro group, respectively. The later is generated in higher yield except for lithium phosphazene **8a**. This carbanion affords equimolecular amounts of both regiosiomers, albeit in very low yield. The poor performance of the reaction of **8a** with nitrobenzene can be ascribed to



Scheme 2. Reagents and conditions: (i) for **6a–c** and **6e** LiBu^n (1 equiv), THF, HMPA (6 equiv), −30 °C, 30 min; for **6d** LiBu^s (1 equiv), THF, HMPA (6 equiv), −90 °C, 30 min; (ii) 1 equiv of **7a**, THF, −90 °C, 12 h.

Table 1. Distribution of products (%) in the reaction of phosphorus-stabilised anions **8a–e** with nitrobenzene

Entry	Nucleophile	R	X	Conversion	S_NAr^{Ha}	**9**[b]	**10**[b]	**11**[b]
1	**8a**	H	=NP(O)(OPh)$_2$	18	100	9 (**a**)	9 (**a**)	
2	**8b**	CH_3	=NP(O)(OPh)$_2$	84	77	11 (**b**)	54 (**b**)	19 (**a**)
3	**8c**	CH_3	=NCO_2Me	76	55	10 (**c**)	32 (**c**)	10 (**b**)
4	**8d**	CH_3	BH_3	58	83	3 (**d**)	45 (**d**)	10 (**c**)
5	**8e**	CH_3	=O	94	20		19 (**e**)	<1% (**d**)

[a] Referred to the % of conversion.
[b] Crude yield.

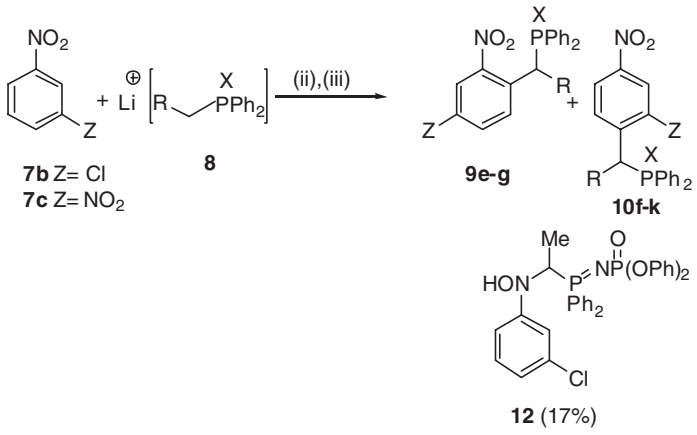
the lower nucleophilicity of the primary carbanion as compared with anions **8b–c**. This behaviour has been noted previously in lithiated *N*-phosphoryl[8e] and *N*-methoxycarbonylphosphazenes.[8c,10]

Besides S_NAr^H products, variable amounts of azoxy derivatives **11** were obtained in the reactions of **8b** and **8c** (Scheme 2, Table 1). Arylation of carbanions via S_NAr reactions with nitroarenes might be complicated by electron-transfer processes as well as the attack of the carbanion to the nitro function.[11] Azoxy compounds have been described[12] as decomposition products of nitroso derivatives formed by reduction of the NO_2 moiety. The formation of compounds **11** suggests that the reaction proceeds in part via a mechanism involving radical-anion species. Addition to the reaction medium of DDQ as an external oxidant did not improved the yield of S_NAr^H products. On the other hand, in absence of the strongly coordinating cosolvent HMPA the yields of **9** and **10** decreased significantly.[7]

We were also interested in studying the feasibility of lithium ethyldiphenylphosphine borane complex **8d** as nucleophiles in S_NAr^H reactions with nitrobenzene **7a**. The BH_3 moiety of phosphine borane complexes has a double function. It enhances the acidity of the protons adjacent to the phosphorus and protects the heteroatom from oxidation.[13] The BH_3 group can be removed in several ways (e.g., heating with triethylamine, DABCO, fluoroboric acid, etc.)[14] and the resulting phosphine can be further transformed. Lithium ethyldiphenylphosphine borane complex **8d** reacted with **7a** in a similar manner to the phosphazenyl carbanions **8b–c**. Although in this case the conversion was slightly lower, the yield of S_NAr^H products and the selectivity in favour of the *para* isomer increased notably (Table 1, entry 4).

We next attempted the reaction between lithiated phosphine oxide **8e** and nitrobenzene **7a** under the same reaction conditions used with phosphazenyl anions **8a–c**. The ^1H and ^{31}P NMR spectra of the crude mixture showed that the conversion was high. However, a complex mixture of products was formed in which compound **10e** represents only a 19% (Table 1, entry 5). After column chromatography (eluent ethyl acetate/hexane 5:1) the azoxy derivative **11d** could be identified although only traces of this compound are present in the crude mixture (Table 1, entry 5). The structures of **10e** and **11d** were confirmed by comparison of their ^1H and ^{31}P NMR data with the products obtained in the acid hydrolysis of **10b** and **11b**, respectively.

3-Chloronitrobenzene **7b** and 1,3-dinitrobenzene **7c** were also reacted with carbanions **8a–e**. The results obtained are shown in Scheme 3 and Table 2. As can be observed in Table 2, the higher electrophilicity of the nitroarenes **7b–c** as compared with nitrobenzene **7a** produced an increase in the yield of S_NAr^H products. Furthermore, although several regioisomers might be formed, the products of substitution at the *para* position with respect to the nitro group **10f–k** were obtained with high (entries 1, 3 and 4) or total regioselectivity (entries 2, 5 and 6). No displacement of halogen was observed in any case. Except for **8a**, the reactions performed well in the absence of coordinating cosolvents. However, the efficient replacement of hydrogen in **7b–c** by anions **8b–d** required the use of DDQ as external oxidant. Otherwise, byproducts arising from nucleophilic



Scheme 3. Reagents and conditions: (ii) $ArNO_2$ 1 equiv, THF, −90 °C, 12 h; (iii) DDQ 1.2 equiv, −90 °C, 15 min then 1 h at room temperature.

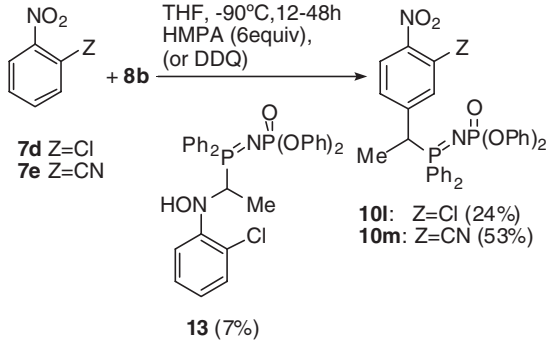
Table 2. Distribution of products (%) in the reaction of anions **8a–e** with **7b** and **7c**

Entry	Nucleophile	R	X	Z	Conversion	**9**[a]	**10**[a]
1	**8a**	H	$=NP(O)(OPh)_2$	Cl	46[b]	5 (**e**)	41 (**f**)
2	**8b**	CH_3	$=NP(O)(OPh)_2$	Cl	62[c]		62 (**g**)
3	**8c**	CH_3	$=NCO_2Me$	Cl	87	8 (**f**)	79 (**h**)
4	**8e**	CH_3	$=O$	Cl	72	7 (**g**)	34 (**i**)
5	**8b**	CH_3	$=NP(O)(OPh)_2$	NO_2	79		79 (**j**)
6	**8d**	CH_3	BH_3	NO_2	54		54 (**k**)

[a] Crude yield.
[b] Metalation in the presence of 6 equiv of HMPA; absence of DDQ.
[c] In the absence of DDQ compound **12** was also formed in 17% yield.

attack to the nitro group are detected. For example, in the reaction of **8b** with *m*-chloronitrobenzene in the absence of DDQ the hydroxylamine **12** was formed in 17% yield. By contrast, the presence of the oxidizing agent in the reaction of the primary carbanion **8a** with *m*-chloronitrobenzene **2c** inhibits almost completely the S_NAr^H process. The lithiated phosphine oxide **8e** proved to be the less efficient nucleophile in terms of substitution products. Either in the presence or absence of DDQ a complex mixture of products was obtained. Compounds **9g/10i** were obtained in a yield of 41% in a ratio of 1:5 (entry 4). From the comparison of Tables 1 and 2 it can be concluded that the regiochemistry is mainly controlled by steric factors. Nevertheless, some electronic effects are also operative, which would explain the higher ratios of *para*:*ortho* products generated in the reactions of lithium phosphine borane complex **8d** as compared with the corresponding phosphazenes (cf. **10d/9d** 10:1 vs **10b/9b** 5:1 and **10c/9c** 3:1).

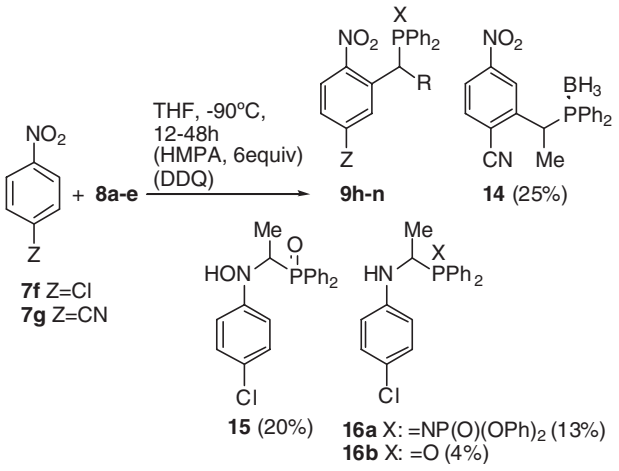
Replacement of hydrogen in *ortho* substituted nitrobenzenes such as *o*-chloronitrobenzene **7d** and *o*-nitrobenzonitrile **7e** by reaction with anion **8b** proceed with some problems. Substitution occurs exclusively at the *para* position to the nitro group to give the nitrobenzylphosphazenes **10l** and **10m**, respectively (Scheme 4). The yields of **10l** were low and the hydroxylamine **13** was persistently formed even when the external oxidizing agent DDQ was used. On the other hand, compound **10m** could be obtained in reasonable yield only when the addition of *o*-nitrobenzonitrile **7e** was carried out in the presence of HMPA. On the light of these results no further assays of these nitroarenes with the other nucleophiles were performed.



Scheme 4. The stoichiometry phosphorylphosphazene/LiBu^n/nitroarene used was 1:1:1 for **7d** and 1:2.5:2.5 for **7e**.

The reactivity of anions **8a–e** towards the *p*-substitued systems 4-chloro- and 4-cyanonitrobenzene was also evaluated. The substituents of these nitroarenes represent a good test of the efficiency of the process. Besides the expected S_NAr^H reactions alternative pathways are possible. Among others, it might occur the displacement of some substituent of the aromatic system,[15] the addition to the CN function,[16] and the competition between the CN and NO_2 groups for directing the nucleophilic attack to the aromatic nucleus.

Lithium phosphazenes **8a–c** react with **7f** and **7g** in THF at −90 °C to give exclusively products of replacement of hydrogen at the *ortho* position with respect to the nitro group **9h,i,k,l,m** (Scheme 5 and Table 3). The reaction conditions required some optimization to obtain the best yields of nitrobenzylphosphazenes **9**. Thus, good yields of **9k** are obtained when the reaction is effected in the presence of HMPA (entry 4). In the absence of coordinating solvent compound **9k** was formed only in 26% yield.[17] The increased reactivity of **8a** induced by the cosolvent may be assigned to the well known deaggregating effect of HMPA.[18] The yield of **9m** increased slightly (from 75 to 81%, entry 6) when the rearomatisation was forced by addition of DDQ to the reaction mixture. Likewise, the use of DDQ in the reaction of **8b** with *para*-chloronitrobenzene **7f** was necessary for the clean formation of **9i**, otherwise the amine **16a** arising from the attack of the nucleophile to the nitro group is also isolated in 13% yield (entry 2). The reaction of the primary carbanion **8a** with **7f** proceeds with low yield and the addition of HMPA promotes the generation of a number of byproducts without increasing the amount of **9h** obtained.



Scheme 5. The stoichiometry used was phosphorous compound **6a–c**, **6e**/LiBu^n/nitroarene 1:1:1 for **7f** and 1:2.5:2.5 for **7g**. Metalation of phosphine borane to give **8d** was performed with LiBu^s and the stoichiometry used was **6d**/LiBu^s/**7g** 1:1.5:1.2.

Once again, the lithium phosphine oxide **8e** was the less efficient nucleophile for S_NAr^H processes. The reaction of **8e** with 4-chloronitrobenzene in the presence of DDQ gives a complex mixture of products, with compound **9j** being obtained in only 27% yield (entry 3). Purification by column chromatography allowed to identify also the hydroxylamine **15** and the amine **16b** formed as byproducts. When 4-cyanonitrobenzene was used as electrophile no products of hydrogen substitution could be unambiguously detected.

The reaction of lithium phosphine borane complex **8d** with *p*-cyanonitrobenzene was remarkable. No evidences of displacement of cyanide or nucleophilic addition to the cyano group were observed. Only products of aromatic hydrogen substitution were detected. The conversion was only of 37%. A 63% of the starting phosphine borane complex remained unreacted even when the metalation was performed in presence of HMPA and DDQ was added as external oxidizing agent prior to the aqueous work-up. However, the most important feature of this reaction concerns its regioselectivity. The reaction products consisted of a mixture of the regioisomers **9n** and **14** in a ratio of

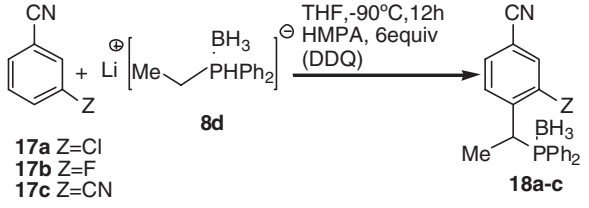
Table 3. Compounds **9h–n** obtained in the reaction of anions **8a–e** with **7f** and **7g**

Entry	Nucleophile	R	X	Z	Yield (%) **9**
1	**8a**	H	$=NP(O)P(OPh)_2$	Cl	28 (**h**)
2	**8b**	CH_3	$=NP(O)P(OPh)_2$	Cl	53 (**i**)[a,b]
3	**8e**	CH_3	$=O$	Cl	27 (**j**)[a,c]
4	**8a**	H	$=NP(O)P(OPh)_2$	CN	64 (**k**)[d]
5	**8b**	CH_3	$=NP(O)P(OPh)_2$	CN	81 (**l**)
6	**8c**	CH_3	$=NCO_2Me$	CN	81 (**m**)[a]
7	**8d**	CH_3	BH_3	CN	12 (**n**)[e,f]

[a] Addition of DDQ (1.2 equiv).
[b] In absence of DDQ a 13% of compound **16a** was also obtained.
[c] Also obtained 20% of compound **15** and 4% of compound **16b**.
[d] Metalation in the presence of 6 equiv of HMPA.
[e] Metalation in the presence of HMPA (6 equiv) and addition of DDQ (1.2 equiv).
[f] Also obtained 25% of compound **14**.

1:2 (Scheme 5, Table 3 entry 7). This means that both the nitro and the cyano groups compete for directing the attack of the incoming nucleophile, with the later being more potent than the nitro function by a factor of 2. Selective replacement of hydrogen in *p*-nitrobenzonitrile using Grignard reagents as nucleophiles has been reported.[19] The presence of the CN group did not improve the efficiency of the substitution compared to the nitrobenzene itself. In other cases, a cyano substituent on a nitroarene makes difficult or prevents to attain the desired products of nucleophilic aromatic substitution of hydrogen.[20] As far as we know this is the first time that such competing effect between a nitro and a cyano group in a S_NAr^H reaction on a phenyl ring is observed.[19,21,22] Hydrogen displacement via VNS reactions of 1-naphthonitrile has been described.[23] We are not aware of S_NAr^H of organolithium reagents with benzonitriles.[24]

These results prompted us to study the reactivity of lithium phosphine borane complex **8d** with a variety of other substituted cyanoarenes. 3-Chlorobenzonitrile **17a**, 3-fluoro benzonitrile **17b**, and 1,3-dicyanobenzene **17c** reacted with **8d** to give exclusively the products of hydrogen substitution at the *para* position to the CN group **18a–c** (Scheme 6, Table 4). The same conditions described for the reaction with **7g** were used, except that the use of the external oxidising agent DDQ was necessary for obtaining high yield of **18a**. Otherwise, the major compound formed is the cyclohexadiene derivative resulting from the [1,6] addition to the aromatic ring (Table 4, entries 1 and 2).[25] The reaction of the fluorinated nitrile **17b** proceeds in a disappointing 25% yield in absence of DDQ and the addition of the oxidant proved to be detrimental for the process (entries 3 and 4). It is worth nothing, however, that no displacement of fluorine was observed in spite of the known high rate of fluorine substitution in fluoroarenes. The higher activation of the aromatic system provided by



Scheme 6. The metalation of phosphine borane was achieved with Bu^{s}Li. Stoichiometry phosphine borane/LiBu^s/benzonitrile 1:1.2:1.2.

the two cyano groups present in **17c** allowed to perform the reaction of this electrophile with **8d** in absence of DDQ affording **18c** in high yield (entry 5).

Table 4. Compounds **18** obtained in the reaction of anion **8d** with cyanoarenes **17a–c**

Entry	**17**	Z	**18**	Yield (%)
1	**a**	Cl	**a**	21
2	**a**[a]	Cl	**a**	64
3	**b**	F	**b**	25
4	**b**[a]	F	**b**	17
5	**c**	CN	**c**	87

[a] Addition of DDQ (1.2 equiv).

2.2. Structural characterization

The structural identification of S_NAr^H products **9**, **10**, **14** and **18** was straightforward based on the correlations observed in the 2D HMBC spectra between the benzylic protons and the carbons of the aromatic system.

For the products of the reaction of **8a–d** with nitrobenzene, the P–C*H* protons of *ortho* regioisomers (**9a–d**) correlate with two quaternary carbons and one methine carbon *meta* with respect to the nitro group. In the *para* isomers (**10a–d**) the benzylic protons show only two correlations corresponding to the C_{ipso} and the two adjacent isochronous CH carbons. From the analysis of the NMR data a rule merged that can be applied to the identification of the substitution pattern: in the ^{1}H NMR spectra the benzylic protons of the *ortho* isomers appear notably deshielded as compared with the *para* derivatives ($\Delta\delta$ (P–C*H*)$_{(ortho-para)} \approx 1$ ppm), whereas the opposite occurs for the corresponding methine carbon in the ^{13}C NMR spectra ($\Delta\delta$ (P–*C*H)$_{(para-ortho)} \approx 7$ ppm).

For compounds **9e–g** and **10f–k**, the P–C*H* protons show correlations with two quaternary carbons and one methine carbon. This fact implies that products of nucleophilic attack at position 2 of the nitroarenes were not formed and that nitrocompounds **10j** and **10k** are the exclusive S_NAr products of the reaction between 1,3-dinitrobenzene and anions **8b** and **8d**, respectively. Substitution products of attack *ortho*, **9e–g**, and *para* to the nitro group of 3-chloronitrobenzene, **10f–i**, give rise to the same set of correlations for the benzylic protons. They can be easily distinguished based on the chemical shifts of the C_{ipso} carbons bonded to the chlorine atom and the nitro group,

the later inducing a much larger downfield shift ($\Delta\delta^{C_{ipso}}$ (NO_2–Cl) ≈ 16 ppm). Similarly, the exclusive replacement of hydrogen at the *ortho* position respect to the nitro group in the reaction of carbanions **8a–c** and nitroarenes **7f–g** was deduced from the correlations observed in the 2D *g*HMBC spectra between the benzylic proton and the C_{ipso} carbon bonded to the nitro group. In all cases, this carbon appears in the ^{13}C NMR spectra as the most downfield signal.

The structural characterization of the new functionalized benzonitriles **18a–c** was realized following the same procedure described for the nitrobenzyl derivatives. The ^{31}P NMR spectra of the products resulting from the hydrogen displacement by lithium phosphine borane complex **8e** are characterized by a very pronounced deshielding of the phosphrus signal respect to the starting phosphine borane complex **6e** ($\Delta\delta_P \approx 7$ ppm). As expected, very broad ^{31}P NMR signals were observed for compounds containing the phosphine borane moiety owing to the combined effect of fast relaxation and unresolved couplings produced by the quadrupolar nuclei $^{10/11}B$.[26]

Compounds **9n** and **14** were isolated by column chromatography (eluent ethyl acetate/hexane 1:5) and characterised by their spectroscopic data. The 2D HMBC spectra provided the proton–carbon connectivity for identifying the position of entering of the nucleophile. The benzylic proton of **14** (δ_H 4.52 ppm, dc, $^3J_{HH}=7.3$ Hz, $^2J_{PH}=15.3$ Hz) correlates with two high field quaternary carbons at δ_C 115.91 ppm (d, $^4J_{PC}=1.5$ Hz) and 118.54 ppm (d, $^3J_{PC}=5.1$ Hz), assigned to the CN and *ipso*-carbon linked to the CN group, respectively. For compound **9n** the replacement of the hydrogen *ortho* to the nitro group is evidenced by the correlation of the P–C*H* proton (δ_H 5.02 ppm, dq, $^3J_{HH}=$ 7.3 Hz, $^2J_{PH}=15.8$ Hz) with the quaternary carbon bonded to the NO_2 group (δ_C 151.21 ppm, d, $^3J_{PC}=5.7$ Hz).

The redox products **11** exhibited the same pattern of carbon–proton correlations found in the precursors **10** with duplicate signals. Thus, the ^{31}P NMR spectrum of **11a** shows two set of signals of very close chemical shifts corresponding to both phosphazene moieties present in this compound. Molecular weight determinations via mass spectrometry supports the assignment made.

Finally, the structure of hydroxylamines **12**, **13** and **15** and the anilines **16a–b** was deduced from the analysis of the mass spectrum, IR and ^1H, ^{31}P, ^{13}C, DEPT, 2D *g*HMQC, and 2D *g*HMBC NMR spectra. Focusing in compound **12**, the molecular weight of 602 is in agreement with the formula $C_{32}H_{29}ClN_2O_4P$. Relevant spectroscopic data of this compound are the O–H stretching absorption in the IR spectrum at 3456 cm^{-1} and the chemical shift of the methine carbon linked to the phosphorus ($\delta_C=63.52$ ppm, d, $^1J_{PC}=85.6$ Hz). This chemical shift indicates that this carbon must be also bonded to a second heteroatom of moderate electronegativity, that is, nitrogen.

3. Conclusions

Non-functionalised carbanions stabilised by *N*-phosphorylphosphazenyl, *N*-methoxycarbonylphosphazenyl, phosphine borane complex, and phosphine oxide groups were used as nucleophiles in reactions of aromatic substitution of hydrogen with a variety of electron-deficient benzene derivatives. The process is strongly influenced by the nature of both the phosphorus functionality linked to the carbanion and the substituents present in the aromatic system. The results obtained indicate that lithium phosphazenes are suitable nucleophiles for the direct preparation of benzyl phosphorus derivatives via S_NAr^H reactions with *ortho*-, *meta*- and *para*-substituted nitrobenzenes. The substituents used were Cl, NO_2, and CN. The new synthetic method provides nitrobenzylphosphazenes in moderate to good yield (range from 24 to 81%) and with high regioselectivity. Products of substitution of hydrogen at the *para* position to the nitro group are predominantly or exclusively formed. Contrary to the VNS protocol, in this case the existence of a nucleofuge at the carbanion centre is not necessary. The reactions of primary anions proceed in lower yields most probably due to the lower nucleophilicity as compared with secondary anions. Generally, higher yields are obtained when the reaction is performed in the presence of HMPA. In some cases, the use of an external oxidising agent such as DDQ to help the departure of hydride ion with subsequent aromatization improved the efficiency of the process. The addition of DDQ to the reactions of **8b** with chloro-substituted nitrobenzenes prevents the formation of byproducts arising from the nucleophilic attack to the nitro group. By contrast, the reactions of the anion of ethyldiphenylphosphine oxide with nitroarenes lead to complex mixtures of compounds, in which S_NAr^H products are detected only in minor amounts.

Lithium phosphine borane complex **8d** is less efficient than phosphazenyl anions in S_NAr^H reactions with nitroarenes. However, it proved to be a good nucleophile for the replacement of hydrogen of benzonitriles such as 3-chlorobenzonitrile, 3-fluorobenzonitrile, and 1,3-dicyanobenzene. Only products of substitution *para* to the CN group were formed in yields of 25–87%. The use of DDQ increased notably the yield of the reaction of **8d** with 3-chlorobenzonitrile, whereas left almost unaffected the reaction with 3-fluorobenzonitrile. In the reaction with *p*-nitrobenzonitrile the replacement of hydrogen took place at *ortho* positions to both activating groups, NO_2 and CN, with the later being produced predominantly.

Aromatic hydrocarbons are very important building blocks in organic synthesis. They are low-cost readily available reagents, which utility depends on the ability of performing the functionalisation of C_{Ar}–H bonds in a regioselective manner. The synthesis here described represents a convenient route for accessing to nitrobenzylphosphazenes and cyanobenzylphosphine borane complexes via S_NAr^H reactions. The method developed allows the regioselective installation of a phosphaalkyl moiety into an electron-deficient aromatic ring providing a substitution pattern generally not accessible through electrophilic aromatic substitution or directed *ortho* metalation processes.[27] The use of non-functionalised phosphorus-stabilised carbanions opens a pathway alternative to VNS reactions for introducing organophosphorus moieties into π-deficient arenes. Both phosphorus functional groups can be further transformed into a variety of other functions with retention

or elimination of the phosphorus atom by known procedures.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen using dried glassware. Solvents were distilled before use. THF was dried with sodium and distilled under nitrogen. Commercial starting materials were purchased from Aldrich. Liquids, except LiBu^n and LiBu^s, were distilled prior use. TLC was performed on Merck plates with aluminium backing and silica gel 60 F_{254}. For column chromatography silica gel 60 (40–63 μm) from Scharlau was used.

Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were obtained in KBr pellets using a Mattson Genesis II FT spectrometer. Mass spectra were determined by APCI (Atmospheric Pressure Chemical Ionization) on a Hewlett-Packard 1100. Microanalysis were performed on a Perkin-Elmer 2400. NMR spectra were measured on a Bruker 300DPX and Bruker Avance 500 spectrometers. Chemical shifts are referred to internal tetramethylsilane for ^{1}H, the deuterated solvent for ^{13}C, and to external 85% H_3PO_4 for ^{31}P. 2D NMR correlation spectra (HMQC and HMBC) were acquired using standard Bruker software and processing routines.

4.2. General procedure for the reaction of phosphorus-stabilised carbanions and electron-deficient aromatic compounds

Phosphazenes **6a–c** were readily synthesised through the Staudinger reaction of commercial methyl and ethyldiphenylphosphine with the corresponding azide.[8c,e,28] Phosphine borane complex **6d** was prepared by complexation of ethyldiphenylphosphine with $BH_3\cdot THF$.[25]

Anions **8a–c** and **8e** were prepared by adding a solution of LiBu^n (0.3–0.8 mL of a 1.6 M solution in hexane, 0.5–1.25 mmol) to a solution of 0.5 mmol of the appropriate phosphorus compound **6a–c** or **6e** in THF (25 mL) at −30 °C. The metalation of the phosphine borane complex (0.5 mmol) to give **8d** was achieved with LiBu^s (0.4–0.5 mL of a 1.3 M solution in cyclohexane) also at −90 °C. In some cases, 0.5 mL (3 mmol) of the co-ordinating agent HMPA was also added.

After 30 min of metalation, the temperature was lowered at −90 °C and the corresponding aromatic compound **7a–g/17a–c** (0.5, 0.6 or 1.25 mmol) was added. The reaction mixture was stirred for 12–48 h at this temperature, monitoring the reaction progress by ^{31}P NMR. Addition of water (25 mL) followed by extraction with ethyl acetate (3×15 mL) and solvent evaporation under vacuum afforded a crude product, which was purified by column chromatography using a mixture of ethyl acetate/hexane or, in the case of **18c**, by precipitation from diethyl ether.

Treatment with external oxidizing agent. Before the hydrolytic work-up, 137 mg (0.6 mmol) of DDQ were added to the reaction crude at −90 °C. The mixture was then stirred for an additional hour at room temperature and processed as it is describe above.

4.2.1. 2-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]methyl}nitrobenzene (9a). Eluent: ethyl acetate/hexane 3:1. Oil. Yield: 9%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1199. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.61 (d, $^2J_{PH}$=14.6 Hz, 2H), 7.08 (m, 2H, H^{ar}), 7.22 (m, 10H, H^{ar}), 7.37 (m, 4H, H^{ar}), 7.46 (m, 2H, H^{ar}), 7.56 (m, 6H, H^{ar}), 7.73 (m, 1H^{ar}), 7.96 (m, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 32.99 (dd, $^1J_{PC}$=60.4 Hz, $^3J_{PC}$=1.7 Hz), 120.58 (d, $^3J_{PC}$=5.1 Hz), 123.77 (d, $^5J_{PC}$=1.2 Hz), 125.02 (d, $^4J_{PC}$=2.4 Hz), 126.37 (d, $^2J_{PC}$=8.7 Hz), 127.64 (dd, $^1J_{PC}$=104.8 Hz, $^3J_{PC}$=5.4 Hz), 128.08 (d, $^4J_{PC}$=3.3 Hz), 128.67 (d, $^3J_{PC}$=12.9 Hz), 129.18 (d, $^4J_{PC}$=0.9 Hz), 131.72 (d, $^2J_{PC}$=10.5 Hz), 132.62 (d, $^4J_{PC}$=2.7 Hz), 133.35 (d, $^5J_{PC}$=3.0 Hz), 134.56 (d, $^3J_{PC}$=4.8 Hz), 148.33 (d, $^3J_{PC}$=5.7 Hz), 152.18 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −7.13 (d, $^2J_{PP}$=31.2 Hz), 17.22 (d, $^2J_{PP}$=31.2 Hz). Anal. Calcd for $C_{31}H_{26}N_2O_5P_2$ (568.51): C, 65.49; H, 4.57; N, 4.93. Found: C, 66.44; H, 4.56; N, 4.90. MS *m*/*z* (%): 569 (100).

4.2.2. 2-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}nitrobenzene (9b). Eluent: ethyl acetate/hexane 3:1. Oil. Yield: 11%. IR (KBr pellets, neat), ν (cm^{-1}): 1260, 1091, 1022. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.69 (dd, $^3J_{HH}$=7.1 Hz, $^3J_{PH}$=17.4 Hz, 3H), 4.92 (dquintet, $^3J_{HH}$=$^2J_{PH}$=7.1 Hz, $^4J_{PH}$=3.2 Hz, 1H), 7.15 (m, 6H, H^{ar}), 7.26 (m, 9H, H^{ar}), 7.55 (m, 6H, H^{ar}), 7.99 (m, 3H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.45 (d, $^2J_{PC}$=3.6 Hz), 34.01 (dd, $^1J_{PC}$=69.4 Hz, $^3J_{PC}$=3.3 Hz), 120.41 (d, $^3J_{PC}$=5.1 Hz), 120.70 (d, $^3J_{PC}$=4.8 Hz), 123.73 (d, $^5J_{PC}$=1.2 Hz), 123.83 (d, $^5J_{PC}$=1.2 Hz), 124.43 (d, $^4J_{PC}$=1.8 Hz), 127.52 (d, $^1J_{PC}$=96.7 Hz), 128.19 (d, $^1J_{PC}$=103.9 Hz), 128.22 (d, $^3J_{PC}$=12.6 Hz), 128.85 (d, $^4J_{PC}$=0.8 Hz), 129.09 (d, $^3J_{PC}$=12.3 Hz), 129.24 (d, $^4J_{PC}$=0.9 Hz), 129.28 (d, $^4J_{PC}$=0.6 Hz), 131.10 (d, $^2J_{PC}$=10.1 Hz), 131.46 (d, $^3J_{PC}$=4.8 Hz), 132.05 (d, $^2J_{PC}$=9.9 Hz), 132.06 (d, $^4J_{PC}$=3.0 Hz), 132.13 (d, $^2J_{PC}$=5.4 Hz), 132.68 (d, $^5J_{PC}$=3.0 Hz), 133.27 (d, $^4J_{PC}$=2.7 Hz), 148.82 (d, $^3J_{PC}$=6.6 Hz), 152.39 (d, $^2J_{PC}$=7.8 Hz), 152.41 (d, $^2J_{PC}$=8.1 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −10.42 (d, $^2J_{PP}$=34.5 Hz), 17.85 (d, $^2J_{PP}$=34.5 Hz). Anal. Calcd for $C_{32}H_{28}N_2O_5P_2$ (582.53): C, 65.98; H, 4.84; N, 4.81. Found: C, 66.21; H, 4.83; N, 4.82. MS *m*/*z* (%): 583 (100).

4.2.3. 2-{1-[(*P*,*P*-Diphenyl)(*N*-methoxycarbonyl)-phosphazenyl]ethyl}nitrobenzene (9c). Eluent: ethyl acetate/hexane 5:1.Oil. Yield: 10%. IR (KBr pellets, neat), ν (cm^{-1}): 1732, 1657, 1260, 1092, 1019. ^{1}H NMR (300.13 MHz, $CDCl_3$): 1.76 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{PH}$=16.3 Hz, 3H), 3.63 (s, 3H), 4.50 (dq, $^3J_{HH}$=7.2 Hz, $^2J_{PH}$=11.2 Hz, 1H), 7.19–7.44 (m, 8H^{ar}), 7.57–7.72 (m, 4H^{ar}), 7.90–8.01 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.48 (d, $^2J_{PC}$=3.0 Hz), 33.04 (d, $^1J_{PC}$=69.7 Hz), 52.72 (d, $^4J_{PC}$=3.6 Hz), 124.48 (d, $^4J_{PC}$=1.8 Hz), 125.94 (d, $^1J_{PC}$=88.3 Hz), 126.76 (d, $^1J_{PC}$=94.9 Hz), 127.99 (d, $^5J_{PC}$=2.4 Hz), 128.31 (d, $^3J_{PC}$=12.0 Hz), 129.00

(d, $^{3}J_{PC}$=11.4 Hz), 131.37 (d, $^{3}J_{PC}$=4.2 Hz), 131.60 (d, $^{2}J_{PC}$=9.0 Hz), 132.06 (d, $^{4}J_{PC}$=3.0 Hz), 132.44 (d, $^{2}J_{PC}$=5.4 Hz), 132.62 (d, $^{2}J_{PC}$=8.4 Hz), 132.65 (d, $^{4}J_{PC}$=3.6 Hz), 132.88 (d, $^{4}J_{PC}$=2.4 Hz), 149.87 (d, $^{3}J_{PC}$=6.6 Hz), 162.46 (d, $^{2}J_{PC}$=1.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 27.32. Anal. Calcd for $C_{22}H_{21}N_2O_4P$ (408.39): C, 64.70; H, 5.18; N, 6.86. Found: C, 64.66; H, 5.17; N, 6.91. MS *m/z* (%): 409 (100), 352 (45).

4.2.4. 2-[1-(*P*,*P*-Diphenylphosphynylborane)ethyl]nitrobenzene (9d). Eluent: ethyl acetate/hexane 1:3, then 1:20. Oil. Yield: 3%. IR (KBr pellets, neat), ν (cm^{-1}): 2385, 1260, 1106, 1063, 1027. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.63 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=15.8 Hz, 3H), 5.1 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=16.5 Hz, 1H), 7.19 (m, 4H^{ar}), 7.34 (m, 1H^{ar}), 7.48 (m, 2H^{ar}), 7.65 (m, 5H^{ar}), 8.01 (m, 3H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.61 (d, $^{2}J_{PC}$=3.6 Hz), 30.21 (d, $^{1}J_{PC}$=31.8 Hz), 124.46 (d, $^{4}J_{PC}$=1.5 Hz), 126.75 (d, $^{1}J_{PC}$=53.2 Hz), 127.56 (d, $^{1}J_{PC}$=53.5 Hz), 127.79 (d, $^{5}J_{PC}$=2.4 Hz), 128.33 (d, $^{3}J_{PC}$=9.6 Hz), 129.08 (d, $^{3}J_{PC}$=9.9 Hz), 131.08 (d, $^{4}J_{PC}$=1.8 Hz), 131.3 (d, $^{3}J_{PC}$=3.9 Hz), 131.81 (d, $^{4}J_{PC}$=2.4 Hz), 132.13 (d, $^{2}J_{PC}$=8.4 Hz), 132.73 (d, $^{4}J_{PC}$=2.1 Hz), 133.12 (d, $^{2}J_{PC}$=8.7 Hz), 133.63, 149.2 (d, $^{3}J_{PC}$=5.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 27.82. Anal. Calcd for $C_{20}H_{21}BNO_2P$ (349.18): C, 68.80; H, 6.06; N, 4.01. Found: C, 68.77; H, 6.03; N, 4.10. MS *m/z* (%): 352 (100).

4.2.5. 3-Chloro-2-{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]methyl}nitrobenzene (9e). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 5%. IR (KBr pellets, neat), ν (cm^{-1}): 1260, 1094, 1020. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.57 (d, $^{2}J_{PH}$=14.1 Hz, 2H), 7.10–7.60 (m, 21H, H^{ar}), 7.72 (m, 1H^{ar}), 7.92 (dd, $^{3}J_{HH}$=8.5 Hz, $^{4}J_{PH}$=2.4 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 32.48 (dd, $^{1}J_{PC}$=59.8 Hz, $^{3}J_{PC}$=1.5 Hz), 120.59 (d, $^{3}J_{PC}$=5.1 Hz), 123.89 (d, $^{5}J_{PC}$=1.2 Hz), 124.82 (d, $^{2}J_{PC}$=9.3 Hz), 125.00 (d, $^{3}J_{PC}$=2.4 Hz), 127.40 (dd, $^{1}J_{PC}$=105.4 Hz, $^{3}J_{PC}$=5.4 Hz), 128.81 (d, $^{3}J_{PC}$=12.9 Hz), 129.22 (d, $^{4}J_{PC}$=0.9 Hz), 131.71 (d, $^{2}J_{PC}$=10.5 Hz), 132.81 (d, $^{4}J_{PC}$=3.0 Hz), 133.36 (d, $^{4}J_{PC}$=3.3 Hz), 133.92 (d, $^{5}J_{PC}$=3.6 Hz), 135.76 (d, $^{3}J_{PC}$=4.5 Hz), 148.52 (d, $^{3}J_{PC}$=5.7 Hz), 152.06 (d, $^{2}J_{PC}$=7.5 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −6.51 (d, $^{2}J_{PP}$=31.8 Hz), 17.55 (d, $^{2}J_{PP}$=31.8 Hz). Anal. Calcd for $C_{31}H_{25}ClN_2O_5P_2$ (602.95): C, 61.65; H, 4.18; N, 4.65. Found: C, 61.71; H, 4.19; N, 4.65. MS *m/z* (%): 603 (100).

4.2.6. 5-Chloro-2-{1-[(*P*,*P*-diphenyl)(*N*-methoxycarbonyl)phosphazenyl]ethyl}nitrobenzene (9f) and 3-chloro-4-{1-[(*P*,*P*-diphenyl)(*N*-methoxycarbonyl)-phosphazenyl]ethyl}nitrobenzene (10h). Solid isolated as a 16:1 mixture after column chromatography using ethyl acetate/hexane 2:1 as eluent. Mp 141–145 °C. IR (KBr), ν (cm^{-1}): 1639, 1303, 1112.

NMR data for **9f**. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.67 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.1 Hz, 3H), 3.56 (s, 3H), 4.95 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=11.7 Hz), 7.18–8.11 (m, 13H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.33 (d, $^{2}J_{PC}$=3.3 Hz), 32.59 (d, $^{1}J_{PC}$=68.8 Hz), 52.76, 124.47 (d, $^{3}J_{PC}$=1.8 Hz), 128.48 (d, $^{3}J_{PC}$=11.7 Hz), 129.02 (d, $^{3}J_{PC}$=11.7 Hz), 130.87 (d, $^{2}J_{PC}$=5.4 Hz), 131.65, 132.31 (d, $^{3}J_{PC}$=3.0 Hz), 132.64 (d, $^{2}J_{PC}$=8.7 Hz), 132.86 (d, $^{4}J_{PC}$=3.6 Hz), 133.82 (d, $^{5}J_{PC}$=3.0 Hz), 149.58 (d, $^{3}J_{PC}$=6.6 Hz), 162.36 (d, $^{2}J_{PC}$=1.5 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 27.28.

NMR data for **10h**. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.64 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.1 Hz, 3H), 3.60 (s, 3H), 4.56 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=11.3 Hz, 1H), 7.18–8.11 (m, 13H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.23 (d, $^{2}J_{PC}$=3.6 Hz), 35.29 (d, $^{1}J_{PC}$=70.6 Hz), 52.84 (d, $^{4}J_{PC}$=3.9 Hz), 121.67 (d, $^{4}J_{PC}$=2.4 Hz), 123.98 (d, $^{4}J_{PC}$=2.1 Hz), 125.77 (d, $^{1}J_{PC}$=88.3 Hz), 126.41 (d, $^{1}J_{PC}$=95.2 Hz), 128.32 (d, $^{3}J_{PC}$=12.0 Hz), 129.08 (d, $^{3}J_{PC}$=11.7 Hz), 131.53 (d, $^{4}J_{PC}$=3.6 Hz), 131.81 (d, $^{2}J_{PC}$=9.0 Hz), 132.39 (d, $^{3}J_{PC}$=2.7 Hz), 132.56 (d, $^{2}J_{PC}$=9.0 Hz), 132.82 (d, $^{4}J_{PC}$=3.0 Hz), 135.04 (d, $^{3}J_{PC}$=7.5 Hz), 143.02 (d, $^{2}J_{PC}$=4.8 Hz), 146.97 (d, $^{5}J_{PC}$=3.0 Hz), 162.41 (d, $^{2}J_{PC}$=1.5 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 26.68.

4.2.7. 5-Chloro-2-[1-(*P*,*P*-diphenylphosphinoyl)ethyl]-nitrobenzene (9g) and 3-chloro-4-[1-(*P*,*P*-diphenylphosphinoyl)ethyl]nitrobenzene (10i). Solid isolated as a 9:1 mixture after column chromatography using ethyl acetate/hexane 2:1 as eluent. Mp 164–168 °C. IR (KBr), ν (cm^{-1}): 1183, 1119, 1022.

NMR data for **9g**. 1.58 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=15.3 Hz, 3H), 4.6 (quintet, $^{3}J_{HH}$=$^{2}J_{PH}$=7.3 Hz, 1H), 7.19–8.27 (m, 13H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.61 (d, $^{2}J_{PC}$=3.6 Hz), 33.90 (d, $^{1}J_{PC}$=66.1 Hz), 124.39 (d, $^{4}J_{PC}$=1.2 Hz), 128.41 (d, $^{3}J_{PC}$=12.0 Hz), 128.92 (d, $^{3}J_{PC}$=11.4 Hz), 130.36 (d, $^{2}J_{PC}$=9.0 Hz), 130.79 (d, $^{5}J_{PC}$=0.6 Hz), 130.67 (d, $^{1}J_{PC}$=97.3 Hz), 131.77 (d, $^{4}J_{PC}$=2.4 Hz), 132.42 (d, $^{3}J_{PC}$=4.8 Hz), 133.11 (d, $^{4}J_{PC}$=2.4 Hz), 133.33 (d, $^{2}J_{PC}$=2.4 Hz), 149.28 (d, $^{3}J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 33.79.

NMR data for **10i**. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.54 (dd, $^{3}J_{HH}$=6.9 Hz, $^{3}J_{PH}$=15.3 Hz, 3H), 4.36 (quintet, $^{3}J_{HH}$=$^{2}J_{PH}$=6.9 Hz, 1H), 7.19–8.27 (m, 13H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.30 (d, $^{2}J_{PC}$=3.0 Hz), 36.11 (d, $^{1}J_{PC}$=66.7 Hz), 121.92 (d, $^{4}J_{PC}$=1.8 Hz), 124.09 (d, $^{4}J_{PC}$=1.8 Hz), 128.30 (d, $^{3}J_{PC}$=12.0 Hz), 128.94 (d, $^{3}J_{PC}$=12.0 Hz), 130.51 (d, $^{2}J_{PC}$=9.6 Hz), 130.86 (d, $^{1}J_{PC}$=97.3 Hz), 131.09 (d, $^{2}J_{PC}$=9.0 Hz), 131.13 (d, $^{3}J_{PC}$=3.0 Hz), 131.89 (d, $^{4}J_{PC}$=3.0 Hz), 132.21 (d, $^{4}J_{PC}$=2.7 Hz), 134.29 (d, $^{3}J_{PC}$=8.1 Hz), 144.32 (d, $^{2}J_{PC}$=4.2 Hz), 146.74 (d, $^{5}J_{PC}$=2.4 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 33.73.

4.2.8. 4-Chloro-2-{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]methyl}nitrobenzene (9h). Eluent: ethyl acetate/hexane 1:1. Oil. Yield: 28%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1095, 1022. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.62 (d, $^{2}J_{PH}$=14.5 Hz, 2H), 7.08 (m, 2H, H^{ar}), 7.31 (m, 13H, H^{ar}), 7.55 (m, 6H, H^{ar}), 7.71 (d, $^{3}J_{HH}$=8.9 Hz, 1H^{ar}), 8.1 (m, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 32.99 (dd, $^{1}J_{PC}$=59.5 Hz, $^{3}J_{PC}$=1.5 Hz), 120.54 (d, $^{3}J_{PC}$=4.8 Hz), 123.82 (d, $^{5}J_{PC}$=1.2 Hz), 126.45 (d, $^{4}J_{PC}$=2.4 Hz), 127.35 (dd, $^{1}J_{PC}$=105.1 Hz, $^{3}J_{PC}$=4.8 Hz), 128.39 ($^{5}J_{PC}$=3.2 Hz), 128.67 (d, $^{2}J_{PC}$=9.0 Hz),

128.77 (d, $^3J_{PC}$=13.2 Hz), 129.19 (d, $^4J_{PC}$=0.8 Hz), 131.71 (d, $^2J_{PC}$=10.8 Hz), 132.79 (d, $^4J_{PC}$=3.0 Hz), 134.24 (d, $^3J_{PC}$=4.8 Hz), 139.84 (d, $^4J_{PC}$=3.6 Hz), 146.57 (d, $^3J_{PC}$=5.4 Hz), 152.15 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −7.08 (d, $^2J_{PP}$= 31.2 Hz), 16.87 (d, $^2J_{PP}$=31.2 Hz). Anal. Calcd for $C_{31}H_{25}ClN_2O_5P_2$ (602.95): C, 61.75; H, 4.18; N, 4.65. Found: C, 61.70; H, 4.21; N, 4.66. MS *m/z* (%): 603 (100).

4.2.9. 4-Chloro-2-{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]ethyl}nitrobenzene (9i). Eluent: ethyl acetate/hexane 1.5:1. Oil. Yield: 53%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1095, 1022. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.66 (dd, $^3J_{HH}$=7 Hz, $^3J_{PH}$=17.7 Hz, 3H, H-8), 5.01 (dquintet, $^3J_{HH}$=$^2J_{PH}$=7.3 Hz, $^4J_{PH}$=1.7 Hz, 1H, H-7), 6.92–7.40 (m, 15H^{ar}), 7.46–7.71 (m, 5H^{ar}), 7.93–8.08 (m, 2H^{ar}), 8.17 (dd, $^4J_{HH}$=$^4J_{PH}$=2.1 Hz, 1H^{ar}, H-3). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.24 (d, $^2J_{PC}$= 3.3 Hz), 34.04 (dd, $^1J_{PC}$=67.9 Hz, $^3J_{PC}$=2.9 Hz), 120.45 (d, $^3J_{PC}$=5.1 Hz), 120.68 (d, $^3J_{PC}$=5.1 Hz), 123.74 (d, $^5J_{PC}$=1.2 Hz), 123.86 (d, $^5J_{PC}$=1.2 Hz), 125.94 (d, $^4J_{PC}$=1.8 Hz), 127.08 (d, $^1J_{PC}$=96.9 Hz), 127.91 (dd, $^1J_{PC}$=105.6 Hz, $^3J_{PC}$=5.3 Hz), 128.23, 128.42 (d, $^3J_{PC}$=12.9 Hz), 129.22 (d, $^3J_{PC}$=12.6 Hz), 129.29 (d, $^4J_{PC}$=0.8 Hz), 130.99 (d, $^2J_{PC}$=10.5 Hz), 131.56 (d, $^3J_{PC}$=4.8 Hz), 132.06 (d, $^2J_{PC}$=10.2 Hz), 132.01 (d, $^4J_{PC}$=3.0 Hz), 132.87 (d, $^4J_{PC}$=3.0 Hz), 134.37 (d, $^2J_{PC}$=5.7 Hz), 139.84 (d, $^4J_{PC}$=3.0 Hz), 147.06 (d, $^3J_{PC}$= 6.6 Hz), 152.38 (d, $^2J_{PC}$=7.8 Hz), 152.45 (d, $^2J_{PC}$= 7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −9.24 (d, $^2J_{PP}$=37.9 Hz), 18.65 (d, $^2J_{PP}$=37.9 Hz). Anal. Calcd for $C_{32}H_{27}ClN_2O_5P_2$ (616.98): C, 62.30; H, 4.41; N, 4.54. Found: C, 62.22; H, 4.37; N, 4.50. MS *m/z* (%): 617 (100).

4.2.10. 4-Chloro-2-[1-(*P*,*P*-diphenylphosphinoyl)ethyl]-nitrobenzene (9j). Eluent: ethyl acetate/hexane 7:1. Oil. Yield: 27%. IR (KBr pellets, neat), ν (cm^{-1}): 1550, 1177. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.62 (dd, $^3J_{HH}$= 7.3 Hz, $^3J_{PH}$=15.3 Hz, 3H), 4.73 (quintet, $^3J_{HH}$=$^2J_{PH}$= 7.3 Hz, 1H), 7.26 (m, 3H, H^{ar}), 7.50 (m, 7H, H^{ar}), 7.96 (m, 2H, H^{ar}), 8.1 (m, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.49 (d, $^2J_{PC}$=3.3 Hz), 34.20 (d, $^1J_{PC}$=65.2 Hz), 125.87 (d, $^4J_{PC}$=1.5 Hz), 127.84 (d, $^5J_{PC}$=2.1 Hz), 128.37 (d, $^3J_{PC}$=11.7 Hz), 128.95 (d, $^3J_{PC}$=11.7 Hz), 130.43 (d, $^2J_{PC}$=9.0 Hz), 131.13 (d, $^3J_{PC}$=4.5 Hz), 131.18 (d, $^2J_{PC}$= 8.7 Hz), 131.74 (d, $^4J_{PC}$=2.7 Hz), 132.22 (d, $^4J_{PC}$= 2.7 Hz), 135.81 (d, $^2J_{PC}$=4.8 Hz), 139.59 (d, $^4J_{PC}$= 2.4 Hz), 147.21 (d, $^3J_{PC}$=6.6 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 32.74. Anal. Calcd for $C_{20}H_{17}NO_3P$ (385.79): C, 62.27; H, 4.44; N, 3.63. Found: C, 62.19; H, 4.46; N, 3.59. MS *m/z* (%): 477 (100).

4.2.11. 3-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]methyl}-4-nitrobenzonitrile (9k).[17] Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 64%. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.59 (d, $^2J_{PH}$=14.5 Hz, 2H), 7.07 (m, 2H, H^{ar}), 7.19 (m, 4H, H^{ar}), 7.25 (m, 5H, H^{ar}), 7.42 (m, 4H, H^{ar}), 7.57 (m, 6H, H^{ar}), 7.79 (d, $^3J_{HH}$=8.9 Hz, 1H^{ar}), 8.26 (t, $^4J_{HH}$=$^4J_{PH}$=1.6 Hz, 1H^{ar}). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.86 (d, $^2J_{PP}$= 31.1 Hz), 17.58 (d, $^2J_{PP}$=31.1 Hz).

4.2.12. 3-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]ethyl}-4-nitrobenzonitrile (9l).[17] Eluent: ethyl acetate/hexane 1:1. Oil. Yield: 81%. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.64 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=17.2 Hz, 3H), 4.83 (dquintet, $^3J_{HH}$=$^2J_{PH}$=7.3 Hz, $^4J_{PH}$=2.6 Hz, 1H), 7.12 (m, 7H, H^{ar}), 7.32 (m, 8H, H^{ar}), 7.63 (m, 5H, H^{ar}), 8.00 (m, 2H, H^{ar}), 8.32 (s, 1H^{ar}). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −7.65 (d, $^2J_{PP}$=35.6 Hz), 19.65 (d, $^2J_{PP}$=35.6 Hz).

4.2.13. 3-{1-[(*P*,*P*-Diphenyl)(*N*-methoxycarbonyl)phosphazenyl]ethyl}-4-nitrobenzonitrile (9m). Eluent: ethyl acetate/hexane 1.5:1. Oil. Yield: 81%. IR (KBr pellets, neat), ν (cm^{-1}): 2233, 1637, 1261, 1090, 1023. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.71 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=15.9 Hz, 3H), 3.58 (s, 3H), 5.1 (dq, $^3J_{HH}$=7.3 Hz, $^2J_{PH}$=12.6 Hz, 1H), 7.36 (m, 2H, H^{ar}), 7.48 (m, 3H, H^{ar}), 7.64 (m, 4H, H^{ar}), 7.81 (m, 4H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.31 (d, $^2J_{PC}$=3.0 Hz), 32.48 (d, $^1J_{PC}$= 66.1 Hz), 52.94 (d, $^4J_{PC}$=3.9 Hz), 116.33 (d, $^4J_{PC}$= 2.7 Hz), 116.51, 124.18 (d, $^1J_{PC}$=94.3 Hz), 125.15 (d, $^4J_{PC}$=2.1 Hz), 125.77 (d, $^1J_{PC}$=94.6 Hz), 128.75 (d, $^3J_{PC}$=12.0 Hz), 129.11 (d, $^3J_{PC}$=12.0 Hz), 131.64 (d, $^5J_{PC}$=2.4 Hz), 131.87 (d, $^2J_{PC}$=9.3 Hz), 132.66 (d, $^4J_{PC}$=3.0 Hz), 132.92 (d, $^2J_{PC}$=9.0 Hz), 133.27 (d, $^4J_{PC}$=3.0 Hz), 133.82 (d, $^2J_{PC}$=5.1 Hz), 134.96 (d, $^3J_{PC}$= 4.2 Hz), 151.69 (d, $^3J_{PC}$=6.6 Hz), 162.53 (d, $^2J_{PC}$= 1.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 27.07. Anal. Calcd for $C_{23}H_{20}N_3O_4P$(433.39): C, 63.74; H, 4.65; N, 9.69. MS, m/z (%): 434 (100), 377 (20).

4.2.14. 3-[1-(*P*,*P*-Diphenylphosphynylborane)ethyl]-4-nitrobenzonitrile (9n). Eluent: ethyl acetate/hexane 1:5. Oil. Yield: 12%. IR (KBr pellets, neat), ν (cm^{-1}): 2384, 2298, 1261, 1097, 1021. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.65 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=15.5 Hz, 3H), 5.02 (dq, $^3J_{HH}$=7.3 Hz, $^2J_{PH}$=15.8 Hz, 1H), 7.27 (m, 5H, H^{ar}), 7.65 (m, 4H, H^{ar}), 7.98 (m, 2H, H^{ar}), 8.20 (m, 1H^{ar}), 8.38 (d, $^3J_{HH}$= 8.9 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.42 (d, $^2J_{PC}$=3.0 Hz), 30.38 (d, $^1J_{PC}$=30.3 Hz), 116.49 (d, $^4J_{PC}$=2.4 Hz), 116.54, 124.22, 124.95 (d, $^5J_{PC}$=1.5 Hz), 125.72 (d, $^1J_{PC}$=53.8 Hz), 126.77 (d, $^1J_{PC}$=53.2 Hz), 128.70 (d, $^3J_{PC}$=9.9 Hz), 129.24 (d, $^3J_{PC}$=9.9 Hz), 131.31 (d, $^4J_{PC}$=2.4 Hz), 131.55 (d, $^4J_{PC}$=2.4 Hz), 132.1 (d, $^2J_{PC}$= 9.0 Hz), 133.08 (d, $^2J_{PC}$=8.7 Hz), 135.24, 135.29 (d, $^3J_{PC}$= 3.9 Hz), 151.21 (d, $^3J_{PC}$=5.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 28.15. Anal. Calcd for $C_{21}H_{20}BN_2O_2P$ (374.19): C, 67.41; H, 5.39; N, 7.49. Found: C, 67.35; H, 5.40; N, 7.53. MS *m/z* (%): 373 (100), 129 (90).

4.2.15. 4-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]methyl}nitrobenzene (10a). Eluent: ethyl acetate/hexane 3:1. Oil. Yield: 9%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1095. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.02 (d, $^2J_{PH}$=13.7 Hz, 2H), 7.17 (m, 2H, H^{ar}), 7.46 (m, 4H, H^{ar}), 7.62 (m, 6H, H^{ar}), 7.88 (m, 2H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 36.57 (dd, $^1J_{PC}$=60.7 Hz, $^3J_{PC}$=1.2 Hz), 120.56 (d, $^3J_{PC}$=4.8 Hz), 123.12 (d, $^4J_{PC}$= 3.0 Hz), 123.85 (d, $^5J_{PC}$=1.2 Hz), 127.96 (dd, $^1J_{PC}$= 105.1 Hz, $^3J_{PC}$=6.0 Hz), 128.86 (d, $^3J_{PC}$=12.9 Hz), 129.15 (d, $^4J_{PC}$=0.6 Hz), 131.29 (d, $^3J_{PC}$=4.8 Hz), 131.64 (d, $^2J_{PC}$=10.2 Hz), 132.79 (d, $^4J_{PC}$=3.0 Hz), 137.88 (d, $^2J_{PC}$=8.4 Hz), 146.87 (d, $^5J_{PC}$=3.9 Hz),

152.04 (d, $^{2}J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −6.31 (d, $^{2}J_{PP}$=31.2 Hz), 16.51 (d, $^{2}J_{PP}$=31.2 Hz). Anal. Calcd for $C_{31}H_{26}N_2O_5P_2$ (568.51): C, 65.49; H, 4.57; N, 4.93. Found: C, 66.50; H, 4.55; N, 4.94. MS *m/z* (%): 569 (100).

4.2.16. 4-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}nitrobenzene (10b). Eluent: ethyl acetate/hexane 3:1. Oil. Yield: 54%. IR (KBr pellets, neat), ν (cm^{-1}): 1522, 1487, 1200, 1108, 1024. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.64 (dd, $^{3}J_{HH}$=7.2 Hz, $^{3}J_{PH}$=17.6 Hz, 3H), 4.04 (m, 1H), 7.03–7.66 (m, 22H^{ar}), 7.82–7.92 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.11 (d, $^{2}J_{PC}$=2.4 Hz), 40.70 (dd, $^{1}J_{PC}$=66.1 Hz, $^{3}J_{PC}$=3.0 Hz), 120.46 (d, $^{3}J_{PC}$=5.4 Hz), 120.62 (d, $^{3}J_{PC}$=5.1 Hz), 122.98 (d, $^{4}J_{PC}$=2.7 Hz), 123.81 (d, $^{5}J_{PC}$=1.2 Hz), 123.86 (d, $^{5}J_{PC}$=1.2 Hz), 126.92 (dd, $^{1}J_{PC}$=97.6 Hz, $^{3}J_{PC}$=2.7 Hz), 128.51 (d, $^{3}J_{PC}$=12.6 Hz), 128.97 (d, $^{3}J_{PC}$=12.3 Hz), 129.22 (d, $^{4}J_{PC}$=0.9 Hz), 129.25 (d, $^{4}J_{PC}$=0.6 Hz), 130.32 (d, $^{3}J_{PC}$=5.1 Hz), 131.57 (d, $^{2}J_{PC}$=10.2 Hz), 132.21 (d, $^{2}J_{PC}$=9.9 Hz), 132.38 (d, $^{4}J_{PC}$=3.0 Hz), 132.78 (d, $^{4}J_{PC}$=3.0 Hz), 144.15 (d, $^{2}J_{PC}$=6.3 Hz), 146.83 (d, $^{5}J_{PC}$=3.3 Hz), 152.29 (d, $^{2}J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −9.51 (d, $^{2}J_{PP}$=34.5 Hz), 18.36 (d, $^{2}J_{PP}$=34.5 Hz). Anal. Calcd for $C_{32}H_{28}N_2O_5P_2$ (582.53): C, 65.98; H, 4.84; N, 4.81. Found: C, 66.15; H, 4.80; N, 4.79. MS *m/z* (%): 583 (100), 284 (20).

4.2.17. 4-{1-[(*P*,*P*-Diphenyl)(*N*-methoxycarbonyl)-phosphazenyl]ethyl}nitrobenzene (10c). Eluent: ethyl acetate/hexane 5:1. Oil. Yield: 32%. IR (KBr pellets, neat), ν (cm^{-1}): 1732, 1657, 1260, 1092, 1019. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm): 1.61 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.7 Hz, 3H), 3.58 (s, 3H), 4.67 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=15.8 Hz, 1H), 7.13 (dd, $^{3}J_{HH}$=8.8 Hz, $^{4}J_{PH}$=2.0 Hz, 2H^{ar}), 7.41–7.70 (m, 8H^{ar}), 7.73–7.82 (m, 2H^{ar}), 8.03 (d, $^{3}J_{HH}$=8.8 Hz, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.42 (d, $^{2}J_{PC}$=2.1 Hz), 37.18 (d, $^{1}J_{PC}$=57.2 Hz), 52.69 (d, $^{4}J_{PC}$=3.8 Hz), 122.96 (d, $^{4}J_{PC}$=2.4 Hz), 123.66 (d, $^{1}J_{PC}$=99.6 Hz), 125.17 (d, $^{1}J_{PC}$=93.4 Hz), 128.41 (d, $^{3}J_{PC}$=11.9 Hz), 128.49 (d, $^{3}J_{PC}$=11.9 Hz), 129.87 (d, $^{3}J_{PC}$=4.8 Hz), 132.49 (d, $^{4}J_{PC}$=3.0 Hz), 132.63 (d, $^{2}J_{PC}$=9.2 Hz), 132.83 (d, $^{4}J_{PC}$=3.0 Hz), 133.19 (d, $^{2}J_{PC}$=8.6 Hz), 144.22 (d, $^{2}J_{PC}$=5.4 Hz), 144.21 (d, $^{5}J_{PC}$=3.5 Hz), 162.63 (d, $^{2}J_{PC}$=2.4 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 29.19. Anal. Calcd for $C_{22}H_{21}N_2O_4P$ (408.39): C, 64.70; H, 5.18; N, 6.86. Found: C, 64.75; H, 5.16; N, 6.93. MS *m/z* (%): 409 (100), 120 (20).

4.2.18. 4-[1-(*P*,*P*-Diphenylphosphynylborane)ethyl]nitrobenzene (10d). Eluent: ethyl acetate/hexane 1:3. Oil. Yield: 45%. IR (KBr pellets, neat), ν (cm^{-1}): 2365, 1261, 1097, 1025. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.62 (d, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=15.8 Hz, 3H), 3.98 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=14.5 Hz, 1H), 7.28 (m, 4H^{ar}), 7.43 (m, 3H^{ar}), 7.58 (m, 3H^{ar}), 7.93 (m, 2H^{ar}), 8.01 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.06 (d, $^{2}J_{PC}$=2.7 Hz), 37.5 (d, $^{1}J_{PC}$=29.7 Hz), 122.93 (d, $^{4}J_{PC}$=2.1 Hz), 126.86 (d, $^{1}J_{PC}$=52.6 Hz), 127.56 (d, $^{1}J_{PC}$=53.2 Hz), 128.51 (d, $^{3}J_{PC}$=9.9 Hz), 129.04 (d, $^{3}J_{PC}$=9.6 Hz), 130.08 (d, $^{3}J_{PC}$=4.5 Hz), 131.42 (d, $^{4}J_{PC}$=2.7 Hz), 131.78 (d, $^{4}J_{PC}$=2.4 Hz), 132.59 (d, $^{2}J_{PC}$=8.7 Hz), 132.94 (d, $^{2}J_{PC}$=8.4 Hz), 145.75 (d, $^{2}J_{PC}$=0.9 Hz), 146.89 (d, $^{5}J_{PC}$=3 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 26.65. Anal. Calcd for $C_{20}H_{21}BNO_2P$ (349.18): C, 68.80; H, 6.06; N, 4.01. Found: C, 68.78; H, 6.10; N, 3.98. MS *m/z* (%): 352 (100), 346 (60).

4.2.19. 4-[1-(*P*,*P*-Diphenylphosphinoyl)ethyl]nitrobencene (10e). Eluent: ethyl acetate/hexane 5:1. Solid. Yield: 19%. Mp 208–210 °C. IR (KBr), ν (cm^{-1}): 1173, 1109. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.61 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=15.7 Hz, 3H), 3.75 (quintet, $^{3}J_{HH}$=$^{2}J_{PH}$=7.3 Hz, 1H), 7.26–7.36 (m, 2H^{ar}), 7.38–7.46 (m, 3H^{ar}), 7.47–7.63 (m, 5H^{ar}), 7.93 (m, 2H^{ar}), 8.05 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.26 (d, $^{2}J_{PC}$=3.0 Hz), 41.05 (d, $^{1}J_{PC}$=65.2 Hz), 123.30 (d, $^{4}J_{PC}$=1.8 Hz), 128.34 (d, $^{3}J_{PC}$=11.7 Hz), 128.85 (d, $^{3}J_{PC}$=11.4 Hz), 129.91 (d, $^{3}J_{PC}$=5.4 Hz), 130.78 (d, $^{2}J_{PC}$=8.7 Hz), 130.92 (d, $^{1}J_{PC}$=96.1 Hz), 131.19 (d, $^{2}J_{PC}$=8.7 Hz), 131.32 (d, $^{1}J_{PC}$=98.5 Hz), 131.75 (d, $^{4}J_{PC}$=2.7 Hz), 132.08 (d, $^{4}J_{PC}$=3.0 Hz), 145.95 (d, $^{2}J_{PC}$=5.4 Hz), 146.79 (d, $^{5}J_{PC}$=2.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 33.17. Anal. Calcd for $C_{20}H_{18}NO_3P$ (351.34): C, 61.54; H, 5.16; N, 3.99. Found: C, 61.79; H, 5.14; N, 4.02. MS *m/z* (%): 352 (100).

4.2.20. 3-Chloro-4-{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]methyl}nitrobenzene (10f). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 41%. IR (KBr pellets, neat), ν (cm^{-1}): 1262, 1096, 1023. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.23 (d, $^{2}J_{PH}$=14.6 Hz, 2H), 7.18 (m, 8H, H^{ar}), 7.42 (m, 5H, H^{ar}), 7.60 (m, 7H, H^{ar}), 7.87 (m, 2H, H^{ar}), 7.97 (d, $^{3}J_{HH}$=2.4 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 33.50 (dd, $^{1}J_{PC}$=61.9 Hz, $^{3}J_{PC}$=1.8 Hz), 120.58 (d, $^{3}J_{PC}$=4.8 Hz), 121.52 (d, $^{4}J_{PC}$=3.0 Hz), 123.97 (d, $^{5}J_{PC}$=1.2 Hz), 124.05 (d, $^{4}J_{PC}$=3.0 Hz), 127.71 (dd, $^{1}J_{PC}$=105.1 Hz, $^{3}J_{PC}$=5.4 Hz), 128.77 (d, $^{3}J_{PC}$=12.6 Hz), 129.27 (d, $^{4}J_{PC}$=1.2 Hz), 131.76 (d, $^{2}J_{PC}$=10.8 Hz), 132.93 (d, $^{4}J_{PC}$=3.0 Hz), 133.39 (d, $^{3}J_{PC}$=4.2 Hz), 135.10 (d, $^{2}J_{PC}$=6.6 Hz), 136.42 (d, $^{3}J_{PC}$=8.4 Hz), 147.07 (d, $^{5}J_{PC}$=3.6 Hz), 152.03 (d, $^{2}J_{PC}$=7.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −6.44 (d, $^{2}J_{PP}$=31.2 Hz), 16.36 (d, $^{2}J_{PP}$=31.2 Hz). Anal. Calcd for $C_{31}H_{25}ClN_2O_5P_2$ (602.95): C, 61.65; H, 4.18; N, 4.65. Found: C, 61.73; H, 4.18; N, 4.67. MS *m/z* (%): 603 (100).

4.2.21. 3-Chloro-4-{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]ethyl}nitrobenzene (10g). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 62%. IR (KBr pellets, neat), ν (cm^{-1}): 1262, 1096, 1023. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.63 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=17.4 Hz, 3H), 4.47 (dquintet, $^{3}J_{HH}$=$^{2}J_{PH}$=7.3 Hz, $^{4}J_{PH}$=3.1 Hz, 1H), 6.92–7.42 (m, 14H, H^{ar}), 7.57 (m, 6H, H^{ar}), 8.01 (m, 3H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.33 (d, $^{2}J_{PC}$=3.3 Hz), 36.2 (dd, $^{1}J_{PC}$=70.3 Hz, $^{3}J_{PC}$=3.6 Hz), 120.39 (d, $^{3}J_{PC}$=5.4 Hz), 120.46 (d, $^{3}J_{PC}$=5.1 Hz), 121.92 (d, $^{4}J_{PC}$=2.7 Hz), 123.80 (d, $^{4}J_{PC}$=1.8 Hz), 123.91 (d, $^{5}J_{PC}$=0.9 Hz), 124.05 (d, $^{5}J_{PC}$=1.2 Hz), 127.31 (d, $^{1}J_{PC}$=96.4 Hz), 127.87 (dd, $^{1}J_{PC}$=104.5 Hz, $^{3}J_{PC}$=4.2 Hz), 128.26 (d, $^{3}J_{PC}$=12.8 Hz), 129.22 (d, $^{3}J_{PC}$=12.3 Hz), 129.36 (d, $^{4}J_{PC}$=0.9 Hz), 129.38 (d, $^{4}J_{PC}$=0.9 Hz), 131.31 (d, $^{2}J_{PC}$=10.8 Hz), 131.46 (d, $^{3}J_{PC}$=4.5 Hz), 132.00 (d, $^{2}J_{PC}$=9.9 Hz), 132.48 (d, $^{4}J_{PC}$=3.3 Hz), 132.91 (d, $^{4}J_{PC}$=3.0 Hz), 134.63 (d, $^{2}J_{PC}$=

7.8 Hz), 142.48 (d, $^3J_{PC}$=5.4 Hz), 146.85 (d, $^5J_{PC}$=3.0 Hz), 152.25 (d, $^2J_{PC}$=7.8 Hz), 152.28 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −9.09 (d, $^2J_{PP}$= 35.6 Hz), 18.29 (d, $^2J_{PP}$=35.6 Hz). Anal. Calcd for $C_{32}H_{27}ClN_2O_5P_2$ (616.98): C, 62.30; H, 4.41; N, 4.54. Found: C, 62.21; H, 4.36; N, 4.45. MS *m/z* (%): 617 (100).

4.2.22. 1-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]ethyl}-2,4-dinitrobenzene (10j). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 79%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1094, 1022. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.74 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=17.8 Hz, 3H), 4.99 (dquintet, $^3J_{HH}$=$^2J_{PH}$=7.3 Hz, $^4J_{PH}$=2.4 Hz, 1H), 7.27 (m, 12H, H^{ar}), 7.66 (m, 6H, H^{ar}), 7.96 (m, 2H, H^{ar}), 8.23 (d, J_{HH}= 1.2 Hz, 2H, H^{ar}), 8.44 (t, J_{HH}=1.2 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.47 (d, $^2J_{PC}$=3.7 Hz), 34.82 (dd, $^1J_{PC}$=67.5 Hz, $^3J_{PC}$=3.7 Hz), 119.66 (d, $^4J_{PC}$= 2.1 Hz), 120.34 (d, $^3J_{PC}$=5.4 Hz), 120.69 (d, $^3J_{PC}$=5.1 Hz), 123.99 (d, $^5J_{PC}$=1.2 Hz), 124.13 (d, $^5J_{PC}$=1.5 Hz), 126.99 (d, $^4J_{PC}$=2.0 Hz), 127.46 (d, $^1J_{PC}$=105.1 Hz), 127.52 (d, $^1J_{PC}$=105.4 Hz), 128.67 (d, $^3J_{PC}$=12.9 Hz), 129.33 (d, $^3J_{PC}$=12.6 Hz), 129.38 (d, $^4J_{PC}$=0.9 Hz), 129.42 (d, $^4J_{PC}$=0.6 Hz), 130.90 (d, $^2J_{PC}$=10.5 Hz), 131.99 (d, $^2J_{PC}$= 9.9 Hz), 132.66 (d, $^4J_{PC}$=3.0 Hz), 133.11 (d, $^4J_{PC}$=3.0 Hz), 133.29 (d, $^3J_{PC}$=4.5 Hz), 139.15 (d, $^2J_{PC}$=5.4 Hz), 146.34 (d, $^5J_{PC}$=2.7 Hz), 148.68 (d, $^3J_{PC}$=6.9 Hz), 152.21 (d, $^2J_{PC}$=7.8 Hz), 152.22 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −9.20 (d, $^2J_{PP}$=35.6 Hz), 18.03 (d, $^2J_{PP}$=35.6 Hz). Anal. Calcd for $C_{32}H_{27}N_3O_7P_2$ (627.53): C, 61.25; H, 4.34; N, 6.70. Found: C, 61.37; H, 4.34; N, 6.69. MS *m/z* (%): 628 (100).

4.2.23. 1-[1-(*P*,*P*-Diphenylphosphynylborane)ethyl]-2,4-dinitrobenzene (10k). Eluent: ethyl acetate/hexane 1:7. Oil. Yield: 54%. IR (KBr pellets, neat), ν (cm^{-1}): 2326, 1261, 1105, 1065, 1027. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.67 (dd, $^3J_{HH}$=7.1 Hz, $^3J_{PH}$=15.6 Hz, 3H), 5.18 (dq, $^3J_{HH}$=7.1 Hz, $^2J_{PH}$=16.0 Hz, 1H), 7.25 (m, 4H, H^{ar}), 7.38 (m, 1H^{ar}), 7.61 (m, 3H, H^{ar}), 8.01 (m, 2H, H^{ar}), 8.19 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{PH}$=1.7 Hz, 1H^{ar}), 8.44 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HH}$=2.4 Hz, 1H^{ar}), 8.5 (d, $^4J_{HH}$=2.4 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.59 (d, $^2J_{PC}$=3.0 Hz), 30.97 (d, $^1J_{PC}$=30.3 Hz), 119.80 (d, $^4J_{PC}$=1.5 Hz), 125.79 (d, $^1J_{PC}$=54.1 Hz), 126.54 (d, $^4J_{PC}$=2.1 Hz), 126.65 (d, $^1J_{PC}$=53.2 Hz), 128.77 (d, $^3J_{PC}$=9.9 Hz), 129.31 (d, $^3J_{PC}$= 9.9 Hz), 131.73 (d, $^4J_{PC}$=2.7 Hz), 132.07 (d, $^2J_{PC}$=8.7 Hz), 132.24 (d, $^4J_{PC}$=2.7 Hz), 132.94 (d, $^3J_{PC}$=3.6 Hz), 133.06 (d, $^2J_{PC}$=8.7 Hz), 140.87, 146.39 (d, $^5J_{PC}$=2.7 Hz), 149.05 (d, $^3J_{PC}$=5.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 28.85. Anal. Calcd for $C_{20}H_{20}BN_2O_4P$ (394.17): C, 60.94; H, 5.11; N, 7.11. Found: C, 60.91; H, 5.12; N, 7.16. MS *m/z* (%): 393 (100).

4.2.24. 2-Chloro-4-{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]ethyl}nitrobenzene (10l). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 24%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1094. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.60 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=17.7 Hz, 3H), 4.00 (ddq, $^3J_{HH}$=7.3 Hz, $^2J_{PH}$=10.6 Hz, $^4J_{PH}$=1.4 Hz, 1H), 7.05–7.64 (m, 21H^{ar}), 7.85 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 14.91 (d, $^2J_{PC}$=2.4 Hz), 40.38 (dd, $^1J_{PC}$=65.5 Hz, $^3J_{PC}$=2.7 Hz), 120.48 (d, $^3J_{PC}$= 5.1 Hz), 120.60 (d, $^3J_{PC}$=5.1 Hz), 123.87 (d, $^4J_{PC}$=1.2 Hz), 123.90 (d, $^4J_{PC}$=1.5 Hz), 125.14 (d, $^4J_{PC}$=2.4 Hz), 126.38 (dd, $^1J_{PC}$=98.5 Hz, $^3J_{PC}$=2.7 Hz), 126.50 (d, $^4J_{PC}$= 2.7 Hz), 127.53 (dd, $^1J_{PC}$=103.3 Hz, $^3J_{PC}$=4.5 Hz), 128.66 (d, $^3J_{PC}$=5.1 Hz), 128.67 (d, $^3J_{PC}$=12.6 Hz), 129.02 (d, $^3J_{PC}$=12.3 Hz), 129.25 (d, $^4J_{PC}$=0.9 Hz), 129.28 (d, $^4J_{PC}$=0.9 Hz), 131.51 (d, $^2J_{PC}$=10.2 Hz), 132.26 (d, $^2J_{PC}$= 9.9 Hz), 132.59 (d, $^4J_{PC}$=3.0 Hz), 132.66 (d, $^3J_{PC}$=5.4 Hz), 132.95 (d, $^4J_{PC}$=3.0 Hz), 143.14 (d, $^2J_{PC}$=6 Hz), 146.37 (d, $^5J_{PC}$=3.6 Hz), 152.23 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −8.32 (d, $^2J_{PP}$=35.6 Hz), 19.39 (d, $^2J_{PP}$=35.6 Hz). Anal. Calcd for $C_{32}H_{27}ClN_2O_5P_2$ (616.98): C, 62.30; H, 4.41; N, 4.54. Found: C, 62.39; H, 4.37; N, 4.50. MS *m/z* (%): 617 (20).

4.2.25. 5-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}-2-nitrobenzonitrile (10m). Eluent: ethyl acetate/hexane 4:1. Oil. Yield: 53%. IR (KBr pellets, neat), ν (cm^{-1}): 2245, 1261, 1096, 1024. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.64 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=17.3 Hz, 3H), 4.13 (quintet, $^3J_{HH}$=$^2J_{PH}$=7.3 Hz, 1H), 7.25 (m, 8H, H^{ar}), 6.38 (m, 5H, H^{ar}), 7.57 (m, 5H, H^{ar}), 7.69 (m, 2H, H^{ar}), 7.85 (m, 2H, H^{ar}), 7.99 (d, $^3J_{HH}$=8.8 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 14.82 (d, $^2J_{PC}$=2.2 Hz), 40.5 (dd, $^1J_{PC}$=63.7 Hz, $^3J_{PC}$=2.7 Hz), 107.07 (d, $^4J_{PC}$=2.4 Hz), 114.58, 120.45 (d, $^3J_{PC}$=5.1 Hz), 120.54 (d, $^3J_{PC}$=5.1 Hz), 124.00 (d, $^5J_{PC}$=1.2 Hz), 125.11 (d, $^4J_{PC}$=2.4 Hz), 125.68 (dd, $^1J_{PC}$=100.2 Hz, $^3J_{PC}$= 3.8 Hz), 127.31 (dd, $^1J_{PC}$=102.7 Hz, $^3J_{PC}$=4.2 Hz), 128.91 (d, $^4J_{PC}$=12.9 Hz), 129.16 (d, $^3J_{PC}$=12.6 Hz), 129.27 (d, $^4J_{PC}$=0.9 Hz), 129.32 (d, $^5J_{PC}$=0.8 Hz), 131.40 (d, $^2J_{PC}$=10.5 Hz), 132.27 (d, $^2J_{PC}$=9.9 Hz), 132.91 (d, $^4J_{PC}$=3.0 Hz), 133.26 (d, $^4J_{PC}$=3.0 Hz), 134.90 (d, $^3J_{PC}$=4.8 Hz), 135.85 (d, $^3J_{PC}$=5.1 Hz), 144.55 (d, $^2J_{PC}$=6.0 Hz), 146.90 (d, $^5J_{PC}$=3.3 Hz), 152.09 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −8.09 (d, $^2J_{PP}$=35.6 Hz), 19.3 (d, $^2J_{PP}$=35.6 Hz). Anal. Calcd for $C_{33}H_{27}N_3O_5P_2$ (607.53): C, 65.24; H, 4.47; N, 6.91. Found: C, 65.29; H, 4.50; N, 6.99. MS *m/z* (%): 608 (100).

4.2.26. 4,4′-Di{1-[(*P*,*P*-diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}azoxybenzene (11a). Eluent: ethyl acetate/hexane 3:1. Oil. Yield: 19%. IR (KBr pellets, neat), ν (cm^{-1}): 1261, 1096, 1022. ^{1}H NMR (500.13 MHz, $CDCl_3$), δ (ppm): 1.66 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=17.5 Hz, 3H), 1.67 (dd, $^3J_{HH}$=7.1 Hz, $^3J_{PH}$= 17.8 Hz, 3H), 3.99 (m, 2H), 7.20 (m, 28H^{ar}), 7.42 (m, 6H^{ar}), 7.53 (m, 4H^{ar}), 7.63 (m, 2H^{ar}), 7.88 (m, 4H^{ar}), 7.95 (d, $^3J_{HH}$=8.5 Hz, 2H^{ar}), 8.05 (d, $^3J_{HH}$=8.5 Hz, 2H^{ar}). ^{13}C NMR (125.76 MHz, $CDCl_3$), δ (ppm): 15.22 (d, $^2J_{PC}$= 2.1 Hz), 15.31 (d, $^2J_{PC}$=1.7 Hz), 40.69 (dd, $^1J_{PC}$=66.9 Hz, $^3J_{PC}$=2.4 Hz), 40.95 (dd, $^1J_{PC}$=67.3 Hz, $^3J_{PC}$=2.4 Hz), 120.58 (d, $^3J_{PC}$=4.9 Hz), 120.61 (d, $^3J_{PC}$=4.9 Hz), 120.72 (d, $^3J_{PC}$=4.5 Hz), 120.77 ($^3J_{PC}$=4.9 Hz), 121.93 (d, $^4J_{PC}$= 2.1 Hz), 123.61, 123.69, 123.74, 125.35 (d, ^4J=2.2 Hz), 127.57 (d, $^1J_{PC}$=101.1 Hz), 127.94 (d, $^1J_{PC}$=116.9 Hz), 128.04 (d, $^1J_{PC}$=106.9 Hz), 128.27 (d, $^3J_{PC}$=12.4 Hz), 128.41 (d, $^3J_{PC}$=12.5 Hz), 128.80 (d, $^3J_{PC}$=10.1 Hz), 128.88 (d, $^3J_{PC}$=10.4 Hz), 129.17 (d, $^4J_{PC}$=1.3 Hz), 129.18 (d, $^4J_{PC}$=2.2 Hz), 129.79 (d, $^3J_{PC}$=5.2 Hz), 129.87 (d, $^3J_{PC}$=5.3 Hz), 131.84 (d, $^2J_{PC}$=10.0 Hz), 132.00 (d, $^2J_{PC}$=9.9 Hz), 132.10 (d, $^4J_{PC}$=2.0 Hz), 132.23 (d, $^4J_{PC}$=2.1 Hz), 132.30 (d, $^2J_{PC}$=10.1 Hz), 132.32

(d, $^{2}J_{PC}$=9.7 Hz), 132.44 (d, $^{4}J_{PC}$=2.4 Hz), 132.59 (d, $^{4}J_{PC}$=2.4 Hz), 138.25 (d, $^{2}J_{PC}$=6.5 Hz), 140.60 (d, $^{2}J_{PC}$=6.0 Hz), 142.92 (d, $^{5}J_{PC}$=3.5 Hz), 147.18 (d, $^{5}J_{PC}$=3.5 Hz), 152.47 (d, $^{2}J_{PC}$=8.7 Hz), 152.52 (d, $^{2}J_{PC}$=6.9 Hz), 152.54 (d, $^{2}J_{PC}$=8.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 18.83 (d, $^{2}J_{PP}$=33.4 Hz), 18.37 (d, $^{2}J_{PP}$=34.5 Hz), −9.43 (d, $^{2}J_{PP}$=33.4 Hz), −9.47 (d, $^{2}J_{PP}$=34.5 Hz). Anal. Calcd for $C_{64}H_{56}N_4O_7P_4$ (1116.56): C, 68.84; H, 5.01; N, 5.02. Found: C, 68.91; H, 5.05; N, 4.92. MS *m/z* (%): 1117 (37), 559 (100).

4.2.27. 4,4′-Di{1-[(*P*,*P*-diphenyl)(*N*-methoxycarbonyl)-phosphazenyl]ethyl}azoxybenzene (11b). Eluent: ethyl acetate/hexane 5:1. Oil. Yield: 10%. IR (KBr pellets, neat), ν (cm^{-1}): 1709, 1651, 1260, 1091, 1019. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.64 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.6 Hz, 3H), 1.65 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.6 Hz, 3H), 3.63 (s, 6H), 4.62 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=12.3 Hz, 1H), 4.67 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=12.3 Hz), 7.05 (m, 4H^{ar}), 7.43 (m, 4H^{ar}), 7.57 (m, 12H^{ar}), 7.79 (m, 4H^{ar}), 7.98 (d, $^{3}J_{HH}$=8.3 Hz, 2H^{ar}), 8.08 (d, $^{3}J_{HH}$=8.5 Hz, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.44 (d, $^{2}J_{PC}$=2.0 Hz), 15.57 (d, $^{2}J_{PC}$=2.0 Hz), 37.14 (d, $^{1}J_{PC}$=57.7 Hz), 37.40 (d, $^{1}J_{PC}$=58.5 Hz), 52.76 (d, $^{4}J_{PC}$=3.9 Hz), 52.80 (d, $^{4}J_{PC}$=3.9 Hz), 121.91 (d, $^{4}J_{PC}$=2.4 Hz), 124.37 (d, $^{1}J_{PC}$=97.6 Hz), 124.89 (d, $^{1}J_{PC}$=95.8 Hz), 125.07 (d, $^{1}J_{PC}$=95.8 Hz), 125.18 (d, $^{1}J_{PC}$=94.9 Hz), 125.33 (d, $^{4}J_{PC}$=2.4 Hz), 128.26 (d, $^{3}J_{PC}$=11.7 Hz), 128.40 (d, $^{3}J_{PC}$=11.7 Hz), 128.49 (d, $^{3}J_{PC}$=12.0 Hz), 128.53 (d, $^{3}J_{PC}$=11.7 Hz), 129.58 (d, $^{3}J_{PC}$=4.8 Hz), 129.61 (d, $^{3}J_{PC}$=5.1 Hz), 132.37 (d, $^{4}J_{PC}$=2.7 Hz), 132.46 (d, $^{4}J_{PC}$=3.0 Hz), 132.55 (d, $^{4}J_{PC}$=3.0 Hz), 132.74 (d, $^{4}J_{PC}$=2.7 Hz), 132 99 (d, $^{2}J_{PC}$=9.0 Hz), 133.15 (d, $^{2}J_{PC}$=9.0 Hz), 133.27 (d, $^{2}J_{PC}$=8.7 Hz), 133.31 (d, $^{2}J_{PC}$=8.7 Hz), 138.31 (d, $^{2}J_{PC}$=5.4 Hz), 140.68, (d, $^{2}J_{PC}$=5.1 Hz), 142.93 (d, $^{5}J_{PC}$=3.6 Hz), 147.18 (d, $^{5}J_{PC}$=3.3 Hz), 162.91 (d, $^{2}J_{PC}$=2.4 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 29.59, 29.76. Anal. Calcd for $C_{44}H_{42}N_4O_5P_2$ (768.79): C, 68.74; H, 5.51; N, 7.29. Found: C, 68.69; H, 5.53; N, 7.33. MS *m/z* (%): 385 (100), 769 (37).

4.2.28. 4,4′-Di[1-(*P*,*P*-diphenylphosphynylborane)ethyl]-azoxybenzene (11c). Eluent: ethyl acetate/hexane 1:3. Oil. Yield: 10%. IR (KBr pellets, neat), ν (cm^{-1}): 2380, 1261, 1101, 1017. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.63 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.1 Hz, 3H), 1.64 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=16.1 Hz, 3H), 3.91 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=12.1 Hz, 1H), 3.95 (dq, $^{3}J_{HH}$=7.3 Hz, $^{2}J_{PH}$=12.1 Hz, 1H), 7.18 (dd, $^{3}J_{HH}$=8.5 Hz, $^{4}J_{PH}$=1.6 Hz, 2H^{ar}), 7.2 (dd, $^{3}J_{HH}$=8.5 Hz, $^{4}J_{PH}$=1.6 Hz, 2H^{ar}), 7.29 (m, 4H^{ar}), 7.41 (m, 4H^{ar}), 7.56 (m, 8H^{ar}), 7.92 (m, 4H^{ar}), 8.00 (d, $^{3}J_{HH}$=8.5 Hz, 2H^{ar}), 8.08 (d, $^{3}J_{HH}$=8.5 Hz, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.17 (d, $^{2}J_{PC}$=3.3 Hz), 16.23 (d, $^{2}J_{PC}$=3 Hz), 37.31 (d, $^{1}J_{PC}$=30.3 Hz), 37.57 (d, $^{1}J_{PC}$=30 Hz), 121.73 (d, $^{4}J_{PC}$=2.1 Hz), 125.19 (d, $^{4}J_{PC}$=2.1 Hz), 127.35 (d, $^{1}J_{PC}$=52 Hz), 127.65 (d, $^{1}J_{PC}$=52 Hz), 127.79 (d, $^{1}J_{PC}$=53.5 Hz), 127.97 (d, $^{1}J_{PC}$=53.5 Hz), 128.27 (d, $^{3}J_{PC}$=8.7 Hz), 128.4 (d, $^{3}J_{PC}$=9 Hz), 128.86 (d, $^{3}J_{PC}$=9.6 Hz), 128.94 (d, $^{3}J_{PC}$=9.6 Hz), 129.55 (d, $^{3}J_{PC}$=5.4 Hz), 129.61 (d, $^{3}J_{PC}$=4.2 Hz), 131.07 (d, $^{4}J_{PC}$=2.4 Hz), 131.23 (d, $^{4}J_{PC}$=2.7 Hz), 131.46 (d, $^{4}J_{PC}$=2.7 Hz), 131.59 (d, $^{4}J_{PC}$=2.4 Hz), 132.72 (d, $^{2}J_{PC}$=8.4 Hz), 132.82 (d, $^{2}J_{PC}$=8.4 Hz), 132.97 (d, $^{2}J_{PC}$=8.2 Hz), 133.00 (d, $^{2}J_{PC}$=8.4 Hz), 139.84 (d, $^{2}J_{PC}$=1.8 Hz), 142.09 (d, $^{2}J_{PC}$=1.5 Hz), 142.78 (d, $^{5}J_{PC}$=3.3 Hz), 147.05 (d, $^{5}J_{PC}$=3.0 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 26.46. Anal. Calcd for $C_{40}H_{42}B_2N_2OP_2$ (650.35): C, 73.87; H, 6.51; N, 4.31. Found: C, 73.81; H, 6.54; N, 4.29. MS *m/z* (%): 634 (100), 673 (M+23, 20%).

4.2.29. 4,4′-Di[1-(*P*,*P*-diphenylphosphinoyl)ethyl]azoxybenzene (11d). Eluent: ethyl acetate/hexane 5:1. Solid. Mp 267–270 °C. IR (KBr), ν (cm^{-1}): 1261, 1098, 1025. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.62 (dd, $^{3}J_{HH}$=7.7 Hz, $^{3}J_{PH}$=15.8 Hz, 6H), 3.71 (m, 2H), 7.33 (m, 10H^{ar}), 7.54 (m, 10H^{ar}), 7.93 (m, 4H, H^{ar}), 8.03 (m, 2H^{ar}), 8.11 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.27 (d, $^{2}J_{PC}$=3.0 Hz), 15.39 (d, $^{2}J_{PC}$=3.0 Hz), 40.80 (d, $^{1}J_{PC}$=66.1 Hz), 41.06 (d, $^{1}J_{PC}$=66.7 Hz), 122.09 (d, $^{4}J_{PC}$=2.1 Hz), 125.57 (d, $^{4}J_{PC}$=1.5 Hz), 128.14 (d, $^{3}J_{PC}$=11.4 Hz), 128.25 (d, $^{3}J_{PC}$=11.7 Hz), 128.69 (d, $^{3}J_{PC}$=11.1 Hz), 128.77 (d, $^{3}J_{PC}$=11.1 Hz), 129.39 (d, J_{PC}=5.4 Hz), 129.46 (d, $^{3}J_{PC}$=5.1 Hz), 130.92 (d, $^{2}J_{PC}$=8.7 Hz), 131.04 (d, $^{2}J_{PC}$=9.0 Hz), 131.25 (d, $^{2}J_{PC}$=8.7 Hz), 131.30 (d, $^{2}J_{PC}$=8.4 Hz), 131.40 (d, $^{1}J_{PC}$=108.7 Hz), 131.46 (d, $^{4}J_{PC}$=2.7 Hz), 131.54 (d, $^{1}J_{PC}$=109.0 Hz), 131.59 (d, $^{4}J_{PC}$=3.0 Hz), 131.80 (d, $^{2}J_{PC}$=2.7 Hz), 131.92 (d, $^{4}J_{PC}$=3.0 Hz), 139.89 (d, $^{2}J_{PC}$=5.7 Hz), 142.19 (d, $^{2}J_{PC}$=5.4 Hz), 142.65 (d, $^{5}J_{PC}$=3.0 Hz), 146.94 (d, $^{5}J_{PC}$=3.0 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 33.65, 33.93. Anal. Calcd for $C_{40}H_{36}N_2O_3P_2$ (654.69): C, 73.38; H, 5.54; N, 4.28. Found: C, 72.98; H, 5.51; N, 4.31. MS *m/z* (%): 655 (100).

4.2.30. *N*-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}-3-chlorohydroxylamine (12). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 17%. IR (KBr pellets, neat), ν (cm^{-1}): 3456, 1260, 1094. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.25 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=14.0 Hz, 3H), 4.43 (dquintet, $^{3}J_{HH}$=$^{2}J_{PH}$=7.3 Hz, $^{4}J_{PH}$=0.6 Hz, 1H), 6.81–7.72 (m, 20H^{ar}), 7.78 (dd, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{PH}$=8.2 Hz, 4H^{ar}), 10 (s, OH). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 8.99 (d, $^{2}J_{PC}$=4.2 Hz), 63.52 (d, $^{1}J_{PC}$=85.6 Hz), 115.98, 120.52 (d, $^{3}J_{PC}$=5.1 Hz), 120.91 (d, $^{3}J_{PC}$=4.8 Hz), 121.25, 123.43 (d, $^{1}J_{PC}$=94.8 Hz), 123.95 (d, $^{5}J_{PC}$=1.2 Hz), 124.14 (d, $^{5}J_{PC}$=1.2 Hz), 124.71 (d, $^{1}J_{PC}$=97.9 Hz), 128.82 (d, $^{3}J_{PC}$=12.6 Hz), 128.86 (d, $^{3}J_{PC}$=12.0 Hz), 129.12 (d, $^{4}J_{PC}$=0.6 Hz), 129.26 (d, $^{4}J_{PC}$=0.9 Hz), 129.49, 131.79 (d, $^{2}J_{PC}$=9.6 Hz), 132.31 (d, $^{2}J_{PC}$=10.5 Hz), 132.57 (d, $^{4}J_{PC}$=2.4 Hz), 132.60 (d, $^{4}J_{PC}$=2.7 Hz), 134.67, 151.85 (d, $^{2}J_{PC}$=7.5 Hz), 152.08 (d, $^{2}J_{PC}$=7.5 Hz), 152.68 (d, $^{3}J_{PC}$=13.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 16.25 (d, $^{2}J_{PP}$=35.6 Hz), −5.43 (d, $^{2}J_{PP}$=35.6 Hz). Anal. Calcd for $C_{32}H_{29}ClN_2O_4P_2$ (602.99): C, 63.74; H, 4.85; N, 4.65. Found: C, 63.71; H, 4.89; N, 4.67. MS *m/z* (%): 625 (M+23, 20%), 434 (100).

4.2.31. *N*-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}-2-chlorophenylhydroxylamine (13). Eluent: ethyl acetate/hexane 2:1. Oil. Yield: 7%. IR (KBr pellets, neat), ν (cm^{-1}): 3490, 1261, 1097. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.56 (dd, $^{3}J_{HH}$=7.0 Hz, $^{3}J_{PH}$=16.1 Hz, 3H), 2.8 (br, 1H, OH), 5.21 (dquintet, $^{3}J_{HH}$=$^{2}J_{PH}$=7.0 Hz, $^{4}J_{PH}$=0.7 Hz, 1H), 6.67 (d, $^{3}J_{HH}$=8.4 Hz, 1H^{ar}), 6.82–7.63 (m, 19H^{ar}), 7.73–8.00 (m, 4H^{ar}).

^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 13.85 (d, $^2J_{PC}$= 2.7 Hz), 79.51 (dd, $^1J_{PC}$=81.4 Hz, $^3J_{PC}$=2.4 Hz), 115.89, 118.91, 120.67 (d, $^3J_{PC}$=5.1 Hz), 120.71 (d, $^3J_{PC}$=4.8 Hz), 122.55, 123.72 (d, $^4J_{PC}$=1.5 Hz), 123.78 (d, $^4J_{PC}$=1.2 Hz), 124.98 (d, $^1J_{PC}$=105.3 Hz), 125.07 (d, $^1J_{PC}$=105.6 Hz), 128.62 (d, $^3J_{PC}$=12.6 Hz), 128.82 (d, $^3J_{PC}$=12.6 Hz), 128.97, 129.05, 129.13 (d, $^4J_{PC}$=0.6 Hz), 12919 (d, $^4J_{PC}$=0.9 Hz), 132.1 (d, $^2J_{PC}$=10.5 Hz), 132.58 (d, $^4J_{PC}$=3 Hz), 132.79 (d, $^4J_{PC}$=3 Hz), 132.93 (d, $^2J_{PC}$= 9.9 Hz), 143.88, 152 (d, $^2J_{PC}$=7.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 15.82 (d, $^2J_{PP}$=33.4 Hz), −7.18 (d, $^2J_{PP}$=33.4 Hz). Anal. Calcd for $C_{32}H_{29}ClN_2O_4P_2$ (602.99): C, 63.74; H, 4.85; N, 4.65. Found: C, 63.69; H, 4.81; N, 4.70. MS *m*/*z* (%): 603 (79), 472 (100).

4.2.32. 2-[1-(*P*,*P*-Diphenylphosphynylborane)ethyl]-4-nitrobenzonitrile (14). Eluent: ethyl acetate/hexane 1:5. Oil. Yield: 25%. IR (KBr), ν (cm^{-1}): 2229, 1262, 1098, 1023. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.67 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=15.3 Hz, 3H), 4.52 (dq, $^3J_{HH}$= 7.3 Hz, $^2J_{PH}$=15.3 Hz, 1H), 7.27 (m, 2H, H^{ar}), 7.38 (m, 3H, H^{ar}), 7.62 (m, 4H, H^{ar}), 8.06 (m, 2H, H^{ar}), 8.14 (m, 1H^{ar}), 8.67 (m, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.47 (d, $^2J_{PC}$=3.0 Hz), 35.53 (d, $^1J_{PC}$=29.7 Hz), 115.91 (d, $^4J_{PC}$=1.5 Hz), 118.54 (d, $^3J_{PC}$=5.1 Hz), 122.35 (d, $^5J_{PC}$=2.4 Hz), 124.64 (d, $^3J_{PC}$=3.3 Hz), 125.43 (d, $^1J_{PC}$=53.5 Hz), 126.59 (d, $^1J_{PC}$=53.2 Hz), 128.56 (d, $^3J_{PC}$=9.9 Hz), 129.31 (d, $^3J_{PC}$=9.9 Hz), 131.63 (d, $^4J_{PC}$=2.7 Hz), 132.29 (d, $^4J_{PC}$=2.7 Hz), 132.60 (d, $^2J_{PC}$= 8.7 Hz), 133.06 (d, $^4J_{PC}$=1.8 Hz), 133.19 (d, $^2J_{PC}$= 8.7 Hz), 144.50, 149.80 (d, $^4J_{PC}$=2.4 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 28.33. Anal. Calcd for $C_{21}H_{20}BN_2O_2P$ (374.19): C, 67.41; H, 5.39; N, 7.49. Found: C, 67.37; H, 5.37; N, 7.51. MS *m*/*z* (%): 374 (30), 148 (35).

4.2.33. *N*-(4-Chlorophenyl)-*N*-[1-(*P*,*P*-diphenylphosphinoyl)ethyl]hydroxylamine (15). Eluent: ethyl acetate/hexane 7:1. Oil. Yield: 20%. IR (KBr pellets, neat), ν (cm^{-1}): 3483, 1094, 799. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.31 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=15.4 Hz, 3H), 4.40 (quintet, $^3J_{HH}$=$^2J_{PH}$=7.3 Hz, 1H), 6.95 (d, $^3J_{HH}$=8.9 Hz, 2H^{ar}), 7.17 (d, $^3J_{HH}$=8.5 Hz, 2H^{ar}), 7.51 (m, 6H^{ar}), 7.86 (m, 4H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 7.86 (d, $^2J_{PC}$=3.0 Hz), 62.01 (d, $^1J_{PC}$=87.7 Hz), 117.43, 126.66, 128.58, 128.65 (d, $^3J_{PC}$=11.7 Hz), 128.75 (d, $^3J_{PC}$=11.4 Hz), 130.06 (d, $^1J_{PC}$= 94.6 Hz), 131.24 (d, $^2J_{PC}$=8.7 Hz), 132.08 (d, $^4J_{PC}$=2.1 Hz), 132.25 (d, $^4J_{PC}$=2.4 Hz), 149.64 (d, $^3J_{PC}$=12.3 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 34.46. Anal. Calcd for $C_{20}H_{19}ClNO_2P$ (371.80): C, 64.61; H, 5.15; N, 3.77. Found: C, 64.10; H, 5.17; N, 3.97. MS *m*/*z* (%): 394 (70), 201 (100).

4.2.34. *N*-{1-[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)-phosphazenyl]ethyl}-4-chloroaniline (16a). Eluent: ethyl acetate/hexane 1.5:1. Oil. Yield: 13%. IR (KBr pellets, neat), ν (cm^{-1}): 3420, 1261, 1094. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.47 (dd, $^3J_{HH}$=6.8 Hz, $^3J_{PH}$=15.8 Hz, 3H), 5.14 (dq, $^3J_{HH}$=6.8 Hz, $^2J_{PH}$=3.6 Hz, 1H), 6.56 (d, $^3J_{HH}$=8.6 Hz, 2H^{ar}), 6.91–7.62 (m, 18H^{ar}), 7.71 (dd, $^3J_{HH}$=7.1 Hz, $^3J_{PH}$=12.2 Hz, 2H^{ar}), 7.83 (dd, $^3J_{HH}$= 7.1 Hz, $^3J_{PH}$=12.2 Hz, 2H^{ar}), 7.92 (s, NH). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 14.03 (d, $^2J_{PC}$=3.0 Hz), 78.7 (d, $^1J_{PC}$=80.5 Hz, $^3J_{PC}$=1.8 Hz), 115.79, 120.65 (d, $^3J_{PC}$=5.1 Hz), 120.70 (d, $^3J_{PC}$=5.1 Hz), 120–133 (14C^{ar}), 146.52, 152.01 (d, $^2J_{PC}$=7.2 Hz), 152.15 (d, $^2J_{PC}$=8.1 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 16.01 (d, $^2J_{PP}$= 32.3 Hz), −7.15 (d, $^2J_{PP}$=32.3 Hz). Anal. Calcd for $C_{32}H_{29}ClN_2O_3P_2$ (586.99): C, 65.48; H, 4.98; N, 4.77. Found: C, 64.95; H, 4.76; N, 4.97. MS *m*/*z* (%): 586 (20), 284 (100).

4.2.35. *N*-[1-(*P*,*P*-Diphenylphosphinoyl)ethyl]-4-chloroaniline (16b). Eluent: ethyl acetate/hexane 7:1. Oil. Yield: 4%. IR (KBr pellets, neat), ν (cm^{-1}): 1092, 1023. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.34 (dd, $^3J_{HH}$=5.6 Hz, $^3J_{PH}$=14.5 Hz, 3H), 4.3 (m, 1H), 6.55 (d, $^3J_{HH}$=8.9 Hz, 2H^{ar}), 7.09 (d, $^3J_{HH}$=8.9 Hz, 2H^{ar}), 7.53 (m, 6H^{ar}), 7.81 (m, 4H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 14.09 (d, $^2J_{PC}$=2.4 Hz), 47.59 (d, $^1J_{PC}$=81.7 Hz), 114.64, 122.76, 128.72 (d, $^3J_{PC}$=11.7 Hz), 129.13, 130.14 (d, $^1J_{PC}$= 92.2 Hz), 131.20 (d, $^2J_{PC}$=8.7 Hz), 131.29 (d, $^2J_{PC}$= 8.7 Hz), 132.1 (d, $^4J_{PC}$=2.7 Hz), 132.21 (d, $^4J_{PC}$= 2.7 Hz), 144.76 (d, $^3J_{PC}$=10.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 33.32. Anal. Calcd for $C_{20}H_{19}ClNOP$ (355.80): C, 67.52; H, 5.38; N, 3.94. Found: C, 68.01; H, 5.35; N, 3.97. MS *m*/*z* (%): 378 (40), 203 (50).

4.2.36. 3-Chloro-4-[1-(*P*,*P*-diphenylphosphynylborane)-ethyl]benzonitrile (18a). Eluent: ethyl acetate/hexane 1:5. Oil. Yield: 64%. IR (KBr pellets, neat), ν (cm^{-1}): 2384, 2226, 1261, 1095. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.54 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=15.9 Hz, 3H), 4.63 (dq, $^3J_{HH}$=7.3 Hz, $^2J_{PH}$=16.1 Hz, 1H), 7.29 (m, 5H, H^{ar}), 7.45 (m, 1H^{ar}), 7.59 (m, 4H, H^{ar}), 7.92 (dd, $^3J_{HH}$=8.1 Hz, $^4J_{HH}$=1.7 Hz, 1H^{ar}), 8.01 (m, 2H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.49 (d, $^2J_{PC}$=3.3 Hz), 32.64 (d, $^1J_{PC}$=31.2 Hz), 112.12 (d, $^5J_{PC}$=2.7 Hz), 117.23, 126.68 (d, $^1J_{PC}$=53.2 Hz), 127.34 (d, $^1J_{PC}$=53.5 Hz), 128.24 (d, $^3J_{PC}$=9.9 Hz), 129.15 (d, $^3J_{PC}$=9.6 Hz), 130.23 (d, $^4J_{PC}$=2.1 Hz), 131.22 (d, $^4J_{PC}$=1.8 Hz), 131.27 (d, $^3J_{PC}$=3.21 Hz), 131.96 (d, $^4J_{PC}$=2.4 Hz), 132.23 (d, $^4J_{PC}$=1.8 Hz), 132.38 (d, $^2J_{PC}$=8.7 Hz), 133.09 (d, $^2J_{PC}$=8.7 Hz), 134.94 (d, $^3J_{PC}$=6.0 Hz), 142.38. ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 27.56. Anal. Calcd for $C_{21}H_{20}BClNP$ (363.63): C, 69.36; H, 5.54; N, 3.85. Found: C, 69.97; H, 5.51; N, 3.79. MS *m*/*z* (%): 364 (40), 221 (100).

4.2.37. 4-[1-(*P*,*P*-Diphenylphosphynylborane)ethyl]-3-fluorobenzonitrile (18b). Eluent: ethyl acetate/hexane 1:10. Oil. Yield 25%. IR (KBr pellets, neat), ν (cm^{-1}): 2391, 1261, 1097. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.57 (dd, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=15.7 Hz, 3H), 4.39 (dq, $^3J_{HH}$=7.3 Hz, $^2J_{PH}$=15.8 Hz, 1H), 7.07 (dd, $^4J_{HH}$= 1.5 Hz, $^3J_{FH}$=9.5 Hz, 1H^{ar}), 7.27 (m, 2H^{ar}), 7.42 (m, 4H^{ar}), 7.56 (m, 3H^{ar}), 7.74 (m, 1H^{ar}), 7.97 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.77 (d, $^2J_{PC}$= 3.3 Hz), 28.31 (dd, $^1J_{PC}$=31.5 Hz, $^3J_{FC}$=1.8 Hz), 112.04 (dd, $^5J_{PC}$=2.7 Hz, $^3J_{FC}$=10.1 Hz), 117.37 (dd, $^6J_{PC}$= 1.5 Hz, $^4J_{FC}$=2.7 Hz), 118.34 (dd, $^4J_{PC}$=2.1 Hz, $^2J_{FC}$= 27.0 Hz), 126.80 (d, $^1J_{PC}$=52.9 Hz), 127.87 (dd, $^4J_{PC}$= 2.4 Hz, $^4J_{FC}$=3.9 Hz), 128.30 (d, $^3J_{PC}$=9.9 Hz), 129.08 (d, $^3J_{PC}$=9.9 Hz), 131.39 (d, $^4J_{PC}$=2.4 Hz), 131.63 (t, $^3J_{PC}$=$^3J_{FC}$=3.3 Hz), 131.86 (d, $^4J_{PC}$=2.4 Hz), 132.01 (d, $^2J_{FC}$=14.1 Hz), 132.29 (dd, $^2J_{PC}$=8.7 Hz, $^6J_{FC}$= 1.2 Hz), 132.87 (d, $^2J_{PC}$=8.4 Hz), 159.23 (dd, $^3J_{PC}$= 5.1 Hz, $^1J_{FC}$=248.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$),

δ (ppm): 26.46. Anal. Calcd for $C_{21}H_{20}BFNP$ (347.18): C, 72.65; H, 5.81; N, 4.03. Found: C, 70.01; H, 5.79; N, 4.55. MS *m*/*z* (%): 370 (10), 344 (100).

4.2.38. 5-Cyano-2-[1-(*P*,*P*-diphenylphosphynylborane)-ethyl]benzonitrile (18c). Solid. Yield: 87%. Mp 172–174 °C. IR (KBr), ν (cm^{-1}): 2261, 2233, 1102. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.62 (dd, $^3J_{HH}=7.3$ Hz, $^3J_{PH}=15.8$ Hz, 3H), 4.47 (dq, $^3J_{HH}=7.3$ Hz, $^2J_{PH}=15.4$ Hz, 1H), 7.31 (m, 4H, H^{ar}), 7.66 (m, 5H, H^{ar}), 7.90 (m, 1H^{ar}), 8.09 (m, 3H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 16.39 (d, $^2J_{PC}=3.6$ Hz), 35.73 (d, $^1J_{PC}=29.4$ Hz), 112.09 (d, $^5J_{PC}=2.4$ Hz), 114.48 (d, $^3J_{PC}=5.4$ Hz), 115.58 (d, $^4J_{PC}=1.8$ Hz), 116.41 (d, $^6J_{PC}=1.5$ Hz), 125.58 (d, $^1J_{PC}=54.1$ Hz), 126.46 (d, $^1J_{PC}=53.5$ Hz), 128.53 (d, $^3J_{PC}=9.6$ Hz), 129.34 (d, $^3J_{PC}=10.2$ Hz), 130.95 (d, $^3J_{PC}=3.0$ Hz), 131.72 (d, $^4J_{PC}=2.4$ Hz), 132.26 (d, $^4J_{PC}=2.4$ Hz), 132.52 (d, $^2J_{PC}=9.0$ Hz), 133.09 (d, $^2J_{PC}=9.0$ Hz), 135.20 (d, $^4J_{PC}=1.2$ Hz), 135.51 (d, $^4J_{PC}=1.8$ Hz), 147.54. ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 28.78. Anal. Calcd for $C_{22}H_{20}BN_2P$ (354.20): C, 74.60; H, 5.69; N, 7.91. Found: C, 74.58; H, 7.93; N, 7.85. MS *m*/*z* (%): 354 (80), 274 (100).

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Synthesis and characterization of 2,6-bis-hydrazinopyridine, and its conversion to 2,6-bis-pyrazolylpyridines

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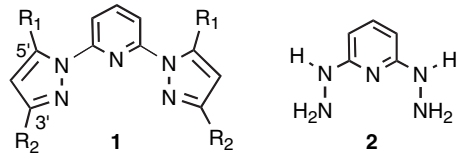
Abstract—2,6-Bis-hydrazinopyridine has been prepared and characterized for the first time. This material is useful for the preparation of a wide variety of 2,6-bis-pyrazolylpyridines. This approach represents the most efficient preparation to date of sterically crowded 2,6-bis-pyrazolylpyridines, and the only method for the preparation of pyrazolylpyridines containing unsymmetrically 3′,5′-disubstituted pyrazoles with the larger groups in the 5′ positions.

1. Introduction

Substituted pyridines have played a remarkably diverse role as chelating ligands in transition metal chemistry.[1] The potentially tridentate 2,6-bis-pyrazolylpyridines (e.g., **1**, Scheme 1) are one such class of ligands that have been recently reviewed.[2] While there are several examples of such ligands with large groups in the 3′ positions,[2–4] including chiral groups,[5] no examples having groups larger than methyl at the 5′ position have been reported, apparently because of difficulties in their preparation. To date, 2,6-bis-pyrazolylpyridines have been made almost exclusively by nucleophilic aromatic substitution reactions of pyrazole anions with 2,6-dihalopyridines.[2–5] Given the low reactivity of aryl halides and the poor nucleophilicity of even unhindered pyrazole anions, these reactions require rather severe conditions. For example, the reaction of 2,6-dibromopyridine with 3,5-dimethylpyrazolyl sodium or potassium required $\geq$110 °C for several days.[3] We have found that these reactions are quite sensitive to steric bulk, with more hindered 3,5-disubstituted pyrazole anions reacting very poorly with pyridyl halides even under forcing conditions. A recent report using similar conditions found that attempted Pd(II) catalysis actually inhibited the reaction.[6] A more efficient preparation of 2,6-bis-pyrazolylpyridines is needed to better explore the chemistry of these ligands.

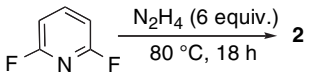


Scheme 1.

Arylhydrazines react readily with 1,3-diketones to provide *N*-arylpyrazoles in high yield.[7] We anticipated that reaction of 2,6-bis-hydrazinopyridine (BHP, **2**, Scheme 1) with 1,3-diketones would efficiently provide the desired 2,6-bis-pyrazolylpyridines. *N*-Arylpyrazoles have been made from 2-hydrazinopyridine[8] and 2-hydrazinoquinoline[9] and 1,3-diketones. However, the literature contains only obscure references to bis-hydrazine **2**,[10] with no details of its preparation or characterization. A recent review has noted both the potential utility of BHP in preparing 2,6-bis-pyrazolylpyridines and the lack of any published routes to it.[2]

2. Results and discussion

The preparation of BHP via reaction of a 2,6-dihalopyridine with hydrazine was studied. The 2,6-dihalopyridines (X=F, Cl, Br) are all commercially available; we chose 2,6-difluoropyridine (Scheme 2) because of its expected higher reactivity and, being the only liquid 2,6-dihalopyridine, it allowed for solvent-free reactions with hydrazine. In addition, ^{19}F coupling to the aryl protons provided



Scheme 2.

Keywords: 2,6-Difluoropyridine; Hydrazine; Hydrazinopyridine; Pyrazolylpyridine.
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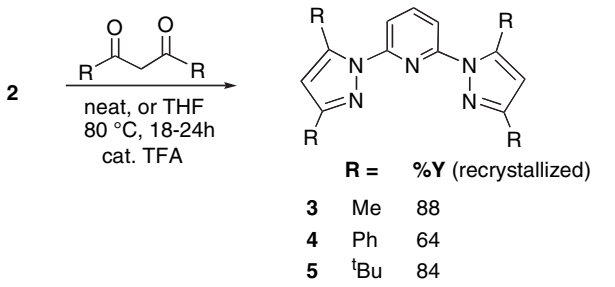
a simple way to monitor the presence of both starting material and the mono-hydrazino intermediate. We employed excess anhydrous hydrazine (6 equiv) to avoid significant amounts of polymer formation.[11] The reaction proceeds readily to the mono-hydrazino stage at room temperature, and disubstitution occurs with moderate warming (70–80°) overnight. Higher temperatures (~100 °C) cause decomposition (darkening) of the product. Surprisingly, these reactions are quite oxygen-sensitive; under argon, the mixtures are colorless to light yellow, while exposure to air rapidly results in extensive brown or black coloration and a dramatic loss in yield. Interestingly, this degradation is not evident by ^{1}H NMR; even largely impure samples are soluble in DMSO-d_6 and exhibit clean proton NMR spectra.

The isolation of pure BHP was not entirely straightforward. Simple recrystallization of the crude reaction mixture directly from deoxygenated water gave feathery yellow plates in an apparent yield of 88%. However, elemental analysis revealed that this material contained only 75–80% BHP, the remainder being $N_2H_4\cdot HF$ and water.[12]

The tendency of HF salts to contaminate BHP led us to study recrystallization from aqueous base, the idea being that neutralization of $N_2H_4\cdot HF$ would eliminate the presence of both hydrazine and fluoride salts. Indeed, neutralization of the HF salts in the crude product with an equimolar amount of aqueous NaOH caused immediate precipitation of the sparingly soluble NaF. After hot filtration (under inert atmosphere), 2,6-bis-hydrazino-pyridine crystallized in 85–95% yield as colorless to brownish rods. Elemental analysis showed no hydrazine, fluoride or water present in this material. These crystals were stable enough to be weighed in air, and appear to be indefinitely stable in the freezer under inert atmosphere. BHP is very soluble in DMSO, somewhat soluble in water and slightly soluble in THF. We have reported the crystal structures of BHP dihydrate, the di-tosylate salt and 2,6-bis-pyrazolylpyridine **5** (described below) elsewhere.[13]



Scheme 3.

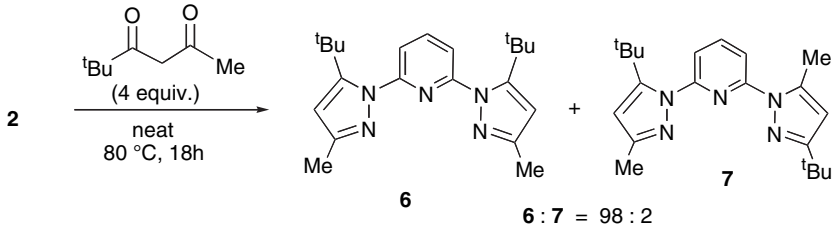
The preparation of 2,6-bis-pyrazoylpyridines from bis-hydrazine **2** is straightforward and generally quite efficient (Scheme 3). Treatment of **2** with an excess (4 equiv) of neat 2,4-pentanedione results in an exothermic reaction, and is easily complete at 80 °C overnight, providing the known[3,14] 2,6-bis-(3′,5′-dimethylpyrazolyl)pyridine (**3**) in 88% yield after recrystallization. More hindered diketones also react efficiently, aided by catalytic amounts of acid. For example, reaction of an excess (4 equiv) of dibenzoylmethane and 0.1 equiv of trifluoroacetic acid with BHP in refluxing THF yielded 64% (recrystallized) of the corresponding 2,6-bis-pyrazolylpyridine **4** after recrystallization. Likewise, neat 2,2,6,6-tetramethyl-3,5-heptanedione (4 equiv) reacted with **2** (80 °C, 0.1 equiv TFA) to yield 84% of 2,6-bis-pyrazolylpyridine **5** after recrystallization. Neither of pyrazolylpyridines **4** or **5** had been reported previously.

BHP also reacts with unsymmetrical 1,3-diketones to provide 2,6-bis-pyrazoylpyridines that are not easily obtained any other way. For example, GC–MS revealed that reaction of 2,2-dimethyl-3,5-hexanedione with BHP (80 °C, 24 h) yielded a 98:2 ratio of pyrazolylpyridines **6** and **7** (Scheme 4), and no detectable amounts (<ca. 0.1%) of the third possible isomer **8** (Scheme 5). Compounds **6** and **8** were easily identified by their proton NMR spectra; both were clearly symmetrical, and the 5′ methyls are more downfield (2.61 ppm) than the 3′ methyls (2.29 ppm), as is commonly observed in pyrazolylpyridines.[6] The regio-chemistry of **6** is easily rationalized by initial reaction of each NH_2 group of BHP with the less-hindered carbonyl group of the diketone, followed by cyclization of the remaining carbonyl onto the NH, placing the larger group immediately adjacent to the pyridine ring. Reactions of mono-amines with 1,3-diketones are known to form imines at the less-hindered carbonyl group.[15]

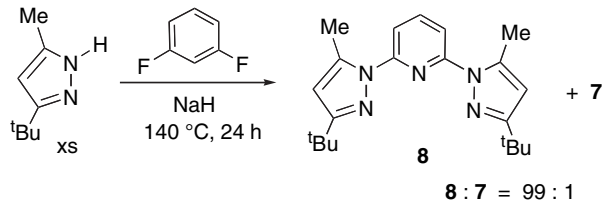
In contrast, unsymmetrical pyrazole anions are well known[5] to undergo arylation selectively at the less-hindered nitrogen, in this case yielding an entirely different isomer than that given by BHP. Reaction of the anion of 3-*tert*-butyl-5-methylpyrazole[16] with 2,6-difluoropyridine (140 °C, 24 h) produced a 99:1 mixture of pyrazolylpyridines **8** and **7** (Scheme 5), and no detectable amounts of **6** by GC–MS.

3. Conclusion

The use of BHP allows the preparation of new 2,6-bis-pyrazoylpyridines, particularly those with large groups at



Scheme 4.



Scheme 5.

the 5′ position of the pyrazole ring. Studies of electronic effects and application of this chemistry to the preparation of chiral non-racemic ligands for possible application in asymmetric synthesis are now in progress. We anticipate that BHP will be useful in several other applications.

4. Experimental

4.1. General

Unless specified otherwise, reagents and solvents were purchased from the Aldrich Chemical Company or from Acros Organics, and were used as received. 2,2-Dimethyl-3,5-heptanedione was obtained from Strem Chemical. NMR spectra were obtained at 300, 360 or 500 MHz for ^{1}H and 75, 90 or 125 MHz for ^{13}C. Spectra obtained in $CDCl_3$ were referenced to TMS (0 ppm) for ^{1}H and to solvent (77.0 ppm) for ^{13}C. Spectra obtained in DMSO-d_6 were referenced to solvent (2.48 ppm for ^{1}H, 39.5 ppm for ^{13}C). Selected IR peaks are reported in cm^{-1}, with the strongest peaks indicated by an (s). GC–MS was done on a Hewlett-Packard GCD using a 30 m×0.25 mm HP-5 capillary column with helium carrier and EI ionization. High-resolution mass spectra were obtained from the University of California, Riverside, mass spectroscopy facility. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Melting points were calibrated against accepted standards.

4.1.1. 2,6-Bis-hydrazinopyridine (BHP, 2). Caution: 2,6-difluoropyridine is poorly miscible in hydrazine and the two-phase mixture can react violently if the addition is too fast or the stirring is not vigorous enough, especially on larger scales.

Under inert atmosphere and with vigorous stirring, 2,6-difluoropyridine (0.5 mL, 5.5 mmol) was cautiously added dropwise to anhydrous hydrazine (1.03 mL, 33 mmol). The mixture was heated to 80 °C for 18–24 h, then cooled to yield a yellow solid. This was treated with deoxygenated aqueous NaOH (2.2 M, 5 mL, 11 mmol, 2 equiv), which immediately yielded a white precipitate of sodium fluoride. The suspension was then warmed to 60–70 °C with stirring and, using a cannula, filtered hot through a small amount of Celite under inert atmosphere. Upon cooling, amber plates formed. After cooling to 0 °C, the supernatant was removed by cannula, the crystals were washed once with cold water and dried under vacuum to yield BHP (0.68 g, 89%), mp (sealed tube) 125–127 °C (dec). ^{1}H NMR (DMSO-d_6): 3.99 (4H, br s), 5.95 (2H, d, J=7.8 Hz), 7.01 (2H, s), 7.20 (1H, t, J=7.8 Hz). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): 94.7, 138.8, 161.6. IR (KBr pellet): 4435, 3295, 3258, 1594 (s), 1465 (s). HRMS: calcd for $C_5H_9N_5$=139.0858, found 139.0853. Anal. Calcd for $C_5H_9N_5$: C, 43.15; H, 6.52; N, 50.33. Found: C, 43.34; H, 6.47; N, 50.33.

4.2. Procedure for the preparation of 2,6-bis-pyrazolyl-pyridines (3–6) from BHP

Under inert atmosphere, BHP (250 mg, 1.8 mmol) was treated with neat 1,3-diketone (7.2 mmol, 4 equiv). Solid diketones were added as a solution in a minimum amount of THF. With hindered diketones, catalytic trifluoroacetic acid (0.18 mmol, 0.1 equiv) was added. The mixture was heated to 80 °C for 18–24 h. Excess diketone was removed by bulb-to-bulb vacuum distillation, and the residue was recrystallized from hexanes or hexanes/ethyl acetate. Column chromatography on silica gel using 20–40% ethyl acetate and 2% triethyl amine in hexanes can also be used. On a smaller scale, the products could be purified by preparative TLC eluted with 5–10% ethyl acetate and 1–2% triethylamine in hexanes.

4.2.1. 2,6-Bis-(3′,5′-diphenylpyrazolyl)pyridine (4). Sixty four percentage yield after recrystallization from ethyl acetate/hexanes, mp 165.5–167 °C. ^{1}H NMR ($CDCl_3$): 6.70 (2H, s), 7.12–7.18 (4H, m), 7.21–7.30 (6H, m), 7.33–7.47 (6H, m), 7.58 (2H, d, J=8 Hz), 7.81–7.91 (5H, m) $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 106.6, 116.3, 125.9, 127.9, 128.0, 128.2, 128.6, 128.8, 130.7, 132.6, 140.2, 145.3, 150.8, 152.4. IR (KBr pellet): 1584, 1454 (s), 1353, 759, 694. Anal. Calcd for $C_{35}H_{25}N_5$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.32; H, 4.85; N, 13.55.

4.2.2. 2,6-Bis-(3′,5′-di-*tert*-butylpyrazolyl)pyridine (5). Eighty four percentage yield after recrystallization from hexanes, mp 161–162 °C. ^{1}H NMR ($CDCl_3$): 1.26 (18H, s), 1.32 (18H, s), 6.05 (2H, s), 7.58 (2H, d, J=8.1 Hz), 7.90 (1H, t, J=8.1 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 30.4, 30.8, 32.0, 32.4, 102.0, 120.0, 139.8, 153.0, 154.1, 161.5. IR (KBr pellet): 2967 (s), 1592, 1465 (s), 1362, 1246, 820. HRMS: calcd for $C_{27}H_{41}N_5$=435.3362, found 435.3356. Anal. Calcd for $C_{27}H_{41}N_5$: C, 74.44; H, 9.49; N, 16.08. Found: C, 74.50; H, 9.68; N, 16.22.

4.2.3. 2,6-Bis-(5′-*tert*-butyl-3′-methylpyrazolyl)pyridine (6). Reaction was done according to the standard procedure using catalytic trifluoroacetic acid. GC–MS (HP-5, 60–300 °C at 10 °C/min, hold 6 min) of the crude product showed two peaks of mass 351, at 24.8 min (98%) and 25.7 min (2%), each having distinctly different fragmentation patterns, especially with respect to the base peaks. After removing excess diketone by Kugelrohr distillation, the residue was passed through a 3 cm column of silica gel using 50% ethyl acetate in hexanes to give **6** as an amber oil in 90% yield. The major product **6** could also be isolated by preparative TLC. ^{1}H NMR ($CDCl_3$): 1.24 (18H, s), 2.29 (6H, s), 6.02 (2H, s), 7.52 (2H, d, J=7.8 Hz), 7.94 (1H, t, J=7.8 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 13.5, 30.7, 32.2, 105.3, 120.7, 140.2, 148.7, 152.9, 154.7. MS (EI): 351, 336, 229 (base), 203, 160, 123. IR (thin film): 2966, 1595, 1579, 1466 (s), 1355, 1014, 814, 792. HRMS: calcd for $C_{21}H_{29}N_5$=351.2423, found 351.2435. The minor isomer **7** gave the following MS: 351, 336 (base), 137.

4.2.4. 2,6-Bis-(3′-*tert*-butyl-5′-methylpyrazolyl)pyridine (8). A conical flask was charged with 3-*tert*-butyl-5-methylpyrazole[16] (112 mg, 0.81 mmol, 2.2 equiv), sodium hydride (43 mg, 1.8 mmol, 5 equiv) and a stir bar. Under inert atmosphere, anhydrous diglyme (0.5 mL) and 2,6-difluoropyridine (33 μL, 0.36 mmol, 1 equiv) were added and the mixture was heated to 140 °C overnight. The crude product was extracted into CH_2Cl_2 and analyzed by GC–MS as for compound **6** above. Two compounds of mass 351 were observed at 25.7 min (1%, **7**) and 27.0 min (99%, **8**), each having very distinct fragmentation patterns. The major isomer was purified by preparative TLC (10% ethyl acetate and 2% triethylamine in hexanes) to yield 29 mg (23%) of **8** as a white solid, mp 131–134 °C. ^{1}H NMR ($CDCl_3$): 1.35 (18H, s), 2.61 (6H, s), 6.08 (2H, s), 7.72 (2H, d, $J=8$ Hz), 7.87 (1H, t, $J=8$ Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 14.3, 30.3, 32.2, 105.7, 113.6, 140.3, 140.6, 151.7, 162.9. MS (EI): 351 (base), 336, 294, 160. IR (KBr pellet): 2964, 1599, 1585, 1487, 1468 (s), 1431, 1363, 1076, 798. HRMS: calcd for $C_{21}H_{29}N_5=351.2423$, found 351.2420.

Acknowledgements

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1,3-Dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP): a powerful condensing reagent for phosphate and phosphonate esters

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Abstract—A novel phosphonium-type condensing reagent, 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP), was designed and synthesized. A ^{31}P NMR study on the condensation reactions of phosphate, alkylphosphonate, boranophosphate, and *H*-phosphonate derivatives with an alcohol in the presence of MNTP demonstrated the versatility and the enhanced activity of the new condensing reagent, compared to the previously reported phosphonium-type condensing reagents. The mechanism of the condensation reactions mediated by MNTP is discussed on the basis of the ^{31}P NMR studies and theoretical calculations.

1. Introduction

Phosphate esters, especially those which play important roles in cells such as nucleic acids,[1,2] phosphoinositols,[3,4] phospholipids,[5] sugar phosphates,[5,6] and phosphopeptides,[7] are one class of important targets in current synthetic organic chemistry. The most frequently used method to synthesize these phosphate esters as well as their analogs is the O-phosphitylation with phosphoramidites (the phosphoramidite method),[8–11] because the reactions proceed rapidly and efficiently under mild acidic conditions. However, this method has some shortcomings. Firstly, care should be taken to store the phosphitylating reagents due to their instability to oxidation and hydrolysis. The reactions have to be carried out under strictly anhydrous conditions for the same reason. Secondly, an additional step, such as oxidation, sulfurization, or boronation, to transform the phosphite intermediates into the corresponding phosphate derivatives is required, which may cause some undesired side reactions depending on substrates (e.g., the dealkylation by I^- and/or hydrolysis of substrates during oxidation with I_2/H_2O, the reduction of substrates caused by a boronating reagent, and so on).[12–16]

In the course of our study to develop new synthetic methods for nucleic acid derivatives, we have been devoting much effort to the design and synthesis of condensing reagents for O-phosphorylations and O-phosphonylations, which have some advantages over the O-phosphitylations by the phosphoramidite method and can be appropriately chosen depending on target molecules.[17–19] The advantages are: (1) condensation reactions can be carried out without strictly anhydrous conditions; (2) the phosphorylating and phosphonylating reagents can be stored for a long period of time without being oxidized or hydrolyzed; (3) an additional step, such as oxidation, is eliminated. These characteristics would enable one to synthesize some functionalized molecules, which are difficult to be synthesized by the phosphoramidite method. As such a successful result, we have developed a new boranophosphorylation reaction of nucleosides mediated by a condensing reagent and could synthesize dinucleoside boranophosphates containing four nucleobases,[18,19] which were difficult to be synthesized by the phosphoramidite method due to serious side reactions on the nucleobases caused by a boronating reagent during the boronation of the phosphite intermediates.[13–16] However, O-phosphorylations and O-phosphonylations (except for the reactions of reactive *H*-phosphonates) suffer from the low reactivity of the phosphorylating and phosphonylating reagents, compared to that of phosphitylating reagents in the phosphoramidite method. This would be a significant drawback, especially when target molecules require multiple phosphorylations or phosphonylations as the synthesis of DNA/RNA analogs. To remedy this drawback and to develop an efficient condensing reagent applicable to a wide variety of phosphate derivatives, we designed

Keywords: Phosphonium-type condensing reagent; Phosphate; Alkylphosphonate; Boranophosphate; *H*-Phosphonate.
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a new phosphonium-type condensing reagent, 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (**1**). In this paper, we report the synthesis of **1** and its application to the synthesis of phosphate and phosphonate esters. The synthesis of the prototype condensing reagent, 3-nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (**2**),[19] is also described in detail.

2. Results and discussion

2.1. Design and synthesis of 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP) and 3-nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyNTP)

Phosphonium-type condensing reagents, which were originally developed for the peptide synthesis,[20–23] have also proven to be effective for the synthesis of phosphate and phosphonate derivatives.[17,19,24–27] For example, 2-(benzotriazol-1-yloxy)-1,3-dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (BOMP) (Fig. 1, **3**) was successfully used for the rapid formation of *H*-phosphonate diesters.[17] The study showed that **3** was much more effective for the activation of *H*-phosphonate monoesters than the parent commercially available condensing reagent, benzotriazol-1-yloxy-2-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP) (Fig. 1, **4**).[21] Although **3** is one of the most active condensing reagents for *H*-phosphonate derivatives at present, we considered that further improvement of the molecular structure would be necessary for the development of a versatile condensing reagent applicable to various phosphate and phosphonate esters, because the activation of the $P–O^-$ functions of phosphates or phosphonates except for *H*-phosphonates with **3** would form rather less active intermediates, 1-benzotriazolyl phosphates or phosphonates.[28] Given this situation, we designed 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP, **1**), in which 3-nitro-1,2,4-triazole was introduced in the place of 1-hydroxybenzotriazole in **3**, as a new condensing reagent, because the effectiveness of 3-nitro-1,2,4-triazole as a nucleophilic catalyst has already been demonstrated with the prototype condensing reagent, 3-nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyNTP, **2**),[19] and because 3-nitro-1,2,4-trialzole has also been used as an efficient nucleophilic catalyst for O-phosphorylations and O-phosphonylations with conventional condensing reagents, such as 1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT).[29]

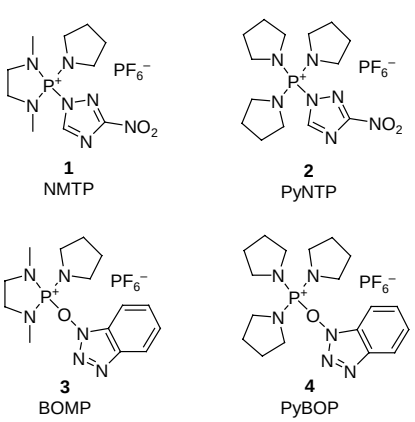
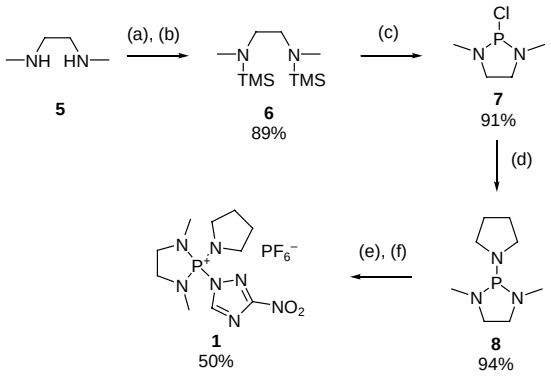


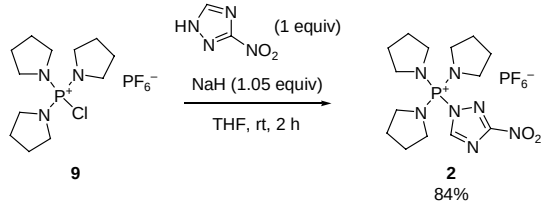
Figure 1. Phosphonium-type condensing reagents.

The synthesis of **1** is outlined in Scheme 1. 1,3-Dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidine (**8**) was prepared from *N*,*N*′-dimethyl-1,2-ethylenediamine (**5**) in three steps,[30] and **8** was allowed to react with 3-nitro-1,2,4-triazole in the presence of carbon tetrachloride, followed by a counteranion exchange to give **1** as a colorless crystalline solid, which could be stored in a vial for at least 12 months at −30 °C.



Scheme 1. Synthesis of MNTP **1**. Reagents and conditions: (a) BuLi (2.1 equiv), Et_2O–hexane, −78 °C then 0 °C, 30 min; (b) TMSCl (2.1 equiv), −78 °C then rt, 2 h; (c) PCl_3 (1 equiv), 0 °C then rt, 6 h; (d) 1-(trimethylsilyl)pyrrolidine (1 equiv), 0 °C then reflux, 1 h; (e) 3-nitro-1,2,4-triazole (1 equiv), CCl_4 (4 equiv), CH_2Cl_2, −78 °C, 1 h then rt, 30 min; (f) KPF_6 (1 equiv), CH_3CN, rt, 1 h.

PyNTP **2** could be synthesized by a much simpler protocol than that for **1** (Scheme 2). The nucleophilic substitution of the chloro group on the phosphorus atom of a commercially available condensing reagent, chlorotri(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyCloP, **9**)[22] with 3-nitro-1,2,4-triazole in the presence of NaH yielded **2** in good yield as a colorless crystalline solid, which could also be stored in a vial for at least 12 months at −30 °C.



Scheme 2. Synthesis of PyNTP **2**.

The optimized geometries of **1** and **2** calculated at the HF/6-31G* level showed that **1** was a little less congested around the phosphorus atom, compared to **2** (Fig. 2). This reduced steric hindrance of **1** may have some positive effect on the reaction rate mediated by this new condensing reagent. The strained five-membered diazaphospholidine ring of **1** may also contribute to an enhanced condensation reaction,

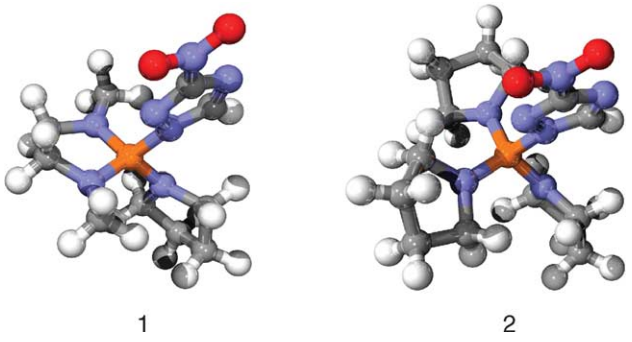


Figure 2. Optimized geometries of **1** and **2** calculated at the HF/6-31G* level.

because nucleophilic attacks to the phosphorus atom of strained five-membered cyclic structures are known to be faster than to that of the corresponding linear organophosphorus compounds.[31]

2.2. Condensation reactions of dimethyl phosphate in the presence of the phosphonium-type condensing reagents 1 and 2

For the validation of our molecular design of the new phosphonium-type condensing reagent, we chose the condensation of dimethyl phosphate **10a** with 2-phenylethanol **11** as a simple model reaction, and compared the condensation activity of **1** with that of **2** and **3**. The phosphate **10a** was allowed to condense with **11** (1.5 equiv) in the presence of **1**, **2** or **3** (3 equiv) and a weak, less nucleophilic base, 2,6-lutidine (10 equiv), as an acid scavenger in CH_3CN–CD_3CN (4/1, v/v) at 20 °C, and the reactions were monitored by ^{31}P NMR. The results clearly demonstrated the superiority of **1** and **2** over **3** with respect to the reaction rate (Fig. 3). Thus, the desired phosphate triester **12a** was formed in 98 and 83% yields after 150 min

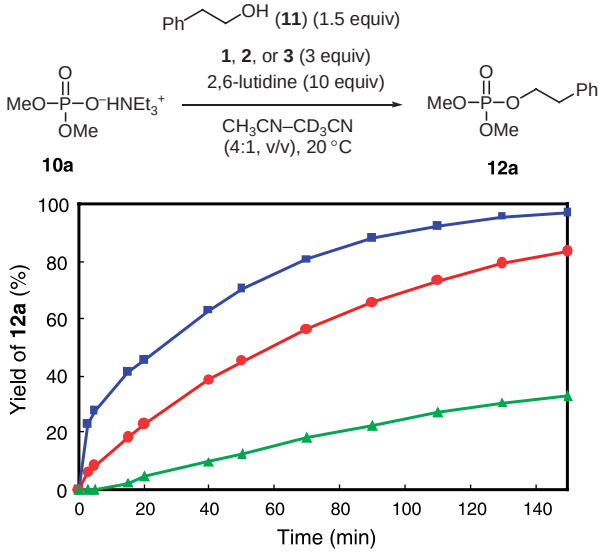


Figure 3. Condensation reactions of dimethyl phosphate **10a** with 2-phenylethanol **11** (1.5 equiv) in the presence of **1**, **2**, or **3** (3 equiv) in CH_3CN–CD_3CN (4/1, v/v) at 20 °C. ■, MNTP **1**; ●, PyNTP **2**; ▲, BOMP **3**.

when **1** and **2** were used, respectively. In the former case, **12a** was isolated in 98% yield after the usual work-up and purification by silica gel column chromatography. On the other hand, only 33% of **12a** was generated within the same time period, when **3** was used.

The condensation reaction of **10a** with **11** mediated by **1**–**3** is most likely to start with the generation of the active intermediate **13a**,**b** (Fig. 4). This type of active intermediate has also been proposed for the PyBOP-mediated activation of phosphonates.[25] There are some possible pathways from **13a**,**b** to the final product **12a**. The pathway via the symmetric pyrophosphate **14a** (path a) undoubtedly exists; the generation of **14a** and its conversion to the final product **12a** could be monitored by ^{31}P NMR (**14a**, δ −9.6;[32] **12a**, δ 1.9, Fig. 5).[33] In the presence of **1** or **2**, the rate-determining step of the path a must be the reaction of **14a** with 3-nitro-1,2,4-triazole (Nt–H) judging from the fact that **14a** was the only intermediate observed by ^{31}P NMR. However, there is not only one pathway, because the reaction rate was affected by the phosphonium skeleton of the condensing reagents (Fig. 3, **1** vs **2**), which is not involved in the rate-determining step of the path a. Our assumption is that there are two other pathways, the paths b and c shown in Figure 4, and the rate constants of the nucleophilic attacks of X–H (path b) and **11** (path c) at the electronically neutral phosphorus atom of **13a** are larger than at that of **13b**. Then, we carried out the ab initio molecular orbital calculations (HF/6-31G* level) for **13a**,**b** to find that the energy levels of the unoccupied molecular orbitals (UMOs) of **13a** were lower in general than those of **13b**.[34] For example, the energy level of the lowest UMO (LUMO) of **13a** was calculated to be 38.7 kcal/mol, whereas that of **13b** was 46.3 kcal/mol. The structures of **1** and **2** may also affect the rate of the nucleophilic attack of **10a** at the electronically neutral phosphorus atoms of **13a**,**b** (path a). However, we consider that the paths b and c, which should originally have larger activating energy values than the path a, would be relatively more affected than the path a.

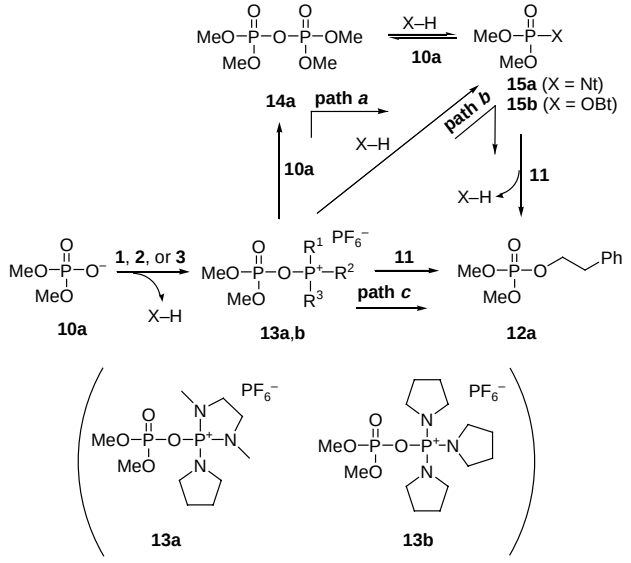


Figure 4. Possible reaction pathways for the reaction of **10a** with **11** in the presence of **1**, **2**, or **3**. X–H=Nt–H=3-nitro-1,2,4-triazole for **1** and **2**; X–H=BtO–H=1-hydroxybenzotriazole for **3**.

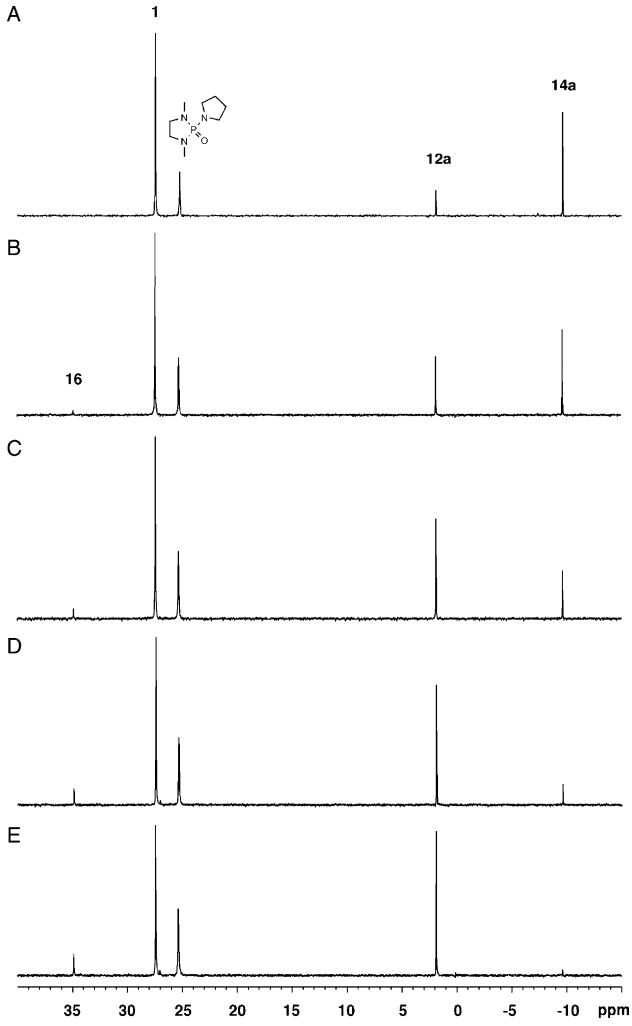
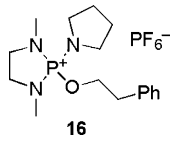


Figure 5. ^{31}P NMR spectra of the reaction mixture obtained by the reaction of **10a** with **11** (1.5 equiv) in the presence of **1** (3 equiv) in CH_3CN–CD_3CN (4/1, v/v) at 20 °C. (A) 3 min; (B) 20 min; (C) 50 min; (D) 90 min; (E) 150 min.

The slow reaction mediated by **3** would be attributed to the less reactive benzotriazol-1-yloxy ester **15b** generated from **10a** and **3**. In fact, the intermediate **15b** was observed throughout the reaction by ^{31}P NMR monitoring (δ 1.4) and gradually consumed to yield **12a**, whereas the reactive intermediate **15a** could not be detected by ^{31}P NMR.[34]

It should be noted that there was a by-product when **1** was used for the condensation reaction of **10a** with **11**. A ^{31}P NMR analysis showed a signal at δ 34.9 (Fig. 5), which was assigned to that of **16** by the independent reaction of **1** with **11**. This side reaction was rather unexpected, because the nucleophilic attack of alcohols to a positively charged phosphorus atom assisted by a weak base, such as 2,6-lutidine, is known to be slow.[17,19,25] In fact, this side reaction was not observed when **2** or **3** was used.[35] This side reaction peculiar to **1** might be attributed to the extreme reactivity toward nucleophiles due to the good leaving group and the strained five-membered ring structure of **1**. The ratio of **16** increased upon using a stronger base; the ratios for **12a** and **16** upon completely consuming **14a** were 45:55 with *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine and 48:52 with triethylamine, while 79:21 with 2,6-lutidine. This result suggests that the condensation of less reactive phosphates with sterically less hindered alcohols should be carried out using more than 1 Mequiv of the alcohols in the absence of a strong base.



16

2.3. Application of MNTP to various phosphate and phosphonate esters

In the next stage, the condensation reactions of various phosphate and phosphonate derivatives with **11** were carried out in the presence of **1**. ^{31}P NMR monitoring studies demonstrated that **1** was more effective for the condensation reactions of **10b–d** with **11** than for the reaction of **10a** with **11** (Fig. 6). Thus, all of the reactions of **10b–d** with **11** were completed within 40 min; especially **10c** and **10d** were completely condensed within 3 and 10 min, respectively. As a result, **12b** and **12c** were isolated in 99 and >99% yields. We confirmed that practically the same reaction rate and yield were obtained on a preparative scale by using the reaction of **12c** and **11** (See the Section 4). The quantitative

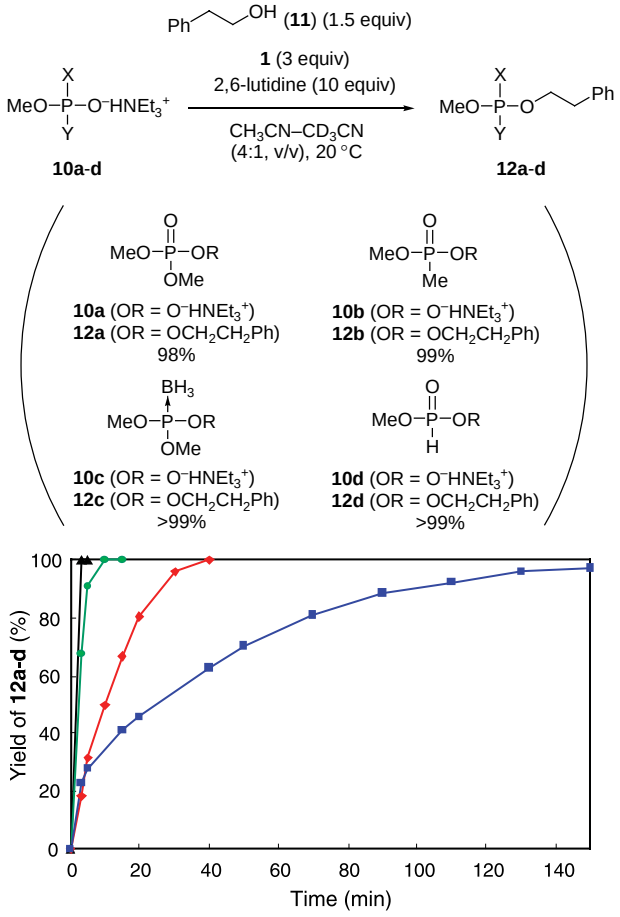


Figure 6. Condensation reactions of **10a–d** with **11** (1.5 equiv) in the presence of **1** (3 equiv) in CH_3CN–CD_3CN (4/1, v/v) at 20 °C. ■, **10a**; ♦, **10b**; ●, **10c**; ▲, **10d**.

formation of **12d** was confirmed by the ^{31}P NMR spectrum, which showed a newly generated signal at 10.6 ppm with a P–H coupling typical of dialkyl *H*-phosphonates ($^{1}J_{PH}$= 691.3 Hz).[34] We also found that the condensation reaction of a secondary alcohol mediated by **1** was completed very rapidly; ^{31}P NMR monitoring showed that the reaction of **12c** with cyclohexanol in the presence of **1** was completed within 10 min as in the case of **11**.[34] In the cases of **10b–d**, any undesired byproducts including **16** were not observed by ^{31}P NMR within the period for the quantitative formation of **12b–d**.[34]

3. Conclusion

MNTP has proven to be a powerful condensing reagent, which mediated the rapid formation of various phosphate and phosphonate esters. Such versatility and enhanced activity of MNTP would reduce the problem of slow and inefficient reactions in the phosphorylation and phosphonylation of alcohols mediated by conventional condensing reagents and make these methods comparable to the phosphitylation by the phosphoramidite method. MNTP and its simpler counterpart PyNTP were found to be good alternatives to the phosphoramidite method, especially for the synthesis of various functionalized phosphate derivatives, which are difficult to be synthesized by the phosphoramidite method. In addition to the synthesis of phosphate derivatives, the new phosphonium-type condensing reagents presented in this paper may also be useful for the rapid assembly of polypeptides as well as carboxylic acid esters, considering the wide-use of phosphonium-type condensing reagents for this purpose.

4. Experimental

4.1. General information

^{1}H NMR spectra were obtained at 300 MHz with tetramethylsilane (TMS) as an internal standard in $CDCl_3$ or CD_3CN. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as an internal standard (δ 77.0) in $CDCl_3$, or with CD_3CN as an internal standard (δ 117.8) in CD_3CN. ^{31}P NMR spectra were obtained at 121 MHz with 85% H_3PO_4 as an external standard in $CDCl_3$ or CD_3CN. Melting points were uncorrected. Silica gel column chromatography was carried out using silica gel 60 N (63–210 μm). Dry organic solvents were prepared by appropriate procedures prior to use. The other organic solvents were reagent grade and used as received. Isolated phosphate and phosphonate derivatives (**12a–c**) were determined to be >95% pure by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies.

Ab initio calculations. Ab initio molecular orbital calculations were carried out using the Gaussian 03[36] and Spartan '04[37] programs on a Dell Precision 650 workstation. Geometry optimizations were carried out at the HF/6-31G* level.

4.1.1. 1,3-Dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP, 1). 1,3-Dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidine **8** (14.2 g, 76 mmol) was added dropwise over 2 h to a stirred solution of 3-nitro-1,2,4-triazole (8.67 g, 76 mmol), which was dried by repeated coevaporations with dry pyridine and dry toluene, and dry CCl_4 (29.3 mL, 304 mmol) in dry CH_2Cl_2 (150 mL) at −78 °C under argon. The mixture was then allowed to warm to rt and concentrated to dryness under argon. The residue was dissolved in dry CH_3CN (75 mL), and a solution of KPF_6 (14.0 g, 76 mmol) in dry CH_3CN (210 mL) was added dropwise over 1 h to the solution with stirring at rt under argon. The resultant white insoluble solid was removed by suction filtration, and the filtrate was concentrated to dryness. AcOEt (400 mL) was added to the residue, and the insoluble solid was collected by suction filtration, washed with AcOEt (50 mL), and dried under vacuum to afford **1** as a colorless crystalline solid (16.9 g, 38 mmol, 50%). Mp 175–177 °C (decomp.). IR (KBr) 3135, 2990, 2898, 1568, 1511, 1280, 1145, 829, 580, 558 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN) δ 8.85 (s, 1H), 3.62–3.33 (m, 8H), 2.89 (J_{PH}=11.7 Hz, 6H), 2.06 (m, 4H). ^{13}C NMR (75 MHz, CD_3CN) δ 166.2, 153.1 (d, J_{PC}=7.5 Hz), 49.6, 47.5 (d, J_{PC}=15.0 Hz), 31.6 (d, J_{PC}=4.5 Hz), 27.0 (d, J_{PC}=9.0 Hz). ^{31}P NMR (121 MHz, CD_3CN) δ 25.0, −144.9 (septet, J_{PF}=701.8 Hz). Anal. Calcd for $C_{10}H_{19}F_6N_7O_2P_2$: C, 26.98; H, 4.30; N, 22.02. Found: C, 26.77; H, 4.40; N, 21.87.

4.1.2. 3-Nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyNTP) 2. To powdery NaH (0.254 g, 10.5 mmol), prepared from NaH dispersion in mineral oil prior to use, was added a solution of 3-nitro-1,2,4-triazole (1.14 g, 10 mmol), which was dried by repeated coevaporations with dry pyridine and dry toluene, in dry THF (40 mL) at rt under argon. The mixture was then added a solution of PyCloP (**9**) (4.22 g, 10 mmol) in dry THF (10 mL) at rt, and the mixture was stirred for 2 h. The insoluble solid was filtered off and thoroughly washed with dry CH_2Cl_2 (ca. 50 mL). The combined filtrate was concentrated under reduced pressure to some extent (ca. 20 mL) and cooled to 0 °C. The resultant precipitate was collected by suction filtration, washed with a small amount of THF, and dried under vacuum to afford **2** (4.19 g, 8.4 mmol, 84%) as a colorless crystals. Mp 161–163 °C (decomp.). IR (KBr) 3118, 2984, 2880, 1566, 1510, 1285, 1143, 854, 590, 557 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN) δ 8.79 (s, 1H), 3.40 (m, 12H), 2.03 (m, 12H). ^{13}C NMR (75 MHz, CD_3CN) δ 165.5, 151.7 (d, J_{PC}=8.3 Hz), 49.0 (d, J_{PC}=4.9 Hz), 26.5 (d, J_{PC}=9.2 Hz). ^{31}P NMR (121 MHz, CD_3CN) δ 19.3, −142.5 (septet, J_{PF}=698.8 Hz). Anal. Calcd for $C_{14}H_{25}F_6N_7O_2P_2$: C, 33.67; H, 5.05; N, 19.64. Found: C, 33.76; H, 5.03; N, 19.58.

4.2. ^{31}P NMR monitoring of the condensation reactions of dimethyl phosphate or its analogs (10a–d) with 2-phenylethanol 11 in the presence of the phosphonium-type condensing reagents

Compound **1**, **2**, or **3** (150 μmol) was placed in an NMR sample tube and dried under vacuum over P_2O_5. Dry CD_3CN (100 μL), an anhydrous CH_3CN solution (400 μL) of triethylammonium dimethyl phosphate (**10a**) or one of its analogs (**10b–d**) (50 μmol), which was dried by repeated coevaporations with dry CH_3CN, dry 2-phenylethanol (**11**) (9.0 μL, 75 μmol), and distilled 2,6-lutidine (58.2 μL,

500 μmol) were added. The sample tube was then sealed, shaken to dissolve the condensing reagent. After 1.5 min, the ^{31}P NMR data accumulation was started. Each measurement was carried out over 1.5 min at every time-point of 3, 5, 15, 20, 40, 50, 70, 90, 110, 130, and 150 min (Figs. 3 and 6). In each measurement, data accumulation was carried out 16 times with a pulse width of 6.3 μs, an acquisition time of 0.5 s, and a pulse delay of 5.0 s. A spectrum was acquired with 71942 data points for a spectral width of 71942 Hz.

4.2.1. Dimethyl 2-phenylethyl phosphate 12a. After the ^{31}P NMR experiment, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with a 1 M HCl aqueous solution (3×3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were washed with a saturated NaCl aqueous solution (2×3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (1/1, v/v)] to afford **12a** (11.3 mg, 49 μmol, 98%) as a colorless oil. ^{1}H, ^{13}C, and ^{31}P NMR spectra were identical to those reported in the literature.[38]

4.2.2. Methyl 2-phenylethyl methylphosphonate 12b. After the ^{31}P NMR experiment, the reaction mixture was diluted with CH_2Cl_2 (3 mL), washed with 0.2 M phosphate buffer (pH 7) (3×3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (1/1, v/v)] to afford **12b** (10.6 mg, 49 μmol, 99%) as a colorless oil. IR (film) 3444, 2956, 1645, 1497, 1455, 1313, 1231, 1016, 912, 818, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.20 (m, 5H), 4.23 (m, 2H), 3.61 (d, J_{PH}=11.1 Hz, 3H), 2.98 (t, J=6.9 Hz, 2H), 1.38 (d, J_{PH}=17.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 128.9, 128.4, 126.6, 66.1 (d, J_{PC}=6.3 Hz), 37.1 (d, J_{PC}=6.3 Hz), 11.4, 9.5. ^{31}P NMR (121 MHz, $CDCl_3$) δ 33.0. FAB-HRMS: *m/z* calcd for $C_{10}H_{15}O_3P$ (M^+) 214.0759, found 214.0752.

4.2.3. Dimethyl 2-phenylethyl boranophosphate 12c. After the ^{31}P NMR experiment, the reaction mixture was diluted with CH_2Cl_2 (3 mL), washed with 0.2 M phosphate buffer (pH 7) (3×3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (4/1, v/v)] to afford **12c** (11.4 mg, 50 μmol, quant) as a colorless oil. IR (film) 2955, 2396, 1455, 1260, 1028, 798, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 4.20 (q, J=7.1 Hz, 2H), 3.61 (d, J_{PH}=11.1 Hz, 6H), 2.98 (t, J=7.1 Hz, 2H), 0.42 (br q, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 128.8, 128.3, 126.5, 67.1 (d, J_{PC}=3.4 Hz), 52.9 (d, J_{PC}=3.5 Hz), 36.8 (d, J_{PC}=5.5 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 117.7 (q, J_{PB}=99.1 Hz). FAB-HRMS: *m/z* calcd for $C_{10}H_{18}BO_3P$ (M^+) 228.1089, found 228.1094.

4.3. Synthesis of dimethyl 2-phenylethyl boranophosphate 12c on a preparative scale

Triethylammonium dimethyl boranophosphate **10c** (0.113 g, 0.50 mmol) was dried by repeated coevaporations with dry CH_3CN, and dissolved in dry CH_3CN (5.0 mL) under argon. Dry 2-phenylethanol (**11**) (0.898 mL, 0.75 mmol), distilled 2,6-lutidine (0.582 mL, 5.0 mmol), and MNTP (**1**) (0.668 g, 1.5 mmol) were added. The reaction mixture was then stirred for 10 min at rt, diluted with CH_2Cl_2 (30 mL), and washed with 0.2 M phosphate buffer (pH 7.0) (3×30 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (30 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (4/1, v/v)] to afford **12c** (0.114 g, 0.50 mmol, quant) as a colorless oil. The ^{1}H and ^{31}P NMR spectra were identical to those described above.

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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.2006.01.084. ^{31}P NMR spectra of the reaction mixtures obtained by the reaction of **10a** with **11** in the presence of **2** or **3**; ^{31}P NMR spectra of the reaction mixtures obtained by the reaction of **10b**,**c**, or **10d** with **11** in the presence of **1**; ^{31}P NMR spectra of the reaction mixtures obtained by the reaction of **10c** with cyclohexanol in the presence of **1**; ^{1}H, ^{13}C, and ^{31}P NMR spectra of **1**, **2**, and **12b**,**c**. Experimental details for the synthesis of **6**–**8**. Optimized geometries and the orbital energies of the reaction intermediates **13a**,**b**.

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34. See the Supplementary data.
35. Compound **2** did not react with alcohols even in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine.
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A novel ruthenium(II) tris(bipyridine)–zinc porphyrin–rhenium carbonyl triad: synthesis and optical properties

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Abstract—A novel ruthenium(II) tris(bipyridine)–zinc porphyrin–rhenium carbonyl triads and its free base porphyrin derivative were synthesized and characterized by ^{1}H, ^{13}C NMR, UV–vis, mass-spectrometry and elemental analysis. The redox potentials of the two compounds were measured and compared to their corresponding reference complexes. The fluorescence and transient absorption spectra of the two complexes revealed the features of two different pathways for possible photoinduced intramolecular electron transfer or energy transfer in the triads.

1. Introduction

The preparation of multicomponent photoactive arrays by logical covalent or noncovalent connection is a rapidly growing field and an important research area in view of the following interests: (i) a better understanding of efficient electron transfer and charge separation in natural photosynthesis;[1] (ii) the construction of the nanometer-scale wires,[2] switches,[3] logic gate,[4] and other components for the development of molecular electronic devices.[5] It has been known that photoexcitation results in charge transfer from Ru^{2+} ion to the bpy ligands in $Ru(bpy)_3X_2$ derivatives, effectively creating a Ru^{3+}-$(bpy)^{-}$ metal to ligand charge transfer state.[6] The Ru^{3+} is an extremely strong oxidant that could potentially promote facile oxidation of an adjacent porphyrin via electron transfer.[7] In recent years, a sizable number of dyads (or larger architectures) comprised of a porphyrin and a $Ru(bpy)_3$ complex[8] or $Ru(tpy)_2$ complex[9] have been designed and synthesized. The photochemical properties of a number of such complexes have been reviewed.[10] In addition, rhenium-containing complexes $Re(CO)_3(bpy)L$, in which L is a halide, have been the subject of a large number of studies. In general, the continuously growing interest for the study of these molecules stems from their ability to act as efficient sensitizers for energy and electron transfer.[11] Herein, we sought to prepare a porphyrin-based triad with $Ru(bpy)_3X_2$ and $[Re(CO)_3(bpy)L]$ covalently attached to porphyrin for the studies of electron transfer or energy transfer in multicomponent systems.

2. Results and discussion

2.1. Synthesis

The procedure for the synthesis of **1** and **1-Zn** was depicted in Scheme 1. The starting porphyrin **2** was synthesized by a mixed condensation of pyrrole, 4-nitrobenzaldehyde and 4-(*t*-butyl)benzaldehyde.[12] The '*ortho*' orientated 5,10-bis-(4-nitrophenyl)porphyrin (**2**) was separated by column chromatography from other multiple porphyrin products, including mono, bis (trans), tris and tetrais nitrophenyl-substituted porphyrins. Gradient elution was used for the multicomponent separation with silica gel and a dichloromethane/hexane solvent system consisting initially of CH_2Cl_2–Hexane (1/1) and gradually ending with 100% of dichloromethane. We did not collect the trans analogue 5,15-bis-(4-nitrophenyl)porphyrin due to its extremely low yield, although TLC analysis of these mixtures indicated that the trans could be separated. The following simultaneous reduction of the two nitro groups was carried out in $CHCl_3$/HOAc by the usual $SnCl_2$/HCl procedure[13] to give amino substituted phenylporphyrin **3** in

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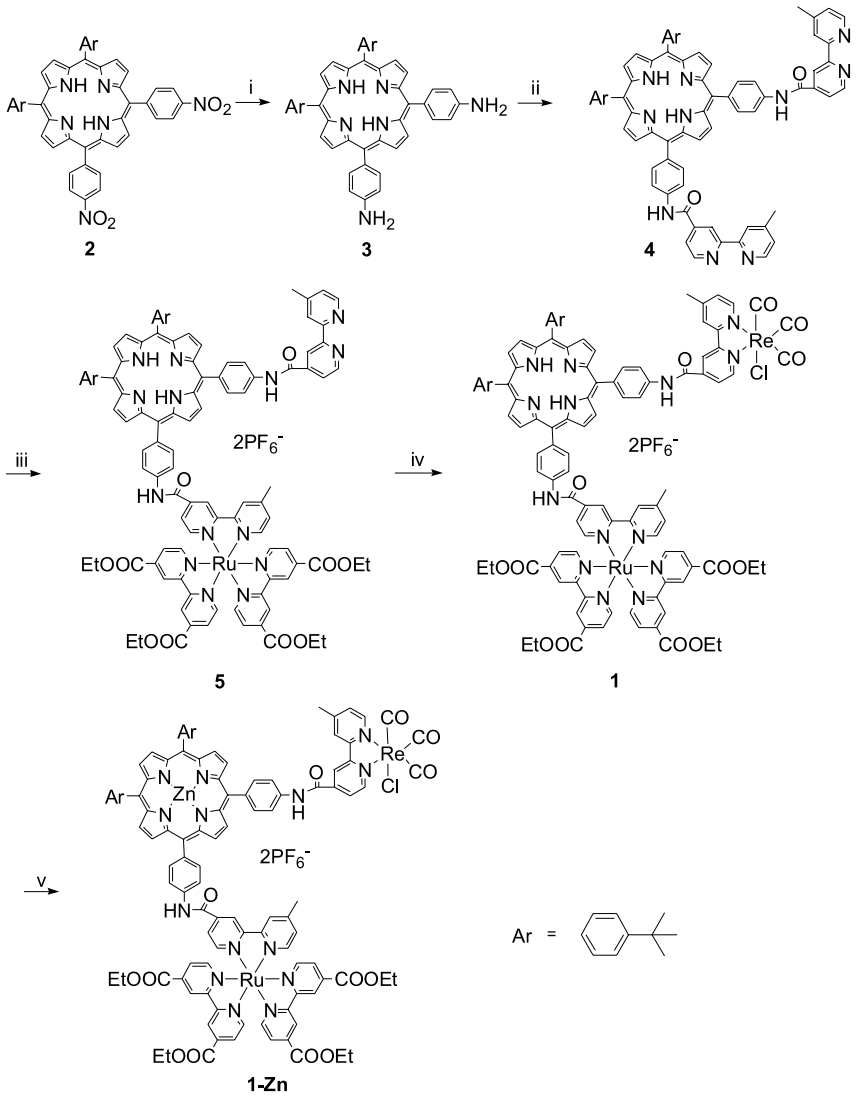


Scheme 1. Synthesis of complex **1-Zn**. Conditions: (i) $SnCl_2$/HCl, $CHCl_3$–HOAc reflux, 12 h, 82%; (ii) 4′-methyl-2,2′-bipyridinyl-4-carbonyl chloride, CH_2Cl_2, reflux, 4 h, 60%; (iii) *cis*-Ru(4-4′-di-COOEt-2,2′-bpy)$_2Cl_2$, HOAc, reflux, 1 h, 32%; (iv) $Re(CO)_5Cl$, toluene, reflux 6 h, 98%; (v) $Zn(OAc)_2\cdot 2H_2O$, $CHCl_3$–EtOH, rt, 12 h, 94%.

82% yield. Porphyrin **3** was then reacted with 4′-methyl-2, 2′-bipyrindyl-4-carbonyl chloride (prepared in situ from 4,4′-dimethyl-2,2′-bipyridine[14]) in the presence of Et_3N to form compound **4** in 60% yield, where the two amidations occurred in the same step. For the next transformation to the complex **5**, the acetic acid solution of 1 equiv of *cis*-Ru(4, 4′-di-COOEt-2, 2′-bpy)$_2Cl_2$[15] was carefully titrated to porphyrin **4** in order to ensure the regioselectivity. The remaining bipyridine subunit was coordinated to Re by treatment of **5** with $Re(CO)_5Cl$ in toluene at reflux to give the binuclear product **1** in 98% yield. The trinuclear target complex **1-Zn** was then formed by stirring the mixture of $Zn(OAc)_2$ and **1** in chloroform in the presence of a little EtOH at room temperature. All of the compounds were insoluble in hexane or alcohols but were easily dissolved in most other organic solvents.

2.2. Steady-state absorption spectra

The absorption spectra of **1** and **1-Zn** were shown in Figure 1. The spectrum of Ru(4,4′-di-COOEt-2,2′-bpy)$_2$(4-Me-4′-COOH-2,2′-bpy) $(PF_6)_2$ (abbreviated as **Ru**[16]) (Fig. 5) was also shown as a comparison. The absorption spectrum of **1-Zn** showed a red-shifted soret band at 428 nm ($S_0 \rightarrow S_2$ transition) with respect to that of **1** (418 nm).

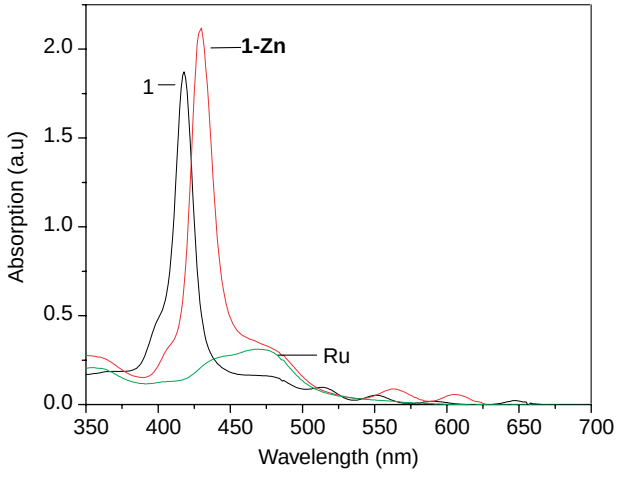


Figure 1. UV–vis absorption spectra of **1**, **1-Zn** and **Ru** in CH_2Cl_2 [5×10^{-6} M].

While the two Q bands ($S_0 \rightarrow S_1$ transition) exhibited typical pattern of regular metal porphyrins. The shoulders at 475 nm for both spectra of **1** and **1-Zn** are mainly from ruthenium moiety, since porphyrins have negligible absorption in this region. In addition, the metal to ligand charge transfer (MLCT) transition of ruthenium moieties in all cases was red shifted (25 nm) relative to the absorption of $Ru(bpy)_3X_2$,[17] due to the introduction of electron-withdrawing substituents in the pyridine rings.

2.3. Emission measurements

The emission spectra of **1** and **1-Zn** were shown in Figure 2a. The emission spectrum of complex **1** showed the typical porphyrin component emission at 656 and 722 nm (0–0 and 0–1 band) upon irradiation at the Q band (552 nm). While the related peaks in the emission spectrum of **1-Zn** were blue-shifted (0–0 and 0–1 band at 614 and 667 nm, respectively) upon irradiation at 558 nm, and the emission intensity was strongly quenched. The emission from Zn porphyrin component in **1-Zn** (Φ_f=0.0005) and porphyrin component in **1** (Φ_f=0.007) were reduced by 62-fold and 14-fold from that of zinc tetraphenylporphyrin (Φ_f=0.031) and tetraphenylporphyrin (Φ_f=0.10) respectively. Since energy transfer to the appended ruthenium or rhenium unit is thermodynamically infeasible, this quenching is mainly attributed to electron transfer to the ruthenium unit.[9] Comparing with a Zn porphyrin–ruthenium complex (Φ_f=0.0011),[18] we deduced that rhenium carbonyl unit also played an important role in the electron transfer by quenching of the emission of zinc porphyrin component in **1-Zn**.

The emission spectra of the complex **Ru** (see Fig. 5) (λ_{ex}=475 nm) and **1-Zn** (λ_{ex}=428, 475, 558 nm) were shown in Figure 2b. We found that the emission profile of **1-Zn** was identical to that of Zn porphyrin, no matter the soret band (λ_{ex}=428 nm) or Q band (λ_{ex}=558 nm) was excited. In addition, no contribution from ruthenium or rhenium moieties could be observed. Thus, the soret band excitation of Zn porphyrin moiety in **1-Zn** did not generate any sensitized ruthenium or rhenium emission, and energy transfer from the S_2 state of Zn porphyrin to ruthenium or rhenium unit therefore could not be significant. When exciting at the ruthenium band (475 nm), the emission profile of **1-Zn** was similar to that of **Ru**. However, the intensity of the emission of **1-Zn** was found to be 50% relative to that of **Ru**. The decrease of emission intensity is attributed to the quenching of ^{3}MLCT state of ruthenium unit by Zn porphyrin via electron or energy transfer.

2.4. Transient absorption

A preliminary time-resolved absorption and emission study of **1-Zn** was carried out in CH_3CN solution using a YAG laser with a 12 ns pulse width and excitation at 532 nm. The spectrum is characteristic of the porphyrin $^3(\pi,\pi^*)$ excited states with intense absorption at 480 nm (Fig. 3). The $^3(\pi,\pi^*)$ spectrum is also marked by a distinct near-infrared absorption peak, which is not found in the $^1(\pi,\pi^*)$ spectrum.[19] However, there is a significant difference between the transient spectra of the **1-Zn** and regular zinc porphyrins at 780 nm, in which transient absorption of the **1-Zn** is stronger than that of regular zinc porphyrins. We attribute it to the mixture of the porphyrin $^3(\pi,\pi^*)$ excited states and the intraligand charge transfer transition (^{3}ILCT) from the porphyrin (π) to bpy (π^*).[11b] A lifetime of 783 ns was obtained for the excited triplet sate of Zn porphyrin by fitting the experimental absorbance decay at 480 nm, while a lifetime of 489 ns was obtained by fitting the experimental absorbance decay at 780 nm. The different lifetime also indicated that the two absorptions at 480 and 780 nm were attributed to different excited states. A detailed investigation of photoinduced electron transfer and energy transfer processes occurring in **1-Zn** will help us to evaluate this molecular triad system as a potential light-driven molecular switch. Femtosecond transient absorption measurements on this complex are in progress.

2.5. Electrochemistry

Redox potentials of the compounds **1**, **1-Zn** and reference compounds **Ru**, **PZnRu**[17] and **PZnRe**[2c] (their formulas were shown in Fig. 5, vide infra) were compiled in Table 1. The different waves of **1** and **1-Zn** could be easily assigned to their individual components by comparison with the redox couples of the reference compounds. Compound **1-Zn** had a good reversible characteristic at all redox processes, in

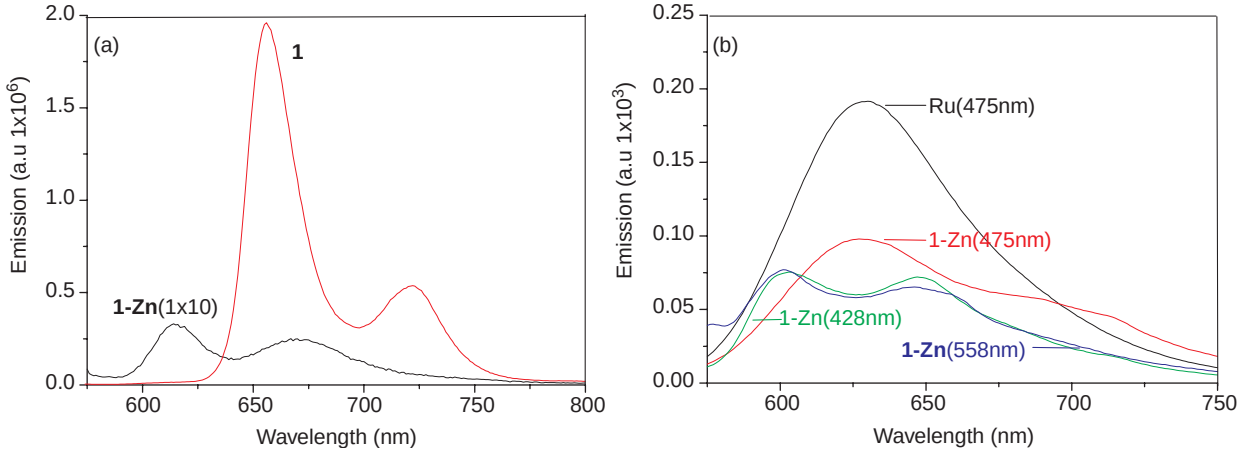


Figure 2. (a) Steady-state emission spectra of **1** (λ_{ex}=552 nm), **1-Zn** (λ_{ex}=558 nm) in CH_2Cl_2 [5×10^{-6} M]; (b) steady-state emission spectra of **1-Zn** (λ_{ex}=558, 428, 475 nm) and **Ru** (λ_{ex}=475 nm) in CH_2Cl_2 [5×10^{-6} M].

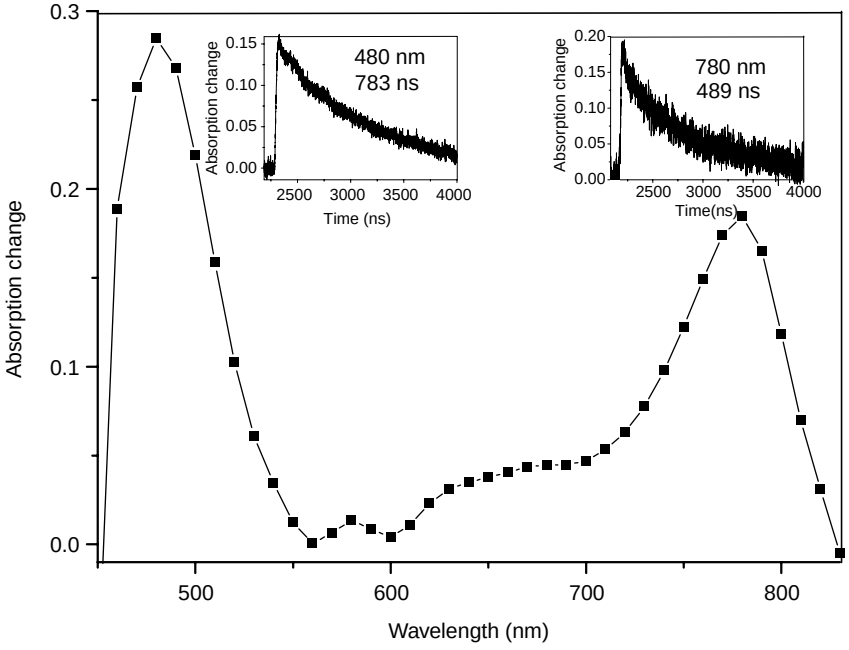


Figure 3. Differential absroption spectrum (visible and near-infrared) obtained upon nanosecond flash photolysis (532 nm) of $\sim 1\times10^{-5}$ M **1-Zn** in deoxygenated CH_3CN solutions.

Table 1. Redox potentials in CH_2Cl_2

	Oxidation $E_{1/2}$ (V vs SCE)				Reduction $E_{1/2}$ (V vs SCE)		
	P/P^+	P^+/P^{2+}	Re^+/Re^{2+}	Ru^{2+}/Ru^{3+}	L/L^-	L'/L'^-	P/P^-
Ru				1.66	−0.76	−1.02	
PZnRe	0.81	1.22	1.53			−1.06	
PZnRu	0.78	1.17		1.68	−0.79	−1.07	−1.43
1-Zn	0.83	1.22	1.51	1.71	−0.76	−1.03	
1	—	—	1.47	1.72	−0.77	−1.14	

which there were two one-electron reductions and four one-electron oxidations (Fig. 4, e.g., **1-Zn**). We can see that potentials of the Ru^{2+}/Ru^{3+}(1.71 V) and Re^+/Re^{2+} (1.51 V) couple are more positive than that of the Zn porphyrin constituent (0.83 V). Thus, the complex has the requisite characteristics to facilitate generation of a porphyrin π-cation radical upon photoexcitation of the Ru or Re subunit, when just considering the redox properties.

This would both quench the fluorescence of the porphyrin and allow the oxidized porphyrin to quench nearby Re part (or Ru subunit) excited states. According to the above analysis, **1-Zn** may be suitable for an all-optical switch.

3. Conclusion

To investigate intramolecular photoinduced electron or energy transfer in large light-harvesting arrays or molecular devices, two new multicomponent arrays based on porphyrin and ruthenium (or rhenium) bipyridine complexes were synthesized and characterized. Detailed

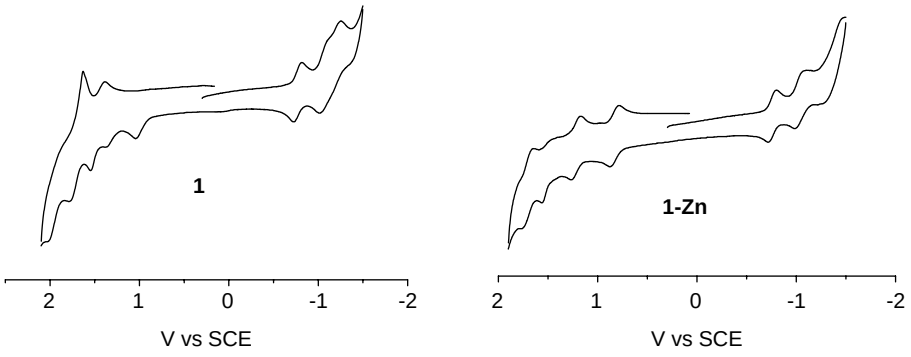


Figure 4. Cyclic voltammogram for complexes **1** and **1-Zn** in 10^{-3} M of CH_2Cl_2/0.1 M $TBAPF_6$ glassy carbon disc electrode at a scan rate of 50 mV/s and reported relative to SCE.

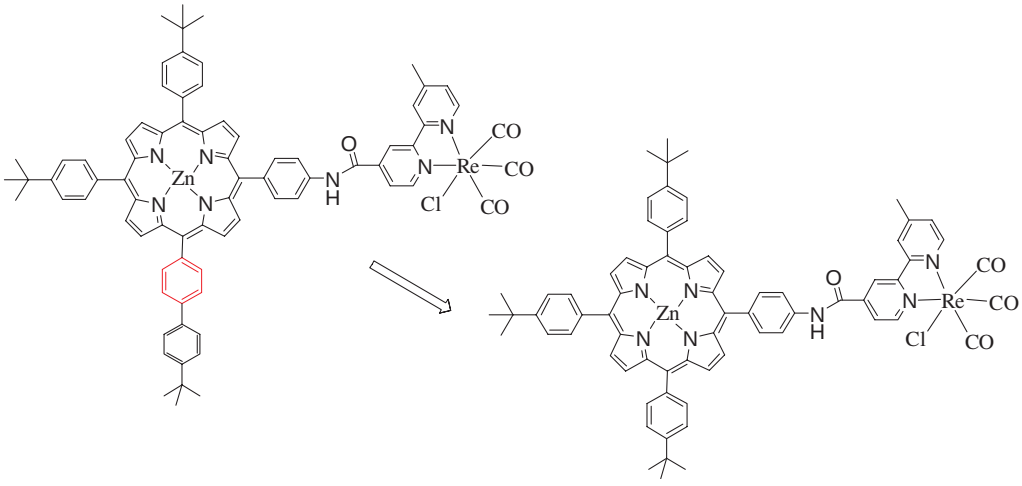


Figure 5. Schematic formulas of reference compounds studied.

photophysical and electrochemical studies of free-base and zinc-metalated multicomponents clearly showed that electronic interactions in each subunit were very weak. In fact, the absorption spectra and the electrochemical properties of the two multicomponent arrays can be described by a superposition of their monomeric subunits. Emission and transient absorption spectra recorded at room temperature showed that intramolecular photoinduced electron or energy transfer might occur.

4. Experimental

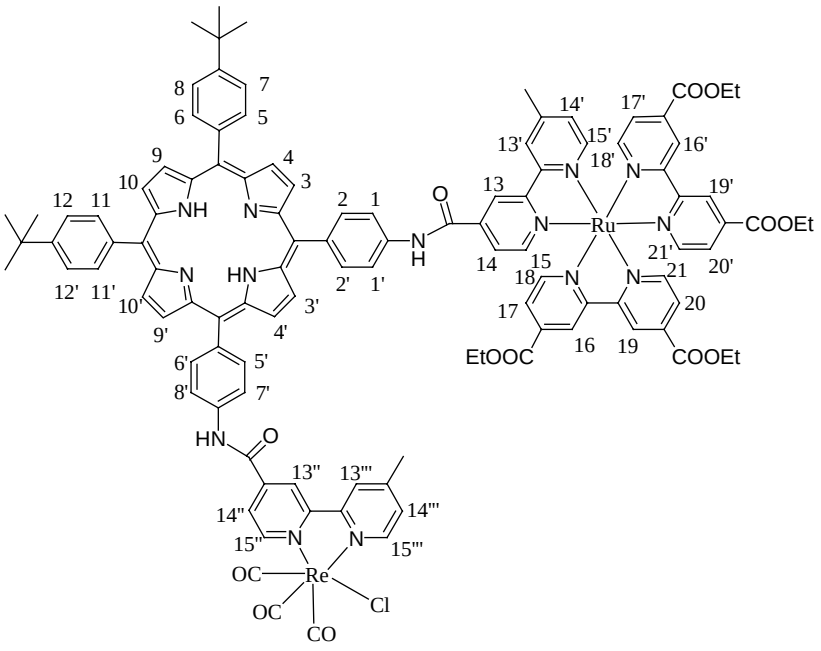
4.1. General

The reference compounds **Ru**, **PZnRu**[17] and **PZnRe**[2c] were prepared according to the literatures. We showed serial numbers of compound **1** so that we can easily assign the signal in ^{1}H NMR (see Fig. 6). All reagents were purchased from Aldrich, and all solvents were purified according to standard methods. Pyrrole was freshly distilled before use. All of the manipulations were performed under N_2. ^{1}H NMR spectra were recorded on a varian 400 spectrometer and reported in parts per million downfield from TMS.

4.1.1. 5,10-Bis(4-nitrophenyl)-15,20-bis(4-*tert*-butylphenyl)porphyrin (2). Pyrrole (0.56 mL, 8.0 mmol), 4-nitrobenzaldehyde (306 mg, 2.0 mmol) and 4-*tert*-butylbenzaldehyde (1.04 mL, 6.0 mmol) were added to CH_2Cl_2 (1000 mL), which was degassed with N_2 for 30 min. After the mixture was stirred under N_2 for a further 30 min, a BF_3/etherate solution (1.0 mL, 2 M in CH_2Cl_2, 2.0 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) (1.82 g, 8.0 mmol) was added to the red-brown solution, and the resulting black mixture was refluxed for 2 h. Et_3N (1.12 mL, 8.0 mmol) was added to the mixture, and the solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2=50:50) to give the desired porphyrin product (196 mg, 12%). Mp>300 °C; ^{1}H NMR ($CDCl_3$) δ 2.78 (s, br, 2H, –NH), 1.61 (s, 18H, *tert*-butyl-H), 7.78 (d, J=8.0 Hz, 4H, H_7, H_8, H_{12}, $H_{12'}$), 8.14 (d, J=8.0 Hz, 4H, H_5, H_6, H_{11}, $H_{11'}$), 8.40 (d, J=8.0 Hz, 4H, H_1, $H_{1'}$, $H_{7'}$, $H_{8'}$), 8.65 (d, J=8.0 Hz, 4H, H_2, $H_{2'}$, $H_{5'}$, $H_{6'}$), 8.73 (d, J=4.8 Hz, 2H, pyrrole), 8.78 (s, 2H, pyrrole), 8.91 (s, 2H, pyrrole), 8.96 (d, J=4.8 Hz, 2H, pyrrole); ^{13}C NMR ($CDCl_3$) δ 31.9, 35.1, 117.1, 122.1, 123.9, 134.7, 135.3, 138.8, 147.9, 149.2, 151.1; UV–vis in CH_2Cl_2 λ_{max} (nm)= 423.0, 518.0, 554.0, 592.0, 647.0; APCI-MS Positive: $[M+H]^+$ (m/z=817.4). Anal. Calcd for $C_{52}H_{44}N_6O_4\cdot 0.1CH_2Cl_2$: C, 75.81; H, 5.40; N, 10.18. Found: C, 76.00; H, 5.52; N, 10.26.

4.1.2. 5,10-Bis(4-aminophenyl)-15,20-bis(4-*tert*-butylphenyl)porphyrin (3). $SnCl_2\cdot 2H_2O$ (915 mg, 4.0 mmol) in concentrated HCl (25 mL) was added to **2** (408 mg, 0.5 mmol) in $CHCl_3$–HOAc (1/2) (45 mL). The mixture was vigorously stirred in a preheated oil bath (65–70 °C) for 30 min, refluxed overnight, and then neutralized with ammonia solution (25%) to pH 8–9. Chloroform (100 mL) was added, and the mixture was stirred for 1 h. The organic phase was separated, and the water phase was extracted with $CHCl_3$ (2×100 mL). The combined organic layer was washed once with dilute ammonia solution, three times with water, and then concentrated to dryness. The residue was purified by column chromatography (silica gel, CH_2Cl_2/CH_3CH_2OH=200:1) to give the desired porphyrin product (309 mg, 82%). Mp>300 °C; ^{1}H NMR ($CDCl_3$) δ −2.72 (s, br, 2H, –NH), 1.60 (s, 18H, *tert*-butyl-H), 3.98 (s, br, 4H, $-NH_2$), 7.03 (d, J=8.4 Hz, 4H, H_5, H_6, H_{11}, $H_{11'}$), 7.74 (d, J=8.0 Hz, 4H, H_7, H_8, H_{12}, $H_{12'}$), 7.99 (d, J=8.0 Hz, 4H, H_2, $H_{2'}$, $H_{5'}$, $H_{6'}$), 8.14 (d, J=8.0 Hz, 4H, H_1, $H_{1'}$, $H_{7'}$, $H_{8'}$), 8.86–8.91 (m, 8H, pyrrole); ^{13}C NMR ($CDCl_3$) δ 31.9, 35.1, 113.6, 120.0, 120.6, 123.8, 131.1, 132.8, 134.7, 135.9, 139.5, 146.1, 150.6; UV–vis in CH_2Cl_2 λ_{max} (nm)=421.0, 517.0, 555.0, 591.0, 650.0; APCI-MS Positive: $[M+H]^+$ (m/z=757.5). Anal. Calcd for $C_{52}H_{48}N_6\cdot 0.75CH_3CH_2OH$: C, 81.18; H, 6.69; N, 10.62. Found: C, 81.58; H, 6.83; N, 10.21.

4.1.3. Porphyrin-(NHCO-bpy)$_2$(4). A mixture of 4-carboxy-4′-methyl-2,2′-bipyridine (350 mg, 1.636 mmol) and $SOCl_2$ (20 mL) was refluxed for 2 h. After removal of the excess $SOCl_2$ by distillation under reduced pressure, the acid chloride product was obtained and dried in vacuum at 70 °C for 1 h. Then dry CH_2Cl_2 (12 mL) was added and the mixture was stirred for 5 min at 50 °C. The resulting light yellow



1

Figure 6. Serial numbers of the complex **1**.

solution was added dropwise to the CH_2Cl_2 solution (30 mL) of **3** (268 mg, 0.35 mmol) in which two drops of Et_3N were added. White smoke was observed in the reaction flask. The mixture was refluxed overnight, and washed with 5% of aqueous ammonia solution and then water. After removing the solvent, the residue was dissolved in $CHCl_3$ (20 mL) and CH_3CN (200 mL) was added dropwise. Precipitate was formed by slowly evaporating $CHCl_3$ under vacuum. The desired product was obtained after column chromatography on silica gel with a mixture of CH_2Cl_2–MeOH (95/5) as eluent to give purple solid (242 mg, 60%). Mp > 250 °C; ^{1}H NMR ($CDCl_3$) −2.75 (s, br, 2H –NH), 1.58 (s, 18H, *tert*-butyl-H), 2.48 (s, 6H, bpy–CH_3), 7.21 (d, J=4.8 Hz, 2H, $H_{14'}$, $H_{14'''}$), 7.71 (d, J=8.0 Hz, 4H, H_5, H_6, H_{11}, $H_{11'}$), 7.96 (d, J=3.2 Hz, 2H, H_{14}, $H_{14''}$), 8.05 (d, J=8.4 Hz, 4H, H_7, $H_{8,}$ H_{12}, $H_{12'}$), 8.09 (d, J=8.0 Hz, 4H, H_2, $H_{2'}$, $H_{5'}$, $H_{6'}$), 8.20 (d, J=8.4 Hz, 4H, H_1, $H_{1'}$, $H_{7'}$, $H_{8'}$), 8.34 (s, 2H, $H_{13'}$, $H_{13'''}$), 8.59 (d, J=5.2 Hz, 2H, $H_{15'}$, $H_{15'''}$), 8.68 (s, 2H, amide–H), 8.85–8.86 (m, 8H, pyrrole-H), 8.88–8.91 (m, 4H, H_{13}, $H_{13''}$, H_{15}, $H_{15''}$); ^{13}C NMR ($CDCl_3$) δ 21.5, 31.9, 35.1, 117.6, 118.8, 119.2, 120.6, 121.7, 122.3, 122.6, 123.5, 125.7, 131.5, 133.3, 134.6, 135.4, 137.4, 139.2, 143.3, 149.1, 150.6, 155.1, 156.9, 163.6; UV–vis in CH_2Cl_2 λ_{max} (nm)=421.0, 518.0, 554.0, 594.0, 647.0; APCI-MS Positive: $[M+H]^+$(m/z=1149.5). Anal. Calcd for $C_{76}H_{64}N_{10}O_2\cdot 0.4CH_2Cl_2$: C, 77.54; H, 5.52; N, 11.84. Found: C, 77.82; H, 5.74; N, 12.00.

4.1.4. Porphyrin-(NHCO-bpy)$_2$-Ru[(bpy)(COOEt)$_2$]$_2$[-PF$_6$]$_2$ (5). A mixture of **4** (100 mg, 0.087 mmol) and Ru[bpy(COOEt)$_2$]$_2$$Cl_2$ (134 mg, 0.174 mmol) in acetic acid (30 mL) was refluxed for 1 h under N_2 in the dark. After removing the solvent, the product was loaded on column of silica gel with a mixture of CH_2Cl_2–MeOH (10/1) as eluent, and the anion was exchanged with NH_4PF_6. The product was obtained as a red-brown solid, which was the desired **5** (60 mg, 32%). Mp > 250 °C; ^{1}H NMR (CD_3CN) δ −2.81 (s, br, 2H, –NH), 1.42–1.46 (m, 12H, –COOCH$_2$*CH*$_3$), 1.53 (s, 18H, *tert*-butyl), 2.48 (s, 3H, bpy–CH_3), 2.63 (s, 3H, Ru unit-bpy-CH_3), 4.48–4.50 (m, 8H, –COO*CH*$_2$CH$_3$), 7.29–7.31 (m, 1H, $H_{14'}$), 7.35–7.37 (m, 1H, $H_{15'}$), 7.58 (d, J=5.2 Hz, 1H, $H_{14'''}$), 7.64–7.70 (m, 4H, H_7, H_8, H_{12}, $H_{12'}$), 7.84–7.88 (m, 4H, H_5, H_6, H_{11}, $H_{11'}$), 7.92–8.16 (m, 20H, H_1, $H_{1'}$, H_2, $H_{2'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$, H_{14}, $H_{14''}$, H_{15}, $H_{15''}$, H_{17}, $H_{17'}$, H_{18}, $H_{18'}$, H_{20}, $H_{20'}$, H_{21}, $H_{21'}$), 8.32 (s, 1H, $H_{15'''}$), 8.59–8.61 (m, 1H, $H_{13'}$), 8.65–8.89 (m, 9H, pyrrole-H, $H_{13''}$), 8.95–8.97 (m, 1H, $H_{13'''}$), 9.04–9.12 (m, 5H, H_{13}, H_{16}, $H_{16'}$, H_{19}, $H_{19'}$), 9.43 (s, 1H, amide-H), 9.51 (s, 1H, Ru unit-amide-H); UV–vis in acetonitrile λ_{max} (nm)=306.0, 418.0, 514.0, 551.0, 594.0, 646; IR (KBr, νCO): 558, 844, 1731, 3422 cm^{-1}; API-ES-MS m/z: $[M-PF_6]^+$1996.3, $[M-2PF_6]^{2+}$925.0. Anal. Calcd for $C_{108}H_{96}F_{12}N_{14}O_{10}P_2$-Ru·1.8$HPF_6$: C, 53.96; H, 4.10; N, 8.16. Found: C, 53.99; H, 3.95; N, 7.98.

4.1.5. Porphyrin-(NHCO-bpy)$_2$-Ru[(bpy)(COOEt)$_2$]$_2$-(Re(CO)$_3$Cl)[PF$_6$]$_2$ (1). A mixture of **5** (100 mg, 0.046 mmol) and $Re(CO)_5Cl$ (25 mg, 0.07 mmol) in toluene (90 mL) was refluxed for 6 h under N_2 in the dark. After removing the solvent, the product was loaded on column of silica gel with a mixture of MeOH–CH_2Cl_2 (1/100) as eluent. The desired product was obtained as a yellow-brown solid (112 mg, 98%). Mp > 250 °C; ^{1}H NMR (CD_3CN) δ −2.81 (s, br, 2H, –NH), 1.40–1.44 (m, 12H, –COOCH$_2$-*CH*$_3$), 1.56 (s, 9H, *tert*-butyl), 1.58 (s, 9H, *tert*-butyl), 2.61 (s, 3H, bpy–CH_3), 2.63 (s, 3H, Ru-bpy–CH_3), 4.45–4.48 (m, 8H, –COO*CH*$_2$CH$_3$), 7.34 (d, J=5.6 Hz, 1H, $H_{14'}$), 7.53 (d, J=6.8 Hz, 2H, $H_{15'}$, $H_{14'''}$), 7.78–7.85 (m, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$ H_{12}, $H_{12'}$), 7.89–8.01 (m, 10H, H_{14}, H_{15}, H_{17}, $H_{17'}$, H_{18}, $H_{18'}$, H_{20}, $H_{20'}$, H_{21}, $H_{21'}$), 8.07–8.28 (m, 12H, H_1, $H_{1'}$, H_2, $H_{2'}$, H_5, $H_{5'}$ H_6, $H_{6'}$, H_{11}, $H_{11'}$, $H_{14''}$, $H_{15''}$), 8.55 (s, 1H, $H_{15'''}$), 8.71 (s, 1H, $H_{13'}$), 8.85–8.91 (m, 8H, Pyrrole-H), 8.95

(s, 1H, $H_{13''}$), 9.07–9.13 (m, 5H, H_{13}, H_{16}, $H_{16'}$, H_{19}, $H_{19'}$), 9.25 (d, 1H, $J=5.2$ Hz, $H_{13''}$), 9.58 (s, br, 1H, amide-H), 9.64 (s, br, 1H, amide-H); UV–vis in acetonitrile λ_{max} (nm)=275.0, 418.0, 515.0, 551.0, 592.0, 646; IR (KBr, νCO): 558, 844, 1729, 1917, 2022, 3398 cm^{-1}; API-ES-MS *m/z*: $[M-PF_6]^+$2300.5, $[M-2PF_6]^{2+}$1078.9. Anal. Calcd for $C_{111}H_{96}ClF_{12}N_{14}O_{13}P_2ReRu\cdot 2CH_2Cl_2$: C, 51.87; H, 3.85; N, 7.49. Found: C, 51.97; H, 3.79; N, 7.29.

4.1.6. Zn-Porphyrin-(NHCO-bpy)$_2$-Ru[(bpy)(COOEt)$_2$]$_2$(Re(CO)$_3$Cl)[PF$_6$]$_2$ (1-Zn). $Zn(OAc)_2\cdot 2H_2O$ (20 mg, 0.100 mmol) in ethanol (2 mL) was added to **1** (61 mg, 0.025 mmol) in chloroform (15 mL), and stirred at room temperature overnight under N_2 in the dark. This mixture was washed with water and extracted with $CHCl_3$. The combined organic phase was evaporated to dryness and purified by CH_2Cl_2–MeOH (10/1). The desired product was obtained as a red-brown solid (58 mg, 94%). Mp>250 °C; ^{1}H NMR (CD_3CN) δ 1.41–1.45 (m, 12H, –$COOCH_2CH_3$), 1.57 (s, 9H, *tert*-butyl), 1.58 (s, 9H, *tert*-butyl), 2.60 (s, 3H, bpy–CH_3), 2.62 (s, 3H, Ru-bpy–CH_3), 4.46–4.50 (m, 8H, –$COOCH_2CH_3$), 7.36 (d, $J=$ 7.6 Hz, 1H, $H_{14'}$), 7.55 (d, $J=5.2$ Hz, 2H, $H_{15'}$, $H_{14'''}$), 7.81–7.87 (m, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$ H_{12}, $H_{12'}$), 7.92–8.02 (m, 10H, H_{14}, H_{15}, H_{17}, $H_{17'}$, H_{18}, $H_{18'}$, H_{20}, $H_{20'}$, H_{21}, $H_{21'}$), 8.03–8.29 (m, 12H, H_1, $H_{1'}$, H_2, $H_{2'}$, H_5, $H_{5'}$ H_6, $H_{6'}$, H_{11}, $H_{11''}$, $H_{14''}$, $H_{15''}$), 8.56 (s, 1H, $H_{15'''}$), 8.73 (s, 1H, $H_{13'}$), 8.87–8.95 (m, 8H, pyrrole-H), 8.98 (s, 1H, $H_{13'''}$), 9.06–9.13 (m, 5H, H_{13}, H_{16}, $H_{16'}$, H_{19}, $H_{19'}$), 9.27 (d, 1H, $J=5.2$ Hz, $H_{13''}$), 9.60 (s, br, 1H, amide-H), 9.65 (s, br, 1H, amide-H); UV–vis in acetonitrile λ_{max} (nm)=308.0, 428.0, 563.0, 605.0; API-ES-MS *m/z*: $[M-PF_6]^+$1904.7, $[M-2PF_6]^{2+}$, 1108.3. Anal. Calcd for $C_{111}H_{94}Cl\ F_{12}N_{14}O_{13}P_2ReRuZn\cdot 1.5CH_2Cl_2$: C, 51.23; H, 3.71; N, 7.43. Found: C, 51.61; H, 3.65; N, 7.10.

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Asymmetric aziridine synthesis by aza-Darzens reaction of *N*-diphenylphosphinylimines with chiral enolates. Part 1: Formation of *cis*-aziridines

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Abstract—The aza-Darzens ('ADZ') reactions of *N*-diphenylphosphinyl ('*N*-Dpp') imines with chiral enolates derived from oxazolidinones and camphorsultam have been studied. Whilst oxazolidinone enolates reacted poorly in terms of aziridination, the use of the chiral enolate derived from both antipodes of *N*-bromoacetyl 2,10-camphorsultam, 2*R*-(**5**) and 2*S*-(**5**), with *N*-diphenylphosphinyl aryl and *tert*-butylimines proceeded in generally good yield to give, respectively, (2′*R*,3′*R*)- or (2′*S*,3′*S*)-*cis*-*N*-diphenylphosphinyl aziridinoyl sultams of high de.

1. Introduction

Though aziridines are regarded as valuable synthetic intermediates, there remain few generally applicable methods for the one-step preparation of these compounds in high enantiomeric purity from readily available precursors.[1,2] Furthermore, the methodology previously described is often compromised by the fact that the substituents present on nitrogen (often sulfonyl groups) frequently are not compatible with further immediate synthetic manipulation.

2. Background

We have previously investigated the preparation and ring-opening reactions of *N*-diphenylphosphinyl aziridines,[3] and were keen to devise an asymmetric synthesis of these aziridines; we were especially interested in facilitating the preparation of chiral 2-carboxyaziridines, because of the potential use of such compounds as precursors to related non-proteinogenic 2-amino acids. We report here in detail the results of our preliminary studies[4] into the aza-Darzens (ADZ) reaction[5] of *N*-Dpp imines with chiral, camphorsultam-derived α-bromoenolates, which show that the routine preparation of chiral *N*-Dpp-2-carboxyaziridines with high levels of diastereomeric and enantiomeric purity is indeed feasible.

Keywords: Aza-Darzens; Aziridination; Imine; Camphorsultam.
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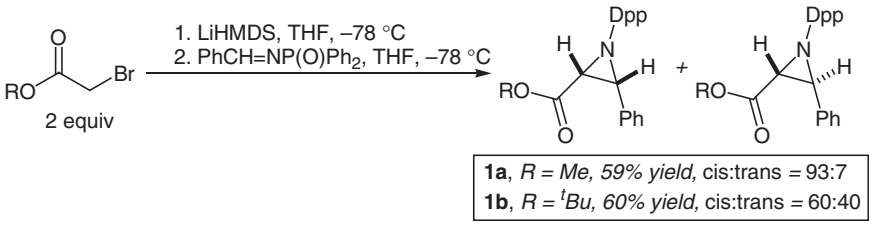
3. Results and discussion

3.1. Feasibility study: reaction of achiral ester enolates with *N*-Dpp imines

ADZ reactions of *N*-Dpp imines had not been reported before we embarked upon our work, which meant that our first task was to assess the feasibility of the proposed reaction using achiral reagents. Thus, when *N*-diphenylphosphinybenzaldimine[6] was added to the lithium enolate of methyl bromoacetate at −78 °C, a diastereoselective reaction was observed, affording methyl *N*-diphenylphosphinyl-2-phenyl aziridine carboxylate **1a** in 60% yield; the product was obtained as 90:10 mixture of cis- and trans-diastereoisomers (J_{cis}=6.5 Hz, J_{trans}=2.8 Hz, Scheme 1). The isomers were separable by flash chromatography; the predominance of the cis-isomer is consistent with results obtained in many other aziridine syntheses.[1]

When a bulkier ester was used in the same procedure, the diastereoselectivity of the reaction was similar (the cis-isomer, *cis*-**1b**, again dominated the product mixture), but lower (cis:trans=60:40, Scheme 1). In this case, a precise measurement of the diastereoselectivity was hampered by the fact that these diastereoisomers could not easily be separated, either by flash chromatography, or by crystallisation.

When NaHMDS was used as base in the preparation of the ^{t}butyl aziridine carboxylate, only *cis*-**1b** was produced, but



Scheme 1.

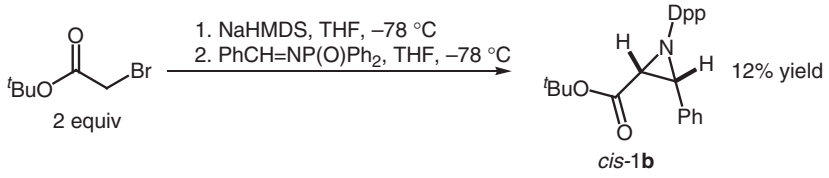
the efficiency of the transformation was greatly reduced (Scheme 2). Under these conditions, the major product of the reaction was the starting imine, even when prolonged reaction time and/or increased temperatures were employed.

Armed with a set of conditions for our new ADZ reaction, we turned to an asymmetric version of these reactions.

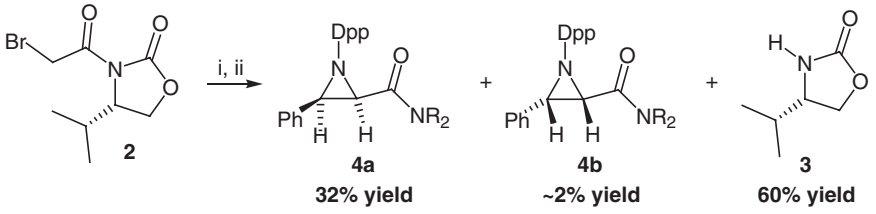
3.2. Aziridination via reaction of 4*S*-*N*-bromoacetyl-4-isopropyloxazolidinone enolates with *N*-Dpp-imines

As a first goal, we sought a reagent-controlled process and chose to examine the use of an Evans' auxiliary. Thus, (4*S*)-*N*-bromoacetyl-4-isopropyloxazolidinone (**2**)[7] was deprotonated at −78 °C in THF by LiHMDS and to the resultant lithium enolate was added a solution of *N*-Dpp benzaldimine. Under these (and a range of other) reaction conditions, no product of Darzens-like reaction were observed: instead, the only product isolated from these reactions was the parent oxazolidinone **3**, its presence presumably resulting from elimination to generate ketene, a reaction pathway known for processes conducted above 0 °C.[8] The use of NaHMDS, thereby furnishing the corresponding sodium enolate, was more encouraging: when the reaction was started at −78 °C and allowed to warm to ambient temperatures, an unequal mixture of two diastereomeric *cis*-aziridines (**4a** and **4b**) was obtained, in mediocre yield (Scheme 3). Again the major reaction pathway furnished oxazolidinone **3**, in 60% yield. These aziridines are non-crystalline, and the analysis of their stereochemistry was carried out using NMR spectroscopy and computer modelling, which led us tentatively to assign the absolute configurations of the new asymmetric centres in the major product **4a** as (2′*R*,3′*R*) (Scheme 3).

In an effort to improve the yield of aziridination at the expense of the elimination pathway, we experimented with many variations of the precise conditions of these reactions, but found little success in these endeavours; noteworthy observations include the obtention of a mixture of **4a** and *trans*-aziridines **4c** and **4d** when using diethyl ether as solvent for the reaction (Scheme 4).

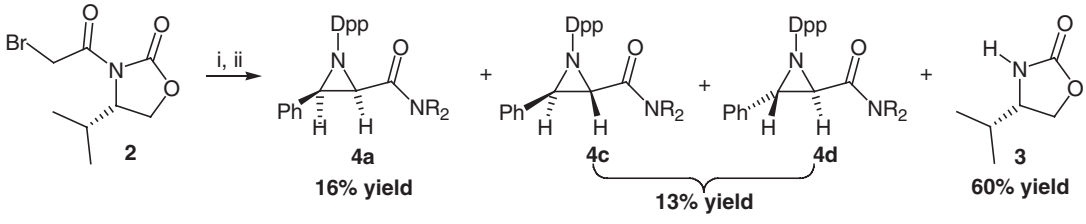


Scheme 2.



Conditions: i. NaHMDS, THF, –78 °C; ii. PhCH=NP(O)Ph2.

Scheme 3.



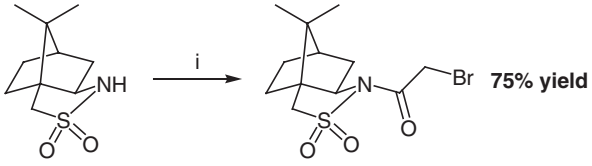
Conditions: i. NaHMDS, Et2O, –78 °C; ii PhCH=NP(O)Ph2.

Scheme 4.

In this case, the *trans*-aziridines were obtained as an inseparable mixture of (2′*R*,3′*R*) and (2′*S*,3′*S*) isomers. Thus, it seemed that the use of chiral oxazolidinones in ADZ reactions was problematic: we turned our attention to another chiral controller.

3.3. Aziridination via reaction of 2*R*-*N*-bromoacetylcamphorsultam enolates with *N*-Dpp-imines

2*R*-*N*-Bromoacetylcamphorsultam (**5**) was prepared in 71% yield in routine fashion (Scheme 5); to our surprise, this compound had not been reported in the literature previously.[9]



Conditions: i. ^{n}BuLi, $BrCH_2C(O)Br$, THF, –78 °C.

Scheme 5.

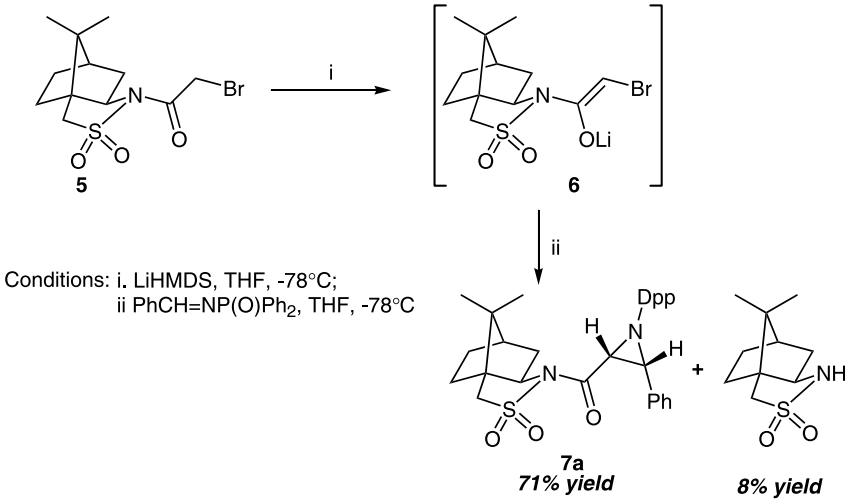
Deprotonation of **5** in THF at −78 °C using LiHMDS gave α-bromo lithioenolate **6**, to which was immediately added a THF solution of *N*-diphenylphosphinylbenzaldimine (Scheme 6). The reaction was allowed to proceed for 3 h at −78 °C, after which aqueous work-up gave aziridinyl sultam **7a**. Spectroscopic examination (^{1}H and ^{13}C NMR) of this crude product indicated that only one, cis-configured (J=6.2 Hz), diastereoisomer had been formed: no evidence of the alternate diastereoisomer could be found. Chromatographic purification subsequently furnished pure (2′*R*,3′*R*)-**7a** in 71% yield, accompanied by a small amount of deacetylated sultam (8%); no trace of any trans-configured aziridine, nor could any of the alternative cis-diastereoisomer be isolated from the reaction.

Single crystal X-ray analysis of **7a** confirmed the stereochemical analysis, and revealed the absolute configurations of the newly-created asymmetric centres to be (2′*R*,3′*R*). This observation implies that the reaction proceed via a *syn*-selective aza-aldol reaction, involving nucleophilic attack of the *si*-face of the enolate upon the *si*-face of the imine, followed by ring-closure. The obtention of aziridine rather than the intermediate aminobromide is noteworthy, because previously-reported asymmetric Darzens and aza-Darzens reactions using boron-containing asymmetric reagents or catalysts did not proceed directly to the heterocyclic product (epoxide, or aziridine, respectively), relying instead on a subsequent, separate, ring-closing step (Scheme 6).

Encouraged by this result, we immediately turned our attention to an examination of the scope of the reaction. The results of the first part of our study are collated in Table 1.

Thus, a range of aromatic imines was found to undergo ADZ reaction in acceptable yield and with virtually complete diastereo- and enantiocontrol. In all these examples (and despite significant variation in reaction conditions), a small amount of deacetylated sultam (<10%) was always isolated in addition to the desired aziridines; presumably this by-product arises by elimination from the initially formed bromoenolate, or by a self-condensation. As expected, the use of the enantiomeric auxiliary (Table 1, entries 10–16) yielded aziridine products of opposite stereochemistry, with similar selectivity. In most of the reactions the yield of aziridine was good, the only exception being the reaction of the *N*-Dpp imine derived from pivaldehyde (vide infra), and spectroscopic analysis of crude products again did not indicate the presence of other diastereoisomers. In the reaction of *N*-Dpp pivaldehyde imine (Table 1, entry 9) the mediocre yield (40%) of aziridine **7i** was due, in part, to the fact that the precursor 1,2-aminobromide **8** (13%) was also isolated (Scheme 7). It would seem that the additional barrier to rotation caused by the presence of a substituent of considerable steric demand retards the necessary bond rotation, which must occur prior to the second step, cyclization to give the aziridine product.

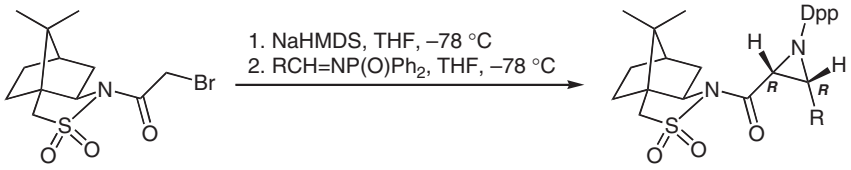
As mentioned above, the identification of *cis*-aziridines as the only products of the reaction was based on analysis of ^{1}H



Conditions: i. LiHMDS, THF, -78°C;
ii PhCH=NP(O)Ph_2, THF, -78°C

Scheme 6.

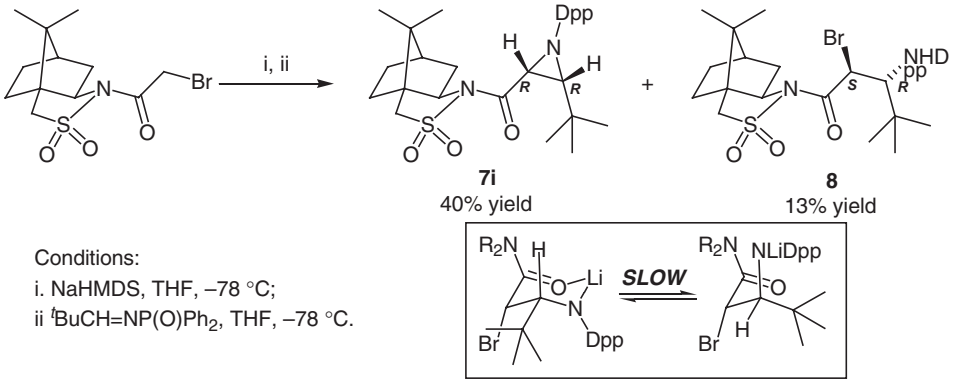
Table 1. Asymmetric aza-Darzens reaction of *N*-bromoacetyl camphorsultams



5 **7a–p**

Entry	R	Yield **7** (%)	cis:trans	dr
1	Ph	**7a** 71	100:0	>95:<5[a]
2	4-O_2N–C_6H_4	**7b** 75	100:0	>95:<5[a]
3	4-MeO–C_6H_4	**7c** 78	100:0	>95:<5[a]
4	2-O_2N–C_6H_4	**7d** 70	100:0	>95:<5[a]
5	4-Br–C_6H_4	**7e** 60	100:0	>95:<5[a]
6	2-Naphthyl	**7f** 72	100:0	>95:<5[a]
7	2-Fluorenyl	**7g** 67	100:0	>95:<5[a]
8	2-Furyl	**7h** 68	100:0	>95:<5[a]
9	^{t}Bu	**7i** 40[b]	100:0	>95:<5[a]
10	Ph[c]	**7j** 71	100:0	>95:< 5[d]
11	4-F–C_6H_4[c]	**7k** 57	100:0	>95:< 5[d]
12	2,6-Cl_2–C_6H_4[c]	**7l** 60	100:0	>95:< 5[d]
13	3-Br–C_6H_4[c]	**7m** 60	100:0	>95:< 5[d]
14	4-MeO–C_6H_4[c]	**7n** 60	100:0	>95:< 5[d]
15	2-Pyridyl[c]	**7o** 67	100:0	>95:< 5[d]
16	CH_2=CH[c]	**7p** 47	100:0	>95:< 5[d]

[a] (2′*R*,3′*R*):(2′*S*,3′*S*).
[b] (2′*S*,3′*R*)-*syn*-(2-Bromo-3-(diphenylphosphinyl)amino)sultam (**8**) also isolated in 13% yield.
[c] (2*S*)-Sultam used as auxiliary.
[d] (2′*S*,3′*S*):(2′*R*,3′*R*).



Scheme 7.

coupling constants (aziridines exhibit $^3J_{cis}$=4.5–7 Hz while $^3J_{trans}$=1.5–3 Hz). In certain cases, however, the relatively restricted rotation induced by the bulky *N*-substituent led to broad and overlapping resonances, which initially precluded assignment of cis- or trans-stereochemistry. Thus, the identification of the product of the reaction of *para*-nitrophenylbenzaldimine **7b** with the camphorsultam enolate (Table 1, entry 5) was complicated by the fact that the ^{1}H resonances of the aziridine protons were not resolved in deuteriochloroform. The signals were, however, resolved in deuteriobenzene, allowing identification of the ^3J coupling constant as 6.4 Hz, again indicative of a cis-configured product (Fig. 1).

A similar situation was encountered in the analysis of the *para*-bromo analogue **7e** (Table 1, entry 2) (Fig. 2): the C_6D_6 spectrum revealed a ^3J value similar in magnitude to the *para*-nitro compound.

3.4. Hydrolytic cleavage of auxiliary from (aziridinyl)acyl sultams

As the utility of the Dpp group as an aziridine activator had already been demonstrated within our group, we next sought to cleave the chiral auxiliary (to give the corresponding *N*-diphenylphosphinyl aziridine carboxylic acids) thereby allowing preparation of simple esters, for use in subsequent synthetic endeavours. Since the acylsultam linkage is labile under basic conditions, whereas the Dpp group is normally removed under acidic conditions, we were confident that this selective hydrolysis would be routine. Reaction of aziridinyl sultams with 1 equiv of lithium hydroxide monohydrate, proceeded smoothly, yielding the corresponding *N*-Dpp aziridine carboxylates **9** in generally good yield (Table 2, Scheme 8). These heterocycles are ideal precursors to a range of aziridine esters or other derivatives, valuable compounds both for synthesis and biological studies.

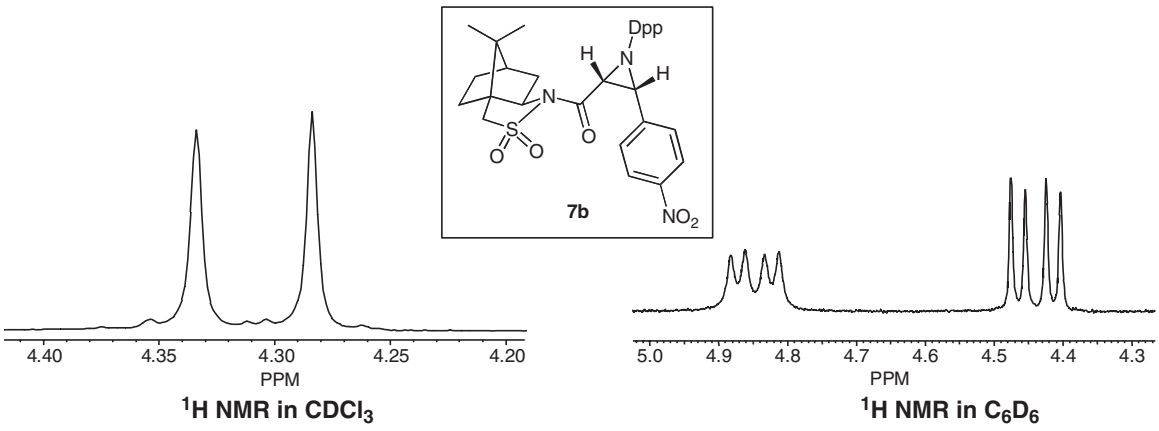


Figure 1.

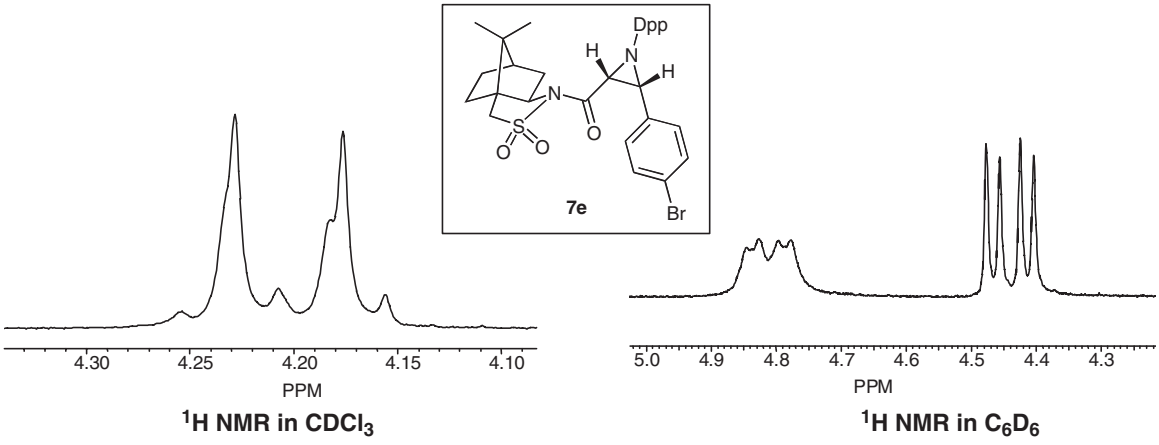
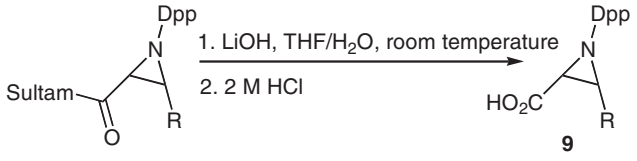


Figure 2.

Table 2. Removal of auxiliary from (aziridinyl)acylcamphorsultams

Entry	R	Sultam configuration	Aziridine configuration	Yield **9** (%)
1	Ph	*R*	(2′*R*,3′*R*)	**9a** 64
2	4-O_2N–C_6H_4	*R*	(2′*R*,3′*R*)	**9b** 60
3	2-O_2N–C_6H_4	*R*	(2′*R*,3′*R*)	**9c** 67
4	4-Br–C_6H_4	*R*	(2′*R*,3′*R*)	**9d** 61
5	2-Naphthyl	*R*	(2′*R*,3′*R*)	**9e** 67
6	^{t}Bu	*R*	(2′*R*,3′*R*)	**9f** 47
7	3-Br–C_6H_4	*S*	(2′*S*,3′*S*)	**9g** 80
8	2,6-Cl_2–C_6H_3	*S*	(2′*S*,3′*S*)	**9h** 45
9	2-Pyridyl	*S*	(2′*S*,3′*S*)	**9i** 100



Scheme 8.

4. Conclusion

We have demonstrated the use of the previously unreported *N*-bromoacylcamphorsultams as efficient precursors to a range of *cis*-*N*-Dpp-aziridine-2-carboxylates by a two-step process; the subsequent paper in this series will describe our observations of factors controlling the diastereoselectivity of the aziridine-forming reactions, and comments concerning the mechanism of the reaction.

5. Experimental

5.1. General techniques

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[10] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40 to 60 °C and 'ether' refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl; toluene from sodium; dichloromethane, triethylamine, acetonitrile from calcium hydride, methanol from magnesium methoxide and diisopropylethylamine from potassium hydroxide. Chemicals were purchased from Aldrich Chemical Co. or prepared by literature methods.

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Spectra were recorded on Perkin Elmer 881 or Paragon 1000 spectrophotometers. Optical rotations were measured using a Perkin Elmer 241 MC polarimeter and are quoted in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on VG9090 or Fisons Autospec mass

spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on Jeol GX-270, Jeol GX-400, Lambda 300, Bruker DPX-250 or Bruker AX-400 spectrometers. Unless otherwise stated, deuterochloroform was used as solvent and tetramethylsilane was the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from tetramethylsilane, and in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (J) are quoted in Hertz.

Reactions involving chemicals or intermediates sensitive to air or moisture were conducted under a nitrogen or argon atmosphere in oven- or flame-dried apparatus. Flash chromatography was performed using Merck Kieselgel 60 or Fluka Kieselgel 60 silica gel. Analytical thin-layer chromatography was performed using either precoated Merck Kieselgel 60 F_{254} glass-backed plates, or precoated Merck Kieselgel 60 F_{254} aluminium backed plates and were visualised under UV at 254 nm and by staining with iodine and/or an acidic ammonium molybdate dip.

^{13}C NMR spectra of *N*-Dpp compounds are complicated by rotameric isomers, which often leads to the appearance of 'excess' resonances in the aromatic region of the spectra; the situation is further complicated by the difficulty in obtaining precise coupling constants. Rather than refer to the entire region of the spectra as being a 'multiplet', the data quoted describes the actual appearance of the spectra.

5.1.1. (±)-Methyl *cis* *N*-diphenylphosphinyl-3-phenylaziridine-2-carboxylate (*cis*-1a). To a solution of methyl 2-bromoacetate (0.18 mL, 1.83 mmol) in THF (10 mL) at −78 °C, was added LiHMDS in THF (1.83 mL, 1.0 M, 1.83 mmol), dropwise. After 30 min, a THF (10 mL) solution of *N*-(phenylmethylene)diphenylphosphinamide (280 mg, 0.92 mmol), cooled to −78 °C, was slowly added. The reaction was then stirred for 2.5 h, before being quenched with water, and diluted with EtOAc at −78 °C. The solution was partitioned between H_2O (10 mL), and EtOAc (2×10 mL), the organic layers separated, washed with brine (15 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to leave a yellow oil. Purification by flash chromatography (EtOAc/petrol 1:1) gave *cis*-**1a** as an oil (190 mg, 55%). R_f 0.7 (EtOAc); IR ν_{max} ($CHCl_3$) 2982, 1751, 1437, 1175, 1126, 729 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 3.48 (3H, s), 3.71 (1H, dd, J_P=14.9 Hz, J=6.5 Hz), 4.16 (1H, dd, J_P=15.8 Hz, J=6.5 Hz), 7.30–7.55 (11H, m), and 7.92–8.18 (4H, m); δ_C (67.5 MHz, $CDCl_3$) 40.7, 41.7, 52.2, 127.5, 128.4, 130.5, 132.4, 137.0, 166.6; *m/z* (CI) 378 (MH^+, 100%), 346 (40), 320 (18), 201 (19), 79 (18); HRMS found: $[MH]^+$378.1260, $C_{22}H_{21}NO_3$ requires 378.1259.

5.1.2. (±)-Methyl *trans* *N*-diphenylphosphinyl-3-phenylaziridine-2-carboxylate (*trans*-1a). *Trans*-**1a** was also isolated from the reaction, as a viscous oil (15 mg, 4%). R_f 0.4 (EtOAc); IR ν_{max} (film) 2924, 1747, 1439, 1211, 1124, 728, 696 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 3.57 (1H, dd, J_P=13.6 Hz, J=2.8 Hz), 3.60 (3H, s), 4.03 (1H, dd, J_P=14.2 Hz, J=2.9 Hz), 7.30–7.46 (11H, m), and 7.65–8.06 (4H, m); *m/z* (CI) 378 (MH^+, 100%), 346 (26), 320 (17), 201 (17), 201 (17), 176 (13); HRMS found: $[MH]^+$378.1274, $C_{22}H_{21}NOP$ requires 378.1259.

5.1.3. (±)-^{t}Butyl *cis*- and *trans*-*N*-diphenylphosphinyl-3-phenylaziridine-2-carboxylate (1b). To a solution of *tert*-butyl 2-bromoacetate (0.08 mL, 0.52 mmol) in THF (10 mL) at −78 °C, was added LiHMDS in THF (0.52 mL, 1.0 M, 0.52 mmol), dropwise. After 30 min, a THF (10 mL) solution of *N*-(phenylmethylene)diphenylphosphinamide (80 mg, 0.26 mmol), was slowly added at −78 °C. The reaction was then stirred for 2.5 h, before being quenched with water, and diluted with EtOAc at −78 °C. The solution was then partitioned between H_2O (10 mL), and EtOAc (2×10 mL), the combined organic layers were then washed with brine (15 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to leave a yellow oil. This was purified by flash chromatography (EtOAc/petrol 1:1) to give a mixture of *cis*-**1b** and *trans*-**1b** (cis:trans=60:40) as a colourless oil (65 mg, 60%). R_f 0.6 (EtOAc); IR ν_{max} ($CHCl_3$) 2985, 1737, 1438, 1369, 1180, 1127, 729, 697 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.15 and 1.35 (9H, 2×s), 3.56 (0.4H, dd, J_P=13.3 Hz, $J_{(trans)}$=2.8 Hz), 3.58 (0.6H, dd, J_P=15.2 Hz, $J_{(cis)}$=6.6 Hz), 4.08 (0.4H, dd, J_P=11.5 Hz, $J_{(trans)}$=2.8 Hz), 4.10 (0.6H, dd, J_P=15.4 Hz, $J_{(cis)}$=6.6 Hz), 7.22–8.21 (15H, m), δ_C (67.5 MHz, $CDCl_3$) 27.7, 27.8, 41.2, 41.4, 43.4, 43.5, 44.7, 44.8, 127.6, 127.9, 128.4, 132.4, 135.1, 165.2, 166.8; *m/z* (CI) 420 (MH^+, 5%), 364 (M−^{t}Bu, 27), 320 (M−CO_2^tBu, 100), 201 (17), 120 (48), 79 (72); HRMS found: $[MH]^+$420.1722, $C_{25}H_{27}NO_3P$ requires 420.1729.

5.1.4. (±)-^{t}Butyl *cis*-*N*-diphenylphosphinyl-3-phenylaziridine-2-carboxylate (*cis*-1b). By following the procedure above, *tert*-butyl 2-bromoacetate (0.2 mL, 1.3 mmol), NaHMDS in THF (1.3 mL, 1.0 M, 1.3 mmol), *N*-(phenylmethylene)diphenylphosphinamide (200 mg, 0.66 mmol), were reacted together in THF (15 mL) at −78 °C for 3 h, to give a yellow oil. Purification by flash chromatography (EtOAc/petrol 1:1) gave *cis*-**1b** as a colourless oil (33 mg, 12%). R_f 0.6 (EtOAc); IR ν_{max} ($CHCl_3$) 2976, 1743, 1439, 1368, 1180, 1127, 729, 697 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.15 (9H, s), 3.58 (1H, dd, J_P=15.4 Hz, J=6.6 Hz), 4.10 (1H, dd, J_P=15.6 Hz, J=6.6 Hz), 7.23–7.56 (11H, m), 7.91–8.21 (4H, m); δ_C (67.5 MHz, $CDCl_3$) 27.8, 41.4, 43.5, 44.8, 127.6, 127.9, 128.4, 132.4, 135.1, 166.8; *m/z* (CI) 420 (MH^+, 18%), 364 (M−^{t}Bu+H^+, 51), 320 (M−CO_2^tBu+H^+, 100), 218 (15), 120 (14); HRMS found: $[MH]^+$420.1720, $C_{25}H_{27}NO_3P$ requires 420.1729.

5.1.5. (4*S*,2′*R*,3′*R*)-(+)-3-[(1′-Diphenylphosphinyl-3′-phenyl-2′-aziridinyl)carbonyl]-4-(1-methylethyl)oxazolidin-2-one (4a).[11] (4*S*)-(+)-3-Bromoacetyl-4-(1-methylethyl)-2-oxazolidinone (150 mg, 0.6 mmol), was dissolved in THF (15 mL), and cooled to −78 °C. NaHMDS in THF (0.66 mL, 1.0 M, 0.66 mmol) was then added dropwise, and the resulting pale yellow solution stirred for 30 min. *N*-(Diphenylmethylene)diphenylphosphinamide (900 mg, 0.3 mmol), was then added at −78 °C as a solution in THF (5 mL). The reaction mixture was then stirred for 3 h and allowed to reach ambient temperature, at which point the reaction was quenched with saturated ammonium chloride solution (20 mL) and EtOAc (20 mL, 2×10 mL), the organic layers were then combined, washed with brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo, to afford a yellow oil. Purification by flash chromatography (gradient 20–80% EtOAc in petrol),

provided a clear oil, which was crystallised from EtOAc/Hexane to afford **4a** as colourless needles (40 mg, 32%). R_f 0.5 (EtOAc); mp 183–184 °C; $[\alpha]_D^{20}$ +110.9 (*c* 1.5, CH_2Cl_2); IR ν_{max} (film) 2964, 1785, 1708, 1439, 1209, 1126, 729, 698 cm^{-1}; δ_H (400 MHz, CD_2Cl_2) 0.00 (3H, d, J=7.0 Hz), 0.61 (3H, d, J=7.0 Hz), 1.71–1.74 (1H, m), 3.94–3.98 and 4.05–4.12 (3H, 2×m), 4.33 and 4.38 (2H, 2×dd, J_P=15.2 Hz, J=6.6 Hz), 7.12–8.19 (15H, m); δ_C (67.5 MHz, $CDCl_3$) 13.1, 17.6, 27.9, 42.1, 42.5, 58.1, 63.7, 127.3, 128.5, 131.4, 132.2, 135.2, 153.2, 164.7; *m/z* (CI) 475 ($[MH]^+$, 100%), 346 (56), 320 (43), 275 (28), 201 (23), 130 (63); HRMS found: $[MH]^+$475.1775, $C_{27}H_{28}N_2O_4P$ requires 475.1787; Found: C, 68.3; H, 5.8; N, 6.1; $C_{27}H_{27}N_2O_4P$ requires C, 68.4; H, 5.8; N, 5.9%.

5.1.6. (4*S*,2′*S*,3′*S*)-(+)-3-[(1′-Diphenylphosphinyl-3′-phenyl-2′-aziridinyl)carbonyl]-4-(1-methylethyl)oxazolidin-2-one (4b). From the reaction described above a small quantity of a different cis diastereoisomer, **4b**, was also isolated (2–3 mg, ~2%), as a colourless oil. This product could not be satisfactorily separated from (4*S*)-4-(1-methylethyl) oxazolidinone generated by enolate decomposition and only partial physical data were collected: R_f 0.6 (EtOAc); δ_H (400 MHz, $CDCl_3$) 0.74 and 0.78 (6H, 2×d, J=7.1 Hz), 2.13–2.20 (1H, m), 3.86–3.91 and 4.09–4.12 (3H, 2×m), 4.27 and 4.45 (2H, 2×dd, J_P=15.4 Hz, J=6.6 Hz), 7.28–8.26 (15H, m); *m/z* (CI) 475 ($[MH]^+$, 65%), 390 (10), 346 (40), 320 (41), 275 (25), 201 (23), 130 (100); HRMS found: $[MH]^+$475.1796, $C_{27}H_{28}N_2O_4P$ requires 475.1787.

5.1.7. *trans*-(4*S*)-3-[(1′-Diphenylphosphinyl-3′-phenyl-2′-aziridinyl)carbonyl]-4-(1-methylethyl)oxazolidin-2-one (4c and 4d). Following the procedure above, (4*S*)-(+)-3-bromoacetyl-4-(1-methylethyl)-2-oxazolidinone (200 mg, 0.8 mmol), NaHMDS in THF (0.9 mL, 1.0 M, 0.88 mmol), and *N*-(phenylmethylene)diphenylphosphinamide (120 mg, 0.4 mmol) were reacted together in ether (25 mL). Purification by flash chromatography (gradient 20–100% EtOAc in petrol), provided **4a** a yellow oil (20 mg, 16%), and a mixture of *trans*-aziridine diastereoisomers, **4c** and **4d** as a clear oil (25 mg, 13%). R_f 0.2 (EtOAc); $[\alpha]_D^{20}$ +59.8 (*c* 0.5, CH_2Cl_2); IR ν_{max} (film) 2965, 1782, 1704, 1438, 1204, 1124, 727, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.64 and 0.79 (6H, 2×d, J=7.2 Hz), 2.14–2.26 (1H, m), 4.11–4.29 (3H, m), 4.39–4.44 (1H, m), 4.81 (1H, dd, J_P=12.6 Hz, J=2.8 Hz), 7.01–7.46 (11H, m), 7.72–7.95 (4H, m); δ_C (100 MHz, $CDCl_3$) 14.6, 17.9, 28.1, 43.2, 45.3, 58.6, 63.9, 127.6, 132.2, 135.9, 153.8, 166.4; *m/z* (CI) 475 ($[MH]^+$, 100%), 346 (39), 320 (13), 275 (10), 201 (10), 130 (26); HRMS found: $[MH]^+$475.1776, $C_{27}H_{28}N_2O_4P$ requires 475.1787.

5.1.8. (2*R*)-(−)-(*N*-Bromoacetyl)bornane-10,2-sultam (*R*-5). (2*R*)-Bornane-10,2-sultam (200 mg, 9.3 mmol), was dissolved in THF (25 mL), under a nitrogen atmosphere and cooled to −78 °C. *n*-BuLi in hexanes (2.5 M, 0.41 mL, 1.0 mmol), was then added dropwise and the solution stirred for 20 min. Bromoacetyl bromide (0.1 mL, 1.0 mmol), was then dissolved in THF (10 mL), and this was then added dropwise to the anion. The reaction was stirred at −78 °C and was determined to be complete by TLC after 2 h. Water (10 mL) was added to quench the reaction, and EtOAc (20 mL) added. The organic layer was partitioned and the aqueous layer washed with EtOAc (2×10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The resulting pale yellow oil was then purified by flash chromatography, (gradient 0–10% EtOAc in hexane), affording (*R*)-**5** as a clear oil, which was crystallised from $CHCl_3$/hexane to provide colourless needles (220 mg, 71%). R_f 0.4 (EtOAc/heptane 3:7); mp 113–114 °C; $[\alpha]_D^{20}$ −118.5 (*c* 1, CH_2Cl_2); IR ν_{max} ($CHCl_3$) 2959, 1705, 1330, 1170 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.98 and 1.16 (6H, 2×s), 1.37–1.43, and 1.90–2.16 (7H, 2×m), 3.44–3.55 (2H, 2×d, J=14.0 Hz), 3.91 (1H, dd, J=7.6, 5.1 Hz), 4.20 and 4.34 (2H, 2×d, J=13.0 Hz); δ_C (100 MHz, $CDCl_3$), 19.9, 20.7, 26.4, 27.5, 32.8, 37.9, 44.5, 47.9, 49.1, 52.7, 65.5, 164.5; *m/z* (CI) 336 ($[MH]^+$, 86%), 258 (16), 192 (42), 135 (100); HRMS found: $[MH]^+$336.0259, $C_{12}H_{19}BrNO_3S$ requires 336.0269; Found: C, 43.0; H, 5.5; N, 4.1; $C_{12}H_{18}BrNO_3S$ requires C, 42.9; H, 5.4; N, 4.2%.

5.1.9. (2*S*)-(+)-(*N*-Bromoacetyl)bornane-10,2-sultam (*S*-5). Bornane-10,2-sultam (1.00 g, 4.7 mmol) was dissolved in anhydrous THF (30 mL) under a nitrogen atmosphere and cooled to −78 °C. *n*-BuLi in hexanes (2.1 mL, 2.5 M, 5.1 mmol) was added dropwise to the solution and left to stir for approximately 1 h. After this time bromoacetyl bromide (0.4 mL, 4.7 mmol) dissolved in anhydrous THF (20 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir for 3 h at −78 °C and the course of the reaction was followed by TLC. Once all starting materials had been consumed, water (20 mL) was added to quench the reaction followed by the addition of ether (20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed in vacuo. Flash chromatography of the resultant colourless solid (petrol/ether, 6:4), affording the desired product as a colourless needles (1.23 g, 77%). R_f 0.34 (petrol/ether, 1:1); mp 113 °C; $[\alpha]_D^{20}$ +118.5 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 2959, 1705, 1330, 1170 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, s), 1.09 (3H, s), 1.25–1.40 and 1.72–2.11 (7H, 2×m), 3.38–3.48 (2H, 2×d, J=13.7 Hz), 3.90 (1H, dd, J=7.5, 5.0 Hz), 4.14 and 4.27 (2H, 2×d, J=13.2 Hz); δ_C (100 MHz, $CDCl_3$) 19.8, 20.7, 26.4, 28.0, 32.7, 37.9, 44.5, 47.8, 49.0, 52.7, 65.4, 164.5; *m/z* (CI) 36 ($[MH]^+$, 86%), 258 (16), 192 (42), 135 (100); HRMS found: $[MH]^+$336.0259, $C_{12}H_{19}BrNO_3S$ requires 336.0269.

5.2. General procedure for asymmetric aza-Darzens reaction using *R*-5

(2*R*)-(−)-(*N*-Bromoacetyl)bornane-10,2-sultam (*R*-**5**), (1.1 equiv), was dissolved in THF (25 mL) and cooled to −78 °C. LiHMDS in THF (1.2 equiv) was then added dropwise, and the resulting pale yellow solution stirred for 30 min. Phosphinylimine, (typically 0.7 mmol) was then added at −78 °C as a solution in THF (10 mL). The reaction mixture was then stirred for over 2 h at −78 °C, after which time the reaction was judged to have reached completion by TLC and the mixture was quenched with saturated ammonium chloride solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL, 2×10 mL), the organic layers were then combined, washed with brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo, to afford the crude aziridine.

5.2.1. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-phenyl-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7a). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (490 mg, 1.4 mmol), LiHMDS in THF (1.6 mL, 1.0 M, 1.6 mmol), and *N*-(phenylmethylene)diphenylphosphinamide (400 mg, 1.3 mmol), were reacted together in THF (35 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–70% EtOAc in petrol containing 0.05% v/v acetic acid) provided a colourless oil. Crystallisation from $CHCl_3$/hexane afforded **7a** as a colourless solid (520 mg, 71%). R_f 0.5 (EtOAc); mp 197–198 °C; $[\alpha]_D^{20}$ −11.3 (*c* 1, CH_2Cl_2); IR ν_{max} ($CHCl_3$) 2961, 1705, 1439, 1336, 1270, 1213, 1137, 837, 654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s), 0.95 (3H, s), 1.20–1.32 and 1.79–1.96 (7H, 2×m), 3.27 and 3.38 (2H, 2×d, *J*=13.6 Hz), 3.57–3.61 (1H, m), 4.18 and 4.27 (2H, 2×dd, J_P=14.4 Hz, *J*=6.1 Hz), 7.19–7.55 (11H, m), and 7.93–8.15 (4H, m), δ_C (75 MHz, $CDCl_3$) 19.8, 19.9, 26.3, 32.5, 38.1, 41.6, 44.0, 44.6, 47.7, 49.0, 52.6, 64.7, 127.7, 128.4, 128.7, 130.9, 131.9, 132.7, 163.7; *m*/*z* (CI) 561 ($[MH]^+$, 72%), 483 (11), 361 (42), 346 (44), 320 (70), 216 (100), 135 (67); HRMS found: $[MH]^+$561.1987, $C_{31}H_{34}N_2O_4PS$ requires 561.1977; Found: C, 66.6; H, 6.0; N, 5.0; $C_{31}H_{33}N_2O_4PS$ requires C, 66.4; H, 5.9; N, 5.0%.

5.2.2. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-(4-nitrophenyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7b). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (250 mg, 0.74 mmol), LiHMDS in THF (0.8 mL, 1.0 M, 0.8 mmol), and *N*-(4-nitrophenylmethylene)diphenylphosphinamide (240 mg, 0.7 mmol), were reacted together in THF (35 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–70% EtOAc in petrol, containing 0.05% v/v acetic acid) provided a colourless oil. Crystallisation from $CHCl_3$/hexane afforded **7b** as a colourless solid (320 mg, 77%). R_f 0.55 (EtOAc); $[\alpha]_D^{20}$ −28.6 (*c* 1, CH_2Cl_2); mp 213 °C (EtOAc/hexane); IR ν_{max} (film) 2960, 1703, 1439, 1347, 1215, 1127, 730, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, s), 0.98 (3H, s), 1.21–1.31 and 1.81–2.05 (7H, 2×m), 3.28 and 3.42 (2H, 2×d, *J*=13.7 Hz), 3.54–3.57 (1H, m), 4.29–4.33 (2H, m), 7.38–7.64 (10H, m) and 7.90–8.15 (4H, m); δ_H (300 MHz, C_6H_6) 0.26 (3H, s), 0.65 (3H, s), 0.53–0.89, 1.07–1.16 and 1.65–1.85 (7H, m), 2.42 and 2.46 (2H, 2×d, *J*=13.9 Hz), 3.14–3.18 (1H, m), 4.44 (1H, dd, J_P=15.4 Hz, *J*=6.4 Hz), 4.85 (1H, dd, J_P=14.8 Hz, *J*=6.4 Hz) 6.93–7.86 and 8.09–8.43 (14H, m); δ_C (75 MHz, $CDCl_3$) 19.8, 20.7, 26.3, 32.5, 38.0, 42.0, 42.8, 44.5, 47.8, 49.1, 52.7, 64.8, 123.0, 128.7, 131.9, 131.9, 131.9, 140.2, 140.2, 147.7, 163.3; *m*/*z* (CI) 606 ($[MH]^+$, 100%), 541 (10), 419 (44), 406 (47), 219 (25), 201 (12), 135 (22); HRMS found: $[MH]^+$606.1824, $C_{31}H_{33}N_3O_6PS$ requires 606.1828; Found: C, 61.8; H, 5.6; N, 6.9; $C_{31}H_{32}N_3O_6PS$ requires C, 61.5; H, 5.3, H, 7.0%.

5.2.3. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-(4-methoxyphenyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7c). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (390 mg, 1.2 mmol), LiHMDS in THF (1.25 mL, 1.0 M, 1.25 mmol), and *N*-(4-methoxyphenylmethylene)diphenylphosphinamide (350 mg, 1.0 mmol), were reacted together in THF (40 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–80% EtOAc in petrol, containing 0.05% v/v acetic acid), provided a colourless oil. Crystallisation from $CHCl_3$/hexane afforded **7c** (460 mg, 74%). R_f 0.5 (EtOAc); mp 138–140 °C; $[\alpha]_D^{20}$ −14.0 (*c* 1, CH_2Cl_2); IR ν_{max} (film) 2964, 3840, 1698, 1439, 1330, 1188, 1275, 1126, 730, 703, 652 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s), 0.94 (3H, s), 1.21–1.30 and 1.79–1.98 (7H, 2×m), 3.28 and 3.39 (2H, 2×d, *J*=14.0 Hz), 3.61 (1H, m), 3.75 (3H, s), 4.11–4.26 (2H, 2×dd, J_P=15.9, 6 Hz, *J*=0.2 Hz), 6.80 (2H, app. d, *J*=8.5 Hz), 7.34–7.54 (8H, m), and 8.10–8.15 (4H, m); δ_C (75 MHz, $CDCl_3$) 19.8, 20.7, 26.3, 32.5, 38.1, 41.7, 43.8, 44.6, 47.7, 49.0, 52.6, 55.1, 64.7, 113.2, 124.7, 124.8, 128.6, 131.5, 131.7, 131.8, 159.4, 163.9; *m*/*z* (CI) 591 ($[MH]^+$, 100%), 526 (15), 419 (47), 373 (32), 219 (36), 135 (14); HRMS found: $[MH]^+$591.2064, $C_{32}H_{36}N_2O_5PS$ requires 591.2082.

5.2.4. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-(2-nitrophenyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7d). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (320 mg, 0.94 mmol), LiHMDS in THF (1.0 mL, 1.0 M, 1.0 mmol), and *N*-(2-nitrophenylmethylene)diphenylphosphinamide (300 mg, 0.9 mmol), were reacted together in THF (35 mL) at −78 °C to produce a yellow solid. Purification by flash chromatography (gradient 20–70% EtOAc in petrol, containing 0.05% v/v acetic acid) provided a colourless oil. Crystallisation from EtOAc/hexane afforded **7d** (380 mg, 72%). R_f 0.55 (EtOAc); $[\alpha]_D^{20}$ −112.4 (*c* 1, CH_2Cl_2); mp 190–192 °C; IR ν_{max} (film) 2960, 1700, 1438, 1342, 1212, 1136, 730, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, s), 0.89 (3H, s), 1.17–1.32 and 1.79–1.96 (7H, 2×m), 3.28 and 3.36 (2H, 2×d, *J*=13.8 Hz), 3.51–3.55 (1H, m), 4.25 (1H, br dd, J_P=14.9 Hz, *J*=5.8 Hz), 5.05 (1H, dd, J_P=15.2 Hz, *J*=6.2 Hz), 7.38–7.58 (10H, m), and 7.80–8.12 (4H, m); δ_C (75 MHz, $CDCl_3$) 19.8, 20.6, 26.3, 32.5, 38.1, 40.8, 42.2, 44.6, 47.8, 49.0, 52.4, 64.5, 124.9, 128.8, 128.9, 128.7, 128.7, 131.0, 131.2, 131.2, 131.6, 131.8, 132.4, 132.9, 148.7, 164.1; *m*/*z* (CI) 606 ($[MH]^+$, 2.5%), 419 (15), 321 (20), 272 (32), 219 (25), 201 (12), 135 (100); HRMS found: $[MH]^+$606.1832, $C_{31}H_{33}N_3O_6PS$ requires 606.1828; Found: C, 61.4; H, 5.35; N, 6.9; $C_{31}H_{32}N_3O_6PS$ requires C, 61.5; H, 5.3, H, 7.0%.

5.2.5. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(3′-(4-Bromophenyl)-1′-diphenylphosphinyl-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7e). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (270 mg, 0.8 mmol), LiHMDS in THF (0.9 mL, 1.0 M, 0.9 mmol), and *N*-(4-bromophenylmethylene)diphenylphosphinamide (280 mg, 0.73 mmol), were reacted together in THF (25 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–80% EtOAc in petrol, containing 0.05% v/v acetic acid) provided a colourless oil. Crystallisation from $CHCl_3$/hexane afforded **7e** as a colourless crystalline solid (300 mg, 65%); mp 135–136 °C ($CHCl_3$/hexane). R_f 0.55 (EtOAc); $[\alpha]_D^{23}$ −16.0 (*c* 1, CH_2Cl_2); IR ν_{max} (film) 2940, 1708, 1442, 1347 and 1170, 1272, 1137, 750, 720, 684 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90, (3H, s), 0.97 (3H, s), 1.22–1.33 and 1.80–1.97 (7H, 2×m), 3.28 and 3.41 (2H, 2×d, *J*=3.7 Hz), 3.58–3.62

(1H, m), 4.17–4.22 (2H, 2×m), 7.31–7.56 (10H, m) and 7.89–8.13 (4H, m); δ_C (300 MHz, C_6D_6) 0.28 (3H, s), 0.68 (3H, s), 0.21–0.56, 0.83–0.93, 1.11–1.29 and 1.65–1.88 (7H, m), 2.45 and 2.59 (2H, 2×d, J=13.9 Hz), 3.10–3.14 (1H, m), 4.43 (1H, dd, J_P=15.8 Hz, J=6.2 Hz), 4.81 (1H, br dd, J_P=14.1 Hz, J=6.2 Hz), 6.92–7.16 (6H, m), 7.26 (4H, d, J=8.6 Hz), and 7.47 (4H, d, J=8.6 Hz), 8.09–8.44 (4H, m); δ_C (75 MHz, $CDCl_3$) 19.8, 20.7, 26.3, 32.5, 38.1, 41.4, 43.3, 44.6, 47.8, 49.0, 52.7, 64.8, 122.2, 128.5, 131.9, 163.5; *m/z* (CI) 641 and 639 ($[MH]^+$, Br isotopic pattern, 24%), 576 (19), 574 (19), 561 (5), 424 (20), 358 (15), 219 (70), 201 (100), 135 (55); HRMS found: $[MH]^+$639.1068, $C_{31}H_{33}BrN_2O_4PS$ requires 639.1082.

5.2.6. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-(2-naphthyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7f). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (370 mg, 1.1 mmol), LiHMDS in THF (1.2 mL, 1.0 M, 1.2 mmol), and *N*-(2-naphthylmethylene)diphenylphosphinamide (350 mg, 1.0 mmol), were reacted together in THF (40 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–70% EtOAc in petrol, containing 0.05% v/v acetic acid), afforded **7f** as a clear oil (440 mg, 73%). R_f 0.55 (EtOAc); $[\alpha]_D^{20}$ −16.6 (*c* 1, CH_2Cl_2); IR ν_{max} (film) 2962, 1702, 1438, 1336, 1214, 1126, 646, 618 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.85 (3H, s), 0.94 (3H, s), 1.15, 1.72–1.93 (7H, 2×m), 3.21 and 3.36 (2H, 2×d, J=13.9 Hz), 3.49–3.51 (1H, m), 4.11 and 4.42 (2H, 2×dd, J_P=15.9 Hz, J=6.2 Hz), 7.31–8.20 (17H, m); δ_C (75 MHz, $CDCl_3$) 19.7, 20.7, 26.2, 32.4, 38.0, 41.8, 44.1, 44.5, 47.6, 48.9, 52.6, 64.6, 125.8, 125.9, 127.2, 127.6, 127.7, 128.4, 131.9, 133.1, 163.6; *m/z* (CI) 611 ($[MH]^+$, 100%), 546 (22), 419 (82), 411 (70), 393 (37), 219 (64), 201 (30), 135 (28); HRMS found: $[MH]^+$611.2126, $C_{35}H_{36}N_2O_4PS$ requires 611.2133.

5.2.7. (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-(2-fluorenyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7g). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (330 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol), and *N*-(fluorenemethylene)diphenylphosphinamide (350 mg, 0.9 mmol), were reacted together in THF (40 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–70% EtOAc in petrol, containing 0.05% v/v acetic acid), afforded **7g** as a pale yellow oil (390 mg, 68%). R_f 0.5 (EtOAc); $[\alpha]_D^{20}$ −20.0 (*c* 1, CH_2Cl_2); IR ν_{max} (film) 2962, 1702, 1439, 1337, 1217, 1127, 730, 646, 619 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, s), 0.95 (3H, s), 1.19–1.21 and 1.76–1.97 (7H, 2×m), 3.25 and 3.38 (2H, 2×d, J=13.9 Hz), 3.58 (1H, m), 3.85 (2H, d, J=3.7 Hz), 4.22 and 4.38 (2H, 2×dd, J_P=15.9 Hz, J=6.2 Hz), 7.26–7.72 and 7.97–8.20 (17H, 2×m); δ_C (75 MHz, $CDCl_3$) 19.7, 20.6, 26.2, 32.4, 38.0, 36.8, 41.9, 44.3, 44.5, 47.6, 48.9, 52.5, 64.6, 119.0, 119.8, 124.9, 126.6, 127.0, 128.6, 131.9, 141.3, 141.6, 142.6, 143.4, 163.6; *m/z* (CI) 649 ($[MH]^+$, 21%), 585 (7), 449 (43), 419 (100), 219 (60), 135 (22); HRMS found: $[MH]^+$649.2282, $C_{38}H_{38}N_2O_4PS$ requires 649.2290.

5.2.8. (2*R*,2′*R*,3′*S*)-(−)-*N*-[(1′-Diphenylphosphinyl-3′-(2-furyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7h). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (500 mg, 1.49 mmol), LiHMDS in THF (1.6 mL, 1.0 M, 1.6 mmol), and *N*-(2-furylmethylene)diphenylphosphinamide (400 mg, 1.4 mmol), were reacted together in THF (35 mL) at −78 °C to produce a pale yellow oil. Purification by flash chromatography (gradient 20–70% EtOAc in petrol, containing 0.05% v/v acetic acid), provided a pale yellow oil. Crystallisation from EtOAc/hexane afforded **7h**, as a colourless crystalline solid (530 mg, 71%). R_f 0.5 (EtOAc); $[\alpha]_D^{20}$ −18.9 (*c* 3, CH_2Cl_2); IR ν_{max} (film) 2961, 1701, 1438, 1336, 1217, 1137, 728, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (3H, s), 0.98 (3H, s), 1.16–1.36 and 1.83–1.89 (7H, 2×m), 3.31 and 3.41 (2H, 2×d, J=13.5 Hz), 3.73–3.76 (1H, m), 4.09–4.22 (2H, 2×dd, J_P=16.1 Hz, J=5.9 Hz), 6.29 (1H, dd, J=3.4, 1.9 Hz), 6.36 (1H, d, J=3.2 Hz), 7.33–7.58 (7H, m), and 7.84–8.12 (4H, m); δ_C (75 MHz, $CDCl_3$) 19.8, 20.6, 26.4, 32.6, 37.6, 38.1, 41.0, 44.6, 47.8, 49.2, 52.5, 64.7, 109.1, 110.5, 128.6, 131.7, 142.8, 148.5, 165.0; *m/z* (CI) 551 ($[MH]^+$, 35%), 487 (15), 447 (10), 419 (70), 351 (100), 219 (80), 201 (12), 135 (30); HRMS found: $[MH]^+$551.1779, $C_{29}H_{32}N_2O_5PS$ requires 551.1770.

5.2.9. (2*R*,2′*R*,3′*R*)-(+)-*N*-[(3′-(*tert*-Butyl)-1′-diphenylphosphinyl-2′-aziridinyl)carbonyl]bornane-10,2-sultam (7i). By following the procedure above, (2*R*)-(−)-(*N*-bromoacetyl)bornane-10,2-sultam (260 mg, 0.77 mmol), LiHMDS in THF (0.8 mL, 1.0 M, 0.8 mmol), and *N*-(*tert*-butylmethylene)diphenylphosphinamide (200 mg, 0.7 mmol), were reacted together in THF (40 mL) at −78 °C to produce a yellow oil. Purification by flash chromatography (gradient 20–70% EtOAc in petrol, containing 0.05% v/v acetic acid) provided a colourless oil. Crystallisation from ethyl acetate/hexane afforded (**7i**) as a colourless crystalline solid (150 mg, 40%). R_f 0.55 (EtOAc); mp 204 °C (EtOAc/hexane); $[\alpha]_D^{20}$ +11.9 (*c* 1, CH_2Cl_2); IR ν_{max} (film) 2960, 1703, 1439, 1339, 1203, 1127, 1064, 729, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82 (9H, s), 0.83 and 0.91 (6H, 2×s), 1.26–1.44 and 1.80–2.08 (7H, 2×m), 3.03 (1H, dd, J_P=17.8 Hz, J=6.3 Hz), 3.36 and 3.42 (2H, 2×d, J=13.7 Hz) 3.61 (1H, br dd, J_P=17.3 Hz, J=5.9 Hz), 3.85 (1H, m), 7.40–7.53 (6H, m), and 7.94–8.10 (4H, m); δ_C (75 MHz, $CDCl_3$) 19.8, 20.4, 27.9, 26.4, 32.6, 38.0, 32.4, 39.6, 44.4, 47.8, 49.0, 52.5, 53.5, 65.1, 128.4, 131.8, 131.7, 132.0, 165.5; *m/z* (CI) 541 ($[MH]^+$, 100), 471 (42), 419 (20), 298 (56), 201 (23), 135 (9); HRMS found: $[MH]^+$541.2294, $C_{29}H_{38}N_2O_4PS$ requires 541.2290; Found: C, 64.6; H, 6.9; N, 5.2; $C_{29}H_{37}N_2O_4PS$ requires C, 64.4; H, 6.9, H, 5.2%.

5.2.10. (2*R*)-*N*-[2′-Bromo-4′-dimethyl-3′-(diphenylphosphinamido)-1′-oxopentyl]bornane-10,2-sultam (8). The above reaction also gave compound **8** as a clear oil (60 mg, 13%). R_f 0.65 (EtOAc); IR ν_{max} (film) 3368, 2960, 1706, 1438, 1332, 1216, 1122, 724, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s), 0.95 (3H, s), 1.24 (3H, s), 1.26–1.41 and 1.80–1.91 (6H, 2×m), 2.37–2.42 (1H, m), 3.37–3.43 and 3.53–3.63 (2H, 27×m), 3.45–3.53 (2H, 2×d, J=13.7 Hz), 3.90 (1H, dd, J=7.8, 4.6 Hz), 5.52 (1H, s), 7.38–7.52 (6H, m), and 7.82–7.94 (4H, m), δ_C (100 MHz, $CDCl_3$) 20.0, 20.8, 27.8, 26.5, 33.1, 37.0, 37.9, 44.6, 47.8, 48.5, 53.1, 53.3, 58.8, 66.4, 128.2, 132.2, 166.2; *m/z* (CI) 623 and 621 ($[MH]^+$, Br isotope pattern, 26%), 543 (14),

485 (27), 326 (17), 270 (100), 216 (20), 57 (54); HRMS found: $[MH]^+$621.1539, $C_{29}H_{39}BrN_2O_4PS$ requires 621.1552.

5.3. General procedure for asymmetric aza-Darzens reactions using *S*-5

Compound *S*-**5** (336 mg, 1.0 mmol) was dissolved in anhydrous THF (20 mL) and cooled to −78 °C under an inert atmosphere. LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) was added dropwise and the resulting yellow solution stirred for approximately 30 min. Phosphinylimine (0.9 mmol) was added as a THF solution (15 mL) to the reaction mixture. The reaction mixture was then left stirring at −78 °C for approximately 3–4 h and followed by TLC. After this time the reaction was quenched via addition of a saturated ammonium chloride solution (20 mL). The aqueous layer was then extracted with ether (3×20 mL) and the organic layers combined, washed with brine, dried ($MgSO_4$), filtered and the solvent removed in vacuo to afford the crude aziridine.

5.3.1. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(phenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7j). Following the general procedure described above, *S*-**5** (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide (275 mg, 0.9 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:9), affording **7j** as a colourless solid (358 mg, 71%). R_f 0.53 (EtOAc); mp 198 °C; $[\alpha]_D^{20}$ +11.3 (*c* 1, CH_2Cl_2); IR ν_{max} (CCl_4) 2961, 1705, 1439, 1336, 1270, 1213, 1137, 837, 654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, s), 0.94 (3H, s), 1.21–1.26 and 1.78–1.96 (7H, 2×m), 3.27, 3.39 (2H, 2×d, J=13.9 Hz), 3.58 (1H, m), 4.25 and 4.29 (2H, 2×dd, J_P=15.8 Hz, J=6.2 Hz), 7.23–7.52 (11H, m), 7.93–7.98 and 8.11–8.15 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.6, 20.5, 26.2, 32.3, 37.9, 41.5, 43.8, 44.4, 47.6, 48.8, 52.5, 64.6, 127.6, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 130.9, 131.0, 131.4, 131.5, 131.6, 131.7, 132.0, 132.1, 132.2, 132.3, 132.5, 132.6, 163.5; *m*/*z* (CI) 561 ($[MH]^+$, 60%), 483 (11), 361 (42), 346 (44), 320 (70), 216 (100), 135 (67); HRMS found: $[MH]^+$561.1987, $C_{31}H_{34}N_2O_4PS$ requires 561.1977.

5.3.2. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(4-fluorophenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7k). Following the general procedure described above, *S*-**5** (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(4-fluorophenylmethylene)-phosphinic amide (323 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:9), affording **7k**, as a colourless solid (328 mg, 57%). R_f 0.51 (EtOAc); mp 197 °C; $[\alpha]_D^{20}$ +8.5 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3056, 2968, 1705, 1441, 1338, 1188, 1267, 1127, 740, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s), 0.96 (3H, s), 1.20–1.29, 1.79–1.81 and 1.95–1.97 (7H, m), 3.28 and 3.40 (2H, 2×d, J=13.6 Hz), 3.57–3.60 (1H, m), 4.19–4.26 (2H, 2×dd, J_P=16.1 Hz, J=6.2 Hz), 6.92–6.97 and 7.35–7.54 (10H, m), 7.91–7.96 and 8.09–8.14 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.7, 20.6, 26.3, 32.4, 37.9, 41.6, 43.2, 44.4, 47.6, 48.9, 52.5, 64.6, 114.5, 114.8, 128.3, 128.5, 128.6, 129.9, 129.9, 130.9, 131.4, 131.4, 131.6, 131.7, 131.9, 132.2, 161.2, 163.6; *m*/*z* (CI) 579 ($[MH]^+$, 14%), 515 (12), 419 (32), 379 (7), 297 (19), 219 (100), 77 (17); HRMS found: $[MH]^+$579.1870, $C_{31}H_{33}FN_2O_4PS$ requires 579.1883.

5.3.3. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2,6-dichlorophenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7l). Following the general procedure described above, *S*-**5** (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2,6-dichlorophenylmethylene)phosphinic amide (337 mg, 0.9 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:1), affording **7l**, as a colourless solid (493 mg, 87%). R_f 0.18 (petrol/EtOAc 1:1); mp 192 °C; $[\alpha]_D^{20}$ +6.2 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2964, 1704, 1441, 1333, 1168, 1274, 1125, 737, 708, 698 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.70–0.83 (6H, m), 1.18 and 1.74–1.93 (7H, m), 3.33 (1H, m), 3.45 and 3.50 (2H, 2×d, J=14.0 Hz), 4.18 and 4.21 (2H, 2×dd, J_P=15.6 Hz, J=5.3 Hz), 7.00–7.10 (3H, m), 7.34–7.44 (6H, m), 7.90–7.96 (3H, m); δ_C (60 MHz, $CDCl_3$) 19.7, 21.1, 26.2, 32.8, 38.2, 38.9, 42.6, 44.7, 47.7, 48.9, 52.7, 65.2, 128.1, 128.2, 128.3, 128.7, 129.1, 131.6, 131.7, 132.1, 132.2, 132.5, 132.6, 135.6, 165.2; *m*/*z* (CI) 629 ($[MH]^+$, 18%), 565 (12), 419 (12), 219 (100), 151 (26), 78 (39); HRMS found: $[MH]^+$629.1197, $C_{31}H_{32}Cl_2N_2O_4PS$ requires 629.1197.

5.3.4. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(3-bromophenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7m). Following the general procedure described above, *S*-**5** (300 mg, 0.89 mmol), LiHMDS in THF (1.0 mL, 1.0 M, 1.0 mmol) and *P*,*P*-diphenyl-*N*-(3-bromophenylmethylene)-phosphinic amide (346 mg, 0.89 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:9), affording **7m**, as a colourless solid (343 mg, 60%). R_f 0.75 (EtOAc); $[\alpha]_D^{20}$ +16.5 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2964, 1705, 1441, 1339, 1188, 1267, 1128, 740, 705 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.90 (3H, s), 0.97 (3H, s), 1.20–1.34 and 1.67–1.98 (7H, 2×m), 3.30 and 3.41 (2H, 2×d, J=13.9 Hz), 3.61–3.64 (1H, m), 4.18 and 4.22 (2H, 2m), 7.11–7.15 and 7.30–7.60 (10H, m), 7.92–7.97 and 8.09–8.14 (4H, m); δ_C (60 MHz, $CDCl_3$) 19.7, 20.6, 26.3, 32.4, 38.0, 41.6, 43.0, 44.5, 47.7, 49.0, 52.6, 64.6, 121.7, 126.6, 127.0, 128.0, 128.1, 128.4, 128.6, 128.7, 129.2, 129.8, 130.7, 130.8, 130.9, 131.1, 131.4, 131.4, 131.5, 131.7, 131.8, 131.9, 132.0, 132.1, 132.2, 135.1, 135.1, 141.0, 163.4; *m*/*z* (CI) 639 ($[MH]^+$, 23%), 573 (28), 419 (57), 359 (10), 219 (100), 135 (24); HRMS found: $[MH]^+$639.1187, $C_{31}H_{33}BrN_2O_4PS$ requires 639.1182.

5.3.5. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(4-methoxyphenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7n). Following the general procedure described above, *S*-**5** (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(4-methoxyphenylmethylene)phosphinic amide (337 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:9), affording **7n**, as a colourless solid (355 mg, 60%). R_f 0.45 (EtOAc); mp 139 °C; $[\alpha]_D^{20}$ +11.4

(c 1, $CHCl_3$); IR ν_{max} (CCl_4) 2964, 1698, 1439, 1330, 1188, 1275, 1126, 730, 703, 652 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s), 0.95 (3H, s), 1.22–1.30, 1.79–1.81 and 1.96–1.97 (7H, m), 3.28 and 3.39 (2H, 2×d, J=13.7 Hz), 3.61 (1H, m), 3.76 (3H, s), 4.11 and 4.25 (2H, 2×dd, J_P=16.1 Hz, J=5.9 Hz), 6.79–6.81 and 7.36–7.52 (10H, m), 7.91–7.96 and 8.10–8.15 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.7, 20.6, 26.3, 32.5, 38.1, 41.6, 43.7, 44.5, 47.7, 48.9, 52.6, 55.1, 64.6, 113.2, 124.7, 124.7, 128.4, 128.5, 128.7, 129.4, 131.1, 131.2, 131.5, 131.6, 131.8, 131.9, 132.1, 132.1, 132.4, 132.5, 159.3, 163.9; m/z (CI) 591 ($[M]^+$, 18%), 419 (37), 219 (92), 148 (100), 77 (49); HRMS found: $[M]^+$591.2089, $C_{32}H_{36}N_2O_5PS$ requires 591.2083.

5.3.6. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2-pyridinyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7o). Following the general procedure described above, *S*-**5** (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-pyridinylmethylene)phosphinic amide (306 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:9), affording **7o**, as a colourless solid (376 mg, 67%). R_f 0.37 (EtOAc); mp 195 °C; $[\alpha]_D^{20}$ +11.8 (c 1, $CHCl_3$); IR ν_{max} (CCl_4) 3059, 2965, 1703, 1440, 1342, 1171, 1268, 1129, 776, 738, 705 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.89 (6H, 2s), 1.21–1.29 and 1.82–2.04 (7H, m), 3.25 and 3.34 (2H, 2×d, J=13.9 Hz), 3.72 (1H, m), 4.11 and 4.34 (2H, 2×dd, J_P=15.8 Hz, J=6.6 Hz), 7.14–7.17 (1H, m), 7.37–7.64 (8H, m), 7.91–7.96 and 8.13–8.18 (4H, m), 8.50–8.51 (1H, m); δ_C (60 MHz, $CDCl_3$) 19.8, 20.5, 26.3, 32.7, 38.2, 41.5, 44.3, 44.8, 47.7, 49.2, 52.2, 64.4, 122.2, 123.1, 128.4, 128.6, 128.6, 128.8, 130.8, 131.4, 131.5, 131.8, 131.9, 132.1, 132.2, 132.3, 136.2, 150.3; m/z (CI) 562 ($[MH]^+$, 100%), 498 (75), 419 (97), 362 (34), 319 (50), 280 (73), 219 (93), 119 (31); HRMS found: $[MH]^+$562.1942, $C_{30}H_{33}N_3O_4PS$ requires 562.1930.

5.3.7. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(ethenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (7p). Following the general procedure described above, *S*-**5** (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(ethenylmethylene)phosphinic amide (255 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography (petrol/EtOAc 1:9), affording **7p**, as a colourless solid (239 mg, 47%). R_f 0.49 (EtOAc); $[\alpha]_D^{20}$ +10.2 (c 1, $CHCl_3$); IR ν_{max} (CCl_4) 3056, 2966, 1704, 1440, 1338, 1168, 1267, 1129, 735, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s), 0.93 (3H, s), 1.08–1.36, 1.77–1.81 and 1.97–2.02 (7H, m), 3.30 and 3.38 (2H, 2×d, J=13.7 Hz), 3.52–3.60 (1H, m), 3.77–3.95 (2H, m), 5.19 (1H, d, $J_{(cis)}$=10.5 Hz), 5.36 (1H, d, $J_{(trans)}$=17.4 Hz), 5.65 (1H, ddd, J=17.4, 10.5, 7.3 Hz), 7.33–7.43 (6H, m), 7.81–7.86 and 7.92–8.00 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.8, 20.3, 26.3, 32.7, 38.2, 39.7, 42.9, 44.6, 47.7, 49.2, 52.7, 64.8, 121.4, 128.3, 128.4, 128.6, 128.7, 130.7, 130.8, 131.2, 131.4, 131.5, 131.6, 131.7, 131.7, 131.8, 132.0, 132.3, 132.4, 132.4, 164.7; m/z (CI) 511 ($[MH]^+$, 30%), 419 (18), 268 (100), 201 (76), 77 (22); HRMS found: $[MH]^+$511.1820, $C_{27}H_{32}N_2O_4PS$ requires 511.1820.

5.4. General procedure for the removal of the sultam auxiliary

(2′*R*,3′*R*)-*N*-Sultamoyl-*N*-diphenylphosphinylaziridines (typically 0.2 mmol) were dissolved in a mixture of THF and water (4:1), 5 mL. Lithium hydroxide monohydrate (0.4 mmol) was then added. The resulting suspension was then stirred vigorously overnight, after which the THF was removed in vacuo, the aqueous layer basified to pH 10 with saturated $NaHCO_3$, and extracted with $CHCl_3$ (30 mL and 2×20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL) dried ($MgSO_4$), filtered and the solvent removed in vacuo. The aqueous layer was then combined with the base washings and acidified to pH 2 with 2 M HCl. Further $CHCl_3$ was added (3×45 mL), the layers separated, the organic layers combined, dried ($MgSO_4$), filtered and the solvent removed in vacuo, to afford the *N*-diphenylphosphinyl-2-substituted-3-carboxyaziridines.

5.4.1. (2′*R*,3′*R*)-*N*-Diphenylphosphinyl-2-carboxy-3-phenylaziridine (9a). By following the general procedure described above (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-diphenylphosphinyl-3′-phenyl-2′-aziridinyl)carbonyl]bornane-10,2-sultam (90 mg, 0.15 mmol) afforded **9a** as a colourless oil (33 mg, 64%). $[\alpha]_D^{20}$ −6.0 (c 1, MeOH); IR ν_{max} (film) 1717, 1438, 1128, 1025, 727, 691 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 3.40 (1H, dd, J_P=15.4 Hz, J=6.6 Hz), 3.97 (1H, dd, J_P=15.9 Hz, J=6.7 Hz), 7.04–8.00 (15H, m); δ_C (75 MHz, d_6-DMSO) 40.5, 40.7, 127.5, 128.6, 131.9, 133.5, 166.9; m/z (CI) 364 ($[MH]^+$, 0.5%), 320 (83), 242 (9), 218 (20), 201 (12), 89 (47), 61 (100); HRMS found: $[MH]^+$364.1113, $C_{21}H_{19}NO_3P$ requires 364.1102.

5.4.2. (2′*R*,3′*R*)-*N*-Diphenylphosphinyl-2-carboxy-3-(4-nitrophenyl)aziridine (9b). By following the general procedure described (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-diphenylphosphinyl-3′-(4-nitrophenyl)-2′-aziridinyl)carbonyl]-bornane-10,2-sultam (100 mg, 0.17 mmol) afforded **9b** as a colourless oil (40 mg, 60%). $[\alpha]_D^{20}$ −4.4 (c 2, DMSO); IR ν_{max} (film) 1719, 1517, 1347, 1437, 1128, 1025, 727, 691 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 3.59 (1H, dd, J_P=15.2 Hz, J=6.8 Hz), 4.49 (1H, dd, J_P=15.0 Hz, J=6.8 Hz), 7.47–8.31 (14H, m); δ_C (75 MHz, d_6-DMSO) 39.5, 124.6, 128.5, 131.9, 135.9, 148.1, 167.2; m/z (CI) 409 ($[MH]^+$, 1%), 365 (1.5), 335 (2), 219 (100), 201 (8) 141 (23); HRMS found: [M−CO_2] 365.1050, $C_{20}H_{18}N_2O_3P$ requires 365.1056.

5.4.3. (2′*R*,3′*R*)-*N*-Diphenylphosphinyl-2-carboxy-3-(2-nitrophenyl)aziridine (9c). By following the general procedure described (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-diphenylphosphinyl-3′-(2-nitrophenyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (100 mg, 0.17 mmol) afforded **9c** as a colourless oil (45 mg, 67%). $[\alpha]_D^{20}$ +2.3 (c 4, DMSO); IR ν_{max} (film) 1718, 1516, 1343, 1436, 1123, 1024, 727, 691 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 3.61 (1H, dd, J_P=15.2 Hz, J=6.6 Hz), 4.26 (1H, dd, J_P=15.4 Hz, J=6.8 Hz), 7.40–8.20 (14H, m); δ_C (75 MHz, d_6-DMSO) 39.5, 123.2, 128.5, 131.4, 134.1, 135.8, 147.4, 167.3; m/z (CI) 409 ($[MH]^+$, 7%), 365 (10), 347 (45), 219 (100), 201 (70), 120 (60); HRMS found: $[MH]^+$409.0956, $C_{21}H_{18}N_2O_5P$ requires 409.0953.

5.4.4. (2′*R*,3′*R*)-*N*-Diphenylphosphinyl-3-(4-bromophenyl)-2-carboxyaziridine (9d). By following the general procedure described (2*R*,2′*R*,3′*R*)-(−)-*N*-[(3′-(4-bromophenyl)-1′-diphenylphosphinyl-2′-aziridinyl)carbonyl]bornane-10,2-sultam (55 mg, 0.09 mmol) afforded **9d** as a colourless oil (26 mg, 61%). $[\alpha]_D^{20}$ −6.6 (*c* 1.5, DMSO); IR ν_{max} (film) 1735, 1437, 1131, 1011, 730, 692 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 3.49 (1H, dd, J_P=15.3 Hz, J=6.6 Hz), 4.08 (1H, dd, J_P=15.8 Hz, J=6.8 Hz), 7.44–8.07 (14H, m); δ_C (75 MHz, d_6-DMSO) 39.5, 122.2, 128.4, 131.7, 167.4; *m/z* (CI) 442 and 444 ($[MH]^+$, bromine isotope pattern, 3.3%) 398 (31), 400 (31), 320 (26), 219 (100), 201 (35), 141 (12); HRMS found: $[MH]^+$442.0201, $C_{21}H_{18}BrNO_3P$ requires 442.0208.

5.4.5. (2′*R*,3′*R*)-*N*-Diphenylphosphinyl-2-carboxy-3-(2-naphthyl)aziridine (9e). By following the general procedure described (2*R*,2′*R*,3′*R*)-(−)-*N*-[(1′-diphenylphosphinyl-3′-(2-naphthyl)-2′-aziridinyl)carbonyl]bornane-10,2-sultam (100 mg, 0.16 mmol) afforded **9e** as a yellow oil (35 mg, 51%). $[\alpha]_D^{20}$ −10.0 (*c* 2, DMSO); IR ν_{max} (film) 1719, 1437, 1129, 1034, 727, 692 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 3.57 (1H, dd, J_P=15.4 Hz, J=6.6 Hz), 4.21 (1H, dd, J_P=15.7 Hz, J=6.6 Hz), 7.44–8.11 (17H, m); δ_C (75 MHz, d_6-DMSO) 39.5, 125.1, 126.1, 126.2, 127.4, 127.6, 128.4, 131.9, 167.3; *m/z* (CI) 414 ($[MH]^+$, 0.5%), 370 (17), 247 (16), 219 (100), 201 (8), 141 (14); HRMS found: $[M-CO_2]$ 370.1350, $C_{24}H_{21}NOP$ requires 370.1361.

5.4.6. (2′*R*,3′*R*)-*N*-Diphenylphosphinyl-3-(*tert*-butyl)-2-carboxyaziridine (9f). By following the general procedure described (2*R*,2′*R*,3′*R*)-(+)-*N*-[(3′-(*tert*-Butyl)-1′-diphenylphosphinyl-2′-aziridinyl)carbonyl]bornane-10,2-sultam (50 mg, 0.1 mmol) afforded **9f** as a colourless oil (15 mg, 47%). $[\alpha]_D^{20}$ +3.7 (*c* 1.5, DMSO); IR ν_{max} (film) 2960, 1718, 1438, 1129, 1027, 730, 675 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 0.72 (9H, s), 2.56 (1H, dd, J_P=16.8 Hz, J=6.8 Hz), 3.06 (1H, dd, J_P=16.6 Hz, J=6.8 Hz), 7.40–8.10 (10H, m); δ_C (75 MHz, d_6-DMSO) 26.7, 39.5, 128.5, 128.6, 131.8, 167.4; *m/z* (CI) 344 ($[MH]^+$, 62%), 298 (22), 274 (23), 219 (100), 201 (54), 141 (12); HRMS found: $[MH]^+$344.1414, $C_{19}H_{23}N_2O_3P$ requires 344.1416.

5.4.7. (2′*S*,3′*S*)-2-Carboxy-*N*-diphenylphosphinyl-3-(3-bromophenyl)aziridine (9g). Following the general procedure described above, *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-bromophenyl)-2-aziridinyl)carbonyl]-bornane-10,2-sultam (128 mg, 0.2 mmol) afforded **9g** as a colourless oil (70 mg, 80%). $[\alpha]_D^{20}$ −12.8 (*c* 1, $CDCl_3$); IR ν_{max} (CCl_4) 1718, 1439, 1131, 1028, 751, 695 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.51 and 3.98 (2H, 2×dd, J_P=15.6 Hz, J=6.6 Hz), 7.06–8.05 (14H, m); δ_C (60 MHz, $CDCl_3$) 42.3, 42.6, 123.5, 128.1, 129.8, 130.1, 130.3, 130.4, 130.5, 130.6, 131.4, 132.0, 132.6, 132.8, 132.8, 133.0, 133.2, 133.4, 134.6, 134.6, 137.4, 169.2; *m/z* (CI) 444 ($[MH]^+$, 10%), 398 (7), 236 (67), 219 (100); HRMS found: $[MH]^+$444.0214, $C_{21}H_{18}BrNO_3P$ requires 444.0188.

5.4.8. (2′*S*,3′*S*)-2-Carboxy-*N*-diphenylphosphinyl-3-(2,6-dichlorophenyl)aziridine(9h). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2,6-dichlorophenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (126 mg, 0.2 mmol) afforded **9h** as a colourless oil (37 mg, 45%). $[\alpha]_D^{20}$ −10.8 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 1718, 1439, 1131, 1028, 751, 714, 695 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.39 and 4.08 (2H, 2×dd, J_P=16.0 Hz, J=6.0 Hz), 7.11–7.92 (13H, m); δ_C (60 MHz, $CDCl_3$) 40.9, 42.6, 129.9, 130.0, 130.1, 130.5, 130.7, 131.2, 132.6, 132.8, 133.2, 133.3, 133.7, 133.8, 134.4, 134.4, 134.6, 134.7, 137.2, 170.7; *m/z* (CI) 432 ($[MH]^+$, 100%), 388 (40), 354 (10), 236 (91), 201 (21), 66 (36); HRMS found: $[MH]^+$432.0303, $C_{21}H_{17}Cl_2NO_3P$ requires 432.0323.

5.4.9. (2′*S*,3′*S*)-2-Carboxy-*N*-diphenylphosphinyl-3-(2-pyridinyl)aziridine (9i). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-pyridinyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (105 mg, 0.187 mmol) afforded **9j** as a yellow oil (68 mg, 99%). $[\alpha]_D^{20}$ −25.8 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 1718, 1439, 1130, 757, 695 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.58 and 4.06 (2H, 2×dd, J_P=15.6 Hz, J=6.6 Hz), 7.22–8.35 (14H, m); δ_C (60 MHz, $CDCl_3$) 42.1, 43.4, 124.5, 125.4, 129.8, 130.0, 130.3, 130.5, 130.6, 130.7, 132.6, 132.8, 132.9, 133.0, 133.1, 133.2, 133.4, 134.5, 134.6, 134.7, 139.3, 149.9, 154.5, 169.1; *m/z* (CI) 321 ($[MH-CO_2]^+$, 13%), 236 (63), 218 (100), 150 (17), 121 (23); HRMS found: $[MH-CO_2]^+$321.1171, $C_{19}H_{17}N_2OP$ requires 321.1157.

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11. The absolute configuration of the aziridine asymmetric centres were tentatively assigned from computer modelling.

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Asymmetric aziridine synthesis by aza-Darzens reaction of *N*-diphenylphosphinylimines with chiral enolates. Part 2: Inversion of diastereoselectivity

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Abstract—The aza-Darzens ('ADZ') reactions of *N*-diphenylphosphinyl ('*N*-Dpp') imines with chiral enolates derived from *N*-bromoacetyl 2*S*-2,10-camphorsultam proceed in generally good yield to give *N*-diphenylphosphinyl aziridinoyl sultams. However, the stereoselectivity of the reaction is dependent upon the structure of the imine substituent: when the chiral enolate was reacted with arylimines substituted in the *ortho*-position, mixtures of *cis*- and *trans*-2′*R*,3′*R*-aziridines were obtained, often with a complete selectivity in favour of the trans-isomer.

1. Introduction

We have recently described our studies of the aza-Darzens reaction ('ADZ') of *N*-diphenylphosphinyl ('*N*-Dpp') imines with enolates derived from *N*-bromoacetylcamphorsultam, which proceed with good efficiency and high levels of stereoselectivity.[1] In the reactions of *N*-Dpp aryl imines with these enolates, in common with other such reactions, there often is an inherent propensity for the formation of *cis*-aziridines as the major products. This is a consequence of the stepwise nature of the mechanism involved (vide infra). In this manuscript, we describe how the presence of sterically-demanding imine substitutents can invert the diastereoselectivity of the ADZ reaction, allowing for the obtention of *trans*-aziridines from this process.

2. Results and discussion

2.1. ADZ reaction of unsaturated imines

The first sign that the ADZ reaction might be tunable according to substituent pattern in the imine was observed in the reactions of α,β-unsaturated imines. Thus, in the reaction of the camphor enolate with Dpp–imine derived from acrolein, *cis*-aziridine[†] **1a** was obtained as the only product of the reaction, in moderate yield. However, when the analogous reaction was carried out using the imine from 3,3-dimethylacrolein, we obtained two products (Scheme 1). The first was **1b**, an aziridine with $^{2}J_{H}=$ 2.9 Hz, indicative of a trans-stereochemistry. The second product was a non-crystalline, non-aziridine product, tentatively identified as pyrroline (**2**, obtained in 20% yield).

The latter compound would be obtained via 1,4-addition of the chiral enolate followed by 5-*exo*-tet cyclization of the resulting amide anion. Despite many attempts, we have been unable to confirm either the gross structure or stereochemistry of the fragile by-product **2**. Given that we had previously observed only cis-configured aziridines (often the products of asymmetric aziridination reactions)[2] in these aza-Darzens reactions, we were intrigued by the observation and we postulated that the inverted stereoselectivity might be due to the extra steric demand present in the more substituted imine due to the *gem*-dimethyl substitution pattern. We set out to examine the scope of the trans-selective reaction.

2.2. ADZ reaction of *ortho*-substituted aryl imines

In the first instance, we chose a range of *ortho*-substituted aryl imines as suitable substrates to provide pertinent information about the breadth of the process. *N*-Dpp-2-chlorobenzaldimine reacted under the standard conditions to give a mixture of

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[†] Decoupling experiments indicated $J\sim 6$ Hz.

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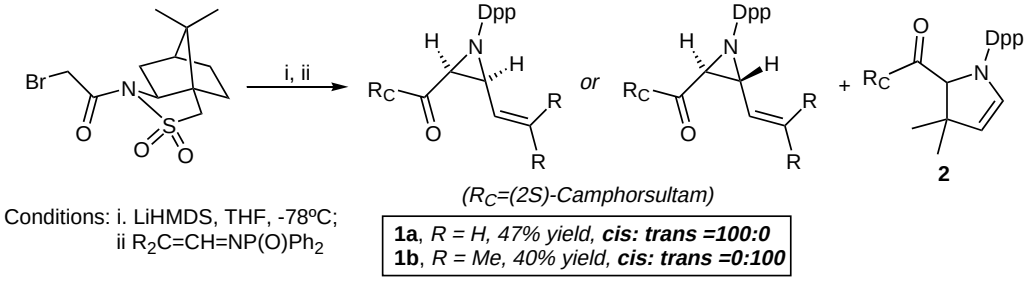
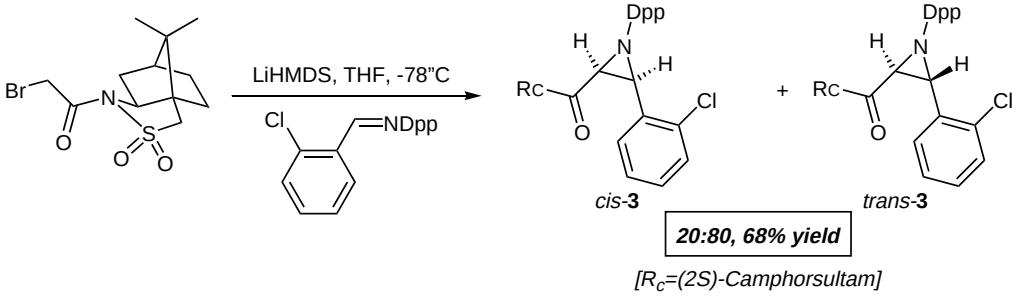
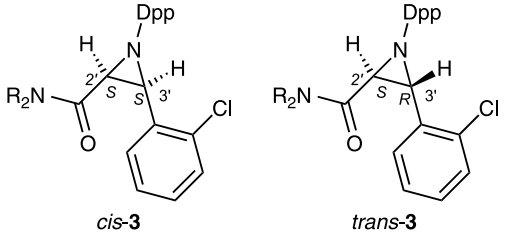


Scheme 1.



Scheme 2.



cis-isomer	64.58	52.46	48.95	47.70	44.56	40.72	40.66	32.49	38.12	26.29	20.55	19.72
trans-isomer	65.11	52.71	48.76	47.59	44.37	43.99	41.27	32.52	37.75	26.29	20.64	19.65
Δδ/ppm	0.53	0.25	-0.11	-0.11	-0.19	3.27	0.61	0.03	-0.37	0.00	0.09	-0.07

Figure 1. Selected ^{13}C NMR data for *cis*-**3** and *trans*-**3**.

cis- and *trans*-aziridines **3** (cis:trans =20:80, J=6.1, 2.8 Hz, respectively) in a combined yield of 68% (Scheme 2).

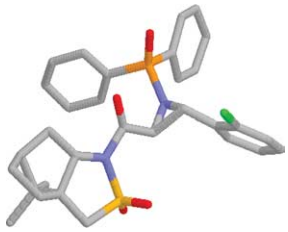
Although the obtention of a mixture of diastereoisomers, and the coupling constants shown by these products, gave a clear indication that the diastereoselectivity of the reaction had been inverted to favour the trans-isomer, *cis*-**3** and *trans*-**3** did not initially produce crystals suitable for analysis by X-ray crystallography. We were, therefore, forced to seek an alternative means to confirm the actual stereochemistry of the compounds. Although we felt it was reasonable to assume that the diastereoface selectivity of the reaction (vide infra) was unaltered (meaning that the absolute stereochemistry at C′-2 would be *S*), we were, of course, motivated to provide more compelling evidence for the stereochemistry engendered by the reaction. As a first means of assessing the compounds, we examined the ^{13}C NMR spectra of *cis*-**3** and *trans*-**3** (Fig. 1).

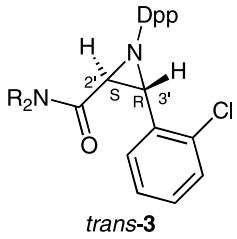
Thus, we observed that in the NMR spectra of *cis*-**3** and *trans*-**3** there was significant (≥5%) divergence in the chemical shift value of only one of the non-aromatic resonances recorded for each compound. Since we had previously demonstrated in an unambiguous manner[‡] that this resonance belonged to the benzylic aziridine carbon (i.e., position 3′), we felt confident in stating that the stereochemistry of *trans*-**3** was (2′*S*, 3′*R*), as shown in Figure 1. To our delight, when we subsequently obtained single crystals of *trans*-**3**, which were suitable for X-ray analysis, our initial stereochemical assignment was vindicated (Fig. 2).

When the reaction was repeated with a range of *ortho*-substituted aryl imines, a pattern began to emerge (Table 1).

In all but one of the ADZ reactions of *ortho*-substituted benzaldimines examined, *trans*-aziridines were observed in the product mixture and in several cases (entries 5–7, 10) the reaction provided only the trans-isomer; only in the reaction of

[‡] Using homo- and heteronuclear correlated spectroscopy.





trans-**3**

Figure 2.

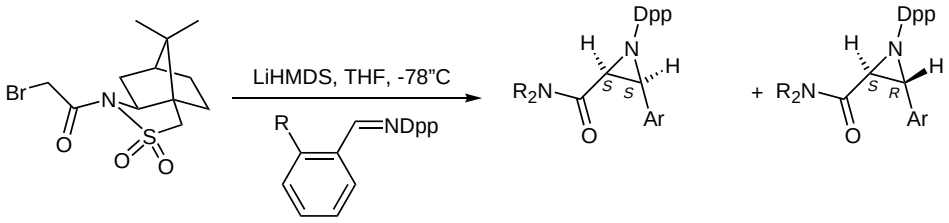
These data are completely at odds with a mechanism controlled by steric demand and may suggest that there are several mechanism at play, as discussed below.

2.3. Mechanism of ADZ Reaction[§]

General principles

Though there are many possible arrangements of reagents, the preferred rationalization for asymmetric aldol reactions

Table 1. Effect of imine substitution upon diastereoselectivity of ADZ reactions



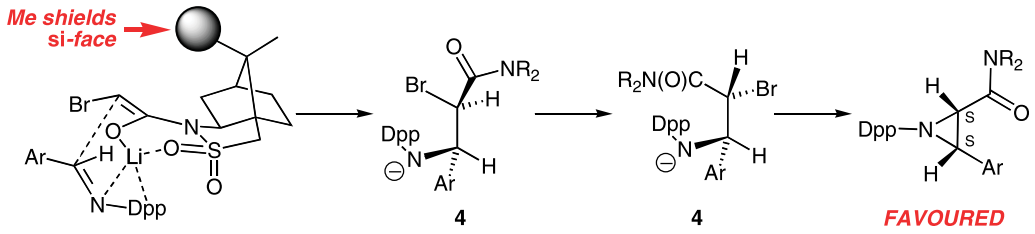
Entry	Ar	Yield (%)	cis:trans	^3J cis/trans (Hz)
1	Ph	71	100:0	6.2
2	2-NO_2–C_6H_4	72	100:0	5.8
3	2-F–C_6H_4	84	50:50	6.2/2.8
4	2-Cl–C_6H_4	68	20:80	6.1/2.8
5	2-Br–C_6H_4	67	0:100	2.6
6	2-I–C_6H_4	73	0:100	2.8
7	2-OMe–C_6H_4	65	0:100	3.1
8	2-Me–C_6H_4	87	50:50	6.0/2.8
9	2-Et–C_6H_4	93	63:37	6.1/2.8
10	2-CF_3–C_6H_4	69	0:100	2.7

the -imine derived from 2-nitrobenzaldehyde was *cis*-aziridine exclusively isolated. The latter observation might lead one to the conclusion that the polarity of the 2-substituent is unimportant in influencing the diastereoselectivity of the reaction and that the formation of *cis*-aziridine is due to the relatively small steric demands of the planar NO_2 substituent. This conclusion is endorsed by the results obtained from the ADZ reactions of the imines derived from *ortho*-halo benzaldehydes (Table 1, entries 3–6), which seem to indicate a clear connection between size and selectivity: 2-fluorobenzaldimine gives a 50:50 mixture of *cis*- and *trans*-aziridines, 2-chlorobenzaldimine a 20:80 ratio (as described above), while the 2-bromo- and 2-iodobenzaldimines furnish only *trans*-aziridines. In all the reactions of the halogenated substrates, the overall yields were similar to, or better than (in the case of the 2-fluoro and 2-iodo compounds) the reaction of the parent imine. The presence of a more powerfully π-donating electronegative substituent, a 2-methoxy group, had a similar effect upon the diastereoselectivity of the reaction, with only *trans*-aziridine obtained. However, when the ADZ reaction was carried out using 2-methylbenzaldimine, in which the substituent has a greater steric demand than any of the halogens, a 50:50 mixture of *cis*- and *trans*-aziridines was obtained, in excellent yield. Given the relative *A*-values (for instance, $A_{Br}=$ 2.01–2.80 kJ mol^{-1}, whereas $A_{Me}=7.28$ kJ mol^{-1}), this result does not tally with a reaction proceeding purely under the control of steric effects (vide infra). Furthermore, the 2-trifluoromethylphenyl imine gave only *trans*-aziridine (entry 9), whereas the ethyl substituted analogue reacted to give the cis-isomer as the dominant product (cis:trans = 1.7:1, entry 10).

mediated by lithium enolates of camphorsultam derivatives invokes a twisted boat-like transition state, in which there is a chelation between one of the S=O bonds and the apical lithium atom of the enolate.[3] Thus, in the (*Z*)-enolate produced by deprotonation of *N*-bromoacetyl-(2*S*)-camphorsultam, the *si*-face is powerfully shielded by the methyl group, which is *syn*- to the sultam unit, and these enolates inherently favour *re*-face interactions with incoming electrophiles.

Although likely to share the general features of aldol reactions, the ADZ reaction is complicated by several additional factors: firstly, the reaction is considerably slower than the aldol reaction. Secondly, there is an additional (and polar) substituent in the shape of the diphenylphosphinyl group. Finally, there is the question of imine stereochemistry: the barrier to imine inversion is variable, but such isomerizations are relatively facile under a range of conditions.[4] As in sultam aldol reactions, the enolate's *re*-face is, in all cases, more accessible: as the imine approaches the enolate, its substituent is placed *anti*- to the sultam sub-unit, leading to the transition state shown in Scheme 3 (note that in any of the chelated transition states there is an unavoidable interaction of the imine substituent and the α-bromo group-vide infra). In addition, it is likely that the Dpp group will coordinate to the lithium atom of the enolate, through the polar P=O bond,

[§] In our original description (McLaren, A. B.; Sweeney, J. B. *Org. Lett.*, **1999**, *1*, 1339) of the trans-selective ADZ reaction, the diagrammatic representaion of the transition states involved were reproduced incorrectly; we thank Professor D. Tanner for drawing our attention to this fact.



Scheme 3.

though this interaction may be weak (a full coordination would form a four-membered ring).

This preferred, *re–re*, interaction would lead to a 2′*S*,3′*S*-aziridine when using (2*S*)-sultam, via the corresponding 2′*R*, 3′*S*-bromoamide **4**: this hypothetical prediction is fulfilled in practice. However, although it is clear that the reaction proceeds via a *re–re* interaction, it is not a trivial matter to deduce the precise nature of the TS: we must consider three options.

Chair, boat or open TS?

As adumbrated above, the face selectivity of the ADZ reaction can be easily ascertained from the stereochemistry of the products (assuming *Z*-configuration in the enolate and *E*-configuration in the imine). It is less clear whether this stereochemical course of action arises from a closed or open transition state: it is even less obvious whether the closed TS would prefer a chair or boat arrangement.

Closed TS, chair or boat conformation

It is difficult to construct a convincing *re–re* Zimmerman–Traxler-like transition state (Scheme 4) for this ADZ reaction: there clearly is a unfavourable interaction between the imine CH and the methylene group adjacent to the C–N bond of the camphor sub-unit. As shown in the figure, this repulsive interaction is not greatly ameliorated by a change in conformation from chair→boat. The tetracyclic TS is configured in this manner when coordination to the lithium atom of the enolate occurs through the pseudoaxial rather than the pseudoequatorial S=O bond.

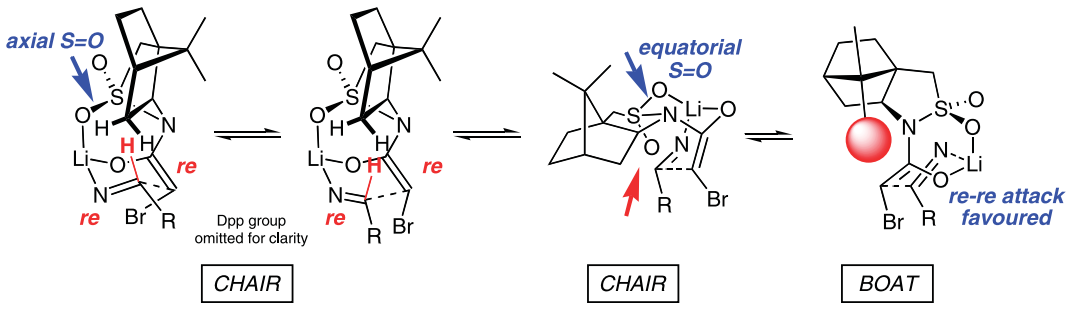
If the pseudoequatorial S=O bond is used in coordination, an alternative Zimmerman–Traxler TS is still accessible, but even more severe steric interactions are evident. Thus, it seems likely that a twisted boat TS is in operation. In this arrangement, one of the *gem*-dimethyl groups of the terpene bridge still provides a powerful shielding influence, the pseudoequatorial S=O–Li interaction is in place and the R substituent is *anti*-to the camphor ring. This is a *re–re* interaction, leading to the 2′*S*,3′*S*-configured aziridine products observed.

Inversion of diastereoselectivity

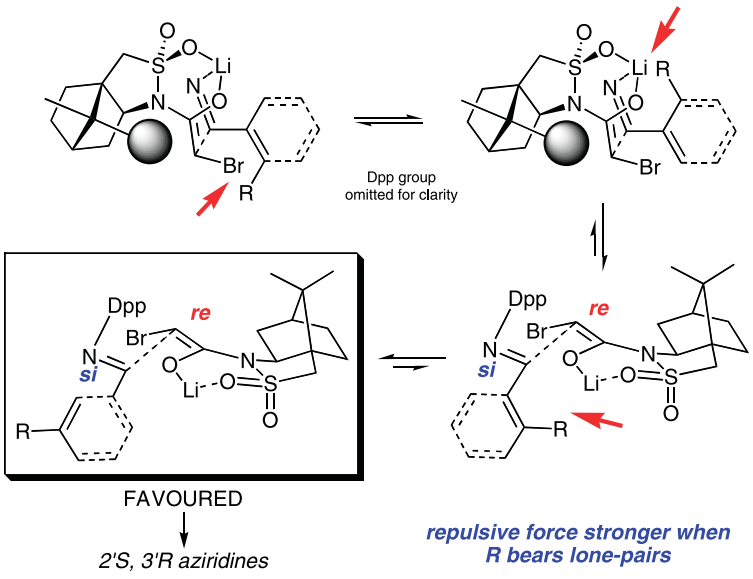
As described above, ADZ reaction of *ortho*-substituted imines can give 2′*S*,3′*R*-aziridines from 2*S*-bromoacyl camphorsultam and we must modify our mechanistic rationâle accordingly. Such products arise from a *re*-enolate–*si*-imine interaction, which cannot be easily accommodated within a closed transition state: the chelated nature of the enolate precludes a simple change in the direction of approach of the reagents. We suggest that an open transition state is in operation, as shown in Scheme 5; this open TS is favoured, we believe, due to the repulsive interaction between the imine γ-substituent (an *ortho*-substituent in the case of aryl imines and an allylic substituent in the case of an α,β-unsaturated imine) and the enolate bromine in a cyclic TS. Thus, there is an equilibrium between conformers in which the R substituent is either *syn*- or *anti*-to the enolate α-bromo substituent.

In both conformers, there are repulsive interactions, which can destabilize the arrangement though the major contributor is certainly the Br–R interaction (indicated by bold arrows on the Scheme). A switch to an open TS, though not without steric interactions, is certainly less compressed than the closed TS, and so a *re*-enolate-*si*-imine interaction is favoured, leading to 2′*S*,3′*R*-configured aziridines.

As alluded to above, the variation in selectivity is not controlled by purely steric demands: recall that the

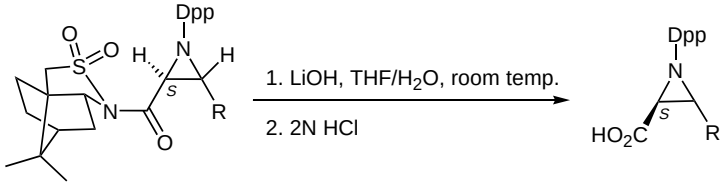


Scheme 4.



Scheme 5.

Table 2. Hydrolytic removal of auxiliary from *cis*- and *trans*-aziridines



Entry	R	Yield (%)
1	*trans*-$Me_2C{=}CH$	50
2	*trans*-2-Cl–C_6H_4	45
3	*trans*-2-F_3C–C_6H_4	57
4	*cis*-2-Me–C_6H_4	81
5	*cis*-2-Et–C_6H_4	65

reaction with R=Me is less selective than with R=OMe, despite the effective smaller size of the methoxy substituent (O vs CH_2). This suggests that there is a polar phenomenon also in play, perhaps due to the lone-pair/lone-pair repulsion, which would be present with oxygen or halogeno substituents, but not with alkyl ones. Such a phenomenon would also rationalize the observation that an *ortho*-CF_3 group causes a complete inversion in stereoselectivity, whereas the *ortho*-CH_3 group engenders a non-selective reaction (giving a 50:50 mixture of cis- and trans-isomers). It does not, however, explain why an *ortho*-ethyl group gives a mixture of aziridines dominated by the cis-form (cis:trans=63:37).

Cleavage of the auxiliary

We have also demonstrated that a representative cross-section of these *trans*-aziridines can be hydrolyzed to give the corresponding aziridine carboxylates, in a manner analogous to that described for the cis-compounds (Table 2). However, the yields of hydrolysis are lower than observed in the hydrolysis of analogous *cis*-aziridines, perhaps reflecting a more hindered trajectory for the incoming nucleophile.

3. Conclusion

We have developed a practical ADZ reaction, which allows the preparation of chiral aziridine derivatives in good yield. Depending on the substitution pattern of the imine, the inherent cis-selectivity of the process can be inverted to give exclusively trans-configured products. We are currently attempting to expand further the scope of this process, and studying the underlying factors responsible for the stereoselectivity observed.

4. Experimental

4.1. General techniques

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[5] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40–60 °C and 'ether' refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl; toluene from sodium; dichloromethane, triethylamine, acetonitrile from calcium hydride, methanol from magnesium methoxide and diisopropylethylamine from potassium

hydroxide. Imines were prepared according to literature methods.[6] Other chemicals were purchased from Aldrich Chemical Co. or prepared by literature methods.

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Spectra were recorded on Perkin Elmer 881 or Paragon 1000 spectrophotometers. Optical rotations were measured using a Perkin Elmer 241 MC polarimeter and are quoted in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on VG9090 or Fisons Autospec mass spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on Jeol GX-270, Jeol GX-400, Lambda 300, Bruker DPX-250 or Bruker AX-400 spectrometers. Unless otherwise stated, deuterochloroform was used as solvent and tetramethylsilane was the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from tetramethylsilane, and in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (*J*) are quoted in Hz.

Reactions involving chemicals or intermediates sensitive to air or moisture were conducted under a nitrogen or argon atmosphere in oven- or flame-dried apparatus. Flash chromatography was performed using Merck Kieselgel 60 or Fluka Kieselgel 60 silica gel. Analytical thin-layer chromatography was performed using either precoated Merck Kieselgel 60 F_{254} glass-backed plates, or precoated Merck Kieselgel 60 F_{254} aluminium backed plates and were visualised under UV at 254 nm and by staining with iodine and/or an acidic ammonium molybdate dip.

X-ray data obtained from *trans*-**3** has been deposited at CCDC (reference number CCDC 291092).

^{13}C NMR spectra of *N*-Dpp compounds are complicated by rotameric isomers, which often leads to the appearance of 'excess' resonances in the aromatic region of the spectra; the situation is further complicated by the difficulty in obtaining precise coupling constants. Rather than refer to the entire region of the spectra as being a 'multiplet', the data quoted describes the actual appearance of the spectra.

4.2. General procedure for aza-Darzens reaction: synthesis of *cis*- and *trans*-2,3 substituted aziridines

(2*R*)-(−)-(*N*-Bromoacetyl)bornane-10,2-sultam, (1.0 equiv), was dissolved in THF (25 mL) and cooled to −78 °C. LiHMDS in THF (1.1 equiv) was then added dropwise, and the resulting pale yellow solution stirred for 30 min. Phosphinylimine (typically 1.0 equiv) was then added at −78 °C as a solution in THF (10 mL). The reaction mixture was then stirred for over 2 h at −78 °C, after which time the reaction was judged to have reached completion by TLC and the mixture was quenched with saturated ammonium chloride solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL, 2×10 mL), the organic layers were then combined, washed with brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo, to afford the crude aziridine.

4.2.1. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2-methylpropenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (*cis*-1b).

Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-methylpropenylmethylene)phosphinic amide (283 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford **1b**, as a colourless solid (214 mg, 40%); R_f 0.55 (EtOAc); $[\alpha]_D^{20}$ +74.1 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3058, 2966, 1698, 1440, 1338, 1168, 1268, 1127, 735, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s), 0.93 (3H, s), 1.13–1.26, 1.76–1.81 and 1.95–2.01 (7H, m), 1.28 (3H, s), 1.53 (3H, s), 3.29 and 3.38 (2H, 2×d, *J*=13.9 Hz), 3.45–3.51 (1H, m), 3.73–3.91 (2H, m), 5.32 (1H, d, *J*=9.2 Hz), 7.29–7.41 (6H, m), 7.76–7.81 and 7.92–7.97 (4H, m); δ_C (100 MHz, $CDCl_3$) 17.5, 25.5, 19.7, 20.6, 26.2, 32.6, 38.2, 40.0, 44.4, 44.5, 47.7, 49.0, 52.6, 64.8, 118.6, 127.9, 128.0, 128.2, 128.4, 128.5, 128.5, 131.2, 131.4, 131.5, 131.6, 131.8, 131.9, 132.1, 132.2, 132.7, 133.0, 134.1, 142.0, 166.7; MS (CI) *m*/*z* 538 ([M]$^+$, 11%), 417 (9), 296 (62), 219 (29), 201 (100), 77 (18); HRMS found: [M]$^+$538.2099 $C_{29}H_{36}N_2O_4PS$ requires 538.2055.

4.2.2. 2*S*-*N*-[1′-Diphenylphosphinyl-4′,4′-dimethyl-2′,3′-dihydro-1*H*-pyrrole-5′-carbonyl]bornane-10, 2-sultam (2).

Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-methylpropenylmethylene)phosphinic amide (283 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford **2** as a colourless solid (109 mg, 20%); R_f 0.36 (EtOAc); $[\alpha]_D^{20}$ +66.4 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3056, 2968, 1687, 1440, 1342, 1168, 1267, 1125, 741, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s), 0.94 (3H, s), 1.23 (3H, s), 1.51 (3H, s), 1.01–1.36 and 1.80–2.11 (7H, 2×m), 3.39 and 3.41 (2H, 2×d, *J*=13.2 Hz), 3.85 (1H, m), 4.17 (1H, m), 4.80 (1H, m), 4.99 (1H, m), 7.36–7.41 (6H, m), 7.82–7.90 (4H, m); δ_C (100 MHz, $CDCl_3$) 18.1, 25.5, 19.7, 20.6, 26.3, 32.8, 38.0, 44.6, 47.7, 48.5, 52.8, 53.3, 56.5, 65.5, 122.3, 128.1, 128.2, 128.3, 128.3, 128.4, 128.6, 131.2, 131.4, 131.5, 131.7, 131.8, 131.9, 132.0, 132.1, 132.2, 132.3, 132.4, 132.4, 133.6, 137.9, 167.2; MS (CI) *m*/*z* 539 ([M]$^+$, 13%), 475 (6), 419 (16), 324 (20), 284 (100), 218 (68), 152 (34); HRMS found: [M]$^+$539.2127, $C_{29}H_{35}N_2O_4PS$ requires 539.2133.

4.2.3. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2-fluorophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 3).

Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-fluorophenylmethylene)phosphinic amide (323 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (243 mg, 42%); R_f 0.50 (petrol/EtOAc 1:3); $[\alpha]_D^{20}$ +16.6 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2964, 1703, 1441, 1340, 1176, 1271, 1129, 758, 733, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89, (3H, s), 0.93 (3H, s), 1.19–1.28 and 1.80–1.99 (7H, 2×m), 3.27 and 3.38 (2H, 2×d, *J*=13.6 Hz), 3.64 (1H, m), 4.18 and 4.48 (2H, 2×dd,

J_P=15.8 Hz, J=6.2 Hz), 6.94–7.59 (10H, m), 7.92–8.15 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.7, 20.6, 26.3, 32.5, 38.0, 38.5, 41.4, 44.6, 47.7, 49.0, 52.4, 64.5, 114.7, 123.4, 128.4, 128.6, 128.7, 129.1, 129.6, 129.7, 130.8, 130.9, 131.5, 131.6, 131.7, 131.8, 132.0, 132.2, 160.8, 163.4; MS (CI) *m/z* 579 ($[MH]^+$, 96%), 515 (42), 419 (40), 379 (27), 297 (28), 218 (100), 135 (30); HRMS found: $[MH]^+$579.1874, $C_{31}H_{33}FN_2O_4PS$ requires 579.1883.

4.2.4. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-fluorophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 3). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-fluorophenylmethylene)phosphinic amide (323 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (243 mg, 42%); R_f 0.45 (petrol/EtOAc 1:3); $[\alpha]_D^{20}$ +83.5 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2964, 1687, 1440, 1339, 1169, 1287, 1139, 742, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, s), 0.87 (3H, s), 1.16–1.36 and 1.70–1.97 (7H, 2×m), 3.03 and 3.36 (2H, 2×d, J= 13.9 Hz), 3.78 (1H, m), 4.20 and 4.33 (2H, 2×dd, J_P= 13.4 Hz, J=2.8 Hz), 6.71–7.90 (14H, m); δ_C (100 MHz, $CDCl_3$) 20.1, 21.0, 26.7, 33.0, 38.2, 40.8, 41.2, 44.8, 48.0, 49.2, 53.1, 65.5, 115.1, 124.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 130.4, 130.4, 131.7, 131.8, 131.9, 132.0, 132.4, 132.5, 163.9, 165.6; MS (CI) *m/z* 579 ($[MH]^+$, 100%), 515 (71), 419 (67), 379 (41), 297 (35), 201 (78); HRMS found: $[MH]^+$579.1902, $C_{31}H_{33}FN_2O_4PS$ requires 579.1883.

4.2.5. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2-chlorophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 4). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-chlorophenylmethylene)phosphinic amide (340 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (81 mg, 13%); R_f 0.63 (EtOAc); $[\alpha]_D^{20}$ +28.7 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2964, 1703, 1440, 1341, 1128, 1266, 1169, 745, 705, 644 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.78–0.83 (6H, m), 1.12–1.20 and 1.72–1.97 (7H, 2×m), 3.22 and 3.30 (2H, 2×d, J=13.9 Hz), 3.57–3.60 (1H, m), 4.11–4.50 (2H, 2×dd, J_P=15.9 Hz, J= 6.1 Hz), 7.10–7.57 and 7.85–8.03 (14H, 2×m); δ_C (100 MHz, $CDCl_3$) 19.7, 20.6, 26.3, 32.5, 38.1, 40.7, 42.3, 44.6, 47.7, 49.0, 52.5, 64.6, 126.0, 128.4, 128.6, 128.7, 129.1, 129.2, 129.6, 130.6, 130.8, 131.6, 131.7, 131.7, 131.8, 131.8, 131.9, 132.1, 132.3, 134.6, 163.7; MS (CI) *m/z* 595 ($[MH]^+$, 66%), 531 (60), 419 (100), 313 (43), 201 (91), 77 (32); HRMS found: $[MH]^+$595.1594, $C_{31}H_{34}N_2O_4PS$ requires 595.1588.

4.2.6. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-chlorophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 4). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-chlorophenylmethylene)phosphinic amide (340 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (325 mg, 55%); R_f 0.56 (EtOAc); $[\alpha]_D^{20}$ +59.4 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3056, 2985, 1705, 1440, 1338, 1168, 1266, 1126, 738, 706, 623 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.75 (3H, s), 0.80 (3H, s), 1.01–1.29 and 1.65–1.89 (7H, 2×m), 3.23 and 3.28 (2H, 2×d, J= 13.6 Hz), 3.72 (1H, m), 4.16 and 4.30 (2H, 2×dd, J_P= 13.3 Hz, J=2.8 Hz), 7.03–7.10 and 7.19–7.34 (10H, 2×m), 7.63–7.67 and 7.79–7.83 (4H, 2×m); δ_C (100 MHz, $CDCl_3$) 19.7, 20.6, 26.3, 32.5, 37.8, 41.3, 44.0, 44.4, 47.6, 48.8, 52.7, 65.1, 126.5, 128.0, 128.1, 128.1, 128.3, 128.4, 128.9, 129.4, 131.2, 131.6, 131.7, 132.5, 133.0, 134.3, 135.5, 164.9; MS (CI) *m/z* 594 ($[M]^+$, 19%), 559 (49), 219 (68), 201 (100), 77 (27); HRMS found: $[M]^+$594.1559, $C_{31}H_{34}N_2O_4PS$ requires 594.1509.

4.2.7. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-bromophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 5). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (336 mg, 1.0 mmol), LiHMDS in THF (1.1 mL, 1.0 M, 1.1 mmol) and *P*,*P*-diphenyl-*N*-(2-bromophenylmethylene)phosphinic amide (386 mg, 1.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (428 mg, 67%); R_f 0.53 (EtOAc); $[\alpha]_D^{20}$ +13.5 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3056, 2966, 1705, 1441, 1336, 1188, 1267, 1128, 740, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, s), 0.89 (3H, s), 1.21–1.38 and 1.80–2.02 (7H, 2×m), 3.37 and 3.42 (2H, 2×d, J= 13.9 Hz), 3.86 (1H, m), 4.24 and 4.43 (2H, 2×dd, J_P= 13.2 Hz, J=2.6 Hz), 7.10–7.14, 7.24–7.28 and 7.35–7.45 (10H, m), 7.78–7.83 and 7.92–7.97 (4H, m); δ_C (100 MHz, $CDCl_3$) 9.8, 20.6, 26.4, 32.7, 37.9, 41.9, 46.1, 44.5, 47.7, 48.8, 52.8, 65.7, 125.4, 127.2, 127.6, 128.1, 128.2, 128.4, 128.4, 128.6, 128.7, 129.5, 129.7, 129.9, 131.3, 131.5, 131.6, 131.7, 131.8, 131.9, 132.4, 132.5, 133.0, 133.3, 133.3, 133.7, 134.4, 134.5, 164.8; MS (CI) *m/z* 639 ($[MH]^+$, 32%), 573 (30), 419 (50), 357 (11), 219 (100), 135 (23); HRMS found: $[MH]^+$639.1089, $C_{31}H_{33}BrN_2O_4PS$ requires 639.1082.

4.2.8. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-iodophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 6). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (202 mg, 0.6 mmol), LiHMDS in THF (0.66 mL, 1.0 M, 0.66 mmol) and *P*,*P*-diphenyl-*N*-(2-iodophenylmethylene)-phosphinic amide (259 mg, 0.6 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (300 mg, 73%); R_f 0.51 (EtOAc); $[\alpha]_D^{20}$ +73.5 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.77 (3H, s), 0.79 (3H, s), 1.07–1.35, 1.70–1.97 (7H, 2×m), 3.03 and 3.37 (2H, m), 3.78 (1H, m), 4.10 and 4.26 (2H, 2×dd, J_P=13.1 Hz, J=2.8 Hz), 6.86 (1H, m), 7.19–7.35 (8H, m), 7.58–7.87 (5H, m); δ_C

(60 MHz, $CDCl_3$) 20.2, 21.2, 26.9, 33.1, 38.3, 43.1, 50.8, 44.9, 48.1, 49.3, 53.3, 65.7, 100.6, 128.5, 128.5, 128.6, 128.7, 128.8, 128.9, 130.4, 131.3, 132.0, 132.2, 132.3, 132.4, 133.0, 133.3, 135.1, 136.9, 136.9, 139.5, 165.0; MS (CI) *m/z* 687 ($[MH]^+$, 10%), 234 (33), 216 (100), 152 (29); HRMS found: $[MH]^+$687.0969, $C_{31}H_{33}IN_2O_4PS$ requires 687.0943.

4.2.9. *trans*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2-methoxyphenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (Table 1, entry 7). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10,2-sultam (202 mg, 0.6 mmol), LiHMDS in THF (0.7 mL, 1.0 M, 0.7 mmol) and *P*,*P*-diphenyl-*N*-(2-methoxyphenylmethylene)phosphinic amide (200 mg, 0.6 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (227 mg, 65%); R_f 0.37 (EtOAc); $[\alpha]_D^{20}$ +86.4 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2965, 1686, 1441, 1343, 1172, 1267, 1124, 735, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, s), 0.83 (3H, s), 1.16–1.29 and 1.72–1.96 (7H, 2×m), 3.23 (3H, s), 3.29 and 3.36 (2H, 2×d, *J*=13.7 Hz), 3.77–3.78 (1H, m), 4.24–4.31 (2H, m), 6.52 (1H, m), 6.81–6.85 (1H, m), 7.12–7.36 (8H, m), 7.69–7.74 and 7.83–7.88 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.7, 20.7, 26.3, 32.6, 38.0, 39.6, 43.4, 44.5, 47.7, 48.8, 52.8, 54.4, 65.1, 109.5, 120.1, 121.8, 121.8, 127.8, 127.9, 128.0, 128.2, 128.3, 129.6, 131.1, 131.3, 131.4, 131.6, 131.6, 131.7, 131.7, 132.0, 133.3, 133.6, 134.9, 158.9, 166.1; MS (CI) *m/z* 591 ($[MH]^+$, 9%), 391 (100), 350 (24), 201 (66), 148 (75), 77 (39); HRMS found: $[MH]^+$591.2072, $C_{32}H_{36}N_2O_5PS$ requires 591.2083.

4.2.10. *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-Diphenylphosphinyl-3-(2-methylphenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (Table 1, entry 8). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10,2-sultam (270 mg, 0.8 mmol), LiHMDS in THF (0.9 mL, 1.0 M, 0.9 mmol) and *P*,*P*-diphenyl-*N*-(2-methylphenylmethylene)phosphinic amide (255 mg, 0.8 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (200 mg, 43%); R_f 0.63 (EtOAc); $[\alpha]_D^{20}$ +34.8 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3059, 2964, 1704, 1440, 1337, 1167, 1268, 1128, 770, 737, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.98 (6H, 2s), 1.30–1.38, 1.87–1.90 and 1.98–2.09 (7H, m), 2.53 (3H, s), 3.37 and 3.49 (2H, 2×d, *J*=13.7 Hz), 3.70–3.73 (1H, m), 4.35 and 4.49 (2H, 2×dd, J_P=11.7 Hz, *J*=6.0 Hz), 7.16–7.28 (3H, m), 7.49–7.63 and 7.73–7.75 (7H, 2×m), 8.10–8.21 (4H, m); δ_C (100 MHz, $CDCl_3$) 19.6, 20.2, 21.0, 26.7, 32.9, 38.4, 40.9, 43.6, 44.9, 48.2, 49.3, 53.1, 65.2, 125.4, 128.2, 128.3, 128.8, 128.9, 129.1, 129.1, 130.1, 130.7, 130.9, 131.0, 131.2, 132.1, 132.2, 132.7, 133.2, 138.3, 164.3; MS (CI) *m/z* 575 ($[MH]^+$, 100%), 510 (12), 375 (24), 201 (59), 131 (25), 77 (16); HRMS found: $[MH]^+$575.2101, $C_{32}H_{36}N_2O_4PS$ requires 575.2134.

4.2.11. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-methylphenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (Table 1, entry 8). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10,2-sultam (270 mg, 0.8 mmol), LiHMDS in THF (0.9 mL, 1.0 M, 0.9 mmol) and *P*,*P*-diphenyl-*N*-(2-methylphenylmethylene)phosphinic amide (255 mg, 0.8 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (200 mg, 43%); R_f 0.49 (EtOAc); $[\alpha]_D^{20}$ +53.0 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 3057, 2965, 1698, 1440, 1337, 1168, 1267, 1125, 740, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.56 (3H, s) 0.59 (3H, s), 0.91–1.07 and 1.48–1.79 (7H, 2×m), 3.06 and 3.11 (2H, 2×d, *J*=14.3 Hz), 3.54 (1H, m), 3.87 and 3.97 (2H, 2×dd, J_P=11.9 Hz, *J*=2.8 Hz), 6.70–7.17 (10H, m), 7.50–7.66 (4H, m); δ_C (100 MHz, $CDCl_3$) 18.7, 19.7, 20.7, 26.3, 32.5, 37.7, 42.2, 44.0, 44.4, 47.6, 48.7, 52.8, 65.2, 125.7, 126.3, 127.9, 128.0, 128.1, 128.2, 128.2, 128.4, 129.7, 131.5, 131.6, 131.6, 131.7, 131.9, 132.1, 132.2, 136.4, 137.9, 165.3; MS (CI) *m/z* 575 ($[MH]^+$, 28%), 511 (25), 419 (37), 219 (100), 131 (16), 77 (19); HRMS found: $[MH]^+$575.2109, $C_{32}H_{36}N_2O_4PS$ requires 575.2134.

4.2.12. *cis*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-ethylphenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (Table 1, entry 9). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10,2-sultam (672 mg, 2.0 mmol), LiHMDS in THF (2.1 mL, 1.0 M, 2.1 mmol) and *P*,*P*-diphenyl-*N*-(2-ethylphenylmethylene)phosphinic amide (667 mg, 2.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (700 mg, 59%); R_f 0.51 (petrol/EtOAc 1:3); $[\alpha]_D^{20}$ +40.0 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.79 (6H, m), 1.07 (3H, t, *J*=7.6 Hz), 1.04–1.20 and 1.68–1.86 (7H, 2×m), 2.53–2.68 and 2.74–2.89 (2H, 2×dt, *J*=15.1, 7.6 Hz), 3.17 and 3.29 (2H, 2×d, *J*=13.8 Hz), 3.52 (1H, m), 4.15 and 4.31 (2H, 2×dd, J_P=15.9 Hz, *J*=6.1 Hz), 7.05–7.09 (3H, m), 7.29–7.40 (H, m), 7.88–8.00 (4H, m); δ_C (60 MHz, $CDCl_3$) 15.0, 20.2, 21.0, 25.3, 26.7, 32.9, 38.4, 41.2, 43.2, 44.9, 48.1, 49.2, 53.0, 65.2, 125.4, 127.9, 128.3, 128.5, 128.8, 128.4, 129.0, 129.1, 130.3, 130.4, 132.0, 132.1, 132.2, 132.2, 132.6, 132.6, 132.7, 144.0, 164.4; MS (CI) *m/z* 589 ($[MH]^+$, 100%), 419 (10), 389 (17), 216 (27), 134 (14), 66 (11); HRMS found: $[MH]^+$589.2295, $C_{33}H_{38}N_2O_4PS$ requires 589.2290.

4.2.13. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-ethylphenyl)-2-aziridinyl)carbonyl]bornane-10,2-sultam (Table 1, entry 9). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10,2-sultam (672 mg, 2.0 mmol), LiHMDS in THF (2.1 mL, 1.0 M, 2.1 mmol) and *P*,*P*-diphenyl-*N*-(2-ethylphenylmethylene)phosphinic amide (667 mg, 2.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (400 mg, 34%); R_f 0.29 (EtOAc); $[\alpha]_D^{20}$ +63.5 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.77 (3H, s), 0.80 (3H, s), 0.95 (3H, t, *J*=7.5 Hz), 1.15–1.27 and 1.71–1.90 (7H, 2×m), 3.27 and 3.33 (2H, 2×d, *J*=13.8 Hz), 3.77 (1H, m), 4.05 and 4.26 (2H, 2×dd, J_P=13.3 Hz, *J*=2.8 Hz), 6.99–7.37 (10H, m), 7.78–7.80 (4H, m); δ_C (60 MHz, $CDCl_3$) 15.1, 20.2, 21.2, 25.6, 26.9, 33.1, 38.2,

43.3, 43.7, 44.9, 48.2, 49.2, 53.3, 65.7, 126.3, 126.5, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 131.7, 132.0, 132.1, 132.2, 132.3, 132.6, 133.2, 133.8, 135.3, 144.2, 165.6; MS (CI) *m/z* 589 ([MH]+, 100%), 387 (17), 334 (10), 201 (39), 135 (11); HRMS found: $[MH]^+$589.2275, $C_{33}H_{38}N_2O_4PS$ requires 589.2290.

4.2.14. *trans*-2*S*,2′*S*,3′*R*-*N*-[(1-Diphenylphosphinyl-3-(2-trifluoromethylphenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (Table 1, entry 10). Following the general procedure described above *N*-bromoacetyl-2*S*-bornane-10, 2-sultam (672 mg, 2.0 mmol), LiHMDS in THF (2.1 mL, 1.0 M, 2.1 mmol) and *P*,*P*-diphenyl-*N*-(2-trifluoromethylphenylmethylene)phosphinic amide (747 mg, 2.0 mmol) were reacted to produce the crude aziridine. The resulting colourless solid was purified by flash chromatography eluting with petrol–EtOAc (1/9) to afford the product, as a colourless solid (860 mg, 69%); R_f 0.50 (EtOAc); $[\alpha]_D^{20}$ +52.6 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.74 (3H, s), 0.80 (3H, s), 1.09–1.33 and 1.72–1.97 (7H, 2×m), 3.31 (2H, m), 3.79 (1H, m), 4.02 and 4.48 (2H, 2×dd, J_P=13.0 Hz, J=2.7 Hz), 7.29–7.46 (10H, m), 7.79–7.87 (4H, m); δ_C (60 MHz, $CDCl_3$) 20.2, 21.2, 26.9, 33.1, 38.1, 41.8, 44.8, 44.9, 48.2, 49.2, 53.3, 65.8, 126.1, 126.2, 127.9, 128.6, 128.7, 128.8, 128.9, 129.9, 130.4, 131.3, 132.0, 132.1, 132.2, 132.3, 132.3, 132.8, 133.3, 134.9, 164.3; MS (CI) *m/z* 629 ($[MH]^+$, 35%), 565 (25), 419 (78), 347 (20), 219 (100), 185 (32), 77 (10); HRMS found: $[MH]^+$629.1843, $C_{32}H_{33}N_2O_4PSF_3$ requires 629.1851.

4.3. General procedure for hydrolytic cleavage of camphorsultam auxiliary

2,3-Disubstituted *N*-diphenylphosphinyl aziridines bearing the camphor sultam moiety (typically 0.2 mmol), were dissolved in a THF–water (4/1) mixture (5 mL). Lithium hydroxide monohydrate (0.4 mmol) was then added and the resulting suspension stirred vigorously overnight. The excess solvent was removed under reduced pressure and the aqueous layer basified to pH 10 with saturated $NaHCO_3$ solution, and extracted with $CHCl_3$ (3×30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the 2*S*-bornane-10, 2-sultam. The aqueous layer was then combined with the base washings and acidified to pH 2 with saturated citric acid solution, and extracted with $CHCl_3$ (3×50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the *N*-diphenylphosphinyl-2-substituted-3-carboxyaziridines.

4.3.1. *trans*-2-Carboxy-*N*-diphenylphosphinyl-3-(2-methylpropenyl)aziridine (Table 2, entry 1). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-methylpropenyl)-2-aziridinyl)-carbonyl]bornane-10, 2-sultam (108 mg, 0.2 mmol) afforded the product as a colourless oil (33 mg, 50%). $[\alpha]_D^{20}$ +17.8 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 1718, 1440, 1127, 1028, 757, 728, 697 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.26 (6H, 2s), 4.26 (1H, dd, J_P=13.4 Hz, J=5.8 Hz), 5.83 (1H, ddd, J=13.4, 13.4, 5.8 Hz), 5.93 (1H, d, J=13.4 Hz), 7.46–7.95 (10H, m); δ_C (60 MHz, $CDCl_3$) 30.0, 30.2, 57.0, 71.4, 125.1, 129.8, 130.1, 130.2, 130.3, 130.4, 132.2, 132.4, 132.6, 132.8, 133.5, 133.6, 133.8, 134.0, 134.3, 134.6, 142.7, 175.1; MS (CI) *m/z* 342 ($[MH]^+$, 15%), 314 (8), 297 (24), 219 (100), 130 (7), 84 (64), 66 (24); HRMS found: $[MH]^+$342.1273, $C_{19}H_{21}NO_3P$ requires 342.1259.

4.3.2. *trans*-2-Carboxy-*N*-diphenylphosphinyl-3-(2-chlorophenyl)aziridine (Table 2, entry 2). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-chlorophenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (119 mg, 0.2 mmol) afforded the product as a colourless oil (34 mg, 45%). $[\alpha]_D^{20}$ +13.6 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 1733, 1439, 1130, 755, 729, 697 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.52 and 4.29 (2H, 2×dd, J_P=13.6 Hz, J=3.0 Hz), 7.12–7.80 (14H, m); MS (CI) *m/z* 354 ($[MH-CO_2]^+$, 35%), 318 (6), 219 (100), 154 (5), 130 (8), 77 (9); HRMS found: $[MH-CO_2]^+$354.0805, $C_{20}H_{18}ClNOP$ requires 354.0815.

4.3.3. *trans*-2-Carboxy-*N*-diphenylphosphinyl-3-(2-trifluoromethylphenyl)aziridine (Table 2, entry 3). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-trifluoromethylphenyl)-2-aziridinyl)carbonyl]bornane-10, 2-sultam (126 mg, 0.2 mmol) afforded the product as a colourless oil (49 mg, 57%). $[\alpha]_D^{20}$ +15.4 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 1723, 1440, 1129, 1036, 757, 730, 695 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.43 and 4.48 (2H, 2×dd, J_P=12.7 Hz, J=2.7 Hz), 7.45–8.00 (14H, m); δ_C (60 MHz, $CDCl_3$) 42.5, 47.3, 123.9, 127.3, 127.3, 128.8, 130.1, 130.2, 130.2, 130.3, 130.4, 130.5, 132.8, 133.0, 133.1, 133.1, 133.2, 133.8, 133.9, 134.0, 169.9; MS (CI) *m/z* 432 ($[MH]^+$, 35%), 388 (21), 235 (100), 201 (11); HRMS found: $[MH]^+$432.0984, $C_{22}H_{18}NO_3PF_3$ requires 432.0976.

4.3.4. *cis*-2-Carboxy-*N*-diphenylphosphinyl-3-(2-methylphenyl)aziridine (Table 2, entry 4). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-methylphenyl)-2-aziridinyl)carbonyl]-bornane-10, 2-sultam (115 mg, 0.2 mmol) afforded the product as a colourless oil (61 mg, 81%). $[\alpha]_D^{20}$ +2.6 (*c* 1, MeOH); IR ν_{max} (CCl_4) 1729, 1439, 1128, 1041, 755, 694 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.16 (3H, s), 3.47 and 3.94 (2H, 2×dd, J_P=15.7 Hz, J=6.6 Hz), 6.88–7.95 (14H, m); δ_C (60 MHz, $CDCl_3$) 19.3, 41.8, 42.1, 126.8, 128.9, 129.5, 130.3, 130.4, 130.5, 130.6, 131.1, 132.6, 132.8, 133.0, 133.1, 133.3, 133.5, 134.4, 134.4, 134.5, 138.4, 169.6; MS (CI) *m/z* 378 ($[MH]^+$, 35%), 334 (100), 235 (9), 201 (19), 134 (17); HRMS found: $[MH]^+$378.1248, $C_{22}H_{21}NO_3P$ requires 378.1259.

4.3.5. *cis*-2-Carboxy-*N*-diphenylphosphinyl-3-(2-ethylphenyl)aziridine (Table 2, entry 5). Following the general procedure described above *cis*-2*S*,2′*S*,3′*S*-*N*-[(1-diphenylphosphinyl-3-(2-ethylphenyl)-2-aziridinyl)carbonyl]-bornane-10, 2-sultam (118 mg, 0.2 mmol) afforded the product as a colourless oil (51 mg, 65%). $[\alpha]_D^{20}$ −5.7 (*c* 1, $CHCl_3$); IR ν_{max} (CCl_4) 1718, 1439, 1130, 756, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, J=7.5 Hz), 2.57 (2H, q, J=7.5 Hz), 3.47 and 4.02 (2H, 2×dd, J_P=15.7 Hz, J=6.6 Hz), 6.66–7.97 (14H, m); δ_C (60 MHz, $CDCl_3$) 15.7, 26.7, 41.8, 42.3, 126.8, 129.2, 129.4, 129.8, 130.3, 130.4, 130.5, 130.6, 132.6, 132.8, 132.9, 133.1, 133.3, 133.4,

134.4, 134.5, 134.6, 144.6, 169.5; MS (CI) *m/z* 348 ([MH−CO_2]$^+$, 100%), 219 (47), 201 (31), 146 (9), 77 (7); HRMS found: [MH−CO_2]$^+$348.1526, $C_{22}H_{22}NOP$ requires 348.1517.

Acknowledgements

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New chiral lithium aluminum hydrides based on biphenyl-2,2′-bisfenchol (BIFOL): structural analyses and enantioselective reductions of aryl alkyl ketones

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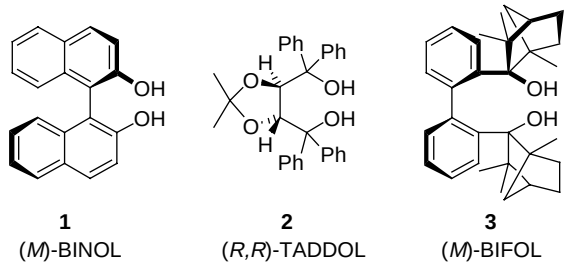
Abstract—A series of new chiral lithium aluminum hydrides based on BIFOL (biphenyl-2,2′-bisfenchol) and various alkyl alcohols (i.e., methanol, *n*-butanol, *tert*-butanol yielding BIFAl-H's) was synthesized and characterized by single crystal X-ray analyses. These investigations point to alkoxide redistribution for BIFAl-H-(O-*t*Bu) (biphenyl-2,2′-bisfenchol aluminum hydride) species. The new BIFAl-H reagents are suitable to reduce aryl alkyl ketones with up to 62% ee. Computational transition structure analyses help to explain the experimentally observed enantioselectivities.

1. Introduction

Lithium aluminum hydride (LAH) represents a powerful reducing agent and is frequently employed in organic synthesis, for example, for conversions of carbonyl functions to alcohols.[1] Appropriate chiral derivates of LAH are widely used as reagents for enantioselective reductions of prochiral ketones.[2] The C_2-symmetric diols BINOL (**1**)[3] and TADDOL (**2**)[4] (Scheme 1) are highly effective for such enantioselective reductions in combination with an alkyl alcohol.[5] The structural characterization of such modified LAH reagents is hence of major interest. Some chiral LAH alkoxides tend to disproportionation and aggravate the syntheses of a well defined reducing species with high enantioselectivity. The use of chelating diols decreases the appearance of multiple LAH species.[5] IR structure analyses of BINOL modified LAH alkoxides by Noyori et al. show that disproportionated LAH species are detectable.[5] Further examinations by Noeth et al. by means of X-ray structure and ^{27}Al NMR analyses show the phenomenon of disproportionation and redistribution of LAH alkoxides.[6]

The chiral chelating diol (*M*)-BIFOL (biphenyl-2,2′-bisfenchol, **3**, Scheme 1), recently developed in our group, exhibits a C_2-axis, which is induced and stabilized by beneficial alignment of the fenchol moieties via hydrogen bonding.[7] As in BINOL (**1**), this flexible biaryl axis can adopt to different metal sizes via rotation around the biaryl axis. Modular aryl fenchols were successfully employed in enantioselective palladium and copper catalyzed C–C-couplings,[8] in organo zinc catalysts[9] and in chiral organo lithium reagents.[10] We here present structural analyses of (*M*)-BIFOL modified lithium aluminum hydrides and their application in enantioselective reductions of aryl alkyl ketones.



1 (*M*)-BINOL **2** (*R,R*)-TADDOL **3** (*M*)-BIFOL

Scheme 1. Chiral C_2-symmetric diols for chiral lithium aluminum hydrides.

2. Results and discussion

A series of enantiopure lithium aluminum hydrides, that is, BIFAl-H-(O-R) (**4a**,**b**,**c**), was prepared from $LiAlH_4$, (*M*)-BIFOL and an alkyl alcohol, that is, methanol, *n*-butanol or *tert*-butanol (Scheme 2).

Keywords: Enantioselective reductions; Chiral lithium aluminum hydrides; X-ray structure analyses; Transition structure analyses.
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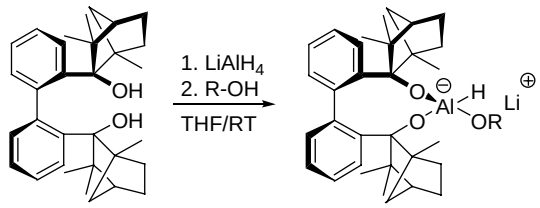
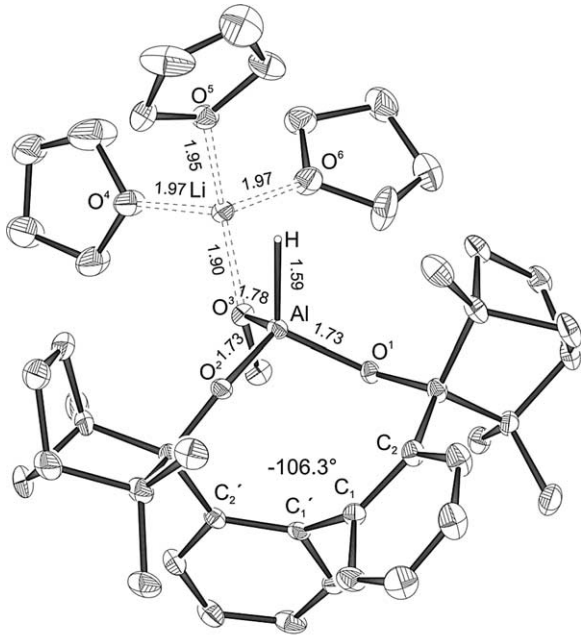


3 (*M*)-BIFOL) (*M*)-BIFAl-H-(O-R)
4a: R=Me
4b: R=*n*Bu
4c: R=*t*Bu

Scheme 2. Synthesis of chiral, BIFOL-based aluminum hydrides, (*M*)-BIFAl-H-(O-R).

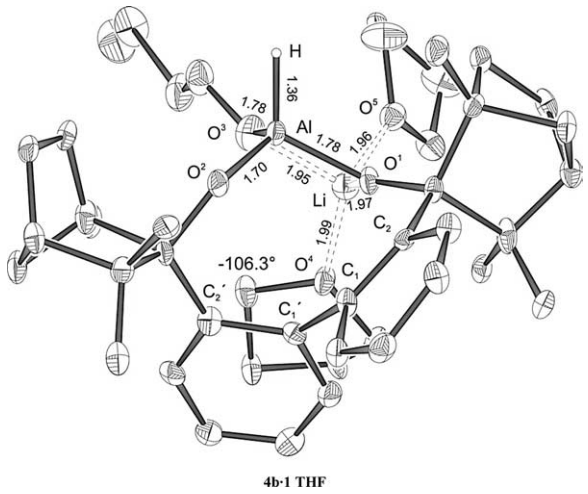
X-ray structures of **4a** and **4b** (Figs. 1 and 2) reveal the formation of the expected reactive hydride species. As observed by the groups of Noyori[5] and Noeth,[6] aging of the reaction solution may give rise to redistribution of hydride components ($LiAlH_{4-n}(RO)_n$, Scheme 3). Indeed, the formation of (*M*)-BIFAl-(O-*t*Bu)$_2$ **5** (Fig. 3) from **4c** points to such a redistribution.



4a·3 THF

Figure 1. X-ray crystal structure of **4a**. Hydrogen atoms are omitted except H1. Thermal ellipsoids represent a 20% probability. Selected atom distances (in Å): Al–H1 1.59, Al–O1 1.73, Al–O2 1.73, Al–O3 1.78, Li–O3 1.90, Li–O4 1.97, Li–O5 1.95, Li–O6 1.97. Biaryl angle: C_2–C_1–C_1'–C_2' −106.3°.

Molecular structures of **4a**, **4b** and **5** (Figs. 1–3) show all tetra coordinated lithium and aluminum ions. In the molecular structure of **4a** (Fig. 1) the Li-ion coordinates to three oxygen atoms of three THF ligands with Li–O distances of 1.97 (O4), 1.95 (O5) and 1.97 Å (O6). The Li–O3 distance to the BIFOL ligand is shorter (1.90 Å) than the distances to the solvent THF. The molecular structure of **4b** shows a Li-ion, which is coordinated by two THF molecules with Li–O distances of 1.96 (O3) and 1.99 Å (O5), one oxygen of the BIFOL ligand (2.06 Å) and the *n*-butoxy unit



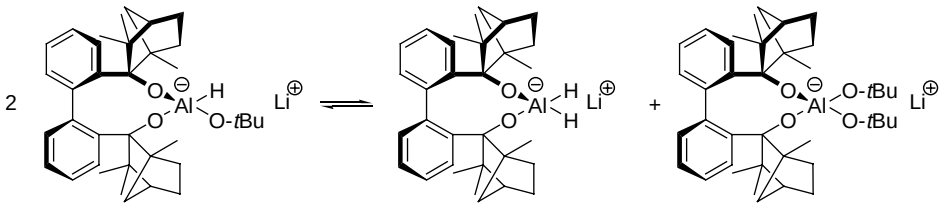
4b·1 THF

Figure 2. X-ray crystal structure of **4b**. Hydrogen atoms are omitted except H1. Thermal ellipsoids represent a 20% probability. Selected atom distances (in Å): Al–H1 1.36, Al–O1 1.78, Al–O2 1.70, Al–O3 1.78, Li–O1 1.97, Li–O3 1.95, Li–O4 1.99, Li–O5 1.96. Biaryl angle: C_2–C_1–C_1'–C_2' −106.3°.

(1.95 Å). In **5** the Li-ion is coordinated by two THF and two oxygen from the *tert*-butanol moieties. The structure of **5** exhibits a shorter Li–O distance to the *tert*-butoxy (1.99 Å (O3), 1.93 Å (O4)) than to the two THF molecules (2.04 Å (O5), 2.05 Å (O6)). All examined BIFAl-H-(O-R) structures crystallize in (*M*) conformations of the chiral biaryl axis. The computed relative energy of the optimized (*M*)-**6-calc** structure is 20.3 kcal/mol lower than its diastereomer (*P*)-**6-calc** (Table 1, Figs. 4 and 5). The dihedral angels of the chiral C_2-axis are very similar (**4a**: −106.3°; **4b**: −106.3°, **5**: −107.4°), which suggest that the influence of the alkyl alcohols are rather small and the steric interactions between the bulky fenchone moieties are high. Hence, the minus biaryl conformations of fenchone moieties in (*M*)-BIFAl-H-(O-R) are more favorable than in the (*P*)-conformations. This parallels the situation in (*M*)-BIFOL, where additional hydrogen bonding contributes to the stabilization of the (*M*)-conformation. Computations and X-ray analyses of BIFAl-H-(O-R) tends to a 100% de of the (*M*) biaryl axis. Similar results were obtained for (*M*)-BIFOL.[7] Enantioselective reduction of aryl alkyl ketones like butyrophenon with (*M*)-BIFAl-H-(O-*n*Bu) yields (*S*)-1-phenylbutane-1-ol in an enantiomeric excess of 62% (Table 2, Scheme 4). Reductions of acetophenon, methylacetophenon and propiophenon result in a range of 3–50% ee.

To predict the sense of enantioselectivity for aryl alkyl ketone reductions, Noyori et al. proposed a six-membered transition state model for the reduction of aryl alkyl ketones with (*M*)-BINAl-H-(O-R).[5] Repulsive p–π interactions between the oxygen lone pairs and the delocalized π-system of the phenyl rest favores (*S*)-configuration of the secondary alcohol (Scheme 5).[5]

This qualitative transition state model was adopted for quantitative transition structure computations of the reduction of different prochiral aryl alkyl ketones with (*M*)-BIFAl-H-(O-R). Each reducing agent and the appropriate substrate yielding the highest enantioselectivity were chosen for transition state optimization. In all three cases the



Scheme 3. Redistribution of (*M*)-BIFAl-H-(O-*t*Bu) according to the attempted synthesis of **4c** and the subsequent detection of **5** via X-ray crystal structure analyses.

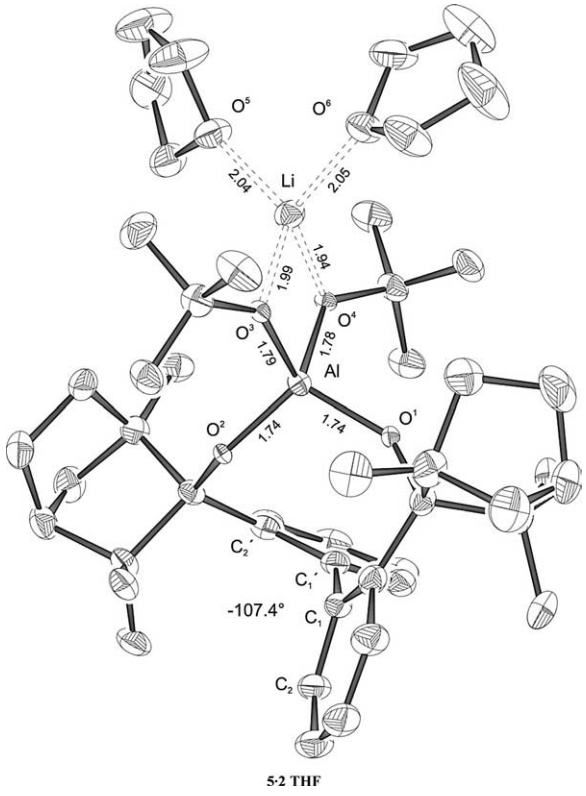


Figure 3. X-ray crystal structure of **5**. Hydrogen atoms are omitted. Thermal ellipsoids represent a 20% probability. Selected atom distances (in Å): Al–O1 1.74, Al–O2 1.74, Al–O3 1.79, Al–O4 1.78, Li–O3 1.99, Li–O4 1.93, Li–O5 2.04, Li–O6 2.05. Biaryl angle: C_2–C_1–C_1'–C_2' −107.4°.

Table 1. Computed relative energies (E_{rel}, kcal/mol) of (*P*)- and (*M*)-conformations of BIFAl-H-(O-R)[a]

R	(*M*)-BIFAl-H-(O-R)-**calc**	(*P*)-BIFAl-H-(O-R)-**calc**
Me (**6**)	0	25.0
*n*Bu	0	23.4
*t*Bu	0	23.2

[a] MNDO optimized, see Refs. 11–13. Relative energies without ZPE correction.

(*S*)-configuration of the corresponding alcohol is more favorable than (*R*)-configuration (Table 3; Figs. 6 and 7).[11,12,13]

3. Conclusions

The new (*M*)-BIFAl-H-(O-R) reagents are efficiently accessible and suitable for the reduction of aryl alkyl ketones with moderate to fairly good enantioselectivities. X-ray structure analyses and computations reveal only (*M*)-conformations of these BIFOL modified lithium aluminum hydrides. The appearance of BIFAl(O-*t*Bu)$_2$ (**5**) provides evidence for hydride–alkoxide redistributions, according to earlier studies on alkoxide modified lithium aluminum

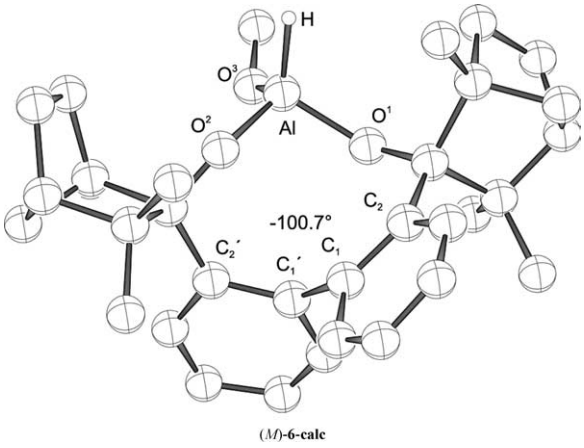


Figure 4. MNDO optimized structure of the (*M*)-BIFAL-H-(O-Me) anion. Biaryl angle: C_2–C_1–C_1'–C_2' −100.7°.

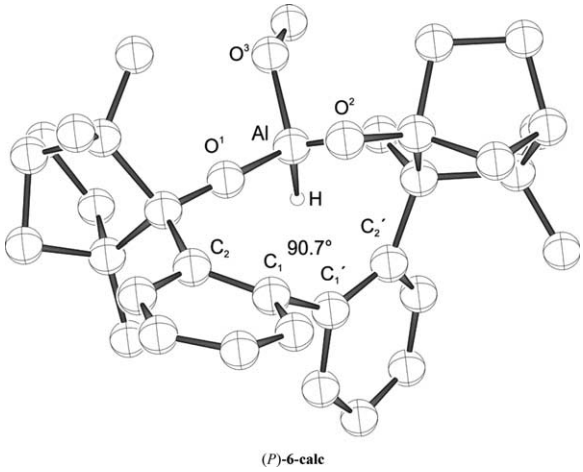
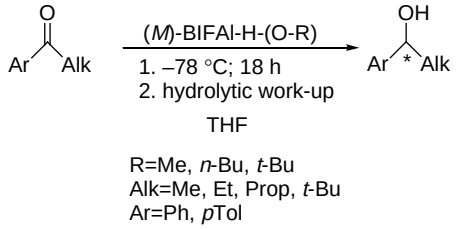


Figure 5. MNDO optimized structure of (*P*)-BIFAL-H (O-Me) anion. Biaryl angle: C_2–C_1–C_1'–C_2' 90.7°.

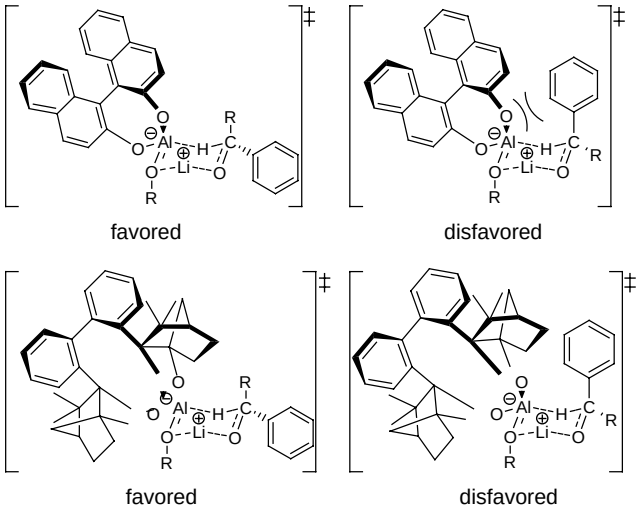
Table 2. Enantioselective reductions of aryl alkyl ketones with BIFAl-H-(O-R) (**4a**,**b**,**c**)[a]

Ketone		(*M*)-**4a**		(*M*)-**4b**		(*M*)-**4c**	
Alk	Ar	conf	ee (%)	conf	ee (%)	conf	ee (%)
Me	Ph	*R*	37	*R*	38	*R*	15
Me	*p*Tol	*S*	22	*S*	39	*S*	38
Et	Ph	*S*	23	*S*	32	*R*	4
Pr	Ph	*R*	24	*S*	62	*R*	17
*t*Bu	Ph	*S*	50	*S*	37	*S*	3

[a] Enantioselectivities were determined by chiral GC (Chiraldex-GTA column). Absolute configurations were determined by POLAR LμP-WR polarimeter. Isolated yields (not optimized) are up to 20%.



Scheme 4. (*M*)-BIFAl-H-(O-R) for enantioselective reductions of prochiral ketones.



Scheme 5. Transition structures of the (*M*)-BINAl-H-(O-R) and (*M*)-BIFAl-H-(O-R) reduction of prochiral aryl alkyl ketones.

Table 3. Computed relative energies (E_{rel}, kcal/mol) and imaginary frequencies (i, cm^{-1}) of six-membered transition structures for alkyl aryl ketone redutions (for **4b** cf. Figs. 6 and 7)[a]

BIFAL-H+alkyl aryl ketones	(*S*) E_{rel}(kcal/mol)	(*R*) E_{rel} (kcal/mol)
4a+*t*Bu, Ph	0 (*i* 846)	1.4 (*i* 807)
4b+Pr, Ph	0 (*i* 716)	0.9 (*i* 439)
4c+Me, *p*Tol	0 (*i* 691)	7.9 (*i* 569)

[a] B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO), see Refs. 11–13. Relative energies without ZPE correction.

hydride disproportionations. Transition state modeling can reflect some origins of enantioselectivity. Besides their application as hydride transfer reagents, the BIFAl-H species are promising chiral Lewis acids. Such properties are currently under investigation.

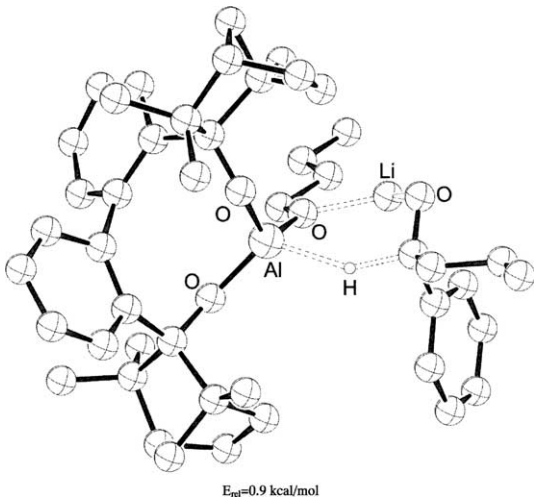


Figure 6. B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO) optimized transition state leading to (*R*)-1-phenylbutanol (disfavored TS).

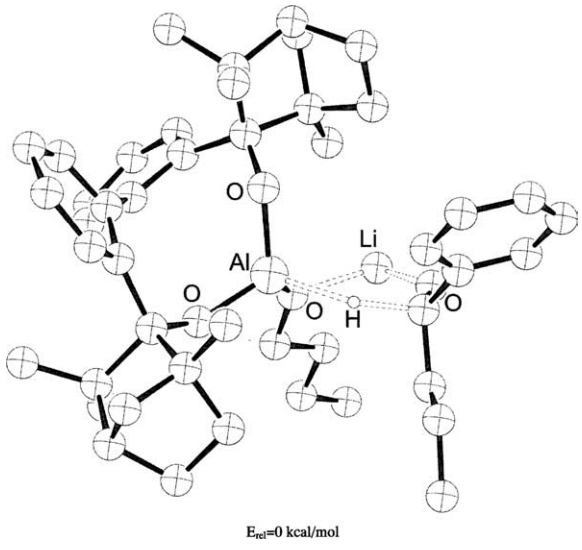


Figure 7. B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO) optimized transition state leading to (*S*)-1-phenylbutanol (favored TS).

4. Experimental

All reactions and crystallization approaches were carried out under argon atmosphere using long necked Schlenk-tubes dried by heatgun. THF was always freshly distilled over sodium under argon atmosphere before use. Methanol was distilled over magnesium under argon. *n*-Butanol and *tert*-butanol (HPLC-Grade) were used without drying. Lithium aluminum hydride (LAH) was used as a 1 M solution in THF commercially available from Aldrich. Enantiomeric excess of the chiral secondary alcohols were measured on a Hewlett Packard HP 6890 GC (chiral capillary column: Chiraldex-GTA, 30 m, 0.25 mm, 0.25 μm); Absolute configuration of the chiral secondary alcohols were determined by POLAR LμP-WR polarimeter (wavelenght: 589 nm); X-ray analysis were recorded with Nonius Kappa CCD diffractometer (Mo Kα; wavelength λ=0.71073Å).

4.1. Synthesis and crystallization of (*M*)-BIFAl-H-(O-Me) 4a·3THF

(*M*)-BIFOL (1 mmol) was dissolved in 5 ml abs THF in a schlenk-tube and 1.2 equiv of a 1 M solution of lithium aluminum hydride in THF was added under few elusion of hydrogen. The mixture was stirred for 30 min. Then 1 mmol abs methanol was added slowly under a rapid stream of hydrogen gas and stirred again for 30 min. For crystallization the solution was cooled down to 4 °C for 3 days and then cooled down to −28 °C for 5 days. White crystals separated. Yield: 0.26 g (35%). X-ray crystal data of **4a**: $C_{45}H_{68}AlLiO_6$; $M=738.91$; space group orthorhombic, $a=9.9449(8)$ Å, $b=19.389(1)$ Å, $c=22.483(1)$ Å, $\alpha=90$, $\beta=90$, $\gamma=90$; $V=4335.3(6)$ Å^3; $Z=4$; $T=293(2)$ K; $\mu=0.091$ mm^{-1}; reflections total: 24407, unique: 9202, observed: 3695 ($I>2\sigma(I)$); parameters refined: 577; $R1=0.0549$, $wR2=0.1097$; GOF=0.895.

4.2. Synthesis and crystallization of (*M*)-BIFAl-H-(O-*n*Bu) 4b·1THF

(*M*)-BIFOL (1 mmol) was dissolved in 5 ml abs THF in a schlenk-tube and 1.2 equiv of a 1 M solution of lithium aluminum hydride in THF was added under few elusion of hydrogen. The mixture was stirred for 30 min. Then 1 mmol *n*-butanol was added slowly under a rapid stream of hydrogen gas and stirred again for 30 min. For crystallization the solution was cooled down to −28 °C for 3 days. White crystals separated. Yield: 0.10 g (14%). X-ray crystal data of **4b**: $C_{44}H_{66}AlLiO_5$; $M=708.89$; space group monoclinic, $a=9.4880(10)$ Å, $b=19.6400(10)$ Å, $c=11.6700(10)$ Å, $\alpha=90$, $\beta=113.157(5)$, $\gamma=90$; $V=1999.4(3)$ Å^3; $Z=2$; $T=100(2)$ K; $\mu=0.094$ mm^{-1}; reflections total: 5582, unique: 2216, observed: 1485 ($I>2\sigma(I)$); parameters refined: 466; $R1=0.0757$, $wR2=0.1783$; GOF=1.049. All THF were disordered. Only one orientation is shown.

4.3. Synthesis and crystallization of (*M*)-BIFAl-(O-*t*Bu)$_2$ 5·2THF

(*M*)-BIFOL (1 mmol) was dissolved in 3 ml abs THF in a schlenk-tube and 1.2 equiv of a 1 M solution of lithium aluminum hydride in THF was added under few elusion of hydrogen. The mixture was stirred for 30 min. Then 1 mmol *tert*-butanol was added slowly under a rapid stream of hydrogen gas and stirred again for 30 min. For crystallization the solution was cooled down to 4 °C for 3 days and then cooled down to −28 °C for 3 days. White crystals separated. Yield: 0.13 g (17%). X-ray crystal data of **4c**: $C_{48}H_{74}AlLiO_6$; $M=789.99$; space group monocline, $a=10.4959(2)$ Å, $b=19.2992(4)$ Å, $c=11.9120(2)$ Å, $\alpha=90$, $\beta=111.476(1)$, $\gamma=90$; $V=2245.39(7)$ Å^3; $Z=2$; $T=293(2)$ K; $\mu=0.091$ mm^{-1}; reflections total: 18192, unique: 9791, observed: 7781 ($I>2\sigma(I)$); parameters refined: 566; $R1=0.0390$, $wR2=0.1218$; GOF=0.656.

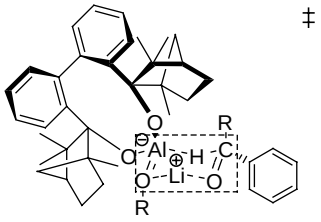
4.4. Enantioselective reduction of the acetophenon, methylacetophenon, propiophenon, butyrophenon, pivalophenon

The respective (*M*)-BIFAl-H-(O-R) reagent was prepared from 2.5 mmol (*M*)-BIFOL and 1 equiv of a 1 M solution of lithium aluminum hydride. After stirring for 30 min, 1 equiv of a primary alkyl alcohol, respectively, methanol, butanol or *tert*-butanol was added slowly under a rapid stream of hydrogen gas. The solution was stirred again for 30 min and cooled down to −78 °C. Then 0.5 equiv of the aryl alkyl ketone was dissolved in 2 ml abs THF was added drop wise. The solution was stirred for 18 h and quenched with 0.5 ml methanol followed by acidic work-up with 2 N HCl and neutral work-up with saturated $NaSO_4$-solution. The secondary alcohol was extracted with diethyl ether. The organic phase was washed with saturated NaCl-solution and dried over $NaSO_4$. The resulting secondary alcohol was distilled and analyzed by chiral GC (Chiraldex-GTA column) and polarimetry.

5. Computational details

All structures were fully optimized and characterized by frequency computations using Gaussian 03[11] with standard basis sets 6-31G*[12] and the B3LYP [13] hybrid-DFT method.

Oniom method is used for transition state computations (Scheme 6).



Scheme 6. B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO) optimized transition state. B3LYP/6-31G* optimized area is framed.

6. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 271631 for compound **4a**; No. 271632 for compound **4b** and No. 271633 for compound **5**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 33) or deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk

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Phosphines catalyzed nucleophilic addition of azoles to allenes: synthesis of allylazoles and indolizines

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Abstract—Triphenylphosphine was used as nucleophilic catalyst for umpolung addition of azoles to electron-deficient allenes. This strategy offers a simple and efficient method for functional allylation of azoles under neutral conditions and affords heterocyclic substituted Michael olefins. Furthermore, this catalytic methodology has been extended to addition–cyclization reactions between electron-deficient allenes or alkynes and pyrrole-2-carboxaldehyde in the presence of catalytic amount of tributylphosphine. In such conditions, substituted indolizine-7-carboxylates are easily obtained.

1. Introduction

The last few years, an impressive development took place in metal free catalytic methods. Exciting results in organocatalyses attracted a deep attention, taking the advantages of often simple, inexpensive and commercially available catalysts.[1] The great potential of organocatalyses was also recently highlighted in reviews as broad and useful methodologies to elaborate complex structures. Among them, nucleophilic organocatalysis was also proved to be efficient for the synthesis of polyfunctionalized structural units and in some recent extensions of the Morita–Baylis–Hillman reaction, high enantioselectivities can be obtained, demonstrating its wide range of synthetic applications.[2]

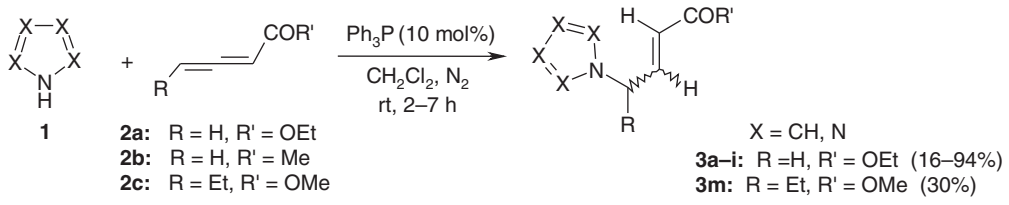
Some years ago, Cristau et al. reported a sequential multistep synthesis using stoichiometric amount of triphenylphosphine for the umpolung γ-addition of various nucleophiles on electron-deficient allenes.[3] Initiated by Trost, the catalytic version of this reaction was expanded till recently to a large set of nucleophiles.[4]

The development of new synthetic methods to functionalize or to construct heterocycles, merely using both tandem reactions and nucleophilic organocatalysis is a question of interest. We report herein the catalytic N-functional allylation of azoles using electron-deficient allenes. In a second time, a catalytic tandem reaction of properly functionalized azoles giving directly indolizines will be presented.

2. Results and discussion

2.1. Functional allylation of azoles

As depicted in Scheme 1, reaction of azoles **1** with activated allenes[5] **2** in the presence of catalytic amount of triphenyl-



1

2a: R = H, R' = OEt
2b: R = H, R' = Me
2c: R = Et, R' = OMe

3a–i: R =H, R' = OEt (16–94%)
3m: R = Et, R' = OMe (30%)

Scheme 1. Allylation of azoles reaction.

Keywords: Phosphines; Nucleophilic catalysis; Allylation; Azoles; Indolizines.
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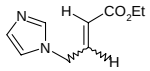
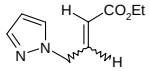
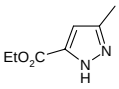
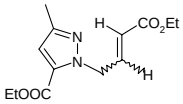
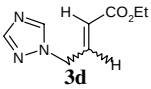
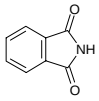
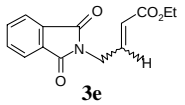
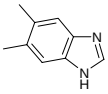
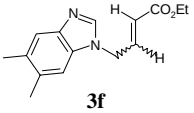
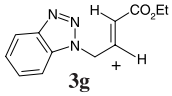
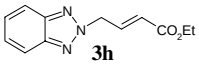
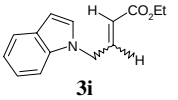
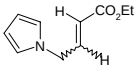
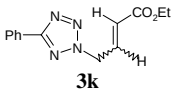
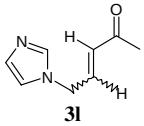
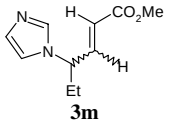
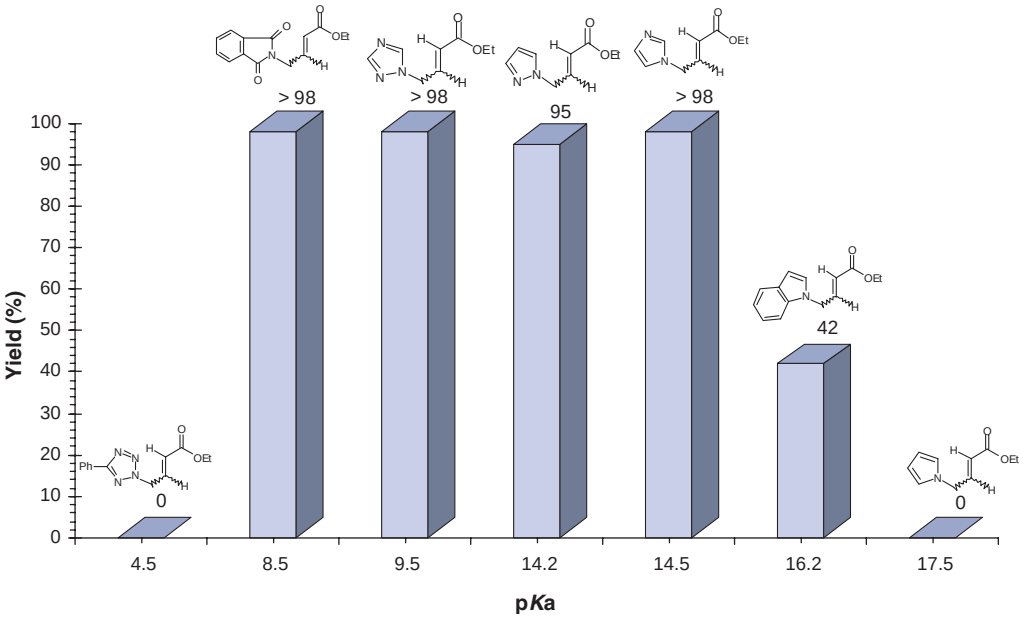
phosphine readily affords the functional 1-allylazoles **3** in excellent to good yields (72–94%) when compounds **1** are imidazole, pyrrazole, triazole, phthalimide and their benzo-analogues (Table 1, entries 1–6).

For the benzotriazole (entry 7), in which a competitive N-allylation either at position 1-N and 2-N is possible, the reaction takes place principally on the position 1 with a ratio 74/26. This experimental result agrees with the ab initio calculations of the charge distribution in the benzotriazolate anion indicating the π-charge is mainly located on the two nitrogen atoms, 1-N and 3-N, adjacent to the benzene ring.[6] The two reaction products **3g** and **3h** are easily identified and assigned by ^{1}H and ^{13}C NMR. Indeed, the resulting addition product **3h** on position 2 presents a plane of symmetry. As a consequence, the ^{1}H and ^{13}C NMR spectra show only two types of signals for the aromatic CH.

Table 1. Triphenylphosphine-catalyzed γ-addition of azoles to electron-deficient allenes

Entry	1	2	3	Yield	Isolated yield (%)	*Z*/*E* ratio[a]
1		**2a**	 **3a**	>98[b]	72	18/82
2		**2a**	 **3b**	95[c]	80	36/64
3		**2a**	 **3c**	92[c]	89	18/82
4		**2a**	 **3d**	>98[b]	79	16/84
5		**2a**	 **3e**	>98[b,c]	94	11/89
6		**2a**	 **3f**	89[c]	72	8/92
7		**2a**	 **3g** +  **3h**	54[c] 20[c]	53 19	0/100 0/100
8		**2a**	 **3i**	42[c]	16	35/65
9		**2a**	 **3j**	—	0	—
10		**2a**	 **3k**	—	0	—
11		**2b**	 **3l**	—	0	—
12		**2c**	 **3m**	>30[b]	30	3/97

[a] *Z*/*E* ratio determined in the reaction mixture by GC/MS or ^{1}H NMR.
[b] Formation yield determined by ^{1}H NMR.
[c] Formation yield determined by GC/MS.



Graph 1. Yield versus pK_a of heterocycles **1** by reaction with ethyl allenoate.

For the reaction between acetylallene **2b**[7] and imidazole, only oligomerization of allene was observed.[8]

Finally, using a γ-substituted allenoate, the desired product is obtained with a lower yield (30%, Table 1, entry 12). The isomerization of the allene into the corresponding diene was the main reaction.[9]

The method provides functional 1-allylazoles with a predominant *E*-stereoselectivity, the *E*/*Z* ratio ranging from 64/36 to 100/0. The stereoselectivity can be easily explained by assuming that the elimination step follows an E1cB mechanism where unfavorable steric hindrance between the azole and the electron withdrawing group induces the preferential formation of the *E*-isomer.[10]

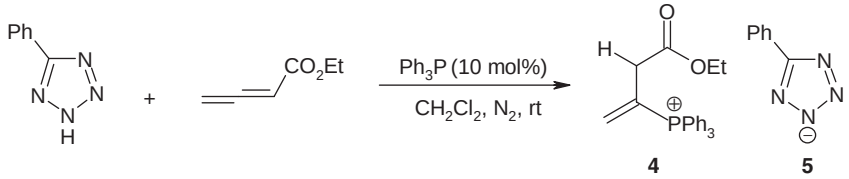
The results described above when ethyl allenoates are used, have been plotted in a histogram representing the yield versus the pK_a of the heterocycle. The higher yields are observed for pK_a ranging from 8 to 14–15 (Graph 1).

Indeed, for phenyltetrazole (pK_a=4.5) (entry 10), only the fast and complete conversion of Ph_3P into a unique product at 25.5 ppm is observed by ^{31}P NMR. It was assigned to the α-substituted vinylphosphonium **4** with tetrazole anion as counter-ion, thanks to the co-addition in the reaction mixture of an authentic sample of the α-substituted vinylphosphonium iodide **4**[11] (Scheme 2). Monitoring the reaction by ^1H NMR and GC/MS shows that the remaining reactants are almost not consumed. Consequently, it can be reasonably proposed that the conjugated base of tetrazole **5** is not nucleophilic enough to add to the vinylphosphonium **4**.

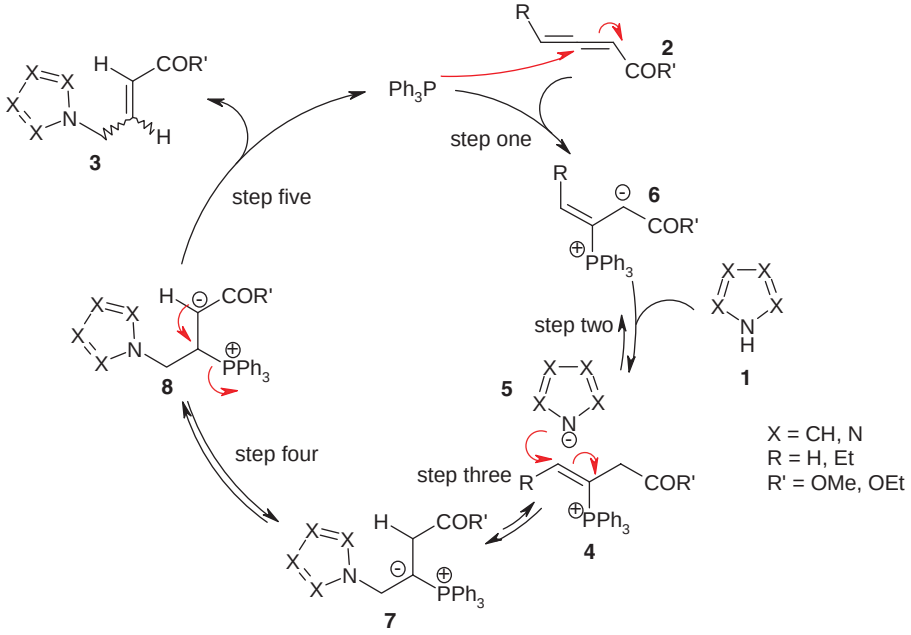
With pyrrole (pK_a 17.5) and indole (pK_a 16.2) (entries 8–9), we mainly observe the formation of a mixture of allene oligomeric products. *N*-allyl indole has been obtained in only 16% yield after chromatography. A possible explanation means the intermediate ylide **6** (see Scheme 3) is not basic enough to deprotonate the azole. As a consequence, the acid–base reaction competes unfavorably with the polymerization of allene.[8] An excess of triphenylphosphine does not improve the yields.

Mechanism

In an attempt to rationalize all these results, the following mechanism can be proposed (Scheme 3). The catalytic cycle might be initiated by a nucleophilic addition of triphenylphosphine to the electron-deficient allene **2**. The enolate **6** then deprotonates the azole **1** generating the nucleophilic species **5** and the vinylphosphonium **4**. Consecutively, nucleophilic addition of **5** to vinylphosphonium **4** leads to the ylide **7**. Finally, enolate **8** is obtained by prototropy and then undergoes a β-elimination affording the final γ-addition allylazole **3** and regenerating the nucleophilic catalyst.



Scheme 2. Formation of the α-substituted vinylphosphonium **4**.



Scheme 3. N-allylation mechanism of azoles.

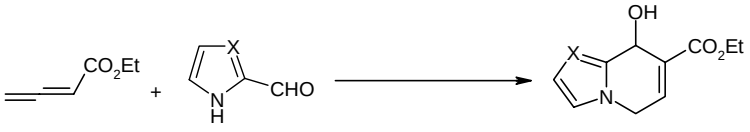
2.2. Addition–cyclization reactions: synthesis of indolizines

In a continuation of our investigations, we took advantage of the intermediate formation of enolate **8** to obtain fused bicyclic compounds. In this regard, another functionality is required on the azoles to react successively as pronucleophile and as electrophile. The commercially available 2-formylazoles **1n–o** could be good candidates for the formation of allylation-Morita–Baylis–Hillman products **9** (see Table 2).

Initial efforts focused on triphenylphosphine-catalyzed addition–cyclization between electron-deficient allenes **2** and 2-formylazoles **1n–o**. In opposition to our expectations, the reaction with imidazole-2-carboxaldehyde **1n** (entry 1) only gave the vinylphosphonium salt **4** resulting from the addition of triphenylphosphine to the electron deficient allene **2**.

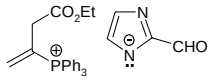
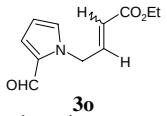
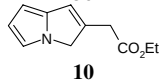
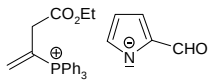
Addition products **3o**-*Z* and **3o**-*E* were obtained in 63% yield by mixing ethyl 2,3-butadienoate with pyrrole-2-carboxaldehyde in the presence of triphenylphosphine

Table 2. Triphenylphosphine-catalyzed reactions of azoles **1n–o** with allene

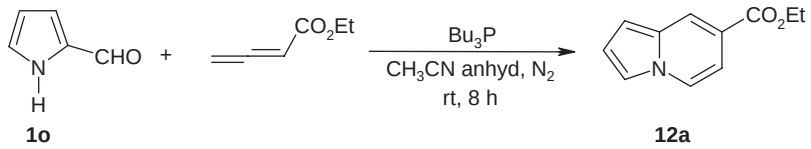


1n (X = N)
1o (X = CH)

9

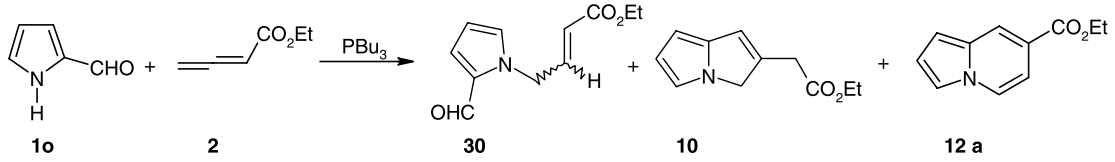
Entry	1	Conditions	Product	Yield (%)	*Z*/*E* ratio[a]
1	**1n**	Ph_3P (10 mol%), DMF, 20 °C, 3 h	 **4**	10[b]	—
2	**1o**	Ph_3P (10 mol%), CH_2Cl_2, 20 °C, 20 h	 **3o**	63[c]	38/62
			 **10**	6[c]	—
3	**1o**	Ph_3P (20 mol%), $BF_3 \cdot Et_2O$ (or $ZnCl_2$) CH_2Cl_2, 20 °C, 16	 **4**	20[c]	—

[a] *Z*/*E* ratio determined in the reaction mixture by GC/MS or ^1H NMR.
[b] One Hundred percentage conversion estimated by ^{31}P NMR.
[c] Isolated yield.



Scheme 4. Synthesis of ethyl indolizine-7-carboxylate **12a**.

Table 3. Optimisation indolizine synthesis **12a**

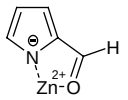


Entry	Ratio **2/1o**	Bu_3P (mol%)	Solvent	T (°C)	t	Conversion (%)[a]		Yield (%)[a]	
						1o	**3o**	**10**	**12a**
1	1	10	CH_2Cl_2	20	20 h	95	77	4	14
2	1	30	CH_2Cl_2	Reflux	3 days	94	44	8	42
3	1.5	30	CH_3CN	20	8 h	93	0	5	88 (54)[b]
4	2.5	30	CH_3CN	20	5 h	100	0	3	97 (57)[b]

[a] Conversion and yield were measured by GC/MS on the reaction mixture.
[b] Yields in brackets correspond to isolated yields.

(10 mol%) (entry 2). From the reaction mixture was also isolated a small fraction (6%) of a bicyclic compound **10**, as the result of a tandem Michael–Wittig reaction.

On the other hand, activation by Lewis acids such as boron trifluoride etherate ($BF_3 \cdot Et_2O$, 100 mol%) or zinc chloride ($ZnCl_2$, 50 mol%) fails to give the expected addition–cyclization reaction (entry 3). Only the vinylphosphonium formation is observed, indicating that activation with Lewis acid decreases dramatically the azole nucleophilicity. A possible explanation could be the formation of stable complexation products as the bidentate complex **11** with zinc.



11

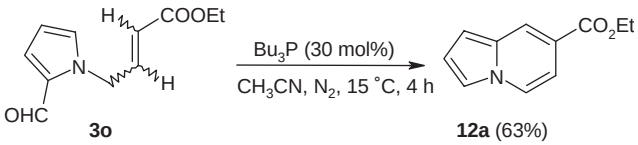
Using tributylphosphine as a more nucleophilic catalyst dramatically changes the behavior of the reaction. Accordingly, addition of a solution of ethyl 2,3-butadienoate to a mixture of pyrrole-2-carboxaldehyde **1o** and tributylphosphine (30 mol%) affords ethyl indolizine-7-carboxylate **12a** isolated in 57% yield after column chromatography (Scheme 4).

To improve the yields, solvent and quantities of reactants were optimized. In dichloromethane with 10 mol% tributylphosphine, addition products **3o** (*Z*/*E*) were obtained as the major products in 77% yield (Table 3, entry 1) together with 4% of Michael–Wittig product **10** and 14% of the expected indolizine **12a** as minor products, while 95% aldehyde was converted. When adding 20 mol% PBu_3 and heating to reflux the latest reaction mixture, cyclization proceeded smoothly and furnished indolizine **12a** in 42% yield (entry 2). In the same way, Wittig product **10** yield also increased to 8%.

In acetonitrile at 20 °C, indolizine **12a** was obtained as the main product in 8 h and in 88% yield, together with small quantities of **10** (5%). Finally, the use of an excess of allene (2.5 equiv) allows the total aldehyde conversion and gives an optimal indolizine yield (97%) after stirring 5 h at 20 °C (entry 4). **12a** was isolated in 57% yield.

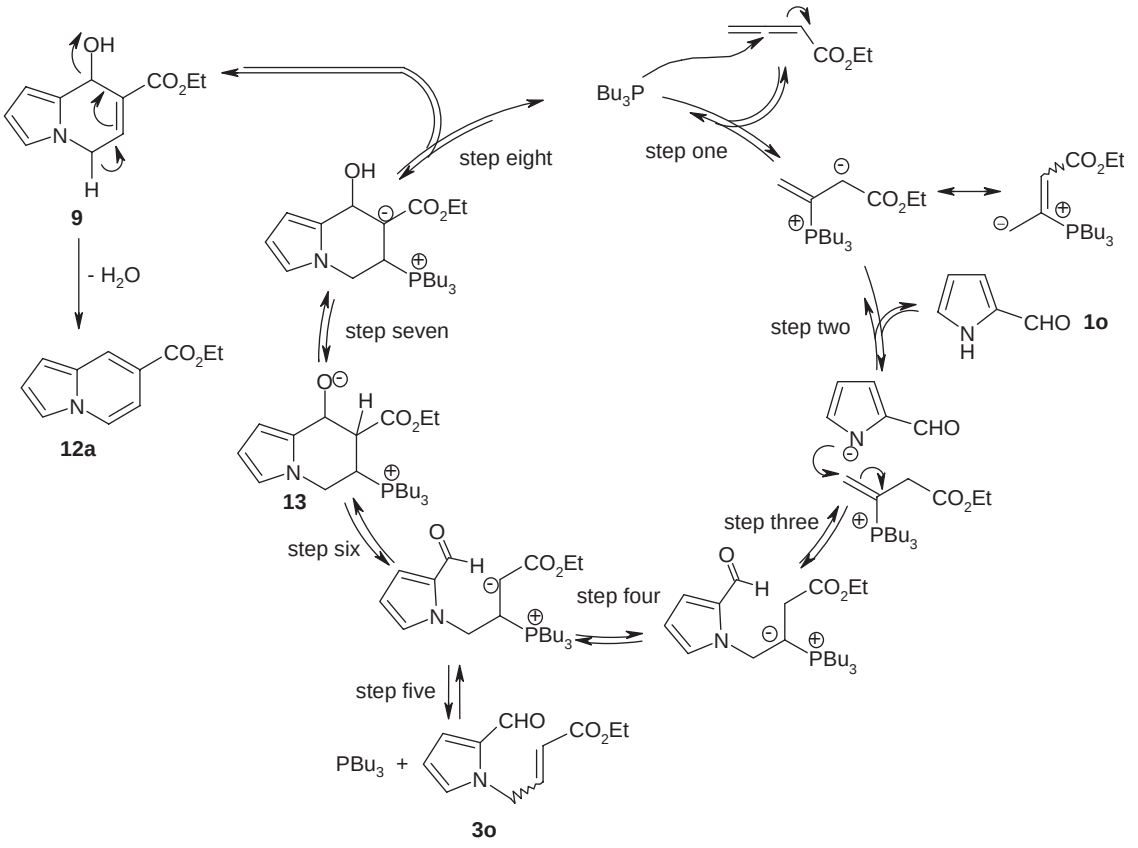
Based on these results, in association with the reactivity observed with triphenylphosphine, the mechanism is most certainly an addition–cyclization sequence. Indeed, in dichloromethane we first observed the formation of allylazole **3o** at room temperature then its cyclization by refluxing the reaction mixture (Table 3, entries 1 and 2).

For confirmation, we ran the following reaction: tributylphosphine was stirred with allylazole **3o** and after 4 h, indolizine **12a** identified by ^1H NMR was formed in 63% yield (Scheme 5).



Scheme 5. Synthesis of indolizine **12a** from **3o**.

In accordance with the previous one (see Scheme 3), the plausible mechanism for this tributylphosphine-catalyzed addition–cyclization reaction is proposed in Scheme 6. The first four steps are similar to those observed previously. When triphenylphosphine is used as catalyst, step five is almost irreversible and allylpyrrole **3o** is preferentially obtained, whereas tributylphosphine is nucleophilic enough to add to the substituted Michael



Scheme 6. Mechanism of formation of indolizine **12a**.

olefin **3o**. Consequently, the aldolization (step six), which is generally considered as the rate limiting step[12] in the Morita–Baylis–Hillman reaction occurs giving the alkoxide **13**.

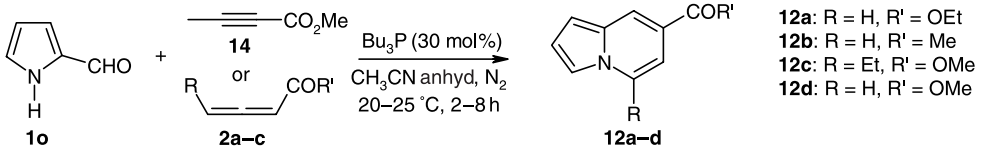
After regeneration of the catalyst (steps seven and eight), the intramolecular Morita–Baylis–Hillman adduct **9** aromatizes spontaneously in the reaction mixture, into indolizine **12a** by elimination of water.

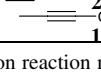
A variety of electron-deficient allenes and also methyl 2-butynoate **14** are then used (see Table 4). Unfortunately, acetylallene **2b** is too reactive and converted essentially into oligomeric products. Indolizine **12b** was formed in poor yield (28%) and isolated in 5% yield.

With methyl 2,3-hexadienoate **2c** (entry 3), the reaction competes with an isomerization into 2,4-dienoate and the indolizine **12c** was obtained in 4% yield.

Finally, more convincing was the reaction with methyl 2-butynoate **14**, which gave the indolizine **12d** in 85% yield (isolated in 50% yield). This new synthetic method to obtain functionalized indolizines seems to fit better with non-isomerizable allenic esters and alkynoates.

Table 4. Synthesis of indolizines **12**



Entry	Reagent	Product	Yield (%)[a]	Isolated yield (%)
1	 **2a**	**12a**	97	57
2	 **2b**	**12b**	28	5
3	 **2c**	**12c**	7	4
4	 **14**	**12d**	85	50

[a] Yield was determined by GC/MS on reaction mixture.

3. Conclusion

In conclusion, nucleophilic phosphinocatalysis offers a simple and efficient method for the functional allylation of azoles under neutral conditions and furnishes attractive heterocyclic substituted Michael olefins. This reaction has been successfully expanded to a variety of azoles. However, there is an optimal range of pK_a in order to avoid the polymerization of allene or the lack of nucleophilicity for the deprotonated azole.

Using the conjunction of pyrrole carboxaldehyde and tributylphosphine with electron deficient allenes or alkynes, we were able to obtain substituted indolizines by a tandem reaction.

4. Experimental

4.1. General remarks

All reactions involving air or moisture sensitive reagents or intermediates were carried out under nitrogen in flame-dried glassware. Reagents and solvents were purified before use and stored under nitrogen atmosphere. All reactions were monitored by GC/MS, ^{31}P or ^{1}H NMR. Flash column chromatography was performed using E. Merck silica gel 60 (35–70 μm) or neutral alumina gel (70–230 μm) and compressed air. Melting points were determined with a Electrothermal Digital Melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1000 Fourier transform spectrometer. For ^{1}H, ^{13}C, and ^{31}P NMR spectra (δ in ppm) a Bruker Avance 400, a Bruker Avance 250 and Bruker AC 200 spectrometers were used. Assignments were made using a combination of 1D and 2D spectra (COSY, HMQC). Mass spectra were run with a Jeol JMS DX-300 spectrometer (positive FAB ionization and exact mass measurements using *p*-nitrobenzyl alcohol matrix). Elemental analyses were performed on a THERMOFINNIGAN Flash EA 1112 apparatus.

4.2. General procedure for functional allylation of azoles

To a mixture of azole (0.3 mol L^{-1}, 1 equiv) and PPh_3 (0.1 equiv) in anhydrous dichloromethane was added dropwise over 2 h at 18 °C a solution of ethyl 2,3-butadienoate (0.3 mol L^{-1}, 1 equiv) in anhydrous dichloromethane. The reaction was monitored by ^{1}H NMR or by GC/MS. After completion of the reaction, the solvent was evaporated under reduced pressure and the product was purified by flash column chromatography of silica gel.

4.2.1. (*E*/*Z*)-Ethyl 4-(imidazol-1′-yl)but-2-enoate (3a). The compound was eluted with dichloromethane–ethanol (99.5/0.5–98/2). Yield: 72% (497 mg), colorless oil; IR (KBr film): ν=3115, 2983, 1722 (C=O), 1499 (C=N) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ= 1.26 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.18 (q, $^{3}J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.72 (dd, $^{3}J_{(H,H)}$=5.0 Hz, $^{4}J_{(H,H)}$=1.9 Hz, 2H, CH_2), 5.70 (dt, $^{3}J_{(H,H)}$=15.5 Hz, $^{4}J_{(H,H)}$=1.9 Hz, 1H, α-CH), 6.90 (dd, $^{3}J_{(H,H)}$=1.3 Hz, $^{4}J_{(H,H)}$=1.3 Hz, 1H, 4-CH), 6.98 (dt, $^{3}J_{(H,H)}$=15.6, 5.1 Hz, 1H, β-CH), 7.10 (dd, $^{3}J_{(H,H)}$=1.1 Hz, $^{4}J_{(H,H)}$=1.1 Hz, 1H, 5-CH), 7.48 (dd, $^{3}J_{(H,H)}$=1.1 Hz, $^{4}J_{(H,H)}$=1.1 Hz, 1H, 2-CH); *Z* isomer δ= 1.32 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.22 (q, $^{3}J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.18 (dd, $^{3}J_{(H,H)}$=6.0 Hz, $^{4}J_{(H,H)}$=2.1 Hz, 2H, CH_2), 5.94 (dt, $^{3}J_{(H,H)}$=11.4 Hz, $^{4}J_{(H,H)}$=2.1 Hz, 1H, α-CH), 6.23 (dt, $^{3}J_{(H,H)}$=6.0, 11.4 Hz, 1H, β-CH), 6.94 (dd, $^{3}J_{(H,H)}$=1.3 Hz, $^{4}J_{(H,H)}$=1.3 Hz, 1H, 4-CH), 7.07 (dd, $^{3}J_{(H,H)}$=1.0 Hz, $^{4}J_{(H,H)}$=1.0 Hz, 1H, 5-CH), 7.51 (dd, $^{3}J_{(H,H)}$=1.1 Hz, $^{4}J_{(H,H)}$=1.0 Hz, 1H, 2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.12 (CH_3), 47.31 (CH_2), 60.78 (CH_2), 119.15 (4-CH), 123.60 (α-CH), 130.05 (5-CH), 137.26 (2-CH), 141.55 (β-CH), 165.37 (1-C); *Z* isomer δ=14.16 (CH_3), 45.11 (CH_2), 60.66 (CH_2), 118.81 (4-CH), 122.18 (α-CH), 129.99 (5-CH), 137.08 (2-CH), 143.19 (β-CH), 165.56 (1-C); FAB (+): *m*/*z* (%)= 181 (100) [M$^+$+H], 135 (3) [M$^+$−OEt], 107 (5) [M$^+$− CO_2Et]; HRMS: calcd for $C_9H_{12}N_2O_2$ 181.0977; found 181.0974.

4.2.2. (*E*/*Z*)-Ethyl 4-(pyrazol-1′-yl)but-2-enoate (3b). The two isomers were separated using hexane–ethyl acetate eluent (95/5 and 92/8). Yield: 80% (165 mg (*Z* isomer) and 426 mg (*E* isomer)), colorless oils; IR (KBr film): *E* isomer ν=3118, 2935, 1721 (C=O) cm^{-1}; *Z* isomer ν=3120, 2984, 2939, 1715 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.18 (q, $^{3}J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.91 (dd, $^{3}J_{(H,H)}$=5.3 Hz, $^{4}J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.71 (dt, $^{3}J_{(H,H)}$=15.6 Hz, $^{4}J_{(H,H)}$=1.8 Hz, 1H, α-CH), 6.31 (t, $^{3}J_{(H,H)}$=2.1 Hz, 1H, 4-CH), 7.04 (dt, $^{3}J_{(H,H)}$=15.6, 5.3 Hz, 1H, β-CH), 7.41 (d, $^{3}J_{(H,H)}$=2.3 Hz, 1H, 3-CH), 7.55 (d, $^{3}J_{(H,H)}$=2.0 Hz, 1H, 5-CH); *Z* isomer δ=1.31 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.22 (q, $^{3}J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.37 (dd, $^{3}J_{(H,H)}$=5.8 Hz, $^{4}J_{(H,H)}$=2.3 Hz, 2H, CH_2), 5.92 (dt, $^{3}J_{(H,H)}$=11.5 Hz, $^{4}J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.26 (t, $^{3}J_{(H,H)}$=2.2 Hz, 4-CH), 6.42 (dt, $^{3}J_{(H,H)}$=11.5, 5.9 Hz, 1H, β-CH), 7.42 (dd, $^{3}J_{(H,H)}$=2.2 Hz, $^{4}J_{(H,H)}$=0.5 Hz, 1H, 3-CH), 7.53 (dd, $^{3}J_{(H,H)}$=2.0 Hz, $^{4}J_{(H,H)}$=0.6 Hz, 1H, 5-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.15 (CH_3), 52.42 (CH_2), 60.61 (CH_2), 106.25 (4-CH), 123.42 (α-CH), 129.41 (5-CH), 139.98 (β-CH), 141.96 (3-CH), 165.60 (C); *Z* isomer δ=14.18 (CH_3), 50.39 (CH_2), 60.47 (CH_2), 105.87 (4-CH), 121.25 (α-CH), 129.30 (5-CH), 139.88 (β-CH), 143.95 (3-CH), 165.78 (C); FAB (+): *m*/*z* (%)=181 (100) [M$^+$+H], 135 (18) [M$^+$−OEt], 107 (11) [M$^+$−CO_2Et]; HRMS: calcd for $C_9H_{12}N_2O_2$ 181.0977; found 181.0988 (*E* isomer).

4.2.3. (*E*/*Z*)-Ethyl 4-(5′-ethoxycarbonyl-3′-methyl-pyrazol-1′-yl)-but-2-enoate (3c). Compound **3c** was eluted with dichloromethane–ethanol (100/0–98/2). Yield: 89% (93 mg (mixture of *E*,*Z* isomers) and 92 mg (*E* isomer)), colorless oils; IR (KBr film): *E* isomer ν=3140, 2982, 1720 (C=O), 1716 (C=O) cm^{-1}; *Z* isomer ν=3120, 3053, 2984, 1715 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 1.40 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 2.28 (d, $^{4}J_{(H,H)}$=0.7 Hz, 3H, CH_3), 4.18 (q, $^{3}J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.40 (q, $^{3}J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.94 (dd, $^{3}J_{(H,H)}$=4.6 Hz, $^{4}J_{(H,H)}$=2.0 Hz, 2H, CH_2), 5.52 (dt, $^{3}J_{(H,H)}$=15.7 Hz, $^{4}J_{(H,H)}$=1.9 Hz, 1H, α-CH), 6.63 (q, $^{4}J_{(H,H)}$=0.8 Hz, 1H, 4-CH), 7.00 (dt, $^{3}J_{(H,H)}$=15.7 Hz, $^{4}J_{(H,H)}$=4.6 Hz, 1H, β-CH); *Z* isomer δ=1.28 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 1.69 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.25 (q,

$^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.41 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.44 (dd, $^3J_{(H,H)}$=5.7 Hz, $^4J_{(H,H)}$=2.2 Hz, 2H, CH_2), 5.95 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.34 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=5.7 Hz, 1H, β-CH), 6.58 (q, $^4J_{(H,H)}$=0.7 Hz, 1H, 4-CH); ^{13}C NMR (63 MHz, $CDCl_3$): *E* isomer δ=11.41 (CH_3), 14.56 (CH_3), 14.80 (CH_3), 50.97 (CH_2), 61.15 (CH_2), 61.37 (CH_2), 109.22 (4-CH), 123.51 (α-CH), 140.56 (5-C), 141.52 (β-CH), 143.60 (s, 3-C), 162.77 (C), 165.87 (C); ^{13}C NMR (100 MHz, $CDCl_3$); *Z* isomer δ=11.26 (CH_3), 14.19 (CH_3), 14.34 (CH_3), 48.47 (CH_2), 60.59 (CH_2), 60.88 (CH_2), 108.59 (4-CH), 121.50 (α-CH), 142.98 (5-C), 143.35 (β-CH), 148.04 (s, 3-C), 162.36 (C), 165.79 (C); FAB (+): *m/z* (%)=289 (20) [M+Na], 267 (70) [M^++H], 221 (100) [M^+−OEt], 193 (12) [M^+−CO_2Et], 147 (10) [M^+−COOEt–OEt+H]; HRMS: calcd for $C_{13}H_{11}N_2O_4$ 267.1345; found 267.1338 (*E*+*Z* isomers).

4.2.4. (*E*/*Z*)-Ethyl 4-([1,2,4]-triazol-1′-yl)but-2-enoate (3d). The two isomers were separated with hexane–ethyl acetate eluent (50/50–45/55). Yield: 79% (79 mg (*Z* isomer), 397 mg (*E* isomer) and 52 mg (mixture of *E*,*Z* isomers)), colorless oils; IR (KBr film): *E* isomer ν=3120, 2983, 1719 (C=O) cm^{-1}; *Z* isomer ν=3121, 2984, 2940, 1713 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.14 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.06 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.88 (dd, $^3J_{(H,H)}$=5.4 Hz, $^4J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.68 (dt, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, α-CH), 6.89 (dt, $^3J_{(H,H)}$=15.8, 5.4 Hz, 1H, β-CH), 7.87 (s, 1H, 5-CH), 8.07 (s, 1H, 3-CH); *Z* isomer δ=1.28 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.18 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.40 (dd, $^3J_{(H,H)}$=5.9 Hz, $^4J_{(H,H)}$=2.1 Hz, 2H, CH_2), 5.96 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.36 (dt, $^3J_{(H,H)}$=11.4, 5.9 Hz, 1H, β-CH), 7.93 (s, 1H, 5-CH), 8.12 (s, 1H, 3-CH); ^{13}C NMR (63 MHz, $CDCl_3$): *E* isomer δ=14.43 (CH_3), 50.13 (CH_2), 61.11 (CH_2), 124.67 (α-CH), 140.36 (β-CH), 143.82 (5-CH), 152.64 (3-CH), 165.50 (C); *Z* isomer δ=14.11 (CH_3), 47.66 (CH_2), 60.62 (CH_2), 122.43 (α-CH), 141.59 (β-CH), 143.21 (5-CH), 152.30 (3-CH), 165.52 (C); FAB (+): *E* isomer *m/z* (%)=182 (98) [M^++H], 136 (52) [M^+−CO_2Et], 69 (55) [triazole]$^+$; *Z* isomer *m/z* (%)=82 (27) [M+H]$^+$, 136 (25%) [M−CO_2Et]$^+$: *m/z*=113 (44%) [$C_6H_8O_2$+H]$^+$; HRMS: calcd for $C_{13}H_{11}N_2O_4$ 182.0930; found 182.0922 (*Z* isomer), 182.0933 (*E* isomer).

4.2.5. (*E*/*Z*)-Ethyl 4-(phtalimid-1′-yl)but-2-enoate (3e). The two isomers were separated with hexane–ethyl acetate eluent (90/10). Yield: 94% (70 mg (*Z* isomer), 508 mg (*E* isomer) and 78 mg (mixture of *E*,*Z* isomers)), white solids; mp 102 °C (*E* isomer), 119 °C (*Z* isomer); IR (KBr): *E* isomer ν=3100, 2989, 2941, 1774 (C=O_{ester}), 1712 (C=O_{amide}) cm^{-1}; *Z* isomer ν=3105, 2983, 1762 (C=O_{ester}), 1708 (C=O_{amide}), 1700 (C=O_{amide}) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.26 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.17 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.45 (dd, $^3J_{(H,H)}$=5.1 Hz, $^4J_{(H,H)}$=1.7 Hz, 2H, CH_2), 5.89 (dt, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.7 Hz, 1H, α-CH), 6.93 (dt, $^3J_{(H,H)}$=15.8, 5.2 Hz, 1H, β-CH), 7.90–7.74 (2 m, 4H, $CH_{aromatic}$); *Z* isomer δ=1.34 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3), 4.24 (q, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 4.95 (dd, $^3J_{HH}$=5.5 Hz, $^4J_{HH}$=2.2 Hz, 2H, CH_2), 5.92 (dt, $^3J_{HH}$=11.4 Hz, $^4J_{HH}$=2.2 Hz, 1H, α-CH), 6.14 (dt, $^3J_{HH}$=11.4, 5.5 Hz, 1H, β-CH), 7.89–7.72 (m, 4H, $CH_{aromatics}$); ^{13}C NMR (50 MHz, $CDCl_3$): *E* isomer δ=14.14 (CH_3), 38.17 (CH_2), 60.55 (CH_2), 123.14 (α-CH), 123.49 (4-CH and 7-CH), 131.90 (3a-C and 7a-C), 134.22 (5-CH and 6-CH), 140.67 (β-CH), 165.54 (C), 167.50 (1-C and 3-C); *Z* isomer δ=14.23 (CH_3), 37.05 (CH_2), 60.43 (CH_2), 121.74 (α-CH), 123.37 (4-CH and 7-CH), 132.05 (3a-C and 7a-C), 134.08 (5-CH and 6-CH), 143.78 (β-CH), 165.70 (C), 167.88 (s, 1-C and 3-C); FAB (+): *E* isomer *m/z* (%)=260 (6) [M^++H], 214 (10) [M^+−OEt], 186 (10) [M^+−CO_2Et]; *Z* isomer *m/z* (%)=260 (20) [M^++H], 214 (23) [M^+−OEt], 186 (31) [M^+−CO_2Et]; elemental analysis calcd (%) for $C_{14}H_{13}NO_4$ (259.26): C 64.86, H 5.05, N 5.40; found: C 64.48, H 5.06, N 5.79 (*E* isomer), C 64.38, H 5.11, N 5.39 (*Z* isomer).

4.2.6. (*E*/*Z*)-Ethyl 4-(5,6-dimethylbenzoimidazol-1′-yl)but-2-enoate (3f). The two isomers were separated with dichloromethane–ethanol eluent (99/1). Yield: 89% (30 mg (*Z* isomer), 310 mg (*E* isomer) and 184 mg (mixture of *E*,*Z* isomers)), colorless oils; IR (NaCl film): *E* isomer ν=3025, 2977, 2939, 1715 (C=O), 1663 (C=N) cm^{-1}; *Z* isomer ν=2990, 2940, 1712 (C=O), 1659 (C=N) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 2.40 (s, 6H, 2 CH_3), 4.18 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.92 (dd, $^3J_{(H,H)}$=4.7 Hz, $^4J_{(H,H)}$=1.9 Hz, 2H, CH_2), 5.68 (dt, $^3J_{(H,H)}$=15.7 Hz, $^4J_{(H,H)}$=1.9 Hz, 1H, α-CH), 7.08 (dt, $^3J_{(H,H)}$=15.8, 4.7 Hz, 1H, β-CH), 7.09 (s, 1H, 7-CH), 7.61 (s, 1H, 4-CH), 7.80 (s, 1H, 2-CH); *Z* isomer δ=1.38 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 2.40 (s, 6H, 2 CH_3), 4.30 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.40 (dd, $^3J_{(H,H)}$=5.8 Hz, $^4J_{(H,H)}$=2.2 Hz, 2H, CH_2), 6.00 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.28 (dt, $^3J_{(H,H)}$=11.4, 5.8 Hz, 1H, β-CH), 7.14 (s, 1H, 7-CH), 7.59 (s, 1H, 4-CH), 7.84 (s, 1H, 2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.13 (CH_3), 20.26 and 20.61 (2 CH_3), 45.33 (CH_2), 60.79 (CH_2), 109.70 (7-CH), 120.56 (α-CH), 123.39 (4-CH), 131.46 (5-C), 132.10 (s, 7a-C), 132.66 (6-C), 141.17 (β-CH), 142.09 (2-CH), 142.40 (3a-C), 165.47 (C); *Z* isomer δ=13.22 (CH_3), 19.23 and 19.55 (2 CH_3), 42.38 (CH_2), 59.69 (CH_2), 108.72 (7-CH), 119.44 (α-CH), 121.21 (4-CH), 130.23 (5-C), 131.10 (7a-C), 131.32 (6-C), 141.05 (β-CH), 141.56 (3a-C), 142.65 (2-CH), 164.77 (C); FAB (+): *E* isomer *m/z* (%)=259 (100) [M^++H], 229 (4) [M^+−C_2H_5], 185 (11) [M^+−CO_2·C_2H_5], 147 (15) [$C_9H_{11}N_2^+$]; *Z* isomer *m/z* (%)=259 (100) [M^++H], 229 (2) [M^+−C_2H_5], 185 (10) [M^+−CO_2 C_2H_5], 147 (15) [$C_9H_{11}N_2^+$]; HRMS: calcd for $C_{15}H_{19}N_2O_2$ 259.1447; found 259.1447 (*E* isomer), 259.1454 (*Z* isomer).

4.2.7. (*E*)-Ethyl 4-(benzotriazol-1′-yl)but-2-enoate (3g). The two regioisomers **3g** and **3h** were separated with dichloromethane–ethyl ether eluent (98/2). Yield: 72% for both regioisomers (214 mg (isomer **3g**), 72 mg (isomer **3h**) and 296 mg (mixture of isomers **3g** and **3h**)), oils; Yield=53% for **3g**; IR (NaCl film): 2982, 2938, 2905, 1716 (C=O), 1663 (C=N) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): 1.27 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.20 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.47 (dd, $^3J_{(H,H)}$=5.1 Hz, $^4J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.75 (dt, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, α-CH), 7.14 (dt, $^3J_{(H,H)}$=15.6, 5.1 Hz, 1H, β-CH), 7.40 (m, 3H, 5-CH+6-CH+7-CH), 8.11 (m, 1H, 4-CH); ^{13}C

NMR (100 MHz, $CDCl_3$): 14.13 (CH_3), 48.55 (CH_2), 60.88 (CH_2), 109.19 (7-CH), 120.30 (4-CH), 124.23 and 124.26 (2s, α-CH+5-CH), 127.86 (s, 6-CH), 132.84 (7a-C), 139.74 (β-CH), 146.13 (3a-C), 165.21 (C); FAB (+): *m/z* (%)= 232 (100) [M^++H], 120 (10) [$M^+-C_6H_4N_3+H$]; HRMS: calcd for $C_{12}H_{14}N_3O_2$ 232.1086; found 232.1081.

4.2.8. (*E*)-Ethyl 4-(benzotriazol-2′-yl)but-2-enoate (3h). This regioisomer was obtained together with **3g**. Yield= 19% for **3h**, oil; IR (NaCl film): 3068, 2982, 2939, 1722 (C=O), 1664 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.16 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.49 (dd, $^3J_{(H,H)}$=5.8 Hz, $^4J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.87 (dt, $^3J_{(H,H)}$=15.7 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, α-CH), 7.18 (dt, $^3J_{(H,H)}$=15.7, 5.8 Hz, 1H, β-CH), 7.39 (ddd, $^3J_{(H,H)}$=8.7, 6.8 Hz, $^4J_{(H,H)}$=1.0 Hz, 2H, 5-CH+6-CH), 7.87 (ddd, $^3J_{(H,H)}$=8.7 Hz, $^4J_{(H,H)}$=1.0 Hz, $^5J_{(H,H)}$= 1.0 Hz, 2H, 4-CH+7-CH); ^{13}C NMR (100 MHz, $CDCl_3$): 14.16 (CH_3), 56.66 (CH_2), 60.78 (CH_2), 118.15 (4-CH +7-CH), 124.79 (α-CH), 126.74 (5-CH +6-CH), 139.42 (β-CH), 144.64 (3a-C+7a-C), 165.24 (C); FAB (+): *m/z* (%)=232 (100) [M^++H], 186 (14) [$M^+-OC_2H_5$], 158 (13) [M^+-CO_2 C_2H_5]; HRMS: calcd for $C_{12}H_{14}N_3O_2$ 232.1086; found 232.1087.

4.2.9. (*E*/*Z*)-Ethyl 4-(indol-1′-yl)-but-2-enoate (3i). The two isomers were separated with hexane–ethyl acetate eluent (98/2). Yield: 53% (142 mg (*Z* isomer), 95 mg (*E* isomer)), colorless oils; IR (NaCl film): *E* isomer ν=3102, 2982, 2937, 2881, 1716 (C=O) cm^{-1}; *Z* isomer ν=3055, 2982, 2880, 2820, 1714 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.18 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.91 (dd, $^3J_{(H,H)}$=4.6 Hz, $^4J_{(H,H)}$=1.9 Hz, 2H, CH_2), 5.62 (dt, $^3J_{(H,H)}$- =15.6 Hz, $^4J_{(H,H)}$=1.9 Hz, 1H, α-CH), 6.59 (dd, $^3J_{(H,H)}$= 3.1 Hz, $^5J_{(H,H)}$=0.8 Hz, 1H, 3-CH), 7.10 (dt, $^3J_{(H,H)}$=15.6, 4.6 Hz, 1H, β-CH), 7.05–7.31 (m, 4H, 2-CH+5-CH+6-CH+7-CH), 7.68 (ddd, $^3J_{(H,H)}$=7.6 Hz, $^4J_{(H,H)}$=1.2 Hz, $^5J_{(H,H)}$=0.8 Hz, 1H, 4-CH); *Z* isomer δ=1.39 (t, $^3J_{(H,H)}$= 7.1 Hz, 3H, CH_3), 4.31 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.41 (dd, $^3J_{(H,H)}$=5.8 Hz, $^4J_{(H,H)}$=2.1 Hz, 2H, CH_2), 5.95 (dt, $^3J_{(H,H)}$=11.5 Hz, $^4J_{(H,H)}$=2.1 Hz, 1H, α-CH), 6.30 (dt, $^3J_{(H,H)}$=11.5, 5.8 Hz, 1H, β-CH), 6.57 (dd, $^3J_{(H,H)}$=3.2 Hz, $^5J_{(H,H)}$=0.8 Hz, 1H, 3-CH), 7.11–7.37 (m, 4H, 2-CH+ 5-CH+6-CH+7-CH), 7.66–7.70 (m, 1H, 4-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.16 (CH_3), 46.97 (CH_2), 60.62 (CH_2), 102.24 (3-CH), 109.29 (7-CH), 119.78–121.14–121.98–122.61 (α-CH, 4-CH, 5-CH, 6-CH), 127.82 (2-CH), 128.65 (3a-C), 135.94 (7a-C), 142.86 (β-CH), 165.85 (C); *Z* isomer δ=14.29 (CH_3), 45.06 (CH_2), 60.57 (CH_2), 101.86 (3-CH), 109.42 (7-CH), 119.63–121.06–121.19–121.75 (α-CH, 4-CH, 5-CH, 6-CH), 127.73 (2-CH), 128.80 (3a-C), 135.92 (7a-C), 145.70 (β-CH), 166.04 (C); FAB (+): *E* isomer *m/z* (%)=230 (55) [M^++H], 229 (100) [M]$^+$, 200 (15) [$M^+-C_2H_5$], 156 (40) [$M^+-CO_2C_2H_5$]; *Z* isomer *m/z* (%)=230 (60) [M^++H], 229 (100) [M]$^+$, 156 (30) [$M^+-CO_2C_2H_5$]; HRMS: calcd for $C_{14}H_{15}NO_2$ 229.1103; found 229.1110 (*E* isomer), 229.1102 (*Z* isomer).

4.2.10. (*E*)-Ethyl 4-(imidazol-1′-yl)hexa-2-enoate (3m). The compound was eluted with hexane–ethyl acetate eluent (98/2). Yield: 30% (228 mg (*E* isomer)), oil; IR (KBr film): ν=3115, 2971, 2880, 1726 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, $^3J_{(H,H)}$=7.4 Hz, 3H, CH_3), 1.85–2.18 (m, 2H, CH_2), 3.69 (s, CH_3), 4.57–4.62 (m, 1H, CH), 5.68 (dd, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.7 Hz, 1H, α-CH), 6.97 (dd, $^3J_{(H,H)}$=15.6, 5.6 Hz, 1H, β-CH), 6.89 (s, 1H, 4-CH), 7.07 (s, 1H, 5-CH), 7.49 (s, 1H, 2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.46 (CH_3), 27.75 (CH_2), 51.78 (CH_2), 59.87 (CH_3), 117.06 (4-CH), 122.30 (α-CH), 129.80 (5-CH), 136.29 (2-CH), 145.79 (β-CH), 160.02 (C); FAB (+): *m/z* (%)=195 (100) [M^++H], 179 (3) [M^+-CH_3], 135 (5) [M^+-COMe]; HRMS: calcd for $C_{10}H_{15}N_2O_2$ 195.1086; found 195.1087

4.2.11. (*E*/*Z*)-Ethyl-4-(2′-formylpyrrol-1′-yl)-but-2-enoate (3o). The two isomers were separated with dichloromethane–ethanol eluent (100/0–98/2). Yield: 63% (112 mg (*Z* isomer), 146 mg (*E* isomer), and 118 mg (mixture of *E*,*Z* isomers)), oils; IR (KBr film): *E* isomer ν=3111, 2982, 2938, 2808, 1721 (C=O_{ester}), 1662 (C=$O_{aldehyde}$) cm^{-1}; *Z* isomer ν=3110, 2982, 2806, 1715 (C=O), 1665 (C=$O_{aldehyde}$) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer δ=1.28 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.18 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.16 (dd, $^3J_{(H,H)}$=4.8 Hz, $^4J_{(H,H)}$=2.0 Hz, 2H, CH_2), 5.53 (dt, $^3J_{(H,H)}$=15.5 Hz, $^4J_{(H,H)}$=2.0 Hz, 1H, α-CH), 6.32 (dd, $^3J_{(H,H)}$=3.9, 2.5 Hz, 1H, 4-CH), 6.94 (ddd, $^3J_{(H,H)}$=2.5 Hz, $^4J_{(H,H)}$=1.0, 1.8 Hz, 1H, 3-CH), 7.00 (dd, $^3J_{(H,H)}$=3.9 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, 5-CH), 7.06 (dt, $^3J_{(H,H)}$=15.5, 4.8 Hz, 1H, β-CH), 9.56 (d, $^4J_{(H,H)}$=1.0 Hz, CH); *Z* isomer δ=1.32 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.23 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.54 (dd, $^3J_{(H,H)}$=6.1 Hz, $^4J_{(H,H)}$=2.0 Hz, 2H, CH_2), 5.87 (dt, $^3J_{(H,H)}$=11.3 Hz, $^4J_{(H,H)}$=2.0 Hz, 1H, α-CH), 6.25 (dd, $^3J_{(H,H)}$=4.1, 2.5 Hz, 1H, 4-CH), 6.27 (dt, $^3J_{(H,H)}$= 11.4, 6.1 Hz, 1H, β-CH), 6.96 (dd, $^3J_{(H,H)}$=4.1 Hz, $^4J_{(H,H)}$=1.6 Hz, 1H, 5-CH), 7.01 (ddd, $^3J_{(H,H)}$=2.5 Hz, $^4J_{(H,H)}$=1.6, 1.0 Hz, 1H, 3-CH), 9.56 (d, $^4J_{(H,H)}$=1.0 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.19 (CH_3), 49.14 (CH_2), 60.59 (CH_2), 110.45 (4-CH), 122.23 (α-CH), 124.86 (5-CH), 131.22 (3-CH), 131.26 (2-C), 143.33 (β-CH), 165.76 (C), 179.45 (CHO); *Z* isomer δ=14.22 (CH_3), 47.21 (CH_2), 60.41 (CH_2), 110.06 (4-CH), 120.92 (α-CH), 124.80 (5-CH), 131.19 (2-C), 131.51 (3-CH), 144.85 (β-CH), 165.87 (C), 179.36 (CHO); FAB (+): *E* isomer *m/z* (%)=208 (40) [M^++H], 134 (100) [$M^+-CO_2C_2H_5$]; *Z* isomer *m/z* (%)=208 (52) [M^++H], 134 (100) [$M^+-CO_2C_2H_5$]; HRMS: calcd for $C_{11}H_{14}NO_3$ 208.0974; found 208.0977 (*E* isomer), 208.0965 (*Z* isomer).

4.2.12. Ethyl (3*H*-pyrrolizin-2-yl)-acetate (10). Yield: 6% (36 mg), oil; IR (NaCl film): ν=3055, 2986, 1731 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 3.44 (d, $^4J_{(H,H)}$=1.0 Hz, 2H, α-CH_2), 4.19 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.51 (ddd, $^4J_{(H,H)}$=1.0, 1.0, 2.0 Hz, 2H, 3-CH_2), 5.88 (dd, $^3J_{(H,H)}$= 3.5 Hz, $^4J_{(H,H)}$=0.8 Hz, 1H, 7-CH), 6.24 (dd, $^3J_{(H,H)}$=2.5, 3.5 Hz, 1H, 6-CH), 6.44 (sextuplet, $^4J_{(H,H)}$=1.0 Hz, 1H, 1-CH), 6.92 (ddd, $^3J_{(H,H)}$=2.5 Hz, $^4J_{(H,H)}$=1.0, 0.8 Hz, 1H, 5-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.22 (s, CH_3), 35.62 (α-CH_2), 53.58 (3-CH_2), 61.09 (CH_2), 97.05 (7-CH), 111.44 (6-CH), 116.95 (5-CH), 121.50 (1-CH), 134.19 (2-C), 140.87 (8-C), 170.40 (C); FAB (+): *m/z* (%)=192

(100) [M^++H], 118 (92) [$M^+-CO_2C_2H_5$]; HRMS: calcd for $C_{11}H_{14}NO_2$ 192.1025; found 192.1061.

4.3. General procedure for indolizines (12) synthesis

To a mixture of pyrrole-2-carboxaldehyde **1o** (0.2 mol L^{-1}, 1 equiv) and tributylphosphine (0.3 equiv) in anhydrous acetonitrile was added dropwise over 2 h at 18 °C a solution of electron-deficient allene or alkyne (0.2 mol L^{-1}, 2 at 2.5 equiv) in anhydrous acetonitrile. The reaction was monitored by ^{1}H NMR or by GC/MS. After completion of the reaction, the solvent was evaporated under reduced pressure and the product was purified by flash column chromatography on silica or alumina gel.

4.3.1. Ethyl indolizine-7-carboxylate (12a). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 113 mg)/Bu_3P (0.3 equiv, 115 mg)/ethyl buta-2,5-dienoate of ethyl (2.5 equiv, 334 mg).

The product was eluted with hexane–ethyl acetate (99/1) on neutral alumina gel. Yield: 30% (128 mg), yellow solid; mp 38 °C; IR (KBr): ν=3125, 3061, 2981, 1705 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.42 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.38 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 6.74 (dddd, $^3J_{(H,H)}$=4.0 Hz, $^4J_{(H,H)}$=1.3, 0.4 Hz, $^5J_{(H,H)}$=1.0 Hz, 1H, 1-CH), 6.89 (dd, $^3J_{(H,H)}$=4.0, 2.6 Hz, 1H, 2-CH), 7.08 (dd, $^3J_{(H,H)}$=7.3 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, 6-CH), 7.44 (ddd, $^3J_{(H,H)}$=2.6 Hz, $^4J_{(H,H)}$=1.3 Hz, $^5J_{(H,H)}$=0.6 Hz, 1H, 3-CH), 7.91 (dt, $^3J_{(H,H)}$=7.3 Hz, $^4J_{(H,H)}$=1.0 Hz, 1H, 5-CH), 8.23 (dddd, $^4J_{(H,H)}$=1.8, 0.4 Hz, $^5J_{(H,H)}$=1.0, 0.6 Hz, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.41 (CH_3), 60.83 (CH_2), 104.42 (1-CH), 109.38 (6-CH), 115.09 (3-CH), 115.31 (2-CH), 118.66 (7-C), 123.13 (8-CH), 124.28 (5-CH), 131.47 (9-C), 166.13 (C); FAB (+): *m/z* (%)=190 (55) [M^++H], 189 (100) [M]$^+$, 161 (30) [$M^+-C_2H_5$+H], 154 (20) [M^+−OEt], 117 (20) [M^+-CO_2Et]; elemental analysis calcd (%) for $C_{11}H_{11}NO_2$ (189.22): C 69.83, H 5.86, N 7.40; found: C 69.50, H 5.83, N 7.53.

4.3.2. 7-Acetylindolizine (12b). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 643 mg)/Bu_3P (0.3 equiv, 410 mg)/acetylallene (2 equiv, 1.11 g).

The product was eluted with hexane–ethyl acetate (99/1–98/2) on silica gel. Yield: 5% (50 mg), yellow solid; mp 49 °C; IR (KBr): ν=3102, 3055, 2964, 1666 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.58 (s, 3H, CH_3), 6.78 (ddd, $^3J_{(H,H)}$=4.1 Hz, $^4J_{(H,H)}$=0.9 Hz, $^5J_{(H,H)}$=1.0 Hz, 1H, 1-CH), 6.90 (dd, $^3J_{(H,H)}$=4.1, 2.4 Hz, 1H, 2-CH), 7.10 (dd, $^3J_{(H,H)}$=7.2 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, 6-CH), 7.45 (m, 1H, 3-CH), 7.90 (ddd, $^3J_{(H,H)}$=7.2 Hz, $^4J_{(H,H)}$=0.7 Hz, $^5J_{(H,H)}$=1.0 Hz, 1H, 5-CH), 8.07 (m, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.68 (CH_3), 105.61 (1-CH), 107.99 (6-CH), 115.59 (2-CH), 115.63 (3-CH), 122.97 (8-CH), 124.59 (5-CH), 126.22 (7-C), 131.02 (9-C), 195.89 (C); FAB (+): *m/z* (%)=160 (80) [M^++H], 159 (100) [M^+], 144 (70) [M^+-CH_3]; HRMS: calcd for $C_{10}H_{19}NO$ 159.0686; found 159.0684.

4.3.3. Methyl 5-ethyl-indolizine-7-carboxylate (12c). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 182 mg)/Bu_3P (0.3 equiv, 116 mg)/methyl hexa-2,3-dienoate (2 equiv, 483 mg).

The product was eluted with hexane–ethyl acetate (98/2) on silica gel. Yield: 4% (17 mg), yellow solid; mp 60 °C; IR (KBr): ν=3154, 3113, 3095, 2970, 2944, 1701 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.48 (t, $^3J_{(H,H)}$=7.4 Hz, 3H, CH_3), 2.88 and 2.89 (2qd, $^3J_{(H,H)}$=7.4 Hz, $^4J_{(H,H)}$=1.1 Hz, 2H, CH_2), 3.94 (s, 3H, CH_3), 6.81 (dddd, $^3J_{(H,H)}$=4.0 Hz, $^4J_{(H,H)}$=1.3, 0.5 Hz, 1H, 1-CH), 6.96 (dd, $^3J_{(H,H)}$=4.0, 2.7 Hz, 1H, 2-CH), 7.00 (m, 1H, 6-CH), 7.41 (ddd, $^3J_{(H,H)}$=2.7 Hz, $^4J_{(H,H)}$=1.3 Hz, $^5J_{(H,H)}$=0.7 Hz, 1H, 3-CH), 8.19 (m, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.21 (CH_3), 24.87 (CH_2), 51.98 (CH_3), 104.97 (1-CH), 105.93 (2-CH), 112.05 (3-CH), 115.25 (8-CH), 118.47 (5-C), 120.87 (6-CH), 132.27 (7-C), 137.34 (9-C), 167.07 (C); FAB (+): *m/z* (%)=204 (55) [M^++H], 203 (100) [M]$^+$, 172 (12) [M^+-OCH_3], 144 (10) [$M^+-CO_2CH_3$]; HRMS: calcd for $C_{12}H_{13}NO_2$ 203.0946; found 203.0936.

4.3.4. Methyl indolizine-7-carboxylate (12d). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 143 mg)/Bu_3P (0.3 equiv, 91 mg)/methyl but-2-ynoate (1.5 equiv, 220 mg).

The product was eluted with hexane–ethyl acetate (99/1) on neutral alumina gel. Yield: 50% (131 mg), yellow solid; mp 102 °C; IR (KBr): ν=3105, 2945, 2850, 1702 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.92 (s, 3H, CH_3), 6.74 (dl, $^3J_{(H,H)}$=3.8 Hz, 1H, 1-CH), 6.90 (dl, $^3J_{(H,H)}$=3.7 Hz, 1H, 2-CH), 7.06 (dd, $^3J_{(H,H)}$=7.3 Hz, $^4J_{(H,H)}$=1.7 Hz, 1H, 6-CH), 7.44 (sl, 1H, 3-CH), 7.91 (d, $^3J_{(H,H)}$=7.3 Hz, 1H, 5-CH), 8.22 (dd, $^4J_{(H,H)}$=1.7 Hz, $^5J_{(H,H)}$=0.9 Hz, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.02 (CH_3), 104.56 (1-CH), 109.33 (6-CH), 115.17 (3-CH), 115.36 (2-CH), 118.29 (7-C), 123.28 (8-CH), 124.32 (5-CH), 131.43 (9-C), 166.59 (C); FAB (+): *m/z* (%)=176 (60) [M^++H], 175 (100) [M^+], 144 (15) [M^+-OCH_3], 116 (10) [$M^+-CO_2CH_3$]; HRMS: calcd for $C_{10}H_{19}O_2$ 175.0633; found 175.0630.

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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.2006.01.055.

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Ab initio study of molecular structures and excited states in anthocyanidins

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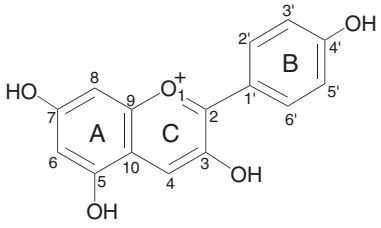
Abstract—The structural and electronic characters of four types of hydroxyl group-substituted anthocyanidins (pelargonidin, cyanidin, delphinidin, and aurantinidin) were examined using quantum chemical calculations. For these cationic molecules, both the planar and non-planar structures in the electronic ground state were determined at the B3LYP/D95 level of theory. We revealed that the planar structure is slightly more stable than the non-planar structure for each molecule. For the optimized planar structures, single excitation–configuration interaction (SE–CI) based on the restricted Hartree–Fock (RHF) wave function was evaluated and the electronic character in the low-excited states was discussed in terms of the MO theory. Symmetry adapted cluster (SAC)/SAC-CI calculations were also carried out to estimate the excitation energies precisely. The results showed that hydroxylation of the phenyl group causes a change in the excitation energies without taking the solvent effects into account. The results are in agreement with spectral experiments and previous MO calculations.

1. Introduction

Anthocyanidins are polyoxygenated derivatives of 2-phenylbenzopyrylium cation, which consist of three six-membered rings, A-, B-, and C-rings, as shown in Figure 1. Glycosylated anthocyanidins, which are called anthocyanins, are most important floral pigments and give rise to a wide range of flower colors from orange to blue. The origin of the variation in flower colors conferred by anthocyanin pigments has been an interesting subject of study since the early twentieth century[1–7] and five main subjects have been discussed to understand the phenomenon to date:

(1) *The structures of anthocyanidins*. Firstly anthocyanidins play a most important role producing flower colors as the chromophore, and three anthocyanidins (pelargonidin, cyanidin, and delphinidin) are well known to be principal and basic skeletons of flower color pigments. The visible absorption spectra of these molecules differ in proportion to the number of hydroxyl groups in the B-rings.[1,2,8,9] Methylation and glycosydation of the hydroxyl groups also affects rather slightly the absorption spectra.[1,2] (2) *Tautomerism*. Secondly anthocyanidins show prototropic equilibria depending on the pH of the solution and change their colors like litmus.[5,6] In strong acid solution, the cationic forms are dominant. At pH 3.0–7.0, neutral quinonoidal forms become predominant while anionic forms exist mainly in alkaline solution. In neutralized aqueous solution, a pseudo-base form is also produced when the hydration reaction occurs. These respective forms have



	$C_{3'}$	$C_{5'}$	C_6	
	–H	–H	–H	**1** (pelargonidin)
	–OH	–H	–H	**2** (cyanidin)
	–OH	–OH	–H	**3** (delphinidin)
	–H	–H	–OH	**4** (aurantinidin)

Figure 1. Structure and atom numbering of the anthocyanidins examined.

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different spectral properties and give specific colors. (3) *Self-association*. It has been thought that the self-association of anthocyanin prevents the hydration reaction in the case of a high-concentration solution and keeps its color stability.[10] (4) *Intra- and inter- molecular copigmentation*. Robinson and Robinson[10,11] showed that anthocyanins make certain complexes (copigmentation) with copigments such as flavone, flavonol, and tannin by intermolecular interaction (intermolecular copigment). The copigmentation protects the anthocyanidin molecule from the hydration reaction, and also controls somewhat its color in response to its tightness. Later, Saito et al.[12,13] found that anthocyanins also make the intramolecular copigments with the aromatic organic acid in their glycosides. (5) *Metal-complex effect*. Shibata et al.[14] suggested that anthocyanin gives a stable blue color upon the formation of a metal-complex. Their metal-complex theory has been the subject of much controversy and the crystal structures of the metal-complex have recently been determined.[15,16]

These factors are considered to contribute to the variation in the structural stabilities and electronic structures of anthocyanins, and therefore flowers show various colors.

To understand the mechanism of the flower color variation, the more accurate information on the chemical nature of anthocyanidins, particularly the electronic structure is needed because all of the above factors are believed to reflect chemical interactions. Some theoretical studies on the stable structures and excitation energies of anthocyanidins have already been reported.[17–28] Pauling[17] applied the resonance concept to anthocyanidins and indicated a close relation between the absorption spectra and π-electron structures. Bendz et al.[18] calculated the π-electron structures of a series of flavylium compounds using the semi-empirical PPP method and discussed electronic character in the ground state in terms of atomic charges and bond orders. Song et al.[19,20] investigated the absorption spectra and electronic structures of anthocyanidin cationic molecules using simple Hückel and PPP methods.

Recently, Rastelli et al.[21] investigated the stabilities of tautomers in three anthocyanidins (apigeninidin, pelargonidin, and cyanidin) using the semi-empirical MO method based on the AM1 Hamiltonian. They found that the cationic, neutral, and anionic forms each show a stable structure and concluded that the important factors in determining these stabilities are both the extent of π-electron delocalization and the classical resonance structures. Pereira et al.[22] examined the flavylium cation and its hydroxylated derivatives using the semi-empirical AM1 and ab initio Hartree–Fock methods and discussed these structures, charge distributions, bond orders, and MOs. They also investigated the electronic structures of hydroxylated derivatives in the B-ring and indicated that hydroxy substitutions in the B-ring, except for the C3′-position, cause an increase in resonance through the C2–C1′ bond.[23] Moreover, they examined the electronic excited states in some anthocyanidins using the semi-empirical INDO1/S and AM1 methods.[24] They concluded that hydroxylation in the B-ring causes a bathochromic shift in the absorption spectra.

Torskangerpoll et al.[25] estimated the excitation energies of 18 derivatives of hydroxyl-substituted anthocyanidins by the semi-empirical ZINDO/S and ab initio CIS methods. Moreover, they applied the multivariate regression model to the quantitative estimation of the visible absorption maxima λ_{max} by using theoretical and positional parameters. Merlin et al.[26] performed a molecular mechanics (MM) study to better understand the results of the resonance Raman spectra of anthocyanidins. Moreover, they clarified the possibility of the intramolecular copigmentation of the hemiacetal form in delphinidin 3-gentiobioside with the hydrogen-bond between the OH of glycoside and the OH of hemiacetal using both the AM1 MO and MM methods.[27,28]

At the present, we investigate theoretically the mechanism of flower color variations in anthocyanins by considering the above five factors. As a first step in a series of theoretical studies on anthocyanin, the structural stabilities and electronic structures of four anthocyanidin molecules (Fig. 1) (pelargonidin, cyanidin, delphinidin, and aurantinidin) are investigated using quantum chemical calculations. To the best of our knowledge, there has been no previous study on anthocyanidin molecules using high-level ab initio calculations. Thus, we examine the structural and electronic characteristics in the solvent-free cationic forms of these anthocyanidins. As shown in Table 1, the absorption maxima λ_{max} of these molecules in acidic media become bathochromic in proportion to hydroxylation in the B-ring, while a hypsochromic shift occurs by hydroxyl substitution at the 6-position in the A-ring. These phenomena are considered to reflect differences in the effects of the position of hydroxylation on the electronic structure.

Table 1. Absorption maxima λ_{max} of anthocyanidins in the visible region[a]

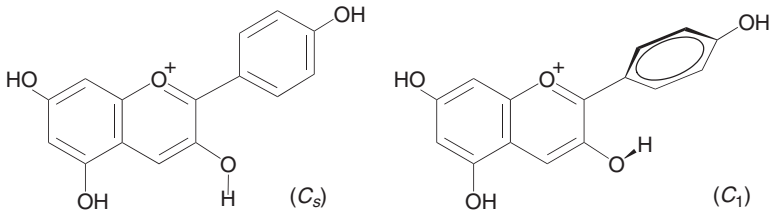
Anthocyanidin	λ_{max} (nm)	
	Methanol–HCl	Ethanol–HCl
Pelargonidin	520	530
Cyanidin	535	545
Delphinidin	546	557
Aurantinidin	499	—

[a] Refs. 1,9.

In the present study, we examined the stable structures of these cationic molecules by the density functional theory (DFT). As shown in Figure 2, we calculated two types of geometries, the planar structure and the non-planar structure, according to the orientation of the 3-OH group. Next, we performed single excitation–configuration interaction (SE–CI) calculations based on the restricted Hartree–Fock (RHF) wave functions to examine the electronic characters in the low-excited states from the perspective of the MO theory. Finally, we carried out symmetry adapted cluster (SAC)/SAC-CI calculations. As a result, we clarified the variation in the lowest excitation energy due to the hydroxy substitution in isolated cationic molecules.

2. Computational details

The stable structures in the ground state were optimized by the DFT using Becke's three-parameter hybrid method[29] with the Lee, Yang, and Parr correlation functional[30]



1a **1b**

Figure 2. Planar (**1a**) and non-planar (**1b**) structures of pelargonidin.

(B3LYP). Dunning's (9s5p/4s)/[4s2p/2s] contracted basis set (D95) was used for the Gaussian basis functions.[31,32] For both the ***n*a** and ***n*b** ($n=1$–4) structures, which differ in the orientation of the 3-hydroxyl group, we adopted the most stable structures within the optimized local minima, which varied in the orientation of the hydroxyl groups, except for 3-OH. The theoretical harmonic vibrational frequencies were obtained from the analytical second derivatives to verify that the equilibrium structures are true minima.

To examine the electronic character in the low-excited states in planar structures ***n*a** ($n=1$–4), SE–CI calculations were carried out using the RHF orbitals as reference orbitals. In the SE–CI calculations, the 1s orbitals of C and O atoms and their antibonding counterparts at the top of the unoccupied space were treated as frozen cores. The basis sets used in the SE–CI calculations were the D95 basis set and D95 plus d-type polarization functions to C ($\alpha=0.75$) and O ($\alpha=0.85$) atoms (D95(d)).[32]

Finally, the ground and singlet A′ excited states at planar structures ***n*a** ($n=1$–4) were calculated by the SAC/SAC-CI SD-*R* method.[33–36] In the SAC/SAC-CI calculations, the D95 basis set was employed and the RHF orbitals were used as the reference orbitals. All valence orbitals were included in the active space and the space of the frozen cores was similar to those in the SE–CI calculations. All single excitations and selected double excitations are included in the linked term. Perturbation selection[37,38] was performed with energy thresholds of 1×10^{-6} a.u. for the ground state and 1×10^{-7} a.u. for the excited states. The resultant dimensions for the SAC/SAC-CI calculations are shown in Table 2. We calculated nine excited A′ states although only the lowest three excited states are shown in the results. For the ground state, the unlinked terms are described as the products of the important linked terms for which the SD–CI coefficients were greater than 0.005. For the singlet excited states, all *S* operators and important *R* operators for which the SD–CI coefficients are greater than 0.05 were included in the unlinked term.

Table 2. Dimensions of the linked terms for SAC/SAC-CI calculations

	Reference state	Before selection	After selection
1a			
Ground state (SAC) A′	1	11,873,732	328,975
Excited state (SAC-CI) A′	9	11,873,732	572,384
2a			
Ground state (SAC) A′	1	14,326,280	353,410
Excited state (SAC-CI) A′	9	14,326,280	597,062
3a			
Ground state (SAC) A′	1	17,135,580	363,787
Excited state (SAC-CI) A′	9	17,135,580	664,113
4a			
Ground state (SAC) A′	1	14,326,280	344,273
Excited state (SAC-CI) A′	9	14,326,280	625,072

All quantum chemical calculations were carried out with the Gaussian03[39] and GAMESS[40] program packages.

3. Results and discussion

3.1. Stable structures

Both the planar structures ***n*a** and non-planar structures ***n*b** ($n=1$–4) are represented in Figure 3. Figure 3 also shows the Mulliken atomic charges[41] based on the Kohn–Sham orbitals. The relative energy difference between ***n*a** and ***n*b**, ΔE, is shown in Table 3. The Mayer bond order[42] and dipole moments are shown in Table 4.

For all molecules, both the planar ***n*a** and non-planar ***n*b** structures were obtained at the B3LYP/D95 level of theory. All of the frequencies for these geometries have real numbers, so that these structures were confirmed to be minima. For pelargonidin, the structure **1a** is more stable than **1b** by 3.4 kcal/mol at the B3LYP/D95(+ZPE) level, as shown in Table 3. For cyanidin and delphinidin, the planar structures, **2a** and **3a**, are more stable than **2b** and **3b** by 3.0 and 3.4 kcal/mol, respectively. Structure **4a** is also more stable than **4b** by 3.6 kcal/mol. Thus, for all of these molecules, the planar structures are more stable than the non-planar structures. Although the trend in the relative stabilities did not change, the ΔE values at the B3LYP/D95(d)//B3LYP/D95(+ZPE) level are smaller than those at the B3LYP/D95(+ZPE) level. Therefore, there is a slight possibility for the existence of non-planar structures in which the B-ring is distorted in response to the orientation of the 3-OH, although these structures are more unstable than the planar structures. The structural variations according to the orientation of the 3-substituent group become important in the case of 3-glucoside forms.

X-ray crystal analyses of pelargonidin and cyanidin bromide monohydrides have been reported.[43,44] Based on both the orientation of 3-OH and the dihedral angle (ϕ(O1C2C1′C2′)=3.8° for pelargonidin and 10.1° for cyanidin), the structures of pelargonidin and cyanidin in the crystals may correspond to structures **1a** and **2a** rather than **1b** and **2b**. The bond lengths calculated at the B3LYP/D95 level are 0.01–0.03 Å longer than those obtained by

the X-ray crystal analysis, except for the C1′–C2 bond. For the C1′–C2 bond, the bond lengths are 1.439 Å in **1a** and 1.443 Å in **2a**, which are shorter than those in the crystals by 0.019 Å in **1a** and 0.010 Å in **2a**. The orientations of the other hydroxyl groups except for 3-OH in **1a** and **2a** are different from those in the crystals. This is because the crystal structures depend on orientations, which are favorable for the formation of the hydrogen-bond network for crystal stability. The calculated planar structure, which corresponds to the orientations of all hydroxyl groups in the crystal structure is more unstable than **2a** by 6.9 kcal/mol.

MM and semi-empirical calculations have also been reported for the anthocyanidin structures[21,26] although these previous studies did not discuss the existence of some conformers according to orientation of the 3-OH group. The results of the MM calculation by Merlin et al.[26] were compared to the present results. The orientation of 3-OH is in agreement with that in **2a**. The bond lengths and orientations of the other OH groups are also consistent with those in planar structure **2a**. However, the dihedral angle, ϕ(O1C2C1′C2′), has been reported to be 28.6°, which is close to that in structure **2b**. Meanwhile, Rastelli et al.[21] reported that the C1′–C2 bond length is 1.433 Å and the dihedral angle ϕ(O1C2C1′C2′) is 0.3° in pelargonidin at the semi-empirical AM1 level. In cyanidin, the C1′–C2 bond length is 1.440 Å, which corresponds to that in planar structure **2a** while the dihedral angle ϕ(O1C2C1′C2′) is 19.0°, which corresponds to that in **2b**.

Next, we discuss the differences between two types of structures, ***n*a** and ***n*b**, in the same molecule. For the C1′–C2 bond, which connects the B-ring to the C-ring, the bond length in **1a** is 1.439 Å, which is shorter than that in **1b** (1.448 Å). In response to the bond length, the bond orders are also different. As shown in Table 4, the bond order of this bond in **1a** is 1.140, while that in **1b** is 1.043. Based on both the bond length and the bond order, it is shown that the bond in **1a** is stronger than that in **1b**. A difference in the bond strength is also seen for the other molecules. This corresponds to the fact that delocalization of the π-bond between two planes (the benzopyrylium ring and the B-ring) is not expected in the non-planar structure. Thus, the bond in **1b** is considered to be a single bond while that in **1a**

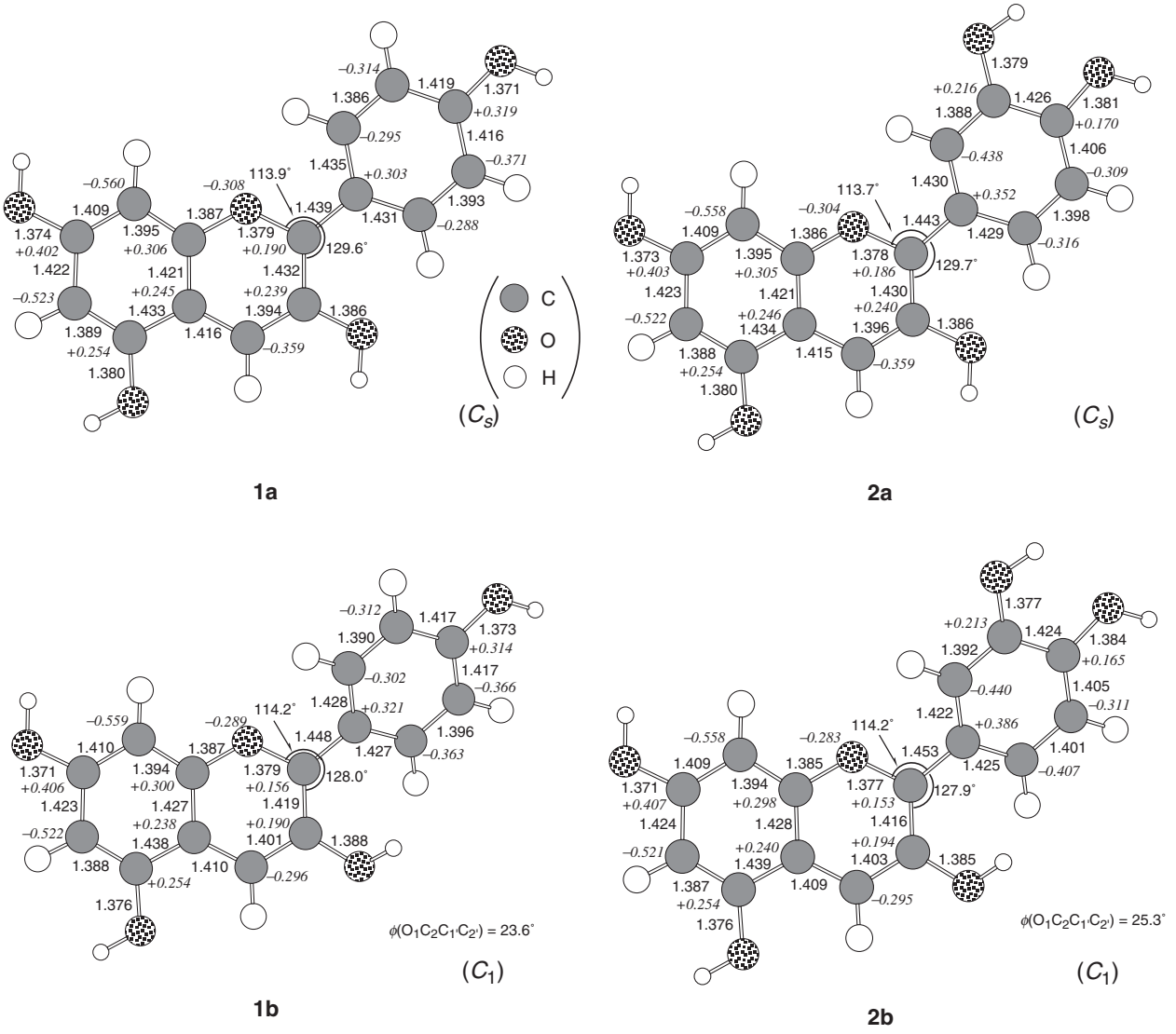


Figure 3. Optimized geometries at the B3LYP/D95 level. Bond length is in Å and bond angle is in degrees. The Mulliken atomic charges are in italics.

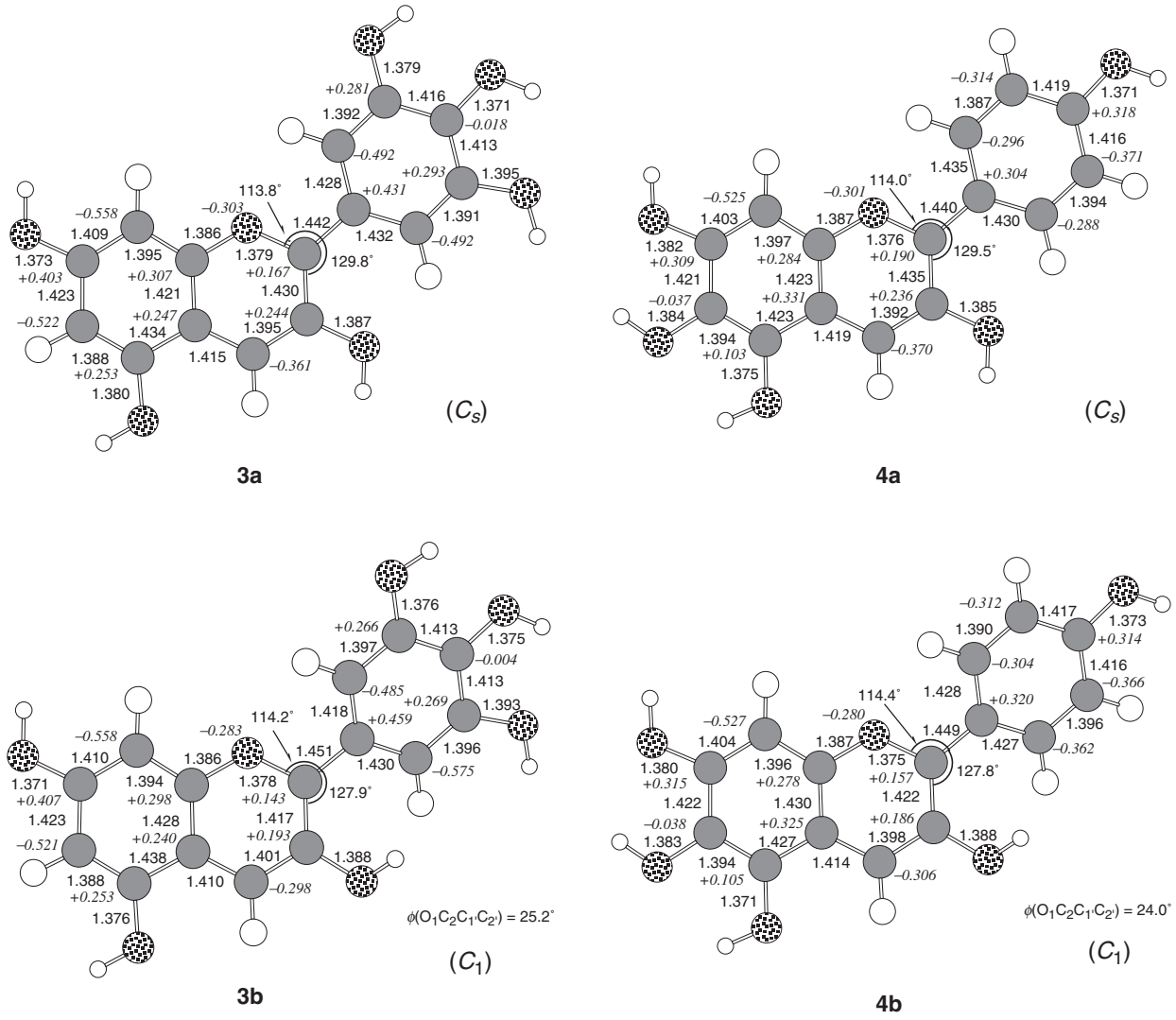


Figure 3 (*continued*)

possesses a slight π-bond character. Structural differences are also seen in the benzopyrylium part (A- and C-rings). The C2–C3 and C4–C10 bonds in planar structure ***n*a** are longer than those in ***n*b**, while the C3–C4, C9–C10, and C5–C10 bonds are shorter. The magnitudes of the bond orders in the C-ring correspond to the bond length. The bond orders of the C3–C4, C9–C10, and C5–C10 bonds in ***n*a** are larger than those in ***n*b** while the bond orders of the O1–C2, C2–C3 and C4–C10 bonds at ***n*a** are smaller. The atomic charges at the C-ring are also mostly different. The atomic charges at the O1 and C4 atoms in ***n*a** are more negative than those in ***n*b**. On the other hand, the charges at the C2 and C3 atoms in ***n*a** are more positive than those in ***n*b**. The C4 atomic charge has the greatest change. The π-bond character in the C2–C1′ bond is not seen in the non-planar structure ***n*b**, so that the distributions of the π-electrons in the C-ring in ***n*b** are different from those in ***n*a**.

Table 3. Relative energies Δ*E* (kcal/mol)

	B3LYP/D95	B3LYP/D95 (+ZPE)	B3LYP/D95(d)// B3LYP/D95(+ZPE)
1a	0.0	0.0	0.0
1b	3.7	3.4	1.8
2a	0.0	0.0	0.0
2b	3.2	3.0	1.3
3a	0.0	0.0	0.0
3b	3.7	3.4	1.5
4a	0.0	0.0	0.0
4b	3.9	3.6	1.9

We now discuss the structural variations due to substitutions of the hydroxyl group. In both the planar and non-planar structures, the C1′–C2 bond lengths in cyanidin are longer than those in pelargonidin, while the bond lengths in delphinidin are slightly shorter than those in cyanidin. The bond order of this bond decreases with successive hydroxyl substitutions. At the same time, the atomic charge at the C1′ atom becomes positive while that at the C2 atom becomes negative. In the case of pelargonidin, the C1′–C2 bond is strengthened by the *para*-OH group in the B-ring. On the other hand, the bond order analysis shows that introduction of the *meta*-OH groups makes the bond weaker. In aurantinidin, a definite change is not observed in comparison with pelargonidin. These variations in bond strength are also observed in the torsional vibrational mode of the

Table 4. Mayer bond orders *I* and dipole moments μ at the B3LYP/D95 level

	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**
I								
O1–C2	1.065	1.085	1.069	1.089	1.077	1.094	1.076	1.098
C2–C3	1.268	1.303	1.281	1.315	1.278	1.312	1.260	1.291
C3–C4	1.390	1.336	1.381	1.323	1.386	1.332	1.406	1.355
C4–C10	1.172	1.221	1.179	1.232	1.177	1.227	1.107	1.155
C9–C10	1.321	1.286	1.317	1.280	1.317	1.282	1.286	1.245
C5–C10	1.164	1.155	1.161	1.151	1.163	1.154	1.167	1.161
C2–C1′	1.140	1.043	1.108	1.005	1.088	0.994	1.136	1.038
C1′–C2′	1.232	1.250	1.256	1.272	1.250	1.269	1.232	1.250
C1′–C6′	1.250	1.243	1.254	1.223	1.280	1.225	1.251	1.245
μ (a.u.)	0.9634	0.1727	1.3967	0.4433	2.0592	1.1405	0.0872	0.9538

planar structures. The torsional vibrational frequencies decrease with successive hydroxylation in the B-ring. These frequencies are 40 cm^{-1} in **1a**, 33 cm^{-1} in **2a**, 28 cm^{-1} in **3a**, and 37 cm^{-1} in **4a**.

We also examined the dipole moment μ in each species. As shown in Table 4, μ increases as the hydroxyl group is introduced into the B-ring. Moreover, μ values for the planar structures ***n*a** are larger than those for the non-planar structures ***n*b** in the case of $n=1$–3. According to Onsager's theory of the reaction field,[45] it is predicted that the planar structures (**1a**–**3a**) are stabilized more by the polar solvent effects than the non-planar structures (**1b**–**3b**). In the case of aurantinidin, μ in **4b** is greater than that in **4a** and this result is different from those in the other molecules.

3.2. Excited states

The SE–CI calculations were performed using the planar structures ***n*a** ($n=1$–4) optimized at the B3LYP/D95 level of theory. The results are shown in Table 5. The orbital energy diagrams near HOMO–LUMO and these MOs in **1a** are shown in Figures 4 and 5, respectively.

In all molecules **1a**–**4a**, the main configuration of the 2A′ state, which corresponds to the first excited state is the HOMO→LUMO excitation, as shown in Table 5. The main configuration of the 3A′ and 4A′ states, which correspond to the second and third excited states are the (HO−1)MO→LUMO and (HO−2)MO→LUMO excitations, respectively. The oscillator strength of the 2A′ state is large while those of the 3A′ and 4A′ states are very small. Therefore, it is predicted that λ_{max} observed in the spectral experiments originates in the 2A′ state.

We now discuss the excitation energies from the ground 1A′ state to the 2A′ state. The excitation energies to the 2A′ state are 3.58 eV in **1a**, 3.56 eV in **2a**, and 3.50 eV in **3a**. These energies decrease with the successive hydroxylations in the B-ring. On the other hand, the excitation energy in **4a** is 3.63 eV, which is greater than that in **1a**. Since this relative trend in the excitation energies is also obtained by calculations using the D95(d) basis set, it is indicated that the polarization function in the basis set have little effect on the results. This result, that is, successive hydroxylations in the B-ring cause a bathochromic shift in the λ_{max} while hydroxy substitution at the 6-position in the A-ring gives a hypsochromic shift, agrees with the experimental[1,9] and theoretical[25] results.

Since the main configuration of the lowest excited state is HOMO→LUMO excitation in all molecules, we notice the orbital energies in HOMO and LUMO. As shown in Figure 4, the HOMO–LUMO gap decreases with the

Table 5. Excited states of **1a**, **2a**, **3a**, and **4a** calculated by the SE–CI method

State	SE–CI/D95			SE–CI/D95(d)	Experimental λ_{max}[a,b]
	Main configuration ($\|C\|>0.2$)	Excitation energy[a]	Oscillator strength	Excitation energy[a]	
1a					
2A′	$0.96(12a''–13a'')$	3.58 (346)	1.2655	3.50 (354)	2.38 (520)
3A′	$0.87(11a''–13a'')-0.27(12a''–14a'')-0.21(10a''–13a'')$	4.83 (257)	0.0232	4.78 (259)	
4A′	$0.88(10a''–13a'')-0.24(10a''–14a'')+0.22(12a''–16a'')+0.20(11a''–13a'')$	4.94 (251)	0.0347	4.98 (249)	
2a					
2A′	$0.92(13a''–14a'')+0.27(12a''–14a'')$	3.56 (348)	1.2369	3.47 (357)	2.32 (535)
3A′	$0.90(12a''–14a'')-0.25(13a''–14a'')$	4.41 (281)	0.0171	4.46 (278)	
4A′	$0.90(11a''–14a'')+0.22(13a''–15a'')$	4.78 (259)	0.0203	4.74 (262)	
3a					
2A′	$0.93(14a''–15a'')$	3.50 (354)	1.2420	3.41 (363)	2.27 (546)
3A′	$0.93(13a''–15a'')-0.20(13a''–16a'')$	4.24 (293)	0.0418	4.27 (290)	
4A′	$0.88(12a''–15a'')+0.24(14a''–16a'')-0.23(11a''–15a'')$	4.69 (264)	0.0181	4.65 (266)	
4a					
2A′	$0.95(13a''–14a'')$	3.63 (341)	1.2883	3.55 (350)	2.48 (499)
3A′	$0.92(12a''–14a'')+0.21(12a''–15a'')$	4.46 (278)	0.0141	4.39 (283)	
4A′	$0.91(11a''–14a'')-0.25(11a''–15a'')$	4.91 (252)	0.0354	4.97 (250)	

[a] In eV (nm).
[b] Refs. 1,9 (methanol–HCl).

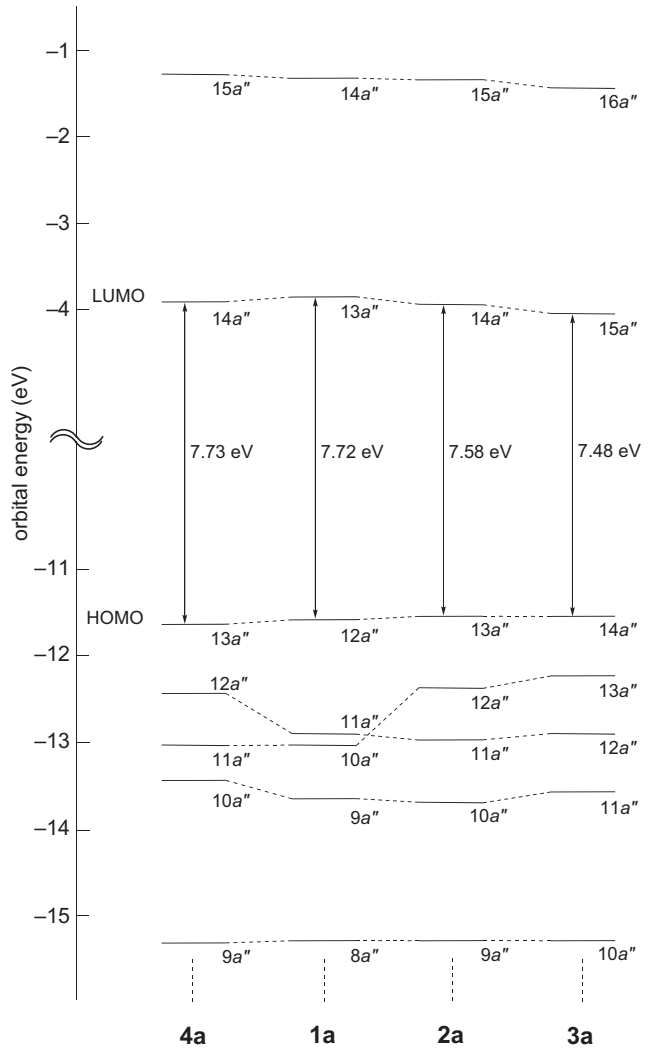


Figure 4. MO energy diagram at the RHF/D95//B3LYP/D95 level.

successive introduction of hydroxyl group in the B-ring (**1a**→**2a**→**3a**). These results correspond to the excitation energies in the SE–CI calculations and previous Hückel calculations.[18] The change in the HOMO–LUMO gap depends mainly on the lowering of the orbital energy in LUMO. On the other hand, the HOMO–LUMO gap in **4a** increases because the lowering of the HOMO energy level is greater than that of the LUMO energy level. In the next section, the variations of the HOMO and LUMO are discussed in terms of the orbital interactions.

As shown in Figure 5, the amplitude of the (HO−2)MO ($10a''$) in **1a** is localized in the B-ring, which originates in the e_{1g} orbital in benzene. The orbitals in **2a** and **3a**, which correspond to the $10a''$ orbital in **1a** are (HO−1)MOs ($12a''$ and $13a''$) and these orbital energies are higher than that of the $10a''$ orbital in **1a**. On the other hand, the (HO−2)MOs in **2a** and **3a**, which correspond to the $11a''$ orbital in **1a** have the same energy levels since these orbitals have large amplitudes in the A-ring part. This result shows that the second excited states in **2a** and **3a** correspond to the $4A'$ state in **1a** while the third excited state in **2a** and **3a** corresponds to the $3A'$ state in **1a**. In the case of **4a**, the (HO−1)MO is destabilized while

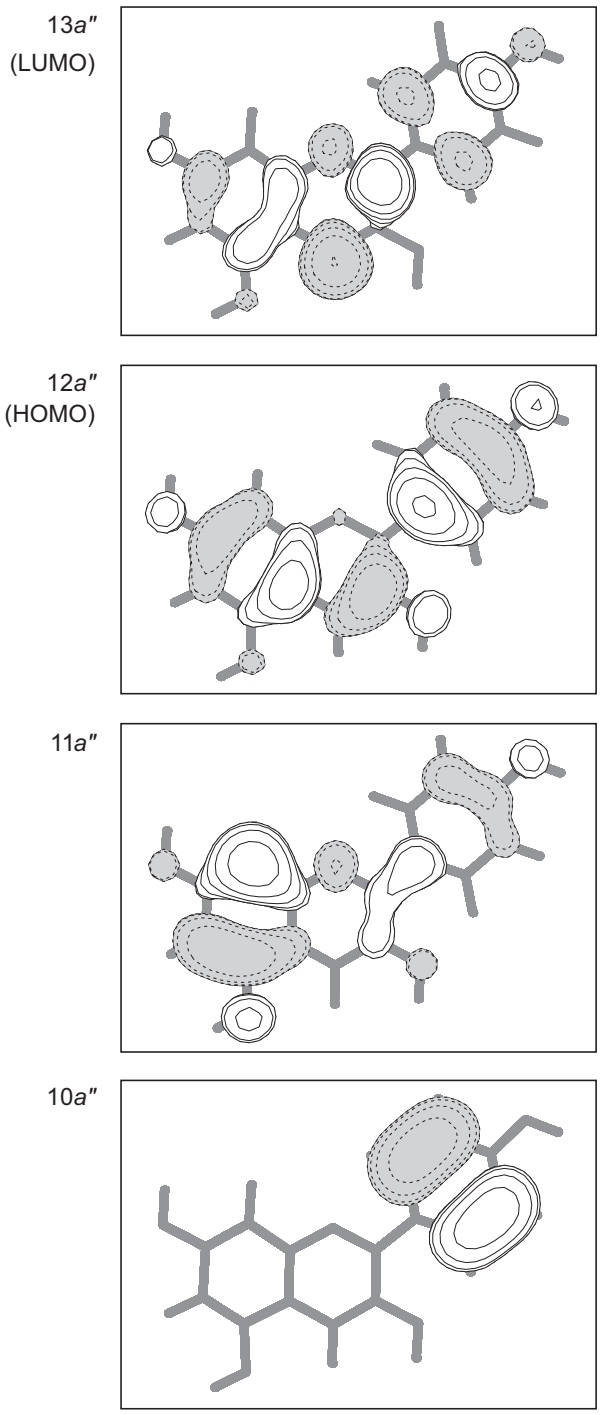


Figure 5. MO contours of **1a** at the RHF/D95//B3LYP/D95 level. MOLDEN[48] program was used for MO visualization.

the stability of the (HO−2)MO in **4a** is not changed in comparison with the orbital energies in **1a**.

We also investigated the strength of the C1′–C2 bond to predict the stable structures in the excited states. The Mayer bond orders at the RHF and SE–CI levels are shown in Table 6. One-particle density matrices are used for calculations at the SE–CI level. The main configuration of the $2A'$ state is excitation from the HOMO to the LUMO. In the HOMO, the C1′–C2 bond has an out-of-phase overlap. On the other hand, the amplitude of the C1′ atom is very

Table 6. Bond order $I(C1'–C2')$ and dipole moments μ

	$I(C1'–C2')$ [a]	μ (a.u.)[a]	μ (a.u.)[b]
1a			
$1A'$	1.044	1.2529	1.2116
$2A'$	1.065	0.9023	0.7561
$3A'$	0.996	2.9368	3.2589
$4A'$	1.091	2.8550	3.1299
2a			
$1A'$	1.003	1.8930	1.8228
$2A'$	1.044	1.4127	1.1036
$3A'$	1.051	3.0089	2.2621
$4A'$	0.977	2.8445	2.3287
3a			
$1A'$	0.985	2.7311	2.6441
$2A'$	1.031	1.9751	1.3352
$3A'$	1.041	2.5726	2.8765
$4A'$	0.949	3.9258	3.9018
4a			
$1A'$	1.043	0.2711	0.2566
$2A'$	1.063	0.4989	0.7143
$3A'$	0.997	4.0211	4.6228
$4A'$	1.092	3.8666	4.1052

[a] RHF/D95 level for the ground $1A'$ state and SE–CI level for the excited states.
[b] SAC level for the ground $1A'$ state and SAC-CI level for the excited states.

small, and therefore the bond overlap is too small in the LUMO. As a result, the bond order increases slightly in all molecules. This indicates that this bond is slightly strengthened by excitation to the $2A'$ state.

3.3. Orbital interactions in HOMO and LUMO

The variations of the HOMO and LUMO by the hydroxylation in the B-ring were examined in terms of the orbital interactions using the fragment molecular orbital (FMO) scheme.[46] At the σ-bond, which connects the B-ring with the C-ring, pelargonidin **1a** was divided into the benzopyrylium cation radical (A) and the phenol radical (B) and each fragment π-MO ($\psi^{A}_{la''}$, $\psi^{B}_{ma''}$) was calculated at the ROHF/D95 level of theory. Then the HOMO and LUMO in **1a** were represented by the linear combination of the obtained fragment π-MOs:

$$\psi_{HOMO} \cong +0.129\psi^{A}_{6a''} + 0.274\psi^{A}_{7a''} + 0.617\psi^{A}_{8a''} - 0.234\psi^{A}_{9a''} - 0.710\psi^{B}_{4a''},$$

$$\psi_{LUMO} \cong -0.901\psi^{A}_{9a''} + 0.179\psi^{B}_{2a''} + 0.422\psi^{B}_{4a''} - 0.239\psi^{B}_{6a''}.$$

Each fragment π-MO and the orbital interaction diagram are shown in Figure 6. In the HOMO, the linkage π-overlap population is -0.0180 and the major components of the population are the negative population between the $\psi^{A}_{8a''}$ and $\psi^{B}_{4a''}$ orbitals (-0.0206) and the positive population between the $\psi^{A}_{9a''}$ and $\psi^{B}_{4a''}$ orbitals ($+0.0197$). On the other hand, the major components of the overlap population in the LUMO (-0.0098) are the negative population between the $\psi^{A}_{9a''}$ and $\psi^{B}_{4a''}$ orbitals (-0.0451) and the positive population between the $\psi^{A}_{9a''}$ and $\psi^{B}_{6a''}$ orbitals ($+0.0569$).

The HOMO and LUMO at cyanidin **2a** and delphinidin **3a** were also examined by the same method. In the overlap populations in the HOMOs, the negative components, which correspond to that between the $\psi^{A}_{8a''}$ and $\psi^{B}_{4a''}$ orbitals in **1a** are -0.0153 (**2a**) and -0.0162 (**3a**). This out-of-phase overlap is weakened by the introduction of the *meta*-OH groups. The positive components ($\psi^{A}_{9a''} - \psi^{B}_{4a''}$ in **1a**) are $+0.0153$ (**2a**) and $+0.0169$ (**3a**), and so that the in-phase overlap is also weakened. For the introduction of the *meta*-OH groups, it is found that the variations of these two major components have the opposite effects on the stability of the HOMO. In the overlap populations in the LUMOs, the negative components ($\psi^{A}_{9a''} - \psi^{B}_{4a''}$ in **1a**) are -0.0392 (**2a**) and -0.0334 (**3a**) and the positive components ($\psi^{A}_{9a''} - \psi^{B}_{6a''}$ in **1a**) are $+0.0593$ (**2a**) and $+0.0636$ (**3a**). In the LUMO, the out-of-phase overlap is weakened while the in-phase overlap is strengthened. Both the components contribute to the stabilization in the LUMO. Here the AO coefficients at $C1'$ atom are not zero in the B-fragment MOs in **2a**, which correspond to the $\psi^{B}_{3a''}$ and $\psi^{B}_{5a''}$ orbitals in **1a**, because these orbitals are mixed with those, which correspond to the $\psi^{B}_{4a''}$ and $\psi^{B}_{6a''}$ orbitals in **1a**, respectively. Then, the negative overlap component in **2a** ($\psi^{A}_{9a''} - \psi^{B}_{4a''}$ in **1a**) is regarded as the sum of the overlap populations ($\psi^{A}_{6a''} - \psi^{B}_{3a''}$ and $\psi^{A}_{9a''} - \psi^{B}_{4a''}$ in **1a**). In the same way, the overlap population in **2a** ($\psi^{A}_{9a''} - \psi^{B}_{6a''}$ in **1a**) is also regarded as the sum of the overlap populations ($\psi^{A}_{9a''} - \psi^{B}_{5a''}$ and $\psi^{A}_{9a''} - \psi^{B}_{6a''}$ in **1a**).

Thus, we obtain the following qualitative explanation for the effects of the *meta*-OH groups. When the OH group is introduced into the *meta*-position at phenol part (B), the AO coefficients at $C1'$ atom decrease in the $\psi^{B}_{4a''}$ orbital while these increase in the $\psi^{B}_{6a''}$ orbital by the electron-withdrawing effect of the *meta*-OH group. Then, in the HOMO the out-of-phase overlaps between the fragment occupied MOs ($\psi^{A}_{6a''}$, $\psi^{A}_{7a''}$, and $\psi^{A}_{8a''}$) and the $\psi^{B}_{4a''}$ orbital is weakened and the in-phase overlap between the $\psi^{A}_{9a''}$ and $\psi^{B}_{4a''}$ orbitals is also weakened. As the result of the balance between these antithetic effects, the HOMO is destabilized. On the other hand, in the LUMO the out-of-phase overlap between the $\psi^{A}_{9a''}$ and $\psi^{B}_{4a''}$ orbitals is weakened and the in-phase overlap between $\psi^{A}_{9a''}$ and $\psi^{B}_{6a''}$ is strengthened, so that the LUMO is stabilized.

3.4. Excitation energies by the SAC/SAC-CI method

The low-excited states of **1a**–**4a** by the SAC/SAC-CI calculations are shown in Table 7. In all molecules, the main configurations of each electronic state by the SAC-CI calculations are consistent with the results of the SE–CI calculations. Thus, the main configurations of the $2A'$, $3A'$, and $4A'$ states are the HOMO→LUMO excitation, the (HO−1)MO→LUMO excitation, and the (HO−2)MO→LUMO excitation, respectively. The oscillator strength of the $2A'$ state is large while the strengths of the other states are very small. Moreover, the excitation energy within the visible region is only the $2A'$ state.

The excitation energies from the ground $1A'$ state to the $2A'$ state are 2.58, 2.56, 2.46, and 2.63 eV in **1a**, **2a**, **3a**, and **4a**, respectively. As shown in Table 1, experimental λ_{max} values observed in methanol–HCl solution are 2.38 eV (520 nm) in pelargonidin, 2.32 eV (535 nm) in cyanidin, 2.27 eV (546 nm) in delphinidin, and 2.48 eV (499 nm) in

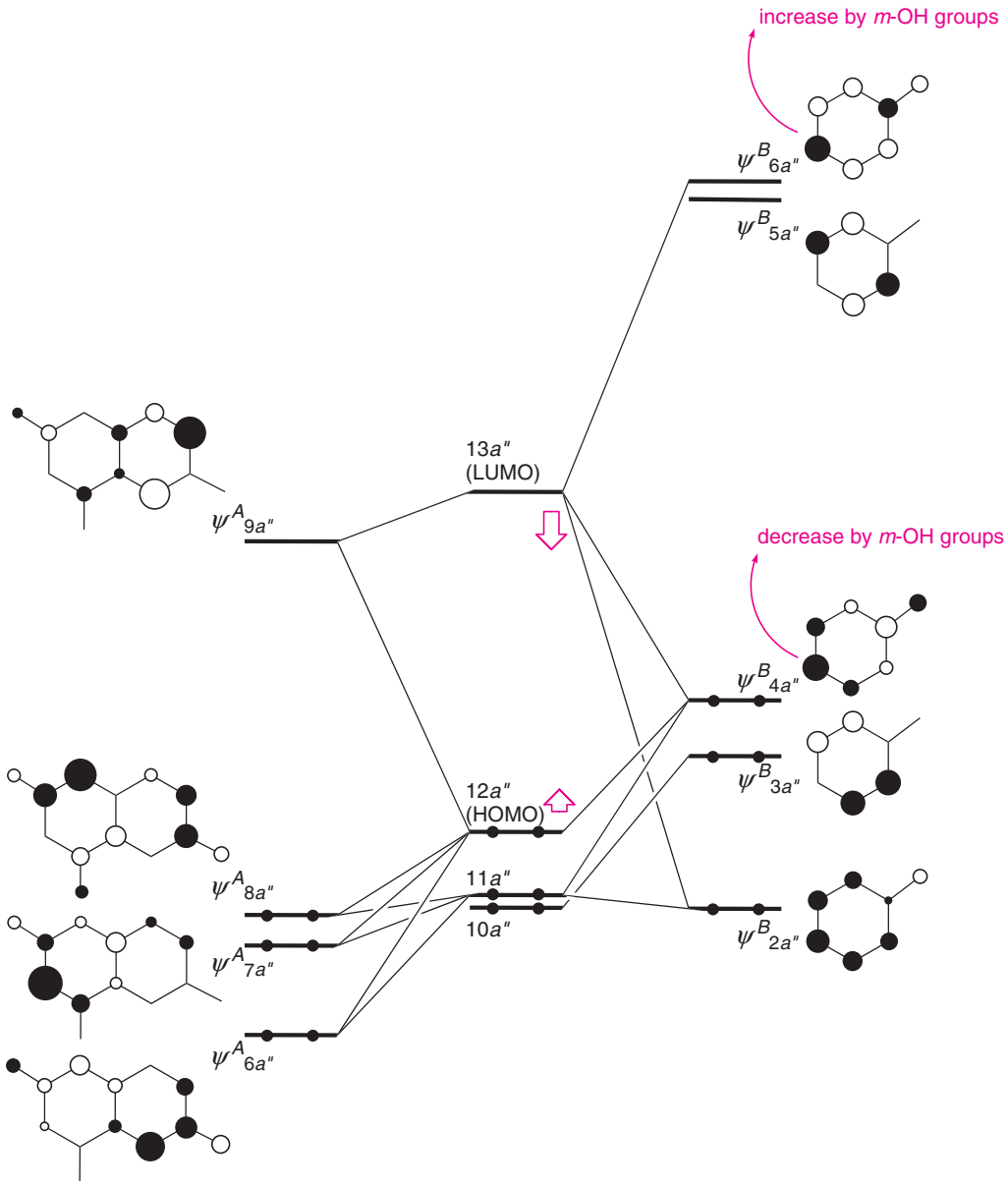


Figure 6. Fragment MO patterns and the orbital interaction diagram in **1a**.

aurantinidin. The SAC/SAC-CI results are better than the SE–CI results and the differences between the experimental λ_{max} and calculated energies are about 0.2 eV. Moreover, the results of these high-level ab initio calculations also show the same tendency as the SE–CI results, in that the lowest excitation ($1A' \rightarrow 2A'$) energy becomes bathochromic with successive hydroxylation in the B-ring while the excitation energy becomes hypsochromic with the 6-OH substitution.

Finally, the dipole moment μ in each electronic state is examined. The μ values calculated by the RHF/SE–CI and SAC/SAC-CI methods are shown in Table 6. In the ground $1A'$ state, the μ values calculated at the B3LYP level are different from the results at the RHF and SAC levels, but the difference between the SE–CI results and SAC-CI results is small. In **1a**, **2a**, and **3a**, the μ values in the $2A'$ state are smaller than those in the $1A'$ state while those in the $3A'$ and $4A'$ states are larger. In the case of **4a**, the μ value in the $1A'$ state is smaller than those in the $1A'$ state of the other molecules and the μ values in the $3A'$ and $4A'$ states are greater than those of the other molecules. According to Onsager's theory of the reaction field, it is predicted that the spectral shift of the $2A'$ state due to the polar solvent is small.

4. Conclusion

Using quantum chemical calculations, we investigated the structural stabilities and electronic structures of four anthocyanidin cationic molecules: pelargonidin, cyanidin, delphinidin, and aurantinidin. First, the stable structures in these molecules were examined at the B3LYP/D95 level of theory. Two stable structures, the planar structure and the non-planar structure, were obtained for each molecule. For all molecules, the planar structures are slightly more stable than the non-planar structures. Next, SE–CI and SAC/SAC-CI calculations were carried out for the planar structures in

Table 7. Excited states of **1a**, **2a**, **3a**, and **4a** calculated by the SAC/SAC-CI method

States	Main configuration ($\|C\|>0.1$)	Excitation energy[a]	Oscillator strength	Experimental λ_{max}[a,b]
1a				
2A′	$0.94(12a''–13a'')-0.12(11a''–13a'')-0.10(12a'',9a''–13a'',13a'')$	2.58 (481)	0.7823	2.38 (520)
3A′	$0.91(11a''–13a'')-0.15(10a''–13a'')-0.12(9a''–13a'')-0.11(12a''–14a'')+0.10(12a''–13a'')$	3.48 (356)	0.0311	
4A′	$0.89\ (10a''–13a'')+0.20(12a''–16a'')+0.15(11a''–13a'')-0.14(10a''–14a'')-0.16(12a'',10a''–13a'',13a'')$	3.89 (319)	0.0159	
2a				
2A′	$0.93(13a''–14a'')+0.16(12a''–14a'')-0.12(11a''–14a'')$	2.56 (484)	0.7211	2.32 (535)
3A′	$0.92(12a''–14a'')-0.16(13a''–14a'')-0.13(11a''–14a'')$	3.19 (388)	0.0121	
4A′	$0.91(11a''–14a'')+0.14(12a''–14a'')-0.12(10a''–14a'')+0.11(12a''–15a'')$	3.56 (348)	0.0482	
3a				
2A′	$0.94(14a''–15a'')+0.12(12a''–15a'')-0.10(13a''–15a'')-0.11(12a'',14a''–15a'',15a'')$	2.46 (504)	0.7339	2.27 (546)
3A′	$0.93(13a''–15a'')+0.12(14a''–18a'')-0.10(13a''–16a'')+0.14(13a'',14a''–15a'',15a'')$	2.99 (414)	0.0119	
4A′	$-0.92(12a''–15a'')+0.17(11a''–15a'')+0.11(14a''–15a'')$	3.36 (369)	0.0057	
4a				
2A′	$0.95(13a''–14a'')-0.15(10a'',13a''–14a'',14a'')$	2.63 (472)	0.8068	2.48 (499)
3A′	$0.94(12a''–14a'')+0.10(12a''–15a'')$	3.01 (412)	0.0156	
4A′	$0.91(11a''–14a'')-0.16(13a''–17a'')-0.16(11a''–15a'')+0.11(13a''–16a'')-0.16(11a'',13a''–14a'',14a'')$	3.87 (321)	0.0169	

[a] In eV (nm).
[b] Refs. 1,9 (methanol–HCl).

all molecules. These high-level ab initio calculations have shown that the lowest excitation energies, which correspond to the visible absorption maxima in the spectral experiments vary according to the existence of hydroxyl groups without taking solvent effects into account. Thus, hydroxy substitution at the 6-position in the A-ring increases the lowest excitation energy while successive hydroxylations in the B-ring decrease the excitation energies.

Now we examine the electronic excited states in not only the anthocyanidin cationic form but also neutral and anionic forms by the TD-DFT method with larger basis sets, including the PCM theory.[47]

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Reactions of (*E*)-1,2-di(3-guaiazulenyl)ethylene and 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene with tetracyanoethylene (TCNE) in benzene: comparative studies on the products and their spectroscopic properties

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Abstract—Reactions of the title ethylene derivatives, (*E*)-1,2-di(3-guaiazulenyl)ethylene (**1**) and 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (**2**), with a 2 M amount of TCNE in benzene at 25 °C for 24 h under argon give new cycloaddition compounds, 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (**3**) from **1** and 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]-azulene (**4**) from **2**, respectively, in 66 and 87% isolated yields. Comparative studies on the above reactions as well as the spectroscopic properties of the unique products **3** and **4**, possessing interesting molecular structures, are reported and, further, a plausible reaction pathway for the formation of these products is described.

1. Introduction

In the previous papers,[1–10] we reported a facile preparation and the crystal structures as well as the spectroscopic, chemical and electrochemical properties of the mono- and dicarbocations stabilized by a 3-guaiazulenyl group. During the course of our investigations, we have recently found (i) that the reduction of the dicarbocation compound, α,α′-bis(3-guaiazulenylmethylium) bis(tetrafluoroborate), with zinc powder in trifluoroacetic acid at 0 °C for 5 min under argon gave (*E*)-1,2-di(3-guaiazulenyl)ethylene (**1**) in 94% isolated yield and, further, the reaction of naturally occurring guaiazulene with 1,2-bis(4-methoxyphenyl)-1,2-ethanediol in methanol in the presence of hydrochloric acid at 60 °C for 3 h under aerobic conditions afforded the pinacol rearrangement product, 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (**2**), in 97% isolated yield;[8] and (ii) that the oxidation potentials of the above ethylene derivatives **1** and **2** in CH_3CN containing 0.1 M $[n\text{-}Bu_4N]BF_4$ as a supporting electrolyte showed that **1** stepwise underwent two-electron oxidation at +0.20 ($E_{1/2}$, reversible) and +0.35 ($E_{1/2}$, reversible) V by CV (and +0.24 and +0.39 V by DPV), generating an electrochemically stable dication-species and, similarly, **2** stepwise underwent two-electron oxidation at +0.52 ($E_{1/2}$, reversible) and +0.73 ($E_{1/2}$, reversible) V by CV (and +0.55 and +0.76 V by DPV), also generating an electrochemically stable dication-species.[8] Thus, the CV and DPV data suggested **1** and **2** serve as an electron donor, respectively, and indicated **1** is more susceptible two-electron oxidation than **2**. Furthermore, we have quite recently reported that the reactions of the *meso* forms, (1*R*,2*S*)-1,2-di(2-furyl)-1,2-di(3-guaiazulenyl)ethane[10] (**A**) [oxidation potential: +0.48 (E_{pa}, irreversible) V by CV and +0.48 (E_p) V by DPV][11] and (1*R*,2*S*)-1,2-di(3-guaiazulenyl)-1,2-di(2-thienyl)ethane[10] (**B**) [oxidation potential: +0.57 (E_{pa}, irreversible) V by CV and +0.56 (E_p) V by DPV],[11] with a 2 M amount of TCNE, which serves as an electron acceptor [−0.75 ($E_{1/2}$, quasi-reversible) V by CV and −0.76 (E_p) V by DPV][12] in benzene at 25 °C for 5 h (for **A**) and 48 h (for **B**) under

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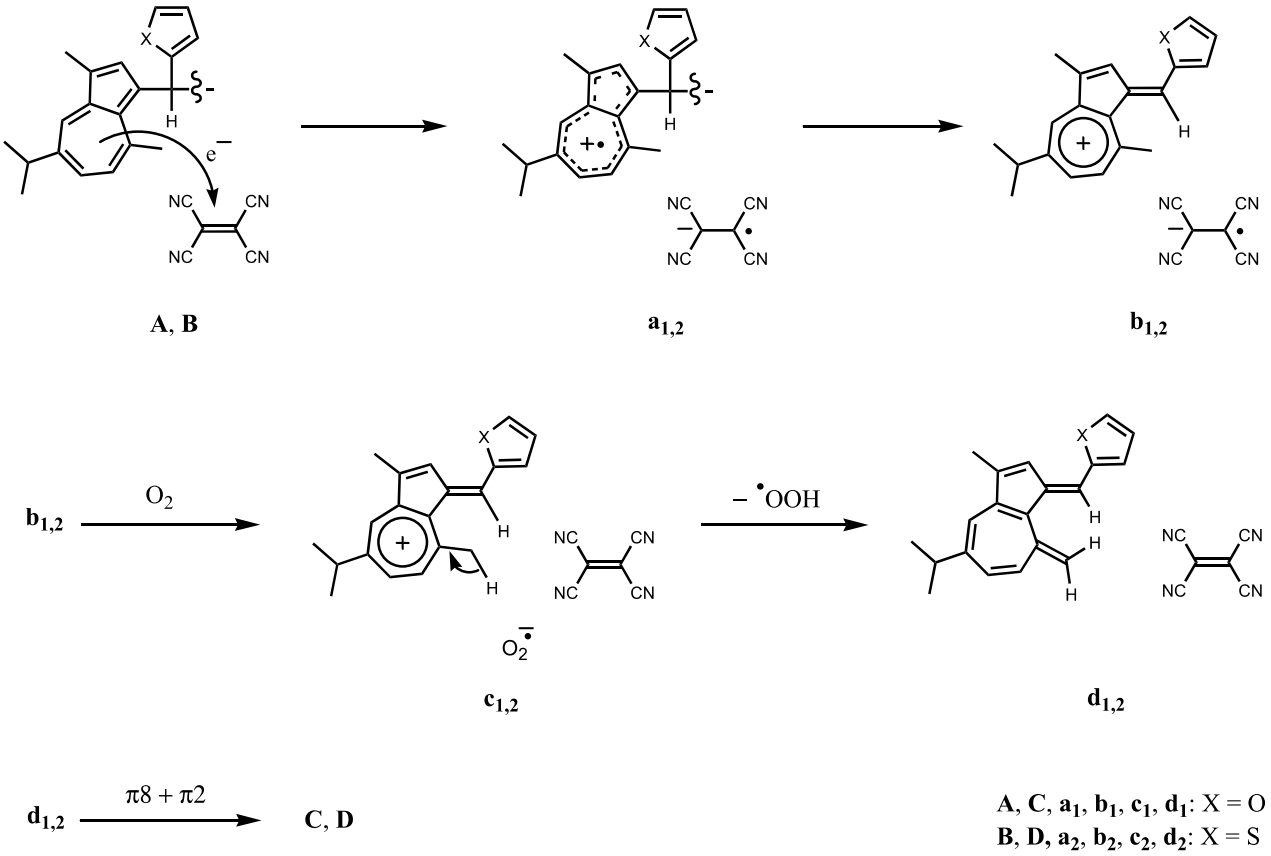


Scheme 1. A plausible reaction pathway for the formation of **C** and **D** yielded by the reactions of the *meso* forms **A** and **B** with a 2 M amount of TCNE in benzene at 25 °C for 5 h (for **A**) and 48 h (for **B**) under oxygen. The partial structures **A**, **B** and $\mathbf{a}_{1,2}$ are illustrated.

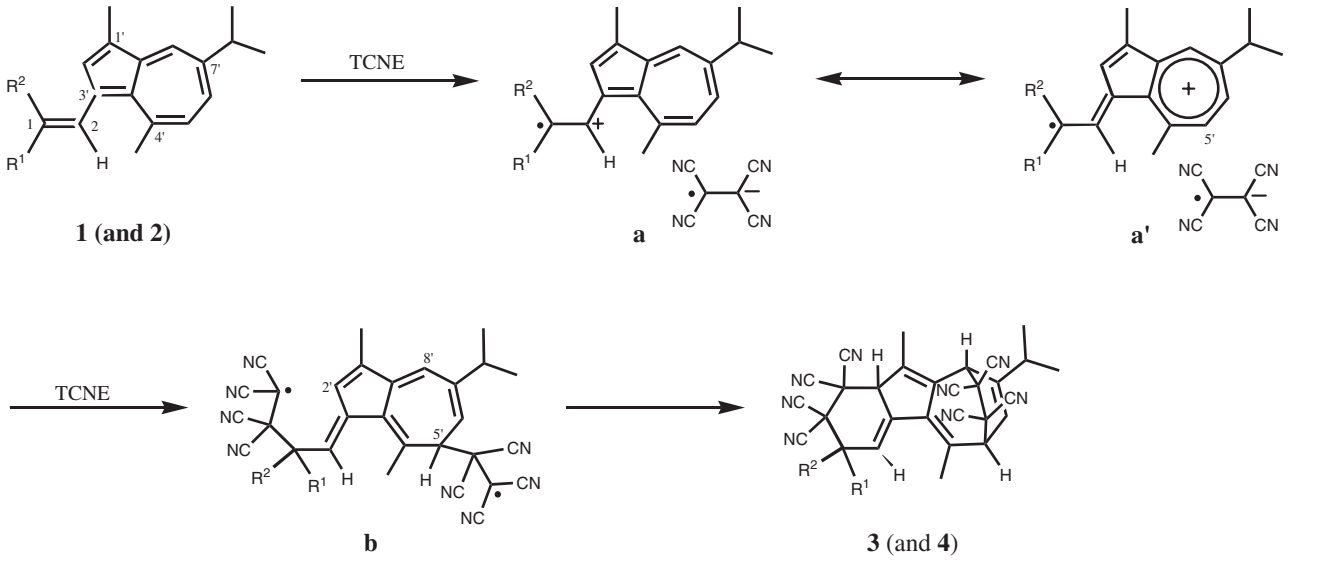
oxygen gave 2,2,3,3-tetracyano-4-(2-furyl)-8-isopropyl-6-methyl-1,2,3,4-tetrahydrocyclohepta[*c*,*d*]azulene (**C**) and 2,2,3,3-tetracyano-8-isopropyl-6-methyl-4-(2-thienyl)-1,2,3,4-tetrahydrocyclohepta[*c*,*d*]azulene (**D**), respectively, in 74 and 21% isolated yields and, further, a plausible reaction pathway for the formation of the unique products **C** and **D**, possessing interesting molecular structures, was described as shown in Scheme 1.[11] Moreover, our interest has quite recently been focused on a comparative study on the title chemistry, the reactions of **1** and **2** with TCNE in benzene at 25 °C under argon. In relation to our basic studies, in 1961 Hafner and Moritz reported that the reaction of guaiazulene in petroleum ether with TCNE in AcOEt at −20 °C gave a 1:1 π-complex in 98% isolated yield, which was converted into 3-tricyanovinylguaiazulene (68% isolated yield) in DMF at room temperature.[13] Furthermore, the addition and cycloaddition reactions of TCNE in organic chemistry[14–18] including azulenes[13,19–21] have been studied to a considerable extent, and a large number of those results and discussion have been well documented. Along with those investigations, we now wish to report the detailed title chemistry, affording the unique products, 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (**3**) from **1** and 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (**4**) from **2**, possessing interesting molecular structures, presumably via charge-transfer and, further, cycloaddtion reactions as shown in Scheme 2.

2. Results and discussion

2.1. Reaction of (*E*)-1,2-di(3-guaiazulenyl)ethylene (1) with TCNE; preparation and spectroscopic properties of 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (3)

Compound **3** was prepared from compound **1** and TCNE using benzene as a solvent as shown in Section 4.1.1, whose molecular structure was established on the basis of elemental analysis and spectroscopic data [UV–vis, IR, exact FAB-MS, ^{1}H and ^{13}C NMR including 2D NMR (i.e., H–H COSY, HMQC=^{1}H detected hetero nuclear multiple quantum coherence and HMBC=^{1}H detected hetero nuclear multiple bond connectivity)].

Compound **3** (66% isolated yield) was blue prisms [R_f=0.39 on silica-gel TLC (hexane/AcOEt=7:3, vol/vol)], mp 159 °C [decomp., determined by the thermal analysis (TGA and DTA)]. The characteristic UV–vis (CH_2Cl_2) absorption bands based on the 3-guaiazulenyl group were observed and the longest visible absorption wavelength appeared at λ_{max} 587 nm (log ε=2.62). The IR (KBr) spectrum showed



1, **3** : R^1 = 3-guaiazulenyl, R^2 = H
2, **4** : $R^1 = R^2 = p$–$CH_3OC_6H_4$–

Scheme 2. A plausible reaction pathway for the formation of **3** and **4** yielded by the reactions of **1** and **2** with a 2 M amount of TCNE in benzene at 25 °C for 24 h under argon.

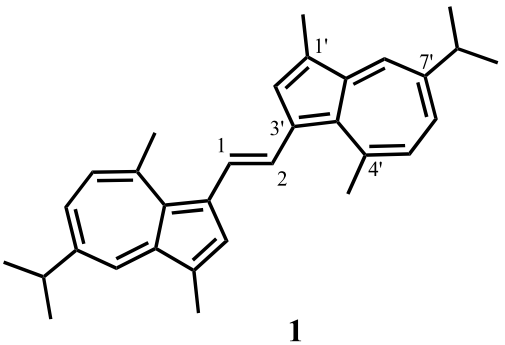
a specific band based on the –C≡N group at ν_{max} 2253 and 2249 cm^{-1}, which coincided with those of **C**[11] and **D**.[11] The protonated molecular formula $C_{44}H_{37}N_8$ ($[M+H]^+$) was determined by the exact FAB-MS (3-nitrobenzyl alcohol matrix) spectrum. The elemental analysis confirmed the molecular formula $C_{44}H_{36}N_8$. The 500 MHz ^{1}H NMR (CD_2Cl_2) spectrum showed signals based on the structure of 8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydrobenz[*a*]azulene possessing a 3-guaiazulenyl group at the C-3 position, which signals (δ and *J* values) were carefully assigned using the H–H COSY technique and the computer-assisted simulation analysis (see Section 4.1.1). The 125 MHz ^{13}C NMR (CD_2Cl_2) spectrum exhibited 36 carbon signals (δ) based on the structure of 3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene and eight carbon signals (δ) based on the –C≡N group, bound at the C-1, 2, 11 and 12 positions, assigned by the HMQC and HMBC techniques (see Section 4.1.1). Thus, the elemental analysis and these spectroscopic data for **3** led to a new molecular structure, 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (see Chart 1).

The crystal structure of **3** was then measured by means of the X-ray diffraction. As a result, although an X-ray crystallographic analysis of **3**, producing accurate structural parameters, has not yet been achieved because of very difficulty in obtaining a single crystal suitable for this purpose (see Ref. 22), the molecular structure of **3** established on the basis of elemental analysis and spectroscopic data could be determined. The crystal structure of **3** with the numbering Scheme, indicating the molecular structure, 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene, is shown in Figure 1. An X-ray crystallographic analysis of **3**, producing accurate structural parameters, is further currently under intensive investigation.

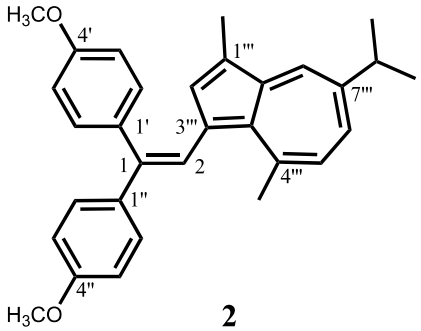
2.2. Reaction of 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (2) with TCNE; preparation and spectroscopic properties of 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (4)

Similarly, as in the case of the preparation of **3**, the target compound **4** was prepared from compound **2** and TCNE using benzene as a solvent as shown in Section 4.1.2, whose molecular structure was established on the basis of similar elemental and spectroscopic analyses to those of **3**.

Compound **4** (87% isolated yield) was white powder [R_f = 0.18 on silica-gel TLC (hexane/AcOEt = 7:3, vol/vol)], mp 140 °C [decomp., determined by the thermal analysis (TGA and DTA)], while a solution of **4** in dichloromethane was pale yellow. The characteristic UV–vis (CH_2Cl_2) absorption bands based on the azulenyl group were not observed and the longest visible absorption wavelength appeared at λ_{max} 410 nm (log ε = 3.08). The IR (KBr) spectrum showed a specific band based on the –C≡N group at ν_{max} 2253 and 2249 cm^{-1}, which coincided with that of **3**. The protonated molecular formula $C_{43}H_{33}N_8O_2$ ($[M+H]^+$) was determined by the exact FAB-MS (3-nitrobenzyl alcohol matrix) spectrum. The elemental analysis confirmed the molecular formula $C_{43}H_{34}N_8O_3$ based on the monohydrate of **4**. The 500 MHz ^{1}H NMR (CD_2Cl_2) spectrum showed signals based on the structure of 8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydrobenz[*a*]azulene possessing two 4-methoxyphenyl groups at the C-3 position, which signals (δ and *J* values) were carefully assigned using the H–H



1



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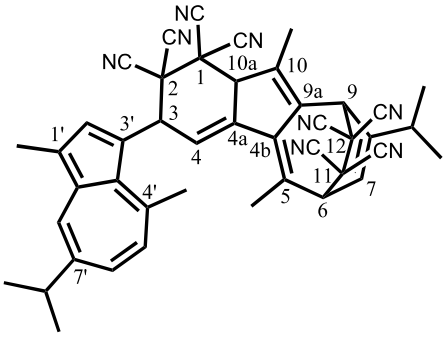

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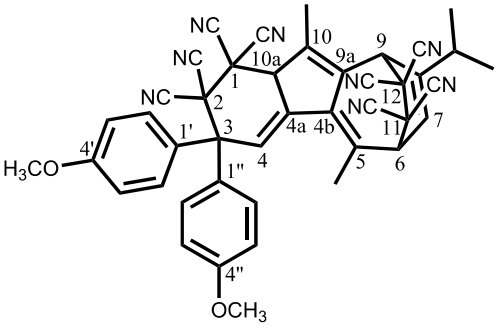
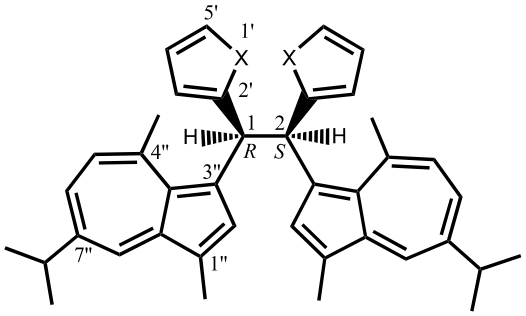
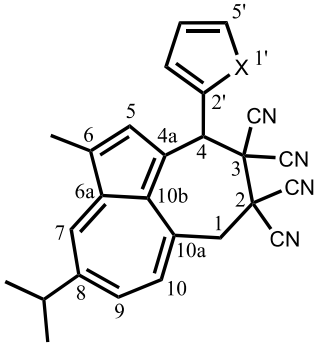


4



A, B



C, D

A, C : X = O
B, D : X = S

Chart 1.

COSY technique and the computer-assisted simulation analysis (see Section 4.1.2). The 125 MHz ^{13}C NMR (CD_2Cl_2) spectrum exhibited 35 carbon signals (δ) based on the structure of 8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz-[*a*]azulene and eight carbon signals (δ) based on the –C≡N group, bound at the C-1, 2, 11 and 12 positions, assigned by the HMQC and HMBC techniques (see Section 4.1.2). Thus, the elemental analysis and these spectroscopic data for **4** led to a new molecular structure, 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (see Chart 1). From a comparative study on the detailed ^{1}H and ^{13}C NMR signals of **3** and **4** (see Sections 4.1.1 and 4.1.2), it can be inferred that the conformation of the 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene unit of **4** assumes similar to that of **3**.

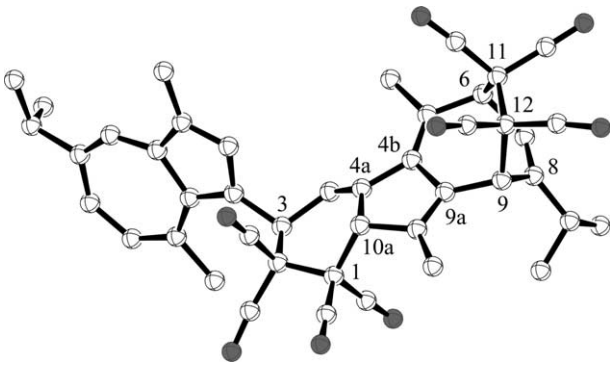


Figure 1. The X-ray crystal structure of **3**. Hydrogen atoms are omitted for reasons of clarity.

2.3. A plausible reaction pathway for the formation of products 3 and 4

From the molecular structures of the resulting products **3** and **4**, obtained by the reactions of the ethylene derivatives **1** and **2**, which serve as an electron donor,[8] with a 2 M amount of TCNE, which serves as an electron acceptor (see Section 1)[12] in benzene at 25 °C for 24 h under argon, a plausible reaction pathway for the formation of compounds **3** and **4** can be inferred as illustrated in Scheme 2; namely, (i) to a solution of TCNE in benzene was added a solution of **1** (and **2**) in benzene under argon, turning the dark-green solution of **1** (and **2**) into a purple solution (for **1**) and into a black solution (for **2**), rapidly. This result suggests that the reaction of **1** (and **2**) with TCNE gives the corresponding charge-transfer (CT) complex **a**, respectively, whose complex has not yet been isolated;[23] and (ii) the above reaction mixture was stirred at 25 °C for 24 h under argon, gradually precipitating a blue solid of **3** from **1**, and gradually precipitating a white solid of **4** from **2**. This result suggests that the CT complex **a** generated is converted into **3** (and **4**) presumably via the CT complex **a′** with the resonance form **a** and, further, the biradical intermediate **b** produced by the addition reaction of **1** (and **2**) with a 2 M amount of TCNE. It is noteworthy that, although the reactions of the ethylene derivatives **1** and **2** with TCNE in benzene at 25 °C do not need oxygen, giving the corresponding cycloaddition products **3** and **4**, oxygen is needed for the reactions of the ethane derivatives **A** and **B** with TCNE in benzene at 25 °C, affording the corresponding cycloaddition products **C**[11] and **D**[11] (see Section 1 and Scheme 1).

3. Conclusion

We have reported the following four points in this paper: (i) reactions of the title ethylene derivatives, (*E*)-1,2-di(3-guaiazulenyl)ethylene (**1**) and 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (**2**), with a 2 M amount of TCNE in benzene at 25 °C for 24 h under argon gave new cycloaddition compounds **3** and **4**, respectively, in 66 and 87% isolated yields; (ii) the detailed elemental and spectroscopic analyses of these products led to the molecular structures, 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene for **3** and 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene for **4**; (iii) although an X-ray crystallographic analysis of **3**, producing accurate structural parameters, has not yet been achieved because of very difficulty in obtaining a single crystal suitable for this purpose, the molecular structure of **3** established on the basis of elemental analysis and spectroscopic data could be determined by means of the X-ray diffraction; and, further, (iv) a plausible reaction pathway for the formation of the unique products **3** and **4**, possessing interesting molecular structures, was described.

4. Experimental

4.1. General

Thermal (TGA/DTA) and elemental analyses were taken on a Shimadzu DTG-50H thermal analyzer and a Yanaco MT-3 CHN corder, respectively. FAB-MS spectra were taken on a JEOL The Tandem Mstation JMS-700 TKM data system. UV–vis and IR spectra were taken on a Beckman DU640 spectrophotometer and a Shimadzu FTIR-4200 Grating spectrometer, respectively. NMR spectra were recorded with a JEOL GX-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) at 25 °C. The ^{1}H NMR spectra were assigned using the computer-assisted simulation analysis (the software: gNMR developed by Adept Scientific plc) on a DELL Dimension XPS T500 personal-computer with a Pentium III processor. Cyclic and differential pulse voltammograms were measured by an ALS Model 600 electrochemical analyzer.

4.1.1. Reaction of (*E*)-1,2-di(3-guaiazulenyl)ethylene (1) with TCNE; preparation and spectroscopic properties of 1,1,2,2,11,11,12,12-octacyano-3-(3-guaiazulenyl)-8-isopropyl-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (3). To a solution of TCNE (19 mg, 148 μmol) in benzene (3 mL) was added a solution of **1** (30 mg, 71 μmol) in benzene (2 mL) under argon, turning the dark-green solution into a purple solution, rapidly. The mixture was stirred at 25 °C for 24 h under argon, gradually giving a blue precipitate of **3**, and then was centrifuged at 2.5 krpm for 1 min. The crude product thus obtained was carefully washed with benzene and hexane, and was recrystallized from dichloromethane–hexane (1/5, vol/vol) (several times) to provide pure **3** as stable crystals (32 mg, 47 μmol, 66% yield).

Compound **3**: blue prisms [R_f=0.39 on silica-gel TLC (hexane/AcOEt=7:3, vol/vol)], mp>159 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 78.10; H, 5.38; N, 16.59%. Calcd for $C_{44}H_{36}N_8$: C, 78.08; H, 5.36; N, 16.56%; UV–vis λ_{max} (CH_2Cl_2) nm (log ε), 246 (4.40), 296 (4.54), 308 (4.51), 357 (3.79), 373 (3.87) and 587 (2.62); IR ν_{max} (KBr) cm^{-1}, 2253 and 2249 (–C≡N); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 677.3168; calcd for $C_{44}H_{37}N_8$: $[M+H]^+$, *m/z* 677.3141; ^{1}H NMR (CD_2Cl_2): δ 1.140, 1.145 (3H each, d, J=6.9 Hz, $(CH_3)_2$CH-8), 1.392, 1.394 (3H each, d, J=6.9 Hz, $(CH_3)_2$CH-7′), 2.26 (3H, brd s, Me-5), 2.39 (3H, brd s, Me-10), 2.62 (1H, sept d, J=6.9, 1.2 Hz, $(CH_3)_2CH$-8), 2.66 (3H, s, Me-1′), 3.09 (3H, s, Me-4′), 3.15 (1H, sept,

J=6.9 Hz, $(CH_3)_2CH$-7′), 3.76 (1H, d, J=7.8 Hz, H-6), 4.32 (1H, d, J=1.4 Hz, H-9), 4.56 (1H, brd q, H-10a), 5.708, 5.716 (0.5H each, brd d, J=2.9 Hz, H-3), 6.245, 6.25 (0.5H each, d, J=2.9 Hz, H-4), 6.35 (1H, ddd, J=7.8, 1.4, 1.2 Hz, H-7), 7.18 (1H, d, J=10.9 Hz, H-5′), 7.55 (1H, dd, J=10.9, 2.0 Hz, H-6′), 7.81 (1H, s, H-2′) and 8.32 (1H, d, J=2.0 Hz, H-8′); ^{13}C NMR (CD_2Cl_2): δ 145.5 (C-8), 143.9 (C-4′), 142.8 (C-7′), 139.8 (C-8a′), 138.2 (C-9a), 137.8 (C-2′), 135.7 (C-4b), 135.6 (C-6′), 134.9 (C-8′), 134.5 (C-10), 133.8 (C-3a′), 132.3 (C-4a), 129.8 (C-5′), 128.0 (C-5), 125.54 (C-1′), 125.51 (C-4), 122.9 (C-7), 113.8 (C-3′), 112.0 (*C*N-11), 111.8 (*C*N-12), 110.76 (*C*N), 110.73 (*C*N), 110.69 (*C*N), 110.5 (*C*N), 109.6 (*C*N-2), 108.1 (*C*N-1), 51.4 (C-10a), 49.5 (C-6), 47.3 (C-2), 45.55 (C-9), 45.51 (C-11), 44.9 (C-12), 42.8 (C-3), 42.4 (C-1), 37.5 ($(CH_3)_2CH$-7′), 34.3 ($(CH_3)_2CH$-8), 27.2 (Me-4′), 24.0, 23.9 ($(CH_3)_2CH$-7′), 23.1 (Me-5), 20.4, 19.7 ($(CH_3)_2CH$-8), 13.1 (Me-10) and 12.4 (Me-1′).

4.1.2. Reaction of 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (2) with TCNE; preparation and spectroscopic properties of 1,1,2,2,11,11,12,12-octacyano-8-isopropyl-3,3-bis(4-methoxyphenyl)-5,10-dimethyl-1,2,3,6,9,10a-hexahydro-6,9-ethanobenz[*a*]azulene (4). To a solution of TCNE (6 mg, 47 μmol) in benzene (1 mL) was added a solution of **2** (10 mg, 23 μmol) in benzene (2 mL) under argon, turning the dark-green solution into a black solution, rapidly. The mixture was stirred at 25 °C for 24 h under argon, gradually giving a white precipitate of **4**, and then was centrifuged at 2.5 krpm for 1 min. The crude product thus obtained was carefully washed with benzene and hexane, and was recrystallized from dichloromethane–hexane (1/5, vol/vol) (several times) to provide pure **4** as stable powder (14 mg, 20 μmol, 87% yield).

Compound **4**: white powder [R_f=0.18 on silica-gel TLC (hexane/AcOEt=7:3, vol/vol)], mp 140 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 72.71; H, 4.71; N, 15.49%. Calcd for $C_{43}H_{34}N_8O_3$ ($C_{43}H_{32}N_8O_2+H_2O$): C, 72.66; H, 4.82; N, 15.77%; UV–vis λ_{max} (CH_2Cl_2) nm (log ε), 233 (4.45), 282 (4.24), 357 (3.14) and 410 (3.08); IR ν_{max} (KBr) cm^{-1}, 2253 and 2249 (–C≡N); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: m/z 693.2704; calcd for $C_{43}H_{33}N_8O_2$: $[M+H]^+$, m/z 693.2727; ^{1}H NMR (CD_2Cl_2): δ 1.13, 1.14 (3H each, d, J=6.9 Hz, $(CH_3)_2CH$-8), 2.36 (3H, brd s, Me-10), 2.43 (3H, brd s, Me-5), 2.62 (1H, sept d, J=6.9, 0.9 Hz, $(CH_3)_2CH$-8), 3.78 (3H, s, MeO-4′), 3.83 (1H, d, J=7.8 Hz, H-6), 3.85 (3H, s, MeO-4″), 4.32 (1H, d, J=1.1 Hz, H-9), 4.40 (1H, brd q, H-10a), 6.39 (1H, ddd, J=7.8, 1.1, 0.9 Hz, H-7), 6.66, 6.67 (0.5H each, br d s, H-4), 6.84 (2H, dd, J=8.5, 2.5 Hz, H-2′,6′), 7.01 (2H, dd, J=8.5, 2.5 Hz, H-2″,6″), 7.39 (2H, dd, J=8.5, 2.5 Hz, H-3′,5′) and 7.53 (2H, dd, J=8.5, 2.5 Hz, H-3″,5″); ^{13}C NMR (CD_2Cl_2): δ 159.9 (C-4″), 159.6 (C-4′), 145.7 (C-8), 138.5 (C-9a), 136.1 (C-4b), 134.6 (C-10), 133.0 (C-1″), 132.2 (C-4a), 131.1 (C-3′,5′), 129.1 (C-4), 129.0 (C-1′), 128.5 (C-3″,5″), 127.9 (C-5), 122.9 (C-7), 114.2 (C-2″,6″), 113.0 (C-2′,6′), 111.9, 111.7, 111.5, 111.1 (*C*N-11 and 12), 110.7 (*C*N-1 or 2), 110.4 (2*C*N-1 or 2), 108.5 (*C*N-1), 55.7 (C-3), 55.1 (MeO-4″), 55.0 (MeO-4′), 51.5 (C-10a), 50.8 (C-2), 49.8 (C-6), 45.4 (C-9,11), 44.8 (C-12), 41.4 (C-1), 34.3 ($(CH_3)_2CH$-8), 23.6 (Me-5), 20.4, 19.7 ($(CH_3)_2CH$-8) and 13.0 (Me-10).

Acknowledgements

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12. The electrochemical measurement conditions of TCNE are as follows: the cyclic and differential pulse voltammograms (potential/V vs SCE) of TCNE (3 mg, 23 μmol) in 0.1 M [*n*-Bu_4N]BF_4, CH_3CN (10 mL) at a glassy carbon (ID: 3 mm) and a platinum wire served as the working and auxiliary electrodes; scan rates 100 mV s^{-1} at 25 °C under argon, respectively. For comparative purposes, the oxidation potential using ferrocene as a standard material showed +0.45 (E_p) V by DPV and +0.42 ($E_{1/2}$, quasi-reversible) V by CV in 0.1 M [*n*-Bu_4N]BF_4, CH_3CN under the same electrochemical measurement conditions as TCNE.
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22. A total 10,210 reflections with $2\theta_{max}=55.0^{\circ}$ were collected on a Rigaku AFC-5R automated four-circle diffractometer with graphite monochromated Mo Kα radiation ($\lambda=0.71069$ Å, rotating anode: 50 kV, 180 mA) at 296 K. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on F^2. All calculations were performed using the teXsan crystallographic software package. Crystallographic data for **3**: $C_{44}H_{36}N_8$ (FW=676.82), blue prism (the crystal size, $0.30\times0.20\times0.30$ mm^3), monoclinic, $P2_1/n$ (#14), $a=12.990(3)$ Å, $b=18.635(3)$ Å, $c=17.095(2)$ Å, $\beta=91.72(1)^{\circ}$, $V=4136(1)$ Å^3, $Z=4$, $D_{calcd}=1.087$ g/cm^3, μ(Mo Kα)=0.66 cm^{-1}, scan width=$(1.26+0.30\tan\theta)^{\circ}$, scan mode=$\omega-2\theta$, scan rate=8.0°/min, measured reflections=10,210, observed reflections=9491, no. of parameters=469, $R1=0.186$, $wR2=0.514$ and Goodness of Fit Indicator =3.49.
23. Although the reactions of **A** and **B** with a 2 M amount of TCNE in toluene at −20 °C under argon gave the corresponding 1:2 CT complexes $\mathbf{a}_{1,2}$ (see Scheme 1),[11] respectively, in 18% isolated yield from **A** and 23% isolated yield from **B**, whose complexes were gradually converted into **C** and **D** (see Scheme 1),[11] respectively, in benzene at 25 °C under oxygen, the CT complexes **a** (see Scheme 2) have not yet been isolated because of very difficulty in obtaining the reactive CT complexes **a** produced by the reactions of **1** and **2** with a 2 M amount of TCNE in toluene at −20 °C under argon.

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Synthesis and structure of 8-hydroxy-6-methoxy-3,7-dimethylisochromane and its analogues

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Abstract—The title compound **1** was obtained by the reaction of alcohol **18** and triethyl orthoformate catalyzed by aluminum chloride followed by catalytic hydrogenation in good yield. Similarly, compounds **1** and **3** were obtained by intramolecular cyclization of MOM ether **19** with titanium(IV) chloride in moderate yields and isochromanes **1**, **3**, **26** and **27** by intramolecular cyclization of ether **20** with titanium(IV) chloride in high yields. The structures of compounds **1**–**3** were elucidated by analysis of spectroscopic data and chemical reactions. The mechanisms on the formation of **1** and **3** are discussed.

1. Introduction

Isochromane **1** is a toxic metabolite of *Penicillium steckii* Zalecki[1] and *Penicillium corylophilum* Dierckx.[2] Compound **1** was highly toxic to 1-day-old chickens (lethal dose 50%: 800 mg/kg)[1] and inhibited growth of etiolated coleoptiles of wheat by 100 and 43% at 10^{-3} and 10^{-4} M, respectively.[2] Hemiacetal **2** was produced by a marine-derived strain of *P. steckii* together with compound **1** and tanzawaic acids E and F.[3] Compound **1** and its regioisomer **3** were synthesized from dimethoxy isochromane **4** as shown in Scheme 1 and the phytotoxic activity of compounds **1** and **3** and their ethers and esters had been investigated in detail (Fig. 1).[4]

Numerous methods have been developed to synthesize isochromanes by using the C–O bond[5]—or the C–C bond[6]—forming cyclization. Practical reactions are shown in Scheme 1. Compound **4**, which was a precursor of isochromanes **1** and **3**, was afforded by heating of **5** with chloromethyl methyl ether and sodium hydride in tetrahydrofuran. Dimethyl ether **4** may be formed via methoxymethyl (MOM) ether of **5** under thermal conditions.[4] Chloroisochromane **7** was obtained by the reaction of **6** with chloromethyl methyl ether in the presence of Lewis acid.[7] Methoxyethoxymethyl (MEM) ethers **8a–d** were converted to isochromanes **9a–d** by intramolecular cyclization catalyzed by titanium(IV) chloride.[8] Compound **10** was obtained by catalytic hydrogenation of compound **11**, which was afforded by formylation of **12** with triethyl orthoformate.[9]

Synthesis and properties of 1-hydroxyisochromanes have been reported by several groups. These compounds were prepared by saponification of 5-formylmellein,[10] reduction of isocoumarins with hydrides,[11] reaction of benzocyclobutenols and aromatic aldehydes in the presence of lithium 2,2,6,6-tetramethylpiperidide,[12] photo-induced hetero Diels–Alder reaction of 2-methylbenzaldehydes,[13] oxidation of 2-hydroxyethyl-5-isopropylbenzyl alcohol[14] or 2-hydroxymethyl-1-(2′-hydroxyphenyl)naphthalene (**13**)[15] with non-activated manganese dioxide or pyridinium chlorochromate (PCC). In the case of compound **13**, a complex mixture of aldehyde **14**, hemiacetal **15** and bisacetal **16** was obtained by oxidation of **13** with PCC as illustrated in Scheme 2 and an equilibrium between compounds **14** and **15** was found.[15] Thus, it is suggested that compound **2** is synthetically equivalent to aldehyde **17**, which would be formed by formylation of the corresponding alcohol **18** (Fig. 2).

In this paper, we wish to describe the synthesis of the title compound **1** by the formylation of alcohol **18** followed by catalytic hydrogenation and by the intramolecular cyclization of MOM ethers **19** and **20** and discuss the reaction

Keywords: Heterocycles; Mycotoxin; Isochromane; Formylation; Catalytic reduction; Intramolecular cyclization.
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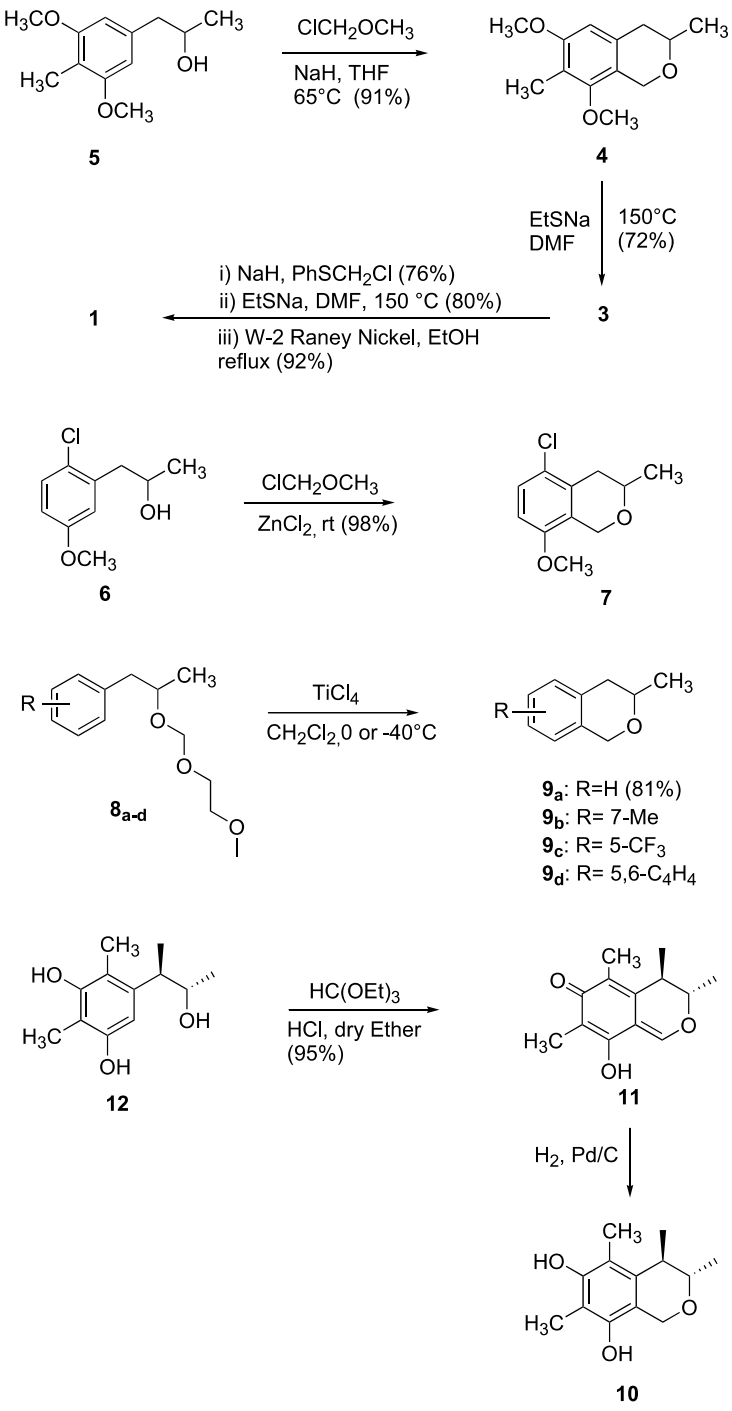
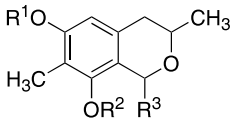


Scheme 1. Synthesis of isochromanes.



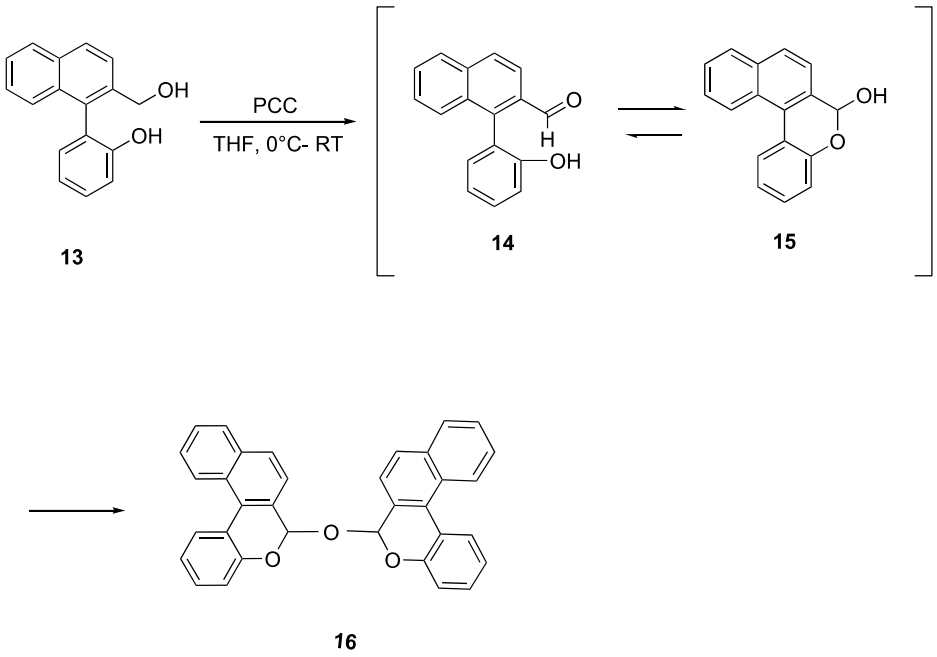
1: R^1=CH_3; R^2=R^3=H
2: R^1=CH_3; R^2=H; R^3=OH
3: R^1=R^3=H; R^2=CH_3
4: R^1=R^2=CH_3; R^3=H

Figure 1.

mechanisms. The structures of compounds **1**–**3** were determined by analysis of spectral data and chemical reactions, though compounds **1**–**3** have been reported till now.

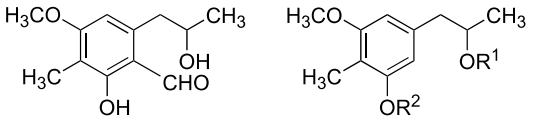
2. Results and discussion

Initially, the synthesis of isochromane **1** was examined as shown in Scheme 3. Ketone **21**[16] was reduced with lithium aluminum hydride in ether at 0 °C to give alcohol **18** in 99.0% yield. Compound **18** was subjected to formylation with triethyl orthoformate catalyzed by anhydrous aluminum chloride in dry toluene at −53 to −30 °C to give aldehyde **17** and bisacetal **22** in 48.9 and 42.6% yields, respectively (Scheme 3). The structure of aldehyde **17** was confirmed by ^{1}H NMR measurement. The ^{1}H NMR spectrum showed the two proton signals of C_1–CHO and C_2–OH at δ 10.21



13 14 15 16

Scheme 2. Syntheses of aldehyde **14**, hemiacetal **15** and bisacetal **16**.



17

18: R^1=R^2=H
19: R^1=MOM, R^2=H
20: R^1=R^2=MOM

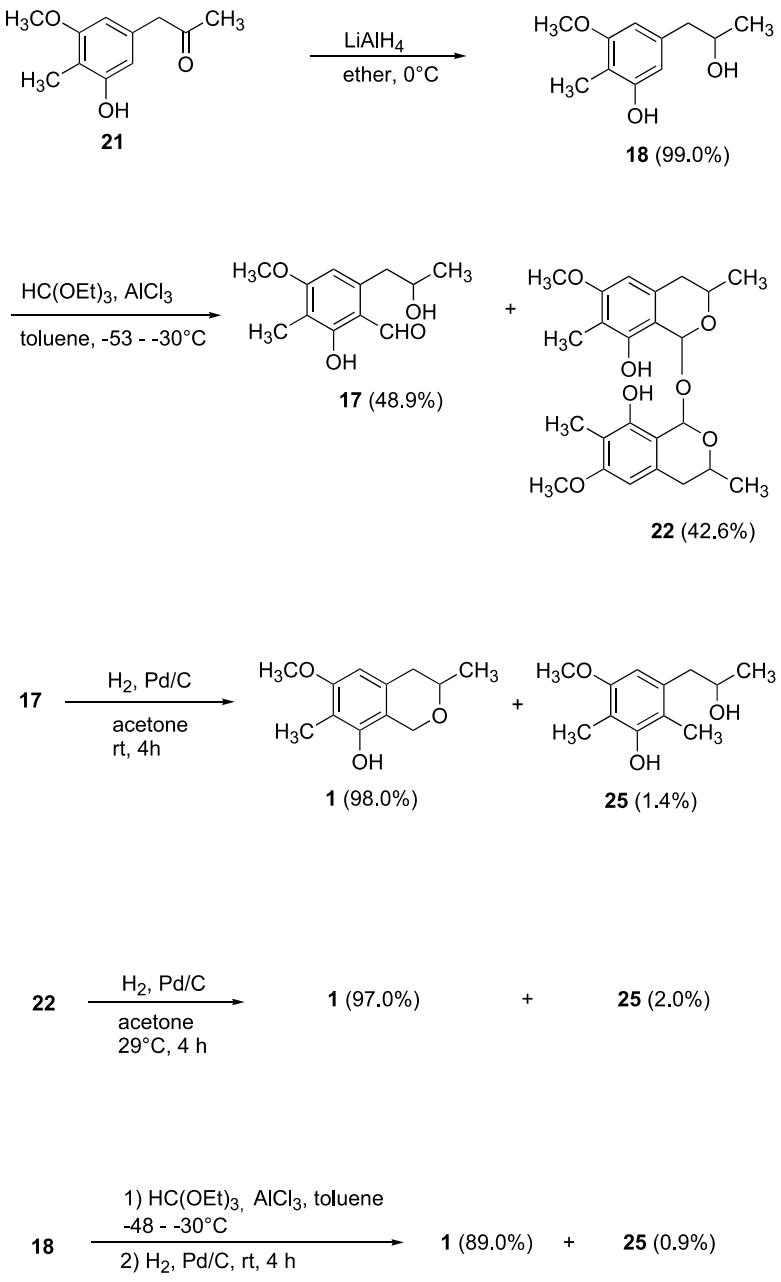
Figure 2.

and 12.65, respectively. The signal for C_2–OH was shifted to downfield because of intramolecular hydrogen bonding with C_1–CHO. The structure of bisacetal **22** was determined by the measurements of ^{1}H NMR, Mass and IR spectra and by the results of elemental analysis. The ^{1}H NMR spectrum showed the methine proton signal of C_1–H at 6.10 ppm. The mass spectrum did not show the molecular ion of **22** (M^+430) but contained two ions at *m*/*z* 223 and 207, which corresponded to the molecular formulas $C_{12}H_{15}O_4$ and $C_{12}H_{15}O_3$, respectively. Furthermore, the absorption band of formyl group was not found in the infrared absorption spectra. Bisacetal **22** was also obtained by heating of aldehyde **17** at 180 °C for 0.5 h.

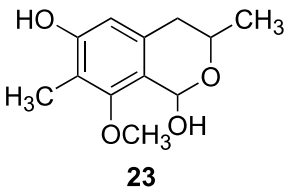
Hemiacetal **2** was not obtained by the formylation of **18** with triethyl orthoformate in the presence of aluminum chloride as described above. Compound **2** would be converted into aldehyde **17** or bisacetal **22** during the treatment of a reaction mixture with the usual way. For this reasons, detection of **2** by the spectroscopic method was carried out. By the ^{1}H NMR measurements of the residue, which was provided by a careful work-up of a reaction mixture, compound **2** was detected together with **17** in a ratio of 81:19, respectively. Hemiacetal **2** was changed partly to aldehyde **17** when a solution of **2** and **17** in acetone-d_6 was left at room temperature for several hours. The methine proton signal of C_1–H was located at 5.64 ppm and the C_1, C_6 and C_8 carbon signals appeared at 96.27, 159.05 and 153.67 ppm for **2** in acetone-d_6, respectively. Those NMR data were not identical with the corresponding signals of an authentic sample obtained from *P. steckii* reported in the literature[3] (C_1–H at 5.51 ppm; C_1, C_6 and C_8 at 95.4, 155.1 and 155.2 ppm, respectively, in methanol-d_4). This compound must be assigned to compound **23** (Fig. 3) because the ^{13}C NMR peaks of C_6 and C_8 carbon atoms were similar to that of **3** and the differences of chemical shifts of C_8 and C_6 carbon atoms was 0.1 ppm as described below. As shown in Scheme 4, aldehyde **17** might be produced by hydrolysis of diethyl acetal **24**, which was obtained exclusively from **18** via intermediate **A** by *ortho*-formylation.[17] Compound **2** is formed by intramolecular hemiacetalization of **17** and dimerized to bisacetal **22**.[15]

To synthesize isochromane **1**, compounds **17** and **22** were hydrogenated as shown in Scheme 3. In the case of **17**, compounds **1** and dimethyl alcohol **25** were obtained in 98.0 and 1.4% yields, respectively, by treatment of **17** with hydrogen in the presence of 10% palladium on charcoal in acetone at room temperature for 4 h. When compound **22** was treated with hydrogen in the presence of 10% palladium on charcoal in acetone at room temperature for 4 h, compounds **1** and **25** were obtained in 97.0 and 2.0% yields, respectively. Additionally, a crude mixture of **2**, **17** and **22** in a ratio of 70:15:15, which was obtained from the reaction of **18** with triethyl orthoformate catalyzed by $AlCl_3$, was stirred in acetone with 10% palladium on charcoal under hydrogen atmosphere at room temperature for 4 h, compounds **1** and **25** were obtained in 89.0 and $<$1.0% yields, respectively. Thus, compound **1** was obtained from **18** in good yield in two steps without purification of the reaction products **2**, **17** and **22**.

The reaction pathways for the formation of compound **1** and **25** by hydrogenation of **2**, **17** and **22** with palladium on charcoal are illustrated in Scheme 5. Hemiacetal **2**, which was formed by intramolecular hemiacetalization of **17** or by



Scheme 3. Synthesis of isochromane **1** and dimethyl alcohol **25**.

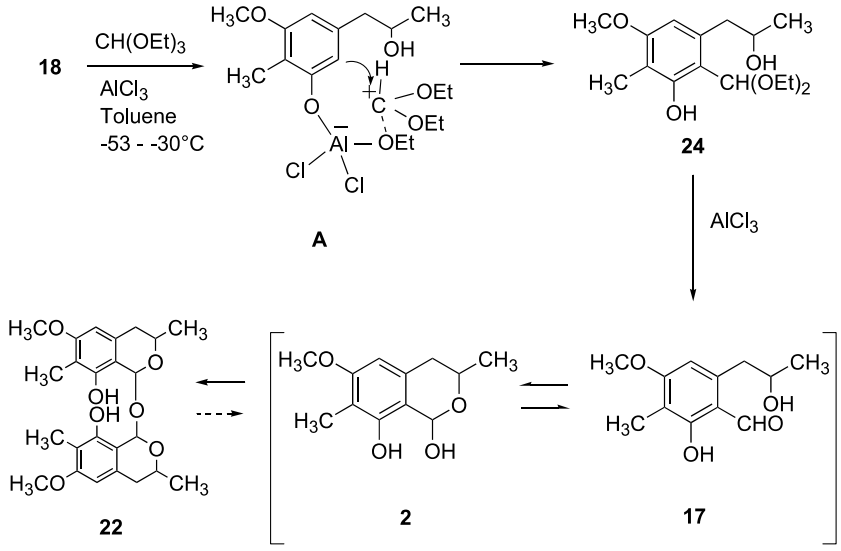


23

Figure 3.

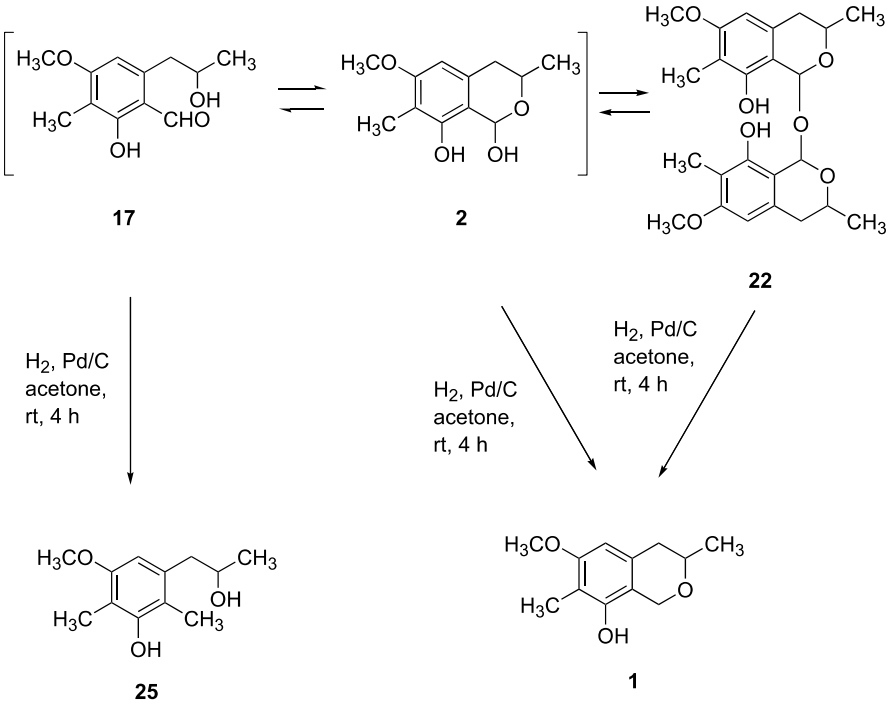
hydrolysis of **22**, is a common intermediate for the production of **1** since isochromane **1** was produced predominantly by catalytic reduction of crude **2**, **17** and **22**, respectively. In the case of **22**, compound **1** would be afforded by catalytic reduction of **22**. On the other hand, dimethyl alcohol **25** must be formed by catalytic reduction of **17**.[18] The structure of **1** was described below.

Next, intramolecular cyclization[8a] of MOM ether **19** was examined to synthesize compound **1** and its regioisomer **3** and to elucidate the structures of **1** and **3**, respectively, since the ^{1}H and ^{13}C NMR spectra of **1**, which was obtained above, did not agree with those of an authentic sample reported in the literature.[1,4] Compounds **19** was obtained by methoxymethylation of **18** with chloromethyl methyl ether and *N*-ethyldiisopropylamine in 39.3% yields together with ether **20** (55.9%) as shown in Scheme 6. When MOM ether **19** was treated with 0.7 equiv of titanium(IV) chloride at −49 °C for 15 min, a mixture of compounds **1** and **3** was obtained in 66.1% yield (the ratio of **1** and **3** was 79:21) (Scheme 6). The ^{1}H and ^{13}C NMR data and selected HMBC correlations for compounds **1** and **3** are summarized in Tables 1 and 2, respectively. The assignment of ^{1}H and ^{13}C NMR spectra of **1** and **3** was

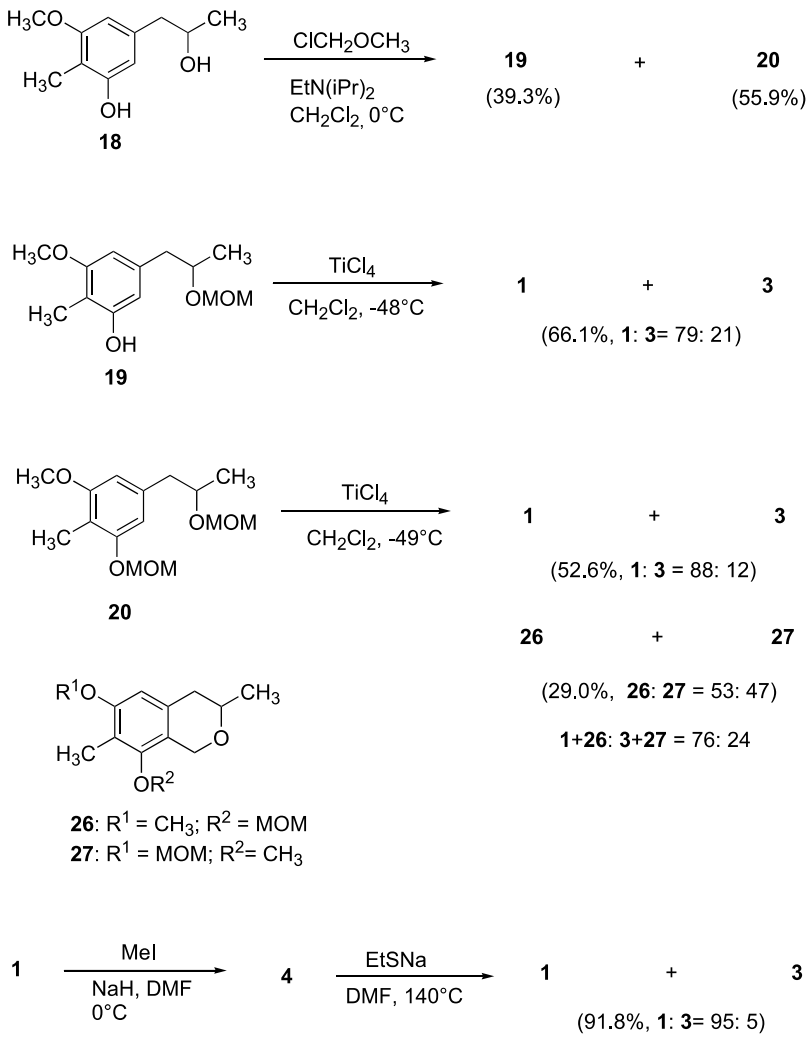


Scheme 4. Reaction pathways for the formation of **2**, **17** and **22** by the formylation of **18**.

confirmed by comparison with the results of NOESY and HMBC experiments, respectively (Figs. 4 and 5). The signal of three protons of methoxy group was located at 3.73 ppm for **1** and at 3.61 ppm for **3**. The ^{13}C NMR showed that the signals of C_6 and C_8 carbon atoms for **1** appeared at 157.68 and 151.60 ppm, respectively. Whereas, the corresponding signals for **3** were 155.91 and 156.73 ppm, respectively. The difference of chemical shift of C_6 and C_8 carbon atoms was 6.08 ppm for **1** and that was 0.82 ppm for **3**. The carbon atom bearing methoxy group was appeared at downfield than that possessing hydroxy group in ^{13}C NMR spectra. The NOESY experiments of **1** showed that three protons of methoxy group attached at C_6 carbon atom had the correlation with aromatic hydrogen attached at C_5 carbon atom (Fig. 4). On the other hand, the correlation between three protons of methoxy group at C_8 carbon atom and two protons at C_1 carbon atom for **3** was observed as shown in Figure 5. It was indicated by HMBC spectra of **1** and **3** that three protons of methoxy group exhibited long-range $^1H/^{13}C$ correlation with C_6 carbon atom for **1**, while the corresponding protons had the same correlation with C_8 carbon atom for **3**. Additionally, the lanthanide induced shifts (LIS) experiments supported the structures of **1** and **3** as shown in Table 3. The large LIS values were observed for C_1–H (2.44 ppm) and C_3–H (2.10 ppm) for **1**. On the other hand, in the case of **3**, C_5–H and C_7–CH_3 had large LIS values of 1.83 and 1.39 ppm, respectively.



Scheme 5. Reaction pathways for the catalytic reduction of compounds **2**, **17** and **22** to isochromane **1** and dimethyl alcohol **25**, respectively.



Scheme 6. Synthesis of MOM ethers **19** and **20** and isochromanes **1**, **3**, **26** and **27**.

Table 1. ^{1}H and ^{13}C NMR data and selected HMBC correlations for isochromane **1** in CD_3CN[a]

C/H	^{13}C	^{1}H	HMBC (H→C)
1	65.10	4.50dt (15.0, 1.5, $H_{a'}$) 4.75d (15.0, $H_{e'}$)	
3	71.19	3.66ddq (10.5, 3.2, 6.3)	C_1–H
4	36.46	2.50dd (16.0, 10.5, $H_{a'}$) 2.60dd (16.0, 3.2, $H_{e'}$)	C_3–CH_3, C_5–H
4a	133.18		C_1–H
5	103.74	6.27s	C_4–H
6[b]	157.68		C_6–OCH_3, C_7–CH_3
7	110.20		C_5–H, C_8–OH
8[c]	151.60		C_1–H, C_7–CH_3
8a	115.67		C_5–H, C_8–OH, C_4–H, C_1–H
C_3–CH_3	21.81	1.24d (6.3)	
C_6–OCH_3[d]	56.18	3.73s	
C_7–CH_3	8.45	1.99s	
C_8–OH		6.02s	

[a] NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Acetonitrile-d_3 was used as an internal reference instead of TMS (^{1}H NMR: δ 1.93 (CHD_2CN), ^{13}C NMR: δ 1.30).
[b] See Ref. 1. The signal of C_6 carbon atom appeared at 153.69 ppm in $CDCl_3$.
[c] See Ref. 1. The signal of C_8 carbon atom appeared at 152.58 ppm in $CDCl_3$.
[d] See Ref. 1. The signal of three protons of methoxy group appeared at 3.66 ppm in $CDCl_3$.

Table 2. ^{1}H and ^{13}C NMR data and selected HMBC correlations for isochromane **3** in CD_3CN[a]

C/H	^{13}C	^{1}H	HMBC (H→C)
1	65.62	4.57dt (14.9, 1.4, $H_{a'}$) 4.79d (14.9, $H_{e'}$)	
3	72.02	3.66ddq (10.7, 3.2, 6.1)	C_1–H
4	36.71	2.47dd (16.4, 10.7, $H_{a'}$) 2.58dd (16.4, 3.2, $H_{e'}$)	C_3–CH_3, C_5–H
4a	120.82		C_1–H
5	111.93	6.33s	C_4–H, C_6–OH
6[b]	155.91		C_7–CH_3
7	116.68		C_5–H, C_6–OH
8[c]	156.73		C_1–H, C_7–CH_3 C_8–OCH_3
8a	134.26		C_4–H
C_3–CH_3	22.48	1.23d (6.1)	
C_6–OH	56.18	6.68s	
C_7–CH_3	9.47	2.03s	
C_8–OCH_3[d]	61.18	3.61s	

[a] NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Acetonitrile-d_3 was used as an internal reference instead of TMS (^{1}H NMR: δ 1.93 (CHD_2CN); ^{13}C NMR: δ 1.30).
[b] See Ref. 4a. The signal of C_6 carbon atom appeared at 149.9 ppm in $CDCl_3$.
[c] See Ref. 4a. The signal of C_8 carbon atom appeared at 156.4 ppm in $CDCl_3$.
[d] See Ref. 4a. The signal of three protons of methoxy group appeared at 3.79 ppm in $CDCl_3$. Chloroform was used as an internal reference instead of TMS (^{1}H NMR: δ 7.26).

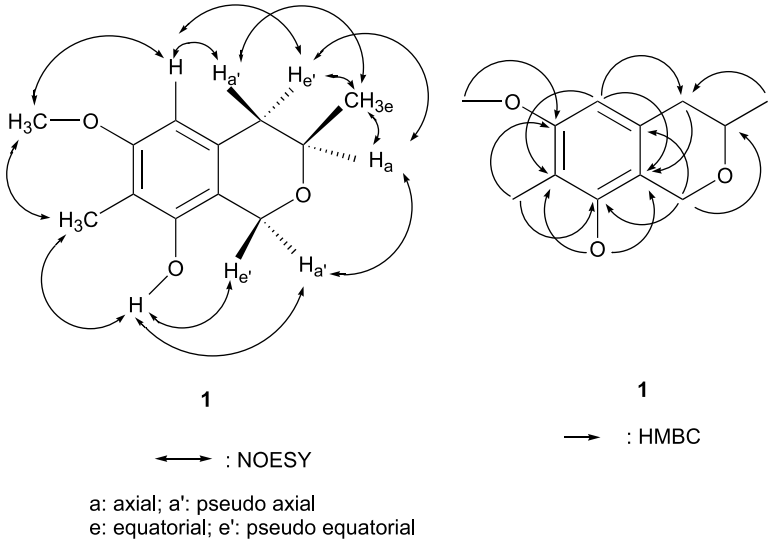


Figure 4. The selective NOESY and HMBC correlations for **1**.

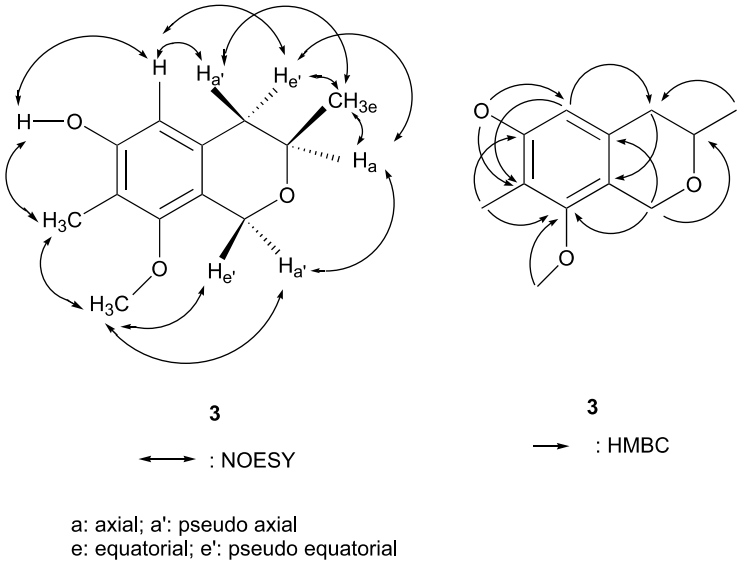
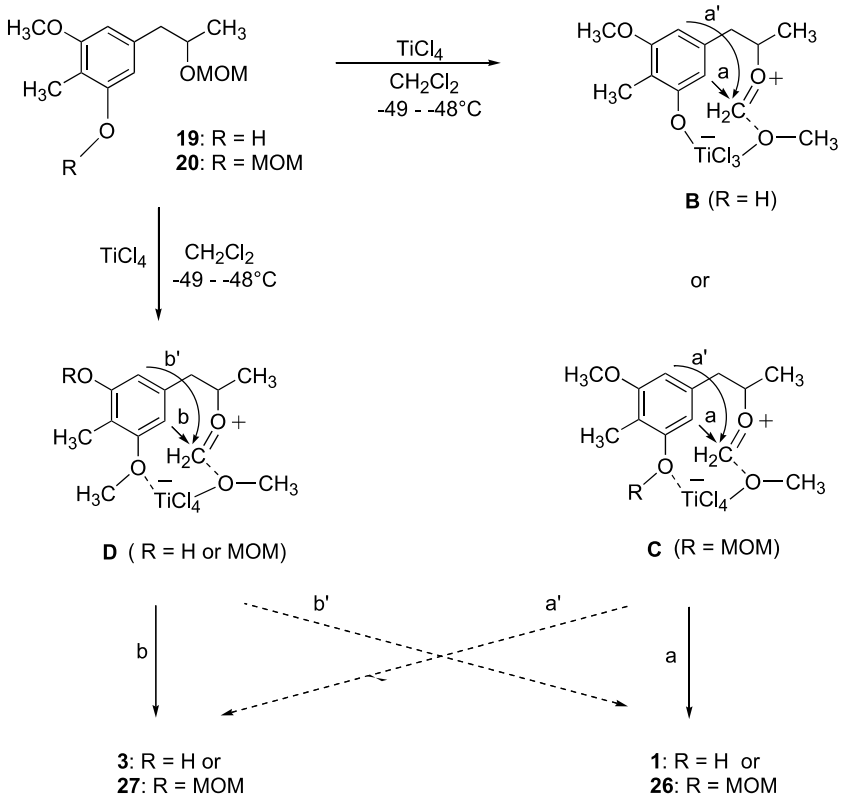


Figure 5. The selective NOESY and HMBC correlations for **3**.

Table 3. Eu(dpm)$_3$ induced shifts (ppm) of isochromanes **1** and **3**[a]

Compound	Proton (shift value/ppm)
1	C_1–H (2.44), C_3–H (2.10), C_3–CH_3 (1.16), C_4–H (1.09), C_5–H (0.31), C_6–OCH_3 (0.27), C_7–CH_3 (0.57), C_8–OH (−[b])
3	C_1–H (0.89), C_3–H (−[c]), C_3–CH_3 (0.78), C_4–H (0.40), C_5–H (1.83), C_6–OH (−[b]), C_7–CH_3 (1.39), C_8–OCH_3 (1.17)

[a] Shift studies were carried out by stepwise addition of known amounts of Eu(dpm)$_3$ to ca. 0.37–0.27 M solutions of substrates in $CDCl_3$. The LIS data were obtained by graphic extrapolation of the observed shifts to a 1:1 shift reagent–substrate ratio.
[b] Signals of hydroxyl group were disappeared by the addition of Eu(dpm)$_3$.
[c] A signal of C_3–H was not measured as it was week and multiple by addition of Eu(dpm)$_3$.



Scheme 7. Plausible mechanisms for the formation of isochromanes **1** and **3** or their MOM ethers **26** and **27**.

Those results indicate that the europium(III) atom is coordinated to the oxygen of C_8 hydroxy group for **1** and to the oxygen of C_6 hydroxy group for **3**, respectively, though the LIS values of phenolic protons were not obtained.

Compounds **1** and **3** were tried to synthesize by an alternate route (Scheme 6). Dimethoxyisochromane **4**, which was obtained by methylation of compound **1** with MeI was treated with sodium ethyl sulfide in *N*,*N*-dimethyformamide (DMF) at 140 °C for 3 h to give a mixture of compounds **1** and **3** (**1**:**3**=95:5) in 91.8% yield.[4,19] Compounds **1** and **3** were identified by comparison of their spectra to those of authentic samples obtained above. The sterically more-hindered C_8 methoxy group was selectively demethylated though the reason is not clear.[†]

Although the structure of compound **1** was elucidated by the substituent effects of hydroxy group to the ^{13}C chemical shifts of **1**,[1] above results indicated that the isochromane, which was obtained from the metabolite of *P. steckii*[1,3] and *P. corylophilum*[2] is compound **3** and the 1-hydroxyisochromane, which was separated from the culture of *P. steckii*[3] is compound **23**. Similarly, isochromanes **1** and **3**, which are shown in Scheme 1 must be corrected to compound **3** and **1**, respectively.

Finally, intramolecular cyclization of ether **20** was carried out by using equimolecular amount of titanium(IV) chloride as catalyst in dry dichloromethane (Scheme 6).[8a] Mixtures of compounds **26** and **27** (29.0%; **26**:**27**=53:47) and **1** and **3** (52.6%; **1**:**3**=88:12) were obtained. Compound **1** or **3** must be obtained by deprotection of MOM ether **26** or **27** with $TiCl_4$. The structures of **26** and **27** were identified by the comparison of their spectra to those of authentic samples obtained by the reaction of **1** and **3** with chloromethyl methyl ether and *N*-ethyldiisopropylamine in dichloromethane, respectively. Plausible mechanisms for the production of **1**, **3**, **26** and **27** are illustrated in Scheme 7. In the case of **19** (R=H), the oxocarbenium intermediate **B** (R=H) must be produced by the interaction of titanium(IV) chloride with the two oxygens of MOM group and C_8 hydroxyl group. On the other hand, the oxocarbenium

[†] Cutler et al.[4] showed that demethylation of compound **4** with sodium ethyl sulfide gave compound **3** because nucleophilic substitution occurred at the less sterically hindered C_6 methoxyl carbon atom (Scheme 1).

intermediate **D** (R=H) must be formed by the interaction of $TiCl_4$ with the two oxygens of MOM group and C_6 methoxy group.[20] By the intramolecular nucleophilic attack of aromatic ring to the carbon atom of intermediates **B** and **D**, compounds **1** and **3** would be afforded, respectively. In the case of **20** (R=MOM), the oxocarbenium intermediates **C** and **D** (R=MOM) were formed by the interactions between $TiCl_4$ with two oxygen atoms of two MOM groups and MOM group and C_6 methoxy group, respectively. MOM ethers **26** and **27** were produced by the intramolecular nucleophilic attack of aromatic ring to the carbon atom of intermediates **C** and **D**, respectively. Compound **1** or **26** would be produced predominantly via path a, whereas compound **3** or **27** would be produced via path b as the yield of **1** or **1** and **26** was larger than that of **3** or **3** and **27** for the reaction of **19** or **20** with $TiCl_4$.[21]

Thus, isochromane **1** was synthesized from the reaction of alcohol **18** with triethyl orthoformate in the presence of $AlCl_3$ followed by catalytic reduction of compounds **2**, **17** and **22** with or without purification in good yields, respectively. On the other hand, mixtures of **1** and **3** or of **1**, **3**, **26** and **27** were obtained from cyclization of MOM ether **19** or ether **20** by treatment with $TiCl_4$, respectively. The structures of **1**–**3** were determined by chemical reaction, ^1H and ^{13}C NMR spectra and NOESY, HMBC, and LIS experiments. The isochromane and the 1-hydroxyisochromanes, which were obtained from the culture of *P. steckii*[1,3]or *P. corylophilum*[2] were 6-hydroxyisochromane **3** and its 1-hydroxy compound **23**, respectively. The structure of demethylated compound obtained by the reaction of **4** with sodium ethyl sulfide in DMF was assigned to compound **1** by comparison with an authentic sample.

3. Experimental

3.1. General

Melting points were determined with a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. IR spectra were recorded on a Hitachi I-3000 spectrophotometer. ^1H NMR spectra were measured with a Hitachi R-24B (60 MHz), a Hitachi R-1200 (60 MHz), a Varian Unity 500plus (500 MHz), or a JEOL ECA 500 (500 MHz) NMR spectrometer. ^{13}C NMR spectra were measured with a Varian Unity 500plus (125 MHz), or a JEOL ECA 500 (125 MHz) NMR spectrometer. Tetramethylsilane was used as internal standard unless otherwise stated. Mass spectra were recorded on a JEOL JMS-AX505WA mass spectrometer using electron-impact mode (70 eV). Shibata glass tube oven model GTO-350RS was employed for heating of aldehyde **17**. Thin-layer chromatography was performed on pre-coated Kieselgel 60 F_{254} plates (Merck) and spots were visualized under UV light. Unless otherwise stated silica gel (Wakogel C-200, Wako) was employed for the column chromatography as the packing materials and anhydrous sodium sulfate as the drying agent. DMF, ethanol and toluene were dried according to the reported procedures.[16] Dichloromethane was refluxed with calcium hydride, distilled and stored over molecular sieves 4 Å under an argon atmosphere. Ether refers to diethyl ether. Tris (2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III) (>95%) was purchased from Tokyo Kasei Kogyo and was used without further purification. Ketone **21** was prepared according to the reported procedure.[16]

3.1.1. 1-(3-Hydroxy-5-methoxy-4-methylphenyl)-2-propanol (18). To a stirred suspension of lithium aluminum hydride (280 mg, 7.38 mmol) in dry ether (66.5 mL) was added a solution of ketone **21** (779 mg, 4.01 mmol) in ether (17.0 mL) dropwise at 0 °C for 32 min. After being stirred for 30 min at 0 °C, the reaction was quenched by addition of 3 M HCl solution (60 mL). Products were extracted with 100 mL of ether twice and the combined organic layer was washed with water and dried over anhydrous magnesium sulfate. By evaporation of solvents in vacuo, the residue (891 mg) was obtained. The residue was chromatographed on silica gel (30 g, Kieselgel 60, Merck). By elution with hexane–acetone (6/1) compound **18** (780 mg, 99.0%) was obtained as colorless crystals, mp 84–85 °C (ether–hexane); IR (KBr): ν_{max} 3404 (OH), 3160 (OH), 2972, 2932, 2832, 1622, 1598, 1518, 1458, 1418, 1232, 1114, 812 cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.12 (3H, d, J=6.5 Hz, –CH(OH)C*H*$_3$), 2.01 (3H, s, C_4–CH_3), 2.52 (1H, dd, J=13.5, 6.5 Hz, –C*H*$_2$CH(OH)–), 2.66 (1H, dd, J=13.5, 6.7 Hz, –C*H*$_2$CH(OH)–), 3.60 (1H, d, J=5.0 Hz, –CH(O*H*)–), 3.80 (3H, s, C_5–OCH_3), 3.94 (1H, m, –C*H*(OH)–), 6.35 (1H, s, C_2–H or C_6–H), 6.38 (1H, s, C_2–H or C_6–H), 8.04 (1H, s, C_3–OH); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 8.32, 23.34, 46.89, 55.75, 69.07, 104.12, 109.89, 110.32, 138.65, 156.41, 159.38. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.22.

3.1.2. 2-Hydroxy-6-(2-hydroxypropyl)-4-methoxy-3-methylbenzaldehyde (17) and 1,1′-oxydi(8-hydroxy-6-methoxy-3,7-dimethylisochromane) (22). To a stirred suspension of anhydrous aluminum chloride (302 mg, 2.15 mmol) and dry toluene (2.6 mL) at −53 °C was added dropwise a solution of alcohol **18** (249 mg, 1.27 mmol) and triethyl orthoformate (4.2 mL, 25.34 mmol) in dry toluene (2.6 mL) over a period of 20 min. The reaction mixture was allowed to warm to −30 °C over a period of 30 min and then stirred for another 35 min at the same temperature. After addition of 6 M HCl solution (7 mL), cooling bath was removed and the resulting mixture was stirred at room temperature for 5 min and then water (10 mL) was added and stirring was continued at room temperature for an another 10 min. The reaction mixture was extracted with ether (100 mL) three times and combined organic layer was washed with brine and dried with anhydrous magnesium sulfate. Solvents were removed by a rotary evaporator at 60 °C to gave 280.1 mg of pale yellow crystals. The crystals were treated with a small portion of ether and insoluble materials were removed by filtration. By fractional recrystallization of insoluble materials from benzene, bisacetal **22** (116 mg, 42.6%) was obtained as colorless short needles and aldehyde **17** (24.4 mg, 8.6%) as colorless crystals, respectively. The residue obtained by concentration of filtrate and the liquor of fractional recrystallization was chromatographed on silica gel (30 g). By elution with benzene–ether (volume ratio was varied from 10/1 to 4/1) followed by recrystallization from benzene, aldehyde **17** (114.5 mg, 40.3%) was afforded.

Compound **17** was transformed to bisacetal **22** by heating at 180 °C for 30 min in a glass tube oven. The IR spectrum of heated compound was same to that of bisacetal **22** obtained above.

Compound **17**: colorless crystals, mp 125–127 °C (benzene); IR (KBr): ν_{max} 3260 (OH), 2980, 2956, 2924, 2904, 2856, 1630, 1574, 1494, 1416, 1404, 1364, 1304, 1256, 1142, 1006, 932, 910, 822, 794, 724, 566 cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.22 (3H, d, J=5.5 Hz, $CHCH_3$), 1.99 (3H, s, C_3–CH_3), 3.00 (1H, dd, J=14.0, 5.0 Hz, Ar-CH_2–), 3.09 (1H, dd, J=14.0, 7.5 Hz, Ar-CH_2–), 3.87 (1H, d, J=4.5 Hz, –CH(O*H*)–, disappeared by D_2O), 3.93 (3H, s, C_4–OCH_3), 3.99 (1H, m, –C*H*(OH)–), 6.56 (1H, s, C_5–H), 10.21 (1H, s, CHO), 12.65 (1H, s, C_2–OH, disappeared by D_2O); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 7.28, 23.81, 41.78, 56.30, 69.40, 106.49, 111.24, 114.64, 145.23, 163.26, 164.67, 195.92; MS: *m/z* (%) 224 (M^+, 49), 206 (61), 191 (58), 180 (98), 179 (100). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found C, 64.41; H, 7.20.

Compound **22**: colorless short needles from benzene, mp 258–260 °C; IR (KBr): ν_{max} 3436 (OH), 3012, 2972, 2928, 2848, 1612, 1590, 1456, 1422, 1330, 1298, 1136, 1106, 980, 920, 876, 844, 830, 804 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz): δ 1.33 (6H, d, J=6.5 Hz, C_3–CH_3×2), 2.25–2.29 (2H, m, C_4–$H_{a'}$×2), 2.43–2.48 (2H, m, C_4–$H_{e'}$×2), 2.77 (6H, s, C_7–CH_3×2), 3.39 (6H, s, C_6–OCH_3×2), 4.62–4.69 (2H, m, C_3–H×2), 6.10 (2H, s, C_1–H×2), 6.16 (2H, s, C_5–H×2). MS: *m/z* (%) 223 (46), 207 (21), 206 (100), 191 (53), 179 (37), 163 (32), 91 (31). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.00; H, 6.83.

3.1.3. Detection of 1,8-dihydroxy-6-methoxy-3,7-dimethylisochromane (2). Alcohol **18** (124 mg, 0.63 mmol) was formylated with triethyl orthoformate (2.1 mL, 12.67 mmol) in the presence of 95% aluminum chloride (156 mg, 1.11 mmol) and the reaction mixture was worked up in a manner similar to that described above. The extracts were concentrated by a rotary evaporator at 60 °C until a small amount of liquor was remained and then volatile materials were removed at room temperature in vacuo to give the residue (152.4 mg) as oily crystals. The residue was dissolved in acetone-d_6 (1.2 mL) and insoluble compound **22** (6.9 mg, 5.0%) was removed by filtration. A ^1H NMR analysis of the filtrate showed that a ratio of **2** and **17** was 81:19, respectively. After the acetone-d_6 solution in a ^1H NMR tube was allowed to stand at room temperature for 7.67 h, the ratio of **2** and **17** was 67:33, respectively. Hemiacetal **2** was changed partly to **17** in acetone-d_6 by standing at room temperature.

Compound **2**: ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.28 (3H, d, J=6.0 Hz, $CHCH_3$), 2.02 (3H, s, C_7–CH_3), 2.49 (1H, dd, J=16.0, 11.0 Hz, Ar-CH_2–), 2.60 (1H, dd, J=16.0, 3.0 Hz, Ar-CH_2–), 3.77 (3H, s, C_6–OCH_3), 4.08 (1H, ddq, J=11.0, 6.0, 3.0 Hz, C_3–H), 5.64 (1H, s, C_1–H), 6.29 (1H, s, C_5–H), 6.94 (1H, s, C_1–OH); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 8.31 (C_7–CH_3), 20.97 (C_3–CH_3), 36.64 (C_4), 55.80 (CH_3O), 64.46 (C_3), 96.27 (C_1), 102.48 (C_5), 111.54 (C_7), 114.39 (C_{4a} or C_{8a}), 134.22 (C_{4a} or C_{8a}), 153.67 (C_8), 159.05 (C_6).

3.1.4. 8-Hydroxy-6-methoxy-3,7-dimethylisochromane (1). *Method A*. A mixture of aldehyde **17** (74 mg, 0.33 mmol), 10% palladium on charcoal (27 mg) and 15.0 mL of acetone was stirred under hydrogen atmosphere at room temperature for 4 h. After removal of insoluble materials by filtration, the filtrate was concentrated under reduced pressure to give the residue (76.1 mg). The residue was chromatographed on silica gel (30 g). By elution with benzene–ether (10/1) isochromane **1** (67.7 mg, 98.0%) was obtained as colorless cubic crystals, mp 153.0–155.3 °C (benzene); R_f: 0.31 (hexane/ether=2:1); IR (KBr): ν_{max} 3324 (OH), 3004, 2972, 2928, 2844, 1622, 1594, 1504, 1470, 1456, 1336, 1274, 1256, 1224, 1204, 1130, 1070, 1052, 918, 856, 820, 756, 608, 566, 488 cm^{-1}; MS: *m/z* (%) 208 (M^+, 100), 207 (54), 166 (33), 165 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.27; H, 7.73.

^1H and ^{13}C NMR data of **1** are summarized at Table 1.

Next, by elution with benzene–ether (5/1) dimethyl alcohol **25** (1.0 mg, 1.4%) was obtained as colorless solid, mp 91.0–93.5 °C; IR (KBr): ν_{max} 3508 (OH), 3420 (OH), 2968, 2928, 2848, 1616, 1588, 1506, 1470, 1418, 1332, 1232, 1128, 1018, 934, 840, 820 cm^{-1}; ^1H NMR (CD_3COCD_3, 60 MHz): δ 1.13 (3H, d, J=6.0 Hz, –CH(OH)CH_3), 2.05 (3H, s, C_2–CH_3 or C_4–CH_3), 2.12 (3H, s, C_2–CH_3 or C_4–CH_3), 2.60–2.77 (2H, m, –CH_2CH(OH)–), 3.44 (1H, d, J=5.4 Hz, –CH(O*H*)–), 3.73 (3H, s, C_5–OCH_3), 3.94 (1H, m, –C*H*(OH)–), 6.38 (1H, s, C_6–H), 6.99 (1H, s, C_3–OH). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found C, 68.61; H, 8.70.

Method B. A mixture of bisacetal **22** (51 mg, 0.12 mmol), 10% palladium on charcoal (18 mg) and acetone (10.0 mL) was stirred under hydrogen atmosphere at room temperature for 4 h. The reaction mixture was worked up in a manner similar to that described above and isochromane **1** (47.6 mg, 97.0%) and dimethyl alcohol **25** (1.0 mg, 2.0%) were prepared, respectively.

Method C. A solution of compound **18** (124 mg, 0.63 mmol) and triethyl orthoformate (2.1 mL, 12.67 mmol) in toluene (1.3 mL) was added dropwise with stirring to a suspension of aluminum chloride (157 mg, 1.12 mmol) in toluene (1.3 mL) at −48 °C under an argon atmosphere. The reaction was carried out similarly as described for the preparation of compounds **17** and **22** and a reaction mixture was worked up in a manner similar to that described for the detection of compound **2** to give the residue (171.6 mg). A ratio of **2** and **17** (82:18) and the yield of **22** (20.5 mg, 15%) in the residue was determined as described for the detection of **2**. A ratio of **2**, **17** and **23**, which was calculated from the above results, was about 70:15:15, respectively. The residue was stirred with 10% Pd on charcoal (60 mg) for 4 h in acetone (26.0 mL) under hydrogen atmosphere without purification. The reaction mixture was worked up in a manner similar to that described for the catalytic hydrogenation of **17** and isochromane **1** (117.5 mg, 89.0%) and dimethyl alcohol **25** (1.2 mg, 0.9%) were obtained, respectively.

3.1.5. 6,8-Dimethoxy-3,7-dimethylisochromane (4). A suspension of isochromane **1** (181 mg, 0.87 mmol), 60% sodium hydride (53 mg, 1.33 mmol) and dry DMF

(12.5 mL) was stirred at 0 °C for 5 min under an argon atmosphere and then methyl iodide (0.54 mL, 8.67 mmol) was added by a syringe. After stirring at the same temperature for 2 h, the reaction mixture was quenched with 3 M HCl solution (30 mL) and extracted with dichloromethane (50 mL) three times. The combined organic layer was washed with brine and dried. The residue obtained by evaporation of solvents in vacuo was chromatographed on silica gel (35 g, Kieselgel 60, Merck). By elution with hexane–ether (15/1) compound **4** (187.6 mg, 97.2%) was obtained as colorless columns, mp 54.5–55.3 °C (hexane) (lit.,[4a] 52.5–54 °C); IR (KBr): ν_{max} 2988, 2968, 2948, 2916, 2844, 1614, 1588, 1490, 1478, 1456, 1364, 1330, 1120, 1086, 1010, 1000, 946, 830, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ 1.34 (3H, d, J= 6.0 Hz, C_3–CH_3), 2.11 (3H, s, C_7–CH_3), 2.59–2.70 (2H, m, C_4–H_2), 3.69 (3H, s, C_8–OCH_3), 3.80 (3H, s, C_6–OCH_3), 4.66 and 5.00 (each 1H, d, J=14.8 Hz, C_1–H_2), 6.39 (1H, s, C_5–H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.35; H, 8.26.

3.1.6. Demethylation of 6,8-dimethoxy-3,7-dimethylisochromane (4).[4,19] To a stirred suspension of 60% sodium hydride (83 mg, 2.07 mmol) in dry DMF (2.0 mL) was added dropwise a solution of ethanethiol (154 μL, 2.07 mmol) in dry DMF (1.0 mL) by a syringe under an argon atmosphere and then stirring was continued for an additional 10 min. Dimethy ether **4** (185 mg, 0.83 mmol) in dry DMF (2.1 mL) was added dropwise to the stirred solution by a syringe and heated at 140 °C for 3 h. After cooling, the reaction mixture was acidified with 1 M HCl solution (50 mL) and extracted with ether (50 mL) three times. The combined organic layer was washed with brine, dried and evaporated in vacuo to give the residue (215.8 mg). The residue was chromatographed on silica gel (30 g, Kieselgel 60, Merck). By elution with hexane–acetone (volume ratio was varied from 30/4 to 10/3) a mixture of compounds **1** and **3** (158.8 mg, 91.8%, 95:5) was obtained as colorless solid. The ratio was determined by ^1H NMR spectroscopy. The structure of **1** and **3** was determined by comparison of their spectra to that of authentic samples obtained above.

3.1.7. 1-(3-Hydroxy-5-methoxy-4-methylphenyl)-2-methoxymethoxypropane (19) and 1-(3-methoxy-5-methoxymethoxy-4-methylphenyl)-2-methoxymethoxypropane (20). To a stirred solution of alcohol **18** (180 mg, 0.92 mmol) and *N*-ethyldiisopropylamine (1.42 mL, 8.16 mmol) in dry dichloromethane (1.0 mL) chrolomethyl methyl ether (0.62 mL, 8.16 mmol) was added by a syringe at 0 °C and continued stirring at room temperature for 18 h. The reaction mixture was poured into ice water and extracted with dichloromethane (50 mL) three times. The combined organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue (277.4 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (30 g, Kieselgel 60, Merck). Firstly, by elution with hexane–ether (10/1) followed by hexane–ether (5/1) ether **20** was obtained in 55.9% yield as colorless oil; IR (KBr): ν_{max} 2936, 1612, 1590, 1454, 1428, 1404, 1150, 1126, 1076, 1030, 920, 844, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19 (3H, d, J=6.0 Hz, –CH(OCH_2OCH_3)CH_3), 2.09 (3H, s, C_4–CH_3), 2.62 (1H, dd, J=13.6, 6.0 Hz, –CH_2CH(OCH_2OCH_3)–), 2.83 (1H, dd, J=13.6, 6.7 Hz, –CH_2CH(OCH_2OCH_3)–), 3.24 (3H, s, –CH(OCH_2OCH_3)–), 3.48 (3H, s, C_3–OCH_2OCH_3), 3.81 (3H, s, C_5–OCH_3), 3.92 (1H, ddq, J=6.7, 6.0, 6.0 Hz, –CH(OCH_2OCH_3)–), 4.54 (1H, d, J=7.0 Hz, –CH(OCH_2 OCH_3)–), 4.64 (1H, d, J=7.0 Hz, –CH(OCH_2CH_3)–), 5.17 (2H, s, C_3–OCH_2OCH_3), 6.42 (1H, s, C_2–H or C_6–H), 6.58 (1H, s, C_2–H or C_6–H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.26, 20.36, 44.01, 55.13, 55.69, 56.01, 74.20, 94.83, 95.00, 105.79, 108.44, 113.48, 137.37, 155.75, 158.20. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.18; H, 8.55.

Secondly, MOM ether **19** was obtained by elution with hexane–ether (2/1) in 39.3% yield as colorless prisms, mp 52.5–53.0 °C (hexane–ether); IR (KBr): ν_{max} 3348, 3016, 2968, 2940, 2896, 2844, 1616, 1600, 1520, 1472, 1422, 1322, 1226, 1142, 1112, 1052, 1026, 898, 826, 796, 672, 644, 608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.18 (3H, d, J=6.0 Hz, –CH(OCH_2OCH_3)CH_3), 2.07 (3H, s, C_4–CH_3), 2.58 (1H, dd, J=13.5, 6.0 Hz, –CH_2CH(OCH_2OCH_3)–), 2.79 (1H, dd, J=13.5, 7.2 Hz, –CH_2CH(OCH_2OCH_3)–), 3.25 (3H, s, –CH(OCH_2OCH_3)–), 3.80 (3H, s, C_5–OCH_3), 3.93 (1H, ddq, J=6.0, 6.0, 7.2 Hz, –CH(OCH_2OCH_3)–), 4.56 (1H, d, J=6.8 Hz, OCH_2O), 4.66 (1H, d, J=6.8 Hz, OCH_2O), 5.34 (1H, s, OH), 6.32 (2H, s, C_2–H and C_6–H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 7.85, 20.29, 43.65, 55.17, 55.71, 74.18, 94.87, 104,28, 109.10, 109.99, 137.40, 154.35, 158.48. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.75; H, 8.44.

3.1.8. The cyclization of MOM ether 19 with $TiCl_4$. A mixture of MOM ether **19** (47 mg, 0.19 mmol) in dry dichloromethane (3.0 mL) was added to a solution of $TiCl_4$ (21 μL, 0.19 mmol) in dichloromethane (3.0 mL) under stirring at −48 °C over a period of 15 min under argon atmosphere and stirred at the same temperature for 15 min. Methanol (0.2 mL) was added to the reaction mixture by a syringe and then 3 M HCl solution (4 mL) was added. After stirring at room temperature, the reaction mixture was extracted with dichloromethane (40 mL) three times. The combined organic layer was washed with brine and dried. The residue (43.8 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (25 g). By elution with hexane–ether (5/1) a mixture of compounds **1** and **3** (26.7 mg, 66.1%, 79:21) was obtained as colorless oil. By repeating chromatography of a mixture of **1** and **3** on silica gel (Kieselgel 60, Merck) eluted with hexane–ether (30/1)[‡] and followed by recrystallization from hexane–ether compound **3** was obtained as colorless crystals, mp 150.5–151.5 °C (hexane–ether); R_f: 0.28 (hexane/ether=2:1); IR (KBr): ν_{max} 3288 (OH), 2980, 2928, 2844, 1616, 1596, 1506, 1460, 1424, 1390, 1366, 1328, 1098, 1048, 1002, 828, 814, 662 cm^{-1}; MS: *m/z* (%) 208 (M^+, 71), 207 (31), 166 (23), 165 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.28; H, 7.84.

The ^1H and ^{13}C NMR data are summarized in Table 2.

[‡] As the difference of R_f values between **1** (R_f: 0.31) and **3** (R_f: 0.28) is small, it is difficult to separate clearly **3** from **1** by column chromatography under the given conditions.

3.1.9. The cyclization of ether 20 with $TiCl_4$. To a stirred solution of $TiCl_4$ (15 μL, 0.14 mmol) in dry dichloromethane (3.0 mL) ether **20** (55 mg, 0.19 mmol) dissolved in dichloromethane (3.0 mL) was added dropwise at −49 °C over a period of 15 min under an argon atmosphere and stirred at the same temperature for 15 min. The reaction mixture was worked up in a manner similar to the reaction of **19** with $TiCl_4$. The residue (42.3 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (25 g). A mixture of compounds **26** and **27** (14.1 mg, 29.0%, 53:47) was obtained by elution with hexane–ether (volume ratio was varied from 20/1 to 10/1). Secondly, a mixture of **1** and **3** (21.1 mg, 52.6%, 88:12) was afforded by elution with hexane–ether (5/1). The structure of **26** and **27** was determined by comparison of their spectra to that of authentic samples obtained by methoxymethylation of **1** and **3**, respectively, as described bellow.

3.1.10. 6-Methoxy-8-methoxymethoxy-3,7-dimethylisochromane (26). To a mixture of compound **1** (71 mg, 0.34 mmol), *N*-ethyldiisopropylamine (217 mg, 1.68 mmol) and dry dichloromethane (1.0 mL) chloromethyl methyl ether (135 mg, 1.68 mmol) was added by a syringe at 0 °C under stirring. After stirring at room temperature for 18 h 45 min, water (10 mL) was added and extracted with dichloromethane (40 mL) three times. The combined organic layer was washed with brine and dried. The residue (89.3 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (25 g). Compound **26** (82.5 mg) was obtained in 96.7% yield by elution with hexane–ether (10/1) followed by hexane–ether (20/1) as colorless oil; R_f: 0.47 (hexane/ether=2:1); IR (neat): ν_{max} 2972, 2936, 2836, 1614, 1590, 1490, 1470, 1362, 1330, 1264, 1160, 1124, 1092, 1050, 982, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.35 (3H, d, J=6.0 Hz, C_3–CH_3), 2.11 (3H, s, C_7–CH_3), 2.65–2.66 (2H, m, C_4–H_2), 3.59 (3H, s, OCH_2OCH_3), 3.75–3.79 (1H, m, C_3–H), 3.80 (3H, s, C_6–OCH_3), 4.73 (1H, d, J=15.0 Hz, C_1–H), 4.92 and 4.94 (each 1H, d, J=6.0 Hz, OCH_2OCH_3), 5.00 (1H, d, J=15.0 Hz, C_1–H), 6.41 (1H, s, C_5–H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.39, 21.53, 35.84, 55.56, 57.33, 64.99, 70.53, 99.38, 106.52, 117.10, 120.41, 132.16, 152.87, 157.12. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.35; H, 7.96.

3.1.11. 8-Methoxy-6-methoxymethoxy-3,7-dimethylisochromane (27). To a stirred solution of compound **3** (20 mg, 0.10 mmol) and *N*-ethyldiisopropylamine (62 mg, 0.48 mmol) in dry dichloromethane (0.8 mL) chloromethyl methyl ether (39 mg, 0.48 mmol) was added by a syringe at 0 °C under stirring and continued stirring at room temperature for 19 h. The reaction mixture was worked up in a manner similar to that described above and compound **27** (19.1 mg, 78.9%) was obtained as colorless oil; R_f: 0.51 (hexane/ether=2:1); IR (neat): ν_{max} 2932, 2852, 1614, 1590, 1486, 1450, 1362, 1324, 1262, 1154, 1118, 1086, 1060, 1002, 924, 854, 816 cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.25 (3H, d, J=6.0 Hz, C_3–CH_3), 2.10 (3H, s, C_7–CH_3), 2.52 (1H, dd, J=16.0, 11.0 Hz, C_4–H), 2.64 (1H, dd, J=16.0, 3.0 Hz, C_4–H), 3.43 (3H, s, OCH_2OCH_3), 3.67 (3H, s, C_6–OCH_3), 3.69 (1H, m, C_3–H), 4.62 and 4.83 (each 1H, d, J=15.0 Hz, C_1–H_2), 5.17 and 5.19 (each 1H, d, J=6.0 Hz, OCH_2OCH_3), 6.63 (1H, s, C_5–H); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 8.99, 21.86, 36.47, 56.09, 60.28, 64.89, 71.23, 95.40, 110.87, 118.46, 122.17, 133.48, 155.76, 155.84. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.76; H, 8.11.

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Platinum-catalyzed allylation of aminonaphthalenes with allylic acetates

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Abstract—The activation of C–O bonds in allylic acetates has been accelerated by carrying out the reactions in the presence of platinum complexes associated with ligands. Platinum-catalyzed allylation of aminonaphthalenes with allylic acetates leads to *N*-allylic aminonaphthalenes in good yields.

1. Introduction

A principal goal of organometallic chemistry is the catalytic synthesis of organic compounds by using the chemistry of organic ligands covalently bound to transition metals. Most organometallic chemistry has focused on complexes with covalent metal–carbon or metal–hydrogen bonds. Transition metals, in particular palladium and rhodium, have been workhorse elements in many commercialized catalytic processes that include hydrogenations, hydroformylations, acetic acid production, and other C–C and C–H bond forming processes.[1] Although carbon–oxygen, carbon–nitrogen, or carbon–sulfur bonds are found in the majority of important organic molecules, catalytic organometallic reaction chemistry that leads to the formation of carbon-heteroatom bonds is less common than that forming carbon–carbon and carbon–hydrogen bonds. Transition metal η^3-allyl complexes, as well as transition metal σ-alkyl complexes, play important roles as active species and key intermediates in many reactions catalyzed by transition metal complexes.[2] The palladium-catalyzed allylation is a powerful tool for C–C, C–N, and C–O bond formation, which has been widely applied to organic chemistry.[3] The processes have been shown to proceed by attack of nucleophiles on intermediate η^3-allylpalladium(II) complexes generated by oxidative addition of allylic compounds including halides,[4] esters,[5] carbonates,[6] carbamates,[7] phosphates,[8] and related derivatives[9] to a Pd(0) complex. Aromatic amines have not been used commonly in allylic amination, presumably because they are less nucleophilic than the more commonly used benzylamine or stabilized anionic nitrogen nucleophiles.[10] We have recently reported our attempts and some successful applications of a process involving the C–O bond cleavage with direct use of allylic alcohols catalyzed by palladium complexes.[11] The reactions should be promoted in the presence of titanium reagent. However, platinum-catalyzed allylation has attracted little attraction.[12] In this paper, we wish to report a novel catalysis of platinum complex, which mediates N-allylation of aminonaphthalenes with allylic acetates.

2. Results and discussion

To evaluate the scope and limitations of the N-allylation of aminonaphthalenes with allylic acetates, we treated a mixture of 1-aminonaphthalene (**1a**, 2 mmol) and allyl acetate (**2a**, 1.6 mmol) in the presence of $Pt(acac)_2$ (1 mol%) and PPh_3 (4 mol%) in benzene under nitrogen, at 50 °C for 3 h, *N*-allyl-1-naphthylamine (**3a**) was formed in only 9% yield (entry 1 in Table 1). The reaction, under reflux, increased the yields of products **3a** and *N*,*N*-diallyl-1-naphthylamine (**4a**) to 75 and 6%, respectively (entry 2). The reaction gave 91% yield under reflux for 6 h (entry 3). It was confirmed that the yield was only 3% in the absence of PPh_3 (entry 4). The reaction did not occur in the absence of the platinum species (entry 5). Among the platinum catalysts including $Pt(acac)_2$ (entry 2), *cis*-$PtCl_2(PhCN)_2$ (entry 6), *cis*-$PtCl_2(PPh_3)_2$ (entry 7), $PtCl_2$ (entry 8), PtI_2 (entry 9), $O[Si(CH_3)_2C{=}CH_2]_2Pt$ (entry 10), $Pt(CH_2{=}CH_2)(PPh_3)_2$ (entries 11 and 12), and $Pt(PPh_3)_4$ (entries 13 and 14) were used. $Pt(acac)_2$, $O[Si(CH_3)_2C{=}CH_2]_2Pt$, and $Pt(CH_2{=}CH_2)(PPh_3)_2$ were found to be

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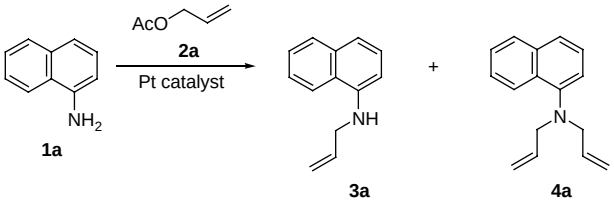
Table 1. Reaction of 1-aminonaphthalene (**1a**) with allyl acetate (**2a**)[a]



Entry	Platinum catalyst	Ligand	Solvent	Yield (%) (**3a**:**4a**)[b]
1	$Pt(acac)_2$	PPh_3	Benzene[c]	9 (100:0)
2	$Pt(acac)_2$	PPh_3	Benzene	81 (93:7)
3	$Pt(acac)_2$	PPh_3	Benzene[d]	91 (93:7)
4	$Pt(acac)_2$	—	Benzene	3 (100:0)
5	—	PPh_3	Benzene	0
6	*cis*-$PtCl_2(PhCN)_2$	PPh_3	Benzene	57 (99:1)
7	*cis*-$PtCl_2(PPh_3)_2$	PPh_3	Benzene	2 (100:0)
8	$PtCl_2$	PPh_3	Benzene	8 (100:0)
9	PtI_2	PPh_3	Benzene	1 (100:0)
10	$O[Si(CH_3)_2C{=}CH_2]_2Pt$	PPh_3	Benzene	88 (86:14)
11	$Pt(CH_2{=}CH_2)(PPh_3)_2$	—	Benzene	66 (99:1)
12	$Pt(CH_2{=}CH_2)(PPh_3)_2$	PPh_3	Benzene	90 (96:4)
13	$Pt(PPh_3)_4$	—	Benzene	5 (100:0)
14	$Pt(PPh_3)_4$	PPh_3	Benzene	68 (87:13)
15	$Pt(acac)_2$	Bu_3P	Benzene	32 (100:0)
16	$Pt(acac)_2$	$(2\text{-}MeC_6H_4)_3P$	Benzene	3 (100:0)
17	$Pt(acac)_2$	$(3\text{-}MeC_6H_4)_3P$	Benzene	82 (97:3)
18	$Pt(acac)_2$	$(4\text{-}MeC_6H_4)_3P$	Benzene	71 (96:4)
19	$Pt(acac)_2$	$(4\text{-}FC_6H_4)_3P$	Benzene	96 (96:4)
20	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Benzene	99 (92:8)
21	$Pt(acac)_2$	$(4\text{-}MeOC_6H_4)_3P$	Benzene	90 (96:4)
22	$Pt(acac)_2$	$[2,6\text{-}(MeO)_2C_6H_3]_3P$	Benzene	1 (100:0)
23	$Pt(acac)_2$	$(2\text{-Furyl})_3P$	Benzene	95 (96:4)
24	$Pt(acac)_2$	$(2\text{-Pyridyl})Ph_2P$	Benzene	91 (97:3)
25	$Pt(acac)_2$	Dppp[e]	Benzene	25 (99:1)
26	$Pt(acac)_2$	Dppb[f]	Benzene	73 (98:2)
27	$Pt(acac)_2$	Dpph[g]	Benzene	69 (98:2)
28	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Benzene[c]	87 (78:22)
29	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Benzene	99 (92:8)
30	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Toluene[c]	82 (87:13)
31	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Toluene	98 (97:3)
32	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	CH_2Cl_2[c]	5 (100:0)
33	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	THF[c]	85 (81:19)
34	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	THF	89 (90:10)
35	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Dioxane[c]	39 (93:7)
36	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	Dioxane	85 (95:5)
37	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	MeCN[c]	52 (83:17)
38	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	MeCN	76 (89:11)
39	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	DMF[c]	58 (85:15)
40	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	DMF	66 (94:6)
41	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	HMPA[c]	38 (93:7)
42	$Pt(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	HMPA	4 (100:0)

[a] Reaction conditions: **1a** (2 mmol), **2a** (1.6 mmol), Pt catalyst (0.02 mmol), ligand (0.08 mmol), and MS 4 Å in a solvent (5 mL) were refluxed for 3 h.
[b] Isolated yield.
[c] Stirred at 50 °C.
[d] Reflux for 6 h.
[e] 1,3-Bis(diphenylphosphino)propane.
[f] 1,4-Bis(diphenylphosphino)butane.
[g] 1,6-Bis(diphenylphosphino)hexane.

superior. The use of $O[Si(CH_3)_2C{=}CH_2]_2Pt$ as catalyst was cheaper than palladium reagents and could give good results. However, using $Pt(CH_2{=}CH_2)(PPh_3)_2$ or $Pt(PPh_3)_4$ with extra PPh_3 as catalyst increased the yield of products (entries 12 and 14). The catalytic reactivity of the phosphine ligands is likely due to improved catalyst stability. In the presence of various monodentate ligands including PPh_3, Bu_3P, $(2\text{-}MeC_6H_4)_3P$, $(3\text{-}MeC_6H_4)_3P$, $(4\text{-}MeC_6H_4)_3P$, $(4\text{-}FC_6H_4)_3P$, $(4\text{-}ClC_6H_4)_3P$, $(4\text{-}MeOC_6H_4)_3P$, $[2,6\text{-}(MeO)_2C_6H_3]_3P$, $(2\text{-furyl})_3P$, and $(2\text{-pyridyl})Ph_2P$ (entries 2, and 15–24) showed that $(4\text{-}FC_6H_4)_3P$ (entry 19), $(4\text{-}ClC_6H_4)_3P$ (entry 20), $(4\text{-}MeOC_6H_4)_3P$ (entry 21), $(2\text{-furyl})_3P$ (entry 23), and $(2\text{-pyridyl})Ph_2P$ (entry 24) were the most effective ligands. The bidentate ligand dppp (entry 25) decreased the yield of products. Dppb (entry 26) and dpph (entry 27) gave moderate yields of products. It was known that several factors, such as the solvent and nature of the nucleophile, can alter the product pattern in metal-catalyzed allylation.[13] At 50 °C, in the presence of $Pt(acac)_2$ and $(4\text{-}ClC_6H_4)_3P$, eight solvents were investigated, CH_2Cl_2, dioxane, and

Table 2. Reaction of aromatic amines (**1b–k**) with allyl acetate (**2a**)[a]

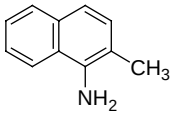
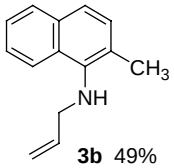
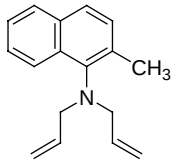
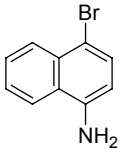
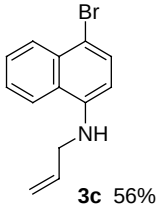
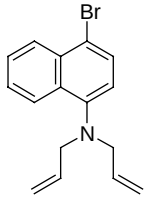
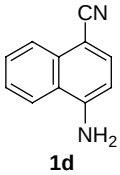
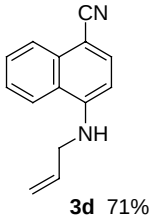
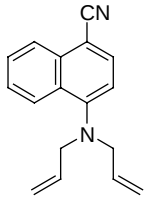
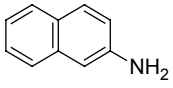
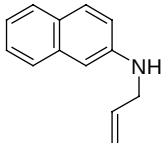
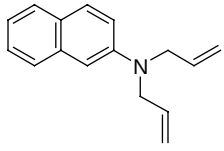
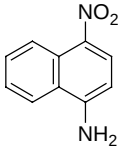
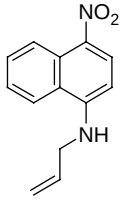
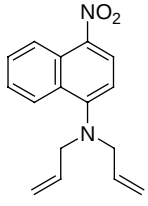
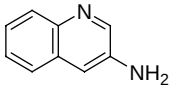
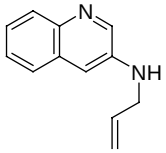
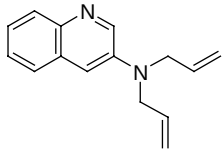
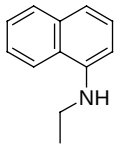
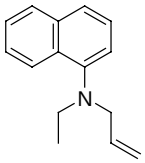
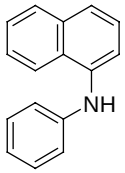
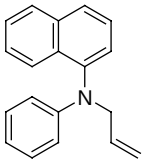
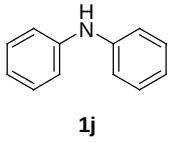
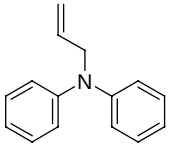
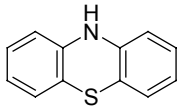
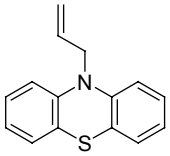
Entry	1	Yields[b]	
1	 **1b**	 **3b** 49%	 **4b** 19%
2[c]	**1b**	**3b** 48%	**4b** 18%
3[d]	**1b**	**3b** 41%	**4b** 42%
4	 **1c**	 **3c** 56%	 **4c** 7%
5[c]	**1c**	**3c** 72%	**4c** 14%
6	 **1d**	 **3d** 71%	 **4d** 5%
7	 **1e**	 **3e** 70%	 **4e** 18%
8	 **1f**	 **3f** 18%	
9[e]	**1f**	**3f** 51%	 **4f** 2%
10	 **1g**	 **3g** 81%	 **4g** 14%

Table 2 (*continued*)

Entry	1	Yields[b]
11	 **1h**	 **3h** 42%
12	 **1i**	 **3i** 30%
13	 **1j**	 **3j** 53%
14	 **1k**	 **3k** 32%

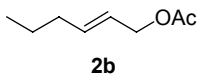
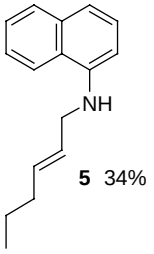
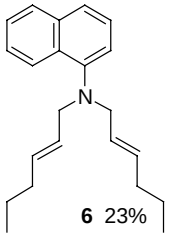
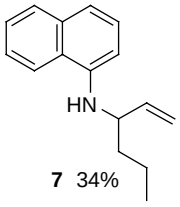
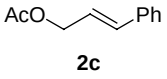
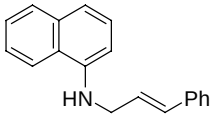
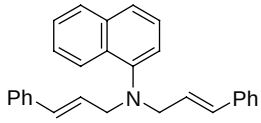
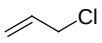
[a] Reaction conditions: **1** (2 mmol), **2a** (1.6 mmol), $Pt(acac)_2$ (0.02 mmol), $(4\text{-}ClC_6H_4)_3P$ (0.08 mmol), and MS 4 Å in benzene (5 mL) were refluxed for 3 h.
[b] Isolated yield.
[c] Compound **2a** (4.0 mmol) was used.
[d] Compound **2a** (8.0 mmol) was used.
[e] Reflux for 24 h.

HMPA gave worst results. The reaction, under reflux, benzene, toluene, and THF gave the best results (entries 28–42).

The results collected in Table 2 show that the amination of allyl acetate (**2a**) with aminonaphthalenes using $Pt(acac)_2$ and $(4\text{-}ClC_6H_4)_3P$, giving general good yields of the corresponding allylic aminonaphthalenes (entries 1–7). As expected, increasing the relative amount of the allyl alcohol favored the formation of the diallylated compound (entries 1–3). Using aminonaphthalenes having strong electron-withdrawing groups, such as the nitro group, gave only 18% lower chemical yields (entry 8). These differences in reactivity could be related to the nucleophilicity of the corresponding aminonaphthalene. 1-Amino-4-nitronaphthalene (**1f**) gave 53% yield under reflux for 24 h (entry 9); the lower yield observed may arise from the nature of the nitro group. The more acidic 1-amino-4-nitronaphthalene (**1f**) is probably less reactive in attack on the π-allyl complex. 3-Aminoquinoline (**1g**) reacted to give the *N*-allylated products in excellent yields (entry 10). The sterically more demanding secondary aminonaphthalenes (**1h** and **1i**) gave lower yields (entries 11 and 12). Secondary aromatic amines, such as diphenylamine (**1j**) and phenothiazine (**1k**), also reacted to give the *N*-allylamine in moderate yield (entries 13 and 14).

The results for amination of a number of derivatives of allylic alcohols **2b–e** with 1-aminonaphthalene (**1a**) using $Pt(acac)_2$ and $(4\text{-}ClC_6H_4)_3P$ are summarized in Table 3. Amination of *trans*-2-hexen-1-yl acetate (**2b**) gave mixtures of monoallylated, diallylated and regioisomeric aminonaphthalenes **5**, **6**, and **7** in yields of 34, 23, and 38%, respectively (entry 1 in Table 1). These products may all be derived from the same π-allyl intermediate which can be attacked at either the C-1 or C-3 position. The reaction is considered to proceed via π-allylplatinum intermediates. The loss of the stereochemistry of the starting acetate **2b** is due to a rapid $\sigma \leftrightarrows \eta^3 \leftrightarrows \sigma$ interconversion of the π-allyl intermediate compared to the rate of amination of this intermediate. Reaction of aromatic allylic acetate **2c**, the corresponding monoallylated and diallylated products were formed in overall 97% yields (entry 2). Increasing the amount of **2c**, favored the formation of the diallylated compound **9** and gave the products in quantitatively yields (entry 3). With the allyl chloride (**2d**), produces only **3a** in 9% yield (entry 4). Allyl carbonate (**2e**) gave products in moderate yields (entry 5).

Table 3. Reaction of 1-aminonaphthalene (**1a**) with allylic compounds (**2b–e**)[a]

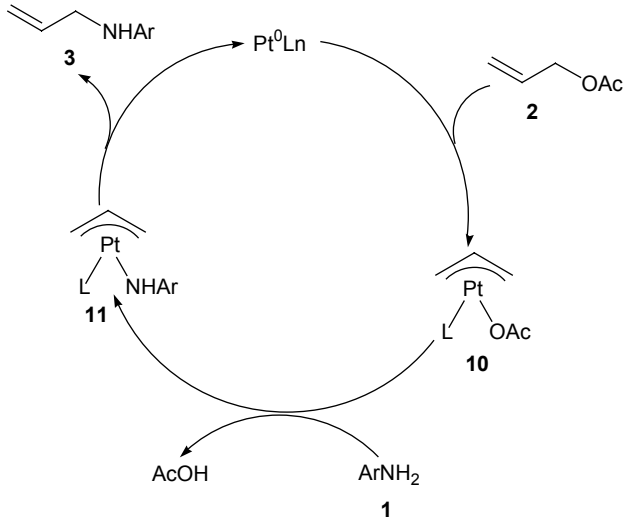
Entry	2	Yields[b]		
1	 **2b**	 **5** 34%	 **6** 23%	 **7** 34%
2	 **2c**	 **8** 89%		 **9** 8%
3[c]	**2c**	**8** 46% **3a** 9%		**9** 54%
4	 **2d**			
5	 **2e**	**3a** 57%		**4a** 4%

[a] Reaction conditions: **1a** (2 mmol), **2** (1.6 mmol), $Pt(acac)_2$ (0.02 mmol), $(4\text{-}ClC_6H_4)_3P$ (0.08 mmol), and MS 4 Å in benzene (5 mL) were refluxed for 3 h.
[b] Isolated yield.
[c] Compound **2a** (4.0 mmol) was used.

A possible mechanism for the formation of *N*-allylanilines from **1** and **2** is illustrated in Scheme 1, in which the substituent on allylic acetate is omitted. Acetate **2** reacts with Pt(0) species generated in situ to afford a π-allylplatinum intermediate (**10**). Subsequently, the reaction of **10** with aminonaphthalene **1** followed by reductive elimination gives *N*-allylaminonaphthalene.

3. Conclusion

In summary, we have shown that platinum-catalyzed allylation of aminonaphthalenes using allylic acetates is a simple and efficient route for C–N bond formation. The reaction did not occur in the absence of the platinum catalyst. The amination of allylic acetates worked well with aminonaphthalenes, giving generally good yields of the corresponding allylic aminonaphthalenes. Aminonaphthalenes with steric constraints gave lower chemical yields.



Scheme 1.

4. Experimental

4.1. General considerations

All reactions were carried out under a nitrogen atmosphere. Solvents were dried and distilled by known methods. Column chromatography was performed on silica gel. All melting points were uncorrected. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer. Proton and carbon-13 NMR were measured with a Unity-400 or Mercury Plus-400 spectrometer. Carbon multiplicities were obtained from DEPT experiments. Chemical shifts (δ) and coupling constants (Hz) were measured with respect to TMS or chloroform-d_1. MS and high-resolution mass spectra (HRMS) were taken on a Thermo-Finnigan trace GC or Finnigan MAT-95XL instrument, with a direct inlet system.

4.2. General procedure for the platinum-catalyzed allylation of aminonaphthalenes. Reaction with 1-aminonaphthalene (1a)

A mixture of 1-aminonaphthalene (**1a**) (283 mg, 2 mmol), allyl acetate (**2a**) (160 mg, 1.6 mmol), $Pt(acac)_2$ (7.8 mg, 0.02 mmol), PPh_3 (21 mg, 0.08 mmol) and MS 4 Å in benzene (5 mL) was refluxed under nitrogen for 3 h. After cooling, the reaction mixture was filtered through Celite and the solvent was distilled under reduced pressure. Column

chromatography (*n*-hexane/chloroform 2:1) of the residue afforded **3a** and **4a** in 75 and 6% yields, respectively.

Products **3j**[11d] and **3k**[11d] are known.

4.2.1. *N*-Allyl-1-naphthylamine (3a). Light yellow thick oil. IR (KBr): ν 3442 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (ddd, J=1.6, 1.6, 5.6 Hz, 2H, CH_2), 4.25 (br s, 1H, NH), 5.12 (ddt, J=1.6, 1.6, 10.0 Hz, 1H, vinyl H), 5.24 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 5.92 (ddt, J=5.6, 10.0, 17.2 Hz, 1H, vinyl H), 6.50 (d, J=7.6 Hz, 1H, ArH), 7.18 (d, J=8.0 Hz, 1H, ArH), 7.26 (d, J=7.6 Hz, 1H, ArH), 7.30 (ddd, J=1.6, 6.8, 8.4 Hz, 1H, ArH), 7.35 (ddd, J=1.6, 6.8, 8.0 Hz, 1H, ArH), 7.63 (d, J=8.4 Hz, 1H, ArH), 7.71 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.5 (CH_2), 104.6 (CH), 116.3 (CH_2), 117.4 (CH), 119.8 (CH), 123.3 (C), 124.5 (CH), 125.5 (CH), 126.4 (CH), 128.5 (CH), 134.1 (C), 134.9 (CH), 142.9 (C). EI-MS: *m*/*z* 183 (M^+), 168, 154, 142, 127, 115, 89, 77. EI-HRMS calcd for $C_{13}H_{13}N$: 183.1048. Found: 183.1049.

4.2.2. *N*,*N*-Diallyl-1-naphthylamine (4a). Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (d, J=5.6 Hz, 4H, $CH_2\times2$), 5.13 (ddt, J=1.6, 1.6, 10.4 Hz, 2H, vinyl H), 5.23 (ddt, J=1.6, 1.6, 17.2 Hz, 2H, vinyl H), 5.86 (ddt, J=6.0, 10.4, 17.2 Hz, 2H, vinyl H), 7.08 (d, J=7.2 Hz, 1H, ArH), 7.36 (dd, J=7.6, 8.0 Hz, 1H, ArH), 7.42–7.47 (m, 2H, ArH), 7.53 (d, J=8.0 Hz, 1H, ArH), 7.81 (dd, J=2.0, 7.2 Hz, 1H, ArH), 8.29 (d, J=7.2 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1 (CH_2), 117.2 (CH_2), 117.6 (CH), 123.3 (CH), 123.9 (CH), 125.2 (CH), 125.3 (CH), 125.7 (CH), 128.3 (CH), 130.0 (C), 134.8 (C), 135.0 (CH), 147.6 (C). EI-MS: *m*/*z* 223 (M^+), 208, 198, 182, 180, 167, 155, 141, 127, 115, 101, 77. EI-HRMS calcd for $C_{16}H_{17}N$: 223.1361. Found: 223.1362.

4.2.3. *N*-Allyl-1-(2-methylnaphthyl)amine (3b). Red thick oil. IR (KBr): ν 3370 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 3.27 (br s, 1H, NH), 3.72 (ddd, J=1.2, 1.6, 6.0 Hz, 2H, CH_2), 5.11 (ddt, J=1.2, 1.6, 10.0 Hz, 1H, vinyl H), 5.30 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 6.03 (ddt, J=6.0, 10.0, 17.2 Hz, 1H, vinyl H), 7.23 (d, J=8.4 Hz, 1H, ArH), 7.35 (ddd, J=1.2, 6.8, 8.0 Hz, 1H, ArH), 7.41 (ddd, J=1.6, 6.8, 8.4 Hz, 2H, ArH), 7.73 (d, J=8.0 Hz, 1H, ArH), 8.04 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8 (CH_3), 52.7 (CH_2), 115.8 (CH_2), 122.6 (CH), 122.7 (CH), 124.8 (CH), 125.3 (CH), 125.4 (C), 128.2 (CH), 128.5 (C), 129.2 (CH), 133.5 (C), 136.6 (CH), 142.2 (C). EI-MS: *m*/*z* 197 (M^+), 182, 180, 168, 156, 141, 129, 115, 102, 89, 77. EI-HRMS calcd for $C_{14}H_{15}N$: 197.1204. Found: 197.1207.

4.2.4. *N*,*N*-Diallyl-1-(2-methylnaphthyl)amine (4b). Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 3.79 (m, 4H, $CH_2\times2$), 4.98 (ddt, J=1.2, 1.6, 10.0 Hz, 2H, vinyl H), 5.08 (ddt, J=1.6, 1.6, 17.2 Hz, 2H, vinyl H), 5.87 (ddt, J=6.8, 10.0, 17.2 Hz, 2H, vinyl H), 7.19 (d, J=8.4 Hz, 1H, ArH), 7.32 (ddd, J=1.2, 6.8, 8.0 Hz, 1H, ArH), 7.41 (ddd, J=1.6, 6.8, 8.4 Hz, 1H, ArH), 7.48 (d, J=8.4 Hz, 1H, ArH), 7.71 (d, J=8.0 Hz, 1H, ArH), 8.17 (d, J=8.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (CH_3), 56.5 (CH_2), 116.2 (CH_2), 124.6 (CH), 124.7 (CH), 125.3 (CH), 125.5 (CH), 128.1 (CH), 129.7 (CH), 133.3 (C), 133.6 (C), 133.8 (C), 136.7 (CH), 144.7 (C). EI-MS: *m*/*z* 237 (M^+), 222, 210, 196, 180, 168, 154, 141, 115, 89. EI-HRMS calcd for $C_{17}H_{19}N$: 237.1517. Found: 237.1520.

4.2.5. *N*-Allyl-1-(4-bromonaphthyl)amine (3c). Claret thick oil. IR (KBr): ν 3445 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.71 (ddd, J=1.2, 1.6, 5.2 Hz, 2H, CH_2), 4.27 (br s, 1H, NH), 5.14 (ddt, J=1.2, 1.6, 10.4 Hz, 1H, vinyl H), 5.24 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 5.90 (ddt, J=5.2, 10.4, 17.2 Hz, 1H, vinyl H), 6.28 (d, J=8.0 Hz, 1H, ArH), 7.32 (ddd, J=1.2, 6.8, 8.4 Hz, 1H, ArH), 7.45 (ddd, J=1.2, 6.8, 8.4 Hz, 1H, ArH), 7.50 (d, J=8.0 Hz, 1H, ArH), 7.61 (d, J=8.4 Hz, 1H, ArH), 8.18 (dd, J=0.8, 8.0 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.4 (CH_2), 105.3 (CH), 109.9 (C), 116.7 (CH_2), 120.1 (CH), 124.5 (C), 125.2 (CH), 126.9 (CH), 127.6 (CH), 130.2 (CH), 131.9 (C), 134.4 (CH), 142.8 (C). EI-MS: *m*/*z* 263 (M^++2), 261 (M^+), 248, 246, 222, 220, 195, 193, 180, 167, 155, 140, 126, 114, 77. EI-HRMS calcd for $C_{13}H_{12}BrN$: 261.0153. Found: 261.0155.

4.2.6. *N*,*N*-Diallyl-1-(4-bromonaphthyl)amine (4c). Amber thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.76 (d, J=6.0 Hz, 4H, $CH_2\times2$), 5.14 (ddt, J=0.8, 1.2, 10.4 Hz, 2H, vinyl H), 5.22 (ddt, J=1.6, 1.6, 17.2 Hz, 2H, vinyl H), 5.84 (ddt, J=6.0, 10.4, 17.2 Hz, 2H, vinyl H), 6.93 (d, J=8.0 Hz, 1H, ArH), 7.55 (ddd, J=1.6, 6.8, 8.0 Hz, 2H, ArH), 7.65 (d, J=8.0 Hz, 1H, ArH), 8.20 (d, J=8.0 Hz, 1H, ArH), 8.32 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.3 (CH_2), 117.0 (C), 117.6 (CH_2), 118.5 (CH), 124.3 (CH), 126.1 (CH), 127.2 (CH), 127.6 (CH), 129.3 (CH), 131.4 (C), 132.9 (C), 134.5 (CH), 147.8 (C). EI-MS: *m*/*z* 303 (M^++2), 301 (M^+), 288, 286, 260, 245, 234, 232, 222, 207, 195, 180, 167, 153, 126, 113, 82. EI-HRMS calcd for $C_{16}H_{16}BrN$: 301.0466. Found: 301.0466.

4.2.7. *N*-Allyl-1-(4-cyanonaphthyl)amine (3d). Light yellow crystal. Mp: 129–131 °C ($CHCl_3$/*n*-hexane). IR (KBr): ν 3393 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.00 (ddd, J=1.6, 1.6, 5.2 Hz, 2H, CH_2), 5.21 (br s, 1H, NH), 5.27 (ddt, J=1.6, 1.6, 10.4 Hz, 1H, vinyl H), 5.36 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 6.02 (ddt, J=5.2, 10.4, 17.2 Hz, 1H, vinyl H), 6.52 (d, J=8.0 Hz, 1H, ArH), 7.52 (ddd, J=1.2, 6.8, 8.4 Hz, 1H, ArH), 7.62 (ddd, J=1.2, 6.8, 8.4 Hz, 1H, ArH), 7.74 (d, J=8.4 Hz, 1H, ArH), 7.83 (d, J=8.4 Hz, 1H, ArH), 8.15 (dd, J=0.8, 8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.1 (CH_2), 96.9 (C), 103.2 (CH), 117.5 (CH_2), 119.6 (C), 120.2 (CH), 122.0 (C), 125.9 (CH), 126.0 (CH), 128.2 (CH), 133.4 (CH), 133.5 (C), 134.6 (CH), 147.1 (C). EI-MS: *m*/*z* 208 (M^+), 193, 181, 167, 154, 140, 125, 113, 90, 77. EI-HRMS calcd for $C_{14}H_{12}N_2$: 208.1000. Found: 208.1003.

4.2.8. *N*,*N*-Diallyl-1-(4-cyanonaphthyl)amine (4d). Light yellow thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (ddd, J=1.6, 1.6, 5.6 Hz, 4H, $CH_2\times2$), 5.21 (ddt, J=1.2, 1.6, 10.4 Hz, 2H, vinyl H), 5.28 (ddt, J=1.6, 1.6, 17.2 Hz, 2H, vinyl H), 5.84 (ddt, J=5.6, 10.4, 17.2 Hz, 2H, vinyl H), 7.01 (d, J=8.0 Hz, 1H, ArH), 7.56 (ddd, J=1.2, 6.8, 8.4 Hz, 1H, ArH), 7.63 (ddd, J=1.2, 6.8, 8.0 Hz, 1H, ArH), 7.78 (d, J=8.0 Hz, 1H, ArH), 8.19 (ddd, J=0.4, 0.8, 8.4 Hz, 1H, ArH), 8.26 (ddd, J=0.4, 0.8, 8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7 (CH_2), 103.3 (C), 115.5 (CH),

118.0 (CH_2), 118.6 (C), 124.7 (CH), 125.7 (CH), 126.4 (CH), 128.2 (CH), 128.6 (C), 132.7 (CH), 133.7 (CH), 134.0 (C), 152.7 (C). EI-MS: *m/z* 248 (M^+), 233, 221, 205, 192, 179, 166, 152, 140, 125, 99, 82. EI-HRMS calcd for $C_{17}H_{16}N_2$: 248.1313. Found: 248.1312.

4.2.9. *N*-Allyl-2-naphthylamine (3e). Brown thick oil. IR (KBr): ν 3417 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (br s, 1H, NH), 3.67 (ddd, J=1.6, 1.6, 5.6 Hz, 2H, CH_2), 5.10 (ddt, J=1.6, 1.6, 10.4 Hz, 1H, vinyl H), 5.21 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 5.85 (ddt, J=5.6, 10.4, 17.2 Hz, 1H, vinyl H), 6.69 (d, J=2.8 Hz, 1H, ArH), 6.71 (d, J=2.4 Hz, 1H, ArH), 7.14 (ddd, J=1.2, 6.8, 8.0 Hz, 1H, ArH), 7.30 (ddd, J=1.2, 6.8, 8.0 Hz, 1H, ArH), 7.54 (m, 2H, ArH), 7.60 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3 (CH_2), 104.6 (CH), 116.1 (CH_2), 117.8 (CH), 121.8 (CH), 125.8 (CH), 126.1 (CH), 127.4 (C), 127.5 (CH), 128.7 (CH), 134.9 (CH), 135.0 (C), 145.5 (C). EI-MS: *m/z* 183 (M^+), 168, 156, 141, 129, 115, 89, 77. EI-HRMS calcd for $C_{13}H_{13}N$: 183.1048. Found: 183.1046.

4.2.10. *N*,*N*-Diallyl-2-naphthylamine (4e). Light yellow thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.02 (ddd, J=1.6, 2.0, 4.8 Hz, 4H, $CH_2\times2$), 5.18 (ddt, J=1.6, 2.0, 10.0 Hz, 2H, vinyl H), 5.24 (ddt, J=1.6, 1.6, 17.2 Hz, 2H, vinyl H), 5.91 (ddt, J=4.8, 10.0, 17.2 Hz, 2H, vinyl H),6.92 (s, 1H, ArH), 7.08 (d, J=8.0 Hz, 1H, ArH), 7.18 (ddd, J=2.0, 6.8, 8.0 Hz, 1H, ArH), 7.31–7.36 (m, 1H, ArH), 7.61 (d, J=8.4 Hz, 1H, ArH), 7.65 (s, 1H, ArH), 7.67 (d, J=2.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9 (CH_2), 106.0 (CH), 116.1 (CH_2), 116.2 (CH), 121.8 (CH), 126.1 (CH), 126.2 (CH), 126.2 (C), 127.4 (CH), 128.7 (CH), 133.9 (CH), 135.5 (C), 146.5 (C). EI-MS: *m/z* 223 (M^+), 208, 196, 180, 167, 155, 141, 127, 115, 101, 89, 77. EI-HRMS calcd for $C_{16}H_{17}N$: 223.1361. Found: 223.1361.

4.2.11. *N*-Allyl-1-(4-nitronaphthyl)amine (3f). Orange-red crystal. Mp: 142–143.5 °C (EtOAc/*n*-hexane). IR (KBr): ν 3391 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.06 (ddd, J=1.6, 1.6, 5.2 Hz, 2H, CH_2), 5.20 (br s, 1H, NH), 5.30 (ddt, J=1.2, 1.6, 10.4 Hz, 1H, vinyl H), 5.37 (ddt, J=1.2, 1.6, 17.2 Hz, 1H, vinyl H), 6.02 (ddt, J=5.2, 10.4, 17.2 Hz, 1H, vinyl H), 6.49 (d, J=8.8 Hz, 1H, ArH), 7.53 (ddd, J=1.2, 6.8, 8.4 Hz, 1H, ArH), 7.69 (ddd, J=1.2, 6.8, 8.8 Hz, 1H, ArH), 7.84 (dd, J=0.8, 8.4 Hz, 1H, ArH), 8.43 (d, J=8.8 Hz, 1H, ArH), 9.02 (dd, J=0.8, 8.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.2 (CH_2), 101.8 (CH), 117.9 (CH_2), 120.0 (CH), 121.8 (C), 124.9 (CH), 125.8 (CH), 127.6 (C), 129.3 (CH), 129.6 (CH), 132.9 (CH), 135.1 (C), 149.3 (C). EI-MS: *m/z* 228 (M^+), 193, 180, 167, 154, 140, 129, 114, 102, 88, 77. EI-HRMS calcd for $C_{13}N_{12}N_2O_2$: 228.0899. Found: 228.0898.

4.2.12. *N*,*N*-Diallyl-1-(4-nitronaphthyl)amine (4f). Orange-red thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.93 (ddd, J=1.2, 1.6, 6.0 Hz, 4H, $CH_2\times2$), 5.24 (ddt, J=1.2, 1.6, 10.0 Hz, 2H, vinyl H), 5.30 (ddt, J=1.6, 1.6, 17.2 Hz, 2H, vinyl H), 5.86 (ddt, J=5.6, 10.4, 17.2 Hz, 2H, vinyl H), 6.99 (d, J=8.8 Hz, 1H, ArH), 7.56 (ddd, J=1.6, 7.2, 8.4 Hz, 1H, ArH), 7.68 (ddd, J=1.6, 7.2, 8.4 Hz, 1H, ArH), 8.27 (d, J=8.4 Hz, 1H, ArH), 8.29 (dd, J=0.8, 8.0 Hz, 1H, ArH), 8.75 (dd, J=0.8, 8.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8 (CH_2), 114.0 (CH), 118.2 (CH_2), 123.9 (CH), 124.8 (CH), 125.6 (CH), 126.1 (CH), 127.4 (C), 128.8 (C), 129.3 (CH), 133.5 (CH), 141.8 (C), 154.6 (C). EI-MS: *m/z* 268 (M^+), 253, 238, 224, 222, 210, 207, 194, 180, 167, 153, 140, 127, 115, 82, 77. EI-HRMS calcd for $C_{16}N_{16}N_2O_2$: 268.1212. Found: 268.1215.

4.2.13. *N*-Allyl-3-quinolylamine (3g). Pale yellow thick oil. IR (KBr): 3410 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.72 (ddd, J=1.6, 1.6, 5.2 Hz, 2H, CH_2), 4.64 (br s, 1H, NH), 5.13 (ddt, J=1.6, 1.6, 10.4 Hz, 1H, vinyl H), 5.24 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 5.86 (ddt, J=5.6, 10.0, 17.2 Hz, 1H, vinyl H), 6.90 (d, J=2.8 Hz, 1H, ArH), 7.32–7.38 (m, 2H, ArH), 7.52–7.56 (m, 1H, ArH), 7.92–7.97 (m, 1H, ArH), 8.43 (d, J=2.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.6 (CH_2), 110.0 (CH), 116.3 (CH_2), 124.5 (CH), 125.7 (CH), 126.6 (CH), 128.3 (CH), 129.3 (C), 133.9 (CH), 141.3 (CH), 141.3 (C), 141.4 (C), 142.9 (CH). EI-MS: *m/z* 185 (M^+), 169, 157, 143, 128, 116, 101, 89, 75, 63. EI-HRMS calcd for $C_{12}H_{12}N_2$: 184.1000. Found: 184.0996.

4.2.14. *N*,*N*-Diallyl-3-quinolinylamine (4g). Yellow thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.05 (ddd, J=1.6, 1.6, 4.8 Hz, 4H, $CH_2\times2$), 5.22 (ddt, J=1.6, 1.6, 10.0 Hz, 2H, vinyl H), 5.24 (ddt, J=1.6, 1.6, 17.6 Hz, 2H, vinyl H), 5.90 (ddt, J=4.8, 10.0, 17.6 Hz, 2H, vinyl H), 7.14 (d, J=2.8 Hz, 1H, ArH), 7.37–7.43 (m, 2H, ArH), 7.58–7.62 (m, 1H, ArH), 7.91–7.95 (m, 1H, ArH), 8.62 (d, J=2.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9 (CH_2), 112.6 (CH), 116.8 (CH_2), 125.0 (CH), 126.0 (CH), 126.8 (CH), 128.7 (CH), 129.2 (C), 133.0 (CH), 141.1 (CH), 141.3 (C), 142.1 (C). EI-MS: *m/z* 224 (M^+), 209, 197, 183, 168, 156, 142, 128, 115, 101, 89, 75, 63. EI-HRMS calcd for $C_{15}H_{16}N_2$: 224.1313. Found: 224.1314.

4.2.15. *N*-Allyl-*N*-ethyl-1-naphthylamine (3h). Light green thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, J=7.2 Hz, 3H, CH_3), 3.18 (q, J=7.2 Hz, 2H, CH_2), 3.70 (ddd, J=1.2, 1.6, 6.0 Hz, 2H, CH_2), 5.09 (ddt, J=1.2, 2.0, 10.4 Hz, 1H, vinyl H), 5.22 (ddt, J=1.6, 2.0, 17.2 Hz, 1H, vinyl H), 5.88 (ddt, J=6.0, 10.4, 17.2 Hz, 1H, vinyl H), 7.06 (dd, J=1.2, 7.6 Hz, 1H, ArH), 7.34 (dd, J=7.6, 8.0 Hz, 1H, ArH), 7.38–7.46 (m, 2H, ArH), 7.50 (d, J=8.4 Hz, 1H, ArH), 7.76 (dd, J=2.0, 7.6 Hz, 1H, ArH), 8.30 (dd, J=1.2, 8.0 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0 (CH_3), 46.7 (CH_2), 57.3 (CH_2), 116.7 (CH_2), 117.6 (CH), 123.3 (CH), 124.0 (CH), 125.1 (CH), 125.4 (CH), 125.6 (CH), 128.2 (CH), 130.6 (C), 134.9 (C), 135.6 (CH), 147.7 (C). EI-MS: *m/z* 211 (M^+), 196, 184, 168, 155, 141, 127, 115, 89, 77, 63. EI-HRMS calcd for $C_{15}H_{17}N$: 211.1361. Found: 211.1360.

4.2.16. *N*-Allyl-*N*-phenyl-1-naphthylamine (3i). Pale yellow thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.38 (ddd, J=1.6, 1.6, 5.2 Hz, 2H, CH_2), 5.18 (ddt, J=1.6, 1.6, 10.4 Hz, 1H, vinyl H), 5.30 (ddt, J=1.6, 1.6, 17.2 Hz, 1H, vinyl H), 6.04 (ddt, J=5.2, 10.4, 17.2 Hz, 1H, vinyl H), 6.58 (dd, J=0.8, 8.0 Hz, 2H, ArH), 6.70 (ddd, J=0.8, 6.8, 7.6 Hz, 1H, ArH), 7.12 (ddd, J=2.0, 7.2, 8.4 Hz, 2H, ArH), 7.39–7.51 (m, 4H, ArH), 7.79 (d, J=8.0 Hz, 1H, ArH), 7.86 (d, J=8.4 Hz, 1H, ArH), 7.90 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2 (CH_2), 113.7 (CH), 116.8

(CH_2), 117.1 (CH), 123.8 (CH), 126.2 (CH), 126.3 (CH), 126.4 (CH), 126.5 (CH), 126.9 (CH), 128.5 (CH), 128.9 (CH), 131.4 (C), 134.5 (CH), 135.2 (C), 143.7 (C), 149.2 (C). EI-MS: *m/z* 259 (M^+), 244, 218, 189, 167, 154, 127, 104, 89, 77. EI-HRMS calcd for $C_{19}H_{17}N$: 259.1361. Found: 259.1359.

4.2.17. *N*-(Hex-2*E*-enyl)-1-naphthylamine (5). Grass-green thick oil. IR (KBr): ν 3432 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J=7.2 Hz, 3H, CH_3), 1.39 (hext, J=7.2 Hz, 2H, CH_2), 2.01 (dt, J=6.4, 7.2 Hz, 2H, CH_2), 3.77 (dd, J=0.8, 6.0 Hz, 2H, CH_2), 4.22 (br s, 1H, NH), 5.63 (dt, J=5.6, 15.2 Hz, 1H, vinyl H), 5.72 (dt, J=6.4, 15.2 Hz, 1H, vinyl H), 6.57 (d, J=7.2 Hz, 1H, ArH), 7.20 (d, J=8.4 Hz, 1H, ArH), 7.30 (dd, J=7.6, 8.0 Hz, 1H, ArH), 7.34–7.40 (m, 2H, ArH), 7.73 (ddd, J=1.2, 8.0, 8.0 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 22.3 (CH_2), 34.4 (CH_2), 46.2 (CH_2), 104.6 (CH), 117.3 (CH), 119.9 (CH), 123.4 (C), 124.5 (CH), 125.6 (CH), 126.5 (CH), 126.5 (CH), 128.5 (CH), 133.6 (CH), 134.2 (C), 143.2 (C). EI-MS: *m/z* 225 (M^+), 196, 182, 168, 165, 143, 127, 115, 89, 77. EI-HRMS calcd for $C_{16}H_{19}N$: 225.1517. Found: 225.1513.

4.2.18. *N*,*N*-Di(hex-2*E*-enyl)-1-naphthylamine (6). Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J=7.2 Hz, 6H, $CH_3\times2$), 1.34 (hext, J=7.2 Hz, 4H, $CH_2\times2$), 1.96 (dt, J=6.8, 7.2 Hz, 4H, $CH_2\times2$), 3.72 (d, J=6.4 Hz, 4H, $CH_2\times2$), 5.46 (dt, J=6.4, 15.2 Hz, 2H, vinyl H), 5.58 (dt, J=6.8, 15.2 Hz, 2H, vinyl H), 7.03 (d, J=7.2 Hz, 1H, ArH), 7.35 (dd, J=7.6, 8.0 Hz, 1H, ArH), 7.40–7.47 (m, 2H, ArH), 7.49 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 22.5 (CH_2), 34.5 (CH_2), 55.2 (CH_2), 117.7 (CH), 122.9 (CH), 124.1 (CH), 125.0 (CH), 125.3 (CH), 125.5 (CH), 126.6 (CH), 128.2 (CH), 130.1 (C), 133.6 (CH), 134.8 (C), 148.1 (C). EI-MS: *m/z* 307 (M^+), 278, 264, 250, 225, 194, 182, 165, 154, 143, 127, 115, 77. EI-HRMS calcd for $C_{22}H_{29}N$: 307.2300. Found: 307.2303.

4.2.19. *N*-(1-Propylallyl)-1-naphthylamine (7). Dark brown thick oil. IR (KBr): ν 3446 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, J=7.2 Hz, 3H, CH_3), 1.45–1.56 (m, 2H, CH_2), 1.73 (dt, J=6.8, 14.4 Hz, 2H, CH_2), 4.01 (dt, J=6.4, 6.4 Hz, 1H, CH), 4.38 (br s, 1H, NH), 5.15 (ddd, J=1.2, 1.2, 10.0 Hz, 1H, vinyl H), 5.25 (d, J=17.2 Hz, 1H, vinyl H), 5.83 (ddd, J=6.0, 10.0, 17.2 Hz, 1H, vinyl H), 6.63 (d, J=6.4 Hz, 1H, ArH), 7.20–7.24 (m, 1H, ArH), 7.31 (dd, J=7.6, 8.0 Hz, 1H, ArH), 7.41–7.46 (m, 2H, ArH), 7.76–7.84 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.2 (CH_2), 38.0 (CH_2), 55.8 (CH), 105.4 (CH), 115.3 (CH_2), 117.1 (CH), 119.7 (CH), 123.3 (C), 124.6 (CH), 125.6 (CH), 126.5 (CH), 128.7 (CH), 134.3 (C), 139.7 (CH), 142.3 (C). EI-MS: *m/z* 225 (M^+), 182, 165, 154, 143, 127, 115, 89, 77. EI-HRMS calcd for $C_{16}H_{19}N$: 225.1517. Found: 225.1513.

4.2.20. *N*-(3-Phenylallyl)-1-naphthylamine (8). Brown crystal. Mp: 78–80 °C. IR (KBr): ν 3431 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (dd, J=1.6, 6.0 Hz, 2H, CH_2), 4.42 (br s, 1H, NH), 6.32 (dt, J=6.0, 16.0 Hz, 1H, vinyl H), 6.56–6.61 (m, 2H, vinyl H and ArH), 7.16–7.42 (m, 9H, ArH), 7.71–7.76 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.2 (CH_2), 104.8 (CH), 117.6 (CH), 119.9 (CH), 123.4 (C), 126.6 (CH), 125.7 (CH), 126.3 (CH), 126.5 (CH), 126.5 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 131.7 (CH), 134.2 (C), 136.7 (C), 143.0 (C). EI-MS: *m/z* 259 (M^+), 242, 215, 181, 168, 154, 143, 127, 117, 91, 77. EI-HRMS calcd for $C_{19}H_{17}N$: 259.1361. Found: 259.1361.

4.2.21. *N*,*N*-Di(3-phenylallyl)-1-naphthylamine (9). Amber thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (d, J=6.0 Hz, 4H, $CH_2\times2$), 6.25 (dt, J=1.6, 16.0 Hz, 2H, vinyl H), 6.54 (d, J=16.0 Hz, 2H, vinyl H), 7.09–7.14 (m, 1H, ArH), 7.16 (dd, J=1.2, 7.2 Hz, 2H, ArH), 7.23 (t, J=7.6 Hz, 4H, ArH), 7.29 (dd, J=1.6, 7.2 Hz, 4H, ArH), 7.34 (dd, J=7.6, 8.0 Hz, 1H, ArH), 7.43 (ddd, J=1.2, 1.6, 8.0 Hz, 1H, ArH), 7.48 (dd, J=1.2, 8.0 Hz, 1H, ArH), 7.51 (d, J=8.0 Hz, 1H, ArH), 7.79 (d, J=8.0 Hz, 1H, ArH), 8.38 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6 (CH_2), 117.7 (CH), 123.4 (CH), 123.9 (CH), 125.3 (CH), 125.4 (CH), 125.7 (CH), 126.3 (C), 126.7 (CH), 127.3 (CH), 128.3 (CH), 128.5 (CH), 129.8 (C), 132.4 (CH), 134.9 (C), 137.0 (C), 147.7 (CH). EI-MS: *m/z* 375 (M^+), 284, 270, 258, 256, 241, 229, 217, 194, 180, 169, 154, 141, 127, 117, 115, 91, 77, 65, 51. EI-HRMS calcd for $C_{28}H_{25}N$: 375.1987. Found: 375.1987.

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Photochemical substitution of olefins and aromatic compounds with difluoromethyl radicals bearing ester and phosphonate groups

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Abstract—Efficient and selective substitution of cyclic and acyclic vinyl ethers with photo-generated difluoromethyl radicals bearing ester and phosphonate groups, in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide was successfully carried out to provide the corresponding regioselective unsaturated difluoromethylene adducts selectively. The reaction involves phenylselenyl transfer at an early stage followed by elimination of phenylselenol from the adducts once formed to provide the unsaturated difluoromethylene adducts selectively. This novel photochemical method was successfully extended to aromatic and heteroaromatic substitutions to provide the corresponding α-aryl-α,α-difluoroacetates and α-aryl-α,α-difluoromethylphosphonates in good to moderate yields.

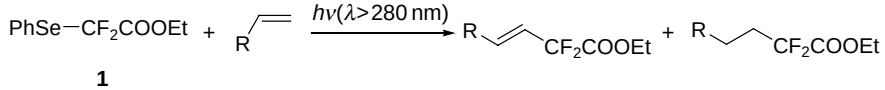
1. Introduction

It is well known that introduction of a fluorine atom into an organic molecule causes dramatic changes in its biological activities, mainly due to the high electoronegativity of fluorine, the strong carbon–fluorine bond, increased solubility in lipids, and mimic effect.[1] Therefore, fluorinated compounds are of great importance in the pharmaceutical and agrochemical industries. In particular, difluoromethylene compounds have attracted a great deal of interest due to their unique biological activities.[2] For example, CF_2/O transposition in methylenephosphonate has proven to be one of the most valuable approaches to the preparation of hydrolytically stable functional groups as phosphonate mimetics.[3] Therefore, their synthesis has become a major interest in organic chemistry. In general, difluorometylene compounds have been prepared using DAST,[4] NFBS,[5] cross-coupling reactions,[6] electrochemical oxidations[7] and radical additions.[8] However, their preparation is still limited.

Previously, we reported photochemical reaction of ethyl α,α-difluoro-α-(phenylseleno)acetate (**1**) with various olefins as shown in Scheme 1.[9]

Interestingly, we obtained not only radical adducts (saturated products) but also difluoromethylene-substituted products (unsaturated products). The formation of difluoromethylene-substituted products prompted us to carry out aromatic and heteroaromatic substitutions with difluoromethyl radicals photo-generated from **1** and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate (**5**) as shown in Scheme 2.[10]

However, the selectivity of the substitution of olefins in Scheme 1 was low,[9] and the yields of aromatic and



Scheme 1.

Keywords: Photoreaction; Difluoromethyl radicals; C–CF_2 bond formation; Group transfer; Selenide.
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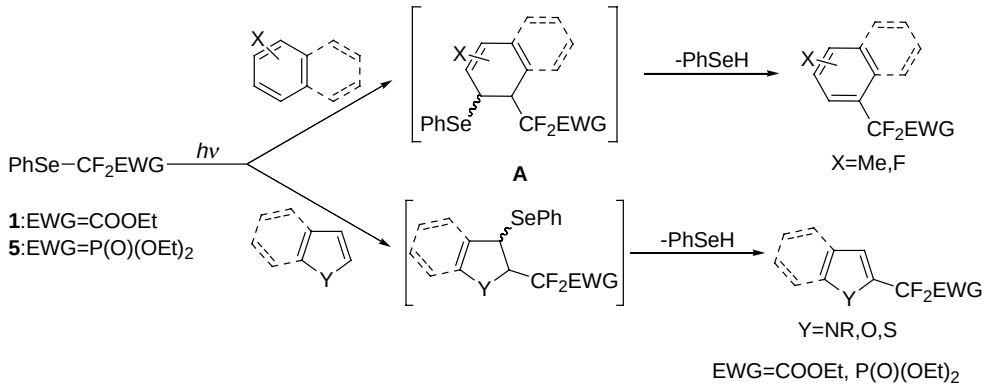


Scheme 2.

heteroaromatic substitutions with difluoromethyl radicals were moderate to low.[10]

In order to improve the selectivity and yields, we investigated photochemical substitutions under various conditions. In this paper, we report the substitution of various vinyl ethers and aromatic compounds with difluoromethylene groups photo-generated from **1** and **5**.

2. Results and discussion

2.1. Photoreaction of ethyl α,α-difluoro-α-(phenylseleno)-acetate (1) with 2,3-dihydrofuran

We attempted the photoreaction of **1** with a large excess amount of 2,3-dihydrofuran as the electron-rich olefin in CH_2Cl_2 (Scheme 3). The reaction was conducted using a 100-W high-pressure mercury-vapor lamp with a Pyrex vessel inside the light source.

As shown in Scheme 3, the group transfer reaction took place to provide a phenylselenyl group transfer adduct **2**, a difluoromethyl-substituted product **3** and a radical adduct **4** in good total yields (25, 28, 28%, respectively). Moreover, the difluoromethyl unit was regioselectively introduced to the 3-position of 2,3-dihydrofuran in all products. Byers et al. obtained always phenylselenyl group transfer products by the photolysis of dialkyl α-(phenylseleno)malonates[11,12] and tetraethyl phenylselenomethylenediphosphonate[13] in the presence of olefins, and they did not obtain selenium-free adducts like **3** and **4** at all. Although the adducts **2** is a single stereoisomer, we could not establish its stereochemistry.

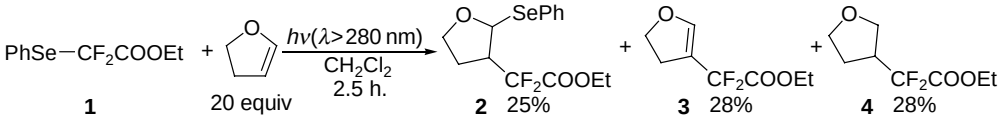
In order to disclose the mechanism for the formation of **3** and **4**, we investigated the photolysis of the phenylselenyl group transfer adduct **2**. We found that compounds **3** and **4** were formed from the adduct **2** (Scheme 4).

This result clearly indicates that the phenylselenyl group transfer adduct **2** is a precursor to compounds **3** and **4**.

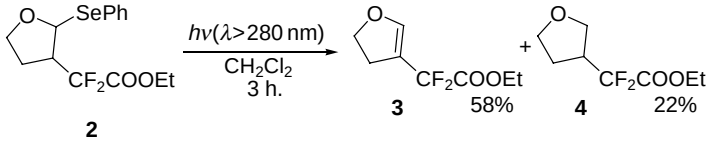
2.2. Time-conversion of the photoreaction of ethyl α,α-difluoro-α-(phenylseleno)acetate (1) with 2,3-dihydrofuran

In order to obtain more information on the reaction mechanism, the yields of **2**–**4** and the recovery of **1** in the time course of the photochemical reaction of **1** in the presence of 2,3-dihydrofuran were investigated and the results are illustrated in Figure 1.

As shown in Figure 1, the starting material **1** was consumed linearly with the photo-irradiation time while the yield of the phenylselenyl group transfer adducts **2** also increased linearly to ca. 50% with the reaction time, and then the yield of **2** gradually decreased. Additionally, difluoromethylene-substituted product **3** also increased gradually with the time and no maximum yield was observed even after long



Scheme 3.



Scheme 4.

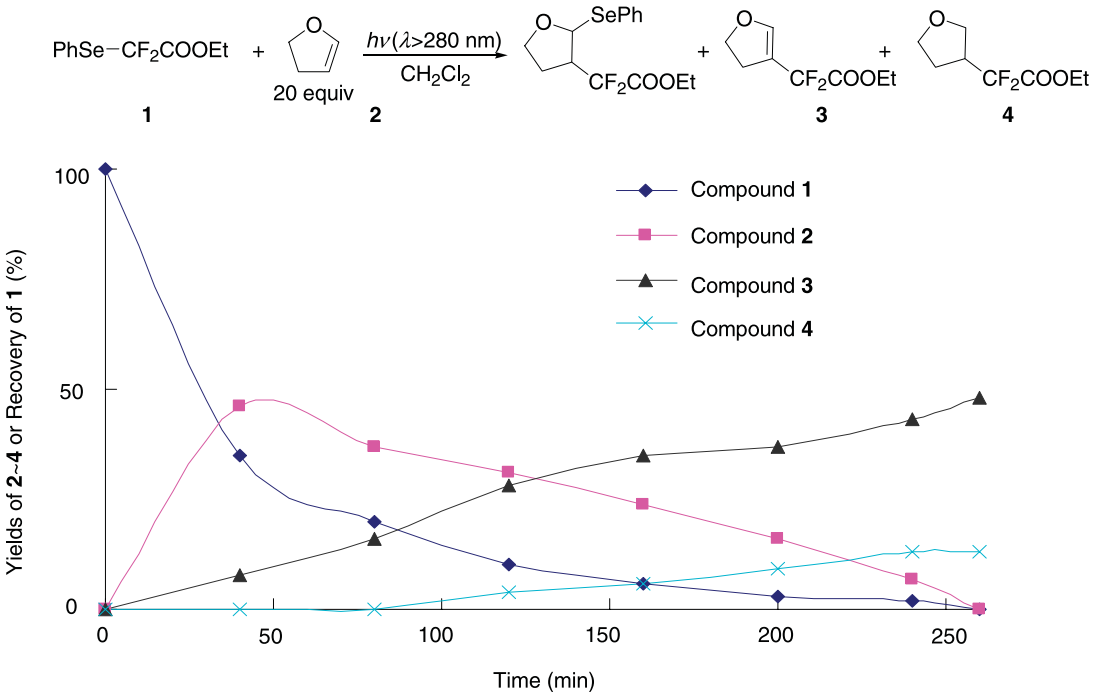


Figure 1. The yields of **2**–**4** and the recovery of **1** in the time-course of the photoreaction of **1** in the presence of 2,3-dihydrofuran.

photo-irradiation. In sharp contrast, the formation of the radical adduct product **4** started after 80 min and gradually increased. When the starting compound **1** and the adduct **2** completely vanished after prolonged photo-irradiation time, the yields of the substituted product **3** and the radical adduct **4** reached maxima. Moreover, a considerable amount of diphenyl diselenide was detected. From the above result, we assumed the substituted product **3** is formed probably by the elimination of phenylselenol from the adduct **2** and the resulting phenylselenol would be involved in the formation of **4** since phenylselenol is a good hydrogen atom donor.

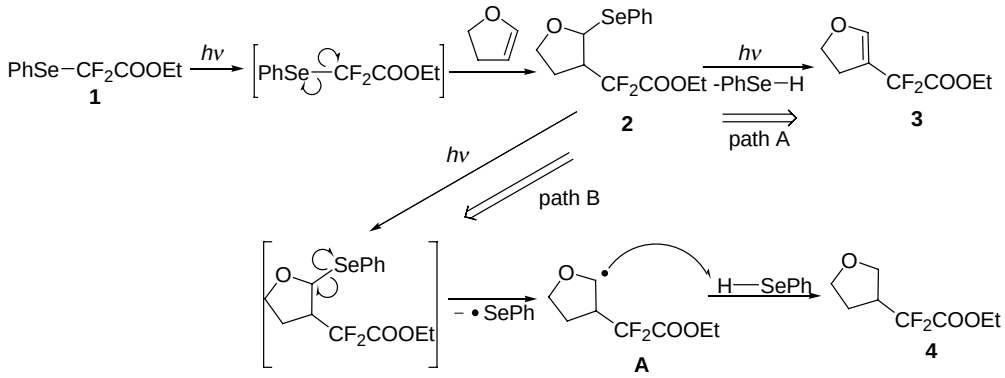
In consideration to the above results and the UV absorption bands of **1** at 265, 217 nm, we propose a plausible reaction mechanism as shown in Scheme 5.

When the homolytic cleavage of the Se–CF_2 bond takes place by photolysis of **1** in the presence of 2,3-dihydrofuran, the phenylselenyl group transfer reaction proceeds quickly to provide **2**, and then further photolysis of **2** once formed results in the formation of the difluoromethyl-substituted product **3** eliminating phenylselenol (path A). Since the formation of **4** required induction time, **4** would be formed by the photochemically homolytic cleavage of the Se–C bond followed by abstraction of a hydrogen atom from phenylselenol (path B).

2.3. Effect of a base

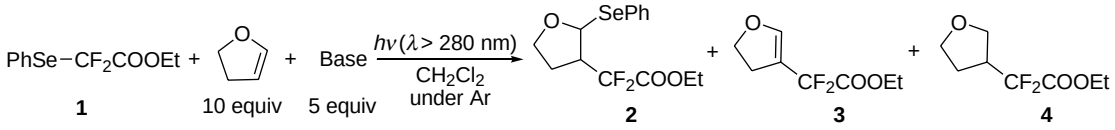
From the above hypothesis, it is expected that when the formation of phenylselenol as a good hydrogen atom donor is inhibited by using a base for deprotonation of phenylselenol, the formation of **4** would be suppressed. Consequently, the selectivity for the formation of **3** would be increased.

In order to confirm our assumption, photochemical reaction of **1** with 2,3-dihydrofuran was investigated in the presence of various bases. The results are summarized in Table 1.



Scheme 5.

Table 1. Photoreaction of **1** in the presence of 2,3-dihydrofuran with various bases



Run	Base	Time (h)	Yield (%)[a]			Ratio **3/4**
			2	**3**	**4**	
1	None	3	—	51	40	1.3
2	DBU	5	—	7	—	—
3	Pyridine	5	—	41	22	1.9
4	DMAP	5	65	20	—	—
5	DMAP	10	31	21	2	10.5
6	Imidazole	10	—	61	18	3.4
7	2,6-Lutidine	10	—	58	32	1.8
8	2,4,6-Trimethylpyridine	10	—	66	15	4.4

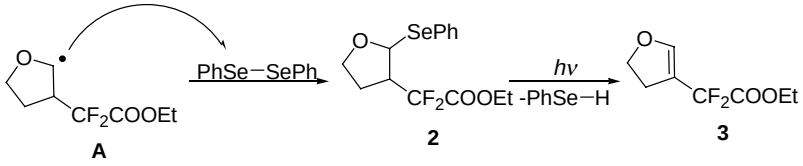
[a] Determined by ^{19}F NMR.

As shown in Table 1, when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used, **3** was formed solely although the yield was extremely low (run 2). When 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) was used, the reaction proceeded smoothly to provide **2** and **3** in good total yield and saturated adduct **4** was not formed at all (run 4). However, in this case, group transfer adduct **2** was mainly formed. Therefore, the reaction time was doubled (10 h). However, the yield of **3** did not increase although the yield of the group transfer adduct **2** decreased (run 5). In sharp contrast, when pyridine and 2,6-lutidine were used, the product selectivity (the ratio of **3** to **4**) was not so different from the case in the absence of a base (run 1, vs runs 3 and 7). The photochemical reaction in the presence of imidazole and 2,4,6-trimethylpyridine provided **3** and **4** in good yields and high product selectivities (runs 6 and 7). Since the addition of 2,4,6-trimethylpyridine resulted in higher selectivity compared with imidazole, 2,4,6-trimethylpyridine was found to be the most suitable base for the selective photochemical reaction.

2.4. Effect of diphenyl diselenide

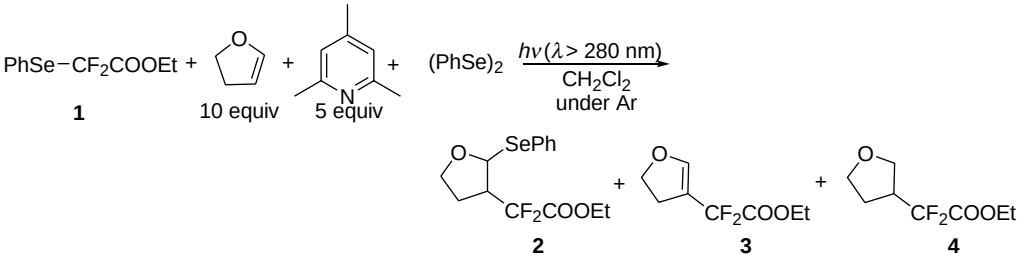
We found 2,4,6-trimethylpyridine as the most suitable base to suppress the formation of **4**, but **4** was still formed. From path B in Scheme 5, we assumed that radical intermediate **A** would also abstract the hydrogen atom from dichloromethane as a solvent. It is expected that the addition of diphenyl diselenide to the reaction system would suppress the hydrogen abstraction of **A** to provide **4** as shown in Scheme 6. In this case, **3** would be formed mainly via **2** derived from **A** and diphenyl diselenide.

In order to suppress the formation of **4**, we investigated the photochemical reaction in the presence of both diphenyl



Scheme 6.

Table 2. Photoreaction of **1** in the presence of diphenyl diselenide and 2,4,6-trimethylpyridine



Run	$(PhSe)_2$ (equiv)	Time (h)	Yield (%)[a]		
			2	**3**	**4**
1	0.1	12	—	68	12
2	0.5	12	—	78	16
3	1	16	—	80 (78)	—

[a] Determined by ^{19}F NMR. Figure in parenthesis shows isolated yield.

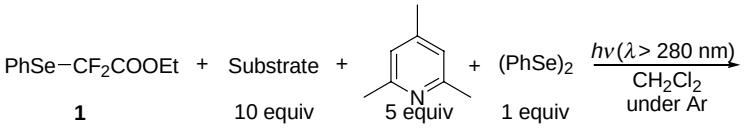
diselenide and 2,4,6-trimethylpyridine. The results are summarized in Table 2.

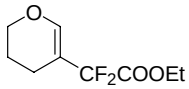
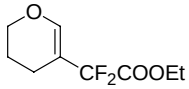
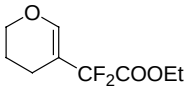
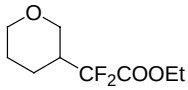
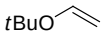
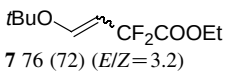
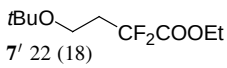
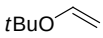
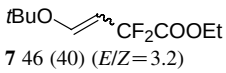
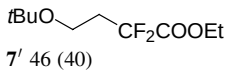
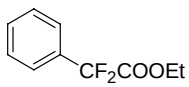
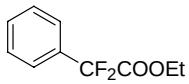
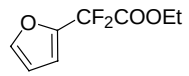
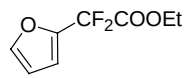
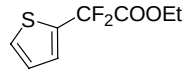
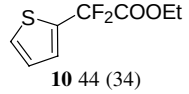
As shown in Table 2, the yield of **3** was increased in all cases. Especially, the photochemical reaction of **1** in the presence of 1 equiv of diphenyl diselenide provided product **3** solely in good yield (run 3) although the reaction time was longer. Therefore, 1 equiv of diphenyl diselenide was found to be the most suitable additive for the selective formation of **3**.

2.5. Photochemical reaction of ethyl α,α-difluoro-α-(phenylseleno)acetate (1) and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate (5) with various unsaturated compounds

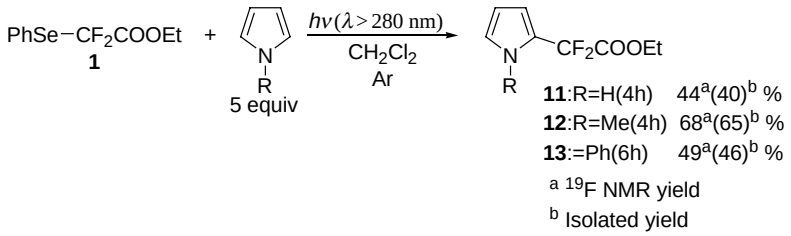
Next, we carried out the photo-induced substitution of **1** with various unsaturated substrates in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide. The results are shown in Table 3.

Table 3. Photoreaction of **1** in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide



Run	Substrate	Time (h)	Recovery of **1** (%)[a]	Yield (%)[a]
1		16	25	 **6** 46 (41)
2		30	25	 **6** 43
3[b]		3	—	 **6** 44 (40)  **6′** 34 (31)
4		18	—	 **7** 76 (72) (*E*/*Z*=3.2)  **7′** 22 (18)
5[b]		3	—	 **7** 46 (40) (*E*/*Z*=3.2)  **7′** 46 (40)
6[c]		25	—	 **8** 79 (70)
7[b,c]		9	—	 **8** 60 (53)
8[c]		25	—	 **9** 72 (67)
9[b,c]		6	—	 **9** 29 (26)
10[c]		25	—	 **10** 62 (53)
11[b,c]		8	—	 **10** 44 (34)

[a] Determined by ^{19}F NMR. Figures in parentheses show islated yields.
[b] Without 2,4,6-trimethylpyridine and diphenyl diselenide.
[c] Neat conditions.



Scheme 7.

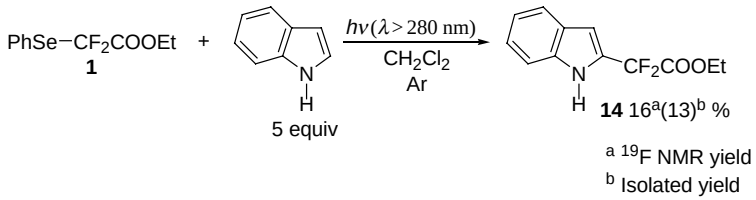
Regardless of substrates, the selectivity of products and yields were improved when 2,4,6-trimethylpyridine and diphenyl diselenide were used. In contrast to run 3, the photochemical reaction with 3,4-dihydro-2*H*-pyran in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide gave a difluoromethyl-substituted product **6** solely in moderate yield and radical adduct **6′** was not formed at all (run 1). In this case, a considerable amount of starting material **1** still remained. In order to obtain better yield, the reaction time was extended to almost double, but the yield of **6** was not increased and the conversion of **1** did not change (run 2). A similar photochemical reaction with *tert*-butyl vinyl ether proceeded to afford difluoromethyl-substituted product **7** in much higher yield (run 4) compared with the reaction in the absence of diphenyl diselenide and a base (run 5). In this case, the product selectivity (**7**/**7′**) was also improved. Photochemical reaction with benzene in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide also gave a much higher yield of the substituted product **8** (run 6) compared with the reaction without these additives (run 7). Moreover, the reaction was applicable to heteroaromatic compounds: the substitution with the difluoromethylene group at the α-position of heteroaromatic compounds proceeded selectivity to provide the corresponding substitution products **9**–**10** in much better yields (runs 8 and 10) compared with the reactions in the absence of the additives (runs 9 and 11). Notably, the yield of **9** was markedly increased.

Next, photochemical substitution with nitrogen-containing heterocycles was investigated. As shown in Schemes 7 and 8, the reactions proceeded to provide the corresponding substitution products in moderate to reasonable yields. Notably, in the case of 1-phenylpyrrole and indole, the substitution at the α-position of the pyrrole ring took place exclusively and the substitution at the benzene ring did not take place at all. In these cases, the yields were not increased in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide, which is in sharp contrast to the cases of furan and thiophene. Even when the reaction time was extended longer in the case of indole, the conversion of **1** did not change and a considerable amount of **1** was recovered. This seems to be due to the formation of dark colored by-products adsorbed on the wall of the Pyrex vessel, which interfered with UV light absorption of **1** to result in the low conversion of **1**.

Finally, we tried similarly the photo-induced substitution of α,αdifluoromethylphosphonate **5** with various unsaturated substrates in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide. The results are summarized in Table 4.

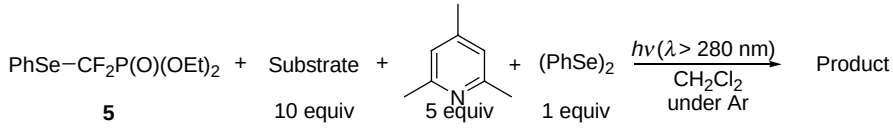
Regardless of substrates, the conversion of **5** became much lower (runs 1 and 3) or lower (run 5 and 7) in the presence of the additives. However, the yields of substitution products based on the consumed **5** increased without exception. Interestingly, substitution product **15** was formed exclusively in the reaction with 1,2-dihydrofuran. Notably, the absolute yield of **17** markedly increased to 55% in the presence of the additives (run 5). These results suggest that the photochemical substitution proceeds selectively in the presence of the additives although the reaction became much slower. However, in the case of 1-methylpyrrole, the yield did not increase even in the presence of additives. In the reactions, diethyl difluoromethylphosphonate, HCF_2-$P(O)(OEt)_2$ was formed as a by-product except for runs 5 and 6 and a considerable amount of diphenyl diselenide was also detected. These facts also clearly indicate that homolytic cleavage of the Se–CF_2 bond took place by photolysis of **5**.

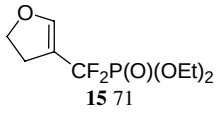
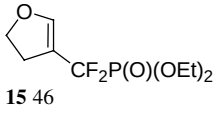
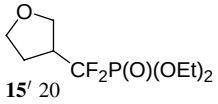
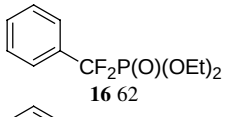
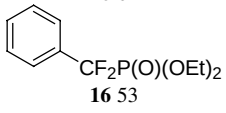
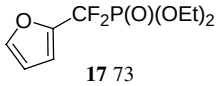
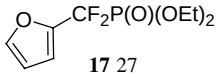
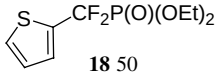
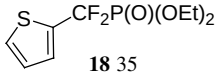
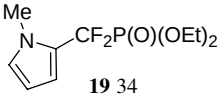
By the way, the substitution of the difluoromethylene group at the α-position of furan proceeded exclusively while the substitution of the difluoromethylene group at the β-position of 2,3-dihydrofuran exclusively. Since the difluoromethyl radicals generated from **1** and **5** are electron deficient, they usually react as electrophiles. Therefore, the regioselectivity of these radical reactions seems to be controlled by SOMO–HOMO interaction between radicals and substrates. The HOMOs of 2,3-dihydrofuran and furan calculated by CAChe MOPAC AM1 are shown in Figure 2.



Scheme 8.

Table 4. Photoreaction of 5 in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide



Run	Substrate	Time (h)	Conversion (%)[a]	Yield (%)[b]
1		18	35	 **15** 71
2[c]		3	69	 **15** 46  **15′** 20
3[d]		60	60	 **16** 62
4[c,d]		9	100	 **16** 53
5[d]		30	75	 **17** 73
6[c,d]		6	96	 **17** 27
7[d]		57	60	 **18** 50
8[c,d]		8	72	 **18** 35
9[c,d]		8	68	 **19** 34

[a] Determined by ^{19}F NMR.
[b] Isolated yield based on consumed starting material **5**.
[c] Without 2,4,6-trimethylpyridine and diphenyl diselenide.
[d] Neat conditions.

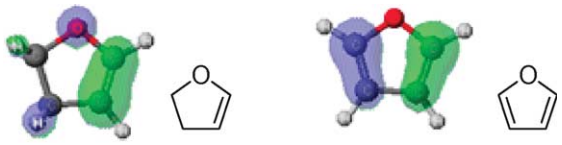


Figure 2. The HOMOs of 2,3-dihydrofuran and furan calculated by CAChe MOPAC AM1.

The β-position of 2,3-dihydrofuran has the largest coefficient of HOMO while the α-position of furan has the largest one. Therefore, the different regioselectivity of the radical reactions with furan and 2,3-dihydrofuran can be reasonably explained.

3. Conclusion

We have developed novel and efficient substitution using photo-generated difluoromethyl radicals with cyclic, acyclic vinyl ethers together with aromatic and heteroaromatic compounds. In the presence of 2,4,6-trimethylpyridine and diphenyl diselenide, the yields and product selectivity were increased in many cases. This method may be highly useful for the preparation of various CF_2-containing building blocks towards biological activities.

4. Experimental

4.1. General procedure for photoreaction

A solution of ethyl α,α-difluoro-α-phenyselenolacetate (**1**)[9] or diethyl α,α-difluoromethyl-α-phenyselenolphosphonate (**5**)[8b] (0.17 mmol) and an olefin (1.70 mmol) in CH_2Cl_2 (40 ml) in the presence of 2,4,6-trimethylpyridine (0.85 mmol) and diphenyl diselenide (0.17 mmol) was bubbled with Ar at room temperature for 0.5 h and then photolyzed with 100-W high-pressure mercury-vapor lamp.

The reaction was conducted using a Pyrex vessel inside the light source. After the photoreaction, the resulting solution was evaporated under vacuum and the residue was purified by silica gel column chromatography (linear gradient of 0–20% EtOAc in hexane) or by HPLC (Develosil ODS-5, MeCN as an eluent) to provide pure products.

4.1.1. 3-(Ethoxycarbonyldifluoromethyl)-2-(phenylselenyl)tetrahydrofuran (2). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62–7.27 (m, 5H), 5.99 (d, 1H, J=3.5 Hz), 4.06–4.01 (m, 2H), 4.32 (q, 2H, J=7.0 Hz), 3.16–2.98 (m, 1H), 2.19–1.98 (m, 2H), 1.33 (t, 3H, J=7.0 Hz); ^{13}C NMR δ 162.96 (t, J=32.4 Hz), 137.21 (t, J=253.8 Hz), 133.98, 128.89, 127.67, 114.76 (t, J=253.20 Hz), 81.89 (t, J=3.9 Hz), 66.81, 63.20, 51.21 (dd, J=23.48, 22.92 Hz), 25.15 (dd, J=3.35, 2.80 Hz), 13.90. ^{19}F NMR (254 MHz, $CDCl_3$) δ −34.10 (dd, 1F, J=257.0, 14.7 Hz), −35.32 (dd, 1F, J=257.0, 14.7 Hz); MS (m/z) 350 (M^+), 305, 277, 77; HRMS m/z Calcd for $C_{14}H_{16}F_2O_3Se$: 350.0233. Found: 350.0203.

4.1.2. 3-(Ethoxycarbonyldifluoromethyl)-2,3-dihydrofuran (3). See Ref. 9.

4.1.3. 3-(Ethoxycarbonyldifluoromethyl)tetrahydrofuran (4). See Ref. 9.

4.1.4. 2*H*-3,4-Dihydro-5-(ethoxycarbonyldifluoromethyl)pyran (6). See Ref. 9.

4.1.5. 2*H*-3,4,5,6-Tetrahydro-3-(ethoxycarbonyldifluoromethyl)pyran (6′). See Ref. 9.

4.1.6. *trans*-Ethyl 5-*t*-butoxy-2,2-difluoro-3-butenoate (7). See Ref. 9.

4.1.7. *cis*-Ethyl 5-*t*-butoxy-2,2-difluoro-3-butenoate (7). See Ref. 9.

4.1.8. Ethyl 5-*t*-butoxy-2,2-difluorobutanoate (7′). See Ref. 9.

4.1.9. Ethyl α,α-difluoro-α-phenylacetate (8). See Ref. 6d.

4.1.10. Ethyl α,α-difluoro-α-[2-(furyl)]acetate (9). ^{1}H NMR δ 7.52 (dd, 1H, J=1.65, 0.82 Hz), 6.76 (dd, 1H, J=3.30, 0.82 Hz), 6.46 (dd, 1H, J=3.30, 1.65 Hz), 4.38 (q, 2H, J=7.02 Hz), 1.36 (t, 3H, J=7.02 Hz); ^{13}C NMR δ 162.25 (t, J=33.5 Hz), 144.73 (t, J=2.2 Hz), 131.86, 111.56 (t, J=3.4 Hz), 110.68 (t, J=1.1 Hz), 108.59 (t, J=248.2 Hz), 63.55, 14.00. ^{19}F NMR δ −25.95 (s, 2F); MS (m/z) 190 (M^+), 117; HRMS Calcd for $C_8H_8F_2O_3$: m/z 190.0442. Found: 190.0424.

4.1.11. Ethyl α,α-difluoro-α-[2-(thienyl)]acetate (10). See Ref. 6b.

4.1.12. Ethyl α,α-difluoro-α-[2-(pyrrolyl)]acetate (11). ^{1}H NMR δ 9.03–8.55 (br, 1H), 6.90 (dd, 1H, J=2.6, 1.8 Hz), 6.55 (dd, 1H, J=3.3, 1.8 Hz), 6.24 (dd, 1H, J=3.3, 2.6 Hz), 4.36 (q, 2H, J=7.3 Hz), 1.37 (t, 3H, J=7.3 Hz). ^{19}F NMR δ −21.32 (s, 2F); MS (m/z) 189 (M^+), 116; HRMS Calcd for $C_8H_9F_2NO_2$: m/z 189.0601. Found: 189.0591.

4.1.13. Ethyl α,α-difluoro-α-[2-(1-methylpyrrolyl)]-acetate (12). ^{1}H NMR δ 6.7 (dd, 1H, J=2.8, 2.0 Hz), 6.4 (dd, 1H, J=3.8, 2.0 Hz), 6.1 (dd, 1H, J=3.8, 2.8 Hz), 4.38 (q, 2H, J=7.0 Hz), 3.76 (s, 3H), 1.37 (t, 3H, J=7.0 Hz); ^{13}C NMR δ 163.28 (t, J=34.1 Hz), 129.06, 126.98 (t, J=2.2 Hz), 112.22 (t, J=5.6 Hz), 111.16 (t, J=245.9 Hz), 107.29, 63.22, 35.48 (t, J=3.4 Hz), 14.03. ^{19}F NMR δ −19.62 (s, 2F); MS (m/z) 203 (M^+), 130; HRMS Calcd for $C_9H_{11}F_2NO_2$: m/z 203.0758. Found: 203.0764.

4.1.14. Ethyl α,α-difluoro-α-[2-(1phenylpyrrolyl)]-acetate (13). ^{1}H NMR δ 7.4–7.3 (m, 5H), 6.9 (dd, 1H, J=2.6, 2.0 Hz), 6.6 (dd, 1H, J=3.6, 2.0 Hz), 6.3 (dd, 1H, J=3.6, 2.6 Hz), 4.13 (q, 2H, J=7.3 Hz), 1.21 (t, 3H, J=7.3 Hz); ^{13}C NMR δ 162.95 (t, J=34.1 Hz), 139.23, 132.42, 128.73, 128.27, 127.16 (t, J=2.2 Hz), 126.86 (t, J=1.6 Hz), 112.90 (t, J=5.0 Hz), 110.62 (t, J=245.4 Hz), 108.36, 63.09, 13.87. ^{19}F NMR δ −15.65 (s, 2F); MS (m/z) 265 (M^+), 192, 77; HRMS Calcd for $C_{14}H_{13}F_2NO_2$: m/z 265.0914. Found: 265.0922.

4.1.15. Ethyl α,α-difluoro-α-[2-(indolyl)]acetate (14). ^{1}H NMR δ 8.68–8.46 (br, 1H), 7.66 (d, 1H, J=7.7 Hz), 7.43 (dd, 1H, J=8.1, 0.7 Hz), 7.30 (dt, 1H, J=7.7, 0.7 Hz), 7.16 (dt, 1H, J=8.1, 0.6 Hz), 6.89–6.86 (m, 1H), 4.38 (q, 2H, J=7.0 Hz), 1.3 (t, 3H, J=7.0 Hz); ^{13}C NMR δ 163.22 (t, J=34.7 Hz), 136.36, 127.814 (t, J=30.7 Hz), 126.18, 124.20, 121.69, 120.72, 111.56, 110.09 (t, J=248.7 Hz), 104.17 (t, J=5.0 Hz), 63.68, 13.99. ^{19}F NMR δ −24.12 (s, 2F); MS (m/z) 239 (M^+), 166; HRMS Calcd for $C_{12}H_{11}F_2NO_2$: m/z 239.0758. Found: 239.0756.

4.1.16. 3-(Diethoxyphosphonyldifluoromethyl)-2,3-dihydrofuran (15). ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.88–6.78(m, 1H), 4.51 (t, 2H, J=9.7 Hz), 4.34–4.23 (m, 4H), 2.87 (ddt, 2H, J=2.0, 2.0, 9.7 Hz), 1.39 (t, 6H, J=7.1 Hz). ^{31}P NMR δ 6.32 (ttt, 1P, J=117.3, 7.4, 7.4 Hz). ^{19}F NMR (254 MHz, $CDCl_3$) δ −27.68 (d, 2F, J=116.7 Hz); MS ((m/z) 256 (M^+), 119; HRMS m/z Calcd for $C_9H_{15}F_2O_4P$: 256.0676. Found: 256.0685.

4.1.17. 3-(Diethoxyphosphonyldifluorometyl)tetrahydrofuran (15′). ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.34–4.23 (m, 4H), 4.00–3.74 (m, 4H), 3.09–2.82 (m, 1H), 2.21–2.01 (m, 2H), 1.39 (t, 6H, J=7.1 Hz). ^{31}P NMR δ 7.03 (tttd, 1P, J=108.4, 7.4, 7.4, 3.0 Hz). ^{19}F NMR (254 MHz, $CDCl_3$) δ −38.53 (ddd, 1F, J=301.5, 109.1, 16.6 Hz), −39.90 (ddd, 1F, J=301.5, 109.1, 16.6 Hz); MS (m/z) 258 (M^+); HRMS m/z Calcd for $C_9H_{17}F_2O_4P$: 258.0833. Found: 258.0848.

4.1.18. Diethyl α,α-difluoromethyl-α-phenylphosphonate (16). See Ref. 6a.

4.1.19. Diethyl α,α-difluoromethyl-α-[2-(furyl)]phosphonate (17). ^{1}H NMR δ 7.55 (dd, 1H, J=1.3, 1.0 Hz), 6.82 (dd, 1H, J=3.6, 1.0 Hz), 6.48 (dd, 1H, J=3.6, 1.3 Hz), 4.35–4.27 (m, 4H), 1.36 (t, 6H, J=6.9 Hz); ^{31}P NMR δ 4.93 (ttt, 1P, J=109.9, 7.4, 7.4 Hz). ^{19}F NMR δ −30.81 (d, 2F, J=109.0 Hz); MS (m/z) 254 (M^+); HRMS Calcd for $C_9H_{13}F_2O_4P$: m/z 254.0520. Found: 254.0539.

See Ref. 14.

4.1.20. Diethyl α,α-difluoromethyl-α-[2-(1-methylpyrrolyl)]phosphonate (19). ^{1}H NMR δ 6.69 (dd, 1H, $J=2.6$, 1.8 Hz), 6.56 (dd, 1H, $J=3.4$, 1.8 Hz), 6.10 (dd, 1H, $J=3.4$, 2.6 Hz), 4.33–4.09 (m, 4H), 3.80 (s, 3H), 1.34 (t, 6H, $J=$ 7.0 Hz); ^{31}P NMR δ 6.36 (ttt, 1P, $J=117.3$, 7.4, 7.4 Hz). ^{19}F NMR δ −24.48 (d, 2F, $J=116.67$ Hz); MS (*m*/*z*) 267 (M^+), 130; HRMS Calcd for $C_{10}H_{16}F_2NO_3P$: *m*/*z* 267.0836. Found: 267.0823.

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