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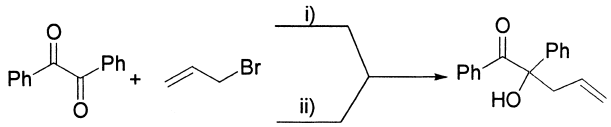
Contents

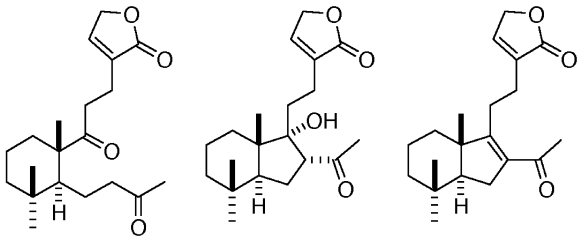
REPORT



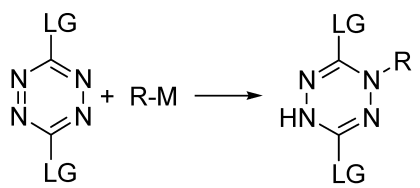
i. In, NaI, DMF, 5 min, 97%
ii. Ga, KI, LiBr, THF, 70 °C, 6 h, 62%

The carbon–carbon bond forming reactions mediated by indium as well as gallium are reviewed.

ARTICLES

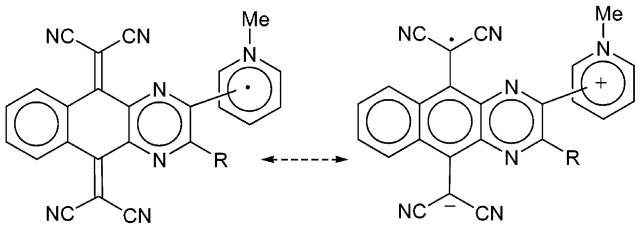


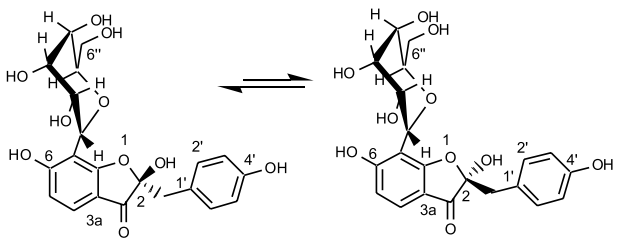
Chapecoderin A B C

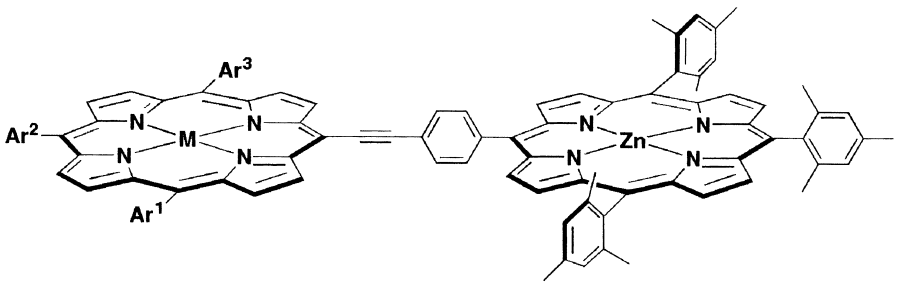


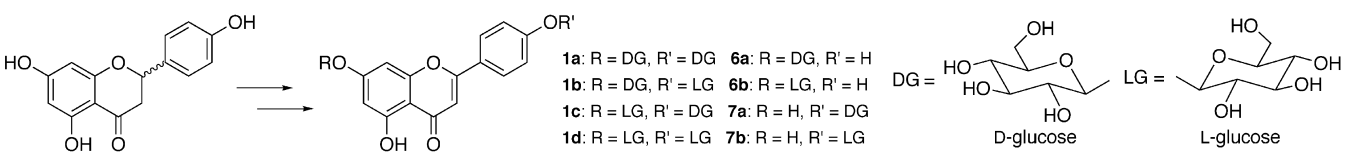
LG: pyrazolyl, SMe,pyridyl morpholino, chloro

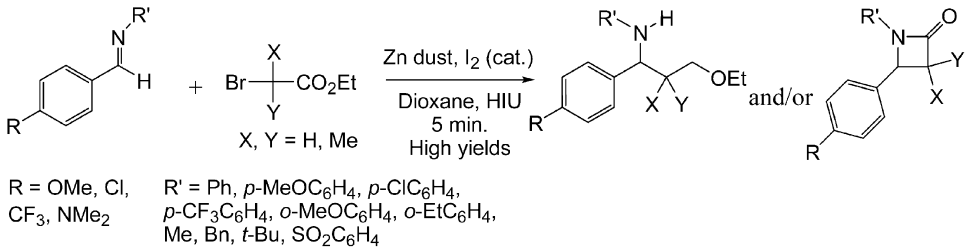
M: Li, Mg, Zn, Cu, In

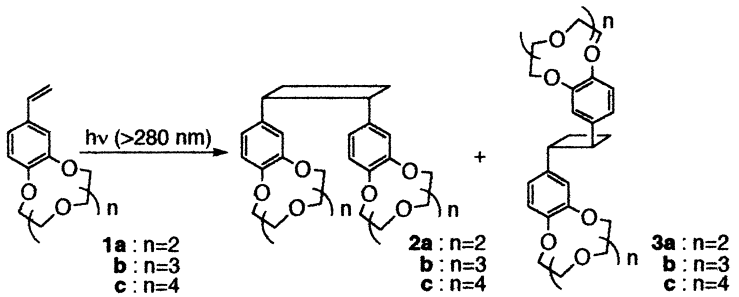


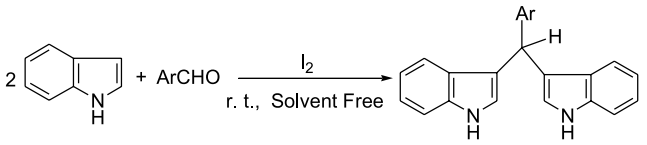


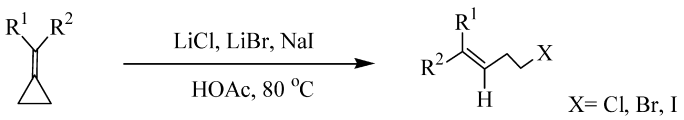




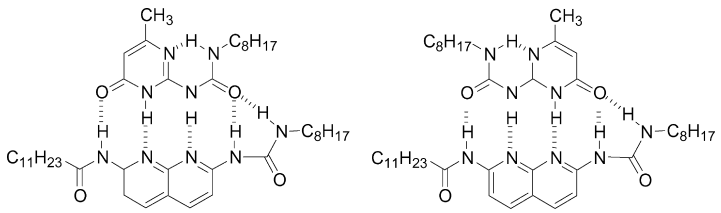


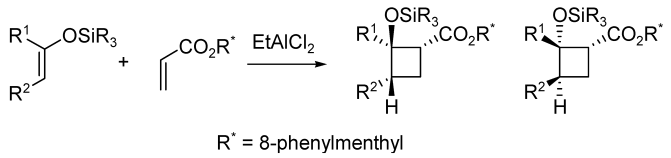


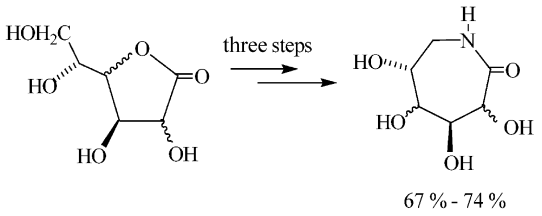


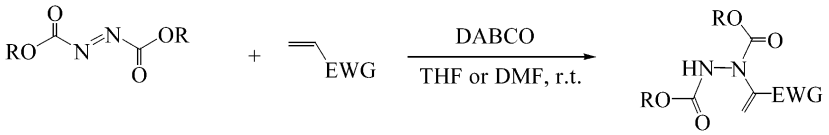


The reactions of MCPs **1** with LiCl, LiBr or NaI in acetic acid at 80 °C produce the corresponding homoallylic halides in good to excellent yields.







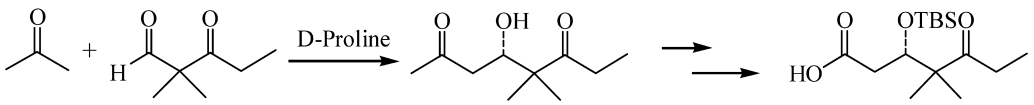


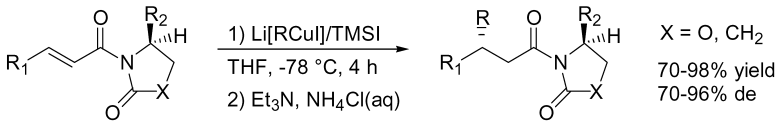
R = ^{i}Pr, Et

EWG= COOMe, COOAr, CN

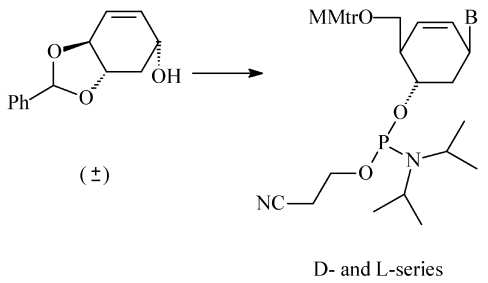
R = ^{i}Pr, Et

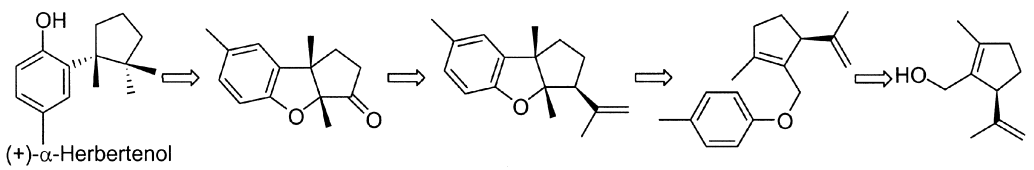
The aza-Baylis–Hillman reaction of DIAD or DEAD with various acrylates and acrylonitrile proceeds smoothly in the presence of DABCO in THF or DMF to give the corresponding adducts in moderate to good yields.

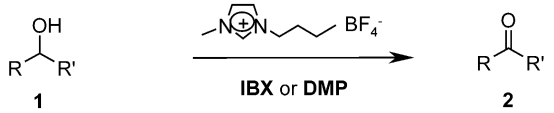


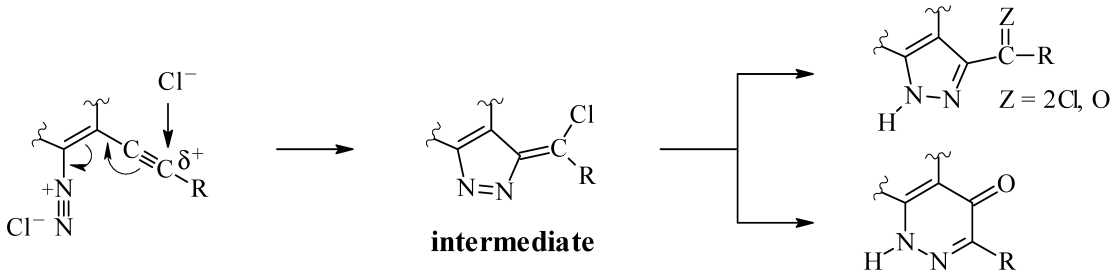


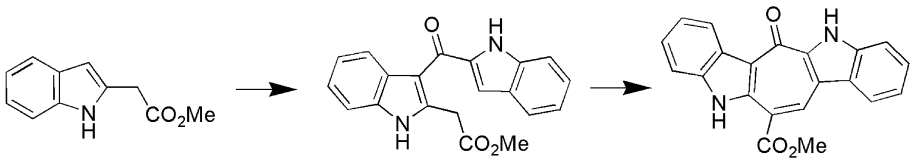
Presence of TMSI in the conjugate additions of Li[RCuI] to various chiral imides are described. TMSI is crucial for the conjugate additions, but only in THF or when 12-crown-4 is used. The reaction is thought not to involve any halosilane in any critical steps in ether. The CuI/DMS complex plays an instrumental role for high yield as well as stereoselectivity.

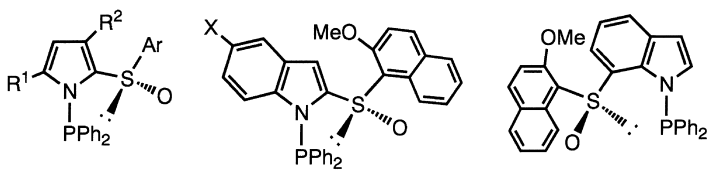


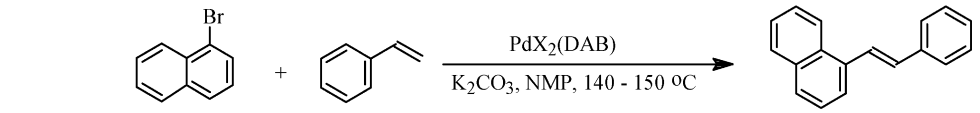












Pd cat : DMG, DAB, 8-Hydroxyquinoline, palladacycles, NHC

27 - (E)

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Indium- and gallium-mediated carbon–carbon bond-forming reactions in organic synthesis

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Contents

1. Introduction

Carbon–carbon bond formation constitutes one of the fundamental processes in organic synthesis and a wide variety of synthetic protocols have been developed to date for effecting this, amongst which organometallic reactions have played a major role since the discovery of Grignard reagents at the turn of the last century. Over the years, organometallic reagents have been developed utilising a range of metals in the Periodic Table, indium and gallium being the latest additions.

2. Indium

Even though indium, named for the luminous indigo line in its spectrum, was discovered in 1863 by Reich,[1] it has emerged as one of the metals of interest in organic synthesis only in the early 1990s. The low natural abundance of indium may have been a deterrent in the explorations involving this metal. Indium, however, enjoys a superior position among other metals as far as its chemical behaviour is concerned and this can be attributed to the following properties:

(1) indium metal is unaffected by air or oxygen at ambient temperatures, this being a major advantage over most of the other metals;
(2) indium is practically unaffected by water, unlike other metals such as Li, Na, etc;
(3) the first ionisation potential of indium (5.8 eV) is at a

Keywords: Organic synthesis; Indium; Galiium; Allylation; Reformatsky reaction; Aldol reaction.
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par with the alkali metals, for example, lithium or sodium (~5 eV), are quite lower when compared to zinc (9.4 eV), tin (7.3 eV) and magnesium (7.6 eV), and indium is therefore an ideal candidate for SET reactions;

(4) indium exhibits low heterophilicity in organic reactions, which makes it a suitable reagent for mediating C–C bond-forming reactions where it can tolerate oxygen and nitrogen functionalities and similarly, indium reagents display low nucleophilicity, thus permitting chemoselective transformations at groups with similar reactivity;

(5) most importantly, the element itself is without any apparent toxicity, whereas organolead and organotin reagents are highly and moderately toxic, respectively.

Cintas has reviewed the chemistry of organoindium reagents in 1995, covering most of the literature available up to that time.[2] In 1999, Li and Chan have summarised the reactions mediated by indium metal and indium compounds in aqueous media.[3a] Since then, reviews dealing with specific areas of indium-mediated reactions, although not exhaustive, have appeared in the literature.[3b,c] After the completion of this account, we came across a fairly comprehensive review on indium which covers the literature up to 2001;[4] a few references in 2002 are also discussed in it. The focus of the present review is on carbon–carbon bond formation mediated by indium, as well as gallium, and the literature coverage is complete through the first-half of 2003.

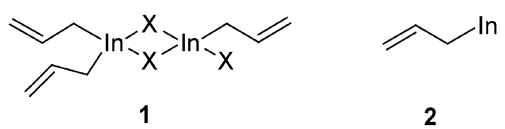
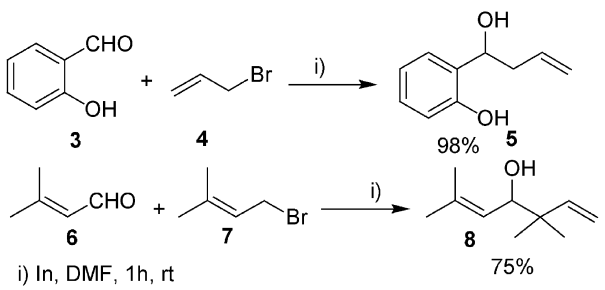


Figure 1.



Scheme 1.

In the late 1980s, Araki and co-workers introduced indium metal for the first time in the Barbier reactions.[5] Since then, indium has been used to mediate a range of reactions which are synthetically useful, amongst which, the carbon–carbon bond-forming reaction occupies a pivotal position. Indium-mediated carbon–carbon bond-forming reactions can be broadly classified into the following categories:

(1) Allylation reactions
(2) Palladium-catalysed reactions
(3) Propargylation reactions
(4) Reformatsky reactions
(5) Aldol reactions
(6) Miscellaneous reactions

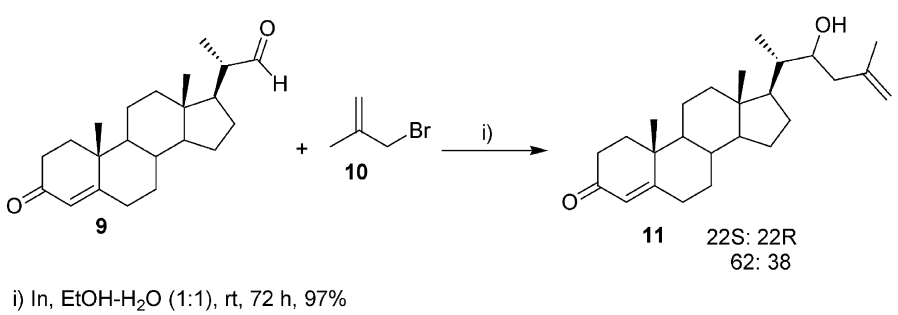
2.1. Allylation reactions

Indium-mediated allylation reactions in highly polar organic solvents such as THF or DMF proceed through an indium sesquihalide, $Allyl_3In_2X_3$ (**1**).[6] Further treatment with KI or KBr enables the isolation of dialkylindium halides. In reactions under aqueous conditions, the existence of allylindium (**2**) as a transient, but discrete, intermediate was established by Chan and Yang (Fig. 1).[7]

2.1.1. Allylation reactions of compounds with carbon–heteroatom multiple bonds

2.1.1.1. With carbon–oxygen multiple bonds. A variety of ketones and aldehydes undergo indium-mediated allylation in DMF to afford the homoallylic alcohols in good yields. Allylic iodides and bromides are equally reactive, but the reactivity of allyl chloride is markedly diminished. Even the less reactive allylic phosphates react with carbonyl compounds in the presence of indium and indium iodide, but ester and cyano groups are not susceptible to allylation under these conditions. It is worthy to note that substrates with active hydrogen such as ethyl acetoacetate and salicylaldehyde can be allylated using indium in good yields. With α,β-unsaturated aldehydes, the addition takes place in a 1,2-fashion (Scheme 1).[5] Indium can also mediate the allylation of aldehydes and ketones efficiently in water.[8] The indium-mediated allylation of aldehydes and ketones in ionic liquids has no significant advantage over similar reactions in conventional solvents.[9] Enantioselectivity can also be induced in indium-mediated reactions using external chiral ligands.[10]

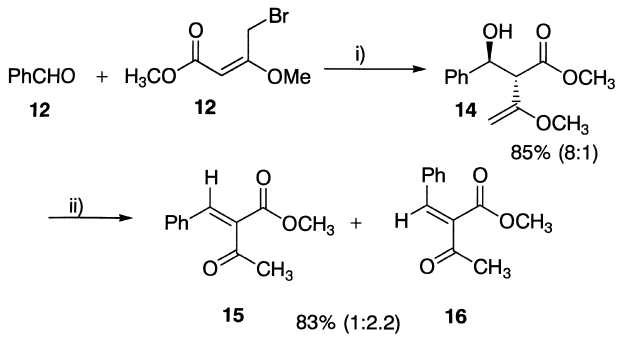
Indium-mediated allylation of the steroidal aldehyde **9** in an aqueous medium provides easy access to a wide variety of



Scheme 2.

22-hydroxysteroids with a moderate to high diastereoselectivity (Scheme 2).[11]

Addition of methyl (*E*)-4-bromo-3-methoxycrotonate to aldehydes in the presence of indium in an aqueous medium delivers the β-hydroxyesters, the acidic hydrolysis of which leads to Knoevenagel-type adducts (Scheme 3).[12]



i) In, NH_4Cl, $THF-H_2O$
ii) CH_3OH, 1N HCl

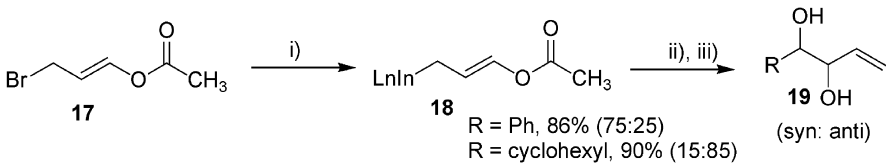
Scheme 3.

Metallic indium adds to 3-bromopropenyl acetate or benzoate either in THF or water, affording the corresponding 3-acyloxyallyl organometallic compounds. This nucleophilic addition to aldehydes opens up a route to the alk-1-ene-3,4-diols in good to excellent yields. The diastereoselectivity depends mainly upon the nature of the carbonyl compound; conjugated aldehydes afford the *syn* adducts, while unconjugated aldehydes display the opposite *anti* stereopreference (Scheme 4).[13]

Whereas the indium-mediated coupling of *E*-(3-bromo-3,3-difluoro-1-propenyl)trimethylsilane with aldehydes gave the corresponding *gem*-difluorohomoallyl alcohols bearing a trimethylsilyl group in high yields, the corresponding reaction of 1,1,3-tribromo-3,3-difluoro-1-propene with aldehydes afforded the coupling-reduction product, **24**. It is assumed that the reaction proceeds through a single allylic indium intermediate and the negative charge in the intermediate resides at the α-carbon (CF_2 site). The α-regioselectivity and the retention of the stereochemistry of the double bond in these reactions were explained on the basis of this (Scheme 5).[14]

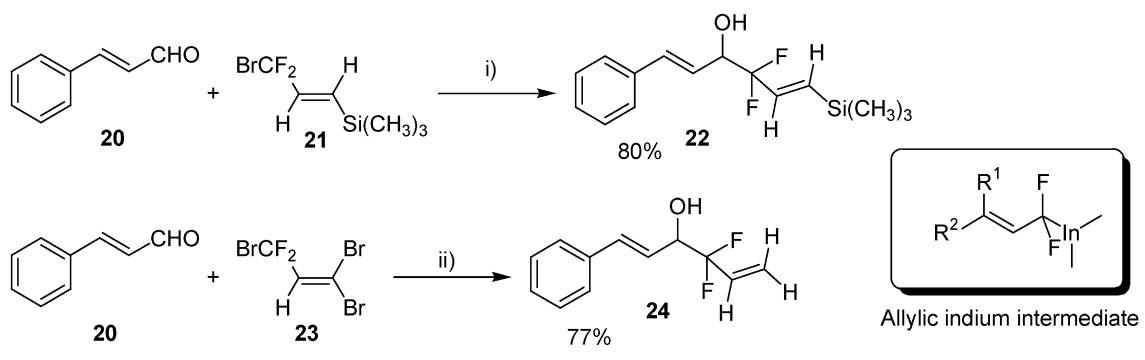
The organoindium reagent derived from 5-bromo-1,3-pentadiene and indium metal reacts with a variety of aldehydes and ketones with excellent regioselectivity to afford the non-conjugated diene products (γ-pentadienylation) in respectable yields. In addition, the trienes derived from the dehydration of condensation products provide a rapid entry into complex multicyclic skeletons via tandem [4+2] cycloadditions (Scheme 6).[15]

Araki and co-workers have shown that the reaction of 1,3-dibromopropene with metallic indium in DMF or DMA produced two types of organoindium species: γ-bromoallylindium and allylic diindium reagents. While the former gave 2-phenyl-3-vinyloxirane upon coupling with benzaldehyde, the latter gave 1-phenylbut-3-en-1-ol. The indium-mediated reaction of 1,3-dibromopropene with carbonyl compounds in water, however, gave the bis-allylation products, with both carbon–carbon bond formations occurring primarily on the same carbon, which effectively constitutes a *gem*-allyl dianion equivalent (Scheme 7).[16] Aromatic aldehydes generally exhibited a higher selectivity than their aliphatic counterparts in product formation during the reaction. Benzaldehyde and analogues bearing electron-withdrawing groups gave mainly the *gem*-bis-allylation products. Interestingly, with those analogues bearing electron-donating groups, the formation of both *gem*- and 1,3-dialkylation products was dramatically decreased and the selectivity was



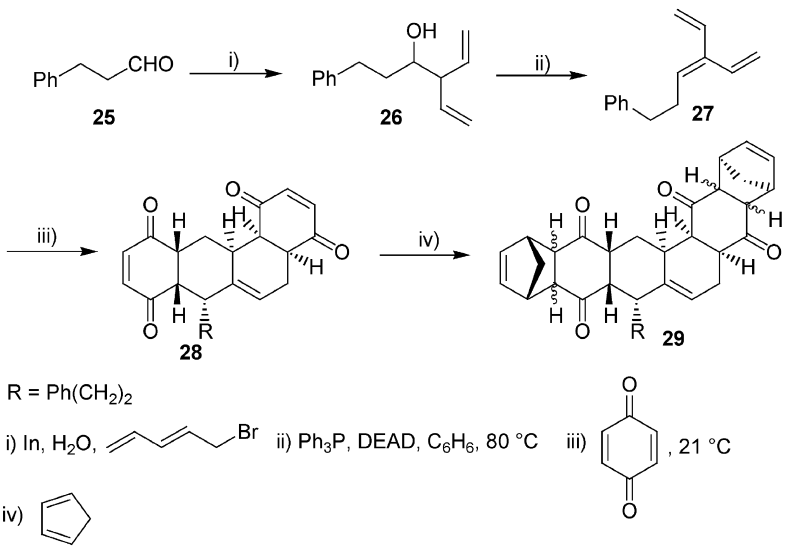
i) In, THF, 0°C-rt, 4h ii) RCHO, 0°C, 4h iii) K_2CO_3, MeOH, Overnight

Scheme 4.

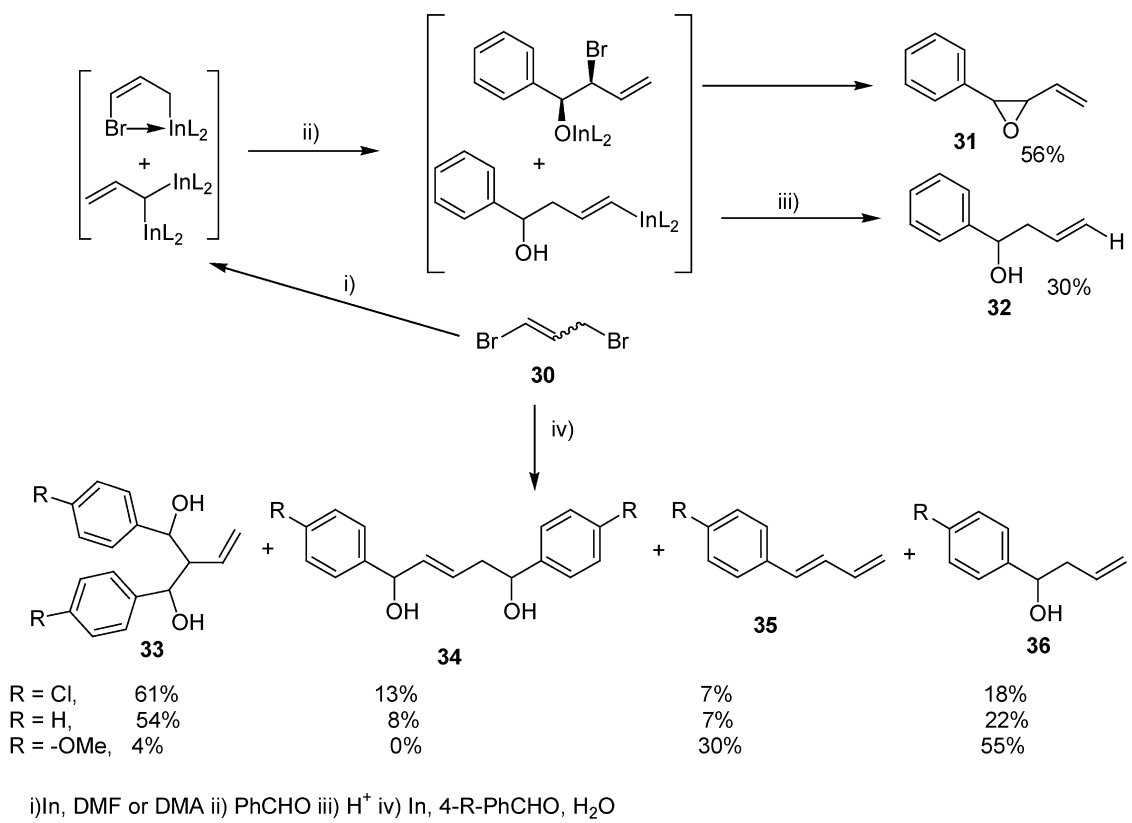


i) In, LiI, DMF, rt ii) In, LiI, DMF, 50 °C

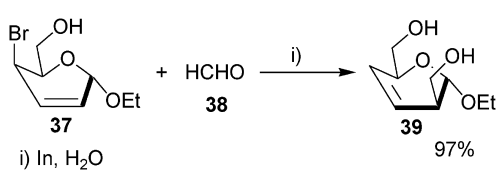
Scheme 5.



Scheme 6.



Scheme 7.

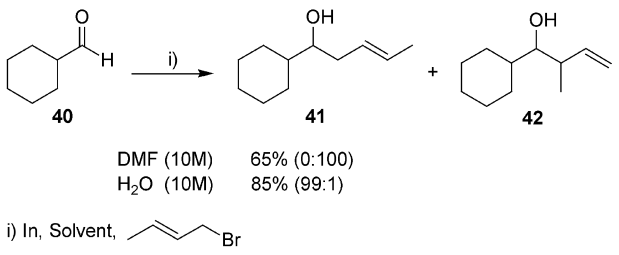


Scheme 8.

reversed compeletely to give the dienes and homoallylic alcohols.

Indium-promoted allylation reactions of aldehydes using 4-bromo-2-eno-pyranoside in aqueous media provided the unsaturated analogues of C-branched sugars or C-disaccharides, which can be elaborated to the branched sugars (Scheme 8).[17]

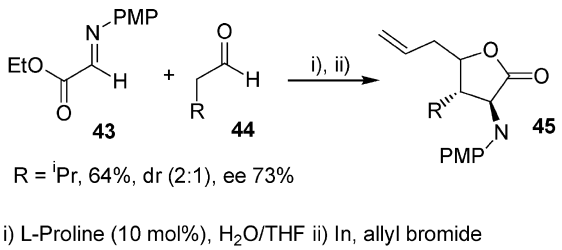
In general, allylation of an aldehyde with a γ-substituted allylic indium reagent occurs regioselectively at the



Scheme 9.

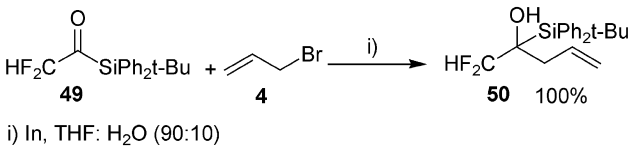
γ-position to afford the γ-homoallylic alcohol in the absence of a sterically-bulky substituent at the carbonyl or allyl bromide. Loh et al., however, have succeeded in synthesising the α-homoallylic alcohol via indium-mediated allylation without the use of a sterically-hindered substituent (Scheme 9).[18] Interestingly, the solvent plays an important role in determining the regioselectivity in these reactions. While water (10 M) and water/dichloromethane (10 M/10 M) exhibit excellent α-selectivity, DMF, ethanol, THF and water (0.5 M) show exclusive γ-selectivity.

A one-pot asymmetric synthesis of a cyclic γ-allyl-substituted α-amino acid derivative was accompolished by combining the proline-catalysed Mannich-type reactions of aldehydes and N-PMP-protected α-imino-ethyl glyoxylate by indium-promoted allylation in aqueous media (Scheme 10).[19] This is the first direct organocatalytic asymmetric Mannich-type reaction in aqueous media.



Scheme 10.

Indole-3-carboxaldehydes, irrespective of the substituents at N-1 and C-2, undergo indium-mediated reactions with allyl bromide and indole to provide the symmetrical and unsymmetrical bisindolylalkanes and with other heterocyclic enamines, viz. pyrrole, pyrazole, 6-aminouracil and imidazole, to provide the indolyl heterocyclic alkanes in excellent yields (Scheme 11).[20] In addition, substituents on the allyl bromide do not affect these ternary reactions. In each case, the allylation proceeds with complete regioselectivity to provide only the γ-addition product.



Scheme 12.

Indium-mediated allylation of difluoroacetyltrialkylsilanes in aqueous media gives the homoallylic alcohols exclusively. It is noteworthy that the common Brook rearrangement, C- to O-silyl group migration, is totally suppressed in these reactions, with no detectable formation of the enol silyl ethers (Scheme 12).[21]

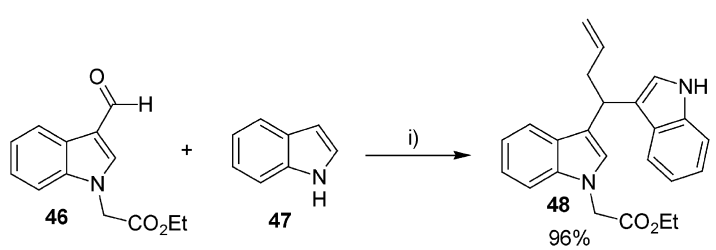
Indium-mediated allylation of α-chloro carbonyl compounds with various allyl bromides in aqueous media gave the corresponding homoallylic chlorohydrins, which could be transformed in to the corresponding epoxides in the presence of a base (Scheme 13).[22] These reactions are strongly dependent on both the substituents at the carbon bearing the chlorine and the allyl bromide.

With α,β-unsaturated ketones, allylindium sesquibromide produced homoallylic indium alkoxide intermediates, which can be induced to undergo a deoxygenative rearrangement that results in vinylcyclopropane derivatives. The overall reaction therefore involves a deoxygenative sequential transfer of two allyl moieties from the indium sesquihalide species to the α,β-unsaturated ketone (Scheme 14).[23]

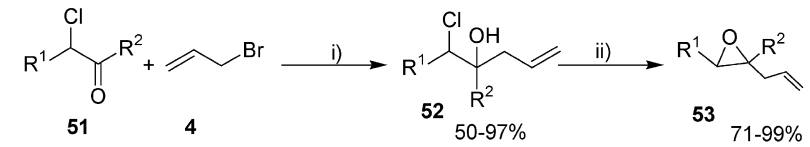
The regioselectivity of the reactions of α,β-enones with allylindium reagents in the presence of TMSCl has also been studied. In the absence of TMSCl, 2-cyclohexen-1-one reacted regioselectively with the allylindium reagent to produce the 1,2-addition product, whereas only the 1,4-addition product was obtained in the presence of TMSCl (Scheme 15).[24]

A variety of organoindium reagents, generated in situ, have been shown to react smoothly with 1,2-diones, resulting in a high-yield synthesis of α-hydroxyketones. For example, benzil, on treatment with indium and allyl bromide, in the presence of sodium iodide in DMF at room temperature, afforded 2-hydroxy-1,2-diphenyl-pent-4-en-1-one in 97% yield (Scheme 16).[25] In the absence of sodium iodide, the reaction was very slow. It is noteworthy that no diallylation occurred, despite the use of an excess of reagent.

In related work, it was shown that an allylindium reagent

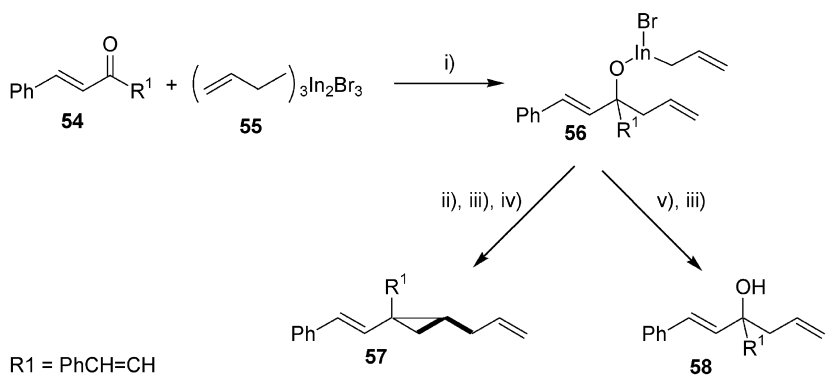


Scheme 11.



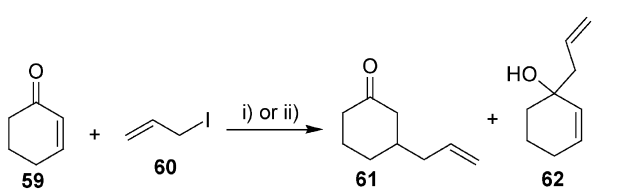
R^1 = H, alkyl, carbonyl compounds
R^2 = aromatic, alkyl, carbonyl compounds
i) In, THF-H_2O
ii) base

Scheme 13.

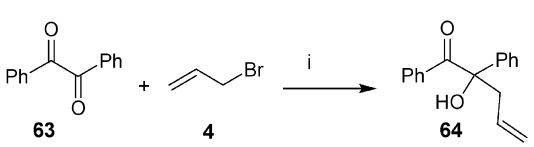


i) THF, 25 °C, ii) LiBr, iii) Et_2O, iv) H_3O^+ (O_2), v) H_3O^+

Scheme 14.



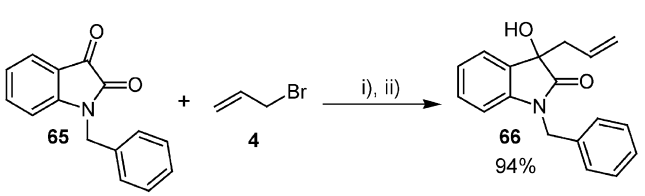
Scheme 15.



i. In, NaI, DMF, 5 min., 97%

Scheme 16.

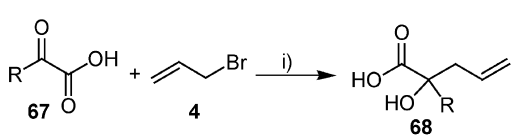
reacts chemoselectively with isatins to afford the oxindole derivatives. In the case of substituted allylic bromides such as cinnamyl and prenyl bromides, exclusive γ-regioselectivity was observed (Scheme 17).[26]



i) In, NaI, DMF, rt, 10 min. ii) H_3O^+

Scheme 17.

2-Oxocarboxylic acids or their sodium salts undergo indium-mediated allylation to provide the corresponding 2-allyl derivatives (Scheme 18).[27] These reactions afford exclusively the γ-addition product. In the reactions with cinnamyl bromide or ethyl 4-bromocrotonate, a high diastereoselectivity is observed.

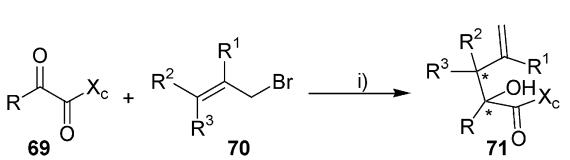


i) In, THF/H_2O, rt

Scheme 18.

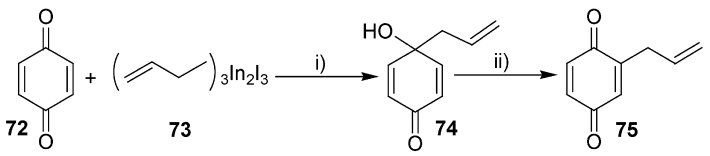
Indium-mediated allylation of α-ketoimides derived from Oppolzer's sultam was accomplished in aqueous THF in good yields and excellent diastereomeric excesses (Scheme 19).[28] This method is very attractive for the preparation of enantiopure α-hydroxyacids.

The reaction of quinones with allylindium reagents deserves special mention (Scheme 20).[29] The reaction of *p*-benzoquinone with allylindium sesquiiodide in DMF at −45 °C

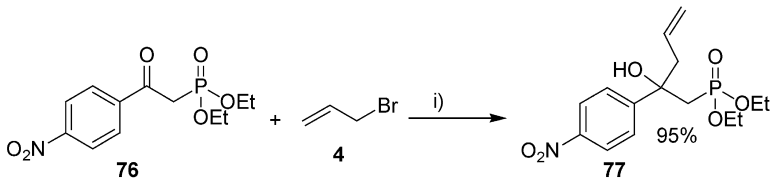


X_c = (+) or (-) Oppolzer's sultam, R = phenyl , thiophenyl , furyl
i) In, aq. THF

Scheme 19.



Scheme 20.

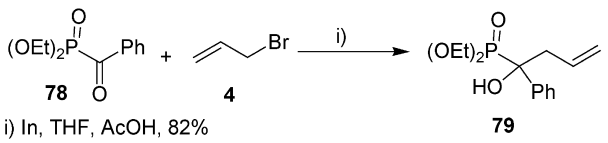


Scheme 21.

gave the allylated product derived from 1,2-addition to the carbonyl group. Treatment of the crude product with silver(I) oxide in refluxing ether induced a [3,3]-sigmatropic rearrangement to give the allylated *p*-benzoquinone **75** in 91% overall yield.

The addition of allylindium species to β-ketophosphonates proceeded to afford the corresponding β-hydroxyphosphonate, both the open-chain and the cyclic β-ketophosphonates reacting equally well (Scheme 21).[30]

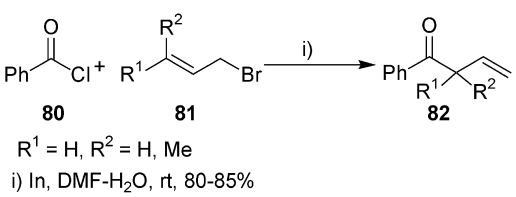
Treatment of aryl phosphonates with allylindium reagents in the presence of acetic acid afforded the corresponding α-hydroxy alkylphosphonates in good yields under mild conditions. This process works well with several different allylic bromides and does not appear to be sensitive to steric hindrance at the β-carbon (Scheme 22).[31]



Scheme 22.

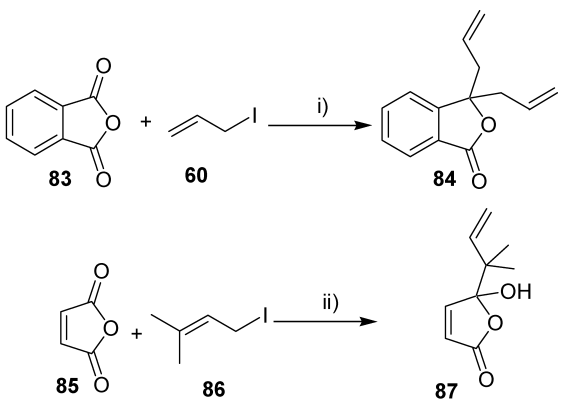
The allylation of acid chlorides with allyl, crotyl or prenyl bromide and indium in DMF at room temperature provides a mild and efficient method for the preparation of β,γ-unsaturated ketones (Scheme 23).[32a] The indium-mediated allylation of acyl cyanides with allyl halides in aqueous media also affords the β,γ-unsaturated ketones in moderate to good yields.[32b]

Allylation of cyclic acid anhydrides with allyl halides and



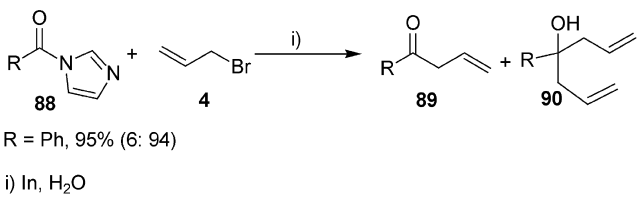
Scheme 23.

indium powder in DMF gives the corresponding *gem*-diallylated derivatives in moderate to good yields (Scheme 24).[33] This strategy offers a novel route to phthalides and butenolides from cyclic anhydrides. With γ-substituted allyl halides, the reaction stopped at the monoallylation stage, presumably due to steric hindrance, affording the hydroxylactones. Unlike acid anhydrides, the behaviour of cyclic imides towards allylindium reagents is rather complicated; the outcome of the reaction depends on the structure of both the imides and the indium reagents and the products are generally obtained in low yields.[5]



Scheme 24.

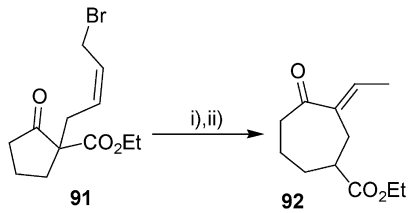
The indium-mediated reaction of allyl bromide with acylimidazoles or pyrazoles in aqueous media gives a mixture of the tertiary alcohol and ketone (Scheme 25).[34] The reaction of simple alkyl and aryl acylimidazoles with



Scheme 25.

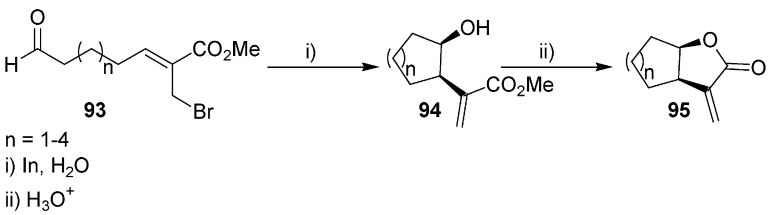
indium and allyl bromide gives predominantly the tertiary alcohol, whereas the reaction of acylpyrazoles under identical conditions results in the predominant formation of the homoallylic ketone.

Indium-mediated intramolecular allylations of carbonyl compounds have also been reported in the literature. Li et al. have described a novel two-carbon ring expansion through the indium-mediated Barbier-type reaction in water (Scheme 26).[35a] They have additionally achieved a one-carbon ring expansion using indium.[35b]



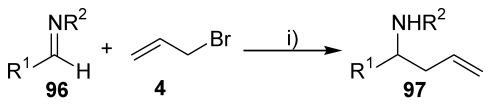
Scheme 26.

Indium-mediated intramolecular carbocyclisation in aqueous media offers a stereoselective route to *cis*-fused α-methylene-γ-butyrolactones; the latter are structural motifs present in many biologically-active natural products (Scheme 27).[36]



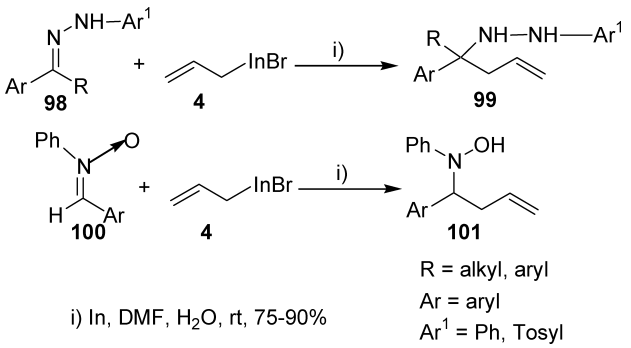
Scheme 27.

2.1.1.2. With carbon–nitrogen multiple bonds. Aldimines can be allylated in a simple Barbier-type reaction using allyl bromide and indium powder in THF to afford the homoallylic amines (Scheme 28).[37]



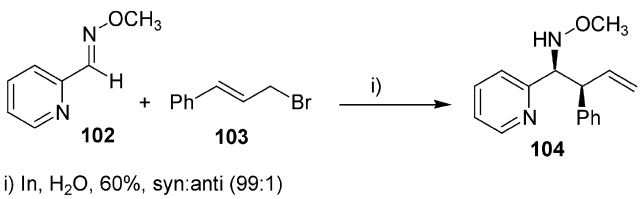
Scheme 28.

Allylindium adds to a variety of tosyl and aryl hydrazones derived from aromatic aldehydes and ketones at ambient temperature in a DMF–H_2O solvent system to afford the homoallylic tosyl hydrazides and homoallylic hydrazines, respectively (Scheme 29).[38] Various aldonitrones also undergo allylation when treated with allylindium reagents to yield the homoallylic hydroxylamines.



Scheme 29.

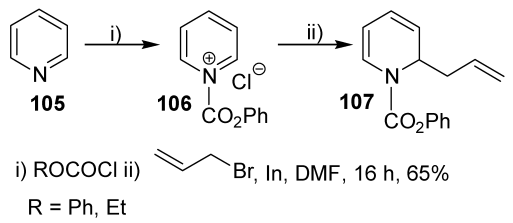
Oxime ethers derived from 2-pyridinecarboxaldehyde and glyoxylic acid can be efficiently allylated in water with allylic bromides promoted by indium (Scheme 30).[39] When the metal is positioned in the proximity of flanking heteroatomic centers, chelation by indium is indeed operative and affects both the reactivity and the stereochemistry. Interestingly, the reaction of oxime ethers derived from 3- and 4-pyridinecarboxaldehyde under similar conditions was unsuccessful. When cinnamyl bromide, crotyl bromide and ethyl bromocrotonate were used, the indium-mediated allylation of oxime ethers occurred with excellent regioselectivity, affording exclusively the γ-adduct. The reaction was found to be highly stereoselective with cinnamyl bromide and ethyl bromocrotonate, whereas, with crotyl bromide, the stereoselectivity was diminished.



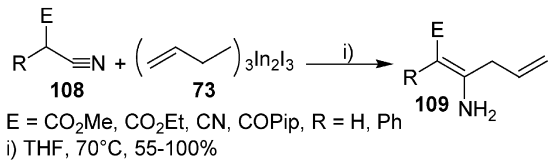
Scheme 30.

Indium-mediated allylation of pyridinium salts with various allylic halides affords the corresponding 2-substituted 1,2-dihydropyridines with complete regioselectivity (Scheme 31).[40] This method has been successfully employed for the synthesis of the alkaloid (±)-dihydropinidine.

The reaction of activated nitriles with allylindium in THF at 70 °C affords the corresponding allylation–enamination products in high to excellent yields (Scheme 32).[41] This reaction provides a useful method for the synthesis of



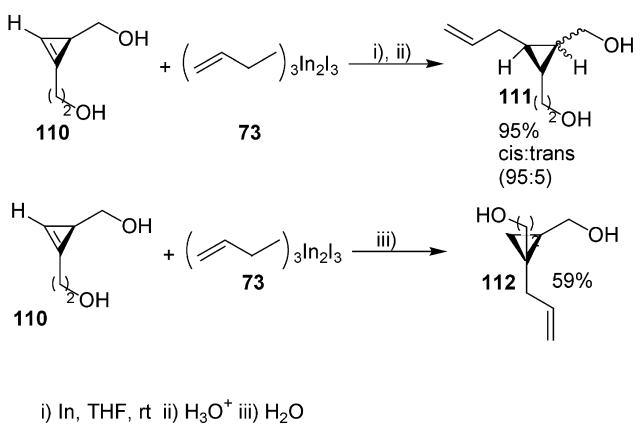
Scheme 31.



Scheme 32.

highly-functionalised enamines, which are not easily accessible by conventional methods.

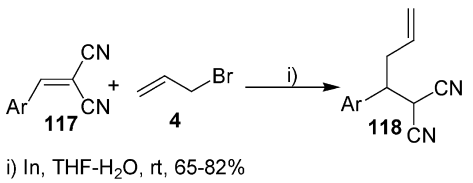
2.1.2. Allylation reactions of compounds with carbon–carbon multiple bonds. The hydroxyl-bearing cyclopropenes undergo clean allylindation with allylindium reagents in both organic and aqueous media, in which chelation of the hydroxyl group to indium plays a central role. The regio- and stereoselectivity have been regulated both by the location of the hydroxyl group in the molecule and the reaction solvents (Scheme 33).[42]



Scheme 33.

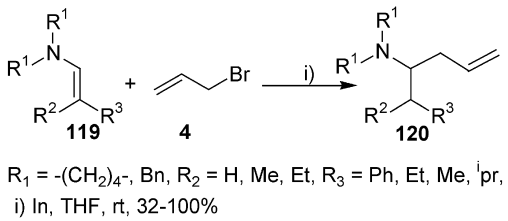
The allylindation of non-activated carbon–carbon double bonds of norbornenols proceeds with high regio- and stereoselectivity to afford the allylated products, together with iodinated and oxygenated products (Scheme 34).[43] The product distribution can be controlled by changing the reaction solvent. In these reactions, the regio- and stereochemistry of the addition of the indium reagents is highly regulated via chelation with the neighbouring hydroxyl group.

Indium-mediated allylation of 1,1-dicyano-2-arylethenes in aqueous media gave the Michael adducts in good yields (Scheme 35).[44] Unfortunately, other electron-deficient alkenes such as 1-cyano-1-ethoxycarbonylstyrene, diethyl maleate and cinnamyl cyanide failed to react under these reaction conditions.



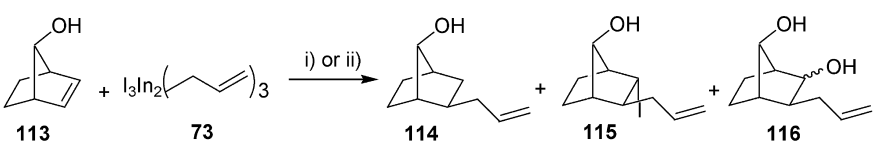
Scheme 35.

The allylation of enamines with allyl bromide in the presence of indium produces the tertiary homoallyl amines (Scheme 36).[45] The reactivity of the enamines is mainly influenced by the substitution (R^1) on nitrogen. Pyrrolidine-derived enamines are more reactive than those derived from morpholine and dibenzylamine. The effect of substitution (R^2 and R^3) on the olefinic carbon β to nitrogen was also studied. Enamines with only one aliphatic substituent R^3 (R^2=H) are more reactive. With two aliphatic substituents R^2 and R^3, the reactivity is moderately decreased. On the other hand, substitution (R^3) by a phenyl group decreases the reactivity considerably.



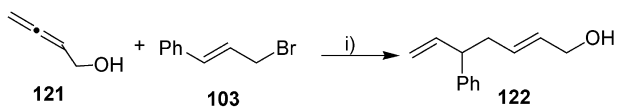
Scheme 36.

The reaction of allylic indium sesquihalides to allenols has been found to proceed with high regio- and stereoselectivity (Scheme 37).[46] Unlike the substituents on the C-4 carbon, substituents on the C-1 carbon of allenols significantly affect the reaction. Secondary allenols show diminished reactivity and the tertiary allenols do not react at all. In addition, protection of the hydroxyl group of the allenol compeletely inhibits the allylindation.



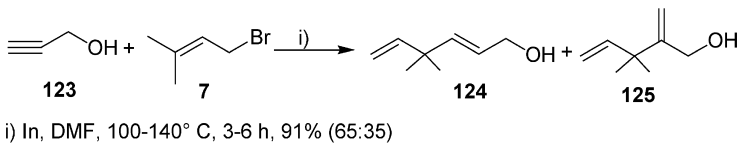
i) THF, reflux	26	16	32
ii) NMP, 180°C	72	0	0

Scheme 34.



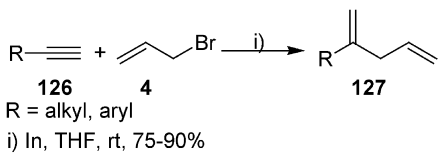
Scheme 37.

Carboindation of alkynols by allylic indium sesquihalides proceeded in DMF at 100–140 °C via a *syn* addition (Scheme 38).[47] Only the terminal alkynols underwent allylindation. This is in sharp contrast to the known carbometallations, in which addition to inner alkynes is very common, whereas addition to terminal alkynes is rare.



Scheme 38.

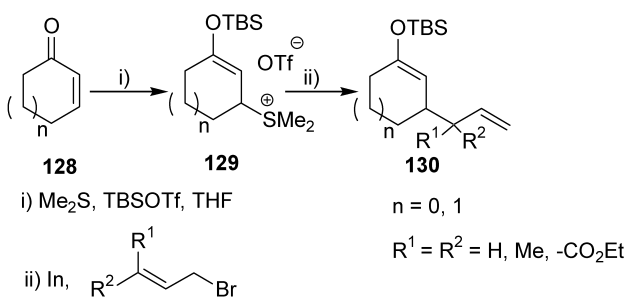
The reaction of unactivated terminal alkynes with allyl bromide and indium in THF at room temperature produces the 1,4-dienes via regioselective addition (Scheme 39).[48] In the case of unprotected alkynols, the regioisomeric outcome is found to depend upon the distance between the hydroxyl group and alkyne moiety; propargylic substrates give linear 1,4-dienes, while the higher homologues afford exclusively the branched 1,4-dienes and the protected compounds always afford the corresponding allylated branched 1,4-dienes.



Scheme 39.

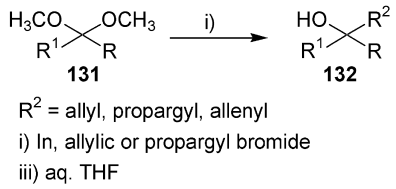
2.1.3. Allylation reactions of compounds with other functional groups. The 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts **129**, derived from the reaction of α,β-enones with dimethyl sulphide in the presence of TBSOTf, undergo a novel nucleophilic substitution with allylindium reagents to afford the silyl enol ethers of γ,ε-unsaturated ketones **130**, which correspond to the Michael addition products, in good yields (Scheme 40).[49]

Acetals and ketals undergo indium-mediated allylation and propargylation reactions with various allyl or propargyl



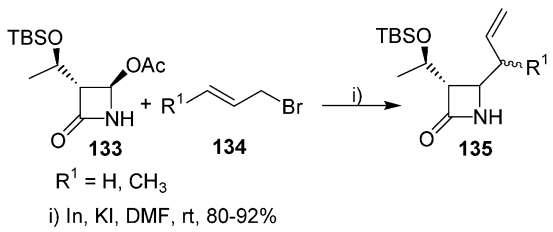
Scheme 40.

bromides in aqueous media to provide the corresponding homoallylic (and allenylic) or homopropargylic alcohols, respectively, in moderate to good yields (Scheme 41).[50] The overall reaction can therefore be shown as a one-pot deprotection-allylation/propargylation.



Scheme 41.

Indium-mediated allylation of 4-acetoxy-2-azetidinones was accomplished by the treatment of indium and allyl bromide in the presence of potassium iodide at room temperature (Scheme 42).[51] It is assumed that azetidinones behaved as the imine equivalent in these reactions to achieve the carbon–carbon bond formation at C-4 position.



Scheme 42.

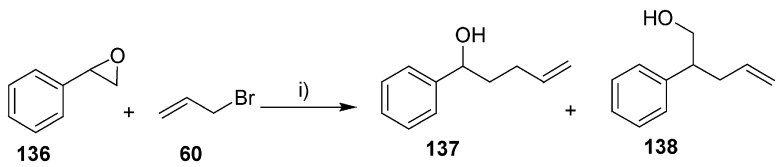
Allylindium, prepared from allyl bromide and indium metal in THF, reacts with terminal epoxides at room temperature to afford the corresponding bishomoallyl alcohols in excellent yields and with good regioselectivity (Scheme 43).[52]

Allylindium, prepared from allyl bromide and indium metal in an aprotic solvent, reacts with terminal vinyl epoxides at room temperature to afford various bishomoallyl alcohols in moderate to high yields via a consecutive 1,2-shift reaction and regioselective allylation (Scheme 44).[53]

2.2. Palladium-catalysed reactions

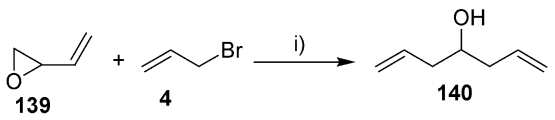
With a variety of organic electrophiles such as aryl and vinyl triflates, vinyl halides, dibromoolefins and alkynyl iodides, allylindiums generated in situ underwent palladium-catalysed allyl cross-coupling reactions (Scheme 45).[54] The presence of various alkyl substituents at the α-and γ-positions did not diminish the efficiency and selectivity of the allyl halides as coupling partners.

The palladium catalysed reactions of aldehydes with allylic compounds such as allyl alcohol, trifluoroacetate, chloride,



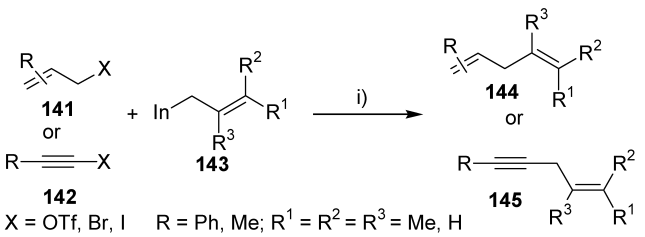
i) In, THF, rt, 90% (90:10)

Scheme 43.



i) In, THF, rt, 87%

Scheme 44.

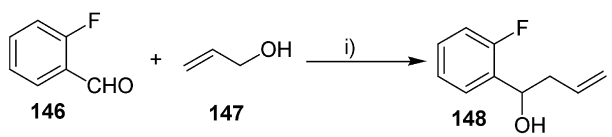


X = OTf, Br, I R = Ph, Me; $R^1 = R^2 = R^3$ = Me, H

i) cat-Pd(0)

Scheme 45.

carbonate, acetate or phenyl sulfone using the indium–indium trichloride system in aqueous media afforded the corresponding homoallylic alcohols. In the case of substituted allyl chloride, acetate and alcohol, the corresponding branched homoallylic alcohols with exclusive *anti* stereoselectivity were obtained. In these reactions, indium(III) chloride plays a role in the formation of π-allyl-palladium complexes from allylic compounds and/or in the in situ-generation of the reactive indium(I) chloride by reaction with indium metal (Scheme 46).[55]

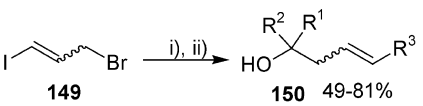


i) In, $InCl_3$, $Pd(PPh_3)_4$, $THF:H_2O$, rt, 100%

Scheme 46.

Araki et al. have shown that the diindium reagent prepared from 3-bromo-1-iodopropene successively coupled with carbonyl compounds and then with aryl, alkenyl or allyl halides in the presence of a Pd(0) catalyst to afford a convenient one-pot synthesis of linear homoallylic alcohols (Scheme 47).[56]

Homoallylic alcohols were obtained in moderate to good yields by the reaction of allylindium species generated by the transmetallation of π-allylpalladium(II) complexes arising from aryl iodides and allenes with aldehydes (Scheme 48).[57a] Imines also reacted under identical conditions to afford the homoallylamines.[57b]



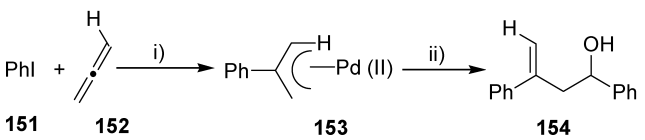
R^1 = alkyl, phenyl, R^2 = H, CH_3,

R^3 = phenyl, cinnamyl, allyl, X = halide

i) In, R^1COR^2, NMP

ii) R^3X, $Pd(PPh_3)_4$, LiCl

Scheme 47.



i) Pd(0) ii) In, PhCHO, 64%

Scheme 48.

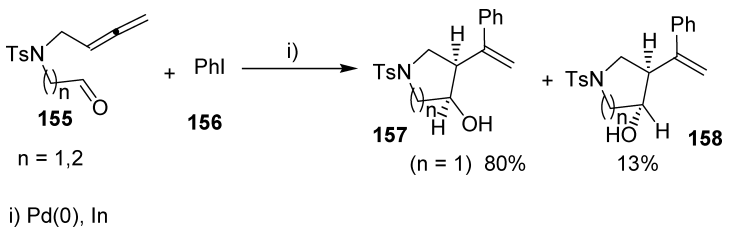
The tandem palladium-catalysed and indium-mediated arylative cyclisation of allenyl aldehydes and ketones to form homoallylic cyclopentanols and cyclohexanols has been reported (Scheme 49).[58a] A similar reaction was observed with allenyl sulfonimines; in contrast to allenyl aldehydes, the *trans* isomer was not obtained in this case.[58b]

Grigg and co-workers have shown that the π-allylpalladium species formed by a palladium-catalysed cyclisation of aryl halides onto proximate alkynes, followed by allene insertion, undergoes transmetallation with indium to afford an allylindium species which then adds to aldehydes to yield carbocyclic and heterocyclic dienes (Scheme 50).[59a] In another study, the same workers generated the π-allylpalladium(II) complex by a palladium-catalysed cyclisation of aryl halides onto proximate 1,3-dienes.[59b]

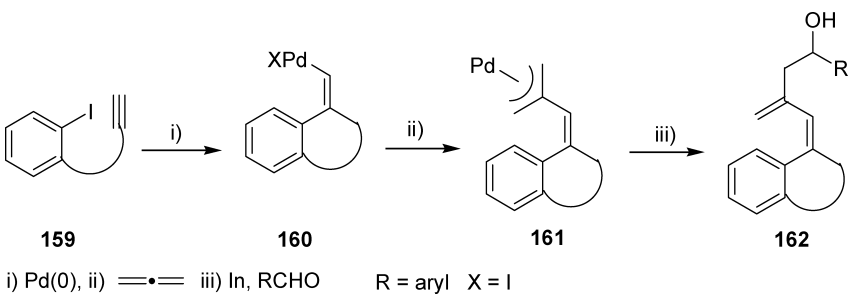
Allenylindium intermediates generated by the reaction of indium with propargyl bromides were employed as effective partners in palladium-catalysed coupling reactions with a variety of electrophiles to produce allenes, polyallenes and unsymmetrical bis(allenes) in excellent yields with complete regio- and chemoselectivity (Scheme 51).[60] Surprisingly, no propargylic cross-coupling product is formed in any of these reactions.

2.3. Propargylation reactions

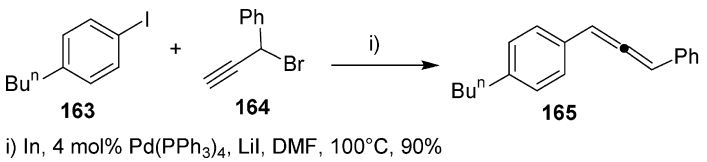
Among the many metals employed for propargylation reactions, indium has attracted special attention, due to its mild reaction conditions, as well as its wide functional group compatibility. Compared to the well-established allylic indium chemistry, however, the synthetic potential



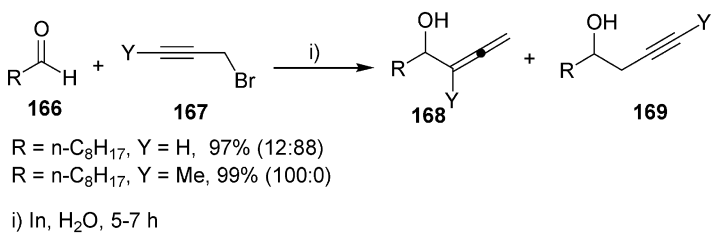
Scheme 49.



Scheme 50.



Scheme 51.



Scheme 52.

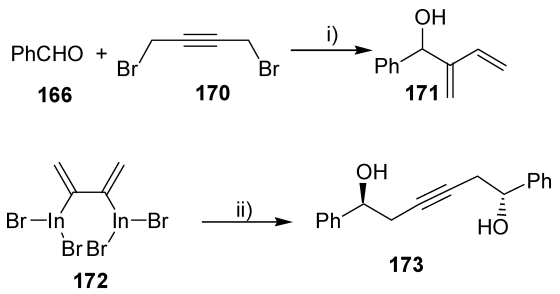
of propargylic indium reagents has not yet been fully exploited.

Indium-mediated coupling of aldehydes with prop-2-ynyl bromides occurs regioselectively to give either homoprop-2-ynyl or allenylic alcohols depending on the γ-substituent of the prop-2-ynyl bromides. With the parent prop-2-ynyl bromide, the indium-mediated coupling with aliphatic or aryl aldehydes affords mainly the homoprop-2-ynyl alcohols in good yields. In contrast, when the prop-2-ynyl bromide is γ-substituted, the coupling products are predominantly or exclusively the allenylic alcohols (Scheme 52).[61]

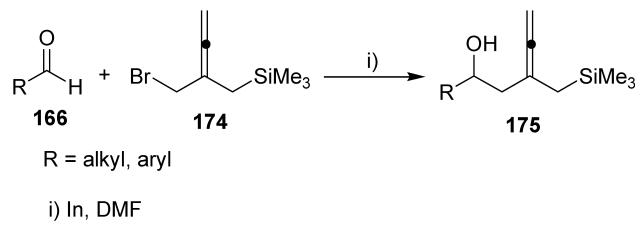
Indium-mediated coupling of 1,4-dibromo-2-butyne with carbonyl compounds in aqueous media proceeded regioselectively to give good yields of the 1,3-butadien-2-ylmethanols. 2,3-Dibutadienyldiindium tetrabromide, formed by the reaction of 1,4-dibromobutyne with indium, adds to different carbonyl compounds in the presence of zinc fluoride to give almost exclusively the acetylenic diol as a single diastereomer (Scheme 53).[62]

Indium-mediated homoallenylation of aldehydes with 4-bromo-3-[(trimethylsilyl)methyl]-1,2-butadiene in DMF afforded 2-(2-hydroxyethyl) homoallenylsilanes in good yields at room temperature (Scheme 54).[63]

The regio- and diastereoselectivity of the indium-mediated reaction of azetidinediones and propargyl bromide in

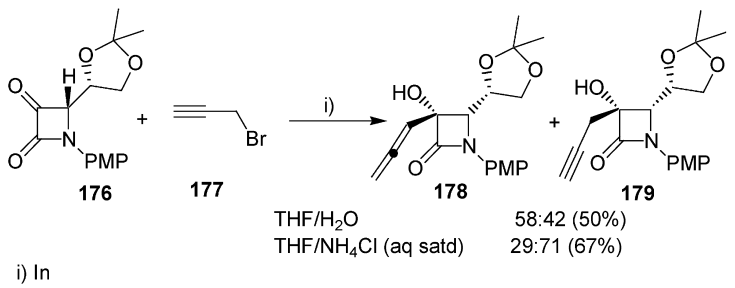


Scheme 53.

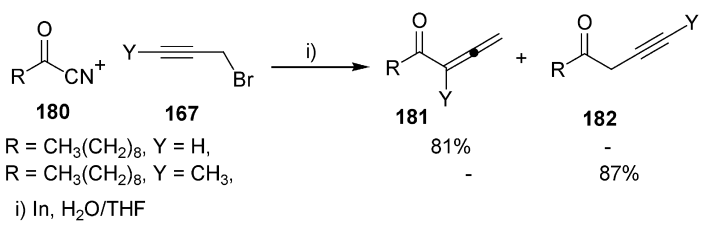


Scheme 54.

Acyl cyanides also undergo indium-mediated propargylation or allenylation to give the corresponding propargylic or allenic ketones in good yields. It may be noted that the regiochemical preference in this case is the opposite of that observed with aldehydes. With the parent propargyl bromide the indium-mediated coupling gives exclusively the allenic ketones, whereas the γ-substituted propargyl bromides give exclusively the acetylenic ketones (Scheme 56).[65]



Scheme 55.



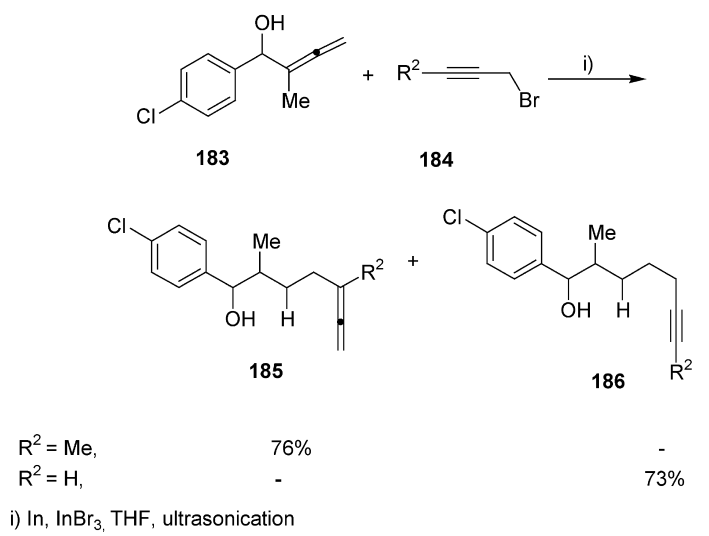
Scheme 56.

aqueous tetrahydrofuran at room temperature have also been reported. In the event, the 3-substituted 3-hydroxy-β-lactam moiety was obtained, but the observed regioselectivity was very poor, with the allenic product slightly predominating. Surprisingly, the regiochemical preference was reversed in the indium promoted reaction by changing the solvent system to a saturated aqueous solution of ammonium chloride in THF, the expected alcohols being obtained as a mixture of regioisomers, with the propargylic alcohol preponderating (Scheme 55).[64]

Allenic alcohols undergo facile allenylation and propargylation in the presence of indium and indium tribromide under ultrasonic irradiation to give *E*-2,5,6-heptatriene and *E*-2-hepten-6-yne compounds in good regio- and stereoselectivity (Scheme 57).[66]

2.4. Reformatsky reactions

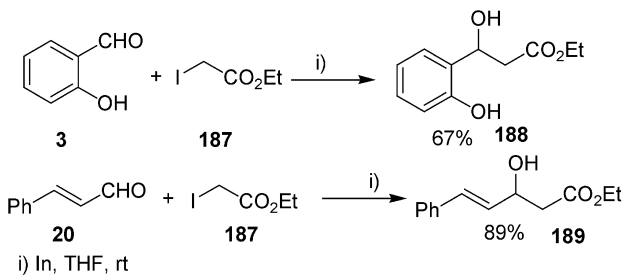
The Reformatsky reaction, because of its selectivity and wide applicability, is a valuable method for the synthesis of



Scheme 57.

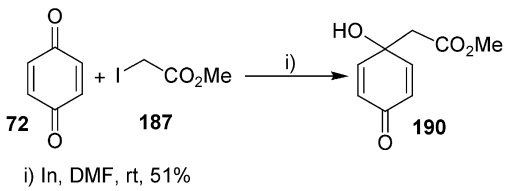
hydroxyesters and their dehydration products. This reaction involves the treatment of an α-bromoester with zinc in the presence of an aldehyde or ketone to afford the β-hydroxyester. Recently, several modified Reformatsky reactions using other metals such as manganese, samarium, etc. have been described.

Indium is also found to effectively promote the Reformatsky reaction of α-iodoesters with carbonyl compounds to furnish the β-hydroxyesters. Although the methodology is limited to the α-iodoesters, it is worthy of note that no elimination products are formed during the process. α,β-Unsaturated carbonyl compounds also undergo exclusive 1,2-addition under modified Reformatsky reaction conditions (Scheme 58).[67]



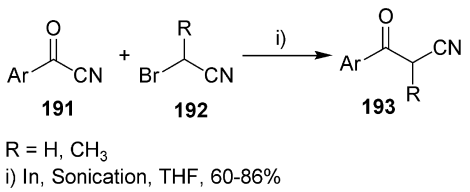
Scheme 58.

Butsugan et al. have applied the Reformatsky reaction to *p*-quinones to give good yields of the β-quinol esters under mild conditions and, using this methodology, the naturally-occurring quinol ester jacaranone **190** was prepared (Scheme 59).[68]



Scheme 59.

Indium-mediated coupling of bromoacetonitrile and 2-bromopropionitrile with a variety of aromatic acyl cyanides afforded the corresponding aromatic α-cyanoketones in moderate to good yields (Scheme 60).[69] Unlike benzaldehyde, the reaction of acyl cyanides with bromoacetonitrile proceeds successfully without additives. It is noteworthy that practically no reaction occurred in the absence of sonication.



Scheme 60.

2.5. Aldol reactions

Carbon–carbon bond formation via the selective reduction of the carbon–halogen bond, an important operation in synthetic organic chemistry, is often accomplished by the aldol reaction. Indium can also promote such synthetically-important aldol reactions. Indium metal as well as indium(I) iodide are found to mediate the aldol condensation between α-haloketones and aldehydes (Scheme 61).[70]

2.6. Miscellaneous reactions

A variety of useful synthetic transformations, besides those described above, have also been accomplished via indium-mediated reactions, illustrating the potential and versatility of the organoindium species.

The indium-promoted pinacol coupling of aromatic carbonyl compounds has been reported to take place in neutral aqueous media under sonication conditions (Scheme 62).[71] In the absence of sonic waves, the reaction occurs much more slowly and the yield of the diols is lower by a factor of 2 to 3-fold. The reaction of solid aldehydes with indium did not take place in *t*-BuOH, and was very slow in water. The reactions of aliphatic aldehydes and ketones with indium were unsuccessful.

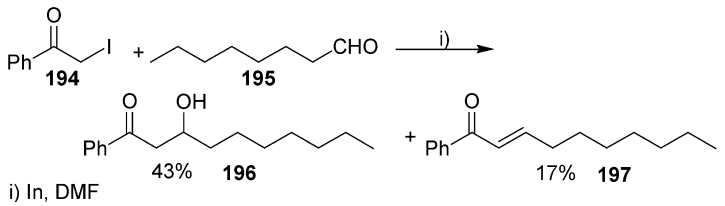
Recently, the In/$InCl_3$-mediated cross-coupling of methyl vinyl ketone with benzaldehydes in aqueous media has been reported (Scheme 63).[72] In this reaction, the end product was the β,γ-unsaturated ketone and not the pinacol.

We have achieved a facile synthesis of unsymmetrical pinacols by the reaction of aldehydes and chalcones in the presence of indium/indium trichloride in aqueous media (Scheme 64).[73] This is the first report of a chalcone participating in pinacol coupling reactions.

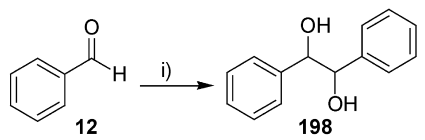
The indium-mediated 1,4-addition of an alkyl radical to β-substituted conjugated alkenes in the presence of the radical hydrogen source 1-ethylpiperidium hypophosphite (EPHP), the surfactant cetyltrimethylammonium bromide (CTAB) and the water-soluble radical initiator 4,4′-azo-bis(4-cyanovaleric) acid (ABCVA) in aqueous media has been developed. The reaction affords the 1,4-addition products from various α,β-enones regiospecifically in high yields (Scheme 65).[74]

Using indium as a radical initiator, the intermolecular alkyl radical addition to imine derivatives in aqueous media has been achieved. The one-pot reaction based on radical addition to glyoxylic hydrazone provides a convenient method for preparing the α-amino acids. The indium-mediated radical addition to an electron-deficient C=C bond also proceeds effectively, to provide a new carbon–carbon bond-forming method in aqueous media (Scheme 66).[75]

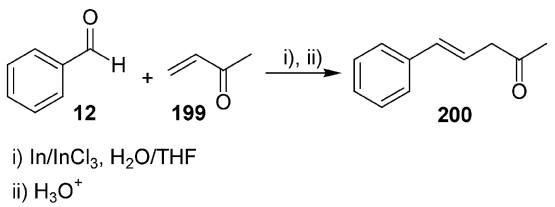
The indium-mediated atom-transfer cyclisations and reductive cyclisations depend upon the ratio of indium and iodine used (Scheme 67).[76] Treatment of an iodoalkyne with indium (0.5 equiv.) and iodine (0.5 equiv.) in methanol promotes the atom-transfer 5-exo cyclisation. In contrast, the reaction with indium (2 equiv.) and iodine (1 equiv.) gives rise to a reductive 5-exo cyclised product. Unfortunately, these atom-transfer or reductive cyclisation reactions are limited to iodoalkynes.



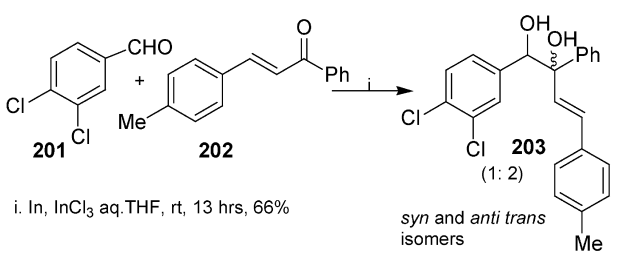
Scheme 61.



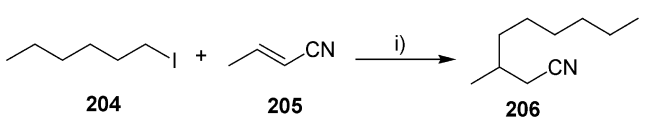
Scheme 62.



Scheme 63.

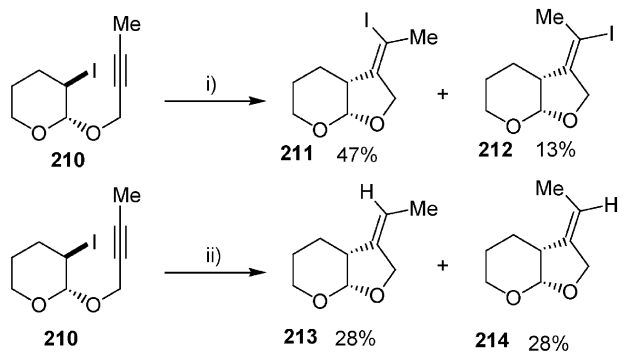


Scheme 64.



Scheme 65.

A simple and general method for the synthesis of tetrahydroquinoline derivatives via a novel domino reaction of aromatic nitro compounds and cyclic enol ethers (2,3-dihydrofurans) mediated and catalysed by indium in water has been reported very recently (Scheme 68).[77]

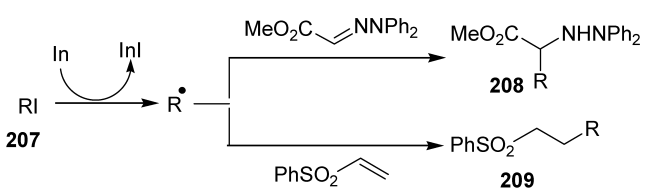


Scheme 67.

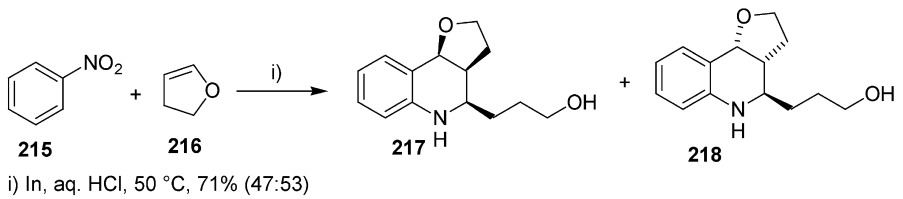
Indium-catalysed aromatic Friedel–Crafts allylation in the presence of $CaCO_3$ and 4 Å molecular sieves results in the formation of the corresponding allylated products in high yields (Scheme 69).[78] The high yields of the reaction in an open vessel, using a catalytic amount of indium which is re-usable after the work up without loss of activity, and the simplicity of the reaction procedure offer advantages over the existing allylation methods. The reactions occur regiospecifically at the α-position of the allyl group and it is therefore assumed that an allylic indium sesquihalide is not involved and that the indium just acts as a Lewis acid catalyst.

Indium mediates a Barbier-type reaction between alkynyl halides and aldehydes or ketones to give the secondary or tertiary propargyl alcohols (Scheme 70).[79] The highest yields were obtained in dichloromethane at reflux, but a mixture of the alcohol and ketone was obtained. It was assumed that the ketone came from the Oppenauer oxidation of the transient indium alkoxide, with the subsequent reduction of benzaldehyde to benzyl alcohol. An increase in the molar amount of benzaldehyde enhanced the Oppenauer oxidation, whereas an excess of the phenylalkynyl iodide prevented the oxidation.

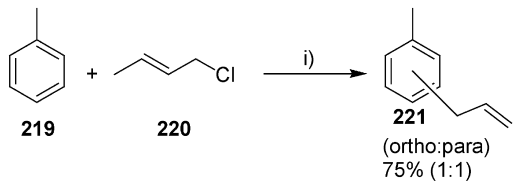
Indium can efficiently mediate the reaction between some β-aminovinyl chlorodifluoromethyl ketones and a series of



Scheme 66.



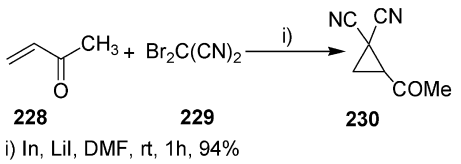
Scheme 68.



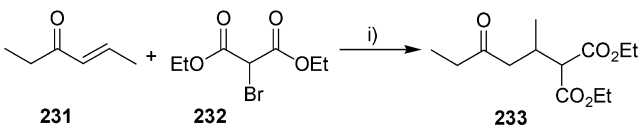
Scheme 69.

heteroaryl aldehydes, to afford the corresponding difluoromethylene compounds in good to high yields (Scheme 71).[80] It is assumed that indium species (In, In^{+} and/or In^{2+}) may act as an electron-transfer reagent to generate a reactive difluorinated enolate. This mild approach seems to be tolerant to a range of substituents and their position on the aromatic ring; this is in sharp contrast to the electrochemical approach, which was only successful with a substituent at the *para* position of the aromatic ring.

Cyclopropanation of electron-deficient alkenes can be accomplished in DMF under mild conditions using methylene dibromide in the presence of indium metal and lithium(I) iodide (Scheme 72).[81] Without the latter salt, the yields are lower and no reaction takes place in ethereal solvents. While electron-deficient alkenes give moderate to good yields of the products, reactions with non-activated and electron-rich alkenes such as cyclohexene and butyl vinyl ether are unsuccessful. The Wideqvist-type synthesis of cyclopropanes from carbonyl compounds can also be achieved using indium.[81]



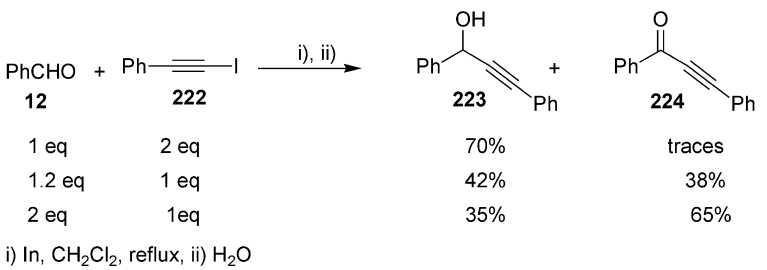
Scheme 72.



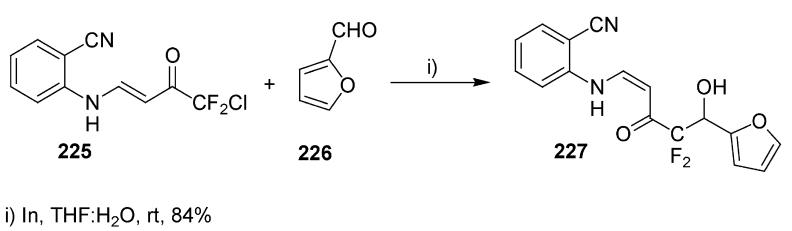
Scheme 73.

Organoindium reagents derived from indium and diethyl bromomalonates were added to a wide range of conjugated enones in a 1,4-fashion in the presence of TMSCl under mild conditions and the corresponding oxo-1,3-diesters were obtained in good to excellent yields (Scheme 73).[82] This protocol is an appealing alternative to the existing two-step Michael reaction route that requires the generation of the anion of diethyl malonate.

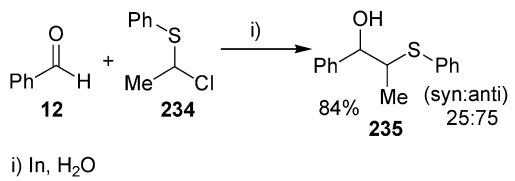
The α-chloro sulfides are used to control the stereoselectivity in indium-promoted C–C couplings at room temperature under aqueous and mixed aqueous/organic



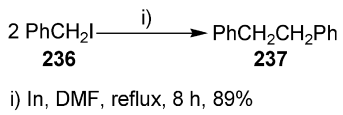
Scheme 70.



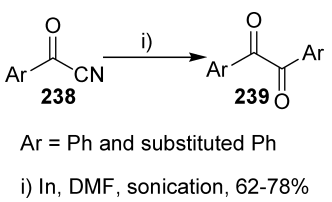
Scheme 71.



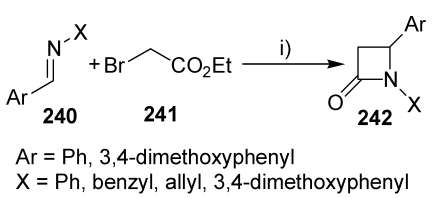
Scheme 74.



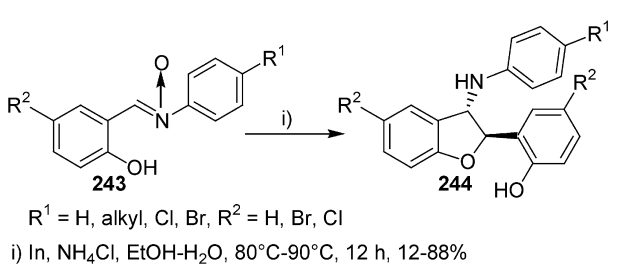
Scheme 75.



Scheme 76.



Scheme 77.



Scheme 78.

conditions. The highest yields were obtained in water or in 50:50 mixtures of water and DMF (Scheme 74).[83]

Reductive homocoupling of alkyl and aryl halides in the presence of indium in DMF gives the dialkyls and biaryls in good yields (Scheme 75).[84]

The indium-mediated reductive coupling of aromatic acyl cyanides affords the corresponding 1,2-diketones in moderate to good yields under neutral and mild conditions (Scheme 76).[85] It is worthy of note that the reaction does not require the exclusion of oxygen or anhydrous conditions as required by SmI_2 for effecting the same transformation.

The indium-mediated reaction of imines with ethyl bromoacetate offers a simple synthesis of 3-unsubstituted β-lactams (Scheme 77).[86] Interestingly, the imines derived from arylalkylamines, allylamine and *p*-anisidine produced only the β-lactams, whereas the imines derived from aniline produced β-aminoesters along with β-lactams.

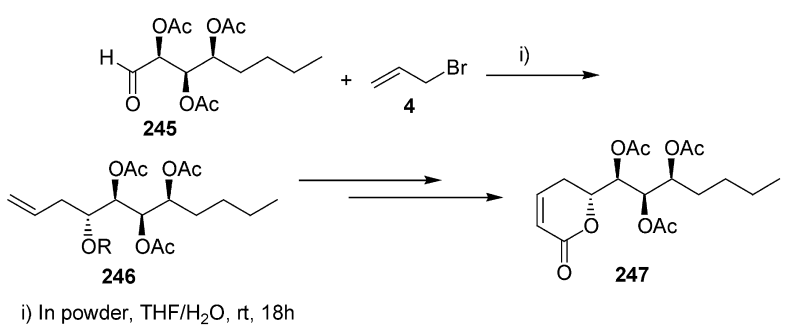
Nitrones undergo deoxygenative reductive coupling and subsequent cyclisation to the 3-arylamino-2,3-dihydrobenzofuran derivatives in the presence of indium under aqueous conditions at ambient temperature (Scheme 78).[87]

3. Application to the synthesis of natural products

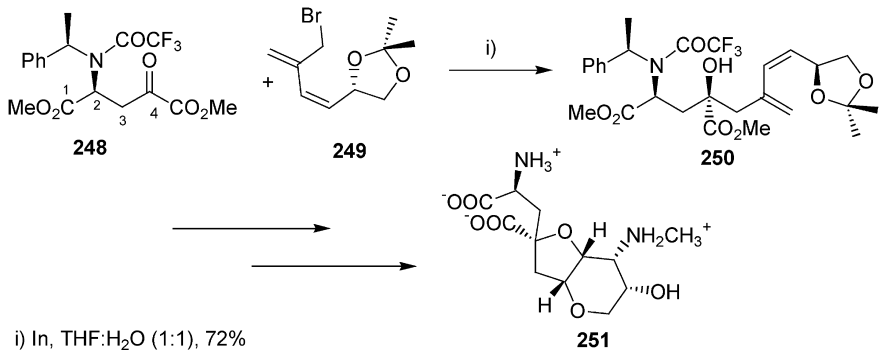
Indium-mediated reactions have found widespread applications in the synthesis of several natural products which are biologically active. This aspect of indium chemistry is briefly described here, with illustrative examples:

The δ-lactone (+)-boronolide **247**, a pharmacologically-active natural product, has been synthesised in an enantiopure form with L-erythulose as the chiral starting material. One of the key steps in this synthesis is the indium-mediated diastereoselective aldehyde allylation (Scheme 79).[88]

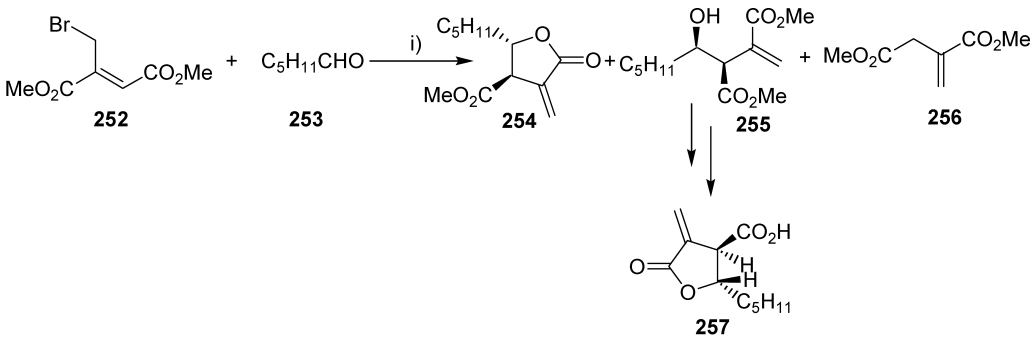
For the total synthesis of dysherbaine **251**, a stereospecific route to the key intermediate based on the indium-mediated allylation reaction in aqueous media has been successfully developed (Scheme 80).[89] A remote phenyl substituent group was used as a control element to achieve a high stereoselectivity of the indium-mediated allylation of the



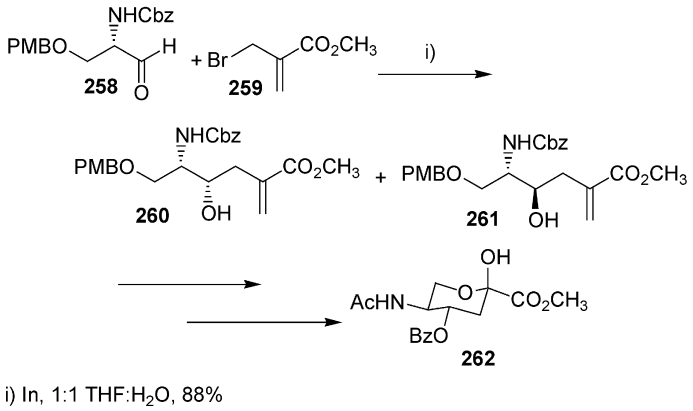
Scheme 79.



Scheme 80.



Scheme 81.



Scheme 82.

ketone ester **248** to set the C-4 quaternary stereocentre in 99% de.

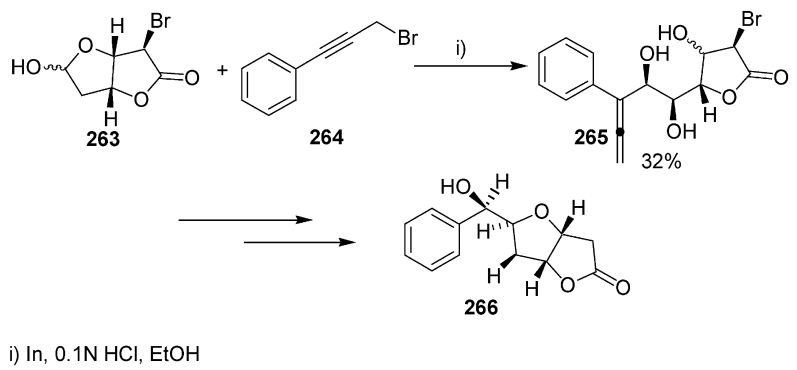
(±)-Methylenolactocin **257**, an antitumour agent, was prepared in five steps in which the indium-mediated allylation reaction forms the key stage (Scheme 81).[90]

In the synthesis of a six-carbon truncated sialic acid, belonging to an important class of monosaccharides, the indium-mediated allyl addition to a serine-derived aldehyde is utilised as a key step (Scheme 82).[91a] Recently, the synthesis of a seven-carbon truncated sialic acid using indium has also been reported.[91b]

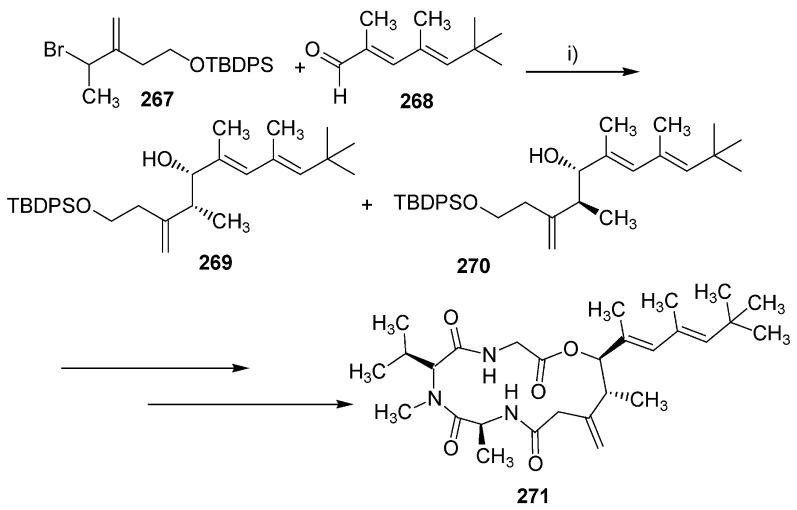
The highly-diastereoselective indium-mediated allenylation of carbonyl compounds bearing an α-hydroxyl group constitutes one of the major steps in the total synthesis of (+)-goniofufurone **266**, a cytotoxic agent (Scheme 83).[92]

Loh et al. have utilised the indium-mediated allylation of aldehydes with a secondary allyl bromide in the presence of $La(OTf)_3$ in aqueous media for delivering a key intermediate in the total synthesis of antillatoxin **271** (Scheme 84).[93] In contrast to the reactions with primary allylic bromides, the indium-mediated allylation of this secondary allylic bromide afforded only the α-adduct.

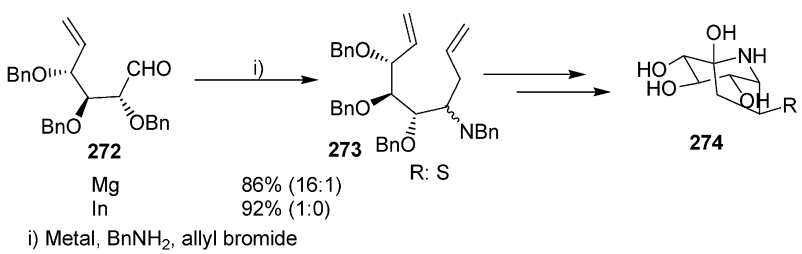
The key step in the total synthesis of calystegine alkaloids employs a zinc-mediated fragmentation of benzyl-protected methyl 6-iodoglycosides, followed by the in situ formation of the benzylimine and Barbier-type allylation with zinc,



Scheme 83.



Scheme 84.



Scheme 85.

magnesium or indium metal. The stereochemistry in the pivotal allylation is controlled by the choice of the metal. When the imine from the glucose- and galactose-derived enal was reacted under Barbier conditions using magnesium, a poor diastereoselectivity was observed, but, when indium was used, the required R isomer was formed exclusively. On the other hand, allylation of the imine from the mannose-derived enal using indium gave only the S isomer (Scheme 85).[94]

4. Gallium

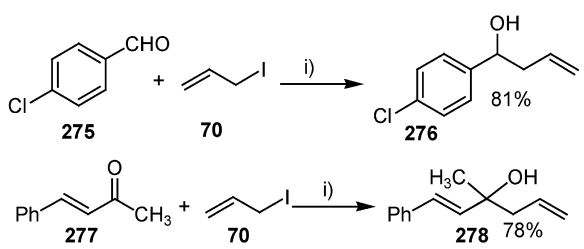
Gallium metal was discovered spectroscopically by the French chemist de Boisbaudran in 1875.[1] The name gallium is coined from the Latin word 'gallio', the former name of France.

The chemical behaviour of gallium is similar to that of aluminium. It is stable towards water, but it reacts vigorously with halogens at low temperature. In contrast to indium, it dissolves in aqueous alkali. It has a very low melting point, but a rather high boiling point and shows the longest liquid range of any element. This makes it a perfect metal to be used in space-based engine controls, where the temperature ranges are great. Gallium easily forms alloys with most metals and has been used to create low-melting alloys. Gallium is used as a doping material for semiconductors and has been used to produce solid-state items such as transistors and light-emitting diodes.

Compared to indium, gallium has not been extensively explored from an organometallic perspective. It is only recently that gallium has been used in allylation and Reformatsky reactions.

4.1. Allylation reactions

The pioneering work by Araki et al. has shown the utility of gallium metal in Barbier-type allylation reactions. The gallium-mediated allylation of aldehydes and ketones with allyl iodide under ultrasonication conditions afforded the homoallylic alcohols (Scheme 86).[95a] Aldehydes gave high yields of the coupling products, whereas the reactivity of ketones was somewhat lower. α,β-Unsaturated compounds underwent exclusive 1,2-addition under these conditions. Allyl bromide was found to be less reactive than allyl iodide. Moreover, the reaction is highly chemoselective; esters, cyanides and acyl chlorides cannot be allylated under the conditions employed. Recently, gallium-mediated allylation has also been reported in an aqueous medium.[95b]



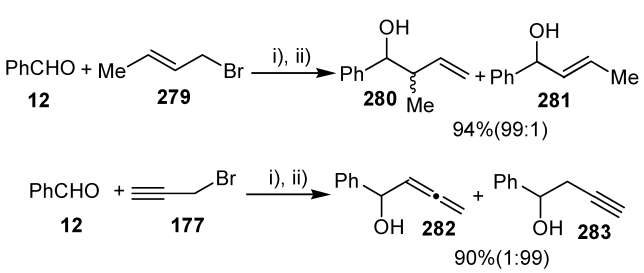
i) Ga, DMF, Ultrasonication, 30 min.

Scheme 86.

Although the nature of the intermediate gallium species in this reaction is not clear, the organogallium sesquiiodide can be considered to be the most likely candidate by analogy with the aluminium- and indium-mediated reactions.

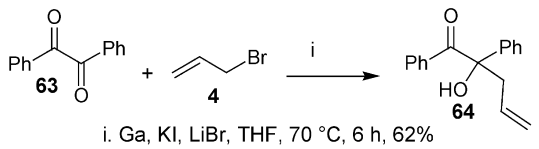
In the presence of potassium iodide, lithium chloride and gallium, aldehydes react with allylic bromides to afford the corresponding α- and γ-adducts (Scheme 87).[96] Interestingly, the reaction shows a very high selectivity towards the γ-adducts. Under the same conditions, the reaction of propargyl bromide with aldehyde exhibits a high acetylenic selectivity.

The gallium-mediated synthesis of α-hydroxy carbonyl compounds in moderate to good yields has been accomplished by the use of the in situ-generated organogallium reagents. For example, benzil, on treatment with allyl bromide and gallium in presence of LiBr and KI in dry THF, furnished 62% of the corresponding α-hydroxy carbonyl compound (Scheme 88).[97]



i) Ga, KI, LiCl, THF, reflux ii) H_2O

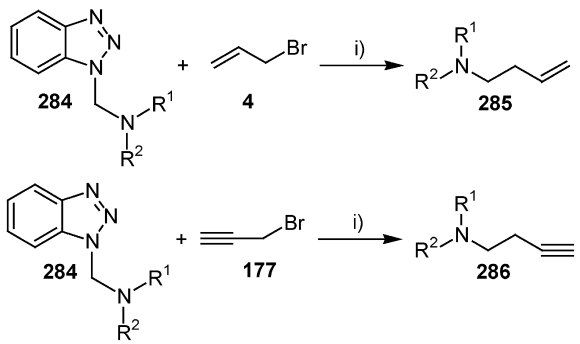
Scheme 87.



i. Ga, KI, LiBr, THF, 70 °C, 6 h, 62%

Scheme 88.

1-(α-Aminoalkyl)benzotriazoles react with allyl and propargyl bromides in the presence of gallium to give the homoallylic and homopropargylic amines in high yields (Scheme 89).[98]



R^1 = aryl, R^2 = CH_3, H

i) Ga, KI, THF, reflux, 72-85%

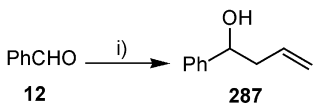
Scheme 89.

Generally, these gallium-mediated Barbier-type allylation reactions in THF require heating at reflux and other methods for the generation of allylgallium species have therefore been developed. These include:

(i) transmetallation of allylmagnesium bromide using gallium trichloride
(ii) transmetallation of allylindium sesquihalides using metallic gallium.

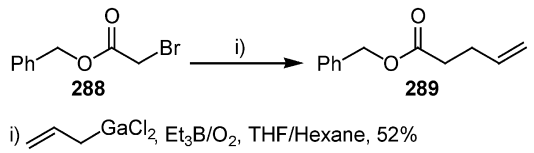
4.1.1. Transmetallation of allylmagnesium bromide using gallium trichloride. The allylic gallium reagents prepared from gallium trichloride and the corresponding allylic Grignard reagent allylated carbonyl compounds in excellent yields in an aqueous medium, as well as in organic solvents (Scheme 90).[99]

Treatment of benzyl bromoacetate with the allylgallium reagent, prepared from allylmagnesium chloride and gallium trichloride in the presence of triethyl borane in THF provided benzyl-4-pentenoate **289** in good yield (Scheme 91).[100] The addition of water as a co-solvent improved the yields of the allylated product. This reaction shows the stability of allylgallium species towards water.



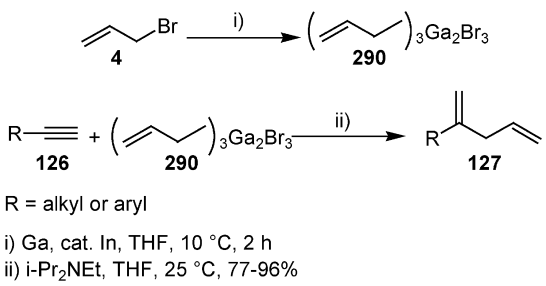
i) $GaCl_2$, THF-Hexane, 0 °C, 30 min., 94%

Scheme 90.



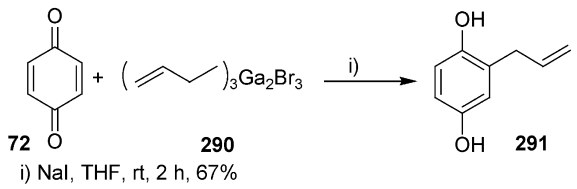
Scheme 91.

4.1.2. Transmetallation of allylindium sesquihalides using metallic gallium. Allylgallium sesquibromide, prepared by the reduction of allyl bromide with gallium metal in the presence of a catalytic amount of indium, adds to terminal alkynes in the presence of a tertiary amine to give the 1,4-dienes (Scheme 92).[101]



Scheme 92.

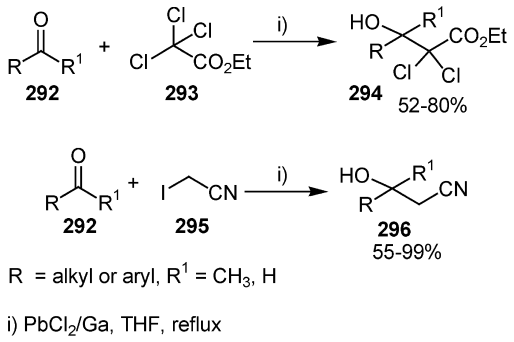
The Grignard-type reaction of 1,4-diones with allylgallium sesquibromide provides a facile and convenient method for the allylation of quinones. Here, the allylgallium sesquihalide is prepared by the reduction of allylic bromides with gallium metal in the presence of a catalytic amount of indium. *p*-Benzoquinone (**72**), for example, was treated with the allylgallium reagent in the presence of sodium iodide in THF to furnish the corresponding 2-allylhydroquinone (**291**) in 67% yield (Scheme 93).[102]



Scheme 93.

4.2. Reformatsky reaction

Gallium metal also mediates the Reformatsky reaction in a bimetallic redox system. In the presence of lead dichloride and a gallium redox system, carbonyl compounds react with ethyl trichloroacetate and iodoacetonitrile to afford the ethyl β-substituted α,α-dichloropropionates and the β-hydroxynitriles, respectively, in moderate to excellent yields (Scheme 94).[103]



Scheme 94.

5. Conclusions and future prospects

This review covers all of the important carbon–carbon bond-forming reactions mediated by indium and gallium. The literature precedents show that the synthetic utility of indium in organic reactions has been explored to a great extent. The higher chemo-, regio- and stereoselectivities shown by the allylindium reagents when compared to the allyl Grignard reagents make them useful alternatives in allylation reactions, especially in targeted syntheses. This domain, however, offers opportunities for further exploration with intriguing possibilities. Compared to indium, the gallium-mediated reactions remain largely under-investigated. It is likely that explorations in the area of gallium-mediated reactions may uncover novel reactivity patterns.

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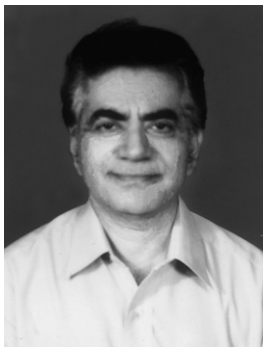
Biographical sketch



Vijay Nair has PhD degrees from the Banaras Hindu University (1967, with Professor R. H. Sahasrabudhey) and the University of British Columbia (1969, with Jim Kutney). Subsequently he was a postdoctoral fellow with Josef Fried at the University of Chicago, Peter Yates in Toronto and with Gilbert Stork at Columbia University. After a 16-year career (Senior Research Chemist and Principal Scientist; outstanding scientist award, 1981) with Lederle Laboratories (American Cyanamid Company) in Pearl River, New York, he returned to his native Kerala State in India, joined the Regional Research Laboratory (CSIR) in 1990 as its Deputy Director, and established an Organic Synthesis Division there. During 1997–2001, he was the Director of the Institute. Presently, he is continuing as a Director-Grade Scientist. In addition, he is an Honorary Professor in the Department of Environmental Sciences, Cochin University of Science and Technology. Dr. Nair's research interests are in the areas of oxidative electron transfer mediated C–C and C–Heteroatom bond forming reactions, multicomponent reactions, heterocyclic synthesis via dipolar cycloadditions, and medicinal chemistry. Dr. Nair has lectured in a number of Universities in Germany in 1998 under the INSA-DFG exchange fellowship. He has been an Invited Speaker at the 17th ICHC in Vienna in 1999, MCR 2000, International Symposium in Munich, the 15th International Conference on Organic Synthesis (ICOS) in Nagoya, Japan in 2004. He was a Visiting Professor at the University of Pernambuco in Brazil in May 2001. He is a Fellow of the Indian Academy of Sciences.

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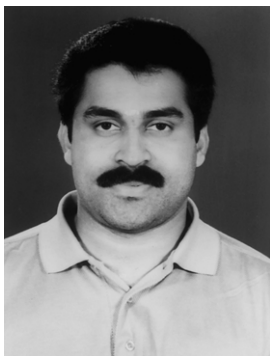

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The first total synthesis and determination of the absolute configuration of chapecoderin A, B and C

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Abstract—The *seco*- and rearranged-labdanes, chapecoderins A **1**, B **2**, and C **3** have been synthesized for the first time starting from (*S*)-(+)-Wieland-Miescher ketone analogue **11**. Their absolute configurations have been determined as depicted in the structures **1**, **2** and **3**.

1. Introduction

Brazilian plants are known to be a rich source of biologically active natural products. In their search for new pharmaceutical agents, Kobayashi and coworkers[1] isolated a new *seco*-labdane type diterpenoid, chapecoderin A **1**, and two new rearranged labdane type diterpenoids, chapecoderin B **2** and C **3** from the leaves of the Brazilian medicinal plant *Echinodorus macrophyllus* (Kunth) Micheli (Alismataceae) which have been used to treat difficulties in urination, hepatitis and rheumatism (Fig. 1). Chapecoderins B **2** and C **3** exhibit cytotoxicity against murine lymphoma L1210 cells with IC_{50} values of 7.2 and 6.0 μg/mL, respectively, while no significant bioactivity was observed in chapecoderin A **1**.

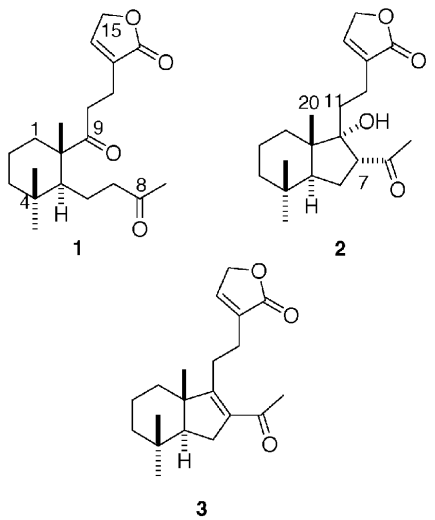

Figure 1.

Their structures were elucidated based on modern NMR techniques and relative stereochemistries were assigned by extensive NOESY correlations unambiguously by Kobayashi et al.[1] Chapecoderins A **1**, B **2** and C **3** possess a characteristic α,β-unsaturated butenolide moiety in the side chain in common. Biosynthetically, chapecoderin C **3** may be derived through dehydration of chapecoderin B **2** which in turn was formed from chapecoderin A **1** through intramolecular aldol condensation. However, their absolute stereochemistries are yet to be clarified. Potential bioactivity and new *seco*- and rearranged-labdane structures as well as our recent interests towards a synthetic study of *seco*-norsesquiterpenoids[2] **4** and **5** (Fig. 2) prompted us to investigate the total synthesis of chapecoderins A **1**,[3] B **2** and C **3**.

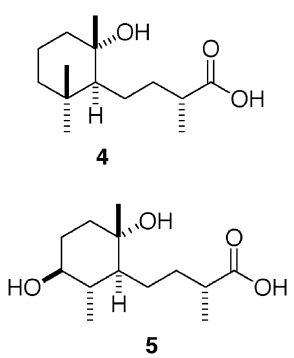

Figure 2.

Keywords: Total synthesis; Labdane diterpenoid; Absolute stereochemistry.
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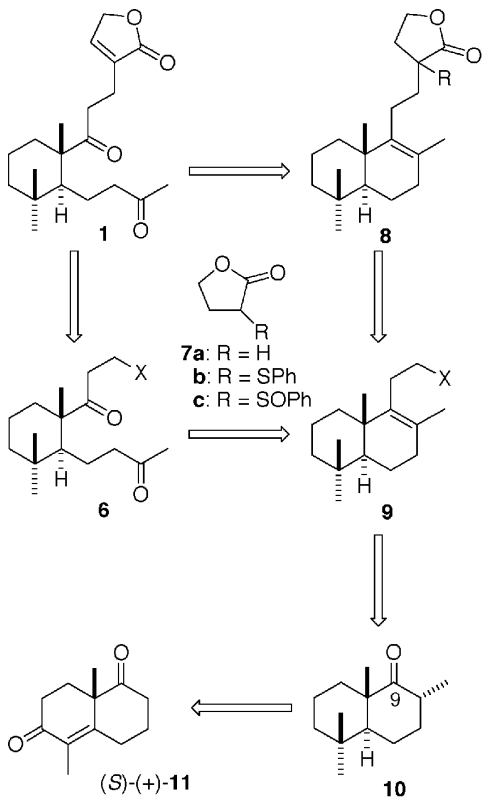


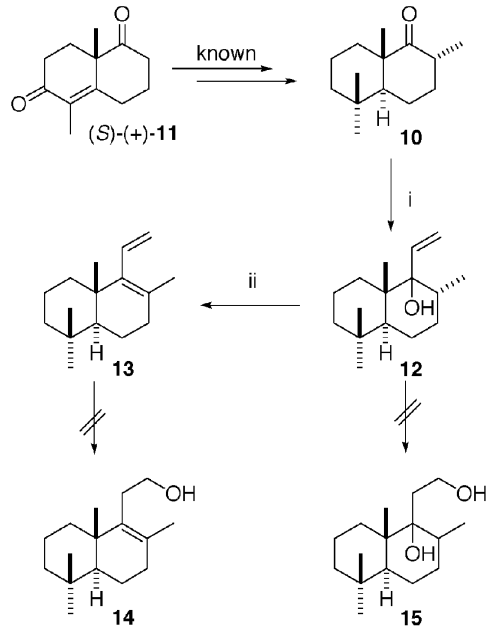
Scheme 1.

Our synthetic design is outlined in Scheme 1. Since enantioselective construction of a substituted cyclohexane ring is not facile due to its conformational flexibility, a route by cleavage of a properly substituted decaline framework was designed. The butenolide ring might be introduced by nucleophilic reaction of γ-butyrolactone derivatives **7** with electrophiles **6** which would be obtained by cleavage of tetrasubstituted olefin **9**. The olefin **9** in turn would be synthesized from the known decalone **10**[2b,4] which has been derived from optically pure Wieland-Miescher ketone analogue **11**.[5] One of the major issues of the present synthetic design is the timing of introduction of the butenolide ring and cleavage of the tetrasubstituted olefin. There are several plausible routes to install the butenolide moiety to the decaline framework by (1) alkylation of α-phenylthio-γ-butyrolactone **7b**, (2) aldol condensation of γ-butyrolactone **7a**, or (3) 1,4-conjugate addition of α-phenylsulfinyl-γ-butyrolactone **7c**.

2. Results and discussion

(*S*)-(+)-Wieland-Miescher ketone analogue **11** was employed as a starting material though there was no knowledge on the absolute stereochemistries of chapecoderins A **1**, B **2** and C **3** (Scheme 2). According to our previously reported procedure,[2b] (*S*)-(+)-Wieland-Miescher ketone analogue **11**[5] was transformed into the decalone **10**.

Initially, introduction of a two carbon unit at C-9 and subsequent manipulation were investigated. Addition of vinylmagnesium bromide to the ketone **10** gave in 90% yield a diastereomeric mixture of alcohol **12** (5.7:1) which



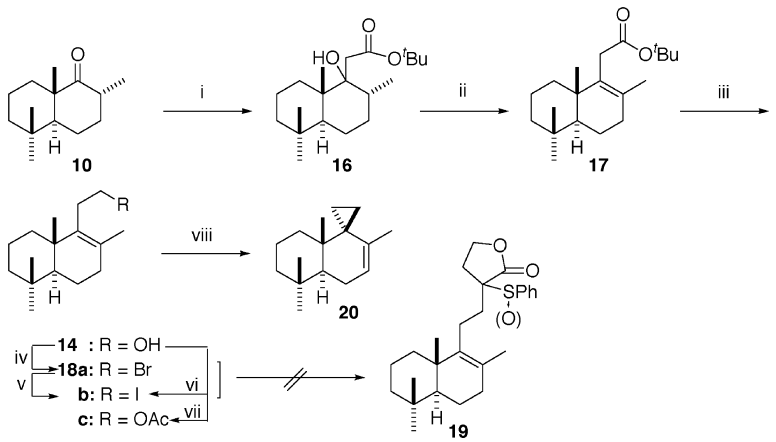
Scheme 2. Reagents, conditions and yields: (i) vinylmagnesium bromide, THF, room temperature, 90%; (ii) $SOCl_2$, DMAP, pyridine, 0 °C, 68%.

was dehydrated with thionyl chloride ($SOCl_2$) to diene **13**[4] in 68% yield. Attempts of selective hydroxylation of the terminal olefin of **12** or **13** resulted in recovery of the starting materials by using bulky reagents such as diisoamylborane or 9-borabicyclo[3.3.1]nonane, while hydroboration by borane-THF complex provided a small amount of the desired primary alcohol **14**.

As an alternative two-carbon addend, reaction of the enolate of *tert*-butyl acetate was investigated in the presence of HMPA to give ester **16** as a mixture of diastereomers (Scheme 3) in 89% yield. Subsequent dehydration by $SOCl_2$ gave unsaturated ester **17** in 97% yield. Reduction of the ester **17** with lithium aluminum hydride (LAH) provided primary alcohol **14** quantitatively. Bromination of the alcohol **14** with carbon tetrabromide and triphenylphosphine (PPh_3) gave in 94% yield bromide **18a** which was further elaborated into iodide **18b** in 96% yield. Since the substitution reaction of the bromide **18a** with sodium iodide required several repeated reactions for complete conversion into iodide **18b**, direct iodination of the alcohol **14** was investigated. Cerium chloride mediated iodination[6] provided the iodide **18b** in 70% yield. Interestingly, an attempt to prepare the more reactive trifluoromethanesulfonate derivative of the alcohol **14** afforded predominantly cyclopropane **20** in 98% yield even at −78 °C.

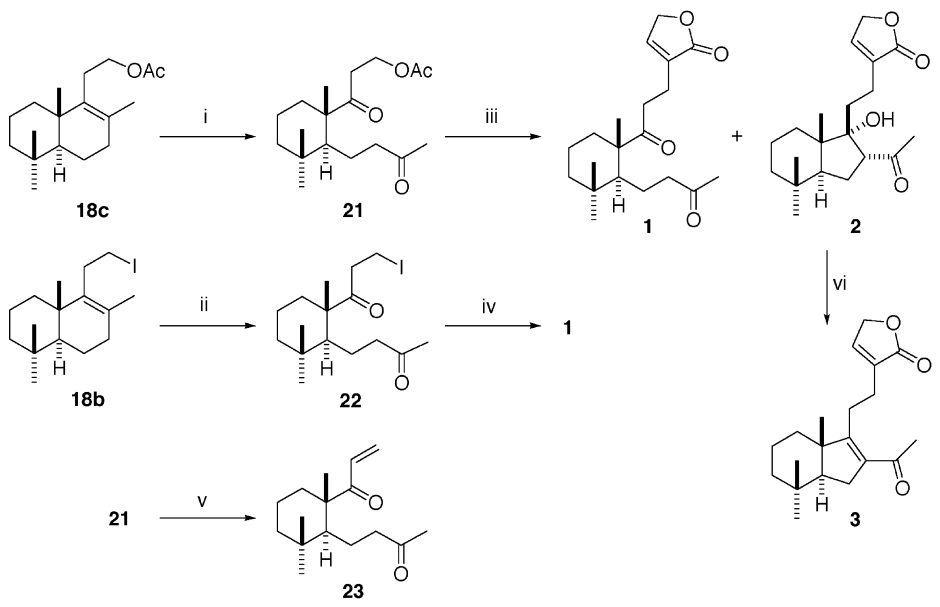
Then, substitution of α-phenylthio- or α-phenylsulfinyl-γ-butyrolactone **7b** or **7c** with the halide **18a** or **18b** were investigated,[7] which resulted in recovery of halides by various combinations of reagents, reaction conditions and substrates. Since the model experiment employing benzyl bromide was successful, the low reactivity of halide **18a** or **18b** might prevent the present reaction.

Although aldol reaction of the aldehyde derived from alcohol **14** with the enolate of lactone **7a** proceeded smoothly, subsequent transformations were unsatisfactory.



Scheme 3. Reagents, conditions and yields: (i) LDA, HMPA, CH_3CO_2t-Bu, −78 °C, 89%; (ii) $SOCl_2$, DMAP, pyridine, room temperature, 97%; (iii) LAH, Et_2O, room temperature, quant; (iv) CBr_4, PPh_3, $CHCl_3$, room temperature, 94%; (v) NaI, acetone, reflux, repeated 3 times, 96%; (vi) NaI, $CeCl_3{\cdot}7H_2O$, CH_3CN, 70%; (vii) acetic anhydride, DMAP, pyridine, room temperature, 88%; (viii) Tf_2O, pyridine, CH_2Cl_2, −78 °C, 98%.

To this end, the order and method of introduction of the butenolide moiety were exchanged (Scheme 4). Ozonolysis of the iodide **18b** provided diketone **22** in 41% yield. While the acetate **18c**, obtained by acetylation of the alcohol **14** in 88% yield (Scheme 3), was also cleaved by ozonolysis in 52% yield in dichloromethane (DCM). The yield was soon improved to 75% by carrying out the reaction in methanol at −20 °C in 0.01 M concentration. The higher yield in dilute solution may be due to preventative formation of polymeric peroxides during the bond reorganization from molozonide to ozonide. Such polymeric peroxides are difficult to decompose to carbonyl compounds. Methanol plays a role in stabilizing intermediates by adding to intermediary zwitter ions.[8] Treatment of the acetoxy diketone **21** and the α-phenylsulfinyl-γ-butyrolactone **7c** with DBU in benzene at room temperature followed by gradual warming to 60 °C furnished chapecoderin A **1** in 39% yield accompanied by 18% of chapecoderin B **2**. The reaction proceeded via three consecutive processes; β-elimination of acetic acid to vinylketone **23** followed by conjugate addition of the α-phenylsulfinyl-γ-lactone **7c** and subsequent elimination of phenylsulfinic acid to chapecoderin A **1**. No other stereoisomers of chapecoderin B **2** were found, which indicates intramolecular aldol condensation proceeded in the desired manner to afford the thermodynamically stable isomer. Vinylketone **23** was actually isolated by treatment of the acetoxy diketone **21** with DBU in 80% yield. The diketo-iodide **22** also provided chapecoderin A **1** in 19% yield by the treatment with α-phenylsulfinyl-γ-lactone **7c** in the presence of potassium carbonate and tetrabutylammonium iodide in DME. Base catalyzed intramolecular aldol condensation of chapecoderin A **1** was difficult due to the instability of the butenolide moiety. Dehydration of chapecoderin B **2** by $SOCl_2$ in the presence of DMAP in pyridine afforded chapecoderin C **3** in 52% yield. Alternatively, treatment of chapecoderin A **1** with pyrrolidine/benzoic acid provided chapecoderin C **3** in 24% yield.



Scheme 4. Reagents, conditons and yields: (i) O_3/O_2, CH_3OH, −20 °C, Me_2S, 75%; (ii) O_3/O_2, DCM, Me_2S, −78°C, 41%; (iii) **7c**, DBU, benzene, room temperature→60 °C, **1**, 39%, **2**, 18%; (iv) **7c**, K_2CO_3, n-Bu_4NI, DME, 0→98 °C, 19%; (v) DBU, benezene, 80%; (vi) $SOCl_2$, pyridine, DMAP, 52%.

Spectral data of the synthetic compounds were identical with those of natural chapecoderin A **1**, B **2** and C **3** kindly supplied by Professors Kobayashi and Shigemori. Since the values and signs of optical rotation of the synthetic compounds were the same as natural compounds, the absolute stereostructures of chapecoderins A **1**, B **2** and C **3** were unambiguously determined as depicted in the structures **1**, **2** and **3**.

Thus, we have completed the first total synthesis of chapecoderin A **1** in 23% overall yield in 8 steps from the known ketone **10**, as well as the total syntheses of chapecoderins B **2** and C **3**, thereby establishing absolute stereochemistries of these natural products.

3. Experimental

3.1. General

Mp was determined with a Yanaco MP hot-stage apparatus and is uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer in carbon tetrachloride unless otherwise indicated. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. *J*-values are in Hz. ^{13}C NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (50 MHz), JEOL EX-270 (67.5 MHz) and Unity 500plus (125 MHz) instruments. Mass spectral data were obtained with a JEOL GC-Mate spectrometer. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for solutions in methanol unless otherwise indicated.

3.1.1. (1*S*,2*RS*,3*R*,6*S*)-1,3,7,7-Tetramethyl-2-vinylbicyclo[4.4.0]decan-2-ol (12).[4] To a stirred solution of the decalone **10** (59 mg, 0.28 mmol) in THF (2.8 mL) was added a solution of vinylmagnesium bromide (590 μL, 0.98 M in THF, 0.56 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 90 min at room temperature, the reaction was quenched by addition of aq. ammonium chloride. Products were extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:10) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:6) provided allyl alcohol **12** (major less polar diastereomer; 51 mg, 76%, minor more polar diastereomer, 9 mg, 13%) as a colorless oil.

More polar diastereomer had $[\alpha]_D^{20}$ −4.82 (*c* 0.39); IR 3625, 2944, 1736, 1460 cm^{-1}; ^{1}H NMR δ (200 MHz) 0.73 (d, 3H, *J*=6.6 Hz), 0.86 (s, 3H), 0.87 (s, 3H), 1.08 (s, 3H), 0.95–1.78 (m, 11H), 1.90 (m, 1H), 5.22 (dd, 1H, *J*=7.3, 1.9 Hz), 5.29 (m, 1H), 6.23 (dd, 1H, *J*=16.5, 11.7 Hz); ^{13}C NMR (67.5 MHz) δ 14.7, 15.9, 18.7, 21.8, 22.0, 31.9, 32.8, 33.4, 33.9, 35.9, 42.0, 42.4, 48.5, 80.8, 115.2, 138.3.

Less polar diastereomer had $[\alpha]_D^{20}$ −5.62 (*c* 1.10); IR 3617, 2946, 1709, 1462 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.72 (d, 3H, *J*=6.7 Hz), 0.84 (s, 3H), 0.88 (s, 3H), 0.98 (s, 3H), 1.10–1.80 (m, 11H), 1.90 (m, 1H), 5.12 (dd, 1H, *J*=4.7, 1.8 Hz), 5.19 (dd, 1H, *J*=2.9, 1.8 Hz), 5.83 (dd, 1H, *J*=17.9, 10.3 Hz); ^{13}C NMR (67.5 MHz) δ 16.2, 17.0, 18.6, 21.7, 22.1, 30.9, 32.4, 33.4, 33.8, 34.1, 41.6, 41.9, 45.5, 79.4, 113.7, 141.9. Anal. calcd for $C_{16}H_{28}O$: C, 81.3; H, 11.9. Found: C, 81.1; H, 11.9.

3.1.2. (1*S*,6*S*)-1,3,7,7-Tetramethyl-2-vinylbicyclo[4.4.0]-dec-2-ene (13).[4] To a stirred solution of the alcohol **12** (39 mg, 0.16 mmol) in pyridine (1.6 mL) was added 4-dimethylaminopyridine (DMAP) (6 mg, 0.049 mmol) and thionyl chloride ($SOCl_2$) (8 μL, 0.25 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 2.5 h, the reaction was quenched by addition of water. Product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:20) gave diene **13** (28 mg, 68%) as a colorless oil; $[\alpha]_D^{20}$ +66.2 (*c* 1.02); IR 3079, 2944, 918 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.84 (s, 3H), 0.88 (s, 3H), 1.00 (s, 3H), 1.05–1.80 (m, 9H), 1.56 (s, 3H), 2.06 (m, 2H), 4.89 (dd, 1H, *J*=17.5, 2.8 Hz) 5.22 (dd, 1H, *J*=11.1, 2.8 Hz), 6.12 (dd, 1H, *J*=17.5, 11.1 Hz); ^{13}C NMR (67.5 MHz) δ 19.0, 19.1, 20.1, 21.2, 21.7, 33.3, 33.4, 33.6, 37.7, 38.2, 41.9, 51.3, 118.2, 126.7, 135.1, 141.9; exact mass calcd for $C_{16}H_{26}$, 218.2035, found 218.2032.

3.1.3. *tert*-Butyl 2-((1*S*,2*RS*,3*R*,6*S*)-2-hydroxy-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-yl)acetate (16). To a stirred solution of LDA prepared from diisopropylamine (305 μL, 2.3 mmol) and *n*-BuLi (1.4 mL, 2.3 mmol, 1.64 M in *n*-hexane) in THF (5 mL) at 0 °C was added a solution of *tert*-butyl acetate (338 μL, 2.5 mmol) in THF (0.5 mL) at −78 °C under nitrogen atmosphere. After being stirred for 20 min, a solution of HMPA (209 μL, 1.2 mmol) in THF (0.5 mL) was added and the resulting solution was stirred for 10 min. To the solution was added the decalone **10** (211 mg, 1.0 mmol) in THF (4 mL). After being stirred for 3 h, the reaction was quenched by addition of aq. ammonium chloride. Product was extracted with ethyl acetate three times and the combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:5) and subsequent MPLC purification (eluent: ethyl acetate–*n*-hexane=1:10) provided hydroxy-ester **16** as a mixture of diastereomers (293 mg, 89%) as a colorless oil.

More polar diastereomer had IR 3459, 2980, 2899, 1705, 1462, 1370, 1152 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.84 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 0.91 (d, 3H, *J*=3.2 Hz), 1.46 (s, 9H), 0.90–2.05 (m, 12H), 2.36 (d, 1H, *J*=16.1 Hz), 2.58 (d, 1H, *J*=16.1 Hz), 5.05 (s, 1H).

Less polar diastereomer had $[\alpha]_D^{20}$ +13.2 (*c* 1.00); IR 3459, 2980, 2870, 1705, 1462, 1370, 1154 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.81 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 0.88 (d, 3H, *J*=2.0 Hz), 1.45 (s, 9H), 0.80–1.80 (m, 12H), 2.21 (d, 1H, *J*=15.9 Hz), 2.49 (d, 1H, *J*=15.9 Hz), 4.89 (s, 1H); ^{13}C NMR (50 MHz) δ 15.9 (q), 16.7 (q), 18.8 (t), 21.6 (t), 21.9 (q), 27.9 (q), 31.2 (t), 32.5 (t), 33.1 (s), 33.6 (q), 36.7 (t), 41.4 (t), 43.1 (s), 44.7 (d), 77.0 (d), 81.5 (s), 174.9 (s).

Anal. calcd for $C_{20}H_{30}O_3$: C, 74.0; H, 11.2. Found: C, 74.3; H, 11.3.

3.1.4. *tert*-Butyl 2-((1*S*,6*S*)-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-en-2-yl)acetate (17). To a stirred solution of the hydroxy-ester **16** (293 mg) in pyridine (9 mL) was added DMAP (33 mg, 0.27 mmol) and $SOCl_2$ (198 μL, 2.7 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 3 h at room temperature, the reaction was quenched by addition of water. Product was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:5) and subsequent MPLC purification (eluent: ethyl acetate–*n*-hexane=1:10) afforded unsaturated ester **17** (269 mg, 97%) as a colorless oil; $[\alpha]_D^{20}$ +72.6 (*c* 1.00); IR 2967, 1734, 1368, 1150 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.43 (s, 9H), 1.57 (s, 3H), 0.80–2.30 (m, 11H), 2.87 (d, 1H, *J*=16.1 Hz), 3.05 (d, 1H, *J*=16.1 Hz); ^{13}C NMR (125 MHz) δ 18.96 (t), 19.7 (q), 20.1 (q), 21.6 (q), 28.0 (q), 33.2 (q), 33.3 (s), 33.6 (t), 36.2 (t), 36.3 (t), 38.5 (t), 41.5 (t), 51.4 (d), 79.9 (s), 129.7 (s), 134.3 (s), 172.2 (s); MS (EI) *m/z* 306 (M^+, 12), 250 (78), 235 (64), 191 (86), 175 (30), 139 (28), 109 (37), 57 (100); exact mass calcd for $C_{20}H_{34}O_2$, 306.2559, found 306.2564.

3.1.5. 2-((1*S*,6*S*)-1,3,7,7-Tetramethylbicyclo[4.4.0]dec-2-en-2-yl)ethan-1-ol (14). To a stirred solution of the unsaturated ester **17** (26 mg, 0.083 mmol) in diethyl ether (1.0 mL) was added LAH (6 mg, 0.16 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 3 h at room temperature, the reaction was quenched by addition of wet diethyl ether. Organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (eleunt: ethyl acetate–*n*-hexane=1:1) followed by MPLC purification (eluent: ethyl acetate–*n*-hexane=1:1) to give alcohol **14** (21 mg, quant.) as a colorless oil; $[\alpha]_D^{20}$ −41.81 (*c* 1.00); IR 3636, 2943, 1368, 1072 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.60–2.10 (m, 11H), 1.61 (s, 3H), 2.30 (m, 2H), 3.60 (t, 2H, *J*=7.5 Hz); ^{13}C NMR (50 MHz) δ 18.95 (t),18.96 (t) 19.9 (q), 20.0 (q), 21.6 (q), 31.4 (q), 33.3 (q), 33.3 (s), 33.6 (t), 37.1 (t), 38.6 (s), 41.7 (t), 51.6 (d), 62.6 (t), 128.5 (s), 136.1 (s); exact mass calcd for $C_{16}H_{28}O$, 236.2140, found 236.2146.

3.1.6. (1*S*,6*S*)-2-(2-Bromoethyl)-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-ene (18a). To a stirred solution of the alcohol **14** (83 mg, 0.36 mmol) in chloroform (2.0 mL) was added triphenylphosphine (PPh_3) (189 mg, 0.72 mmol) and carbon tetrabromide (CBr_4) (239 mg, 0.72 mmol) and the solution was stirred for 11 h at room temperature under nitrogen atmosphere. Extra PPh_3 (95 mg, 0.36 mmol) and CBr_4 (120 mg, 0.36 mmol) were added and stirring was continued for 1 h. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate–*n*-hexane=1:20) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:20) provided bromide **18a** (102 mg, 94%) as a colorless oil; $[\alpha]_D^{20}$ +45.5 (*c* 0.91); IR 2930, 1389, 1206 cm^{-1}; ^1H NMR (200 MHz) δ 0.82 (s, 3H), 0.88 (s, 3H), 0.90 (s, 3H), 1.59 (s, 3H), 0.80–2.10 (m, 11H), 2.35–2.72 (m, 2H), 3.20–3.45 (m, 2H); MS (EI) *m/z* 298 (M^+, 6.6), 235 (59), 203 (87), 109 (77), 69 (98), 55 (100); exact mass calcd for $C_{16}H_{27}Br$ 298.1296, found 298.1295.

3.1.7. (1*S*,6*S*)-2-(2-Iodoethyl)-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-ene (18b). *Method 1*. To a stirred solution of the bromide **18a** (86 mg, 0.29 mmol) in acetone (2.8 mL) was added sodium iodide (65 mg, 0.43 mmol) and the solution was heated at reflux for 15 h. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate–*n*-hexane=1:20) gave almost a 1:1 inseparable mixture of the bromide **18a** and iodide **18b**. A solution of the residue and sodium iodide (86 mg, 0.57 mmol) in acetone (5 mL) was refluxed for 14 h. After evaporation of the solvent followed by column chromatography gave a 1:3 mixture of the bromide **18a** and the iodide **18b**. The same procedure was repeated once again to give the iodide **18b** (96 mg, 96%).

Method 2. To a stirred solution of the alcohol **14** (33 mg, 0.14 mmol) in acetonitrile (2.0 mL) was added sodium iodide (25 mg, 0.17 mmol) and cerium chloride heptahydrate (78 mg, 0.21 mmol) under nitrogen atmosphere and the resulting solution was heated at reflux temperature for 10 h. After being cooled to room temperature, the resulting slurry was diluted with ethyl acetate. After addition of 0.5 M HCl (1.5 mL), the organic layer was washed with aq. sodium hydrogen carbonate twice and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:20) provided the iodide **18b** (34 mg, 70%) as a colorless oil; $[\alpha]_D^{20}$ +10.8 (*c* 1.12); IR 2965, 1468, 1165 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.56 (s, 3H), 0.80–2.10 (m, 11H), 2.40–2.70 (m, 2H), 2.97–3.14 (m, 2H); ^{13}C NMR (67.5 MHz) δ 5.3, 19.0, 19.1, 19.9, 20.1, 21.7, 22.7, 31.7, 33.3, 33.4, 33.7, 37.2, 38.7, 41.7, 51.8, 129.0, 140.9; MS (EI) *m/z* 346 (M^+, 27), 203 (99), 191 (98), 107 (100); exact mass calcd for $C_{16}H_{27}I$, 346.1158, found 346.1163.

3.1.8. (1*S*,6*S*)-1,3,7,7-Tetramethylspiro[bicyclo[4.4.0]-decane-2,1′-cyclopropane]-3-ene (20). To a stirred solution of the alcohol **14** (19.5 mg, 0.083 mmol) in anhydrous DCM (1.0 mL) was added anhydrous pyridine (20 μL, 0.25 mmol) and trifluoromethanesulfonic anhydride (208 μL, 0.12 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 2 h at −78 °C, the reaction was quenched by addition of phosphate buffer (pH 7). Product was extracted with *n*-hexane and the organic layer was washed with water, aq. sodium hydrogen carbonate, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography of the residue (eluent: *n*-hexane) provided cyclopropane **20** (18 mg, 98%) as a colorless oil; $[\alpha]_D^{20}$ −88.8 (*c* 1.08); IR 2965, 2849, 1549, 1335, 1389 cm^{-1}; ^1H NMR (200 MHz) δ 0.40–0.55 (m, 2H), 0.64–0.78 (m, 2H), 0.80–1.72 (m, 7H), 0.87 (s, 3H), 0.89 (s, 3H), 0.96 (s, 3H), 1.39 (m, 3H), 1.87–2.21 (m, 2H), 5.45 (m, 1H); ^{13}C NMR (50 MHz) δ 5.5 (t), 8.6 (t), 18.4 (t), 19.0 (q), 19.3 (q), 22.1 (q), 24.3 (t), 32.5 (q), 32.9 (t), 33.1 (s), 33.2 (s), 34.9 (s), 42.5 (t), 47.8 (d), 121.2 (d), 135.1 (s); MS (EI) *m/z* 218 (M^+, 13), 119 (68), 55 (48), 44 (100), 41 (82); exact mass calcd for $C_{16}H_{26}$, 218.2035, found 218.2029.

3.1.9. 4-[(1*S*,6*S*)-6-(3-Iodopropanoyl)-2,2,6-trimethylcyclohexyl]butan-2-one (22). To a stirred solution of the iodide **18b** (68 mg, 0.19 mmol) in DCM (3.0 mL) was passed O_3/O_2 at −78 °C for 2 h. After addition of dimethylsulfide (2.0 mL), the resulting solution was stirred for 1 h at −78 °C and allowed to stand overnight until ambient temperature. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:3) afforded *seco*-iodide **22** (29 mg, 41%) as a colorless oil; $[\alpha]_D^{20}$ +13.50 (*c* 0.51); IR 2932, 1717, 1462, 1356, 1327, 1267, 1165 cm^{-1}; ^1H NMR (200 MHz) δ 0.92 (s, 3H), 0.93 (s, 3H), 1.10–1.79 (m, 9H), 1.22 (s, 3H), 2.10 (s, 3H), 2.32–2.67 (m, 2H), 3.07–3.18 (m, 2H), 3.29 (t, 2H, *J*=6.4 Hz); ^{13}C NMR (67.5 MHz) δ−2.9, 17.1, 18.1, 22.4, 22.6, 30.1, 33.5, 34.4, 37.2, 41.2, 41.6, 45.8, 47.4, 52.9, 208.8, 213.8; MS (EI) *m/z* 378 (M^+, 3.8), 195 (31), 177 (100), 149 (38). exact mass calcd for $C_{16}H_{27}O_2I$, 378.1056, found 378.1060.

3.1.10. 2-((1*S*,6*S*)-1,3,7,7-Tetramethylbicyclo[4.4.0]dec-2-en-2-yl)ethyl acetate (18c). To a solution of the alcohol **14** (28 mg, 0.12 mmol) in dry pyridine (2.0 mL) was added DMAP (1.4 mg, 0.012 mmol) and acetic anhydride (35 μL, 0.35 mmol) under nitrogen atmosphere and the solution was stirred at room temperature for 1 h. The reaction was quenched by addition of water and product was extracted with ethyl acetate twice. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:2) gave acetate **18c** (29 mg, 88%) as a colorless oil; $[\alpha]_D^{20}$ +32.6 (*c* 1.02); IR 2965, 2940, 1742, 1237, 1030 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.94 (s, 3H), 1.62 (s, 3H), 0.95–1.74 (m, 9H), 1.80–2.14 (m, 2H), 2.05 (s, 3H), 2.15–2.48 (m, 2H), 4.00 (t, 2H, *J*=7.9 Hz); ^{13}C NMR (50 MHz) δ 18.9 (t), 19.0 (t), 19.9 (q), 20.0 (q), 21.6 (q), 31.4 (t), 33.3 (q), 33.3 (s), 33.6 (t), 37.1 (t), 38.6 (s), 41.7 (t), 51.6 (d), 62.6 (t), 128.5 (s), 136.1 (s). Anal. calcd for $C_{18}H_{30}O_2$: C, 77.7; H, 10.9. Found: C, 77.5; H, 11.2.

3.1.11. 3-[(1′*S*,2′*S*)-1′,3′,3′-Trimethyl-2′-(3″-oxobutyl)-cyclohexyl]-3-oxopropyl acetate (21). To a solution of the acetate **18c** (26 mg, 0.095 mmol) in anhydrous methanol (10 mL) was passed into O_3/O_2 at −20 °C for 35 min. After flushing the solution with N_2, dimethylsulfide (2.0 mL) was added and the resulting solution was stirred at −20 °C for 2 h. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:2) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=7:8) afforded *seco*-acetate **21** (22 mg, 75%) as a colorless oil; $[\alpha]_D^{20}$ −56.7 (*c* 1.00); IR 2953, 2872, 1745, 1719, 1238 cm^{-1}; ^1H NMR (200 MHz) δ 0.92 (s, 3H), 0.93 (s, 3H), 1.22 (s, 3H), 1.28–1.75 (m, 9H), 2.02 (s, 3H), 2.10 (s, 3H), 2.46 (m, 2H), 2.82 (td, 2H, *J*=6.5, 4.1 Hz), 4.00 (t, 2H, *J*=7.9 Hz); ^{13}C NMR (50 MHz) δ 17.1 (q), 18.6 (t), 20.9 (q), 22.2 (t), 22.5 (q), 29.9 (q), 33.3 (q), 34.3 (s), 36.7 (t), 37.2 (t), 41.0 (t), 45.5 (t), 47.3 (d), 52.9 (s), 59.9 (t), 170.9 (s), 208.9 (s), 213.8 (s). Anal. calcd for $C_{18}H_{30}O_4$: C, 69.6; H, 9.7. Found: C, 69.6; H, 10.0.

3.1.12. Chapecoderin A (1). To a stirred solution of the acetate **21** (54 mg, 0.173 mmol) in benzene (1.7 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (31 μL, 0.208 mmol) and the solution was stirred for 1 h at room temperature under nitrogen atmosphere. To the solution were added γ-lactone **7c** (55 mg, 0.266 mmol) and DBU (39 μL, 0.260 mmol) and the resulting solution was stirred for 1 h. The solution was then heated at 60 °C for 2 h. The reaction was quenched by addition of 1 M HCl and extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:2) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=2:1) furnished chapecoderin A (**1**) (23 mg, 39%) and chapecoderin B (**2**) (10 mg, 18%) as amorphous solids.

Chapecoderin A **1** had $[\alpha]_D^{23}$ +6.0 (*c* 0.86) {lit. $[\alpha]_D^{23}$+5.5 (*c* 0.86)}; IR 2934, 1765, 1717, 1699, 1072 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (s, 3H), 0.92 (s, 3H), 1.16–1.22 (m, 2H), 1.22 (s, 3H), 1.31–1.38 (m, 1H), 1.40–1.43 (m, 1H), 1.46–1.52 (m, 2H), 1.53–1.63 (m, 2H), 1.73 (t, 1H, *J*=4.9 Hz), 2.10 (s, 3H), 2.44 (t, 2H, *J*=8.2 Hz), 2.56 (td, 2H, *J*=7.0, 1.4 Hz), 2.76 (dt, *J*=18.2, 6.9 Hz), 2.87 (dt, *J*=18.2, 7.3 Hz), 4.76 (dd, 2H, *J*=2.0, 1.5 Hz), 7.17 (t, *J*=1.5 Hz); ^{13}C NMR (125 MHz) δ 17.1 (q), 18.1 (t), 20.2 (t), 22.2 (t), 22.5 (q), 29.8 (q), 33.4 (q), 34.3 (q), 34.9 (t), 37.1 (t), 41.1 (t), 45.5 (t), 47.6 (d), 53.5 (s), 70.1 (t), 132.9 (s), 145.7 (d), 174.1 (s), 208.9 (s), 215.2 (s).

Peaks at 30.0 (C-7) and 19.5 (C-20) ppm in original paper[1] were mistyped and should be corrected to 45.8 and 17.3 ppm, respectively, according to private communication from Professor Shigemori.

Chapecodeirn B (**2**) had $[\alpha]_D^{23}$ −11.9 (*c* 0.31) {lit. $[\alpha]_D^{23}$ −4.6 (*c* 0.38)}; ^1H NMR (500 MHz) δ 0.72 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 1.12 (m, 1H), 1.34 (m, 2H), 1.40 (m, 1H), 1.52 (m, 1H), 1.54 (m, 1H), 1.75 (m, 1H), 1.78 (m, 1H), 1.80 (s, 3H), 2.04 (dt, 1H, *J*=5.0, 12.4 Hz), 2.27 (dd, 1H, *J*=8.1, 12.7 Hz), 2.29 (m, 1H), 2.47 (td like), 2.56 (dd, 1H, *J*=5.0, 12.1 Hz), 3.77 (s, 2H), 5.90 (s, 1H); ^{13}C NMR (125 MHz) δ 16.1, 19.8, 21.0, 21.4, 27.1, 31.1, 31.2, 33.2, 33.6, 35.6, 41.5, 49.4, 51.4, 53.7, 69.4, 84.7, 134.4, 143.6, 173.8, 215.5. Inconsistency of value of optical rotations may arise from different purity of synthetic chapecoderin B (**2**).

3.1.13. Chapecoderin C (3). To a stirred solution of chapecoderin B (**2**) (21 mg, 0.06 mmol) and DMAP (2.3 mg, 0.018 mmol) in pyridine (0.6 mL) was added $SOCl_2$ (7 μL, 0.9 mmol) at 0 °C under nitrogen atmosphere and the resulting solution was stirred for 1.5 h at 0 °C. The reaction was quenched by addition of water and extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC (eluent: ethyl acetate–*n*-hexane=2:1) furnished chapecoderin C (**3**) (10 mg, 52%) as an amorphous solid; $[\alpha]_D^{23}$ +11.6 (*c* 1.10) {lit. $[\alpha]_D^{23}$ +5.7 (*c* 1.10)}; ^1H NMR (500 MHz) δ 0.78 (s), 0.87 (s), 0.92 (s), 1.05 (td, *J*=13.1, 3.8 Hz), 1.24 (td, *J*=13.1, 3.8 Hz), 1.34 (dd, *J*=6.6, 11.7 Hz), 1.38 (td, *J*=3.8, 13.1 Hz), 1.48 (m), 1.57 (tq, *J*=3.8, 13.1 Hz), 1.70 (td, *J*=3.8,13.1 Hz), 1.94 (s), 2.10

(dd, J=6.6, 14.0 Hz), 2.15 (dd, J=11.7, 14.0 Hz), 2.36 (dt, J=4.2, 11.5 Hz), 2.50 (m), 2.67 (m), 2.93 (dt, J=5.2, 11.5 Hz), 3.86 (s), 6.37 (s); ^{13}C NMR (125 MHz) δ 16.8, 19.9, 21.4, 25.3, 25.7, 29.6, 30.8, 32.9, 33.0, 34.4, 41.6, 50.1, 57.6, 69.5, 133.9, 135.3, 144.3, 165.9, 173.6, 197.4.

3.1.14. 1-[(1′*S*,2′*S*)-1′,3′,3′-Trimethyl-2′-(3″-oxobutyl)-cyclohexyl]prop-2-en-1-one (23). A solution of diketo-acetate **21** (30 mg, 0.096 mmol) and DBU (22 μL, 0.145 mmol) in benzene (1 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction was quenched by addition of 1 M HCl. Product was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) afforded vinyl-ketone **23** (19 mg, 80%) as a colorless oil which had IR 2938, 1721, 1690, 1609, 1399, 1356, 1161 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.94 (s, 6H), 1.20 (s, 3H), 1.15–1.8 (m, 9H), 2.06 (s, 3H), 2.23–2.58 (m, 2H), 5.67 (dd, 1H, J=10.3, 1.1 Hz), 6.34 (dd, 1H, J=16.9, 1.1 Hz), 6.91 (dd, 1H, J=16.9, 10.3 Hz); ^{13}C NMR (50 MHz) δ 17.0 (q), 18.0 (t), 21.9 (t), 22.5 (q), 29.8 (q), 33.2 (q), 34.4 (s), 35.8 (t), 41.1 (t), 44.9 (t), 47.3 (d), 51.5 (s), 128.5 (t), 131.4 (d), 205.0 (s), 208.9 (s).

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The azaphilic addition of organometallic reagents on tetrazines: scope and limitations☆

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Abstract—A series of tetrazines were reacted with organometallic reagents. Depending on the nature of the metal azaphilic addition, reduction of the tetrazine or simple complex formation was the predominant transformation and usually high selectivity was observed.

1. Introduction

The chemistry of tetrazines has gained increased attention in the last few decades,[1] due mostly to their applications in organic synthesis,[2] crop protection[3,4] and materials science.[5] Their basic structural feature, the electron-deficient heterocyclic core, is the key to their most extensively utilized transformation, the 'inverse electron-demand' Diels–Alder reaction, that provides an attractive route to pyridazines,[6–8] pyrroles,[9] and other condensed[10,11] and strained heterocyclic ring systems.[12] Another characteristic feature of the electron deficient aromatic ring is its reactivity towards nucleophiles that has been utilized in the preparation of non-symmetrically substituted tetrazines through their addition onto the ring[13] or substitution of leaving groups, such as chloro,[14,15] methylthio[16,17] or dimethylpyrazolyl[15,18,19] with nitrogen, oxygen or sulfur nucleophiles. The analogous reactions introducing carbon nucleophiles would also be of synthetic importance, but there are only a few know examples utilizing potassium cyanide[15] or malonates.[20,21] The cross-coupling reactions on tetrazines, also recently reported have only a limited scope.[22]

The use of reactive carbon nucleophiles, such as organolithium or Grignard reagents in an attempt to substitute 3,6-bis(methylthio)tetrazine led to the addition of the organic group onto a ring nitrogen atom.[23] The transformation, coined 'azaphilic addition' is quite unprecedented for other heterocycles, but had been reported previously for 3,6-diphenyltetrazine too.[24–27] A common feature of the published reactions is that they utilize either organolithium or Grignard reagents, and apparently no rationalization has been provided so far for this unusual transformation. To explore the generality of this reaction we decided to react a series of tetrazines with organometallic reagents. In the light of the fact that on the same tetrazine soft carbanions can initiate nucleophilic substitution,[20,21] while hard carbanions give azaphilic addition selectively,[23] we also wanted to explore the territory between this two 'extremes'. We planed to achieve this aim by reacting a series of organometallic reagents containing different metal residues with a tetrazine that is capable of undergoing nucleophilic substitution.

2. Results and discussion

The first tetrazine selected to test the generality of the azaphilic route was 3,6-bis(3′,5′-dimethylpyrazolyl)-tetrazine (**1**). The choice of **1** was based on two facts: the ease and economy of its preparation[28] and its well documented reactivity towards nitrogen and oxygen nucleophiles.[5,14,18,19] The first experiments, including the reaction of butyllithium, phenyllithium and phenylmagnesium chloride (Table 1, entries 1–3) with **1**, led to the formation of 1-butyl-1,4-dihydro-3,6-bis(dimethylpyrazolyl)tetrazine (**6a**) or 1-phenyl-1,4-dihydro-3,6-bis(dimethylpyrazolyl)-tetrazine (**6b**) in good yield, if the reaction mixtures were quenched at −78 °C, supporting the generality of the azaphilic pathway. On prolonged standing of the reaction mixture on air or letting it warm to room temperature, the yield of **6a** decreased considerably, especially when organolithium reagents were used. In entry 1, the formation

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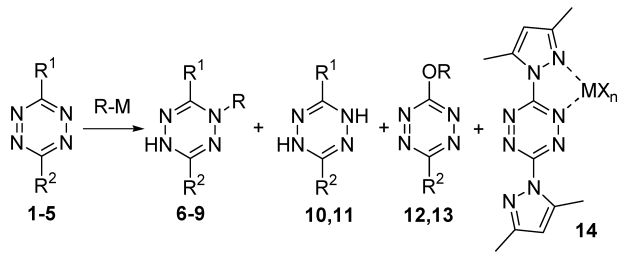
Table 1. Product distribution in the azaphilic addition of tetrazines **1-5** with organometallic reagents



1,6,10,12: R^1=R^2=3,5-dimethyl-pyrazol-1-yl; **2,7,11**: R^1=R^2=3-pyridyl
3,8,13: R^1=3,5-dimethyl-pyrazol-1-yl, R^2=morpholino; **4,9**: R^1=R^2=methyltio
5: R^1=morpholino, R^2=chloro

No.	SM	RM	**6-9**[a] (%)	**10**, **11** (%)	**12**, **13** (%)	**14**[b] (%)
1	**1**	BuLi	70[c]	5		
2	**1**	PhLi	62			
3	**1**	PhMgCl	85			
4	**1**	BuCuLiI[d]	60			40
5	**1**	BuZnBr[d]	85			15
6	**1**	PhZnBr	90			
7	**1**	PhZnBr[d]	45			35
8	**1**	$(C_3H_5)_3In_2Br_3$[e]	60			
9	**1**	$(C_3H_5)_3In_2Br_3$[f]	50[g]	50[g]		
10	**2**	BuLi	13	32		
11	**2**	BuMgI	96			
12	**2**	PhLi	35	25		
13	**2**	PhMgCl	58			
14	**3**	BuLi	13[h]		80	
15	**3**	BuMgI	43[h]		56	
16	**3**	PhLi	85[h]			
17	**3**	PhMgCl	90[h]			
18	**4**	BuLi	90			
19	**4**	PhLi	80			
20	**4**	PhMgCl	94			
21	**5**	PhMgCl	dec.			

[a] Numbers refer to isolated yields unless otherwise stated.
[b] Estimated value based on recovered starting material. Reverts to **1** on acidic workup.
[c] Converts partially to **12** on standing in air.
[d] Prepared by transmetallation form the appropriate lithiumorganic reagent and anhydrous metal halide.
[e] Prepared from In and allyl bromide.
[f] Barbier conditions (In, allyl bromide, THF/aq. NH_4Cl).
[g] Determined by NMR.
[h] Converts partially to **13** on standing in air.

of traces of the reduced starting material (**10**) was also observed.

Extension of the scope of the reaction by using Gilmann or organozinc reagents, prepared by the mixing of one equivalent of copper(I) iodide (entry 4) or zinc bromide (entry 5) with butyllithium prior to the addition to the tetrazine, led also to the formation of **6a**. The use of phenylzinc bromide, prepared through oxidative addition, gave **6b** in excellent yield (entry 6), while the same reagent prepared through transmetallation gave only a moderate yield of **6b** (entry 7). In each reaction, where the reagent was prepared by transmetallation (entries 4,5 and 7), we observed the formation of a salt-like byproduct, schematically represented as **14**, which reverted to **1** on acidic workup. The stability of **14** in the presence of organometallic reagents[29] is exacerbated by the addition of butyllithium to the preformed complex of **1** and CuI at −78 °C leading to marginal conversion to **6a**, which suggests that the coordinating ability of **1** to the organometallic reagent might also play an important role in the course of the azaphilic addition.

The reaction of allylindium reagents (entries 8 and 9) showed a marked dependence on the way the reagent was formed. Allylindium bromide, prepared from allyl bromide and indium in DMF (entry 8), gave good conversion and led only to azaphilic addition (**6c**). In the same reaction, using Barbier-type conditions[30] (entry 9), we also achieved full conversion but the crude product was a 1:1 mixture of the azaphilic adduct **6c** and reduced starting material (**10**) by NMR. We attributed the observed difference to the different mechanisms operating under the applied conditions.

In an attempt to broaden the scope of the azaphilic addition process other selected tetrazine derivatives (**2-5**) were also reacted with organometallic reagents (Table 1, entries 10–21). To our surprise, unlike in the case of **1**, organozinc and Gilmann reagents either failed to react with **2-5** or gave only poor conversion, which means that they are only of limited use from preparative point of view. Organolithium and Grignard reagents on the other hand reacted readily, and even the least reactive tetrazine (**2**) gave full conversion at ambient temperature. Our general observation in these experiments (entries 10–21) is the favored attack of the nucleophile at the ring nitrogen atom (azaphilic addition) although the different tetrazines showed characteristic side reactions too. 3,6-Di(3′-pyridyl)tetrazine (**2**) for example also underwent a competing reduction in the presence of organolithium reagents (entries 10 and 12, cf. with entry 1), while the analogous organomagnesium reagents gave only azaphilic addition. Another feature of **2** is the observation that this compound was the least reactive of the tetrazines examined. Complete conversion of **2** to **7a** or **7b** required warming of the reaction mixtures to ambient temperature.

The addition of the organometallic reagents onto 3-(3′,5′-dimethylpyrazol-1′-yl)-6-morpholino-tetrazine (**3**) had two interesting aspects (entries 14–17). The reaction proceeded regioselectively, as established by NOE experiments, and only the formation of adducts bearing the incoming nucleophile on a nitrogen atom next to the pyrazole moiety was observed. We attribute the selectivity of the addition to the coordinating ability of the pyrazole moiety which might anchor the organometallic reagent in the proximity of the site of observed attack. The intermediates and products formed in the reaction underwent a so far unprecedented transformation in the presence of oxygen. Their solution, when contacted with air, turned red and the formation of the appropriate butoxy- (**13a**) or phenoxy-morpholino-tetrazine (**13b**) was observed. The oxidative transformation proceeded the fastest when the reaction mixture containing **3** and an organolithium reagent was contacted with air and was the slowest in case of the oxidation of solutions of purified **8a** or **8b**. Although we have no sound mechanistic proposal for this oxidative transformation the above findings suggest that the opening step of the process is the electrophilic attack of oxygen on the tetrazine ring.

The reactions of 3,6-bis(methylthio)-tetrazine (**4**) with organolithium and Grignard reagents (entries 18–20) held

no surprise, and in analogy with an earlier report,[23] the azaphilic adducts **9a**,**b** were isolated in excellent yield in each case. Likewise, compounds **1** and **4** also reacted readily with the organometallic reagents even at −78 °C. On the other hand, we saw no sign of double addition or follow-up reactions when using organolithium reagents.[23]

In an attempt to extend the azaphilic addition to chloro-tetrazines, 3-chloro-6-morpholino-tetrazine (**6**)[14] was also reacted with organolithium and Grignard reagents. The former led to the decomposition of the starting material even at −78 °C, probably due to the presence of a lithium–chlorine exchange reaction, while in case of organomagnesium reagents, TLC analysis of the reaction mixtures revealed the formation of a new product, showing an azaphilic adduct-like behavior, that decomposed during workup.

Having demonstrated that organolithium and Grignard reagents initiate, in most cases, azaphilic addition on tetrazines we turned our attention to other organometallic reagents. In the next set of experiments the easily available and reactive dipyrazolyl-tetrazine (**1**) was reacted with a series of organometallic reagents prepared by transmetallation from butyllithium or phenyllithium and the appropriate metal halide.

Tuning the reactivity of butyllithium with cobalt or manganese salts (entries 22 and 23) led to a significant change in reactivity. Besides the formation of substantial amounts of the complex **14**, another product was isolated in both cases. The spectral data of this newly formed compound indicated substitution of one of the pyrazolyl units, but multidimensional NMR and MS experiments verified that it possesses a butoxy substituent (**12**) instead of the expected butyl group. Interestingly, when we carried out the same reaction using phenyllithium instead of butyl-lithium (entry 24) three products were formed: the azaphilic adduct (**6b**), the butoxy substituted tetrazine (**12**) and the complex (**14**), which suggests that the butoxy moiety in **12** is not coming from the organolithium reagent as in entry 14, which leaves tetrahydrofuran as the only potential source of butoxide ions. The capability of THF to undergo reductive ring opening is known[31,32] and the reducing ability of the butyl-metal-halides used might be further enhanced through β-hydride elimination under the applied conditions,[33] yielding the more reactive metal hydrides. By changing the solvent to diethyl ether in the same experiment we observed only complex formation, also supporting this hypothesis.[34]

Table 2. Product distribution in the reaction of **1** with other organo-metallic reagents

No.	SM	RM	**6**[a] (%)	**10** (%)	**12**[a] (%)	**14**[b] (%)
22	**1**	BuCoBr[c]			60	40
23	**1**	BuMnCl[c]			40	60
24	**1**	PhMnCl[c]	20		15	40
25	**1**	BuPbCl[c]	25		30	35
26	**1**	BuSnCl[c]		100[d]		
27	**1**	PhSnCl[c]		100[d]		
28	**1**	BuFeCl[c]		100[d]		
29	**1**	$BuCrCl_2$[c]		100[d]		

[a] Numbers refer to isolated yields unless otherwise stated.
[b] Estimated value based on recovered starting material. Reverts to **1** on acidic workup.
[c] Prepared by transmetallation form the appropriate lithiumorganic reagent and anhydrous metal halide.
[d] Determined by NMR. >99.9% means that no other identifiable compound was detected in the crude product.

A similar behavior was observed when butyllithium was mixed with lead(II) bromide (entry 25) prior to its addition to **1**. At the end of the reaction the azaphilic adduct (**6a**), the butoxy substituted tetrazine (**12**) and starting material (**1**), recovered after the decomposition of **14**, were isolated in similar yields.

The last group of organometallic reagents examined (entries 26–29) initiated the reduction of the tetrazine core selectively. Even careful investigation of the crude reaction mixtures revealed only the presence of **12** besides some highly polar decomposed material. It is worth mentioning that this transformation was selective, not only for butylmetal halides (entries 26,28, and 29) that are capable of producing metal hydrides through β-hydride elimination,[33] but also for phenyltin chloride (entry 27). The fact that these reagents reduced the tetrazine core and not the solvent, as in entries 22–25, is not well understood but might probably be attributed to the different complex forming aptitude of the added metal ions.

In summary, a series of organometallic reagents were reacted with different tetrazine derivatives and selective transformations, such as azaphilic addition, reduction or in certain cases nucleophilic displacement were observed. More polar organometallic reagents, especially lithium, magnesium and zinc derivatives, showed a marked affinity towards the nitrogen atom of the tetrazine core, a behaviour fairly unusual in heterocyclic chemistry. The oxidative rearrangement of the azaphilic adducts to alkoxy/aryloxy tetrazines was also observed in certain cases.

3. Experimental

3.1. General

Melting points were determined on a hotplate and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-250 or DRX-500 spectrometer in $CDCl_3$ and CH_3SOCH_3. For ^1H NMR spectra the residual peak of $CHCl_3$ (7.26 ppm) and CH_3SOCH_3 (2.50 ppm) were used as the internal reference, while for ^{13}C NMR spectra the central peak of $CDCl_3$ (77.0 ppm) and the central peak CD_3SOCD_3 (39.43 ppm) were used as the reference. The IR spectra were obtained on a Bruker IFS-55 FTIR spectrometer. Combination gas chromatography and low resolution mass spectrometry was obtained on a Hewlett–Packard 5790A Gas Chromatograph (30 m×0.25 mm column with 0.25 μm RH-5 MS+coating, He carrier gas) and VG 12-250 Mass Spectrometer (Ion source: EI+, 70 eV, 250 °C; interface: 250 °C). Flash silica gel (0.040–0.063 mm) was used for flash column chromatography.

3.2. General procedure for the reaction of tetrazines 1-4 with organometallic reagents

All reactions were carried out under argon, using dry

glassware. THF was distilled from potassium/benzophenone. When the organometallic reagent was prepared by transmetallation a mixture of 1.1 mmol of the appropriate salt in abs. THF (3 mL) was treated with 1.1 mmol of the organolithium reagent and after stirring for 1 h at −40 °C the resulting mixture was added via a canula to the slurry of 1 mmol of the appropriate tetrazine in dry THF (3 mL) at −78 °C. The reaction was followed by TLC and upon completion (which in certain cases required warming to room temperature) it was quenched with aq. NH_4Cl, extracted with DCM, the combined organic phases were dried oveg $MgSO_4$ and the solvent was evaporated. The products were isolated by flash column chromatography using hexane–ethyl acetate mixtures as eluent.

3.2.1. 1-Butyl-3,6-bis(3′,5′-dimethylpyrazol-1′-yl)-1,4-dihydro-1,2,4,5-tetrazine (6a). Yellow oil, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (s, 1H), 5.88 (s, 1H), 5.82 (s, 1H), 3.03 (t, 2H, J=6.9 Hz), 2.40 (s, 3H), 2.22 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 1.48 (qi, 2H, J=6.9 Hz), 1.25 (sex, 2H, J=6.9 Hz), 0.77 (t, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.19, 150.43, 146.09, 145.91, 143.30, 142.81, 110.44, 107.41, 50.80, 30.30, 19.98, 14.47, 14.11, 14.02, 13.88, 11.70; MS (EI, 70 eV) m/z for $C_{16}H_{24}N_8$ (rel. intensity, ion): 328 (100, M^+), 271 (10), 189 (22), 164 (52), 151 (22), 122 (72), 97 (19), 81 (10); 54 (12); IR (KBr) ν_{max}: 3357, 2958, 2929, 2870, 2154, 1666, 1639, 1569, 1300, 1216, 1135, 1067, 1029, 970, 937, 900, 789 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{24}N_8$: m/z 328.2124. Found: m/z 328.2137.

3.2.2. 1-Phenyl-3,6-bis(3′,5′-dimethylpyrazolyl-1′-yl)-1,4-dihydro-1,2,4,5-tetrazine (6b). Yellow solid, mp: 45–46 °C (decomposition); ^{1}H NMR ($CDCl_3$, 250 MHz) 8.41 (br s, 1H), 7.18 (t, 2H, J=7.2 Hz), 6.97 (t, 1H, J=7.2 Hz), 6.92 (d, 2H, J=7.2 Hz), 6.05 (s, 1H), 5.79 (s, 1H), 2.64 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 151.45, 150.93, 149.79, 142.79, 142.47, 141.38, 140.05, 128.57, 122.90, 117.04, 110.72, 107.73, 14.21, 13.58, 13.53, 11.05; MS (EI, 70 eV) m/z for $C_{18}H_{20}N_8$ (rel. intensity, ion): 348 (65, M^+), 272 (9, M-Ph), 198 (63), 122 (100), 77 (41); IR (KBr): 3350, 2926, 1663, 1639, 1599, 1582, 1570, 1496, 1457, 1414, 1399, 1366, 1077, 995, 969, 754, 693 cm^{-1}. HRMS (EI) Calcd for $C_{18}H_{20}N_8$: m/z 348.1811. Found: m/z 348.1819.

3.2.3. 1-Allyl-3,6-bis(3′,5′-dimethylpyrazol-1′-yl)-1,4-dihydro-1,2,4,5-tetrazine (6c). Yellow solid, mp: 84–85 °C (decomposition); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.05 (s, 1H), 5.96 (s, 1H), 5.89 (s, 1H), 5.84 (ddt, 1H, J=16.9, 10.5, 6.4 Hz), 5.14 (dqa, 1H, J=16.9, 1.6 Hz), 5.08 (dqa, 1H, J=10.5, 1.6 Hz), 3.84 (dt, 2H, J=6.4, 1.6 Hz), 2.49 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 150.94, 150.21, 145.90, 145.00, 143.16, 142.72, 133.96, 117.33, 110.11, 107.12, 53.99, 14.06, 13.68, 13.55, 11.49; MS (EI, 70 eV) m/z for $C_{15}H_{20}N_8$ (rel. intensity, ion) 312 (88, M^+), 271 (56, M-allyl), 215 (29), 164 (25), 122 (85), 97 (100); IR (KBr): 3209, 3138, 3075, 2961, 2927, 1690, 1571, 1490, 1415, 1362, 1261, 1172, 1078, 1025, 973, 798 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{20}N_8$: m/z 312.1811. Found: m/z 312.1809.

3.2.4. 1-Butyl-3,6-bis(3′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (7a). ^{1}H NMR ($CDCl_3$, 250 MHz) 9.33 (dd, 1H, J=2.2, 0.8 Hz), 8.78 (dd, 1H, J=4.9, 1.7 Hz), 8.57 (br s, 1H), 8.50 (d, 1H, J=5.1 Hz), 8.42 (ddd, 1H, J=8.0, 2.2, 1.8 Hz), 7.49 (ddd, 1H, J=8.0, 4.9, 0.9 Hz), 7.23–7.14 (m, 3H), 2.78 (t, 2H, J=7.6 Hz), 1.62 (qi, 2H, J=7.7 Hz), 1.35 (sex, 2H, J=7.6 Hz), 0.91 (t, 3H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 151.56, 151.07, 150.06, 149.92, 148.17, 147.96, 136.79, 133.85, 127.90, 126.35, 123.68, 123.63, 52.63, 30.98, 19.99, 14.15; MS (EI, 70 eV) m/z for $C_{16}H_{18}N_6$ (rel. intensity, ion): 294 (5, M+), 224 (22), 161 (39), 145 (50), 132 (42), 118 (90), 104 (37), 78 (47), 51 (44), 43 (100).

3.2.5. 1-Phenyl-3,6-bis(3′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (7b). Yellow solid, mp: 180–181 °C (decomposition); ^{1}H NMR ($CDCl_3$, 250 MHz) 9.03 (d, 1H, J=1.3 Hz), 8.65 (dd, 1H, J=4.3, 0.9 Hz), 8.55 (d, 1H, J=1.6 Hz), 8.46 (dd, 1H, J=4.9, 1.4 Hz), 8.07 (dt, 2H, J=7.8, 1.9 Hz), 7.39 (dt, 1H, J=8.2, 2.1 Hz), 7.31 (dd, 1H, J=8.0, 4.9 Hz), 7.17–7.04 (m, 5H, J=16.5 Hz), 6.93 (tt, 1H, J=7.1, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 151.67, 150.10, 150.01, 149.94, 147.45, 146.01, 141.14, 136.16, 134.01, 128.64, 128.30, 125.55, 123.64, 123.53, 122.81, 119.28; MS (EI, 70 eV) m/z for $C_{18}H_{14}N_6$ (rel. intensity, ion): 314 (55, M^+), 283 (12), 208 (14), 181 (30), 105 (100), 77 (70), 51 (65); IR (KBr): 3426, 3223, 3062, 3033., 2920.8, 1625, 1596, 1491, 1466, 1413, 1348, 1338, 1096, 1021, 988, 812, 764, 713, 697 cm^{-1}. HRMS (EI) Calcd for $C_{18}H_{14}N_6$: m/z 314.1280. Found: m/z 314.1270.

3.2.6. 4-Butyl-3-(3′,5′-dimethylpyrazol-1′-yl)-6-(*N*-morpholino)-1,4-dihydro-1,2,4,5-tetrazine (8a). Yellow oil, ^{1}H NMR ($CDCl_3$, 250 MHz) 7.60 (s, 1H), 5.95 (s, 1H), 3.72 (t, 4H, J=4.7 Hz), 3.37 (t, 2H, J=7.0 Hz), 3.04 (t, 4H, J=4.7 Hz), 2.46 (s, 3H), 2.19 (s, 3H), 1.68 (qi, 2H, J=14.7 Hz), 1.43 (sex, 2H, J=18.5 Hz), 0.94 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz): 154.22, 150.42, 149.82, 141.94, 109.74, 66.41, 49.70, 48.44, 30.65, 19.59, 13.73; MS (EI, 70 eV) m/z for $C_{15}H_{25}N_7O$ (rel. intensity, ion): 319 (45, M^+), 262 (65), 122 (83), 57 (50), 42 (100).

3.2.7. 4-Phenyl-3-(3′,5′-dimethylpyrazol-1′-yl)-6-(*N*-morpholino)-1,4-dihydro-1,2,4,5-tetrazine (8b). Yellow solid, mp: 170–171 °C (decomposition); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.56 (s, 1H), 7.13 (dd, 2H, J=8.1, 7.2 Hz), 6.91 (t, 1H, J=7.2 Hz), 6.88 (d, 2H, J=8.1 Hz), 5.77 (s, 1H), 3.66 (t, 4H, J=4.8 Hz), 3.30 (t, 4H, J=4.8 Hz), 2.20 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.08, 150.23, 142.41, 140.28, 139.43, 127.48, 121.44, 115.89, 106.66, 65.14, 45.34, 12.65, 10.02; MS (EI, 70 eV) m/z for $C_{17}H_{21}N_7O$ (rel. intensity, ion): 339 (7, M^+), 154 (95), 121 (38), 105 (35), 94 (86), 77 (24), 43 (100), 39 (53); IR (KBr): 3307, 2960, 2852, 1595, 1568, 1389, 1369, 1121, 761, 732, 698, 688 cm^{-1}. HRMS (EI) Calcd for $C_{17}H_{21}N_7O$: m/z 339.1808. Found: m/z 339.1802.

3.2.8. 1-Butyl-3,6-bis(methylthio)-1,4-dihydro-1,2,4,5-tetrazine (9a). Pink solid, mp: 39–40 °C (decomposition); ^{1}H NMR ($CDCl_3$, 250 MHz) 6.50 (s, 1H), 3.32 (t, 2H, J=7.3 Hz), 2.43 (s, 3H), 2.35 (s, 3H), 1.71 (qi, 2H, J=7.2 Hz), 1.38 (sex, 2H, J=7.2 Hz), 0.93 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 154.25, 150.43, 51.27, 29.98, 29.86, 19.87, 14.40, 13.38; MS (EI, 70 eV) m/z for $C_8H_{16}N_4S_2$ (rel. intensity, ion): 232 (100, M^+), 189 (50),

176 (17), 161 (7), 87 (6), 74 (48), 57 (7), 41 (15); IR (KBr): 3265, 2961, 2929, 2861, 1603, 1588, 1467, 1440, 1416, 1374, 1268, 1190, 1149, 1129, 776, 608 cm^{-1}. HRMS (EI) Calcd for $C_8H_{16}N_4S_2$: *m/z* 232.0816. Found: *m/z* 232.0814.

3.2.9. 1-Phenyl-3,6-bis(methylthio)-1,4-dihydro-1,2,4,5-tetrazin (9b). Pale orange solid, mp: 117–118 °C (decomposition); ^1H NMR ($CDCl_3$, 250 MHz) 7.36 (d, 2H, *J*=8.1 Hz), 7.27 (dd, 2H, *J*=8.1, 7.2 Hz), 7.13 (t, 1H, *J*=7.2 Hz), 7.10 (s, 1H), 2.40 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 152.25, 151.95, 142.14, 128.24, 125.97, 123.48, 14.74, 14.20; MS (EI, 70 eV) *m/z* for $C_{10}H_{12}N_4S_2$ (rel. intensity, ion): 252 (100, M^+), 150 (12), 135 (11), 91 (7), 74 (50), 65 (6), 51 (14); IR (KBr): 3282, 3258, 3054, 2926, 1613, 1590, 1490, 1416, 1283, 1170, 1151, 1070, 951, 764, 696 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{12}N_4S_2$: *m/z* 252.0503. Found: *m/z* 252.0502.

3.2.10. 3,6-Bis(3′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (11).[35] ^1H NMR ($CDCl_3$, 250 MHz) 9.35 (s, 2H), 8.99 (d, 2H, *J*=1.8 Hz), 8.67 (dd, 2H, *J*=4.9, 1.6 Hz), 8.18 (dt, 2H, *J*=8.5, 1.8 Hz), 7.50 (dd, 2H, *J*=7.4, 4.7 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 113.98, 110.14, 109.22, 96.43, 88.95, 86.58; MS (EI, 70 eV) *m/z* for $C_{12}H_{10}N_6$ (rel. intensity, ion): 238 (100, M^+), 105 (62), 78 (34), 51 (23); HRMS (EI) Calcd for $C_{12}H_{10}N_6$: *m/z* 238.0967. Found: *m/z* 238.0965.

3.2.11. 3-Butoxy-6-(3′,5′-dimethylpyrazol-1′-yl)-1,2,4,5-tetrazine (12). Red solid, mp: 28–29 °C; ^1H NMR ($CDCl_3$, 500 MHz) 6.08 (s, 1H), 4.60 (t, 2H, *J*=6.9 Hz), 2.57 (s, 3H), 2.29 (s, 3H), 1.86 (qi, 2H, *J*=6.9 Hz), 1.49 (sex, 2H, *J*=6.9 Hz), 0.94 (t, 3H, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.66, 159.68, 153.81, 143.31, 11.37, 70.62, 30.98, 19.35, 14.54, 14.15, 14.05; MS (EI, 70 eV) *m/z* for $C_{11}H_{16}N_6O$ (rel. intensity, ion): 248 (24, M^+), 194 (5), 163 (6), 122 (100), 96 (7), 57 (18); IR (KBr): 2961, 2873, 1577, 1484, 1431, 1370, 1351, 1084, 953 cm^{-1}. HRMS (EI) Calcd for $C_{11}H_{16}N_6O$: *m/z* 248.1386. Found: *m/z* 248.1381

3.2.12. 3-Butoxy-6-(*N*-morpholino)-1,2,4,5-tetrazine (13a). Red solid, mp: 53–54 °C; ^1H NMR ($CDCl_3$, 250 MHz) 4.47 (t, 2H, *J*=6.6 Hz), 3.88–3.79 (m, 8H, *J*=11.1 Hz), 1.85 (qi, 2H, *J*=14.2 Hz), 1.50 (sex, 2H, *J*=18.7 Hz), 0.96 (t, 3H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 164.32, 161.33, 68.80, 66.34, 44.17, 30.69, 18.96, 13.67; MS (EI, 70 eV) *m/z* for $C_{10}H_{17}N_5O_2$ (rel. intensity, ion): 239 (93, M^+), 149 (71), 111 (67), 85 (100), 81 (49), 67 (67), 53 (88), 44 (66), 30 (57); IR (KBr): 2967, 2959, 2936, 2917, 2906, 2865, 1769, 1717, 1530, 1479, 1460, 1330, 1302, 1249, 1120, 1018, 967, 957, 936, 852, 569, 553 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{17}N_5O_2$: *m/z* 239.1382. Found: *m/z* 239.1371.

3.2.13. 3-Phenoxy-6-(*N*-morpholino)-1,2,4,5-tetrazine (13b). Red solid, mp: 95–97 °C; ^1H NMR ($CDCl_3$, 250 MHz) 7.91 (d, 2H, *J*=7.7 Hz), 7.50–7.35 (m, 3H), 3.87 (t, 4H, *J*=5.2 Hz), 3.76 (t, 4H, *J*=5.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz); 149.93, 146.95, 138.18, 128.00, 122.30, 120.42, 65.14, 43.99; MS (EI, 70 eV) *m/z* for $C_{12}H_{13}N_5O_2$ (rel. intensity, ion): 259 (5, M^+), 153 (52), 119 (100), 112 (3), 41 (38).

4. Supplementary Material

^1H and ^{13}C NMR spectra of the new compounds reported in Tables 1 and 2.

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34. Although careful reinvestigation of the analogous reaction of **1** with butyllithium revealed that minor amounts (<2%) of **12** are also formed in the process demonstrating the presence of the same chemistry, we believe that the formation of significant amounts of **12** in entries 22–25 and the transformation of **8a** into **13a** occur by different mechanism.
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Pyrazino-tetracyanonaphthoquinodimethanes: sterically deformed electron acceptors affording zwitterionic radicals

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Abstract—The X-ray analyses of the title electron acceptors (**1**) revealed their butterfly-shaped deformed geometry, which is not affected by the pyridyl group attached at 2-position of the pyrazino-TCNNQ skeleton. Small differences between the first and second reduction potentials (ca. 0.1 V) in pyrazino-TCNNQs show that their anion radicals ($\mathbf{1}^{-\cdot}$) are prone to disproportionate into the neutral (**1**) and dianionic ($\mathbf{1}^{2-}$) species. The thermodynamically unstable anion radical species based on the pyrazino-TCNNQ skeleton could be isolated as inner salts upon electrochemical reduction of the derivatives having an *N*-methylpyridinium moiety at 2-position ($\mathbf{2}^{+}$). The zwitterionic open-shell species ($\mathbf{2}^{\cdot}$) constitute a novel class of radicals that exhibit semiconducting behavior as a single component thanks to the high electrochemical amphotericity.

1. Introduction

7,7,8,8-Tetracyanoquinodimethane (TCNQ) has been known as a representative organic electron acceptor due to its strong oxidizing ability as well as stability of the negatively charged species. Many of its anion radical salts and charge-transfer complexes were proven highly conductive, and the discovery of the first organic metal[1] composed of TCNQ and tetrathiafulvalene (TTF) initiated the vast development of the research on organic conductors. While the TTF skeleton has been featured very often as an strong electron-donating moiety in materials science,[2] the chemistry of TCNQ has been less explored.[3–7] One of the reasons for this scarcity is the easy deformation of the skeleton by the steric hindrance between the Y-shaped dicyanomethylene groups and the substituents attached on the lateral C=C double bond, as exemplified by the severely non-planarized geometry of tetramethyl-TCNQ,[4] which no longer exhibits intrinsic redox properties of TCNQ. Accordingly, the π-extended analogs had to be designed with special care[5] in order to avoid steric factors[6] because simple benzannelation again induced butterfly-shaped deformation as shown by X-ray analyses of 11,11,12,12-tetracyanoanthraquinodimethanes (TCNAQs).[7] It seems the general view that the redox systems with a sterically deformed π-framework are inappropriate in developing organic solids with special properties such as electrical conductivity. That is, steric repulsion in neutral and/or charged species induces geometrical changes upon electron transfer,[8] thus decreasing the thermodynamic stability of ion radicals by easy disproportionation to the corresponding neutral and doubly-charged species.[9] On the contrary, when such unstable ion radicals could be isolated as salts, they provide a unique opportunity for further understanding of the physical properties of organic solids. Among the rare examples are the highly conductive cation radical salts of butterfly-shaped TTF derivatives, one of which exhibits metallic behavior.[10] With these in mind, we have decided to study on the anion radical species of the title electron acceptors with a non-planar geometry. The pyrazino-tetracyanonaphthoquinodimethanes (pyrazino-TCNNQs, **1**) are the 1,4-diaza derivatives of heavily deformed TCNAQ and were designed in anticipation of more flattened structure by partial reduction of the steric repulsion between dicyanomethylene groups and *peri*-hydrogens. It has been revealed in this study that the anion radicals of **1** could be successfully isolated when the pyridinium unit acting as a counter cation is attached on the periphery of the skeleton as in the inner salts $\mathbf{2Z}^{\cdot}$ (Scheme 1). They are new members of stable neutral radicals[11] with a polar structure.[12,13] Noteworthy is that radicals $\mathbf{2}^{\cdot}$ exhibit semiconducting behavior as a single

Keywords: Redox system; Inner salt; Electron acceptor; Tetracyanoquinodimethane; Organic conductor; Deformation; Anion radical; Zwitterion.
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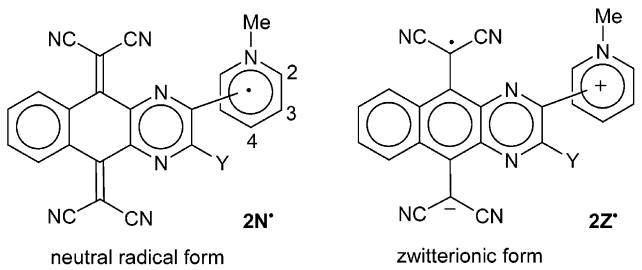


Scheme 1. Two forms of neutral radicals **2**•.

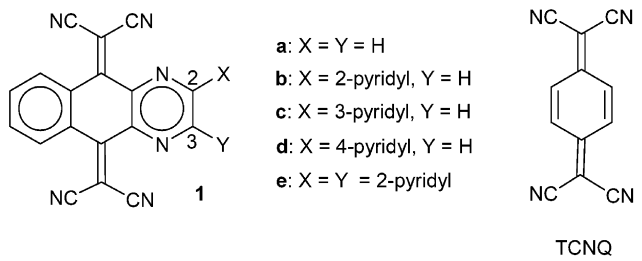


Chart 1.

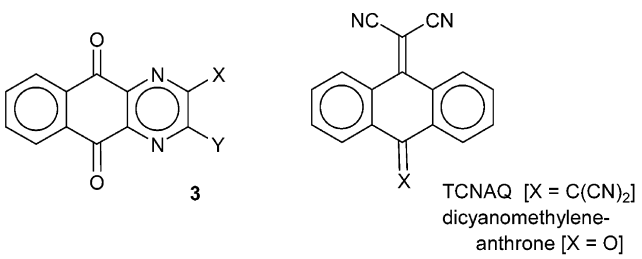


Chart 2.

component[12–14] thanks to the high electrochemical amphotericity (Charts 1 and 2).

2. Results and discussion

2.1. Preparation and molecular geometries of pyrazino-TCNNQs (1)

Condensation of pyrazino-naphthoquinones **3a-d** with malononitrile in the presence of $TiCl_4$[15] gave the corresponding naphthoquinodimethanes **1a-d** as slightly soluble yellow crystals.[16] The X-ray structural analysis of parent **1a** showed the butterfly-shaped deformation as expected (Fig. 1). The central six-membered ring adopts a boat-like conformation. The dihedral angle (α) defined by two fused aromatic rings is 148.0°, which is larger than those in TCNAQs (144.6° for parent;[7a] 143.3° for 2-chloro-TCNAQ[7b]) and rather close to the value in 9-dicyanomethyleneanthrone (152°).[17] Substituents on the fused pyrazine ring do not induce any significant structural change of pyrazino-TCNNQ skeleton, as shown by the quite similar molecular geometry of **1d** with a 4-pyridyl group at 2-position. Thus, not only the dihedral angle (α) but also the tilting (β) and twisting angles (γ) of exomethylene bonds are close to each other (Scheme 2). The pyridine pendant in **1d** lies nearly on the same plane to the fused pyrazine ring with a small torsion angle (δ) of 25.3°, which

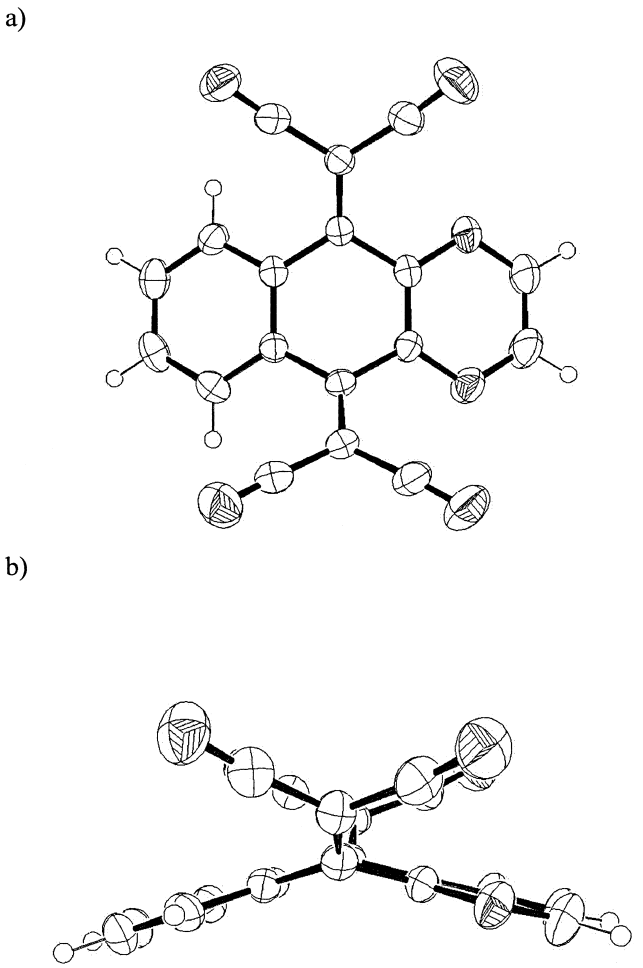
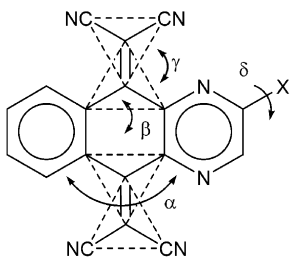


Figure 1. Molecular structure of **1a** determined by X-ray analysis: (a) top view; (b) side view.

indicates the π-conjugation between the two nitrogen heterocycles.

2.2. Redox properties of pyrazino-TCNNQs (1) and quaternary cations (2^+)

In contrast to the one-wave two-electron reduction process observed in heavily deformed TCNAQ (E^{red}, −0.37 V vs. SCE), pyrazino-TCNNQ **1a** with a less deformed structure undergoes two-stage one-electron reduction. The first reduction potential (E_1^{red}, −0.23 V) is more positive than TCNAQ, indicating the higher electron-accepting properties due to the electron-withdrawing nature of a pyrazine ring



	1a	1d	2d+
X	H	4-py	1-Me-4-py+
α (°)	148.0	148.9	152.8
β (°)	33.4 28.5	32.0 24.7	28.3 25.6
γ (°)	6.9 5.4	5.2 4.3	5.5 5.1
δ (°)	-	25.3	11.1

Scheme 2. Molecular geometries determined by X-ray analyses.

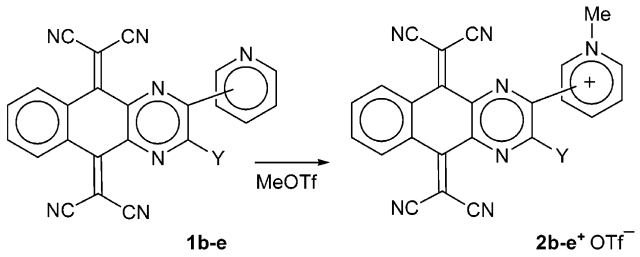
Table 1. Redox potentials of **1a-e** and **2b-e**$^+$ measured in MeCN[a]

	Substituent	E_1^{red}	E_2^{red}	E_3^{red}
1a	None	−0.23	−0.32	< −1.5
1b	2-(2-Pyridyl)	−0.20	−0.30	< −1.5
1c	2-(3-Pyridyl)	−0.19	−0.30	< −1.5
1d	2-(4-Pyridyl)	−0.19	−0.30	< −1.5
1e	2,3-(2-Pyridyl)	−0.18	−0.27	< −1.5
2b$^+$	2-(2-Pyridinium)	−0.12	−0.23	−1.03
2c$^+$	2-(3-Pyridinium)	−0.12	−0.24	−1.16
2d$^+$	2-(4-Pyridinium)	−0.13	−0.27	−0.96
2e$^+$	2-(2-Pyridinium)-3-(2-pyridyl)	−0.10	−0.22	−1.23

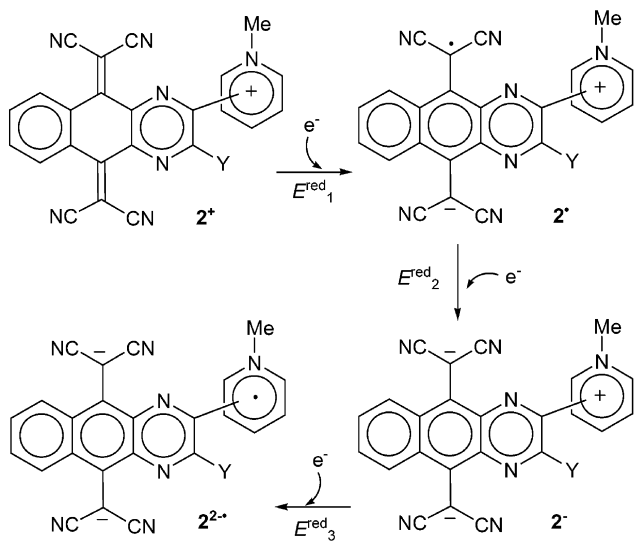
[a] *E*/*V* versus SCE, Pt electrode, scan rate 100 mV s^{-1}.

(Table 1). Although the two reduction peaks were observed separately in the cyclic voltammogram, the potential difference of ca. 0.1 V is much smaller than those of planar acceptors such as the corresponding quinone precursor **3a** (0.56 V) or TCNQ (0.54 V). The narrow separation corresponds to easy disproportionation of **1a**$^{-\cdot}$ to **1a** and **1a**$^{2-}$, as indicated by the small semiquinone formation constant (K_{sem}=[**1a**$^{-\cdot}$]^2/[**1**][**1a**$^{2-}$]=35).[18] Voltammograms of **1b**-**1d** with a pyridyl substituent as well as **1e**[13c] with two 2-pyridyl substituents at 2,3-positions are very similar to that of **1a**, showing the marginal electronic effects by the substituents on the redox behavior. However, considerable positive shifts of E_1^{red} and E_2^{red} were observed when the pyridine rings were converted to pyridinium groups with stronger electron withdrawing properties.

Quaternization of **1b**-**1e** with MeOTf resulted in the N-methylation at the pyridine pendant, and cations **2b**$^+$–**2e**$^+$ were isolated as pale yellow OTf$^-$ salts (Scheme 3). The X-ray analysis of the iodide salt of **2d**$^+$ showed that the molecular geometry of this cation resembles the neutral precursor **1d** (Scheme 2). Coplanarity of the pyridinium unit with the pyrazine ring (δ=11.1°) in **2d**$^+$ suggests full conjugation between the two nitrogen heterocycles, thus enhancing the electron-accepting properties of TCNNQ. In fact, cations **2**$^+$ are stronger oxidants than **1** and undergo two-stage one-electron reduction as in **1** (Table 1). Noteworthy is that cations **2**$^+$ undergo the third one-electron reduction process around −1 V, whose potential is close to E_1^{red} of *N*-methylpyridinium (−1.31 V). These results indicate that LUMO of **2**$^+$ mostly localizes on the pyrazino-TCNNQ skeleton, whereas the third electron is mainly accepted at the pyridinium unit (Scheme 4).



Scheme 3. N-methylation of **1b**-**1e** to cations **2b**-**e**$^+$.



Scheme 4. Multi-stage redox behavior of cations **2**$^+$.

2.3. Generation and properties of radicals (2$^{\cdot}$)

Electrochemical reduction of cations **2b**$^+$–**2e**$^+$ gave deeply colored solid which were assigned as the one-electron reduction products **2b**$^{\cdot}$–**2e**$^{\cdot}$. By considering that the similar electrolysis of **1a** did not afford its anion radical as a salt, coexistence of the counter cation within the pyrazino-TCNNQ skeleton plays an important role in isolating the anion radicals that undergo easy disproportionation.

The very low solubility of **2b**$^{\cdot}$–**2d**$^{\cdot}$ in common solvents prevents from examining their properties in solution. However, UV–vis spectrum of **2e**$^{\cdot}$ could be obtained in MeCN that exhibits absorptions in the longer-wavelength region [λ_{max} (log ε) 606 (4.00, sh) and 674 (4.22) nm] (Fig. 2). These bands are characteristic to the anion radical species of TCNQ derivatives, suggesting that the extra electron is mainly located at the TCNQ skeleton in **2**$^{\cdot}$. The CN stretching frequencies of **2**$^{\cdot}$ (2162–2167 cm^{-1}) were quite lower than those of the corresponding cationic precursors **2**$^+$ (2218–2220 cm^{-1}), indicating the delocalization of a negative charge over the dicyanomethylene moieties. These results suggest that the main contributor for the radicals **2**$^{\cdot}$ is the zwitterionic structure **2Z**$^{\cdot}$ but not the neutral radical form **2N**$^{\cdot}$ (Scheme 1) in consonant with the idea deduced from the redox potentials of cations **2**$^+$ (Scheme 4).

Many attempts to obtain single crystalline specimen of **2**$^{\cdot}$ were unsuccessful, thus lacking the experimental information on the detailed molecular structure of the radicals. However, the redox potentials of **2e**$^{\cdot}$ [E_1^{ox}=−0.10 V, E_1^{red}=−0.22 V, E_2^{red}=−1.23 V] clearly show that the radical is not dimeric but monomeric at least in solution. Thus,

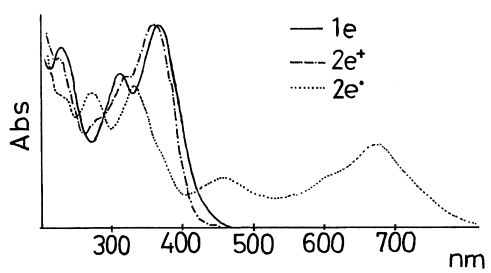


Figure 2. UV–vis spectra of **1e**, **2e**$^+$ and **2e**$^{\cdot}$ in MeCN.

these values correspond well to the reduction potentials (E_1^{red}, E_2^{red} and E_3^{red}) of the precursor $\mathbf{2e}^+$, respectively. Noteworthy is that the difference between E_1^{red} and E_2^{red} of $\mathbf{2}^+$ (ca. 0.1 V) is identical to the difference between E_1^{ox} and E_1^{red} (E_{sum}) of $\mathbf{2}^{\cdot}$. The E_{sum} value of ca. 0.1 V indicates very high electrochemical amphotericity of the resulted radicals $\mathbf{2}^{\cdot}$. There have been several papers reporting that highly amphoteric neutral radicals act as semiconductors as a single component,[12,13] and this is also the case. The electric conductivities of $\mathbf{2b}^{\cdot}$–$\mathbf{2e}^{\cdot}$ measured on the compaction samples by a two-probe method at room temperature are 8.4×10^{-8}, 2.1×10^{-7}, 9.0×10^{-8} and 2.0×10^{-6} S cm^{-1}, respectively. The values are not spectacular but comparable to those in other single-component organic semiconductor without any metal elements.[12b–c,14a–c] Furthermore, these radicals are ones of the rare examples[19] that sterically deformed electron acceptors afford organic conducting material.

3. Conclusion

This work has revealed that pyrazino-TCNNQs **1** with a sterically deformed geometry undergo reversible two-stage one-electron reduction. Although their anion-radicals $\mathbf{1}^{-\cdot}$ are thermodynamically unstable, they could be successfully isolated as inner salts $\mathbf{2}^{\cdot}$ by attaching the pyridinium unit acting as a counter cation within the molecule. This method provided a unique technique to study the solid-state properties of the ion radicals of pyrazino-TCNNQ that are otherwise unable to isolate.

4. Experimental

4.1. General

Melting points are uncorrected. Chemical shifts of ^{1}H NMR spectra are reported in ppm based on TMS (0 ppm). IR spectra were measured in KBr disks. Some compounds prepared here include solvent molecules (dichloroethane, acetonitrile, water) upon crystallization, which is rather common for non-planar molecules. Partial desolvation could be one of the reasons for the unsatisfactory analytical values (deviation >0.4%) observed in some compounds even after through purification. Another factor causing the disagreement is sensitivity toward moisture in the case of cations $\mathbf{2}^+$ and radicals $\mathbf{2}^{\cdot}$ due to their highly polar structures.

4.2. Preparation of pyrazino-TCNNQs (1)

4.2.1. 5,10-Bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazine (1a).[16] To a solution of quinone **3a**[20] (400 mg, 1.90 mmol) in 40 mL of dry $CHCl_3$ was added $TiCl_4$ (0.8 mL, 7.3 mmol) under N_2. To the resultant suspension of the complex was then added dropwise a solution of malononitrile (400 mg, 6.1 mmol) and dry pyridine (6 mL, 50 mmol) in 20 mL of dry $CHCl_3$ over 2.3 h at −20 °C. After the entire mixture was stirred at this temperature for 3.5 h, it was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent and chromatographic separation on SiO_2 (CH_2Cl_2/acetone, 10:1) followed by recrystallization from acetone–ether gave **1a** (77 mg) as yellow cubes in 13% yield: mp >260 °C decomp.; MS (EI) *m/z* (relative intensity) 306 (M^+, 100) and 252 (20); IR ν_{max} 2216 (CN) cm^{-1}; UV–vis (MeCN) λ_{max} (log ε) 295 (4.05) and 350 (4.36) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (2H, s), 8.53–8.49 (2H, AA′BB′) and 7.90–7.85 (2H, AA′BB′). Anal. Calcd for $C_{18}H_6N_4$: C, 70.59; H, 1.97; N, 27.44. Found: C, 70.61; H, 1.73; N, 26.66.

4.2.2. 2-(2-Pyridyl)-5,10-bis(dicyanomethylidene)-naphtho[2,3-*b*]pyrazine (1b). To a solution of quinone **3b**[13c] (501 mg, 1.74 mmol) in 20 mL of dry CH_2Cl_2 was added $TiCl_4$ (1.15 mL, 10.5 mmol) under N_2. To the resultant suspension of the complex was then added dropwise a solution of malononitrile (692 mg, 10.5 mmol) and dry pyridine (2.5 mL, 30.9 mmol) in 50 mL of dry CH_2Cl_2 over 2.3 h at −78 °C. After the entire mixture was stirred at −20 °C for 4.5 h, it was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent and chromatographic separation on SiO_2 (CH_2Cl_2) followed by recrystallization from 1,2-dichloroethane–MeOH gave **1b** (191 mg) as orange cubes in 29% yield. 3-Pyridyl (**1c**) and 4-pyridyl (**1d**) derivatives were obtained from the corresponding quinones[13c] by similar procedures to **1b**: mp 225–240 °C decomp.; MS (EI) *m/z* (relative intensity) 383 (M^+, 84), and 382 (100); IR ν_{max} 2210 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.07 (1H, s), 8.88 (1H, ddd, *J*=4.7, 2.0, 1.2 Hz), 8.71 (1H, ddd, *J*=7.9, 1.2, 1.0 Hz), 8.58–8.54 (2H, m), 7.98 (1H, ddd, *J*=7.9, 7.8, 2.0 Hz), 7.89–7.84 (2H, m) and 7.50 (1H, ddd, *J*=7.8, 4.7, 1.2 Hz). Anal. Calcd for $C_{23}H_9N_7\cdot H_2O$: C, 68.83; H, 2.76; N, 24.43. Found: C, 68.86; H, 2.58; N, 24.21.

4.2.3. 2-(3-Pyridyl)-5,10-bis(dicyanomethylidene)-naphtho[2,3-*b*]pyrazine (1c). Yellow rods (yield 22%): mp 213–227 °C decomp.; MS (EI) *m/z* (relative intensity) 383 (M^+, 100), and 382 (62); IR ν_{max} 2217 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.47 (1H, s), 9.45 (1H, dd, *J*=2.4, 0.9 Hz), 8.84 (1H, dd, *J*=4.9, 1.8 Hz), 8.72 (ddd, *J*=8.1, 2.4, 1.8 Hz), 8.59–8.53 (2H, m), 7.90–7.85 (2H, m) and 7.59 (1H, ddd, *J*=8.1, 4.9, 0.9 Hz). Anal. Calcd for $C_{23}H_9N_7\cdot 0.25H_2O$: C, 71.22; H, 2.47; N, 25.28. Found: C, 71.57; H, 2.49; N, 25.17.

4.2.4. 2-(4-Pyridyl)-5,10-bis(dicyanomethylidene)-naphtho[2,3-*b*]pyrazine (1d). Yellow rods (yield 39%): mp 180–200 °C decomp.; MS (EI) *m/z* 383 (M^+); IR ν_{max} 2218 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.48 (1H, s), 8.94–8.90 (2H, AA′XX′), 8.58–8.52 (2H, m), 8.18–8.15 (2H, AA′XX′) and 7.92–7.88 (2H, m). Anal. Calcd for $C_{23}H_9N_7\cdot 0.75H_2O$: C, 69.61; H, 2.67; N, 24.70. Found: C, 69.87; H, 2.74 N, 24.43.

4.3. Preparation of quaternary salts (2^+)

4.3.1. 1-Methyl-2-{5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridinium triflate ($2c^+OTf^-$). To a hot solution of pyrazino-TCNNQ **1b** (41 mg, 0.11 mmol) in 12.5 mL of dry 1,2-dichloroethane was added MeOTf (60 μL, 0.53 mmol) under N_2. After the mixture was stirred for 4.5 h at 23 °C, filtration of the

deposited precipitates gave **2b**$^{+}$OTf^{-} as a pale yellow powder (10 mg) in 16% yield. 3-Pyridyl (**1c**) and 4-pyridyl (**1d**) derivatives were also converted to the corresponding quaternary salts by similar procedures to **2b**$^{+}$OTf^{-}: mp 183–190 °C decomp.; MS (FAB) *m/z* 398 (M^{+}); IR ν_{max} 2219 (CN) cm^{-1}; ^{1}H NMR (200 MHz, CD_3CN) δ 9.24 (1H, s), 8.87 (1H, dd, *J*=6.2, 1.8 Hz), 8.69 (1H, ddd, *J*=8.0, 7.9, 1.8 Hz), 8.54–8.47 (2H, m), 8.26 (1H, dd, *J*=8.0, 1.4 Hz), 8.19 (1H, ddd, *J*=7.9, 6.2, 1.4 Hz), 7.96–7.91 (2H, m) and 4.36 (3H, s). Anal. Calcd for $C_{25}H_{12}N_7F_3SO_3\cdot1.5H_2O$: C, 52.27; H, 2.63; N, 17.07. Found: C, 52.35; H, 2.35; N, 16.97.

4.3.2. 1-Methyl-3-{5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridinium triflate (2c^{+}OTf^{-}). A pale yellow powder (yield, 90%): mp 210–223 °C decomp.; MS (FAB) *m/z* 398 (M^{+}); IR ν_{max} 2220 (CN) cm^{-1}; ^{1}H NMR (200 MHz, CD_3CN) δ 9.56 (1H, s), 9.54 (1H, s), 9.29 (1H, dd, *J*=8.3, 1.4 Hz), 8.78 (1H, dd, *J*=6.2, 1.4 Hz), 8.57–8.50 (2H, m), 8.24 (1H, dd, *J*=8.3, 6.2 Hz), 7.95–7.90 (2H, m) and 4.42 (3H, s). Anal. Calcd for $C_{25}H_{12}N_7F_3SO_3\cdot1.5H_2O$: C, 52.27; H, 2.63; N, 17.07. Found: C, 52.67; H, 2.40; N, 16.85.

4.3.3. 1-Methyl-4-{5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridinium triflate (2d^{+}OTf^{-}). A pale yellow powder (yield, 88%): mp 167–200 °C decomp.; MS (FAB) m/z 398 (M+); IR ν_{max} 2218 (CN) cm^{-1}; ^{1}H NMR (200 MHz, CD_3CN) δ 9.65 (1H, s), 8.88–8.83 (2H, AA′BB′), 8.82–8.77 (2H, AA′BB′), 8.58–8.49 (2H, m), 7.96–7.91 (2H, m) and 4.36 (3H, s). Anal. Calcd for $C_{25}H_{12}N_7F_3SO_3\cdot C_2H_4Cl_2$: C, 50.17; H, 2.50; N, 15.17. Found: C, 49.75; H, 2.40; N, 15.42.

4.3.4. 1-Methyl-2-{3-(2-pyridyl)-5,10-bis-(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridinium triflate (2e^{+}OTf^{-}). To a solution of 2,3-bis(2-pyridyl) substituted pyrazino-TCNNQ **1e**[13c] (103 mg, 0.224 mmol) in 20 mL of dry benzene was added MeOTf (25 mL, 0.22 mmol) in benzene (0.5 mL) under N_2. After the mixture was stirred for 2 h at 23 °C, filtration of the deposited precipitates gave **2e**$^{+}$OTf^{-} as a pale yellow powder in 94% yield. When the reaction was conducted in CH_2Cl_2, by-production of bis(quaternary) salt made it difficult to isolate **2e**$^{+}$OTf^{-}: mp 173–187 °C decomp.; MS (FAB) *m/z* 475 (M^{+}); IR ν_{max} 2218 (CN) cm^{-1}; UV–vis (MeCN) λ_{max} (log ε) 194 (4.59), 222 (4.42), 282 (4.23, sh), 318 (4.36, sh) and 358 (4.50) nm; ^{1}H NMR (200 MHz, CD_3CN) δ 8.89 (1H, dd, *J*=6.3, 0.6 Hz), 8.69 (1H, ddd, *J*=7.9, 1.1, 1.0 Hz), 8.60–8.52 (2H, m), 8.21 (1H, ddd, *J*=4.8, 1.7, 1.0 Hz), 8.11 (1H, ddd, *J*=7.9, 6.3, 1.6 Hz), 8.01 (1H, ddd, *J*=7.9, 7.8, 1.7 Hz), 7.98–7.93 (2H, m), 7.80 (1H, dd, *J*=7.9, 1.6 Hz), 7.40 (1H, ddd, *J*=7.8, 4.8, 1.1 Hz) and 4.19 (3H, s). Anal. Calcd for $C_{30}H_{15}N_8F_3SO_3\cdot0.25H_2O$: C, 57.28; H, 2.48; N, 17.81. Found: C, 57.30; H, 2.60; N, 17.39.

4.4. Conversion of cations (2^{+}) to radicals (2$^{\cdot}$)

4.4.1. 1-Methyl-2-{5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridyl (2b$^{\cdot}$). The constant current electrochemical reduction (15 μA) of a solution of **2b**$^{+}$OTf^{-} (24 mg, 0.043 mmol) in MeCN containing 0.05 mol dm^{-3} nBu$_4$NBF$_4$ as a supporting electrolyte gave a black powder of low soluble radical **2b**$^{\cdot}$ (5 mg) in 29% yield. Cationic salts of **2d**$^{+}$OTf^{-} and **2d**$^{+}$OTf^{-} were also converted to the corresponding radicals by similar procedures to **2b**$^{\cdot}$: mp 293–302 °C decomp.; IR ν_{max} 2162 (CN) cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_7\cdot1.5H_2O$: C, 67.76; H, 3.55; N, 23.05. Found: C, 67.74; H, 3.06; N, 23.38.

4.4.2. 1-Methyl-3-{5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridyl (2c$^{\cdot}$). A black powder (yield 25%): mp 223–226 °C decomp.; IR ν_{max} 2167 (CN) cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_7\cdot2H_2O$: C, 66.36; H, 3.71; N, 22.57. Found: C, 66.70; H, 3.59; N, 21.78.

4.4.3. 1-Methyl-4-{5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridyl (2d$^{\cdot}$). A black powder (yield 65%): mp 220–265 °C decomp.; IR ν_{max} 2162 (CN) cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_7\cdot2H_2O$: C, 66.36; H, 3.71; N, 22.57. Found: C, 66.58; H, 3.46; N, 22.16.

4.4.4. 1-Methyl-2-{3-(2-pyridyl)-5,10-bis(dicyanomethylidene)naphtho[2,3-*b*]pyrazin-2-yl}pyridyl (2e$^{\cdot}$). The constant potential electrochemical reduction (−0.05 to −0.08 V vs. SCE) of a solution of **2e**$^{+}$OTf^{-} (50 mg, 0.081 mmol) in CH_2Cl_2 containing 0.1 mol dm^{-3} nBu$_4$NBF$_4$ as a supporting electrolyte gave dark blue fine needles of **2e**$^{\cdot}$ (29 mg) in 71% yield: mp 205–231 °C decomp.; IR ν_{max} 2163 (CN) cm^{-1}; UV–vis (MeCN) λ_{max} (log ε) 196 (4.67), 238 (4.41), 272 (4.42), 334 (4.45), 368 (4.20, sh), 462 (3.98), 606 (4.00, sh) and 674 (4.22) nm. Anal. Calcd for $C_{29}H_{15}N_8\cdot0.5H_2O$: C, 71.89; H, 3.72; N, 23.13. Found: C, 71.89; H, 3.48; N, 23.64.

4.5. Redox potential measurement

Redox potentials were measured by cyclic voltammetry in dry MeCN containing 0.1 mol dm^{-3} Et_4NClO_4 as a supporting electrolyte. Ferrocene undergoes one-electron oxidation at +0.38 V under the same conditions.

4.6. Crystallographic analyses

4.6.1. X-ray analysis of 1a. Single crystalline yellow cubes were obtained by recrystallization from MeCN. Crystal data are as follows: $C_{18}H_6N_6$, *M* 306.29, triclinic, *P*1bar, *a*=7.231(1) Å, *b*=10.122(2) Å, *c*=11.133(2) Å, α=69.05(1)°, β=75.41(1)°, γ=72.00(1)°, *U*=714.5(2) Å^3, D_c (*Z*=2)=1.424 g cm^{-1}, μ=0.92 cm^{-1}. A total of 3160 unique reflection data ($2\theta<55°$) were collected by a Rigaku AFC-7R diffractometer with a rotating anode (50 kV, 200 mA, Mo Kα, *T*=290 K) and a CCD camera. The structure was solved by the direct method, and non-hydrogen atoms were refined with the anisotropic temperature factors by the full-matrix least-squares method. Positions of hydrogen atom were calculated geometrically and verified by the electron density map. Their positions were not refined. The final *R* value is 0.036 for 1436 independent reflections with $I>1.5\sigma I$ and 217 parameters.

4.6.2. X-ray analysis of 1d. Single crystalline yellow needles were obtained by recrystallization from $CHCl_3$. Crystal data are as follows: $C_{23}H_9N_7$, *M* 383.37, monoclinic, *P*21/*c*, *a*=9.887(3) Å, *b*=12.431(3) Å, *c*=15.367(4) Å, β=106.605(2)°, *U*=1809.9(8) Å^3, D_c (*Z*=4)=1.407 g cm^{-1}, μ=0.90 cm^{-1}. A total of 4110

unique reflection data ($2\theta<55°$) were collected by a Rigaku AFC-7R diffractometer with a rotating anode (50 kV, 200 mA, Mo Kα, T=290 K) and a CCD camera. The structure was solved by the direct method, and non-hydrogen atoms were refined with the anisotropic temperature factors by the full-matrix least-squares method. Positions of hydrogen atom were calculated geometrically and verified by the electron density map. Their positions were not refined. The final R value is 0.037 for 1607 independent reflections with $I>1.5\sigma I$ and 271 parameters.

4.6.3. X-ray analysis of 2d$^+$I$^-$·CH$_3$CN solvate. Single crystalline black needles were obtained by metathesis of **2d**$^+$OTf$^-$ and Et_4NI in MeCN in 88% yield: mp 135 °C decomp.; IR ν_{max} 2218 (CN) cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_7I{\cdot}CH_3CN$: C, 55.14; H, 2.67; N, 19.79. Found: C, 54.99; H, 2.87; N, 19.96. Crystal data are as follows: $C_{26}H_{15}N_8I$, M 566.37, triclinic, $P\bar{1}$, a=10.269(3) Å, b=15.255(9)Å, c=9.186(3) Å, α=91.34(4)°, β=113.76(4)°, γ=92.93(4)°, U=1311.2(9) Å^3, D_c (Z=2)=1.435 g cm^{-1}, μ=12.336 cm^{-1}. A total of 5745 unique reflection data ($2\theta<55°$) were collected by a Rigaku AFC-5R four-circle diffractometer with a rotating anode (45 kV, 200 mA, Mo Kα, T=290 K). The structure was solved by the direct method, and non-hydrogen atoms were refined with the anisotropic temperature factors by the block-diagonal least-squares method. Hydrogen atoms were not included in the analysis. Positions of solvent molecules are disordered. The final R value is 0.068 for 4575 independent reflections with $I>3\sigma I$ and 344 parameters.

5. Supplementary Material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 219213 (**1a**), 219214 (**1d**), and 219608 (**2d**$^+$**I**$^-$ salt). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Dynamic NMR investigation of two new interconvertible diasteriomeric epimers of natural 2-benzyl-2-hydroxybenzofuranone derivative from *Pterocarpus marsupium*☆,☆☆

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Abstract—The first example of a pair of interconvertible diastereomeric epimers 2α/2β-hydroxy-2-*p*-hydroxybenzyl-3(2*H*)-benzofuranone-7-C-β-D-glucopyranoside isolated from the heartwood of *Pterocarpus marsupium* is reported. The predominance of **1a** over **1b** was supported by dynamic exchange rates and activation parameters obtained from NMR studies. The mechanism of this unique phenomenon is thought to be operative by the formation of diketone as suggested by deuterium exchange.

1. Introduction

Wooden tumbler made up of heartwood of *Pterocarpus marsupium* also known as Indian kino or Bijay sar is used for drinking water as a traditional remedy in India because of its medicinal property[1,2] and notably for controlling blood sugar level. The plant is reported to be rich in polyphenolic compounds.[3] To determine the chemical basis for traditional cures, we have isolated constituents from the aqueous extract of the freshly prepared wooden tumbler as described in Section 4. Herein, we report a new pair of exchangeable diastereomeric epimers **1a** and **1b** which are interconverting so readily that they exist as an inseparable, equilibrium mixture at room temperature.

2. Results and discussion

2.1. NMR analysis and structural determination

The diastereomeric marsuposide **1a** and **1b**, (2α/2β-hydroxy-2-*p*-hydroxybenzyl-3(2*H*)-benzofuranone-7-C-β-D-glucopyranoside), gave the molecular composition as $C_{21}H_{22}O_{10}$ (FAB-MS, *m/z* 435 $[M+H]^+$), and was supported by ^1H and ^{13}C NMR spectroscopic data. The ^1H NMR indicated the material as a mixture of two epimeric diasteromeric compounds. Unfortunately, these proved to be inseparable by HPLC using several solvent combinations. ^{13}C NMR along with DEPT spectra provided further evidence for the presence of two isomeric compounds, showing four similar chemical shifts in their 18-carbon system. The ^1H NMR in CD_3OD indicated the presence of two anomeric protons at 4.71 and 4.75 ppm, along with other sugar and aliphatic resonances between 2.90 and 4.80 ppm. In the aromatic region two sets of *ortho* coupled aromatic protons at 6.59, 7.13 and 6.59, 7.03 ppm and a pair of A_2B_2 system at 6.47, 7.28 and 6.46, 7.29 ppm, respectively. The integral of two distinct signals at 7.03 and 7.13 ppm suggested the ratio of the diastereomers as 1.00:0.78. The complete structure determination was carried out by the combination of COSY, HMQC and HMBC (See Supporting information) spectra. The COSY cross peaks correlation was straight forward, having two sets of *ortho*-coupled spin system in the aromatic region. In HMQC spectra, the anomeric protons correlated with a carbon at 75.1 ppm, characteristic of C_1-substituted glucosides. The starting point for the assignment and evaluating the positions of the various functional moieties in the benzofuranone system was the benzylic methylene proton which appeared as two sets of AB quartets at 3.08, 3.11 and 3.02, 3.11 having a geminal coupling of 13.7 Hz.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.01.012

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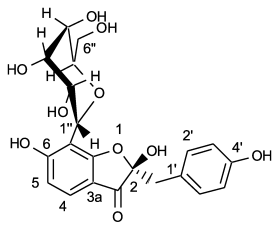


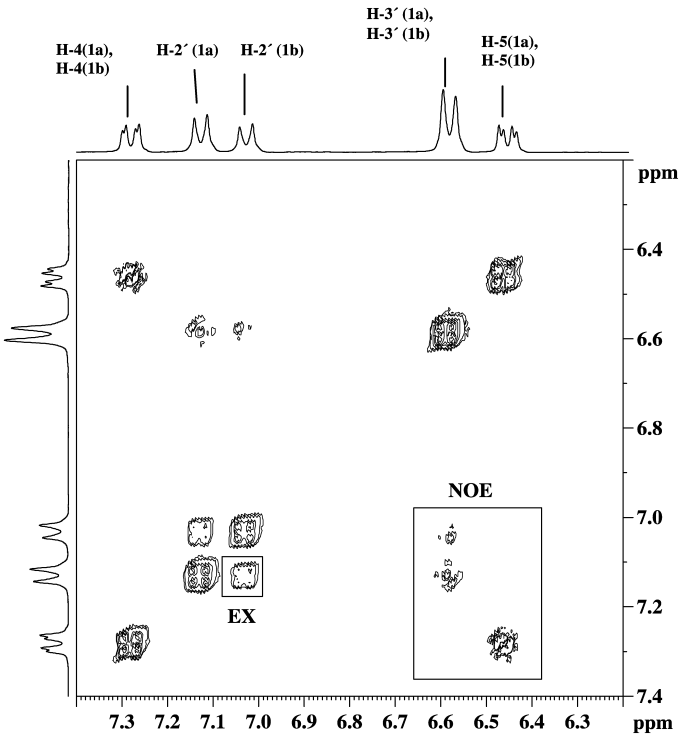
1a

1b = C-2 epimer

In the HMBC spectrum these protons showed cross peaks with the carbonyl carbon of the benzofuranone at 199.7 ppm, the aromatic CH carbons of the phenyl ring (125.8, 133.2, 132.7 ppm) and with the quaternary carbons at 107.6 and 107.8 ppm, respectively. These quaternary carbons were assigned to be C-2 of the benzofuranone ring having hydroxyl and benzylic phenol as substituents. The point of attachment of the C-glucose and a hydroxyl function furan was relatively straightforward as H-1″ of the glucose gave cross peaks with the sets of carbons at (107.8, 107.6), (168.1, 168.0) and (173.3, 173.2) ppm in the HMBC corresponded to the C-7, C-6 bearing hydroxyl function and C-7a, respectively. Thus specific and detailed ^{1}H and ^{13}C assignments of both the isomers could be differentiated from HMBC cross peak correlations and is provided in Section 4. The relative stereochemistry at C-2 could not be defined, even with ROESY and HSQMBC.[4] Moreover, an unusual exchange positive cross peak between H-2′ of **1a** and **1b** was observed in the ROESY spectrum. This prompted us to re-investigate its internal dynamics by two-dimensional exchange spectroscopy (NOESY) in deuterated methanol, and acetonitrile. Cross peaks appear with a positive sign (Fig. 1) between the corresponding protons of different epimers (Ex), whereas NOE peaks appear as negative sign between different protons of the same epimer. The interconversion was also observed in deuterated acetone at room temperature as found from the 2D exchange spectroscopy and in DMSO-d_6 at 353 K, respectively. The higher temperature required in DMSO-d_6 can be attributed to the formation of hydroxy–DMSO complex[5] and hence stabilizing the cyclic hemiacetal form, which prevents the interconversion at room temperature. Whereas, weak intermolecular hydrogen bond interaction may not restrict the interconversion in case of acetone-d_6.

Further, it is pertinent to point out here that in the case of maesopsin and related bioflavonoid, reported by Ferreira[6] and co-workers stated the complexity of the resulting fraction as mixtures by ^{1}H NMR spectrum and proposed derivatization being prerequisite for sample purity, suggested that this was consistent with the existence of epimeric mixtures. Methylation of the compound resulted in the separation of the epimeric diasteromers using FCC by the above-mentioned workers, indicated methylation stops the interconversion.

With due course of time, change in the ^{1}H and ^{13}C NMR pattern of benzylic methylene (CH_2) Figure 2(a) was observed in CD_3OD thus indicating the incorporation of deuterium, respectively. This was further confirmed by ^{2}H NMR, FAB-MS and ES-MS. ^{1}H NMR integration ratio showed 75% of total deuterium incorporation. Whereas in ES-MS the break up percentage of native form, one deuterated incorporated and two deuterium incorporated at the benzylic position was found to be 9.6, 39.4 and 50.9%, respectively. The important feature of the ^{2}H NMR spectra Figure 2(b) was the observation of a broad peak between



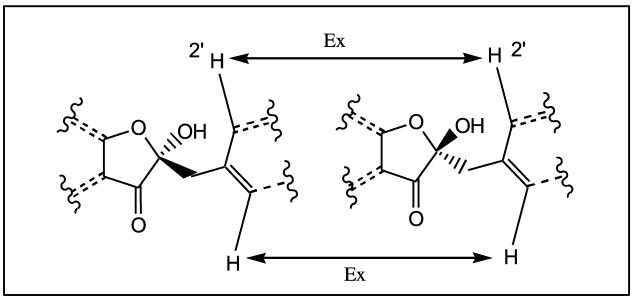


Figure 1. Portion of the NOESY spectrum showing the exchange cross peaks amongst epimers in CD_3OD at 298 K (mixing time of 400 ms).

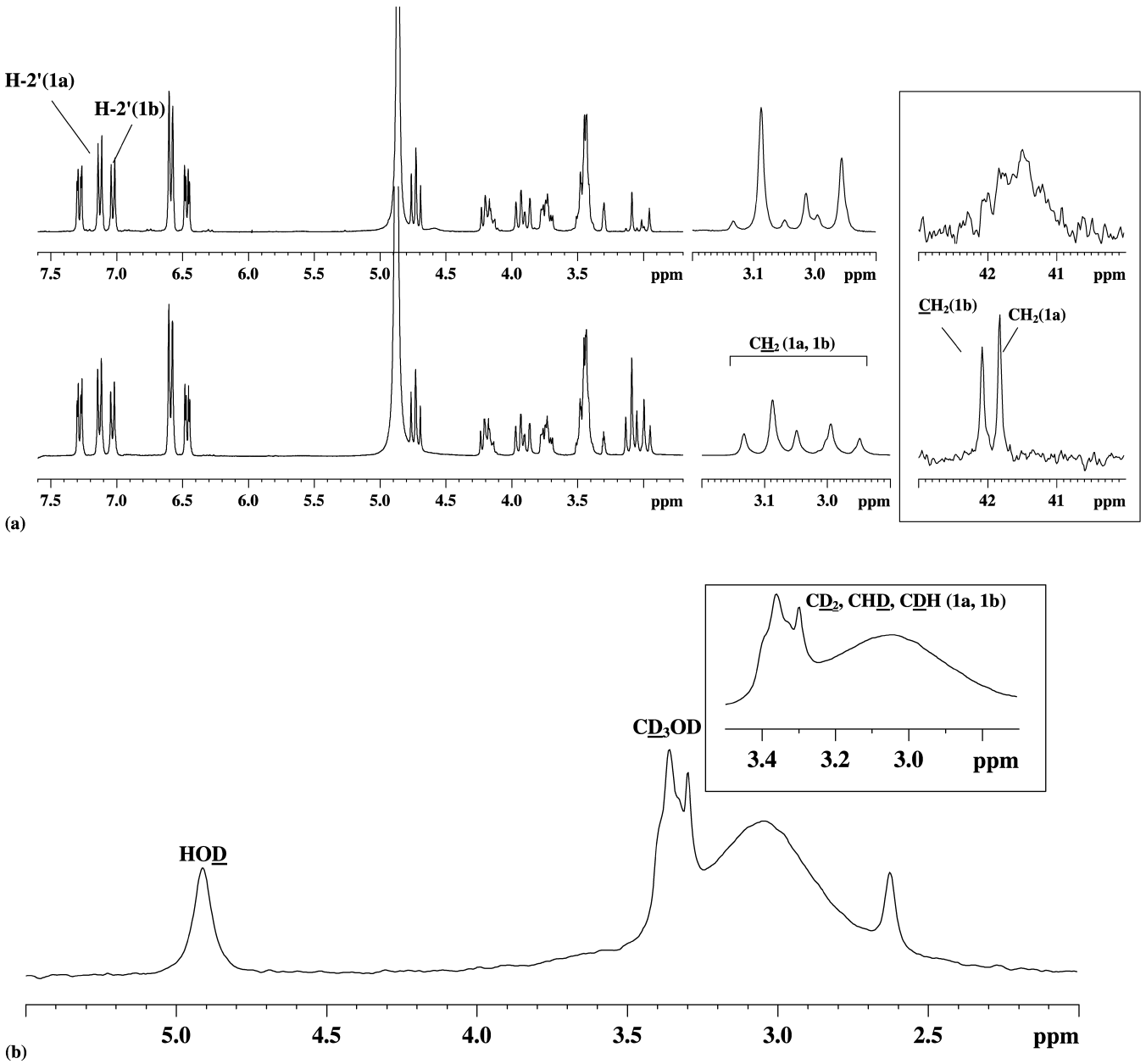


Figure 2. (a) ^{1}H and part of ^{13}C NMR in CD_3OD before (below) and after (above) deuterium exchange. (b) ^{2}H NMR in CH_3OH after deuterium exchange.

2.90 and 3.20 ppm along with other expected signals representing different deuterated species. No peaks were observed beyond δ 2.0 and 5.5 ppm. Furthermore, the ES-MS in CH_3OH showed peaks at *m/z* 435, 436 and 437 and in CD_3OD at *m/z* 464, 465 and 466 $[M+7+Na]^+$ corresponding to **1a** or **1b** in native form, **1a** or **1b** with one deuterium incorporated, **1a** or **1b** with two deuterium incorporated depicting the presence of sets of isomers. Seven corresponds to the number of exchangeable –OH protons in CD_3OD (Supporting information). In order to define the relative stereochemistry at C-2, CD spectrometry[6,7] was carried out. The CD spectra (Fig. 3) of the mixture of epimers provided the resultant spectrum, since the racemization will lead to proportional diminishing of the transition.[8]

Negative amplitude cotton effect for $\pi\rightarrow\pi^*$ transition at 320 nm and positive amplitude cotton effect for $n\rightarrow\pi^*$ transition at 350 nm of the CD spectra[6,7] suggested 2*R* (**1a**) is in excess with 2*S* (**1b**), respectively, and is in accord with the ^{1}H NMR spectrum. To establish the kinetic order character of the exchange process, the concentration dependence of the NOESY spectra has been studied. We found no change in the intensity of the peak upon changing the 55.3 mM concentration to half at 298 K with a mixing

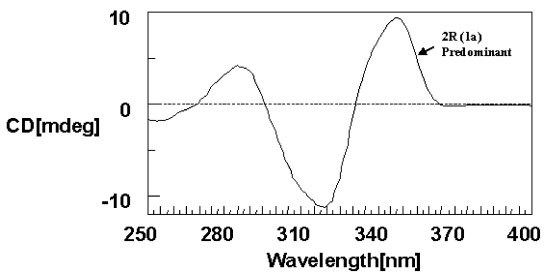


Figure 3. Resultant CD spectra of marsuposides **1a** and **1b**.

time of 400 ms. Under these conditions, the exchange was about 22% complete, and a substantial change in the rate constants would have been immediately reflected in the intensity of the exchange peak for a higher order reaction. It was concluded that the exchange process follows first-order kinetics. The rate of the first order kinetics was calculated by performing phase sensitive 2D-NOESY using 200, 300 and 400 ms as mixing time at five different temperatures; 293, 298, 303, 313 and 318 K in CD_3OD. The values of the rate constants have been obtained by Eq. 1[9] and are presented in Table 1.

Table 1. Rate constants determined by using Eq. 1[9]

T/K	293	298	303	313	318
k_1 (s^{-1})	0.38±0.01	0.51±0.06	0.69±0.12	1.29±0.34	1.54±0.49
k_{-1} (s^{-1})	0.47±0.02	0.61±0.12	0.76±0.20	1.52±0.38	1.71±0.75

$$K \simeq 1/[t_M(I_D/I_C + 1)] \quad (1)$$

Similarly, rates were calculated in CD_3CN using 200, 300 and 400 ms mixing times at five different temperatures; 268, 273, 278, 283 and 288 K (Table 2).

Table 2. Rate constants determined by using Eq. 1[9]

T/K	268	273	278	283	288
k_1 (s^{-1})	0.32±0.07	0.46±0.13	0.68±0.22	1.01±0.22	1.35±0.54
k_{-1} (s^{-1})	0.42±0.03	0.58±0.10	0.84±0.22	1.23±0.20	1.61±0.45

The temperature chosen in case of CD_3CN was based on the fact that at 298 K the peaks were broad due to the presence of fast exchange between **1a** and **1b**. At temperatures lesser than 293 K, good separation of H-2′ signal of **1a** and **1b** was observed.

Notably, different rates were observed in $(CD_3)_2C{=}O$ and DMSO-d_6 depicting the effect of the solvent. Since the reaction rate constants have been determined at different temperatures in CD_3OD and CD_3CN an estimation of the activation parameters were possible using the Eyring's equation (Eq. 2).[10]

$$\ln(k/T) = 23.76 - (-\Delta H^{\ddagger}/RT) + (\Delta S^{\ddagger}/R) \quad (2)$$

The straight line in the Erying plot (Figs. 4 and 5) suggested that the two rate constants have the real physical meaning rather than just being fit parameters, thereby adding credibility to the exchange process.

The activation parameters determined from Eyring plot are given in Table 3. With regard to mechanistic interpretation,

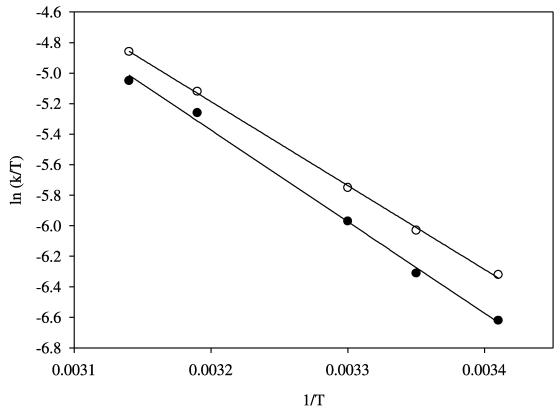


Figure 4. Eyring plot of the rate constants in CD_3OD with 200 ms mixing time determined by fitting the rate constants k_1 and k_{-1} to the experimental data at different temperatures.

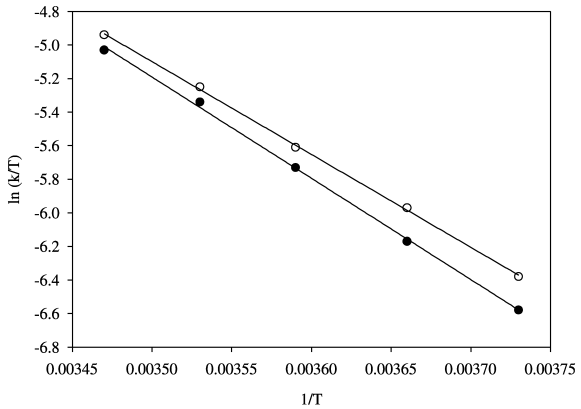


Figure 5. Eyring plot of the rate constants in CD_3CN determined with 200 ms mixing time by fitting the rate constants k_1 and k_{-1} to the experimental data at different temperatures.

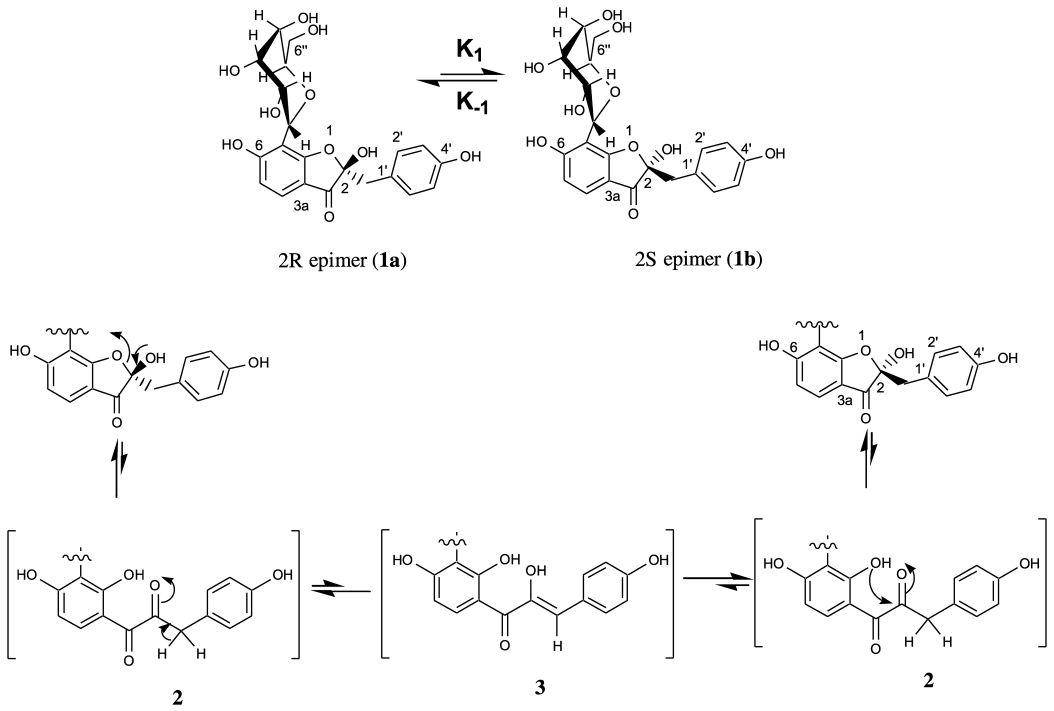
a rationalization is given in Scheme 1 involving **2** as a conceivable intermediate which converted into the enol form. Hence, the key pathway for the deuterium incorporation in CD_3OD was envisaged to be keto enol tautomerism (Scheme 2).

Consistent with this proposal, the $\Delta H^{\ddagger}$ of isomerization clearly suggests that **1a** would be more populated than **1b**, as borne out from the NMR measurements (Tables 1 and 2). However, no characteristics signals in ^1H and ^{13}C NMR spectra were observed in our efforts to trace the intermediates diketo **2** and enol form **3** at the lowest possible temperature of 223 K in CD_3OD and 233 K in CD_3CN. This suggested that the relative concentration of **2** is lower than the NMR dynamic range (NMR detection limit) and for **3** the equilibrium lies well over towards the keto form. Hence the experimental evidence for **2** and **3** could not be achieved.

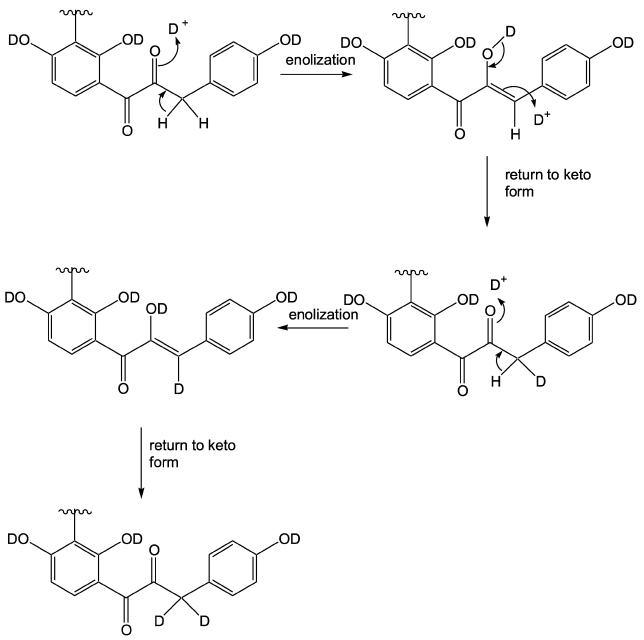
Table 3. Activation parameters obtained from Eyring analysis by using Eq. 2 for rate constants given in Tables 1 and 2[a]

	CD_3OD		CD_3CN	
	k_1	k_{-1}	k_1	k_{-1}
$\Delta H^{\ddagger}$ (kJ/mol)	42.0±7.4	39.5±10.2	44.9±15.1	41.7±10.1
$\Delta S^{\ddagger}$ (J/mol K)	−107.3±25.4	−114.2±34.0	−83.8±48.1	−93.6±43.1

[a] The indicated standard errors of regression take into account the error margins of the individual rate constants.



Scheme 1. Mechanism of interconvertibility.



Scheme 2. Proposed mechanism of deuterium incorporation.

3. Conclusion

In summary, we have demonstrated the exchange between new diastereomeric epimers 2α/2β-hydroxy-2-*p*-hydroxybenzyl-3(2*H*)-benzofuranone-7-C-β-D-glucopyranoside by NMR exchange spectroscopy (NOESY) at different temperatures in different solvents. The first order rates confirmed 2*R* to be more populated. The mechanism of exchange involves ring opening to form diketone followed by keto enol tautomerism which was evident by deuterium incorporation in CD_3OD as studied by ^2H NMR and ES-MS. Due to the exchange property of the molecule, attempts to isolate the individual native diastereomeric epimers at room temperature are unlikely to succeed even using chiral columns.

4. Experimental

4.1. Extraction

The freshly prepared wooden tumbler was purchased from the local Indian market. It was crushed, powdered and was exhaustively extracted with hot water (4×16 ml). The concentrated, extract (500 g) was suspended in H_2O (2.0 l) and successively partitioned with EtOAc and *n*-BuOH. Part (65 g) of the *n*-BuOH extract (170 g) on repeated flash chromatography over silica gel using $CHCl_3$–MeOH (9:1) as solvent, and HPLC separation afforded marsuposide (**1a/1b**, 50 mg).

4.2. General procedure

Melting points was recorded with melting point apparatus and is uncorrected. IR spectra were recorded with FTIR spectrometer (Perkin–Elmer RXI) as a KBr pallet (expressed in cm^{-1}). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in CD_3OD, CD_3CN, $(CD_3)_2CO$ and DMSO-d_6 (Aldrich) as solvent on a Bruker Avance DRX-300 calibrated with TMS. ^2H NMR (46 MHz) was recorded in CH_3OH as solvent in unlock mode by online shimming of the sample using interactive 1D ^1H NMR spectrum. NMR chemical shifts determined from HMQC and HMBC data are reported in δ (ppm) were referenced to TMS (0.0 ppm) for proton and carbon. Optical rotation was measured with a polarimeter (Rudolf Autopol III) using sodium light (D line 589.3 nm) at 25 °C. CD data were recorded in MeOH on a JASCO J-710 spectropolarimeter at

25 °C. ES-MS was recorded in CD_3OD and CH_3OH on a Micromass Quattro II. The FAB-MS was recorded using a Jeol SX-120/DA6000 mass spectrometer using Ar as the FAB gas. TLC was performed on a precoated Merck Aluminium sheets (silica gel 60 PF_{254}) and the column chromatography was performed on 200–400 mesh silica gel.

Marsuposide, light yellow crystalline, mp 156–158 °C, $[\alpha]_D^{26}$ +8.4° (*c* 0.225, CH_3OH) IR (KBr, $\nu\,cm^{-1}$) 3300, 1680, 1608, 1510, 1444.

4.2.1. Compound 1a. ^1H NMR (300 MHz, CD_3OD): 3.11 (1H, d, *J*=13.9 Hz, CH_{2a}), 3.08 (1H, d, *J*=13.9 Hz, CH_{2b}), 7.28 (1H, d, *J*=8.4 Hz, H-4), 6.47 (1H, d, *J*=8.4 Hz, H-5), 7.13 (1H, d, *J*=8.4 Hz, H-2′), 6.59 (1H, d, *J*=8.4 Hz, H-3′), 4.75 (1H, d, *J*=10.3 Hz, H-1″), 4.20 (1H, m, H-2″), 3.44 (1H, m, H-3″), 3.45 (1H, m, H-4″), 3.45 (1H, m, H-5″), 3.11(1H, dd, *J*=12.1, 2.2 Hz, H-6″a), 3.76 (1H, dd, *J*=10.3, 5.9 Hz, H-6″b). ^{13}C NMR (75 MHz, CD_3OD): 107.6 (C-2), 199.7 (C-3), 41.8 (CH_2), 113.3 (C-3a), 126.8 (C-4), 112.8 (C-5), 168.1 (C-6), 110.3 (C-7), 173.4 (C-7a), 125.8 (C-1′), 133.2 (C-2′), 115.9 (C-3′), 157.3 (C-4′), 75.0 (C-1″), 72.5 (C-2″), 80.3 (C-3″), 72.4 (C-4″), 82.7 (C-5″), 63.7 (C-6″).

4.2.2. Compound 1b. ^1H NMR (300 MHz, CD_3OD): 3.11 (1H, d, *J*=13.9 Hz, CH_{2a}), 3.02 (1H, d, *J*=13.9 Hz, CH_{2b}), 7.29 (1H, d, *J*=8.4 Hz, H-4), 6.46 (1H, d, *J*=8.4 Hz, H-5), 7.03 (1H, d, *J*=8.4 Hz, H-2′), 6.59 (1H, d, *J*=8.4 Hz, H-3′), 4.71 (1H, d, *J*=10.3 Hz, H-1″), 4.10 (1H, m, H-2″), 3.44 (1H, m, H-3″), 3.45 (1H, m, H-4″), 3.45 (1H, m, H-5″), 3.88 (1H, dd, *J*=12.1, 2.2 Hz, H-6″a), 3.71 (1H, dd, *J*=10.0, 4.8 Hz, H-6″b). ^{13}C NMR (75 MHz, CD_3OD): 107.8 (C-2), 199.7 (C-3), 42.1 (CH_2), 113.2 (C-3a), 126.8 (C-4), 113.0 (C-5), 167.9 (C-6), 109.9 (C-7), 173.3 (C-7a), 125.8 (C-1′), 132.7 (C-2′), 116.0 (C-3′), 157.4 (C-4′), 75.2 (C-1″), 72.7 (C-2″), 80.3 (C-3″), 71.8 (C-4″), 82.7 (C-5″), 63.1 (C-6″).

FAB-MS; *m*/*z* 435.0 $[M+H]^+$. Anal. calcd for $C_{21}H_{22}O_{10}$: C, 58.06; H, 5.10. Found C, 57.99; H, 5.04%.

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Synthesis of phenylethyne-linked porphyrin dyads

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Abstract—Four new porphyrin dyads have been prepared for studies in artificial photosynthesis. The two porphyrins are joined at the *meso* positions via a phenylethyne linker and are present in zinc/zinc or zinc/free base metalation states. The porphyrin bearing the ethynyl unit incorporates zero, one, or two pentafluorophenyl groups at non-linking *meso* positions for tuning the porphyrin redox potentials. The synthetic approach entailed Pd-mediated coupling of porphyrin building blocks that bear a single ethynylphenyl or bromo/iodo substituent.

1. Introduction

Molecular architectures that incorporate multiple porphyrinic pigments can serve as prototype light-harvesting antennas and charge-separation devices for studies in artificial photosynthesis.[1–8] In covalently linked architectures, the chief function of the linker is to anchor the porphyrinic units in a defined location. In addition to this mechanical role, the linker can interact electronically with the porphyrin (altering redox potentials, absorption/emission spectra, and excited-state lifetimes) and also provide a conduit for electronic communication between the porphyrins.

In studies of multiporphyrin light-harvesting arrays, we found that the use of aryl linkers with *meso*-substituted porphyrins resulted in multiporphyrin arrays with visible absorption spectra that were essentially unchanged from those of benchmark reference porphyrins. However, excited-state energy transfer between a zinc porphyrin and a free base porphyrin occurred with high efficiency: the rate was found to be $(38\ \text{ps})^{-1}$, $(24\ \text{ps})^{-1}$, or $(3.5\ \text{ps})^{-1}$ for the porphyrin dyad joined by a 4,4′-diphenylbutadiyne,[9] 4,4′-diphenylethyne,[10] or 1,4-phenylene linker,[11] respectively (Chart 1). The mechanism of energy transfer was found to be dominated by a through-bond contribution (mediated by the linker) rather than a through-space contribution (which would be independent of linker).[12] To investigate the effects of a slightly stronger coupling, we considered the use of a linker that contains an ethynyl unit attached directly to the porphyrin macrocycle.

The study of ethynyl-porphyrins originated with the work of Arnold, who synthesized a nickel(II)octaethylporphyrin bearing an ethynyl group at the *meso* position.[13] Further work by the group of Hevesi[14] and by Anderson[15] led to tetraalkynyl-substituted porphyrins. Ethynyl- or butadiynyl-linked multiporphyrin arrays have been synthesized and characterized by the groups of Arnold,[16–22] Anderson,[23–27] and Therien.[28,29] The general features of alkynyl porphyrins are as follows: (i) significantly red-shifted absorption spectra, (ii) intensified Q-bands relative to the Soret bands, and (iii) less negative reduction potentials.

Milgrom extended this work to porphyrins bearing arylethynyl substituents at the four *meso* positions.[30–35] The

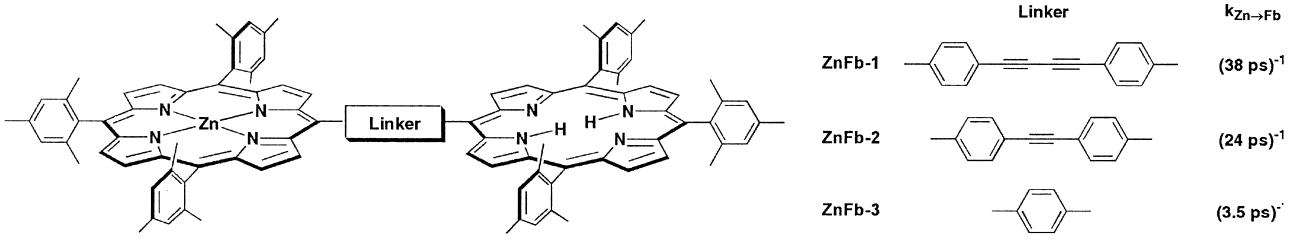

Chart 1.

Keywords: Porphyrin; Dipyrromethane; Ethyne; Phenylethyne; Energy transfer.
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arylethynyl units enable incorporation of a variety of substituents on the aryl unit for electronic modulation or increased solubility of the porphyrin,[30–44] and cause a greater red shift and intensification of the Q bands versus that of ethynyl groups alone. Indeed, the spectral perturbation is so pronounced for *meso*-tetrakis(phenylethynyl)-porphyrin versus *meso*-tetraphenylporphyrin that the former afford green solutions, prompting Milgrom to term the former 'chlorphyrins'.[30] Nakano et al. reported the synthesis and energy-transfer properties of all-zinc porphyrin triads wherein the linker was a phenylethynyl unit, or the central porphyrin was substituted with two non-linking phenylethynyl groups.[45] The phenylethynyl-substituted porphyrin exhibits red-shifted spectral features and functions as the low energy-trapping component in the light-harvesting array. In general, in a phenylethyne-linked dyad composed of identical porphyrin components, the ethyne-substituted porphyrin is shifted to lower energy and serves as the acceptor while the phenyl-substituted porphyrin is energetically unperturbed and serves as the donor.

In this paper, we describe the synthesis of porphyrin dyads where the porphyrins are joined by a phenylethyne linker and the two porphyrins are in zinc/free base or zinc/zinc metalation states (Chart 2). The dyads enable the role of the phenylethyne linker in mediating excited-state energy transfer to be probed, particularly by comparison with the dyads described in Chart 1. In addition, we prepared a set of dyads wherein one porphyrin contains one or two pentafluorophenyl groups at non-linking *meso* positions. The pentafluorophenyl groups enable tuning of the energy levels of the porphyrin, thereby opening the possibility of employing the dyads as charge-separation units. For comparison purposes, we have also prepared and characterized a set of benchmark porphyrins containing one or two *meso*-phenylethynyl groups. The electronic and

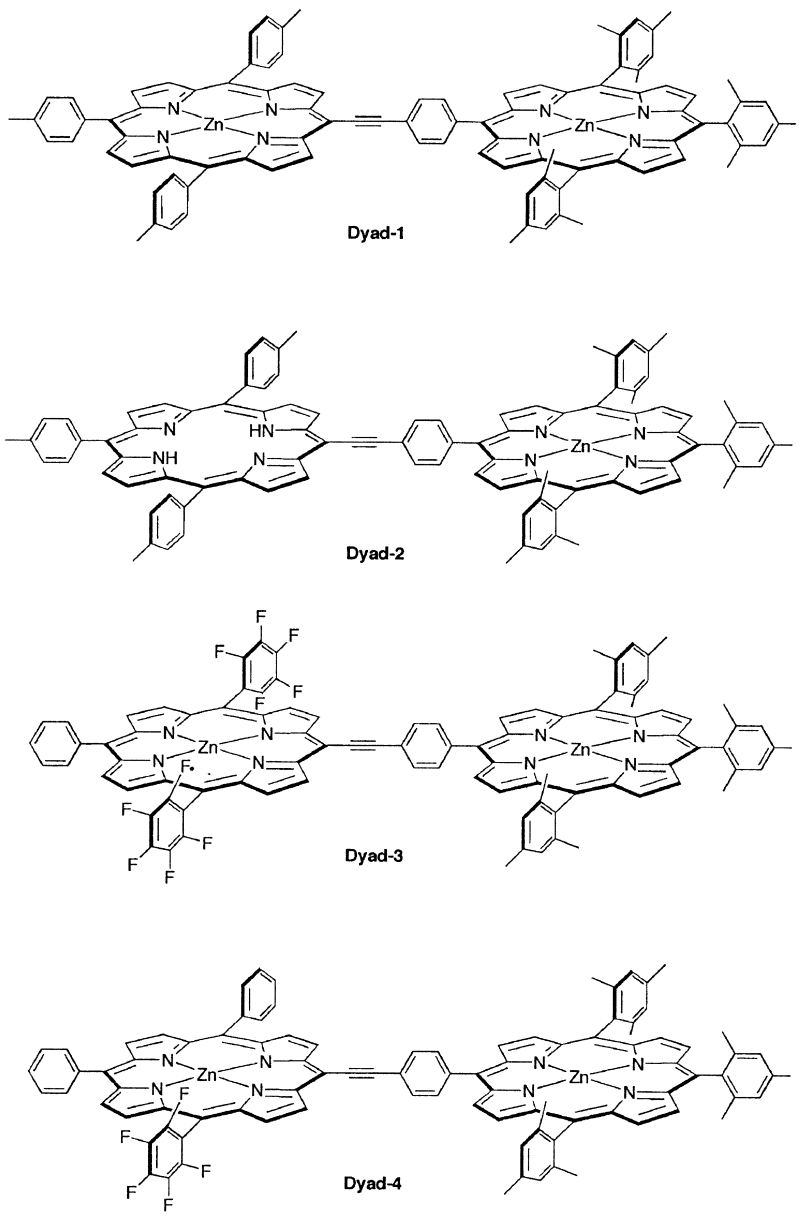


Chart 2.

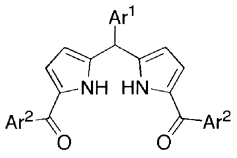
photochemical properties of the dyads and benchmarks are reported elsewhere.[46]

2. Results and discussion

The synthetic route to the phenylethyne-linked porphyrin dyads relies on three methods: (1) the rational synthesis of porphyrin building blocks that bear distinct patterns of substituents,[47,48] including a single ethynylphenyl group or one free *meso* position, (2) halogenation of the lone *meso* position,[49,50] and (3) Pd-mediated coupling of an ethynylphenyl-porphyrin and a halo-porphyrin.[51,52] This route affords control over the metalation state and substituent pattern in each porphyrin in the dyad. While each method is well established, this approach to phenylethyne-linked dyads composed of zinc and free base porphyrins has not been investigated previously.

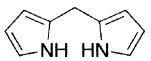
2.1. Synthesis of building blocks

The *meso*-halo-substituted porphyrin building blocks incorporate zero, one, or two pentafluorophenyl substituents to systematically increase the oxidation potential of the porphyrin. The porphyrins with zero or two pentafluorophenyl groups are *trans*-AB_2-porphyrins while those with one pentafluorophenyl group are *cis*-AB_2-porphyrins. The



1a-c

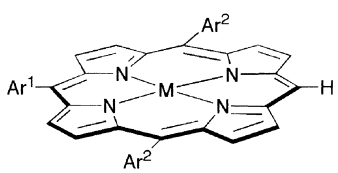
(1) $NaBH_4$, THF, MeOH (10:1)
(2)



2a

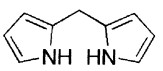
$Yb(OTf)_3$ or $InCl_3$, CH_2Cl_2, rt
20-30 min
(3) DDQ, rt, 1 h

and (optional)
(4) $Zn(OAc)_2 \cdot 2H_2O$
$CHCl_3$, MeOH, rt



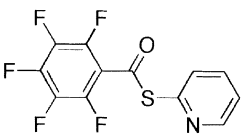
Reactant	Porphyrin	Ar^1	Ar^2	M	Yield (%)
1a ⟶	**Fb3a**	*p*-Tol	*p*-Tol	H,H	14
1b ⟶	**Zn3b**	Ph	Ph	Zn	12
1c ⟶	**Zn3c**	Ph	C_6F_5	Zn	14

Scheme 1.



2a

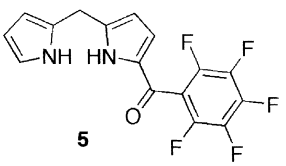
(1) EtMgBr, THF, -78 °C
(2)



4

59%

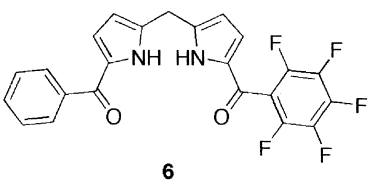
-78 °C



5

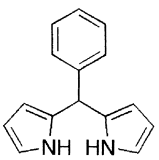
81%

(1) EtMgBr, toluene, rt
(2) benzoyl chloride
toluene



6

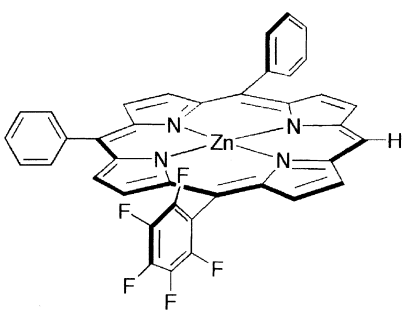
(1) $NaBH_4$, THF, MeOH (10:1)
30 min
(2)



2b

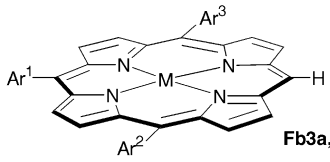
18%

$InCl_3$, CH_2Cl_2
rt, 30 min
(3) DDQ, rt, 1 h
(4) $Zn(OAc)_2 \cdot 2H_2O$
$CHCl_3$, MeOH, rt, 16 h



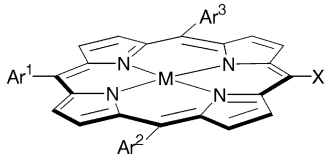
Zn3d

Scheme 2.



Fb3a, Zn3a-d

NBS, pyridine, $CHCl_3$
0 °C, 30 min
or
I_2, [Bis(trifluoroacetoxy)iodo]benzene
$CHCl_3$, pyridine, rt, 1h



Reactant		Porphyrin	Ar^1	Ar^2	Ar^3	M	X	Yield (%)
Fb3a	→	**Fb7a**	*p*-Tol	*p*-Tol	*p*-Tol	H,H	Br	98
Zn3b	→	**Zn7b**	Ph	Ph	Ph	Zn	Br	77
Zn3c	→	**Zn7c**	Ph	C_6F_5	C_6F_5	Zn	Br	96
Zn3d	→	**Zn7d**	Ph	Ph	C_6F_5	Zn	Br	91
Fb3a	→	**Fb8a**	*p*-Tol	*p*-Tol	*p*-Tol	H,H	I	82

Scheme 3.

synthesis of both types of porphyrins proceeds by condensation of a dipyrromethane-dicarbinol and a dipyrromethane followed by oxidation.[47]

The synthesis of the *trans*-AB_2-porphyrins begins with known diacyldipyrromethanes. Thus, reduction of a diacyldipyrromethane (**1a**–**c**)[47,53] with $NaBH_4$ in dry THF/methanol at room temperature gave the corresponding dipyrromethane-dicarbinol. Condensation of the latter with dipyrromethane (**2a**) under new catalysis conditions[54] that employ a mild Lewis acid ($InCl_3$ or $Yb(OTf)_3$ in CH_2Cl_2 at room temperature) followed by oxidation with DDQ afforded the free base porphyrin. In one case, the free base porphyrin was purified (**Fb3a**) while in others, the crude product was treated with zinc acetate and the corresponding zinc porphyrin was obtained (**Zn3b** and **Zn3c**) (Scheme 1). It is noteworthy that earlier synthetic procedures were developed for preparing the triphenylporphyrin **Fb3a** and its zinc chelate **Zn3a**, including (1) mixed-aldehyde condensation of benzaldehyde, paraformaldehyde, and pyrrole,[55] (2) reaction of 5,15-diphenylporphyrin with a phenyl lithium reagent;[56] and (3) Suzuki coupling of phenylboronic acid and Zn(II)-5-bromo-10,20-diphenylporphyrin.[57]

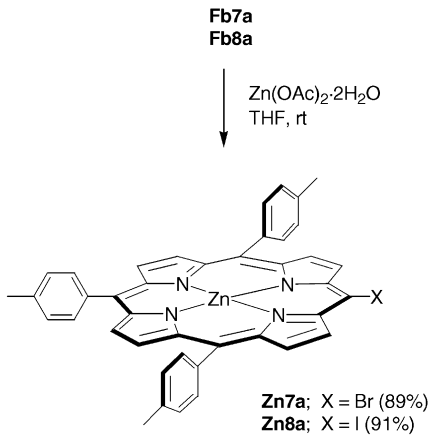
The synthesis of the *cis*-AB_2-porphyrin requires access to an appropriate 1,9-diacyldipyrromethane, which was prepared following the general procedures for the synthesis of ABCD-porphyrins.[47] Thus, dipyrromethane (**2a**)[58,59] was treated with *S*-2-pyridyl pentafluorobenzothioate (**4**)[48] in the presence of EtMgBr in THF, affording the 1-acyl-dipyrromethane **5** in 59% yield. The reaction of **5** with the more potent acylating agent benzoyl chloride in the presence of EtMgBr in toluene gave the 1,9-diacyldipyrromethane **6** in 81% yield. Reduction of **6** with $NaBH_4$ in dry THF/methanol at room temperature gave the corresponding dipyrromethane-dicarbinol, which was condensed with 5-phenyldipyrromethane (**2b**) in the presence of $InCl_3$ in CH_2Cl_2. Subsequent oxidation with DDQ and metalation with $Zn(OAc)_2{\cdot}2H_2O$ afforded the pentafluorophenyl-substituted porphyrin **Zn3d** in 18% yield (Scheme 2).

The availability of porphyrins with a single free *meso* position facilitated preparation of the mono-halo-substituted porphyrins. We prepared both *meso*-bromo and *meso*-iodo porphyrins. Bromination was carried out with either zinc or free base porphyrins (**Fb3a**, **Zn3b**–**d**) using NBS in $CHCl_3$/pyridine for 30 min at 0 °C,[49] in each case affording the mono-brominated porphyrin in high yield. The presence of one or two pentafluorophenyl groups had no adverse effect on the yield of halogenation. Iodination was carried out in one case on a free base porphyrin (**Fb3a**) using [bis(trifluoroacetoxy)iodo]benzene in $CHCl_3$/pyridine for 1 h at room temperature,[50] affording **Fb8a** in 82% yield (Scheme 3). Both procedures are straightforward and the mono-halo-porphyrins are obtained without apparent formation of poly-halogenated products.

The mono-halo-porphyrins are stable to routine handling and manipulation. The free base bromo-porphyrin **Fb7a** was metalated with zinc acetate to give **Zn7a** in 89% yield. The zinc iodo-porphyrin **Zn8a**, prepared by iodination of the zinc porphyrin, also could be prepared by zincation of the free base iodo-porphyrin **Fb8a** in 91% yield (Scheme 4).

2.2. Synthesis of phenylethyne-linked porphyrin dyads

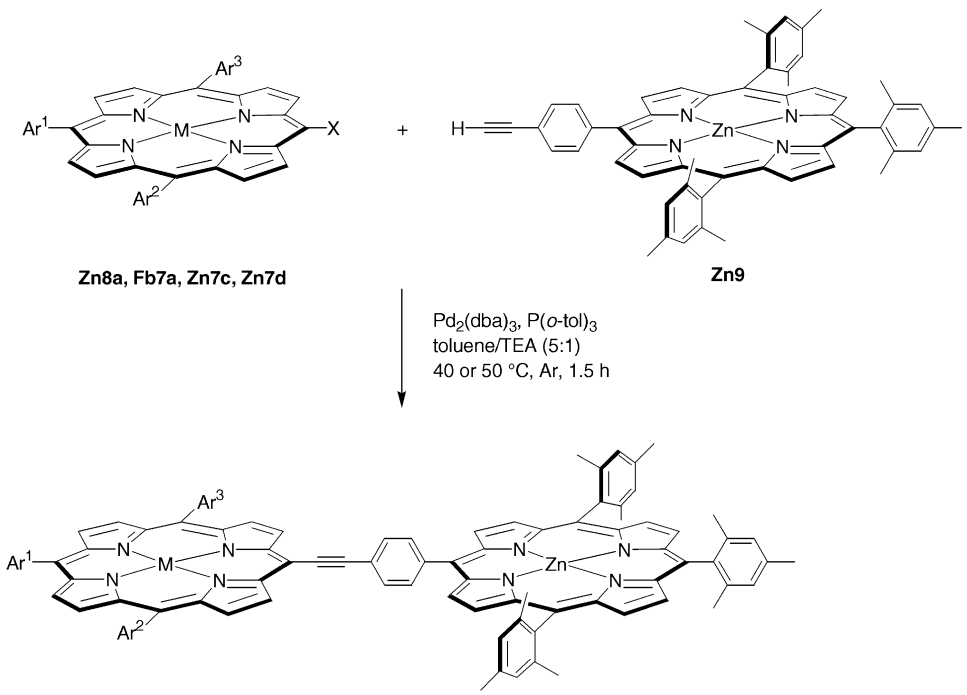
We previously developed conditions for the Sonogashira



Scheme 4.

coupling of an ethynylphenyl-porphyrin and an iodophenyl-porphyrin to give the diphenylethyne-linked porphyrin dyad.[51,52] The key features of the reaction conditions developed for this Pd-mediated coupling reaction were (1) the use of equimolar quantities of the two porphyrins, (2) the reaction in dilute solution, typically 2.5 mM for each porphyrin, (3) the use of low temperatures (e.g., 35 °C), and (4) the absence of copper, which can readily metalate free base porphyrins. We also extended this method to include bromoaryl-porphyrins.[60] The coupling reactions typically afford the desired diphenylethyne-linked porphyrin array in ~60% yield in addition to a sizable quantity of high molecular weight material (HMWM). The purification protocol entails removal of palladium reagents by silica-pad filtration, separation of the target array and HMWM by gravity-flow size exclusion chromatography (SEC), and final silica-gel chromatography to remove residual impurities (including those introduced from the SEC column).

The coupling of ethynylphenyl-porphyrin **Zn9**[51] and iodoporphyrin **Zn8a** under the standard conditions (0.38 mM $Pd_2(dba)_3$ and 3.0 mM P(*o*-tol)$_3$ in toluene/TEA (5:1) at 40 °C with 2.5 mM of each porphyrin) afforded **Dyad-1** in 56% yield accompanied by HMWM as judged by analytical SEC. Several modifications to the reaction conditions were investigated with yields estimated by analytical SEC. Reaction under continuous sonication, replacement of P(*o*-tol)$_3$ with $AsPh_3$, or an increased concentration of the porphyrin building blocks (10 mM) each gave **Dyad-1** in lower yield (~40–45%). On the other hand, reaction with a decreased concentration of the porphyrin building blocks (1.25 or 0.63 mM) gave **Dyad-1** in 60 or 65%. Alternatively, addition of samples of **Zn9** in four portions at 20 min intervals to the reaction mixture gave **Dyad-1** in 65% yield. On the basis of these results, the dyad-forming reactions were performed under Pd-coupling conditions with equimolar quantities of the two porphyrins at 0.63 mM.



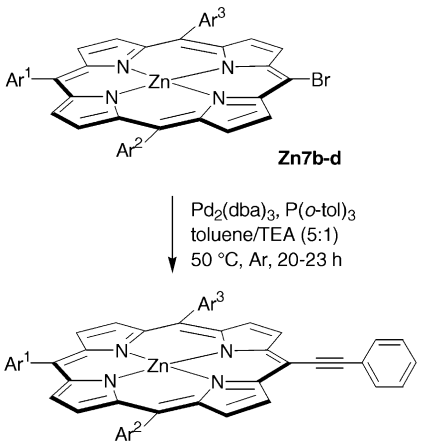
Porphyrins	Ar^1	Ar^2	Ar^3	M	X	Product	Yield (%)
Zn8a + Zn9	*p*-Tol	*p*-Tol	*p*-Tol	Zn	I	**Dyad-1**	41
Fb7a + Zn9	*p*-Tol	*p*-Tol	*p*-Tol	H, H	Br	**Dyad-2**	47
Zn7c + Zn9	Ph	C_6F_5	C_6F_5	Zn	Br	**Dyad-3**	62
Zn7d + Zn9	Ph	Ph	C_6F_5	Zn	Br	**Dyad-4**	48

Scheme 5.

The dilute-solution Pd-coupling conditions were applied to prepare **Dyad-1** as shown in Scheme 5. The same coupling conditions were employed with bromo-porphyrins to give **Dyads-2–4**, although the temperature was increased from 40 to 50 °C due to the use of a *meso*-bromo-porphyrin in place of a *meso*-iodo-porphyrin. After chromatographic workup (three column procedure: silica, SEC, silica), **Dyads-1–4** were obtained in 41–62% yield. The dyads were stable to routine handling.

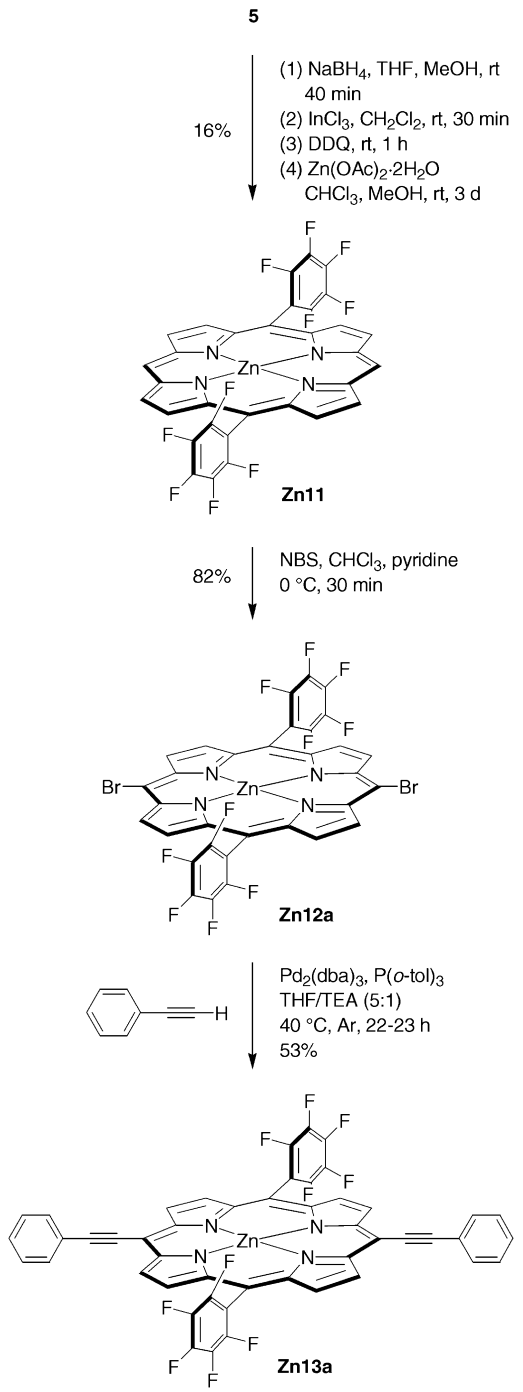
2.3. Synthesis of benchmark porphyrins

For comparison purposes, a series of porphyrins was prepared wherein each porphyrin contains one phenylethynyl group. Thus, the coupling reaction of phenylacetylene and a bromo-porphyrin (**Zn7b–d**) was performed under a slight modification to the standard conditions for bromoaryl-porphyrins [$Pd_2(dba)_3$ and P(*o*-tol)$_3$ in toluene/TEA (5:1) at 50 °C];[60] the modification entailed (1) initial reaction of 2.5 mM porphyrin and 10 mM phenylacetylene, and (2) later addition of an equal quantity of phenylacetylene. After chromatographic workup, phenylethynyl-substituted porphyrins **Zn10b–d** were obtained in 52–74% yield (Scheme 6).



Porphyrin	Ar^1	Ar^2	Ar^3	Yield (%)
Zn10b	Ph	Ph	Ph	52
Zn10c	Ph	C_6F_5	C_6F_5	74
Zn10d	Ph	Ph	C_6F_5	73

Scheme 6.

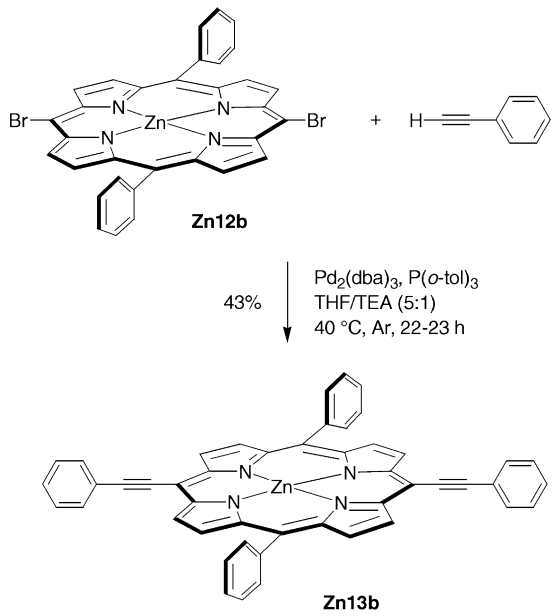


Scheme 7.

2.4. Synthesis of bis(phenylethynyl)porphyrins

Porphyrins bearing two phenylethynyl groups in a *trans*-configuration at the *meso* positions were prepared following a general procedure for the synthesis of *trans*-A_2B_2-porphyrins (Scheme 7).[48] Reduction of 1-acyldipyrromethane **5** with $NaBH_4$ in dry THF/methanol at room temperature afforded the corresponding dipyrromethane-monocarbinol, which underwent self-condensation in CH_2Cl_2 containing $InCl_3$. Subsequent oxidation with DDQ and metalation with zinc acetate afforded porphyrin **Zn11** in 16% yield. Treatment of **Zn11** with NBS afforded dibromo-porphyrin **Zn12a** in 82% yield. **Zn12a** is a known compound but the synthetic procedure has not been described.[61]

Porphyrins **Zn12a** and **Zn12b**[49] were each coupled with excess phenylacetylene in the presence of $Pd_2(dba)_3$ and P(*o*-tol)$_3$ in THF/TEA (5:1) at 40 °C. The solvent THF was employed owing to the limited solubility of the dibromo-porphyrins in toluene (Scheme 8). Upon chromatographic workup, **Zn13a** and **Zn13b** were obtained in 53 and 43% yields, respectively.



Scheme 8.

2.5. Characterization

Each porphyrin was characterized by absorption spectroscopy, laser-desorption mass spectrometry, FAB-MS, ^{1}H NMR spectroscopy, and ^{13}C NMR spectroscopy. Each dyad was examined for purity by analytical SEC and characterized by absorption spectroscopy, fluorescence spectroscopy, laser-desorption mass spectrometry, FAB-MS, ^{1}H NMR spectroscopy, and ^{13}C NMR spectroscopy (except for **Dyad-2**). It is noteworthy that the ^{13}C NMR spectra showed chemical shifts typical of porphyrins bearing four identical *meso* substituents,[62] with multiple resonances consistent with the expected pattern of substituents about the porphyrin perimeter. In the case of zinc porphyrins, characteristic signals of the α-,β-, and *meso*-carbons were easily observed. The signals of the pyrrole α-carbons were observed at 149–153 ppm, while the pyrrole β-carbons gave signals at 130–134 ppm. The chemical shifts of the *meso*-carbons depend on the adjacent substituents: *meso*-H (106 ppm), *meso*-aryl (120 ppm), *meso*-Br (103–104 ppm), *meso*-I (77 ppm), and *meso*-ethyne (100 ppm). In phenylethyne-substituted porphyrins, characteristic signals (93 and 96 ppm) of the ethyne moiety were observed.

3. Conclusions

The synthetic route employed herein relies on the rational synthesis of porphyrin building blocks followed by joining of an ethynylphenyl-porphyrin and a bromo/iodo-porphyrin in a Pd-mediated coupling reaction. The resulting phenylethyne-linked dyads contain porphyrins with defined metalation states and substitution patterns. The phenylethynyl group perturbs the optical and electronic properties of the attached porphyrin. In multiporphyrin arrays, the phenylethyne linker provides a conduit for excited-state energy transfer. The availability of rational synthetic routes to phenylethyne-linked porphyrins enables the phenylethynyl motif to be employed where appropriate in artificial photosynthetic systems.

4. Experimental

4.1. General

^{1}H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) NMR spectra were recorded in $CDCl_3$ or THF-d_8. Mass spectra of porphyrins were obtained by high-resolution fast atom bombardment (FAB-MS), by laser desorption mass spectrometry (LD-MS) with neat samples,[63] and/or by matrix assisted laser desorption mass spectrometry (MALDI-MS). Absorption and emission spectra were collected in toluene unless noted otherwise. Elemental analyses were performed by Atlantic Microlab, Inc. Melting points are uncorrected. Silica gel (Baker 40 μm average particle size) was used for column chromatography. Preparative SEC was performed using BioRad Bio-Beads SX-1 (200–400 mesh) beads. Analytical SEC was performed using an HP 1100 Series Liquid Chromatograph (column size=300 mm, 1000 Å; flow rate=0.800 mL/min; solvent=THF; quantitation at 420 and 450 nm; reference at 680 nm; oven temperature=25 °C).[64] All Pd-mediated reactions were performed using a Schlenk line. The conditions for Sonogashira reactions with porphyrins use tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) and the ligand P(*o*-tol)$_3$ in the absence of any copper reagents.[51,52] Palladium insertion and transmetalation have not been observed with these conditions. Toluene and triethylamine (TEA) were freshly distilled from CaH_2 and sparged of oxygen prior to use. Chloroform contained 0.8% ethanol as a stabilizer.

4.2. Non-commercial compounds

Compounds **1a**,[53] **1b**,[47] **1c**,[53] **2a**,[58,59] **2b**,[59] **4**,[48] **Zn9**,[51] and **Zn12b**[49] were prepared according to the literature.

4.3. Pd-coupling conditions

The standard Pd-coupling conditions[51,52,60] for use with metalloporphyrins and free base porphyrins were modified slightly for the reactions performed herein. The following dilute-solution coupling method was identified for use with an ethynylphenyl-porphyrin and a *meso*-iodo-porphyrin: [ethynylphenyl-porphyrin]=[iodo-porphyrin]=0.63 mM, [$Pd_2(dba)_3$]=0.38 mM, [P(*o*-tol)$_3$]=3.0 mM in toluene/TEA (5:1) at 40 °C. The dyad-forming reactions with a bromo-porphyrin were performed at 50 °C. The reaction of phenylacetylene and a bromo-porphyrin was carried out in a similar manner but with 2.5 mM porphyrin and a 5 or 6-fold molar excess of phenylacetylene (with accompanying Pd-coupling reagents) added in two batches.

4.4. Porphyrin building blocks

4.4.1. 5,10,15-Tris(4-methylphenyl)porphyrin (Fb3a). Following a standard procedure,[47,54]a solution of diacyldipyrromethane **1a** (1.00 g, 2.12 mmol) in dry THF/methanol (50 mL, 10:1) was treated with $NaBH_4$ (1.59 g, 42.4 mmol) at room temperature for 55 min. The reaction was quenched with aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated to dryness. The resulting dipyrromethane-dicarbinol and dipyrromethane **2a** (310 mg, 2.12 mmol) were dissolved in CH_2Cl_2 (848 mL) and treated

with $InCl_3$ (60 mg, 0.32 mmol) at room temperature for 20 min. DDQ (1.44 g, 6.36 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with TEA and concentrated to dryness. Chromatography [silica, CH_2Cl_2/hexanes (2:1)] afforded a purple solid (177 mg, 14%): ^{1}H NMR ($CDCl_3$) δ −2.97 (s, 2H), 2.70–2.75 (br s, 9H), 7.56 (d, J=7.6 Hz, 2H), 8.11 (d, J=7.6 Hz, 2H), 7.60 (d, J=7.6 Hz, 4H), 8.14 (d, J=7.6 Hz, 4H), 8.89–8.95 (m, 4H), 9.05 (d, J=4.4 Hz, 2H), 9.33 (d, J=4.4 Hz, 2H), 10.20 (s, 1H); ^{13}C NMR (THF-d_8) δ 20.77 (two peaks have overlapped), 104.68, 119.60, 120.54, 127.33, 127.62, 130.2–130.5 (broadening due to NH tautomerism), 131.0–131.6 (broadening due to NH tautomerism), 134.43, 134.66, 137.46 (two peaks have overlapped), 139.22, 140.07, 145.2–145.6 (broadening due to NH tautomerism); LD-MS obsd 580.4; FAB-MS obsd 580.2635, calcd 580.2627 ($C_{41}H_{32}N_4$); λ_{abs} 414, 509, 544, 585, 641 nm.

4.4.2. Zn(II)-5,10,15-triphenylporphyrin (Zn3b). Following a standard procedure[47,54] a solution of **1b** (300 mg, 0.700 mmol) in dry THF/methanol [30 mL (10:1)] was treated with $NaBH_4$ (526 mg, 14.0 mmol) at room temperature for 40 min. The resulting dipyrromethane-dicarbinol and **2a** (102 mg, 0.700 mmol) were dissolved in CH_2Cl_2 (280 mL) and treated with $Yb(OTf)_3$ (555 mg, 0.896 mmol) at room temperature for 20 min. DDQ (477 mg, 2.10 mmol) was added and the mixture was stirred at room temperature for 1 h. After standard workup, chromatography [silica, CH_2Cl_2/hexanes (2:1)] afforded the free base porphyrin. The resulting porphyrin was treated with $Zn(OAc)_2{\cdot}2H_2O$ (154 mg, 0.700 mmol) in $CHCl_3$ (10 mL) and methanol (3 mL) at room temperature for 15 h. Standard workup, chromatography [silica, $CHCl_3$/hexanes (2:1)], and trituration (hexanes) afforded a purple solid (49 mg, 12%): ^{1}H NMR ($CDCl_3$) δ 7.72–7.80 (m, 9H), 8.21–8.25 (m, 6H), 8.97 (d, J=4.4 Hz, 2H), 8.99 (d, J=5.1 Hz, 2H), 9.09 (d, J=4.4 Hz, 2H), 9.39 (d, J=4.4 Hz, 2H), 10.24 (s, 1H); ^{13}C NMR (THF-d_8) δ 105.43, 120.10, 120.96, 126.32, 126.43, 127.29 (two peaks have overlapped), 131.27, 131.39, 131.49, 132.01, 134.59, 134.71, 143.72, 143.92, 149.78, 150.10, 150.18, 150.23; LD-MS obsd 598.56 [M^+]; FAB-MS obsd 600.1307, calcd 600.1292 ($C_{38}H_{24}N_4Zn$); λ_{abs} 418, 543 nm; λ_{em} (λ_{ex}=540 nm) 590, 637 nm.

4.4.3. Zn(II)-5,15-bis(pentafluorophenyl)-10-phenylporphyrin (Zn3c). Following a standard procedure,[47,54] a solution of **1c** (750 mg, 1.23 mmol) in dry THF/methanol [40 mL (10:1)] was treated with $NaBH_4$ (924 mg, 24.6 mmol, 20 M equiv.) at room temperature for 40 min. The resulting dipyrromethane-dicarbinol and **2a** (180 mg, 1.23 mmol) were dissolved in CH_2Cl_2 (492 mL) and treated with $InCl_3$ (35.0 mg, 0.157 mmol) at room temperature for 30 min. DDQ (838 mg, 3.69 mmol) was added and the mixture was stirred at room temperature for 1 h. After standard workup, chromatography [silica CH_2Cl_2/hexanes (3:1)] afforded the free base porphyrin. The resulting porphyrin was treated with $Zn(OAc)_2{\cdot}2H_2O$ (360 mg, 1.64 mmol) in $CHCl_3$ (40 mL) and methanol (10 mL) at room temperature for 4 h. Standard workup, chromatography [silica, $CHCl_3$/hexanes (2:1) then $CHCl_3$/hexanes (3:2)], and trituration (hexanes) afforded a purple solid (132 mg, 14%): ^{1}H NMR ($CDCl_3$) δ 7.77–7.82 (m, 3H), 8.20–8.23 (m, 2H), 8.93 (d, J=5.1 Hz, 2H), 9.05–9.08 (m, 4H), 9.52 (d, J=5.1 Hz, 2H), 10.36 (s, 1H); ^{13}C NMR (THF-d_8) δ 101.63, 106.47, 117.6–118.1 (m), 122.19, 126.48, 127.65, 129.90, 130.68, 133.04, 133.22, 134.61, 135.9–136.3 (m), 139.2–139.6 (m), 143.22, 143.4–143.8 (m), 145.1–145.5 (m), 147.3–147.6 (m), 148.3–148.7 (m), 149.46, 149.68, 150.49, 150.97; MALDI-MS (dithranol) obsd 776.60 [M^+]; FAB-MS obsd 780.0391, calcd 780.0350 ($C_{38}H_{14}F_{10}N_4Zn$); λ_{abs} 416, 542, 576 nm; λ_{em} (λ_{ex}= 540 nm) 583, 637 nm.

4.4.4. 1-(Pentafluorobenzoyl)dipyrromethane (5). Following a standard procedure,[48] a solution of dipyrromethane **2a** (731 mg, 5.00 mmol) in THF (5.0 mL) was treated with EtMgBr (12.5 mL, 12.5 mmol, 1.0 M solution in THF) under argon at −78 °C for 10 min. A solution of **4** (1.53 g, 5.00 mmol) in THF (5.0 mL) was added over 1 min. The reaction mixture was stirred at −78 °C for 10 min, then at room temperature for 30 min. Standard workup and chromatography [silica, CH_2Cl_2/ethyl acetate (98:2)] afforded a colorless solid (826 mg, 59%): mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 2H), 6.04–6.07 (m, 1H), 6.11–6.14 (m, 1H), 6.18–6.20 (m, 1H), 6.66–6.68 (m, 1H), 6.69–6.72 (m, 1H), 8.80 (s, 1H), 11.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.8, 107.2, 108.7, 111.9, 118.1, 125.0, 126.8, 131.0, 136.1–136.3 (m), 139.2–139.7 (m), 140.6–140.9 (m), 142.2–142.5 (m), 143.9–144.3 (m), 144.5, 145.5–145.8 (m), 172.0; FAB-MS obsd 340.0632, calcd 340.0635 ($C_{16}H_9F_5N_2O$). Anal. Calcd: C, 56.48; H, 2.67; N, 8.23. Found: C, 56.44; H, 2.71; N, 8.22.

4.4.5. 1-Benzoyl-9-pentafluorophenyldipyrromethane (6). Following a standard procedure,[48] a solution of **5** (830 mg, 2.44 mmol) in toluene (5 mL) was treated with EtMgBr (4.88 mL, 4.88 mmol, 1.0 M solution in THF) at room temperature under argon. After 5 min, a solution of benzoyl chloride (343 mg, 2.44 mmol) in toluene (5 mL) was added and the mixture was stirred at room temperature for 10 min. A subsequent addition of EtMgBr (2.44 mL, 2.44 mmol, 1.0 M solution in THF) and a solution of benzoyl chloride (343 mg, 2.44 mmol) in toluene (5 mL) was performed. Standard workup, chromatography [silica, CH_2Cl_2/ethyl acetate (97:3→95:5)], and precipitation (CH_2Cl_2/hexanes) afforded colorless crystals (882 mg, 81%): mp 166–168 °C; ^{1}H NMR (THF-d_8) δ 4.15 (s, 2H), 5.50–5.51 (m, 1H), 6.05–6.11 (m, 1H), 6.62–6.67 (m, 1H), 6.74–6.75 (m, 1H), 7.42–7.54 (m, 3H), 7.84–7.86 (m, 2H), 11.34 (s, 1H), 11.69 (s, 1H); ^{13}C NMR (THF-d_8) δ 27.2, 110.3, 111.4, 120.2, 122.9, 129.0, 129.7, 132.2, 132.5, 136.8–137.2 (m), 137.4, 140.1–140.5 (m), 141.0–141.4 (m), 142.0, 143.1–143.3 (m), 144.5–144.6 (m), 146.3–146.6 (m), 171.4, 184.2; FAB-MS obsd 444.0892, calcd 444.0897 ($C_{23}H_{13}F_5N_2O_2$). Anal. Calcd: C, 62.17; H, 2.95; N, 6.30. Found: C, 60.36; H, 2.96; N, 6.04.

4.4.6. Zn(II)-5-pentafluorophenyl-10,15-diphenylporphyrin (Zn3d). Following a standard procedure,[47,54] a solution of **6** (420 mg, 0.945 mmol) in dry THF/methanol [25 mL (10:1)] was treated with $NaBH_4$ (712 mg, 18.9 mmol, 20 M equiv.) at room temperature for 30 min. The resulting dipyrromethane-dicarbinol and **2b** (210 mg, 0.945 mmol) were dissolved in CH_2Cl_2 (378 mL) and treated with $InCl_3$ (26.0 mg, 0.118 mmol, 0.32 mM) at

room temperature for 30 min. DDQ (645 mg, 2.84 mmol) was added and the mixture was stirred at room temperature for 1 h. After standard workup, chromatography [silica CH_2Cl_2/hexanes (3:1)] afforded the free base porphyrin. The resulting porphyrin was treated with $Zn(OAc)_2{\cdot}2H_2O$ (170 mg, 0.780 mmol) in CH_2Cl_2 (20 mL) and methanol (5.0 mL) at room temperature for 16 h. Standard workup, chromatography [silica, CH_2Cl_2/hexanes (2:1)], and trituration (hexanes) afforded a purple solid (120 mg, 18%): ^{1}H NMR ($CDCl_3$) δ 7.74–7.83 (m, 6H), 8.20–8.22 (m, 4H), 8.90–8.91 (m, 1H), 8.96–8.98 (m, 2H), 9.00–9.02 (m, 1H), 9.06 (d, J=4.4 Hz, 1H), 9.35 (d, J=4.4 Hz, 1H), 9.48 (d, J=5.1 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR (THF-d_8) δ 99.82, 106.06, 118.1–118.4 (m), 121.68, 121.98, 126.42, 126.48, 127.59 (two peaks have overlapped), 129.38, 130.13, 131.57, 131.68, 131.80, 132.66, 132.99, 133.07, 134.59, 134.70, 136.3–136.9 (m), 138.8–139.4 (m), 140.4–140.8 (m), 143.0–143.4 (m), 143.41, 143.56, 145.4–146.0 (m), 147.8–148.4 (m), 149.56, 149.78, 149.90, 150.06, 150.17, 150.31, 150.43, 150.66; MALDI-MS (dithranol) obsd 692.87 [M^+], 679.76 [$(M-F)^+$]; FAB-MS obsd 690.0850, calcd 690.0821 ($C_{38}H_{19}F_5N_4Zn$); λ_{abs} 417, 543 nm; λ_{em} (λ_{ex}=540 nm) 585, 636 nm.

4.4.7. 5-Bromo-10,15,20-tris(4-methylphenyl)porphyrin (Fb7a). Following a standard procedure,[49] a solution of **Fb3a** (581 mg, 1.00 mmol) in $CHCl_3$ (250 mL) was treated with NBS (178 mg, 1.00 mmol) and pyridine (1.0 mL) at 0 °C for 15 min. Acetone (20 mL) was added. The reaction mixture was concentrated to dryness. Chromatography [silica, $CHCl_3$/hexanes (3:1)] and recrystallization ($CHCl_3$/methanol) afforded a purple solid (645 mg, 98%): ^{1}H NMR ($CDCl_3$) δ −2.72 (s, 2H), 2.70–2.74 (br s, 9H), 7.54–7.60 (m, 6H), 8.05–8.11 (m, 6H), 8.80–8.83 (m, 4H), 8.93 (d, J=4.8 Hz, 2H), 9.67 (d, J=4.8 Hz, 2H); ^{13}C NMR (THF-d_8) δ 20.76 (two peaks have overlapped), 102.09, 121.01, 121.30, 127.57 (two peaks have overlapped), 134.38, 134.54, 137.70, 137.74, 139.15, 139.26, resonances from the α- and β-carbons of the porphyrin were not observed due to NH tautomerism; LD-MS obsd 659.3; FAB-MS obsd 658.1749, calcd 658.1732 ($C_{41}H_{31}BrN_4$); λ_{abs} 423, 486, 520, 554, 597, 655 nm.

4.4.8. Zn(II)-5-bromo-10,15,20-triphenylporphyrin (Zn7b). Following a standard procedure,[49] a solution of **Zn3b** (44 mg, 73 μmol) in $CHCl_3$ (15 mL) was treated with NBS (13 mg, 73 μmol) and pyridine (21 μL) at 0 °C for 30 min. Standard workup, chromatography [silica, $CHCl_3$/hexanes (2:1)], and trituration (hexanes) afforded a purple solid (38.0 mg, 77%): ^{1}H NMR ($CDCl_3$) δ 7.77–7.78 (m, 9H), 8.11–8.27 (m, 6H), 8.85–8.92 (m, 4H), 8.98–8.99 (m, 2H), 9.68–9.80 (m, 2H); ^{13}C NMR (THF-d_8) δ 103.54, 121.45, 121.63, 126.48, 126.59, 127.47, 127.50, 131.828, 121.832, 132.26, 132.74, 134.46, 134.62, 143.33, 143.41, 149.68, 150.55, 150.62, 150.69; LD-MS obsd 678.45 [M^+]; FAB-MS obsd 678.0397, calcd 678.0398 ($C_{38}H_{23}BrN_4Zn$); λ_{abs} 426, 555 nm. **Zn7b** is a known compound but the synthetic procedure has not been described.[61]

4.4.9. Zn(II)-5-bromo-10,20-bis(pentafluorophenyl)-15-phenylporphyrin (Zn7c). Following a standard procedure,[49] a solution of **Zn3c** (110 mg, 0.141 mmol) in $CHCl_3$ (30 mL) was treated with NBS (25 mg, 0.14 mmol) and pyridine (41 μL) at 0 °C for 30 min. Standard workup, chromatography [silica, $CHCl_3$/hexanes (2:1)⟶(3:1)], and trituration (hexanes) afforded a purple solid (116 mg, 96%): ^{1}H NMR ($CDCl_3$) δ 7.74–7.82 (m, 3H), 8.16–8.19 (m, 2H), 8.84 (d, J=5.1 Hz, 2H), 8.95 (d, J=4.4 Hz, 2H), 8.99 (d, J=5.1 Hz, 2H), 9.86 (d, J=5.1 Hz, 2H); ^{13}C NMR (THF-d_8) δ 103.00, 104.62, 117.4–117.7 (m), 122.63, 126.62, 127.81, 130.53, 131.39, 133.50, 133.93, 134.52, 135.9–136.5 (m), 139.2–139.7 (m), 140.4–140.7 (m), 142.77, 143.6–144.1 (m), 144.9–145.7 (m), 148.1–148.6 (m), 149.95, 150.00, 150.40, 151.53;- MALDI-MS (dithranol) obsd 855.46 [M^+]; FAB-MS obsd 857.9459, calcd 857.9455 ($C_{38}H_{13}BrF_{10}N_4$-Zn); λ_{abs} 425, 552 nm.

4.4.10. Zinc(II)-5-bromo-20-pentafluorophenyl-10,15-diphenylporphyrin (Zn7d). Following a standard procedure,[49] a solution of **Zn3d** (100 mg, 0.145 mmol) in $CHCl_3$ (30 mL) was treated with NBS (26 mg, 0.15 mmol) and pyridine (42 μL) at 0 °C for 30 min. Standard workup, chromatography [silica, $CHCl_3$/hexanes (3:1)], and trituration (hexanes) afforded a purple solid (102 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 7.74–7.78 (m, 6H), 8.17–8.18 (m, 4H), 8.81–8.82 (m, 1H), 8.90–8.93 (m, 3H), 8.98–9.01 (m, 2H), 9.76 (d, J=4.4 Hz, 1H), 9.85 (d, J=4.4 Hz, 1H); ^{13}C NMR (THF-d_8) δ 101.15, 104.23, 117.6–118.1 (m), 122.26, 123.39, 126.56, 126.59, 127.67, 127.72, 130.02, 130.95, 132.05, 132.42, 132.46, 133.24, 133.41, 133.85, 134.52, 134.66, 136.3–136.9 (m), 138.8–139.4 (m), 140.5–141.1 (m), 143.08, 143.1–143.6 (m), 143.12, 145.4–146.0 (m), 147.8–148.4 (m), 149.92, 150.12, 150.18 (two peaks have overlapped), 150.51, 150.61, 150.91, 151.32; MALDI-MS (dithranol) obsd 770.67 [M^+], 753.64 [$(M-F)^+$], 694.55 [$(M-Br)^+$]; FAB-MS obsd 767.9951, calcd 767.9926 ($C_{38}H_{18}BrF_5N_4Zn$); λ_{abs} 426, 553, 594 nm.

4.4.11. 5-Iodo-10,15,20-tris(4-methylphenyl)porphyrin (Fb8a). Following a standard procedure,[50] a solution of porphyrin **Fb3a** (871 mg, 1.50 mmol) and I_2 (267 mg, 1.05 mmol) in $CHCl_3$ (210 mL) was treated with a solution of [bis(trifluoroacetoxy)iodo]benzene (478 mg, 1.20 mmol) and pyridine (1.3 mL) in $CHCl_3$ (30 mL). The mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous $Na_2S_2O_3$, and dried (Na_2SO_4). The solution was concentrated to ~100 mL, then 30 mL of hexanes was added. The resulting purple precipitate was filtered, washed (CH_2Cl_2, hexanes) and dried to give a purple powder (618 mg). The filtrate was concentrated and chromatographed [silica, warm toluene/hexanes (7:3)] affording an additional amount of the title compound (253 mg). The total yield is 871 mg (82%): ^{1}H NMR ($CDCl_3$) δ −2.70 (s, 2H), 2.69–2.74 (br s, 9H), 7.53–7.59 (m, 6H), 8.04–8.09 (m, 6H), 8.78–8.83 (m, 4H), 8.89 (d, J=4.8 Hz, 2H), 9.67 (d, J=4.8 Hz, 2H); ^{13}C NMR (THF-d_8) δ 20.77 (two peaks have overlapped), 77.92, 121.04, 121.45, 127.53, 127.59, 134.41, 134.53, 137.72 (two peaks have overlapped), 139.71, 139.28, resonances from the α-and β-carbons of the porphyrin were not observed due to NH tautomerism; LD-MS obsd 706.9; FAB-MS obsd 706.1613, calcd 706.1593 ($C_{41}H_{31}IN_4$); λ_{abs} 424, 520, 557, 598, 656 nm.

4.4.12. Zn(II)-5-bromo-10,15,20-tris(4-methylphenyl)-porphyrin (Zn7a). A solution of porphyrin **Fb7a**

(594 mg, 0.900 mmol) in THF (60 mL) was treated with $Zn(OAc)_2{\cdot}2H_2O$ (988 mg, 4.50 mmol). The mixture was heated (~50 °C) for a few minutes and then stirred at room temperature for 11 h. Standard workup, chromatography [silica, $CHCl_3$/hexanes (3:2)] and recrystallization (hexanes/CH_2Cl_2) afforded a purple solid (582 mg, 89%): ^{1}H NMR ($CDCl_3$) δ 2.67 (s, 3H), 2.70 (s, 6H), 7.52–7.60 (m, 6H), 8.00–8.08 (m, 6H), 8.78–8.82 (m, 4H), 8.91 (d, J=4.8 Hz, 2H), 9.68 (d, J=4.8 Hz, 2H); ^{13}C NMR (THF-d_8) δ 20.78, 20.80, a resonance from the C–Br carbon was not observed, 119.88, 120.03, 127.02, 127.07, 128.44, 131.11, 131.28, 131.80, 134.44, 134.47, 136.73, 136.77, 140.97, 141.07, 149.86, 149.96, 150.23, 150.42; LD-MS obsd 723.8; FAB-MS obsd 720.0901, calcd 720.0867 ($C_{41}H_{29}BrN_4Zn$); λ_{abs} 427, 555, 595 nm.

4.4.13. Zn(II)-5-iodo-10,15,20-tris(4-methylphenyl)porphyrin (Zn8a). A solution of **Fb8a** (353 mg, 0.500 mmol) in THF (60 mL) was treated with $Zn(OAc)_2{\cdot}2H_2O$ (1.10 g, 5.00 mmol). The mixture was heated (~50 °C) for a few minutes and then stirred at room temperature for 8 h. Standard workup, chromatography [silica, $CHCl_3$/hexanes (1:1)], and recrystallization (hexanes/CH_2Cl_2) afforded a purple solid (349 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 2.67–2.70 (br s, 9H), 7.53–7.59 (m, 6H), 8.01–8.06 (m, 6H), 8.76–8.80 (m, 4H), 8.86–8.91 (m, 2H), 9.72 (d, J=4.4 Hz, 2H); ^{13}C NMR (THF-d_8) δ 20.79, 20.80, 79.54, 121.51, 121.92, 127.16 (two peaks have overlapped), 131.16, 131.70, 131.83, 132.98, 134.55 (two peaks have overlapped), 137.07, 137.10, 140.47, 140.56, 150.70 (two peaks have overlapped), 151.29, 152.13; LD-MS obsd 770.5; FAB-MS obsd 768.0760, calcd 768.0728 ($C_{41}H_{29}IN_4Zn$); λ_{abs} 429, 519, 556, 596 nm.

4.5. Porphyrin dyads

4.5.1. Dyad-1. Samples of **Zn9** (11 mg, 13 μmol), **Zn8a** (10 mg, 13 μmol), $Pd_2(dba)_3$ (7.1 mg, 7.7 μmol), and P(o-tol)$_3$ (19 mg, 62 μmol) were placed into a 100 mL Schlenk flask which was then pump-purged three times with argon. Toluene/TEA [20.6 mL (5:1)] was added, and the reaction mixture was stirred at 40 °C for 1.5 h. The reaction mixture was concentrated to dryness. The resulting residue was passed through a pad of silica ($CHCl_3$). The eluant was concentrated and then further purified by preparative SEC (THF) and adsorption chromatography [silica, $CHCl_3$/hexanes (2:1)]. The desired fraction was concentrated to dryness and then triturated with methanol. Filtration afforded the title compound as a purple solid (7.3 mg, 41%): ^{1}H NMR ($CDCl_3$) δ 1.86–1.88 (m, 18H), 2.63–2.64 (m, 9H), 2.72 (s, 3H), 2.74 (s, 6H), 7.29 (s, 2H), 7.30 (s, 4H), 7.56 (d, J=8.1 Hz, 2H), 7.60 (d, J=8.1 Hz, 4H), 8.09 (d, J=8.1 Hz, 2H), 8.14 (d, J=8.1 Hz, 4H), 8.41–8.46 (m, 4H), 8.71–8.74 (m, 4H), 8.84 (d, J=5.1 Hz, 2H), 8.90–8.93 (m, 4H), 9.05 (d, J=4.4 Hz, 2H), 9.12 (d, J=4.4 Hz, 2H), 10.03 (d, J=4.4 Hz, 2H); ^{13}C NMR (THF-d_8) δ 20.80 (two peaks have overlapped), 20.82 (two peaks have overlapped), 21.27, 21.33, 94.40, 95.89, 99.10, 118.18, 118.33, 119.31, 121.89, 122.78, 123.78, 127.15, 127.22, 127.71 (two peaks have overlapped), 129.50, 130.16, 130.43, 130.46, 130.57, 131.32, 131.66, 131.75, 132.44, 132.47, 134.37, 134.54, 135.03 (two peaks have overlapped), 137.08, 137.30, 139.14 (two peaks have overlapped), 139.85, 139.95, 140.52, 140.62, 143.91, 149.74, 149.78, 149.86, 149.88, 150.04, 150.16, 150.80, 152.47; MALDI-MS (dithranol) obsd 1465.84 [M^+]; FAB-MS obsd 1466.4607, calcd 1466.4619 ($C_{96}H_{74}N_8Zn_2$); λ_{abs} 442, 445, 553, 618 nm; λ_{em} (λ_{ex}=550 nm) 627, 681 nm.

4.5.2. Dyad-2. A mixture of **Zn9** (25 mg, 30 μmol), **Fb7a** (20 mg, 30 μmol), $Pd_2(dba)_3$ (17 mg, 18 μmol), and P(o-tol)$_3$ (44 mg, 0.14 mmol) in toluene/TEA [48 mL (5:1)] was stirred at 50 °C for 1.5 h under argon. Standard workup, preparative SEC (THF), chromatography [silica, $CHCl_3$/hexanes (2:1)], and trituration (THF/hexanes) afforded a purple solid (19 mg, 47%): ^{1}H NMR ($CDCl_3$) δ −2.23 (s, 2H), 1.86–1.89 (m, 18H), 2.63–2.65 (m, 9H), 2.71 (s, 3H), 2.73 (s, 6H), 7.28–7.30 (m, 6H), 7.56 (d, J=7.3 Hz, 2H), 7.60 (d, J=8.1 Hz, 4H), 8.08 (d, J=8.1 Hz, 2H), 8.13 (d, J=8.1 Hz, 4H), 8.40 (d, J=8.1 Hz, 2H), 8.45 (d, J=8.1 Hz, 2H), 8.72–8.73 (m, 4H), 8.80–8.81 (m, 4H), 8.83 (d, J=4.4 Hz, 2H), 9.01–9.04 (m, 4H), 9.93 (d, J=5.1 Hz, 2H); MALDI-MS (dithranol) obsd 1409.27 [$(M+H)^+$]; FAB-MS obsd 1404.5476, calcd 1404.5484 ($C_{96}H_{76}N_8Zn$); λ_{abs} 422, 439, 550, 578, 672 nm; λ_{em} (λ_{ex}=550 nm) 675, 747 nm.

4.5.3. Dyad-3. A mixture of **Zn9** (20 mg, 24 μmol), **Zn7c** (21 mg, 24 μmol), $Pd_2(dba)_3$ (13 mg, 14 μmol), and P(o-tol)$_3$ (35 mg, 0.11 mmol) in toluene/TEA [38 mL (5:1)] was stirred at 50 °C for 1.5 h under argon. Standard workup, preparative SEC (THF), chromatography [silica, $CHCl_3$/hexanes (2:1→3:1)], and trituration (hexanes) afforded a purple solid (24 mg, 62%): ^{1}H NMR ($CDCl_3$) δ 1.87–1.89 (m, 18H), 2.63–2.66 (m, 9H), 7.28–7.29 (m, 2H), 7.30–7.32 (m, 4H), 7.75–7.82 (m, 3H), 8.21 (d, J=7.3 Hz, 2H), 8.42 (d, J=7.3 Hz, 2H), 8.47 (d, J=8.1 Hz, 2H), 8.73–8.75 (m, 4H), 8.84–8.86 (m, 4H), 9.00 (d, J=5.1 Hz, 2H), 9.03–9.05 (m, 4H), 10.12 (d, J=4.4 Hz, 2H); ^{13}C NMR (THF-d_8) δ 20.83 (two peaks have overlapped), 21.30, 21.35, 93.37, 96.74, 100.86, 103.43, 117.5–117.8 (m), 118.25, 118.38, 119.14, 123.25, 123.58, 126.62, 127.71, 127.74, 127.82, 129.70, 130.08, 130.20, 130.52, 130.63, 131.09, 131.70, 132.30, 133.32, 134.52, 135.11, 136.4–137.0 (m), 137.32 (two peaks have overlapped), 139.0–139.6 (m), 139.14 (two peaks have overlapped), 139.84, 139.94, 140.5–141.0 (m), 142.85, 143.1–143.6 (m), 144.42, 145.3–145.9 (m), 147.8–148.4 (m), 149.46, 149.77, 149.78, 149.82, 149.87, 149.89, 150.88, 153.13; MALDI-MS (dithranol) obsd 1604.77 [M^+]; FAB-MS obsd 1604.3187, calcd 1604.3208 ($C_{93}H_{58}F_{10}N_8Zn_2$); λ_{abs} 422, 445, 553, 607 nm; λ_{em} (λ_{ex}=550 nm) 616, 678 nm.

4.5.4. Dyad-4. A mixture of **Zn9** (12 mg, 15 μmol), **Zn7d** (12 mg, 15 μmol), $Pd_2(dba)_3$ (9.0 mg, 9.0 μmol), and P(o-tol)$_3$ (22 mg, 0.072 mmol) in toluene/TEA [24 mL (5:1)] was stirred at 50 °C for 1.5 h under argon. Standard workup, preparative SEC (THF), and chromatography [silica, $CHCl_3$/hexanes (2:1)] afforded a purple solid (11 mg, 48%): ^{1}H NMR ($CDCl_3$) δ 1.86–1.89 (m, 18H), 2.62–2.65 (m, 9H), 7.29–7.30 (m, 6H), 7.74–7.83 (m, 6H), 8.19–8.22 (m, 2H), 8.24–8.26 (m, 2H), 8.41–8.47 (m, 4H), 8.71–8.74 (m, 4H), 8.81–8.85 (m, 3H), 8.89–8.93 (m, 2H), 8.99 (d, J=4.4 Hz, 1H), 9.02 (d, J=5.1 Hz, 1H), 9.04 (d, J=5.1 Hz, 2H), 9.12 (d, J=4.4 Hz, 1H), 10.05 (d, J=4.4 Hz,

1H), 10.13 (d, J=5.1 Hz, 1H); ^{13}C NMR (THF-d_8) δ 20.82 (two peaks have overlapped), 21.28, 21.33, 93.79, 96.40, 100.21, the *meso*-carbon adjacent to the pentafluorophenyl group was not observed, 118.20, 118.35, 119.20, 123.23, 123.46, 123.64, 126.55, 126.57, 127.66 (two peaks have overlapped), 127.72 (two peaks have overlapped), 129.52, 129.60, 129.52, 129.60, 130.17, 130.48, 130.59 (two peaks have overlapped), 131.71, 131.93, 132.14 (two peaks have overlapped), 132.94, 133.16, 134.47, 134.63, 135.07 (two peaks have overlapped), 137.30 (two peaks have overlapped), 139.14 (two peaks have overlapped), 139.84, 139.94, 143.13, 143.15, 144.20, 149.75, 149.78, 149.84, 149.87, 150.59, 152.75, resonances from some of the α-carbons of the porphyrin were not observed clearly, and resonances from the carbons of the pentafluorophenyl group were not observed; MALDI-MS (dithranol) obsd 1518.39 [M$^+$]; FAB-MS obsd 1514.3712, calcd 1514.3679 ($C_{93}H_{63}F_5N_8Zn_2$); λ_{abs} 422, 446, 553, 611 nm; λ_{em} (λ_{ex}= 550 nm) 618, 675 nm.

4.6. Benchmark phenylethynyl-porphyrins

4.6.1. Zn(II)-5-(phenylethynyl)-10,15,20-triphenylporphyrin (Zn10b). A mixture of **Zn7b** (30 mg, 44 μmol), phenylacetylene (24 μL, 0.22 mmol), $Pd_2(dba)_3$ (6.1 mg, 6.7 μmol), and P(*o*-tol)$_3$ (16 mg, 53 μmol) in toluene/TEA [18 mL (5:1)] was stirred at 50 °C under argon. After 6 h, phenylacetylene (24 μL, 0.22 mmol), $Pd_2(dba)_3$ (6.1 mg, 6.7 μmol), and P(*o*-tol)$_3$ (16 mg, 53 μmol) were added. After 14 h, the reaction mixture was concentrated to dryness. Chromatography [silica, CH_2Cl_2/hexanes (3:2)] and trituration (hexanes) afforded a blue-purple solid (16 mg, 52%): ^{1}H NMR ($CDCl_3$) δ 7.46–7.51 (m, 1H), 7.54–7.59 (m, 2H), 7.70–7.82 (m, 9H), 8.03 (d, J=7.3 Hz, 2H), 8.17–8.22 (m, 6H), 8.86–8.87 (m, 4H), 9.01 (d, J=4.4 Hz, 2H), 9.84 (d, J=4.4 Hz, 2H); ^{13}C NMR (THF-d_8) δ 92.95, 96.48, 100.49, 122.27, 122.99, 124.45, 126.82, 126.88, 127.86 (two peaks have overlapped), 128.65, 128.91, 131.15, 131.85, 132.16, 132.46, 133.13, 134.52, 134.64, 142.66, 142.77, 150.12, 150.27, 150.77, 152.53; LD-MS obsd 700.15 [M$^+$]; FAB-MS obsd 700.1610, calcd 700.1605 ($C_{46}H_{28}N_4Zn$); λ_{abs} 440, 567, 611 nm; λ_{em} (λ_{ex}= 560 nm) 618, 673 nm.

4.6.2. Zn(II)-5-pentafluorophenyl-10,15-diphenyl-20-(phenylethynyl)porphyrin (Zn10c). A mixture of **Zn7c** (20 mg, 26 μmol), phenylacetylene (14 μL, 0.13 mmol), $Pd_2(dba)_3$ (3.7 mg, 4.0 μmol), and P(*o*-tol)$_3$ (9.9 mg, 32 μmol) in toluene/TEA [10.4 mL (5:1)] was stirred at 50 °C under argon. After 5 h, phenylacetylene (14 μL, 0.13 mmol), $Pd_2(dba)_3$ (3.7 mg, 4.0 μmol), and P(*o*-tol)$_3$ (9.9 mg, 32 μmol) were added. After 15 h, the reaction mixture was concentrated to dryness. Chromatography [silica, CH_2Cl_2/hexanes (3:2)] and trituration (hexanes) afforded a purple solid (15 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 7.49–7.58 (m, 3H), 7.72–7.81 (m, 6H), 8.00–8.03 (m, 2H), 8.16–8.22 (m, 4H), 8.79 (d, J=5.1 Hz, 1H), 8.86–8.89 (m, 2H), 8.93 (d, J=4.4 Hz, 1H), 8.96 (d, J=5.1 Hz, 1H), 9.02 (d, J=4.4 Hz, 1H), 9.83 (d, J=5.1 Hz, 1H), 9.92 (d, J= 4.4 Hz, 1H); ^{13}C NMR (THF-d_8) δ 92.35, 96.26, 100.68, 103.33, 117.5–117.8 (m), 123.52, 124.33, 126.59, 127.79, 128.67, 128.85, 130.03, 130.95, 131.69, 132.13, 133.28, 134.48, 136.5–137.1 (m), 138.8–139.4 (m), 140.6–1401.1 (m), 142.81, 143.0–143.5 (m), 145.2–145.8 (m), 147.8–148.3 (m), 149.37, 149.81, 150.82, 152.96; MALDI-MS (dithranol) obsd 793.71 [(M+H)$^+$], 775.58 [(M−F)$^+$]; FAB-MS obsd 790.1099, calcd 790.1134 ($C_{46}H_{23}F_5N_4Zn$); λ_{abs} 442, 567, 606 nm; λ_{em} (λ_{ex}=560 nm) 612, 671 nm.

4.6.3. Zn(II)-5,15-bis(pentafluorophenyl)-10-phenyl-20-(phenylethynyl)porphyrin (Zn10d). A mixture of **Zn7d** (40 mg, 46 μmol), phenylacetylene (25 μL, 0.23 mmol), $Pd_2(dba)_3$ (6.4 mg, 7.0 μmol), and P(*o*-tol)$_3$ (17 mg, 55 μmol) in toluene/TEA [18 mL (5:1)] was stirred at 50 °C under argon. After 5 h, phenylacetylene (25 μL, 0.23 mmol), $Pd_2(dba)_3$ (6.4 mg, 7.0 μmol), and P(*o*-tol)$_3$ (17 mg, 55 μmol) were added. After 18 h, the reaction mixture was concentrated to dryness. Chromatography [silica, CH_2Cl_2/hexanes (3:2)] and trituration (hexanes) afforded a purple solid (30 mg, 74%): ^{1}H NMR (THF-d_8) δ 7.50–7.54 (m, 1H), 7.57–7.62 (m, 2H), 7.72–7.79 (m, 3H), 8.08 (d, J=6.6 Hz, 2H), 8.16–8.19 (m, 2H), 8.85 (d, J= 5.1 Hz, 2H), 8.88 (d, J=5.1 Hz, 2H), 9.03 (d, J=5.1 Hz, 2H), 9.88 (d, J=4.4 Hz, 2H); ^{13}C NMR (THF-d_8) δ 92.79, 95.95, 100.05, 101.58, 117.9–118.1 (m), 123.17, 123.55, 124.54, 126.53, 126.55, 127.65 (two peaks have overlapped), 128.48, 128.81, 129.49, 130.47, 130.62, 131.61, 131.84, 131.89, 131.99, 132.82, 133.12, 134.45, 134.59, 136.5–137.0 (m), 138.8–139.3 (m), 140.3–140.8 (m), 143.10, 143.13, 143.2–143.4 (m), 145.4–1445.8 (m), 147.8–148.4 (m), 149.47, 149.84, 149.90, 150.22, 150.53, 150.58, 152.67, 152.69; MALDI-MS (dithranol) obsd 882.07 [M$^+$]; FAB-MS obsd 880.0638, calcd 880.0663 ($C_{46}H_{18}F_{10}N_4Zn$); λ_{abs} 443, 566, 602 nm; λ_{em} (λ_{ex}= 565 nm) 616, 674 nm.

4.6.4. Zn(II)-5,15-bis(pentafluorophenyl)porphyrin (Zn11). Following a standard procedure,[48,54] a solution of **5** (681 mg, 2.00 mmol) in dry THF/methanol [66 mL, (10:1)] was treated with $NaBH_4$ (1.50 g, 40.0 mmol) at room temperature for 40 min. The resulting dipyrromethane-monocarbinol was dissolved in CH_2Cl_2 (400 mL) and treated with $InCl_3$ (28 mg, 0.13 mmol, 0.32 mM) at room temperature for 30 min. DDQ (681 mg, 3.00 mmol) was added and the mixture was stirred at room temperature for 1 h. Standard workup and chromatography [silica, CH_2Cl_2/hexanes (3:1)] afforded a mixture of free base porphyrin and chlorin. The mixture was dissolved in toluene (100 mL) and reoxidized with DDQ (681 mg, 3.00 mmol) under reflux for 1 h. The reaction mixture was cooled, diluted with hexanes (100 mL), and filtered. The resulting porphyrin was treated with $Zn(OAc)_2{\cdot}2H_2O$ (3.29 g, 15.0 mmol) in $CHCl_3$ (800 mL) and methanol (30 mL) at room temperature for 3 days. Standard workup and trituration (methanol) afforded a purple solid (114 mg, 16%): ^{1}H NMR (THF-d_8) δ 9.12 (d, J=4.4 Hz, 4H), 9.52 (d, J=4.4 Hz, 4H), 10.39 (s, 2H); ^{13}C NMR (THF-d_8) δ 100.08, 106.75, 130.52, 133.13, 149.50, 150.45, resonances from the C–F carbons of the pentafluorophenyl group were not observed; MALDI-MS (dithranol) obsd 704.23 [M$^+$], 686.20 [(M−F)$^+$]; FAB-MS obsd 704.0049, calcd 704.0037 ($C_{32}H_{10}F_{10}N_4Zn$); λ_{abs} (THF) 409, 541, 575 nm; λ_{em} (λ_{ex}=540 nm, THF) 581, 633 nm.

4.6.5. Zn(II)-5,15-dibromo-10,20-bis(pentafluorophenyl)porphyrin (Zn12a). Following a standard procedure,[49]

a solution of **Zn11** (100 mg, 0.142 mmol) in $CHCl_3$ (30 mL) was treated with NBS (50 mg, 0.28 mmol) and pyridine (0.1 mL) at 0 °C for 30 min. Standard workup, chromatography [silica, THF/hexanes (3:17)], and trituration (methanol) afforded a purple solid (101 mg, 82%): ^{1}H NMR (THF-d_8) δ 9.00 (d, J=5.1 Hz, 4H), 9.75 (d, J=5.1 Hz, 4H); ^{13}C NMR (THF-d_8) δ 103.69, 105.33, 116.8–117.5 (m), 131.85, 134.32, 136.3–136.9 (m), 138.8–139.4 (m), 140.7–141.3 (m), 143.2–143.7 (m), 145.3–145.9 (m), 147.7–148.4 (m), 150.31, 150.98; MALDI-MS (dithranol) obsd 862.16 [M^+], 844.27 [$(M-F)^+$], 782.45 [$(M-Br)^+$]; FAB-MS obsd 859.8242, calcd 859.8247 ($C_{32}H_8Br_2F_{10}N_4Zn$); λ_{abs} (THF) 427, 562, 608 nm.

4.6.6. Zn(II)-5,15-bis(pentafluorophenyl)-10,20-bis-(phenylethynyl)porphyrin (Zn13a). A mixture of **Zn12a** (90 mg, 0.10 mmol), phenylacetylene (69 μL, 0.62 mmol), $Pd_2(dba)_3$ (29 mg, 32 μmol), and P(o-tol)$_3$ (76 mg, 0.13 mmol) in THF/TEA [42 mL (5:1)] was stirred at 40 °C under argon. After 4 h, phenylacetylene (69 μL, 0.22 mmol), $Pd_2(dba)_3$ (29 mg, 32 μmol), and P(o-tol)$_3$ (76 mg, 0.13 mmol) were added. After 18 h, the mixture was concentrated to dryness. Chromatography [silica, THF/hexanes (3:17)] and trituration [$CHCl_3$/hexanes (1:1), then methanol] afforded a blue-purple solid (50 mg, 53%): ^{1}H NMR (THF-d_8) δ 7.63–7.68 (m, 2H), 7.71–7.75 (m, 4H), 8.19–8.22 (m, 4H), 9.10 (d, J=5.1 Hz, 4H), 9.95 (d, J=5.1 Hz, 4H); ^{13}C NMR (THF-d_8) δ 92.24, 96.86, 102.26, 104.27, 117.1–117.9 (m), 124.14, 128.83, 128.86, 130.92, 131.73, 132.27, 136.4–137.0 (m), 138.9–139.5 (m), 140.6–141.2 (m), 143.1–143.7 (m), 145.3–145.9 (m), 147.7–148.3 (m), 149.55, 152.76; MALDI-MS (dithranol) obsd 904.35 [M^+], 885.40 [$(M-F)^+$]; FAB-MS obsd 904.0646, calcd 904.0663 ($C_{48}H_{18}F_{10}N_4Zn$); λ_{abs} 454, 585, 627 nm; λ_{em} (λ_{ex}=585 nm) 633, 697 nm.

4.6.7. Zn(II)-5,15-diphenyl-10,20-bis(phenylethynyl)porphyrin (Zn13b). A mixture of **Zn12b** (100 mg, 0.146 mmol), phenylacetylene (96 μL, 0.88 mmol), $Pd_2(dba)_3$ (40 mg, 44 μmol), and P(o-tol)$_3$ (107 mg, 350 μmol) in THF/TEA [58 mL (5:1)] was stirred at 40 °C under argon. After 6 h, phenylacetylene (96 μL, 0.88 mmol), $Pd_2(dba)_3$ (40 mg, 44 μmol), and P(o-tol)$_3$ (107 mg, 350 μmol) were added. After 17 h, the mixture was concentrated to dryness. Chromatography [silica, THF/hexanes (3:17), then CH_2Cl_2/hexanes (2:1)] and trituration (hexanes) afforded a blue-purple solid (46 mg, 43%). Analytical data were identical to those described in the literature for the synthesis using copper as a cocatalyst.[37]

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Total synthesis of apigenin 7,4′-di-*O*-β-glucopyranoside, a component of blue flower pigment of *Salvia patens*, and seven chiral analogues

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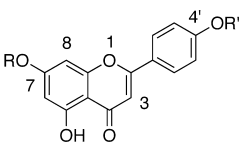
Abstract—We have succeeded in the first total synthesis of apigenin 7,4′-di-*O*-β-D-glucopyranoside (**1a**), a component of blue pigment, protodelphin, from naringenin (**2**). Glycosylation of **2** according to Koenigs–Knorr reaction provided a monoglucoside **4a** in 80% yield, and this was followed by DDQ oxidation to give apigenin 7-*O*-glucoside (**12a**). Further glycosylation of 4′-OH of **12a** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**5a**) was achieved using a Lewis acid-and-base promotion system ($BF_3{\cdot}Et_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, and 1,1,3,3-tetramethylguanidine) in 70% yield, and subsequent deprotection produced **1a**. Synthesis of three other chiral isomers of **1a**, with replacement of D-glucose at 7 and/or 4′-OH by L-glucose (**1b**–**d**), and four chiral isomers of apigenin 7-*O*-β-glucosides (**6a**,**b**) and 4′-*O*-β-glucosides (**7a**,**b**) also proved possible.

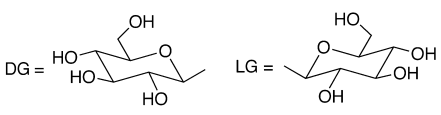
1. Introduction

Flavonoid glycosides are widely distributed in the plant kingdom[1] and show a wide range of biological activities,[1,2] as antioxidants,[3] hepatoprotectants,[4] protecting against UV-light,[5] and acting as feeding[6] and ovipositional[7] stimulants for insects. To generate useful materials, many attempts of glycosylation of phenolic hydroxyl groups of flavonoids have been performed since 1938.[8–12] However, most glycosylations were limited to the monoglycoside at the 7-OH position,[10] while only two methods of glycosylation of 4′-OH of apigenin to the 4′-*O*-glycoside, giving unsatisfactory yields by the Koenigs–Knorr[11a] and phase-transfer-catalyzed systems,[12] have been reported. It is thought that the nucleophilicity of the phenolic hydroxyl group at 7-OH is much higher than that at other positions in flavonoids. Actually, a glycosylation of flavanone using excess sugar halide and silver salt gave only flavanone 7-mono-*O*-glycosides in good yield, and not the polyglycoside (vide infra).

Some flavone diglycosides are involved in flower-color development as co-pigments.[13,14] Apigenin 7,4′-di-*O*-β-D-glucopyranoside (**1a**), one of the components of protodelphin, a blue pigment from flower of *Salvia patens*[14] which is a metalloanthocyanin, stoichiometric supramolecule, composed of six molecules of malonylawobanin as the anthocyanin, six molecules of **1a** as a copigment and two atoms of Mg^{2+} (Fig. 1). The components self-assemble in aqueous solution and become arranged chirally to develop a beautiful blue color.[14b] Formation of the supramolecule was reflected by chiral fitting on the basis of molecular recognition due to the chirality of the sugar linked to the chromophores. To establish the role of chirality of the sugar on the apigenin as a co-pigment, synthesis of chiral analogues bearing D- or L-glucose is necessary (Scheme 1). For this purpose regioselective stepwise glycosylation of the two hydoxyl groups of the flavonoid



1a: R = DG, R' = DG (apigenin 7,4'-di-O-β-D-diglucopyranoside)
1b: R = DG, R' = LG
1c: R = LG, R' = DG
1d: R = LG, R' = LG
6a: R = DG, R' = H
6b: R = LG, R' = H
7a: R = H, R' = DG
7b: R = H, R' = LG



D-glucose L-glucose

Scheme 1. Structure of apigenin 7,4′-di-*O*-D-β-glucopyranoside (**1a**) and its analogues.

Keywords: Glycosylation of phenol; Apigenin 7,4′-di-*O*-glucoside; Flavone; Antipode; L-Glucose; 2,6-Di-*tert*-butyl-4-methylpyridine; Lewis acid-and-base promotion.

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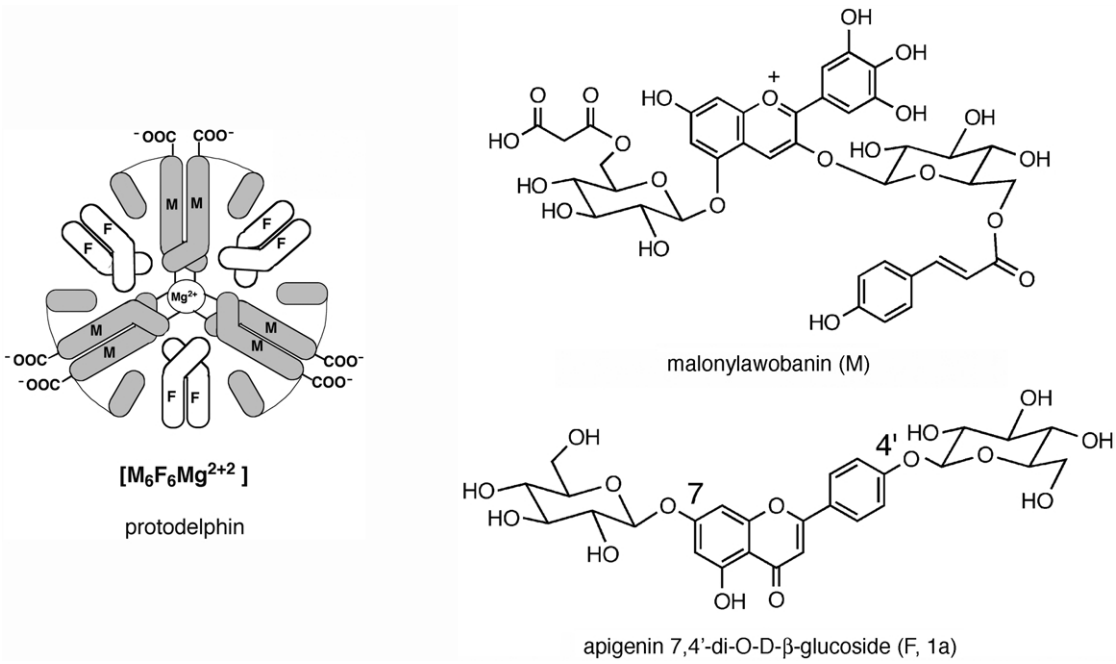


Figure 1. The gross structure and the structure of components of protodelphin.

needs to be performed, requiring a new glycosylation methodology for 4′-OH. We have achieved efficient glycosylation of 4′-OH using acetylglucosyl fluoride **5a** by promotion with $BF_3{\cdot}Et_2O$ as a Lewis acid and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a Lewis base in the presence of 1,1,3,3-tetramethylguanidine (TMG), to succeed in total synthesis of the natural occurring apigenin 7,4′-di-*O*-β-D-glucoside (**1a**) and a number of chiral analogues (**1b**–**d**, **6a**,**b**, **7a**,**b**).[14b]

2. Results and discussion

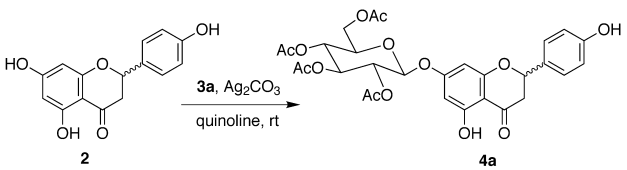
2.1. Synthesis of apigenin 7,4′-di-*O*-β-D-glucopyranoside (1a) and three non-naturally occurring apigenin 7,4′-di-*O*-β-glucopyranosides (1b–d)

Our strategy for synthesis of apigenin of 7,4′-di-*O*-β-glucoside was high yield with short steps, to prepare four chiral isomers, apigenin 7,4′-D,D- (**1a**), 7,4′-D,L- (**1b**), 7,4′-L,D- (**1c**) and 7,4′-L,L-di-β-glucopyranoside (**1d**). The first key reaction is transformation of naringenin to the apigenin derivative; the second, regioselective stepwise-glycosylation with efficient glycosylation of phenolic hydroxyl groups by promotion with a Lewis acid-and-base combination.

We examined glycosylation of (±) naringenin (**2**) with acetobromoglucose **3a** in the presence of Ag_2CO_3 in quinoline under Koenigs–Knorr condition[9a,11b] directly to obtain naringenin 7-*O*-β-D-glucoside (**4a**), which is a 1:1 diastereo-mixture and has a $J_{1,2}$=7.8 Hz. As a result of optimization, 1.5 equiv. of **3a** relative to **2** gave **4a** in 80% yield. However, in spite of using 2.2 equiv. of **3a**, only **4a** was detected, but no diglucoside predicted by the previous report[11b] (Table 1). This direct glycosylation of **2** is exclusively regioselective at 7-OH and the effort to synthesize the diglucoside by a Koenigs–Knorr reaction was not fruitful.

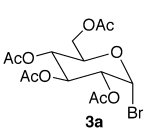
To examine 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of naringenin to apigenin,[15] **2** was protected with 1 equiv. of *t*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole in DMF to give the 7-*O*-TBDMS **8** and 7,4′-di-*O*-TBDMS **9** in 53 and 7% yields, respectively (Scheme 4). Thus, the above results

Table 1. Regioselective glycosylation of naringenin (**2**) to the 7-*O*-β-D-glucoside **4a** by Koenigs–Knorr method

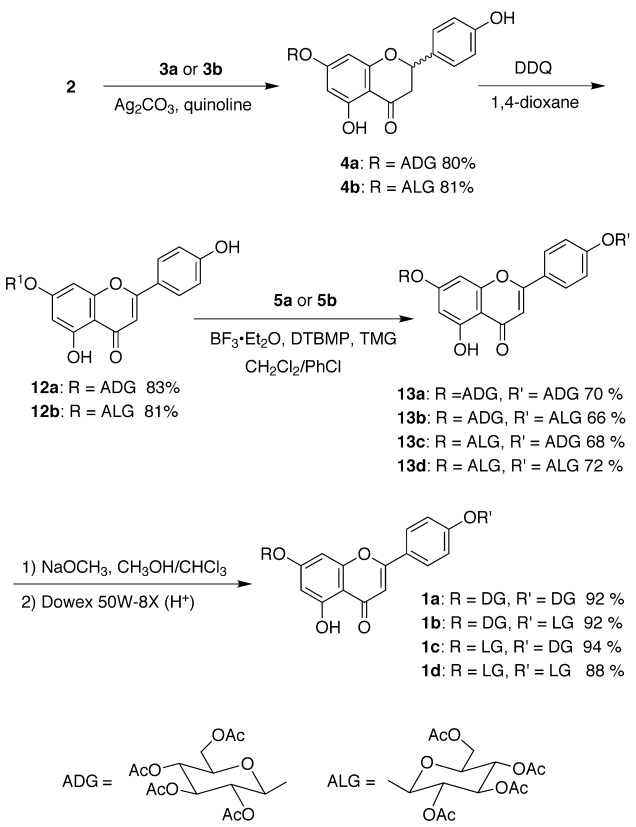


2 **4a**

Entry	**3a** (equiv.)	Ag_2CO_3 (equiv.)	Yield (%)	
1	1	1	48	
2	1.5	1.5	80	
3	2.2	2.2	80	



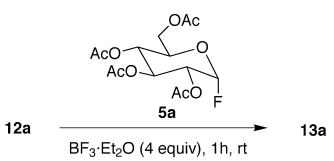
3a



Scheme 2. Synthesis of apigenin 7,4′-di-*O*-D-β-glucopyranosides (**1a**–**d**).

indicated the reactivity of phenolic hydroxyl groups of naringenin to be in the order of 7-OH⩾4′-OH⩾5-OH. **8** was treated with DDQ to give the 7-*O*-TBDMS **10** in 81% yield, but from **9** the corresponding 7,4′-di-*O*-TBDMS **11** was obtained in a lower 44% yield (Table 3, entries 1 and 2). 4′-OH free naringenin **8** was readily dehydrogenated, but the di-TBDMS **9** was very resistant, suggesting that the oxidation of the benzyl proton at C-2 with DDQ favors 4′-OH against protected one. Thus, transformation of **4a** to the corresponding apigenin 7-*O*-glucoside (**12a**), before glycosylation of 4′-OH should be carried out to avoid an unsatisfaction yield and stereo-complications due to glycosylated products. When **4a** was oxidized with 2 equiv. of DDQ in dioxane at 110 °C, a single compound, **12a** was generated in 83% yield (Scheme 2). For glycosylation of 4′-OH of **12a**, a Koenigs–Knorr reaction[9a,11b] or Yamaguchi's method[16] using acetylglucosyl fluoride **5a**, $BF_3{\cdot}Et_2O$ and TMG (Table 2, entries 1 and 2) was then applied, but no diglucoside was produced, indicating the nucleophilicity of the 4′-OH of apigenin to be very low so that the phenolic OH requires activation with a promoter for glycosylation.

Table 2. Glycosylation of 4′-OH of **12a** under various conditions



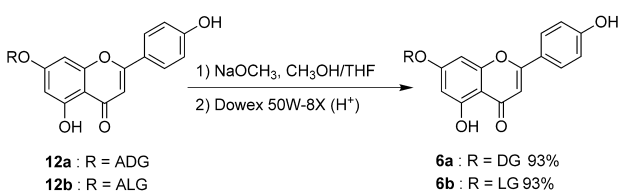
Entry	**5a** (equiv.)	Base (equiv.)	Solvent (v/v)	Yield (%)
1	1	TMG (4)	CH_3CN	0
2	1	TMG (4)	CH_2Cl_2	0
3	1	DTBMP/TMG (4/1)	CH_2Cl_2	30
4	1	DTBMP/TMG (4/1)	$PhCl/CH_2Cl_2$ (6/1)	41
5	2	DTBMP/TMG (4/1)	$PhCl/CH_2Cl_2$ (6/1)	70

Recently, we established highly efficient β-glycosylation of a phenoic hydroxyl group with acetylglucosyl fluoride **5a**, using a combination of $BF_3{\cdot}Et_2O$ and a hindered Lewis base, DTBMP.[17] In this reaction, activation of **5a** with $BF_3{\cdot}Et_2O$ and generation of a phenolate from a less reactive phenolic OH by using DTBMP occurs simultaneously, and consequently the phenolic OH can be efficiently glycosylated. The reaction is influenced by the solvent polarity, and CH_2Cl_2 gave the best results.[17] For glycosyation of **12a** our modified methodology was applied because **12a** was hardly soluble in CH_2Cl_2, toluene, or CH_3CN. Surprisingly, addition of TMG allowed **12a** to go into solution in a non-polar solvent. TMG might play a role as a hydrogen bonding blocker because the lack of solubility of **12a** is conceivably due to strong hydrogen bonding among flavones.

Glycosylation of 4′-OH of **12a** by a combination of $BF_3{\cdot}Et_2O$ (4 equiv.) and DTBMP (4 equiv.)/TMG (1 equiv.) in CH_2Cl_2 gave the desired di-glucoside **13a** in 30% yield, the anomeric configuration being almost β with only trace amounts of the α-isomer (Table 2, entry 3). On screening of several solvents, less polar gave the best results. Though PhCl could not dissolve **12a**, a mixed solvent system of $PhCl/CH_2Cl_2$ improved the glycosylation to give a 41% yield (Table 2, entry 4). When a mole ratio of the donor sugar **5a** to **12a** was changed from 1:1 to 2:1, the yield increased to 70% (Table 2, entry 5), but the higher ratio became plateau of the yield. Finally, deprotection of **13a** with $NaOCH_3$ afforded apigenin 7,4′-di-*O*-β-D-glucoside (**1a**) identical to the natural one[18] in 92% yield (Scheme 2). We thus succeeded in development of the effective short-step synthesis of apigenin 7,4′-di-*O*-β-D-glucoside (**1a**). The new glycosylation using **12a** and 2 equiv. of **5a** (twice to **12a**) in the presence of $BF_3{\cdot}Et_2O$, DTBMP and TMG in CH_2Cl_2/PhCl (1/6 v/v) allowed a route to be opened for synthesis of the following chiral analogues having D- and/or L-glucose. Three chiral isomers, three non-natural apigenin 7,4′-di-*O*-β-glucopyranosides (**1b**–**d**) were synthesized by alternative replacement of D- and/or L-glucose (Scheme 2).

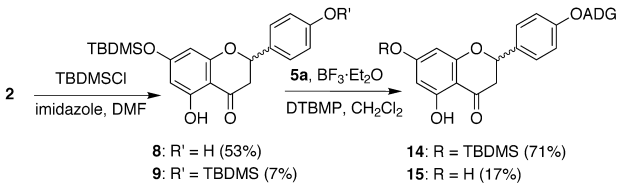
2.2. Synthesis of apigenin 7-*O*-β-D-glucopyranoside (6a) and apigenin 7-*O*-β-L-glucopyranoside (6b)

Apigenin 7-*O*-β-D-glucopyranoside (**6a**) was obtained by deprotection of **12a** by treatment with $NaOCH_3$ quantitatively (Scheme 3). Also, **6b**, the antipode of **6a**, was synthesized via the naringenin 7-*O*-L-glucoside (**4b**), derived from **2** and L-acetobromoglucose **3b** by Koenigs–



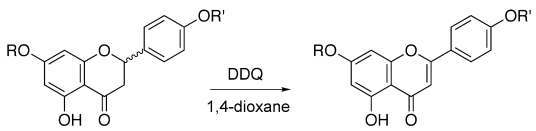
Scheme 3. Deprotection of **12a**,**b**.

Knorr reaction (Scheme 2), according to the same procedure as that for **6a** (Scheme 3).

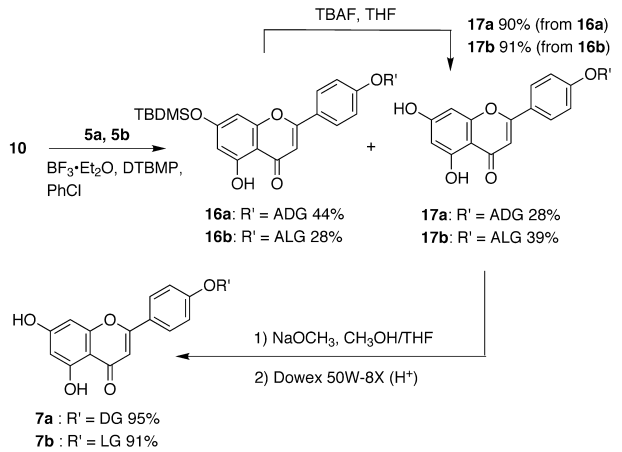


Scheme 4. Synthesis of naringenin 4′-*O*-D-β-glucopyranosides (**14**, **15**).

Table 3. Transformation of naringenin to the corresponding apigenin



Entry	R	R′	Substrate	Product	Yield (%)
1	TBDMS	H	**8**	**10**	81
2	TBDMS	TBDMS	**9**	**11**	44
3	TBDMS	ADG	**14**	**16a**	9
4	H	ADG	**15**	**17a**	25



Scheme 5. Synthesis of apigenin 4′-*O*-β-D- and L-glucopyranosides (**7a**,**b**).

2.3. Synthesis of apigenin 4′-*O*-β-D-glucopyranoside (7a) and apigenin 4′-*O*-β-L-glucopyranoside (7b)

On the basis of the difference of the reactivity among phenolic hydroxyl groups of naringenin (**2**), synthesis of apigenin 4′-*O*-β-D-glucopyranoside (**7a**) was performed as follows: first, regioselective silylation of 7-OH of **2** (Scheme 4); second, DDQ oxidation to 7-*O*-TBDMS apigenin (**10**) (Table 3, entry 1); and finally our glycosylation using **5a** and then deprotection (Scheme 5).

The 7-*O*-TBDMS naringenin (**8**) was glycosylated by using a combination of $BF_3{\cdot}Et_2O$ and DTBMP in CH_2Cl_2 to produce the β-monoglucoside **14** and its de-TBDMS **15** in 71% and 17% yields, respectively (Scheme 4). Treatment of **4a**, **14**, and **15** with DDQ gave the corresponding apigenin products **12a** (83%), **16a** (9%), and **17a** (25%), respectively (Scheme 2 and Table 3). Thus, it was indicated that DDQ oxidation reactivity from naringenin to apigenin depends on the number and the position of the free phenolic OH and the free 4′-OH of the flavanone is optimal for this purpose.

8 was oxidized with DDQ followed by glycosylation using **5a** in the presence of $BF_3{\cdot}Et_2O$ and DTBMP in PhCl to give the corresponding β-glucoside **16a** and the desilylated **17a** in 44 and 28% yields, respectively. During the glycosylation, desilylation occurred partially. Also, **16a** was deprotected with TBAF in THF to give **17a** in 90% yield. Finally, deprotection of **17a** with $NaOCH_3$ afforded a desired apigenin 4′-*O*-β-D-diglucoside (**7a**) in yield 95% (Scheme 5). By the same procedure, apigenin 4′-*O*-β-L-diglucoside (**7b**) was synthesized (Scheme 5).

3. Conclusions

Total synthesis of apigenin 7,4′-*O*-β-D-diglucoside (**1a**) is achievable using a combination of our new glycosylation method and the Koenigs–Knorr reaction. One naturally and three non-naturally occurring apigenin 7,4′-di-*O*-β-glucosides (**1a**–**d**) bearing D-and/or L-glucose could be prepared using this approach. Furthermore, based on differences in reactivity between the 7- and 4′-OH of naringenin, apigenin *O*-monoglucosides **6a**,**b** and **7a**,**b** were synthesized. The finding for total synthesis of **1a** suggests that many kinds of mono- or poly-glycosyl-flavonoids could be synthesized in the same way.

4. Experimental

4.1. General

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured on JASCO P-1010-GT polarimeter. IR spectra were measured on a Perkin–Elmer PARAGON 1000 spectrometer. ^1H and ^{13}C NMR spectra were measured on JEOL JNM-GX 500 spectrometer at 500 and at 125 Hz, respectively. ^1H and ^{13}C chemical shifts are referenced to the internal deuterated solvent. Elemental analyses were performed on Perkin Ellmer CHN 2400-2 or YANACO MT-6 elemental analyser. EI and FAB mass spectra were obtained using JEOL JMX 700 mass spectrometer. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM). Thin layer chromatography was performed on Merck silica gel 60 F_{254}. Solvents were dried following standard methods. L-glucose was purchased from Sigma-Aldrich, D-glucose and naringenin from Tokyo kaei kogyo co., ltd.

4.1.1. 2,3,4,6-Tetra-*O*-acetyl-α-L-glucopyranosyl bromide (3b). According to Lemieux's method,[19] the bromide **3b** was synthesized from L-glucose: mp 87–88 °C; $[\alpha]_D^{24}=-197.3°$ (*c* 1.0, $CHCl_3$); IR (KBr) 1745, 1384, 1229, 1108, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.01 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 4.11 (1H, dd, *J*=12.2, 2.0 Hz), 4.28 (1H, ddd, *J*=10.0, 4.2, 2.0 Hz), 4.31 (1H, dd, *J*=12.2, 4.2 Hz), 4.82 (1H, dd, *J*=10.0, 4.2 Hz), 5.14 (1H, t, *J*=10.0 Hz), 5.54 (1H, t, *J*=10.0 Hz), 6.59 (1H,

d, J=4.2 Hz, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5, 20.6 (×3), 61.0, 67.2, 70.2, 70.6, 72.1, 86.5, 169.4, 169.8 (×2), 170.5; HRMS (FAB) calcd for $C_{14}H_{19}O_9BrNa$ (M+Na^+) 433.0110. Found 433.0111. Anal. calcd for $C_{14}H_{19}O_9Br$: C, 40.89; H, 4.66. Found: C, 40.78; H, 4.67.

4.1.2. 7-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-naringenin (4a). A solution of D-glucosyl bromide **3a** (617 mg, 1.5 mmol), Ag_2CO_3 (414 mg, 1.5 mmol) and **2** (272 mg, 1.0 mmol) in quinoline (7 ml) was stirred for 3 h at room temperature. After being poured into CH_3OH, the solution was filtered through a short pad of silica gel and evaporated in vacuo. The residue was dissolved into AcOEt and washed successively with 1 N HCl and brine, and dried over anhydrous $MgSO_4$. After evaporation, the resulting crude product was purified by flash column chromatography (hexane–AcOEt 1:1) to afford **4a** (483 mg, 80%) as a white foam. The product was an inseparable mixture of diastereomers (1:1); IR (KBr) 3421, 1756, 1644, 1374, 1227 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.95 (4.5H, s), 1.97 (1.5H, s), 2.00 (6H, s), 2.74 (1H, dd, J=17.3, 2.5 Hz), 3.35 (0.5H, dd, J=17.3, 11.8 Hz), 3.38 (0.5H, dd, J=17.3, 11.8 Hz), 4.05 (1H, dd, J=12.2, 2.0 Hz), 4.15 (1H, dd, J=12.2, 6.4 Hz), 4.28 (1H, ddd, J=9.8, 6.4, 2.0 Hz), 4.97 (1H, t, J=9.8 Hz), 5.05 (1H, dd, J=9.8, 7.8 Hz), 5.35 (0.5H, t, J=9.8 Hz), 5.36 (0.5H, t, J=9.8 Hz), 5.51 (0.5H, dd, J=11.8, 2.5 Hz), 5.52 (0.5H, dd, J=11.8, 2.5 Hz), 5.64 (0.5H, d, J=7.8 Hz, 1-H), 5.66 (0.5H, d, J=7.8 Hz, 1-H), 6.10 (1H, d, J=2.0 Hz), 6.14 (0.5H, d, J=2.0 Hz), 6.15 (0.5H, d, J=2.0 Hz), 6.79 (2H, d, J=8.8 Hz), 7.31 (2H, d, J=8.8 Hz), 9.58 (0.5H, s, OH), 9.59 (0.5H, s, OH), 12.02 (0.5H, s, OH) 12.04 (0.5H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.3, 20.4 (×2), 42.1, 42.2, 61.7, 68.1, 70.5, 71.1, 71.9, 78.9 (×2), 95.4, 95.5, 96.1 (×2), 96.5, 103.9 (×2), 115.2, 128.4, 128.5 (×2), 128.6, 157.9 (×2), 162.9, 163.0, 163.8 (×2), 169.1, 169.4, 169.6, 170.0, 197.5 (×2); HRMS (FAB) calcd for $C_{29}H_{30}O_{14}Na$ (M+Na^+) 625.1533. Found: 625.1548.

4.1.3. 7-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-L-glucopyranosyl)-naringenin (4b). According to the procedure described for **4a**, **2** (0.545 g, 2.0 mmol) was glycosylated with L-glucosyl bromide **3b** (1.234 g, 3.0 mmol) to afford **4b** (0.975 g, 81%) as a white foam. The product was an inseparable mixture of diastereomers (1:1); IR (KBr) 3385, 1757, 1644, 1374, 1224 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.95 (4.5H, s), 1.96 (1.5H, s), 2.00 (6H, s), 2.73 (1H, dd, J=17.1, 2.9 Hz), 3.35 (0.5H, dd, J=17.1, 11.8 Hz), 3.37 (0.5H, dd, J=17.1, 11.8 Hz), 4.04 (1H, dd, J=12.2, 2.5 Hz), 4.15 (1H, dd, J=12.2, 6.5 Hz), 4.27 (1H, ddd, J=9.8, 6.5, 2.5 Hz), 4.97 (1H, t, J=9.8 Hz), 5.04 (1H, dd, J=9.8, 7.8 Hz), 5.34 (0.5H, t, J=9.8 Hz), 5.35 (0.5H, t, J=9.8 Hz), 5.50 (0.5H, dd, J=11.8, 2.5 Hz), 5.51 (0.5H, dd, J=11.8, 2.5 Hz), 5.64 (0.5H, d, J=7.8 Hz, 1-H), 5.65 (0.5H, d, J=7.8 Hz, 1-H), 6.10 (1H, d, J=2.0 Hz), 6.14 (0.5H, d, J=2.0 Hz), 6.15 (0.5H, d, J=2.0 Hz), 6.78 (2H, d, J=8.8 Hz), 7.31 (2H, d, J=8.8 Hz), 9.57 (0.5H, s, OH), 9.58 (0.5H, s, OH), 12.01 (0.5H, s, OH), 12.03 (0.5H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3 (×2), 42.0, 42.1, 61.6, 67.9, 70.4, 71.0, 71.8, 78.7, 78.8, 95.3, 95.4, 96.0 (×2), 96.4, 103.7, 103.8, 115.1, 128.3, 128.4 (×2), 128.5, 157.8 (×2), 162.8, 163.0, 163.6, 163.7, 169.0, 169.3, 169.5, 169.8, 197.4 (×2); HRMS (FAB) calcd for $C_{29}H_{30}O_{14}Na$ (M+Na^+) 625.1533. Found 625.1555. Anal. calcd for $C_{29}H_{30}O_{14}$: C, 57.81; H, 5.02. Found: C, 57.81; H, 5.20.

4.1.4. 2,3,4,6-Tetra-*O*-acetyl-α-L-glucopyranosyl fluoride (5b).[20] According to Noyori's method,[21] **5b** was synthesized from L-glucose: mp 106–107 °C; $[\alpha]_D^{25}$ −89.1° (c 1.0, $CHCl_3$); IR (KBr) 1747, 1380, 1229, 1041, 923 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.00, (3H, s), 2.01 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 4.12 (1H, dd, J=12.3, 2.2 Hz), 4.16 (1H, ddd, J=10.0, 4.2, 2.2 Hz), 4.26 (1H, dd, J=12.3, 4.2 Hz), 4.93 (1H, ddd, J=24.2, 10.0, 2.9 Hz), 5.12 (1H, t, J=10.0 Hz), 5.47 (1H, t, J=10.0 Hz), 5.72 (1H, dd, J=52.8, 2.9 Hz, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5 (×2), 20.6, 61.2, 67.4, 69.4, 69.8, (d, J=4.6 Hz), 70.2 (d, J=23.8 Hz), 103.7 (d, J=227.8 Hz), 169.4, 169.9 (×2), 170.5; HRMS (FAB) calcd for $C_{14}H_{19}O_9FNa$ (M+Na^+) 373.0911. Found 373.0913. Anal. calcd for $C_{14}H_{19}O_9F$: C, 48.00; H, 5.47. Found: C, 48.14; H, 5.48.

4.1.5. 7-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-apigenin (12a). A solution of **4a** (90 mg, 0.15 mmol) and DDQ (68 mg, 0.3 mmol) in 1,4-dioxane (5 ml) was refluxed for 15 h at 110 °C. The reaction mixture was purified by flash column chromatography (hexane–AcOEt 1:2) to afford **12a** (75 mg, 83%) as a white solid: mp 207–208 °C; $[\alpha]_D^{26}$ −28.8° (c 0.3, DMSO); IR (KBr) 3431, 1748, 1654, 1603, 1233 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.97 (3H, s), 2.01 (6H, 2s), 2.02 (3H, s), 4.11 (1H, dd, J=12.2, 2.0 Hz), 4.19 (1H, dd, J=12.2, 5.9 Hz), 4.33 (1H, ddd, J=9.8, 5.9, 2.0 Hz), 5.01 (1H, t, J=9.8 Hz), 5.10 (1H, dd, J=9.8, 8.3 Hz), 5.39 (1H, t, J=9.8 Hz), 5.74 (1H, d, J=8.3 Hz, 1-H), 6.43 (1H, d, J=2.0 Hz), 6.78 (1H, d, J=2.0 Hz), 6.87 (1H, s), 6.92 (2H, d, J=8.8 Hz), 7.94 (2H, d, J=8.8 Hz), 10.39 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3, 20.4, 61.6, 67.9, 70.4, 71.1, 71.8, 95.1, 96.4, 99.2, 103.2, 105.9, 116.0, 120.9, 128.6, 156.8, 161.3, 161.4, 161.5, 164.4, 169.0, 169.3, 169.5, 169.9, 182.0; HRMS (FAB) calcd for $C_{29}H_{28}O_{14}Na$ (M+Na^+) 623.1377. Found 623.1391. Anal. calcd for $C_{29}H_{28}O_{14}$: C, 58.00; H, 4.70. Found: C, 58.01; H, 4.92.

4.1.6. 7-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-L-glucopyranosyl) apigenin (12b). According to the procedure described for **12a**, **4b** (1.145 g, 1.9 mmol) was treated with DDQ (863 mg, 3.8 mmol) to afford **12b** as a white solid (0.919 g, 81%): mp 207–208 °C; $[\alpha]_D^{27}$ +28.7° (c 0.3, DMSO); IR (KBr) 3422, 1748, 1659, 1607, 1246 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.97 (3H, s), 2.01 (6H, 2s), 2.02 (3H, s), 4.11 (1H, dd, J=12.2, 2.0 Hz), 4.19 (1H, dd, J=12.2, 5.9 Hz), 4.34 (1H, ddd, J=9.6, 5.9, 2.0 Hz), 5.01 (1H, t, J=9.6 Hz), 5.10 (1H, dd, J=9.6, 8.3 Hz), 5.39 (1H, t, J=9.6 Hz), 5.74 (1H, d, J=8.3 Hz, 1-H), 6.44 (1H, d, J=2.0 Hz), 6.79 (1H, d, J=2.0 Hz), 6.89 (1H, s), 6.93 (2H, d, J=8.8 Hz), 7.95 (2H, d, J=8.8 Hz), 10.40 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3, 20.4, 61.6, 68.0, 70.4, 71.1, 71.8, 95.1, 96.4, 99.2, 103.2, 105.9, 116.0, 120.9, 128.6, 156.8, 161.3, 161.4, 161.5, 164.4, 169.0, 169.3, 169.5, 169.9, 182.0; HRMS (FAB) calcd for $C_{29}H_{30}O_{14}Na$ (M+Na^+) 623.1377. Found 623.1400. Anal. calcd for $C_{29}H_{28}O_{14}$: C, 58.00; H, 4.70. Found: C, 58.02; H, 4.94.

4.1.7. 7,4′-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)apigenin (13a).[12] To a solution of D-glucosyl fluoride **5a** (105 mg, 0.3 mmol), **12a** (90 mg, 0.15 mmol) and TMG (17 mg, 0.15 mmol) and DTBMP (123 mg, 0.6 mmol) in CH_2Cl_2 (0.5 ml) and chlorobenzene (3 ml) was added $BF_3{\cdot}Et_2O$ (80 μl, 0.6 mmol) at room temperature. The solution was stirred for 1 h at room temperature. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo, and purified by thin layer chromatography (AcOE–$CHCl_3$ 1:4 and then hexane–AcOEt 1:1) to afford **13a** as a white foam (98 mg, 70%); $[\alpha]_D^{27}-43.1°$ (*c* 0.1, $CHCl_3$); IR (KBr) 1752, 1656, 1615, 1237, 1042 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.97 (6H, s), 2.02 (18H, s), 4.08 (1H, dd, *J*=12.7, 2.5 Hz), 4.11 (1H, dd, *J*=12.7, 2.5 Hz), 4.18 (1H, dd, *J*=12.7, 5.9 Hz), 4.19 (1H, dd, *J*=12.7, 5.9 Hz), 4.32 (2H, m), 5.01 (1H, t, *J*=9.8 Hz), 5.02 (1H, t, *J*=9.8 Hz), 5.10 (2H, dd, *J*=9.8, 7.8 Hz), 5.39 (1H, t, *J*=9.8 Hz), 5.41 (1H, t, *J*=9.8 Hz), 5.75 (1H, d, *J*=7.8 Hz, 1-H), 5.76 (1H, d, *J*=7.8 Hz, 1-H), 6.46 (1H, d, *J*=2.2 Hz), 6.82 (1H, d, *J*=2.2 Hz), 7.03 (1H, s), 7.17 (2H, d, *J*=8.8 Hz), 8.09 (2H, d, *J*=8.8 Hz), 12.90 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.4, 20.5 (×2), 20.6 (×2), 61.7, 61.8, 68.1, 70.7, 70.8, 71.2, 71.4, 72.1 (×2), 95.5, 96.6, 96.7, 99.5, 104.8, 106.2, 116.9, 125.0, 128.7, 157.1, 159.3, 161.5, 161.8, 163.8, 169.4 (×2), 169.6, 169.7, 169.9, 170.3 (×2), 182.3; HRMS (FAB) calcd for $C_{43}H_{47}O_{23}$ ($M+H^+$) 931.2508. Found 931.2499. Anal. calcd for $C_{43}H_{46}O_{23}$: C, 55.48; H, 4.98. Found: C, 55.47; H, 5.07.

4.1.8. 7-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4′-*O*-(2,3,4,6-tetra-*O*-acetyl-β-L-glucopyranosyl)-apigenin (13b). According to the procedure described for **13a**, **12a** (120 mg, 0.2 mmol) was glycosylated with L-glucosyl fluoride **5b** (140 mg, 0.4 mmol) to afford **13b** as a white foam (123 mg, 66%); $[\alpha]_D^{25}-25.5°$ (*c* 0.1, $CHCl_3$); IR (KBr) 1757, 1657, 1619, 1233, 1039 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.97 (6H, s), 2.02 (18H, s), 4.08 (1H, dd, *J*=12.2, 2.2 Hz), 4.11 (1H, dd, *J*=12.7, 2.4 Hz), 4.18 (1H, dd, *J*=12.2, 6.4 Hz), 4.19 (1H, dd, *J*=12.7, 5.9 Hz), 4.33 (2H, m), 5.01 (1H, t, *J*=9.8 Hz), 5.02 (1H, t, *J*=9.8 Hz), 5.10 (2H, dd, *J*=9.8, 7.8 Hz), 5.39 (1H, t, *J*=9.8 Hz), 5.42 (1H, t, *J*=9.8 Hz), 5.75 (1H, d, *J*=7.8 Hz, 1-H), 5.76 (1H, d, *J*=7.8 Hz, 1-H), 6.47 (1H, d, *J*=2.0 Hz), 6.83 (1H, d, *J*=2.0 Hz), 7.04 (1H, s), 7.17 (2H, d, *J*=8.8 Hz), 8.10 (2H, d, *J*=8.8 Hz), 12.91 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3, 20.4 (×2), 20.5, 61.6 (×2), 67.9, 70.4, 70.6, 71.0, 71.1, 71.8, 71.9, 95.3, 96.4, 99.2, 104.6, 106.0, 116.6, 124.8, 128.5, 156.9, 159.1, 161.3, 161.6, 163.5, 169.0, 169.1, 169.3 (×2), 169.5, 169.6, 169.9 (×2), 182.1; HRMS (FAB) calcd for $C_{43}H_{47}O_{23}$ ($M+H^+$) 931.2508. Found 931.2501. Anal. calcd for $C_{43}H_{46}O_{23}$: C, 55.48; H, 4.98. Found: C, 55.49; H, 5.07.

4.1.9. 7-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-L-glucopyranosyl)-4′-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-apigenin (13c). According to the procedure described for **13a**, **12a** (90 mg, 0.15 mmol) was glycosylated with **5a** (105 mg, 0.3 mmol) to afford **13c** as a white foam (95 mg, 68%); $[\alpha]_D^{25}+25.8°$ (*c* 0.1, $CHCl_3$); IR (KBr) 1756, 1657, 1618, 1233, 1039 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.97 (6H, s), 2.02 (18H, s), 4.08 (1H, dd, *J*=12.2, 2.2 Hz), 4.11 (1H, dd, *J*=12.7, 2.4 Hz), 4.19 (1H, dd, *J*=12.2, 6.4 Hz), 4.20 (1H, dd, *J*=12.7, 5.9 Hz), 4.33 (2H, m), 5.01 (1H, t, *J*=9.8 Hz), 5.02 (1H, t, *J*=9.8 Hz), 5.10 (2H, dd, *J*=9.8, 7.8 Hz), 5.39 (1H, t, *J*=9.8 Hz), 5.42 (1H, t, *J*=9.8 Hz), 5.75 (1H, d, *J*=7.8 Hz), 5.76 (1H, d, *J*=7.8 Hz), 6.47 (1H, d, *J*=2.0 Hz), 6.83 (1H, d, *J*=2.0 Hz), 7.03 (1H, s), 7.18 (2H, d, *J*=8.8 Hz), 8.09 (2H, d, *J*=8.8 Hz), 12.91 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3 (×3), 20.4, 61.6 (×2), 67.9, 70.4, 70.6, 71.0, 71.1, 71.8, 71.9, 95.3, 96.4, 99.3, 104.6, 106.0, 116.6, 124.8, 128.5, 156.9, 159.1, 161.3, 161.6, 163.4, 169.0 (×2), 169.2, 169.3, 169.5 (×2), 169.9 (×2), 182.1; HRMS (FAB) calcd for $C_{43}H_{47}O_{23}$ ($M+H^+$) 931.2508. Found 931.2504. Anal. calcd for $C_{43}H_{46}O_{23}$: C, 55.48; H, 4.98. Found: C, 55.48; H, 5.20.

4.1.10. 7,4′-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-L-glucopyranosyl)apigenin (13d). According to the procedure described for **13a**, **12b** (90 mg, 0.15 mmol) was glycosylated with **5b** (105 mg, 0.3 mmol) to afford **13d** as a white foam (101 mg, 72%); $[\alpha]_D^{26}+43.0°$ (*c* 0.1, $CHCl_3$); IR (KBr) 1755, 1656, 1611, 1234, 1042 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.97 (6H, s), 2.01 (6H, s), 2.02 (12H, s), 4.08 (1H, dd, *J*=12.7, 2.5 Hz), 4.12 (1H, dd, *J*=12.7, 2.5 Hz), 4.19 (1H, dd, *J*=12.7, 5.9 Hz), 4.20 (1H, dd, *J*=12.7, 5.9 Hz), 4.32 (2H, m), 5.01 (1H, t, *J*=9.8 Hz), 5.02 (1H, t, *J*=9.8 Hz), 5.10 (2H, dd, *J*=9.8, 8.3 Hz), 5.39 (1H, t, *J*=9.8 Hz), 5.42 (1H, t, *J*=9.8 Hz), 5.75 (1H, d, *J*=7.8 Hz), 5.76 (2H, d, *J*=7.8 Hz), 6.47 (1H, d, *J*=2.0 Hz), 6.83 (1H, d, *J*=2.0 Hz), 7.03 (1H, s), 7.18 (2H, d, *J*=8.8 Hz), 8.09 (2H, d, *J*=8.8 Hz), 12.91 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3 (×3), 20.4, 61.5, 61.6, 67.9, 70.4, 70,6, 71.0, 71.1, 71.8 (×2), 95.3, 96.4, 99.3, 104.6, 106.0, 116.6, 124.8, 128.5, 156.9, 159.1, 161.3, 161.6, 163.4, 169.0 (×2), 169.2, 169.3, 169.5 (×2), 169.9 (×2), 182.1; HRMS (FAB) calcd for $C_{43}H_{47}O_{23}$ ($M+H^+$) 931.2508. Found 931.2529. Anal. calcd for $C_{43}H_{46}O_{23}$: C, 55.48; H, 4.98. Found: C, 55.49; H, 5.07.

4.1.11. 7,4′-Di-*O*-(β-D-glucopyranosyl)apigenin (1a). To a solution of **13a** (102 mg, 0.11 mmol) in a mixture of CH_3OH (2 ml) and $CHCl_3$ (1 ml) was added $NaOCH_3$ (30 mg) at room temperature. After stirring for 2 h, the reaction mixture was neutralized with Dowex 50W-8X(H^+), filtered, and evaporated in vacuo. The residue was recrystallized from EtOH to afford **1a** as a white solid (60 mg, 92%): mp 180–181 °C; $[\alpha]_D^{28}-55.5°$ (*c* 0.1, DMSO); IR (KBr) 3422, 1656, 1609, 1242, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.17 (2H, m), 3.40 (1H, m), 3.46 (5H, m), 3.70 (4H, m), 5.03 (1H, d, *J*=7.3 Hz, 1-H), 5.06 (1H, d, *J*=7.8 Hz, 1-H), 6.45 (1H, d, *J*=2.0 Hz), 6.86 (1H, d, *J*=2.0 Hz), 6.98 (1H, s), 7.20 (2H, d, *J*=8.8 Hz), 8.06 (2H, d, *J*=8.8 Hz), 12.88 (1H, s, OH). Signals of four protons were overlapped with the signals of H_2O; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 60.6 (×2), 69.5, 69.6, 73.0, 73.1, 76.4, 76.5, 77.1, 94.9, 99.6, 99.8 (×2), 104.0, 105.4, 116.6, 123.8, 128.2, 157.0, 160.4, 161.1, 163.0, 163.6, 182.0; HRMS (FAB) calcd for $C_{27}H_{31}O_{15}$ ($M+H^+$) 595.1663. Found 595.1659.

4.1.12. 7-*O*-(β-L-Glucopyranosyl)-4′-*O*-(β-D-glucopyranosyl)apigenin (1b). According to the procedure described for **1a**, **13b** (93 mg, 0.1 mmol) was treated with $NaOCH_3$

and recrystallized to afford **1b** as a white solid (54 mg, 92%): mp 190–191 °C; $[\alpha]_D^{26}$ −11.9° (*c* 0.3, DMSO); IR (KBr) 3393, 1660, 1609, 1242, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.17 (2H, m), 3.40 (1H, m), 3.46 (5H, m), 3.70 (4H, m), 5.03 (1H, d, *J*=7.3 Hz, 1-H), 5.06 (1H, d, *J*=7.8 Hz, 1-H), 6.45 (1H, d, *J*=2.0 Hz), 6.86 (1H, d, *J*=2.0 Hz), 6.97 (1H, s), 7.20 (2H, d, *J*=8.8), 8.06 (2H, d, *J*=8.8 Hz), 12.88 (1H, s, OH). Signals of four protons were overlapped with the signals of H_2O; ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6 (×2), 69.5, 69.6, 73.1 (×2), 76.4, 76.5, 77.1, 94.9, 99.6, 99.8, 99.9, 104.1, 105.4, 116.6, 123.8, 128.2, 157.0, 160.4, 161.1, 163.0, 163.6, 182.0; HRMS (FAB) calcd for $C_{27}H_{31}O_{15}$ ($M+H^+$) 595.1663. Found 595.1664.

4.1.13. 7-O-(β-D-Glucopyranosyl)-4′-*O*-(β-L-glucopyranosyl)apigenin (1c). According to the procedure described for **1a**, **13c** (56 mg, 0.06 mmol) was treated with $NaOCH_3$ and recrystallized to afford **1c** as a white solid (34 mg, 94%): mp 190–191 °C; $[\alpha]_D^{26}$ +11.9° (*c* 0.3, DMSO); IR (KBr) 3490, 1666, 1609, 1241, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.17 (2H, m), 3.40 (1H, m), 3.46 (5H, m), 3.70 (4H, m), 5.03 (1H, d, *J*=7.3 Hz, 1-H), 5.06 (1H, d, *J*=7.8 Hz, 1-H), 6.45 (1H, d, *J*=2.0 Hz), 6.86 (1H, d, *J*=2.0 Hz), 6.97 (1H, s), 7.20 (2H, d, *J*=8.8), 8.06 (2H, d, *J*=8.8 Hz), 12.88 (1H, s, OH). Signals of four protons were overlapped with the signals of H_2O; ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6 (×2), 69.5, 69.6, 73.0, 73.1, 76.4, 76.5, 77.1, 94.9, 99.6, 99.8, 99.9, 104.1, 105.4, 116.6, 123.8, 128.2, 157.0, 160.4, 161.1, 163.0, 163.6, 182.0; HRMS (FAB) calcd for $C_{27}H_{31}O_{15}$ ($M+H^+$) 595.1663. Found 595.1668.

4.1.14. 7,4′-Di-*O*-(β-L-glucopyranosyl)apigenin (1d). According to the procedure described for **1a**, **13d** (93 mg, 0.1 mmol) was treated with $NaOCH_3$ and recrystallized to afford **1d** as a white solid (52 mg, 88%): mp 180–181 °C; $[\alpha]_D^{27}$ +54.8° (*c* 0.1, DMSO); IR (KBr) 3420, 1663, 1609, 1242, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.17 (2H, m), 3.40 (1H, m), 3.46 (5H, m), 3.70 (4H, m), 5.03 (1H, d, *J*=7.3 Hz, 1-H), 5.06 (1H, d, *J*=7.8 Hz, 1-H), 6.45 (1H, d, *J*=2.0 Hz), 6.86 (1H, d, *J*=2.0 Hz), 6.97 (1H, s), 7.20 (2H, d, *J*=8.8), 8.06 (2H, d, *J*=8.8 Hz), 12.87 (1H, s, OH). Signals of four protons were overlapped with the signals of H_2O; ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6 (×2), 69.5, 69.6, 73.1 (×2), 76.4, 76.5, 77.1, 94.9, 99.6, 99.8 (×2), 104.1, 105.4, 116.6, 123.8, 128.2, 157.0, 160.4, 161.1, 163.0, 163.6, 182.0; HRMS (FAB) calcd for $C_{27}H_{31}O_{15}$ ($M+H^+$) 595.1663. Found 595.1673.

4.1.15. 7-*O*-(β-D-Glucopyranosyl)apigenin (6a). To a solution of **12a** (30 mg, 0.05 mmol) in a mixture of CH_3OH (3 ml) and THF (3 ml) was added $NaOCH_3$ (15 mg) at room temperature. After stirring for 13 h, the reaction mixture was neutralized with Dowex 50W-8X(H^+), filtered, and evaporated in vacuo. The residue was recrystallized from EtOH to afford **6a** (20 mg, 93%) as a white solid: mp 238–239 °C; $[\alpha]_D^{28}$ −42.1° (*c* 0.2, DMSO); IR (KBr) 3452, 1656, 1608, 1178, 1073 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz); δ 3.1–3.2 (1H, m), 3.4–3.5 (2H, m), 3.6–3.7 (1H, m), 5.05 (1H, d, *J*=7.3 Hz, 1-H), 6.44 (1H, d, *J*=2.2 Hz), 6.82 (1H, d, *J*=2.2 Hz), 6.86 (1H, s), 6.93 (2H, d, *J*=8.8 Hz), 7.95 (2H, d, *J*=8.8 Hz), 10.37 (1H, s, OH), 12.95 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6, 69.5, 73.1, 76.4, 77.1, 94.8, 99.5, 99.9, 102.9, 105.3, 116.0, 120.7, 128.5, 156.9, 161.1, 162.9, 164.3, 181.9; HRMS (FAB) calcd for $C_{21}H_{21}O_{10}$ ($M+H^+$) 433.1135. Found 433.1133.

4.1.16. 7-*O*-(β-L-Glucopyranosyl)apigenin (6b). According to the procedure described for **6a**, **12b** (30 mg, 0.05 mmol) was treated with $NaOCH_3$ and recrystallized to afford **6b** (20 mg, 93%) as a white solid: mp 238–239 °C; $[\alpha]_D^{25}$ −43.6° (*c* 0.2, DMSO); IR (KBr) 3443, 1655, 1612, 1177, 1085 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.1–3.2 (1H, m), 3.4–3.5 (2H, m), 3.6–3.7 (1H, m), 5.05 (1H, d, *J*=7.3 Hz, 1-H), 6.43 (1H, d, *J*=2.0 Hz), 6.82 (1H, d, *J*=2.0 Hz), 6.85 (1H, s), 6.93 (2H, d, *J*=8.8 Hz), 7.95 (2H, d, *J*=8.8 Hz), 10.37 (1H, s, OH), 12.95 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6, 69.5, 73.1, 76.4, 77.1, 94.8, 99.5, 99.9, 103.1, 105.3, 115.9, 121.0, 128.5, 156.9, 161.1, 161.3, 162.9, 164.2, 181.9; HRMS (FAB) calcd for $C_{21}H_{21}O_{10}$ ($M+Na^+$) 433.1135. Found 433.1115.

4.1.17. 7-*O*-*tert*-Butyldimethylsilylnaringenin (8) and 7,4′-di-*O*-(*tert*-butyldimethylsilyl) naringenin (9). To a solution of **2** (1.361 g, 5.0 mmol) and imidazole (0.681 g, 10.0 mmol) in DMF (10 ml) was added *tert*-butyldimethylsilyl chloride (0.754 g, 5.0 mmol) at room temperature. After stirring for 13 h, the reaction mixture was diluted with Et_2O and washed with brine. After being dried over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (hexane–AcOEt 2:1) to afford **8** (1.033 g, 53%) and **9** (0.185 g, 7%) as a yellow amorphous powder, respectively. Data for **8**: IR (KBr) 3612, 2958, 2935, 1638, 1179 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.22 (6H, s), 0.95 (9H, s), 2.76 (1H, dd, *J*=17.1, 3.0 Hz), 3.07 (1H, dd, *J*=17.1, 12.8 Hz), 4.96 (1H, s, OH), 5.33 (1H, dd, *J*=12.8, 3.0 Hz), 5.96 (1H, d, *J*=2.2 Hz), 5.99 (1H, d, *J*=2.2 Hz), 6.87 (2H, d, *J*=8.8 Hz), 7.31 (2H, d, *J*=8.8 Hz), 11.92 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ −4.4, 18.2, 25.5, 43.3, 78.9, 99.9, 101.3, 103.6, 115.7, 128.0, 130.7, 156.1, 162.8, 163.9, 165.0, 196.1; HRMS (EI) calcd for $C_{21}H_{26}O_5Si$ (M^+) 386.1550. Found 386.1546. Data for **9**: IR (KBr) 2957, 2935, 1642, 1166, 839 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.19 (6H, s), 0.22 (6H, s), 0.97 (9H, s), 0.94 (9H, s), 2.75 (1H, dd, *J*=17.1, 2.9 Hz), 3.07 (1H, dd, *J*=17.1, 13.2 Hz), 5.32 (1H, d, *J*=2.2 Hz), 5.96 (1H, d, *J*=2.2 Hz), 5.99 (1H, d, *J*=2.2 Hz), 6.86 (1H, d, *J*=8.6 Hz), 7.29 (1H, d, *J*=8.6 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz); δ −4.4, 18.2, 25.5, 25.6, 43.4, 79.0, 99.9, 101.2, 103.6, 120.4, 127.6, 131.0, 156.3, 162.9, 163.9, 165.0, 196.2; HRMS (EI) calcd for $C_{27}H_{40}O_5Si_2$ (M^+) 500.2414. Found 500.2434.

4.1.18. 7-*O*-*tert*-Butyldimethylsilyl-4′-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) naringenin (14) and 4′-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)naringenin (15). To a solution of **5a** (263 mg, 0.75 mmol), **8** (193 mg, 0.5 mmol) and DTBMP (411 mg, 2.0 mmol) in CH_2Cl_2 (3 ml) was added $BF_3{\cdot}Et_2O$ (0.25 ml, 2.0 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by thin layer chromatography

(hexane–AcOEt 3:2 (for **14**) and hexane–AcOEt 1:1 (for **15**)) to give **14** (253 mg, 71%) as a white amorphous powder and **15** (51 mg, 17%) as a white foam, respectively. Both **14** and **15** were an inseparable mixture of diastereomers (1:1): Data for **14**: IR (KBr) 2958, 1755, 1644, 1370, 1223 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.22 (3H, s), 0.94 (6H, s), 2.02 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.77 (1H, dd, J=17.1, 3.0 Hz), 3.04 (0.5H, dd, J=17.1, 12.7 Hz), 3.05 (0.5H, dd, J=17.1, 12.7 Hz), 3.85 (1H, ddd, J=9.8, 5.4, 2.0 Hz), 4.15 (0.5H, dd, J=12.2, 2.0 Hz), 4.16 (0.5H, dd, J=12.2, 2.0 Hz), 4.27 (1H, dd, J=12.2, 5.4 Hz), 5.08 (0.5, d, J=7.8 Hz, H-1), 5.09 (0.5H, d, J=7.8 Hz, H-1), 5.16 (1H, t, J=9.8 Hz), 5.26 (1H, dd, J=9.8, 7.8 Hz), 5.29 (1H, t, J=9.8 Hz), 5.36 (1H, dd, J=12.7, 3.0 Hz), 5.95 (1H, d, J=2.2 Hz), 5.99 (1H, d, J=2.2 Hz), 7.02 (2H, d, J=8.8 Hz), 7.37 (2H, d, J=8.8 Hz), 11.88 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.4, 18.2, 20.5, 20.6, 20.7, 25.5, 43.3, 61.9, 68.3, 71.2, 72.1, 72.7, 99.0, 99.8, 101.3, 103.6, 117.3, 127.7, 133.4, 157.1, 162.6, 164.0, 165.0, 169.2, 169.4, 170.2, 170.5, 195.7; HRMS (FAB) calcd for $C_{35}H_{44}O_{14}SiNa$ (M+Na^+) 739.2398. Found 739.2380.

Data for **15**: IR (KBr) 3422, 2961, 1755, 1641, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.02 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.78 (1H, dd, J=17.1, 3.0 Hz), 3.04 (1H, dd, J=17.1, 12.7 Hz), 4.16 (1H, dd, J=9.5, 5.3, 2.0 Hz), 4.27 (1H, dd, J=12.2, 5.3 Hz), 5.09 (1H, d, J=7.8 Hz, H-1), 5.16, (1H, t, J=9.5 Hz), 5.26 (1H, dd, J=9.5, 7.8 Hz), 5.29 (1H, t, J=9.5 Hz), 5.37 (1H, dd, J=12.7, 3.0 Hz), 5.85 (1H, br, OH), 5.95 (1H, d, J=2.2 Hz), 5.98 (1H, d, J=2.2 Hz), 7.02 (1H, d, J=8.8 Hz), 7.36 (1H, d, J=8.8 Hz), 11.99 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6, 20.7, 43.1, 61.9, 68.3, 71.2, 72.1, 72.7, 78.6, 95.5, 96.8, 98.9, 103.1, 117.2, 117.3, 127.7, 133.3, 157.1, 163.0, 164.3, 165.0, 169.4, 169.5, 170.4, 170.7, 195.6; HRMS (FAB) calcd for $C_{29}H_{30}O_{14}Na$ (M+Na^+) 625.1533. Found 625.1512.

4.1.19. 7-*O*-*tert*-Butyldimethylsilylapigenin (10). A solution of **8** (387 mg, 1.0 mmol) and DDQ (454 mg, 2.0 mmol) in 1,4-dioxane (5 ml) was refluxed for 15 h at 110 °C. The reaction mixture was purified by flash column chromatography (hexane–AcOEt 3:2) to afford **10** (310 mg, 81%) as a white solid: mp 176–177 °C; IR (KBr) 3452, 2957, 2933, 1653, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.26 (6H, s), 0.98 (9H, s), 5.79 (1H, s, OH), 6.28 (1H, d, J=2.2 Hz), 6.41 (1H, d, J=2.2 Hz), 6.55 (1H, s), 6.94 (2H, d, J=8.8 Hz), 7.78 (2H, d, J=8.8 Hz), 12.69 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.4, 18.2, 25.5, 98.8, 103.9, 104.0, 105.9, 116.2, 123.3, 128.4, 157.6, 159.6, 161.9, 162.4, 164.5, 182.7; HRMS (EI) calcd For $C_{21}H_{24}O_5Si$ (M^+) 384.1393. Found 384.1388.

4.1.20. 7,4′-di-*O*-(*tert*-Butyldimethylsilyl)apigenin (11). A solution of **9** (100 mg, 0.2 mmol) and DDQ (91 mg, 0.4 mmol) in 1,4-dioxane (5 ml) was refluxed for 17 h at 110 °C. The reaction mixture was purified by flash column chromatography (hexane–AcOEt 6:1) to afford **11** (44 mg, 44%) as a white solid: mp 99–100 °C; IR (KBr) 2932, 1655, 1604, 1272, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.23 (6H, s), 0.26 (6H, s), 0.99 (18H, s), 6.28 (1H, d, J=2.0 Hz), 6.41 (1H, d, J=2.0 Hz), 6.55 (1H, s), 6.93 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.8 Hz), 12.7 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.4, 18.2, 25.5, 25.6, 98.7, 103.9, 104.3, 106.0, 120.6, 124.1, 128.1, 157.6, 159.3, 162.0, 162.3, 164.2, 182.6; HRMS (EI) calcd for $C_{27}H_{38}O_5Si_2$ (M^+) 498.2258. Found 498.2239.

4.1.21. 7-*O*-*tert*-Butyldimethylsilyl-4′-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) apigenin (16a) from 14. A solution of **14** (93 mg, 0.13 mmol) and DDQ (59 mg, 0.26 mmol) in 1,4-dioxane (5 ml) was refluxed for 17 h at 110 °C. The reaction mixture was purified by flash column chromatography (hexane–AcOEt 3:2) to afford **16a** (8 mg, 9%) as a white amorphous powder; $[\alpha]_D^{24}$ −18.3° (*c* 0.2, $CHCl_3$); IR (KBr) 2958, 2936, 1759, 1608, 1234 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.28 (6H, s), 0.97 (9H, s), 1.97 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 4.08 (1H, dd, J=12.3, 2.0 Hz), 4.20 (1H, dd, J=12.3, 5.6 Hz), 4.31 (1H, ddd, J=10.0, 5.6, 2.0 Hz), 5.02 (1H, t, J=9.8 Hz), 5.10 (1H, dd, J=9.8, 7.8 Hz), 5.43 (1H, t, J=9.8 Hz), 5.76 (1H, d, J=7.8 Hz, 1-H), 6.27 (1H, d, J=2.5 Hz), 6.68 (1H, d, J=2.5 Hz), 7.00 (1H, s), 7.16 (2H, d, J=9.3 Hz), 8.12 (2H, d, J=9.3 Hz), 12.84 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ −3.2, 17.7, 20.3, 20.4, 20.5, 25.8, 61.6, 68.0, 70.6, 71.0, 71.9, 94.1, 96.5, 99.0, 103.8, 104.3, 116.6, 125.2, 128.4, 157.4, 159.0, 161.4, 162.8, 164.4, 169.1, 169.3, 169.6, 170.0, 181.8; HRMS (FAB) calcd for $C_{35}H_{43}O_{14}Si$ (M+H^+) 715.2422. Found 715.2435.

4.1.22. 4′-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)apigenin (17a) from 15. A solution of **15** (271 mg, 0.45 mmol) and DDQ (204 mg, 0.9 mmol) in 1,4-dioxane (5 ml) was refluxed for 14 h at 110 °C. The reaction mixture was purified by flash column chromatography (hexane–AcOEt 1:2) to afford **17a** as a white solid (67 mg, 25%): mp 154–155 °C; $[\alpha]_D^{24}$ −21.0° (*c* 0.2, THF); IR (KBr) 3421, 1755, 1656, 1620, 1233 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.97 (3H, s), 2.01 (3H, s), 2.02 (6H, s), 4.08 (1H, dd, J=12.2, 2.0 Hz), 4.20 (1H, dd, J=12.2, 5.4 Hz), 4.30 (1H, ddd, J=9.8, 5.4, 2.0 Hz), 5.02 (1H, t, J=9.8 Hz), 5.10 (1H, dd, J=7.8, 9.8 Hz), 5.42 (1H, t, J=9.8 Hz), 5.74 (1H, d, J=7.8 Hz, 1-H), 6.20 (1H, d, J=2.0 Hz), 6.51 (1H, d, J=2.0 Hz), 6.92 (1H, s), 7.16 (2H, d, J=8.8 Hz), 8.07 (2H, d, J=8.8 Hz), 10.86 (1H, s, OH), 12.85 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 20.2, 20.3, 20.4, 61.5, 67.9, 70.6, 71.0, 71.8, 94.0, 96.5, 98.9, 103.8, 104.3, 116.6, 125.1, 128.4, 157.3, 158.9, 161.4, 162.8, 164.3, 169.0, 169.3, 169.5, 169.9, 181.8; HRMS (FAB) calcd for $C_{29}H_{29}O_{14}$ (M+H^+) 601.1557. Found 601.1554.

4.1.23. Glycosylation of 10 to 16a and 17a. To a solution of **5a** (140 mg, 0.4 mmol), **10** (77 mg, 0.2 mmol), and DTBMP (164 mg, 0.8 mmol) in PhCl (3 ml) was added $BF_3{\cdot}Et_2O$ (0.1 ml, 0.8 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$, evaporated in vacuo, and purified by thin layer chromatography (hexane–AcOEt 3:2 (for **16a**) and hexane–AcOEt 1:2 (for **17a**)) to afford **16a** (63 mg, 44%) and **17a** (34 mg, 28%), respectively.

4.1.24. Glycosylation of 10 to 16b and 17b. According to the procedure described for **16a** and **17a**, **10** (77 mg, 0.2 mmol) was glycosylated with L-glucosyl fluoride **5b**

(140 mg, 0.4 mmol) to afford **16b** (40 mg, 28%) as a white amorphous powder and **17b** (47 mg, 39%) as a white solid: Data for **16b**: $[\alpha]_D^{24}$+18.3° (*c* 0.2, $CHCl_3$); IR (KBr) 2960, 2934, 1753, 1655, 1607, 1235 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 0.27 (6H, s), 0.96 (9H, s), 1.97 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 4.08 (1H, dd, *J*=12.3, 2.2 Hz), 4.20 (1H, dd, *J*=12.3, 5.5 Hz), 4.31 (1H, ddd, *J*=9.8, 5.5, 2.2 Hz), 5.03 (1H, t, *J*=9.8 Hz), 5.10 (1H, dd, *J*=9.8, 7.9, Hz), 5.43 (1H, t, *J*=9.8 Hz), 5.75 (1H, d, *J*=7.9 Hz, 1-H), 6.26 (1H, d, *J*=2.2 Hz), 6.67 (1H, d, *J*=2.2 Hz), 6.99 (1H, s), 7.16 (2H, d, *J*=9.2 Hz), 8.11 (2H, d, *J*=9.2 Hz), 12.83 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ −4.7, 17.9, 20.2, 20.3, 20.4, 25.3, 61.5, 67.9, 70.6, 71.0, 71.9, 96.4, 98.8, 103.2, 104.4, 105.4, 116.5, 124.9, 128.5, 157.0, 159.1, 161.2, 161.6, 163.2, 169.0, 169.2, 169.5, 169.9, 182.0; HRMS (FAB) calcd for $C_{35}H_{43}O_{14}Si$ ($M+H^+$) 715.2422. Found 715.2420.

Data for **17b**: mp 154–155 °C; $[\alpha]_D^{23}$+21.2° (*c* 0.2, $CHCl_3$); IR (KBr) 3397, 1754, 1656, 1619, 1234 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz); δ 1.97 (3H, s), 2.01 (3H, s), 2.02 (6H, s), 4.08 (1H, dd, *J*=12.2, 2.2 Hz), 4.20 (1H, dd, *J*=12.2, 5.4 Hz), 4.30 (1H, ddd, *J*=9.8, 5.4, 2.2 Hz), 5.02 (1H, t, *J*=9.8 Hz), 5.10 (1H, dd, *J*=9.8, 8.3 Hz), 5.42 (1H, t, *J*=9.8 Hz), 5.74 (1H, d, *J*=8.3 Hz, 1-H), 6.20 1H, (1H, d, *J*=2.0 Hz), 6.51 (1H, d, *J*=2.0 Hz), 6.92 (1H, s), 7.16 (2H, d, *J*=8.8 Hz), 8.07 (2H, d, *J*=8.8 Hz), 10.85 (1H, s, OH), 12.85 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.2, 20.3, 20.4, 61.5, 67.9, 70.6, 70.9, 71.8, 94.0, 96.5, 98.9, 103.8, 104.3, 116.6, 125.1, 128.3, 157.3, 158.9, 161.4, 162.7, 164.3, 169.0, 169.2, 169.5, 169.9, 181.7; HRMS (FAB) calcd for $C_{29}H_{29}O_{14}$ ($M+H^+$) 601.1557. Found 601.1548.

4.1.25. Desilylation of 16a to 17a. To a solution of **16a** (36 mg, 0.05 mmol) in THF (2 ml) was added TBAF·$3H_2O$ (63 mg, 0.2 mmol) at room temperature. After 20 min, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by thin layer chromatography (hexane–AcOEt 1:1) to afford **17a** (27 mg, 90%).

4.1.26. Desilylation of 16b to 17b. According to the procedure described for **17a**, **16b** (114 mg, 0.16 mmol) was desilylated with TBAF·$3H_2O$ to afforded **17b** (87 mg, 91%).

4.1.27. 4′-*O*-(β-D-Glucopyranosyl)apigenin (7a). To a solution of **17a** (30 mg, 0.05 mmol) in a mixture of CH_3OH (3 ml) and THF (1 ml) was added $NaOCH_3$ (30 mg) at room temperature. After stirring for 15 h, the reaction mixture was neutralized with Dowex 50W-8X(H^+), filtered, and evaporated in vacuo. The residue was recrystallized from EtOH to afford **7a** as a white solid (21 mg, 95%): mp 173–174 °C; $[\alpha]_D^{27}$−29.0° (*c* 0.2, DMSO); IR (KBr) 3449, 1656, 1610, 1168, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz); δ 3.1–3.2 (1H, m), 3.3–3.4 (1H, m), 3.4–3.5 (1H, m), 3.6–3.7 (1H, m), 5.02 (1H, d, *J*=7.3 Hz, 1-H), 6.20 (1H, d, *J*=2.0 Hz), 6.51 (1H, d, *J*=2.0 Hz), 6.89 (1H, s), 7.18 (2H, d, *J*=8.8 Hz), 8.03 (2H, d, *J*=8.8 Hz), 10.85 (1H, s, OH), 12.89 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6, 69.6, 73.1, 76.5, 77.1, 94.0, 98.9, 99.8, 103.8, 103.8, 116.5, 123.9, 128.1, 157.3, 160.2, 161.4, 163.1, 164.2, 181.8; HRMS (FAB) calcd for $C_{21}H_{21}O_{10}$ ($M+H^+$) 433.1135. Found 433.1137.

4.1.28. 4′-*O*-(β-L-Glucopyranosyl)apigenin (7b). According to the procedure described for **7a**, **17b** (30 mg, 0.05 mmol) was treated with $NaOCH_3$ and recrystallized to afford **7b** as a white solid (20 mg, 91%): mp 173–174 °C; $[\alpha]_D^{25}$+29.1° (*c* 0.2, DMSO); IR (KBr) 3456, 1656, 1609, 1168, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.1–3.2 (1H, m), 3.3–3.4 (1H, m), 3.4–3.5 (1H, m), 3.6–3.7 (1H, m), 5.02 (1H, d, *J*=7.6 Hz, 1-H), 6.19 (1H, d, *J*=2.0 Hz), 6.50 (1H, d, *J*=2.0 Hz), 6.88 (1H, s), 7.18 (2H, d, *J*=8.8 Hz), 8.03 (2H, d, *J*=8.8 Hz), 10.91 (1H, s, OH), 12.89 (1H, s, OH); ^{13}C NMR (MDSO-d_6, 125 MHz) δ 60.6, 69.6, 73.1, 76.5, 77.1, 94.0, 98.9, 99.8, 103.7, 103.8, 116.5, 123.9, 128.1, 157.3, 160.2, 161.4, 163.0, 164.3, 181.7; HRMS (FAB) calcd for $C_{21}H_{21}O_{10}$ (M^+) 433.1135. Found 433.1138.

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Synthesis of β-lactams and β-aminoesters via high intensity ultrasound-promoted Reformatsky reactions☆

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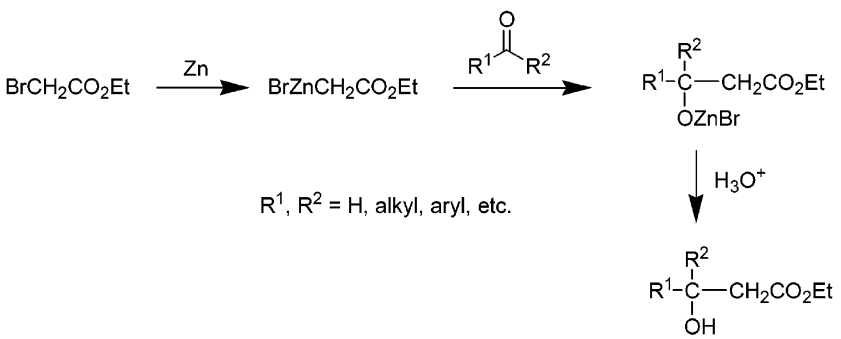
Abstract—Reformatsky reactions of an imine, an α-bromoester, zinc dust and a catalytic amount of iodine in dioxane under high intensity ultrasound (HIU) irradiation from an ultrasonic probe are explored. A series of 16 aldimines with varying electronic demands is evaluated as potential electrophiles for reactions with three α-bromoesters of differing steric demands. This HIU method is successful for both enolizable and non-enolizable imines affording in short reaction times high yields of a β-lactam, the corresponding β-aminoester or a mixture of the two products depending on the identity of the imine and α-bromoester.

1. Introduction

A classic reaction in organic chemistry is the zinc-induced formation of β-hydroxyesters from α-haloesters and aldehydes or ketones known as the Reformatsky reaction (Scheme 1).[1] The scope of the Reformatsky reaction has progressed through the years and is the subject of several reviews.[2–5] An underlying problem with the classical protocol of using zinc dust is its low reactivity. It is necessary to 'activate' the zinc dust to initiate the reaction. Control of the resulting exothermic reaction has also been a problem. Improvements in yields of the Reformatsky reaction have been achieved when freshly prepared zinc powder,[6] a heated column of zinc dust,[7] a trimethyl borate–THF solvent system,[8] a copper–zinc couple,[9] acid-washed zinc,[10] and trimethylchlorosilane[11] were utilized.

The Reformatsky reaction is not limited to aldehydes and ketones as acceptors. Gilman and Speeter[12] first described formation of β-lactams from imines. Functioning as electrophiles in Reformatsky reactions with α-haloesters, imines can provide β-lactams, the corresponding β-aminoesters, or a mixture of the two products (Scheme 2). Kapoor and co-workers[13] report that the relative abundances of these two products are sensitive to the electron-withdrawing nature of the nitrogen atom in the imine. In addition, Dardoize and co-workers[14] found that the relative amounts of β-lactam and β-aminoester to be temperature dependent in ethereal solvents.

In some cases, ultrasonic irradiation can be utilized as an alternative energy source for organic reactions ordinarily accomplished by heating.[15,16] Boudjouk and Han[17] were



Scheme 1. The Reformatsky reaction.

☆ Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tet.2004.01.002

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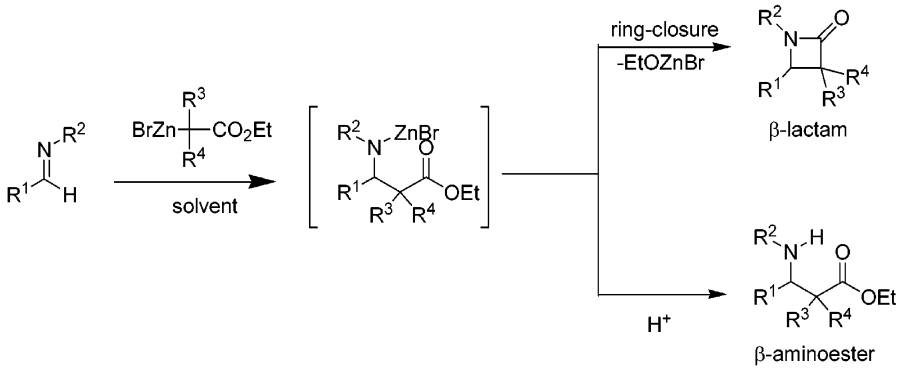


Scheme 2. Potential products in the Reformatsky reaction of imines and α-bromoesters.

first to report that low intensity ultrasound (LIU) from a laboratory cleaning bath greatly improved the rates and yields from Reformatsky reactions of simple aldehydes and ketones with ethyl bromoacetate. However, the zinc dust still had to be 'activated' using the 'Cava' method[18] and the reported conditions called for dried, distilled dioxane as the optimal solvent. Several years later, Bose and co-workers[19] reported a considerable increase in yield, when compared to thermal methods, of β-lactams in LIU-promoted Reformatsky reactions of a series of aryl-substituted imines with methyl bromoacetate in dioxane at room temperature for 4–10 h. However, when this ester component was replaced with methyl α-bromopropionate or methyl α-bromo-β-phenylpropionate, no β-lactam formation was observed although the reactants were consumed. Therefore, the LIU procedure is limited to formation of γ-unsubstituted β-lactams. It is also important to note that the zinc used by Bose and co-workers was 'activated' by washing with nitric acid in order to achieve high yields. When un-activated zinc granules were employed under LIU irradiation, the yields were comparable to those from thermal Reformatsky reactions.

LIU from an ultrasonic cleaner has considerably less power when compared to high intensity ultrasound (HIU) from a direct immersion horn,[20] which can lead to reproducibility problems due to the lower power involved for the former.[21] We have previously reported[22–24] the utility of HIU for Reformatsky reactions of ketones and α-bromoesters and now wish to present the results from our study of HIU-initiated Reformatsky reactions with imines.

2. Results and discussion

2.1. Preparation of imine reactants

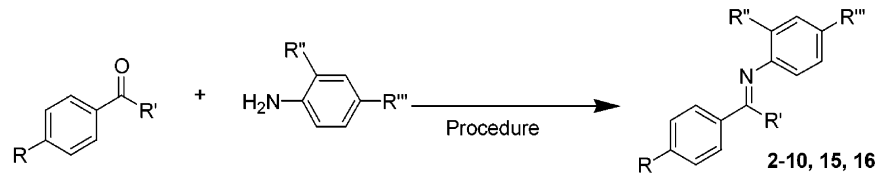
The benzal- or anilino-substituted *N*-benzylideneanilines **2**–**10** and ketone anils **15** and **16** (Table 1) were prepared by adapting two different literature procedures.[25,26] Imines **2**, **3** and **7** were synthesized by Procedure A,[25] which involved stirring the two neat reactants at room temperature. However, for benzaldehyde and *o*-methoxyaniline (entry 8), the reaction was incomplete. Addition of benzene to the neat reactants and refluxing for three days also failed to give complete reaction. Changing to Procedure B,[26] which involved the addition of 5 Å molecular sieves and benzene to the two reactants and stirring at room temperature for 24 h, gave imine **9** in 98% yield. By Procedure B, imines **4**–**6**, **8**–**10**, **15** and **16** were obtained in very high to quantitative yields. Treatment of benzophenone with aniline by Procedure A (entry 12) failed to give the condensation product. Changing to Procedure B produced the corresponding imine in quantitative yield (entry 13). In similar fashion, the imine from acetophenone and aniline was obtained in 98% yield by Procedure B (entry 11).

2.2. HIU Reformatsky reactions

The HIU Reformatsky reactions were conducted in a 20 °C thermostatted cooling bath to control the exothermic reaction and cool the contents from frictional heating produced by direct introduction of HIU irradiation. The reaction flask was partially immersed in the cooling bath during ultrasonication and the in situ temperature rose to 41–42 °C, as determined by a calorimetry experiment. The HIU Reformatsky reactions were performed with unactivated zinc dust, an imine, the α-bromoester, and a catalytic amount of iodine in reagent-grade dioxane with no additional stirring. A series of 16 imines with varying electronic properties was evaluated as potential electrophiles for reactions with three α-bromoesters of differing steric demands.

The investigation began with commercially available *N*-benzylideneaniline (**1**), 1.5 equiv. ethyl bromoacetate, 0.2 equiv. of iodine and 1.8 equiv. of zinc dust in reagent-grade dioxane. The LIU procedure by Bose,[19] which reportedly gave a 70% yield of the corresponding β-lactam **23** was repeated. In our hands, LIU irradiation gave only a very small amount of β-aminoester **17** (2% by GC) together with large amounts of unreacted starting materials. Upon changing from LIU to HIU, complete consumption of the reactants was achieved within 5 min. Results from the initial reactions of *N*-benzylideneaniline (**1**) with ethyl bromoacetate under HIU irradiation are presented in Table 2. For entry 1, the crude product mixture contained a 1:1 mixture of β-aminoester **17** and β-lactam **23**. When a longer reaction time was employed (entry 2), the relative proportion of β-lactam increased. Due to the aforementioned temperature dependence noted by Dardoize and co-workers[14] that influenced the relative amounts of β-lactam and β-aminoester in thermal Reformatsky reactions, the effect of temperature was examined for the HIU-promoted reaction. Lowering of the bath temperature from 20 to 0 °C (entry 3) gave a larger proportion of

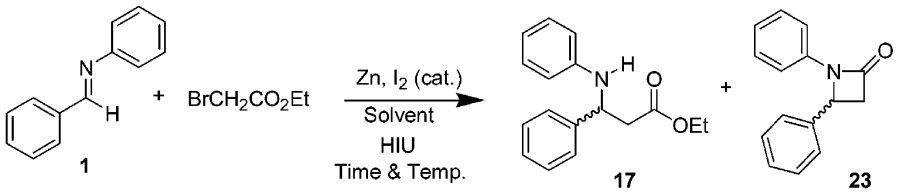
Table 1. Preparation of imines **2**–**10**, **15**, and **16** for Reformatsky reactions



Entry	R	R′	R″	R‴	Prod.[a]	Proc.[b]	Yield[c] (%)
1	Cl	H	H	H	**2**	A	95
2	MeO	H	H	H	**3**	A	96
3	CF_3	H	H	H	**4**	B	98
4	$N(CH_3)_2$	H	H	H	**5**	B	99
5	H	H	H	Cl	**6**	B	97
6	H	H	H	MeO	**7**	A	100
7	H	H	H	CF_3	**8**	B	99
8	H	H	OMe	H	**9**	A	I[d]
9	H	H	OMe	H	**9**	B	98
10	H	H	Et	H	**10**	B	98
11	H	Me	H	H	**15**	B	98
12	H	Ph	H	H	—	A	NR[e]
13	H	Ph	H	H	**16**	B	100

[a] Spectroscopic data are given in Supplementary Material.
[b] Procedure A (*Organic Syntheses*; Wiley: New York, 1941; Coll. Vol. I, p 80); Procedure B (*J. Org. Chem.* **1971**, *36*, 1570).
[c] Isolated yield.
[d] Incomplete reaction as determined by ^{1}H NMR spectroscopy.
[e] No reaction after refluxing in benzene.

Table 2. Reaction of **1** with ethyl bromoacetate



Entry	Time (min)	Temperature (°C)[a]	Solvent	**17/23** ratio[b]
1	5	20	Dioxane	1.0
2	60	20	Dioxane	0.4
3	5	0	Dioxane	5.2
4	60	50	Dioxane	0.2
5	30	20	THF	0.6

[a] Bath temperature.
[b] Ratio determined by GC analysis of the crude reaction product mixture.

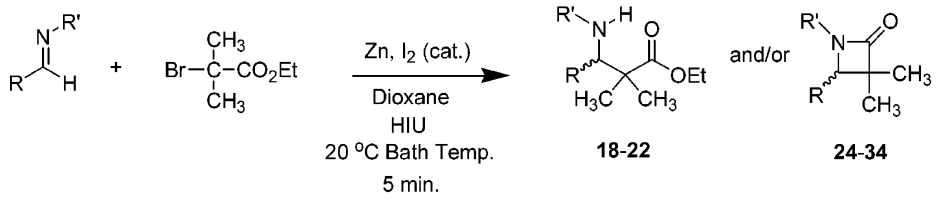
β-aminoester **17** (5.2 times). Entry 4 shows the effect of increasing the bath temperature from 20 to 50 °C with sonication for 60 min. When compared to entry 2, the higher temperature resulted in an enhanced proportion (2 times) of β-lactam **23**. Shankar and co-workers[27] reported that LIU-induced reactions of this type in dioxane gave predominantly the β-aminoester with only traces of β-lactam. Since THF has been used in the synthesis of β-lactams in thermal Reformatsky reactions,[28] it was examined as a solvent for the HIU-promoted reaction resulting in a slightly greater proportion of β-lactam **23** than observed in dioxane (compare entries 2 and 5).

Unsuccessful in our attempts to obtain solely the β-lactam or β-aminoester product from ethyl bromoacetate, the more hindered DL-ethyl α-bromopropionate was tested. This ester provided 3.8 times as much β-aminoester as β-lactam.

The even more hindered ester ethyl α-bromoisobutyrate was then evaluated in reaction with **1** and afforded a 94% isolated yield of β-lactam **24** after 5 min of HIU irradiation. In light of this result, ethyl α-bromoisobutyrate was selected as the α-bromoester component for a series of HIU-initiated Reformatsky reactions designed to probe the importance of electronic effects of substituents in the imine component.

To determine the influence of substituents on the benzal- or anilino-ring of *N*-benzylideneaniline (**1**) upon β-lactam formation, a series of imines was examined (Table 3). Substituents of *p*-Cl, *p*-OMe, *p*-CF_3 and *p*-NMe_2 on the benzal ring (entries 2–5) and *p*-Cl, *p*-OMe, *p*-CF_3, *o*-OMe and *o*-Et on the anilino ring (entries 6–10) were chosen. These substituents provide electron-donating (OMe and NMe_2), weakly electron-withdrawing (Cl), and strongly electron-withdrawing (CF_3) groups. With *p*-Cl, *p*-OMe, or

Table 3. β-Lactams/β-aminoesters (AE) prepared via HIU Reformatsky reactions



Entry	R	R′	Prod (s).	Yield (%)[a]	
				β-AE	β-Lactam
1	Ph	Ph	**24**	0	94
2	*p*-ClC_6H_4	Ph	**25**	0	72
3	*p*-$MeOC_6H_4$	Ph	**26**	0	86
4	*p*-$CF_3C_6H_4$	Ph	**27**	0	79
5	*p*-$Me_2NC_6H_4$	Ph	**28**	0	72
6[b]	Ph	*p*-ClC_6H_4	**18**,**29**	1.0	4.5
7	Ph	*p*-$MeOC_6H_4$	**30**	0	79
8	Ph	*p*-$CF_3C_6H_4$	**19**	82	0
9	Ph	*o*-$MeOC_6H_4$	**20**	92	0
10	Ph	*o*-EtC_6H_4	**31**	0	82
11[b]	Ph	Me	**21**,**32**	1.0	10
12	Ph	*t*-Bu	**33**	0	93
13	Ph	Bn	**34**	0	92
14	Ph	$SO_2C_6H_4$	**22**	98	0

[a] Isolated yield.
[b] Ratio determined by GC analysis of the crude product mixture.

p-CF_3 or *p*-NMe_2 on the benzal-ring (entries 2–5), only the corresponding β-lactams **25**–**28** were isolated in 72–86% yields after 5 min of HIU irradiation. However, when the analogous substituents were present on the anilino-ring, a substituent effect was observed. For entry 7, the *p*-OMe substituent gave only β-lactam **30** in 79% yield. With *p*-Cl (entry 6), a mixture of β-aminoester **18** and β-lactam **29** was produced. GC and ^{1}H NMR analysis of the crude product after workup revealed 4.5 times as much β-lactam as β-aminoester. With *p*-CF_3 (entry 8), only β-aminoester **19** was produced in 82% yield. This substituent effect can be explained by consideration of the mechanism (Scheme 2) and the electronic properties of the substituent. A lack of sensitivity to substituents on the benzal-ring arises from their inability to affect the nucleophilicity of the nitrogen atom. However, when these substituents are present on the anilino-ring, they have a direct inductive effect on the nitrogen atom, and, therefore, can influence ring closure to the β-lactam. For electron-donating *p*-OMe, ring-closure to form β-lactam **30** is favored. Weakly electron-withdrawing *p*-Cl reduces the nucleophilicity of the nitrogen atom, thereby decreasing the amount of β-lactam **29** formed. Strongly electron-withdrawing *p*-CF_3 markedly diminishes the nucleophilicity of the nitrogen atom, which eliminates the ring-closure reaction altogether with β-aminoester **19** as the sole product.

An *o*-OMe substituent on the anilino ring has been shown by Adrian and co-worker[29] to give preferentially β-aminoesters with a variety of imines and methyl bromoacetate in dichloromethane at room temperature in a 'silent' reaction. The preference for β-aminoester isolation was attributed to 'an inductive effect arising from close proximity of the *o*-OMe substituent to the nitrogen–zinc bond, thus reducing its nucleophilic character.' In the present study, the *o*-OMe substituent on the anilino ring under HIU irradiation with ethyl α-bromoisobutyrate gave the corresponding β-aminoester **20** in 92% yield (entry 9). To probe the influence of steric effects in the production of β-aminoester **20**, another reaction was performed in which *o*-OMe was replaced by *o*-Et (entry 10). In this case, β-lactam **31** was produced in 82% yield, which reveals that steric effects are not solely responsible for formation of the β-aminoester, since Et and OMe substituents are similar in size.

Entries 11–14 demonstrate that the HIU method is not limited to *N*-aryl imines. Enolizable imines (entries 11 and 13) are also compatible with this HIU method. *N*-benzylidenemethylamine gave a 10:1 favoring of β-lactam **32** over β-aminoester **21** (entry 11). Hindered aliphatic *N*-benzylidene-*t*-butylamine yielded 93% of β-lactam **33** after 5 min of HIU irradiation (entry 12). *N*-Benzylidenebenzylamine gave a 92% yield of β-lactam **34** (entry 13). When *N*-benzylidenebenzenesulfonamide was used as the imine component (entry 14), only β-aminoester **22** was isolated in 98% yield. This results from electron-withdrawal by the sulfonyl group thereby reducing the nitrogen atom nucleophilicity and eliminating the ring closure reaction.

To probe the scope of these HIU-promoted Reformatsky reactions further, two ketimines were examined as potential electrophiles. Acetophenone anil (**15**) failed to react with the simplest ester, ethyl bromoacetate, in 5 min of HIU irradiation with recovery of unreacted imine, acetophenone and aniline (from hydrolysis during workup). Benzophenone anil (**16**) gave no reaction with either ethyl bromoacetate after 5 or 60 min of HIU irradiation or ethyl α-bromoisobutyrate after 5 min of HIU irradiation with recovery of unreacted imine. Therefore, ketone anils are judged to be too hindered to react under these HIU

conditions. Benzophenone anil has been reported to be an ineffective electrophile with lithium enolates as well.[30]

In further effort to define the scope of the HIU-promoted Reformatsky-type reaction, two cyclic α-bromoesters were examined. *N*-Benzylideneaniline (**1**) was reacted with commercially available methyl α-bromocyclohexanecarboxylate for both 5 and 60 min and ethyl α-bromocyclobutanecarboxylate for 5 min under HIU irradiation in attempts to form spiro-lactams. However, neither of these cyclic α-bromoesters reacted and only unreacted starting materials were recovered. Thus, cyclic α-bromoesters are found to be unreactive under these HIU reaction conditions. Bergbreiter and Newcomb[30] report that the thermal reaction between the lithium enolate of ethyl cyclohexanecarboxylate and *N*-benzylideneaniline gave a good yield of the corresponding spirolactam.

3. Conclusions

HIU-induced Reformatsky reactions of various imines and α-bromoesters have been examined. The HIU-induced reactions of aldimines with ethyl α-bromoisobutyrate afford good yields of either a β-aminoester or β-lactam, in most cases depending on the identity of the imine, in short reaction times. The HIU procedure was successful for both enolizable and non-enolizable imines. Only when the reactants become bulky did the HIU method fail. It was not necessary to 'activate' the zinc and reagent-grade dioxane was used as the solvent. These factors, as well minimal purification of the crude products, make this HIU method attractive for performing Reformatsky reactions.

4. Experimental

Zinc dust (Fisher, 99.9%) was used directly unless otherwise noted. THF was distilled from sodium-benzophenone ketyl radical. Iodine crystals were used as obtained from a commercial source (Mallickrodt). Dioxane (EM Science) was used without drying. The imines and α-bromoesters were utilized as obtained from commercial sources or prepared by published procedures[25,26] and were utilized without purification. All compounds gave satisfactory physical and spectral data. ^{1}H NMR and ^{13}C NMR spectra were recorded at 499.7 or 300.1 and 125.7 MHz, respectively) in $CDCl_3$ with TMS as internal standard. HIU was provided by an ultrasonic processor probe system (20 kHz, 600 W, 13 mm tip diameter at a power level of 7) from Sonics and Materials, Inc. (Newton, CT) that was modified in-house for insertion into a custom-designed and -fabricated, four-armed, 25-mL, glass sonochemical reaction vessel. During irradiation, the reaction vessel was cooled in a 20 °C circulating temperature bath. LIU (Low Intensity Ultrasound) was produced with a Branson Model 2510 ultrasonic laboratory cleaner (117 V, 100 W, 40 kHz). GC analyses was performed on a HP-1 19091Z-413E 30 m×0.32 mm×0.25 μm capillary column using a temperature ramp program from 45 to 250 °C at 10 °C/min. Elemental analyses were performed by Desert Analytics, Inc. (Tucson, AZ).

4.1. General procedure for Reformatsky reactions under HIU irradiation

The 25-mL, 4-armed sonochemical reaction vessel flask was capped with rubber septa and flushed with nitrogen for several minutes. Then zinc dust (1.18 g, 18 mmol) and iodine (0.50 g, 2.0 mmol) were added. Half of the dioxane (12.5 mL) solvent was added and nitrogen was bubbled through the mixture. The imine (10 mmol) and α-bromoester (15 mmol) were added, followed by the remaining solvent (12.5 mL). The flask was attached to the probe and the lower portion was immersed in a 20 °C ethylene glycol/water (1:1) constant temperature bath. The reaction mixture was sonicated for the specified period in a 6 s pulse mode. At the end of the reaction period, the flask was detached from the probe and the contents were poured into a beaker containing distilled water/ice (200 mL). The mixture was transferred to a 1-L separatory funnel. The beaker was rinsed with 100 mL of 2% hydrochloric acid and the rinsings were added to the separatory funnel. The sonochemical flask was rinsed with CH_2Cl_2 and the rinsings were added to the separatory funnel. The mixture in the separatory funnel was extracted with CH_2Cl_2 (2×200 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was dried in vacuo to give the crude product that was subjected to short path column chromatography on alumina with EtOAc–hexane (1:1/v:v) as eluent and, if necessary, Kugelrohr evaporation of the remaining volatile impurities under high vacuum (0.3 Torr) to give the product.

4.1.1. 3,3-Dimethyl-1,4-diphenyl-2-azetidinone (24). The title compound was prepared in 94% yield after chromatography and recrystallization from methanol; white solid; mp 145–148 °C (lit. mp 147.5–148.5 °C);[30] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.52 (s, 3H), 4.80 (s, 1H), 6.99–7.08 (m, 1H), 7.16–7.22 (m, 2H), 7.22–7.27 (m, 2H), 7.28–7.40 (m, 5H); ^{13}C NMR δ 17.9, 22.7, 55.3, 66.4, 117.2, 123.6, 126.5, 127.9, 128.6, 128.9, 135.5, 137.8, 171.4. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.38; H, 6.54; N, 5.60.

4.1.2. 4-(4-Chlorophenyl)-3,3-dimethyl-1-phenyl-2-azetidinone (25). The title compound was obtained in 72% yield after chromatography, flash Kugelrohr distillation up to 124 °C and recrystallization from hexanes; peach solid; mp 87–89 °C (lit. mp 91–92.5 °C);[30] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.50 (s, 3H), 4.78 (s, 1H), 6.90–7.09 (m, 1H), 7.09–7.18 (m, 2H), 7.18–7.26 (m, 2H), 7.26–7.37 (m, 4H); ^{13}C NMR δ 17.8, 22.5, 55.3, 66.5, 116.9, 123.6, 127.8, 128.7, 128.9, 133.6, 134.0, 137.4, 170.9. Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.79; H, 5.70; N, 4.93.

4.1.3. 4-(4-Methoxyphenyl)-3,3-dimethyl-1-phenyl-2-azetidinone (26). The title compound was realized in 86% yield after chromatography, flash Kugelrohr distillation up to 144 °C and recrystallization from hexanes; white solid; mp 88–90 °C (lit. mp 87–89 °C);[30] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.50 (s, 3H), 3.78 (s, 3H), 4.75 (s,

1H), 6.83–6.93 (m, 2H), 6.96–7.07 (m, 1H), 7.07–7.16 (m, 2H), 7.19–7.29 (m, 2H), 7.29–7.36 (m, 2H); ^{13}C NMR δ 17.9, 22.7, 55.1, 55.3, 66.1, 114.0, 117.2, 123.5, 127.3, 127.7, 128.9, 137.8, 159.3, 171.5. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.14; H, 6.86; N, 5.06.

4.1.4. 3,3-Dimethyl-1-phenyl-4-(4-trifluoromethylphenyl)-2-azetidinone (27). The title compound was prepared in 79% yield after chromatography, flash Kugelrohr distillation up to 130 °C, and recrystallization from hexanes; white solid; mp 91–94 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H), 1.55 (s, 3H), 4.87 (s, 1H), 7.01–7.14 (m, 1H), 7.20–7.31 (m, 4H), 7.34 (d, J=7.9 Hz, 2H), 7.62 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 17.9, 22.7, 55.7, 65.8, 117.0, 123.9, 125.64, 125.66, 125.69, 125.73, 126.9, 137.5, 139.8, 170.9. Anal. Calcd for $C_{18}H_{16}F_3NO$: C, 67.70; H, 5.05; N, 4.39. Found: C, 67.93; H, 5.03; N, 4.39.

4.1.5. 4-(4-Dimethylaminophenyl)-3,3-dimethyl-1-phenyl-2-azetidinone (28). The title compound was obtained in 72% yield after chromatography and recrystallization from hexanes; white solid; mp 139–141 °C (lit. mp 141–142 °C);[28] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.47 (s, 3H), 2.92 (s, 6H), 4.71 (s, 1H), 6.67 (d, J=8.7 Hz, 2H), 6.95–7.03 (m, 1H), 7.05 (d, J=8.5 Hz, 2H), 7.14–7.28 (m, 2H), 7.28–7.41 (m, 2H); ^{13}C NMR δ17.8, 22.6, 40.2, 55.2, 66.3, 112.1, 117.2, 122.4, 123.3, 127.4, 128.8, 137.9, 150.0, 171.8. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.82; H, 7.56; N, 9.60.

4.1.6. 1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenyl-2-azetidinone (30). The title compound was realized in 79% yield after chromatography and recrystallization from dichloromethane–hexanes; light purple solid; mp 140–144 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1748 cm^{-1}; ^{1}H NMR^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.51 (s, 3H), 3.74 (s, 3H), 4.77 (s, 1H), 6.72–6.85 (m, 2H), 7.13–7.23 (m, 2H), 7.23–7.29 (m, 2H), 7.29–7.39 (m, 3H); ^{13}C NMR δ 17.9, 22.7, 55.31, 55.33, 66.5, 114.2, 118.4, 126.5, 127.9, 128.6, 131.4, 135.6, 155.8, 170.8. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.08; H, 6.71; N, 5.00.

4.1.7. Ethyl 2,2-Dimethyl-3-phenyl-3-(4-trifluoromethylphenylamino)propionate (19). The title compound was prepared in 82% yield after chromatography, flash Kugelrohr distillation up to 135 °C, and recrystallization from hexanes; yellow solid; mp 52–54 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 3405, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.11–1.20 (m, 6H), 1.30 (s, 3H), 4.06–4.19 (m, 2H), 4.46 (d, J=7.6 Hz, 1H), 5.32 (d, J=7.4 Hz, N–H), 6.50 (d, J=8.7 Hz, 2H), 7.15–7.35 (m, 7H); ^{13}C NMR δ 14.0, 20.7, 24.8, 46.6, 61.0, 64.2, 112.4, 126.34, 126.37, 126.40, 126.43, 127.7, 128.1, 128.2, 138.5, 149.4, 176.4. Anal. Calcd for $C_{20}H_{22}F_3NO_2$: C, 65.74; H, 6.07; N, 3.83. Found: C, 65.53; H, 6.12; N, 3.82.

4.1.8. Ethyl 3-(2-methoxyphenylamino)-2,2-dimethyl-3-phenylpropionate (20). The title compound was obtained in 92% yield after chromatography, flash Kugelrohr distillation up to 132 °C and recrystallization from hexanes; light yellow solid; mp 63–64 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 3429, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09–1.21 (m, 6H), 1.25 (s, 3H), 3.84 (s, 3H), 4.02–4.19 (m, 2H), 4.55 (d, J=7.6 Hz, 1H), 5.36 (d, J=7.4 Hz, N–H), 6.25–6.36 (m, 1H), 6.48–6.58 (m, 1H), 6.58–6.67 (m, 1H), 6.67–6.73 (m, 1H), 7.11–7.21 (m, 1H), 7.21–7.34 (m, 4H); ^{13}C NMR δ 13.9, 20.5, 24.2, 46.9, 55.5, 60.7, 64.0, 109.2, 110.6, 116.1, 120.9, 127.2, 127.8, 128.3, 136.9, 139.4, 146.7, 176.3. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.58; H, 7.72; N, 4.35.

4.1.9. 1-(2-Ethylphenyl)-3,3-dimethyl-4-phenyl-2-azetidinone (31). The title compound was prepared in 82% yield after chromatography and recrystallization from hexanes; white solid; mp 104–105 °C; IR (deposit from CH_2Cl_2 on a NaCl plate) 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.28 (t, J=7.6 Hz, 3H), 1.53 (s, 3H), 2.73–2.90 (m, 2H), 5.04 (s, 1H), 7.07–7.13 (m, 2H), 7.14–7.19 (m, 2H), 7.19–7.24 (m, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR δ 14.0, 18.3, 22.5, 24.9, 54.5, 68.1, 122.5, 126.1, 126.2, 126.5, 127.7, 128.4, 129.3, 134.1, 136.1, 137.2, 171.9. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.76; H, 7.58; N, 5.03.

4.1.10. 1-*tert*-Butyl-3,3-dimethyl-4-phenyl-2-azetidinone (33). The title compound was realized in 93% yield after chromatography and recrystallization from hexanes; light yellow solid; mp 81–83 °C (lit. mp 85.5–87 °C);[29] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3H), 1.31 (s, 9H), 1.35 (s, 3H), 4.34 (s, 1H), 7.20–7.32 (m, 3H), 7.32–7.41 (m, 2H); ^{13}C NMR δ17.3, 22.6, 53.3, 53.7, 66.1, 123.5, 126.8, 127.6, 128.1, 138.6, 174.6. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.86; H, 9.22; N, 6.11.

4.1.11. 1-Benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (34). The title compound was prepared in 92% yield after chromatography, flash Kugelrohr distillation up to 140 °C and hexanes wash; colorless oil; IR (neat) 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (s, 3H), 1.35 (s, 3H), 4.42 (dd, J=14.9, 14.9 Hz, 2H), 4.10–4.20 (s, 1H), 7.08–7.19 (m, 4H), 7.22–7.33 (m, 4H), 7.33–7.41 (m, 2H); ^{13}C NMR δ 17.6, 22.2, 44.0, 56.0, 65.7, 126.7, 127.5, 127.8, 128.3, 128.5, 128.6, 135.7, 135.9, 174.0. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.20; H, 7.15; N, 5.23.

4.1.12. Ethyl 3-benzenesulfonylamino-2,2-dimethyl-3-phenylpropionate (22). The title compound was obtained in 98% yield after chromatography and recrystallization from ethyl acetate–hexanes; white solid; mp 128–130 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 3269, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.19 (t, J=7.2 Hz, 3H), 1.28 (s, 3H), 4.08 (q, J=7.1 Hz, 2H), 4.45 (d, J=9.9 Hz, 1H), 6.45 (d, J=9.8 Hz, NH), 6.81–6.96 (m, 2H), 6.96–7.09 (m, 3H), 7.10–7.22 (m, 2H), 7.25–7.36 (m, 1H), 7.44–7.63 (m, 2H); ^{13}C NMR δ 13.9, 22.1, 24.3, 46.9, 61.0, 64.6, 126.7, 127.3, 127.7, 127.9, 128.3, 131.7, 136.7, 140.4, 175.9. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.28; H, 6.49; N, 3.94.

4.2. General procedure for Reformatsky reactions under LIU irradiation

A 50-mL, round bottom flask was flushed with nitrogen for several minutes. Zinc (Cava-activated or dust) (1.18 g, 18 mmol) and iodine (0.50 g, 2 mmol) were added to the flask. Half of the dioxane (12.5 mL) solvent was added. The imine (10 mmol) and α-bromoester (15 mmol) were added followed by the remaining solvent (12.5 mL). The flask was partially submerged in the ultrasonic cleaning bath in a position of maximum ultrasonic intensity. The reaction mixture was sonicated for the specified period in a continuous irradiation mode and was not thermostatted. At the end of the reaction, the contents were poured into a beaker containing distilled water/ice (200 mL). The mixture was transferred to a 1-L separatory funnel. The beaker was rinsed with 100 mL of 2% hydrochloric acid and the rinsings were added to the separatory funnel. The flask was rinsed with CH_2Cl_2 and the rinsings were added to the separatory funnel. The mixture in the separatory funnel was extracted with CH_2Cl_2 (2×200 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was dried in vacuo to give the crude product, which was analyzed by ^1H NMR spectroscopy and GC.

Acknowledgements

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Complexing properties of two benzocrown-ether moieties arranged at a cyclobutane ring system

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Abstract—Biscrown ethers **2a**–**c** and **3a**–**c** arranged at a cyclobutane ring were prepared by intermolecular [2+2] photocycloaddition of vinylated benzocrown ethers. The complexing behavior of **2a**–**c** toward alkali metal cations was evaluated by ESI-MS analysis, liquid–liquid extraction, and the comparison of complexing stability constant. An intramolecular sandwich-type 1:1 (host/guest) complexation was observed by ESI-MS analysis in the competitive system where **2a**-Na^+, **2b**-K^+, and **2c**-Cs^+ were formed selectively. In the liquid–liquid extraction, however, **2a** hardly extracted any cation, while both **2b** and **2c** efficiently extracted larger cations such as K^+, Rb^+, and Cs^+. It was found that the complexing stability constant of **2a**-Na^+ is lower than that of benzo-15-crown-5-Na^+ though extraordinarily high values were obtained for **2b**-K^+ and **2c**-Cs^+ complexes compared with those of 18-crown-6-K^+ and dibenzo-24-crown-8-Cs^+ complexes, respectively. Hence, the excellent complexing ability was achieved by using the cyclobutane ring, which strongly preorganized two benzocrown-ether moieties for the larger alkali metal cations.

1. Introduction

The preorganization of a host molecule toward a certain guest compound is one of the most important strategies to increase its complexing ability.[1,2] Among them the attachment of an oligo(oxyethylene) chain to a crown ether is the simplest method. Gokel and co-workers called such crown compounds lariat ethers.[3] Along the strategy, often two crown ether moieties are connected by various kinds of spacers to construct biscrown ethers,[4] since biscrown ethers are known to bind larger cations than size-fitting one to the crown unit due to sandwich complexation, and to enhance the complexing ability including ion-selectivity and ion-affinity. Those have been also widely investigated for their complexing behavior.[5] Bis(benzocrown ether)s possessing a flexible spacer forming sandwich-type complexes with alkali metal cations have been thoroughly studied by Kikukawa and co-workers.[6] Biscrown ethers as pre-organized hosts having both rigid spacer and suitable geometry can selectively and efficiently form stable sandwich-type complexes with larger species, compared with conventional biscrown ethers.

Despite many examples related to biscrown ethers,[7] there is no report regarding to bis(benzocrown ether)s arranged at a cyclobutane ring system. Recently, we have successfully prepared crown compounds bridged by a cyclobutane ring by means of intramolecular [2+2] photocycloaddition of styrene derivatives possessing an oligo(oxyethylene) linkage,[8] and have reported that this cyclization is also a useful method to prepared rigid crown compounds.[9] In this paper we describe the preparation of the title compounds by intermolecular [2+2] photocycloaddition of vinylated benzocrown ethers and the examination of their specific complexation to alkali metal cations in a homogeneous phase and a liquid–liquid two-phase system.

2. Results and discussion

2.1. Synthesis of bis(benzocrown ether)s

The photodimerization of styrene[10,11] and *p*-methoxystyrene[12] offered *cis*- and *trans*-isomers in a certain ratio under conditions given. It was considered that when vinylated benzocrown ethers **1** were used as starting materials the dimerization could give us **2** and **3** which would have induced-fitting ability to make a sandwich-type complexation with larger cations. Therefore, the photodimerization of **1** was carried out by using a 400-W high-pressure mercury lamp through Pyrex filter (Scheme 1).

To obtain target compounds in good yields, the reaction was carried out with or without a template in various solvents and with cyclodextrins (CDs) in aqueous media. Precursor **1b** was chosen as a representative and the time-course of its

Keywords: Bis(crown ether)s; Photosynthesis; Extraction experiment; Complexing ability.
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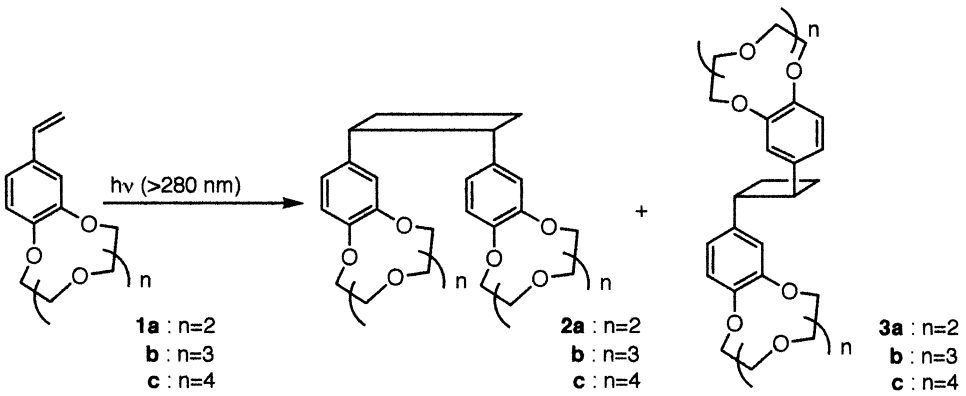


Scheme 1.

Table 1. Preparation of bis(benzocrown ether)s from **1b**

Solvent	Concentration (additive)	Yield (%)	
		2b	**3b**
Cyclohexane	100 mM	23	3
Benzene	100 mM	55	11
Benzene	100 mM ([KBF_4]=1.00 M)	23	8
Benzene	100 mM ([CsBr]=1.00 M)	51	12
Benzene	100 mM ([CH_3COOCs]=1.00 M)	41	7
Toluene	100 mM	51	8
Acetonitrile	100 mM	38	19
Acetonitrile	100 mM ([KBF_4]=1.00 M)	78	4
Acetonitrile	100 mM ([CsBr]=1.00 M)	40	8
Acetonitrile	100 mM ([$CH_3COOHCs$]=1.00 M)	55	11
Acetonitrile	2 mM	0	9
Acetonitrile	2 mM ([KBF_4]=60 mM)	63	2
Water	2 mM	0	0
Water	2 mM ([γ-CD]=0.5 mM, [CsBr]=20 mM)	0	0

reaction was followed by ^{1}H NMR and HPLC analyses. Yields of **2b** and **3b** increased with the conversion of **1b**, then reached at plateau, and decreased sharply due to formation of polymeric material which was not characterized. Hence, the irradiation should be ceased at the plateau.

It is apparent that the yields clearly depended on the polarity of solvent used as shown in Table 1. Good yields and high selectivity for **2b**/**3b** were recorded in benzene and toluene. Since, alkali metal cation often shows an important role as a template in crown ether syntheses,[13–15] we applied the cations in this synthesis. Remarkable template effect by potassium cation was observed in acetonitrile.

Although γ-CD can accommodate two vinyl phenyl moieties,[16] it did not effect this particular reaction.

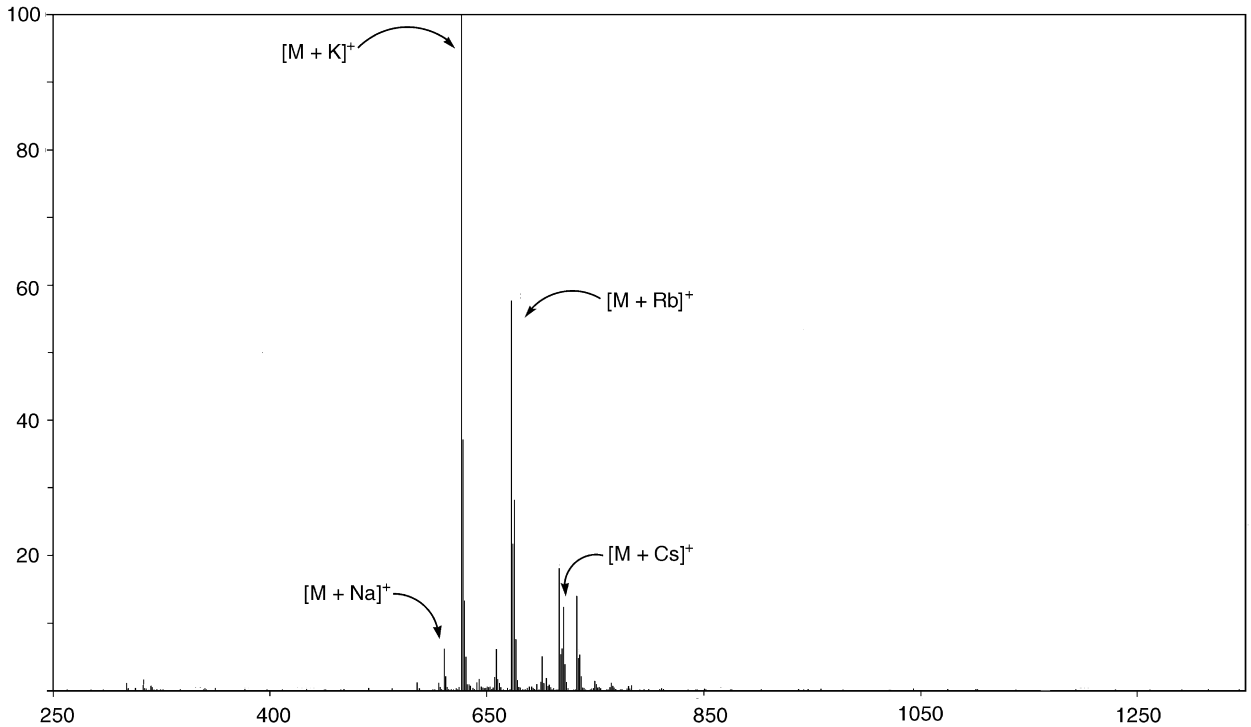


Figure 1. ESI-MS spectrum of **2b** in 4:1 (v/v) $CH_3CN–H_2O$ containing an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$, and $CsClO_4$.

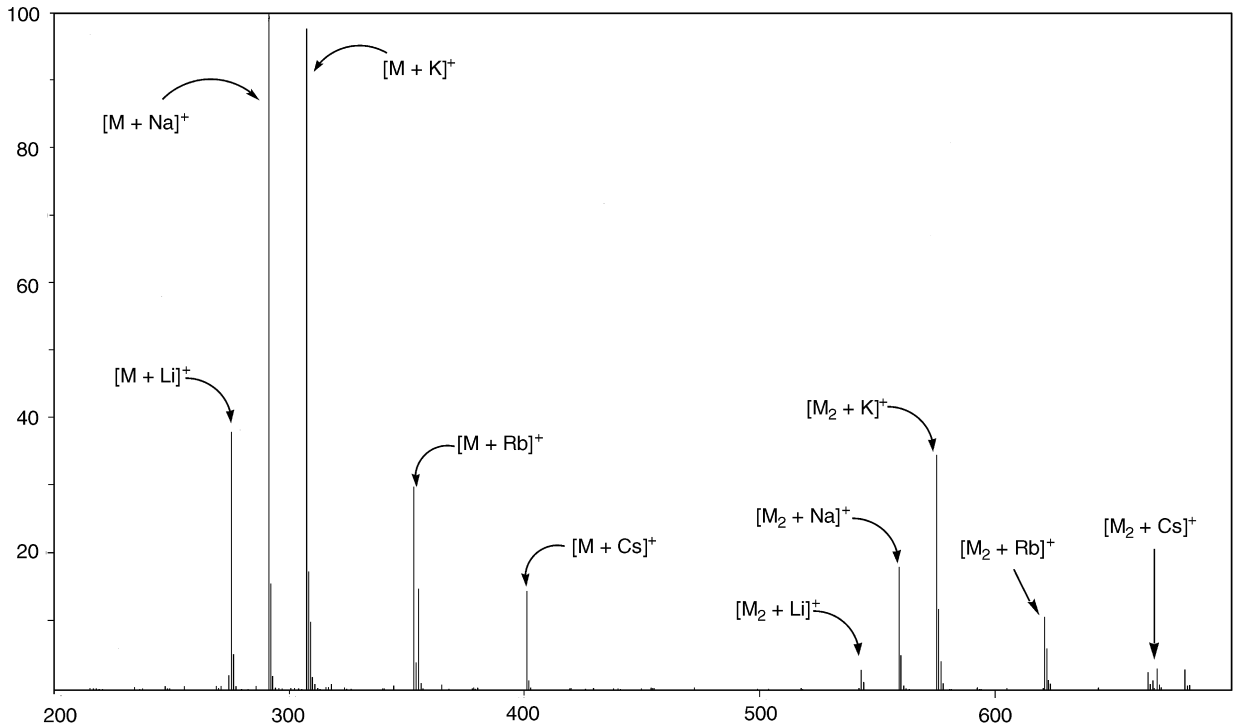


Figure 2. ESI-MS spectrum of **5** in 4:1 (v/v) CH_3CN-H_2O containing an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$, and $CsClO_4$.

2.2. Complexing behavior of bis(benzocrown ether)s

Complexing ability of relatively rigid compounds **2a–c** was evaluated by the liquid–liquid extraction, electrospray ionization mass spectroscopy (ESI-MS) and equilibrium stability in homogeneous systems as described in the following.

2.2.1. Complexation of bis(benzocrown ether)s with alkali metal cations in homogeneous solution. ESI-MS is one of the most simple and useful methods to disclose the complexing behavior of host compounds with cations in a polar homogeneous system.[17–19] The interaction between the bis(benzocrown ether)s and alkali metal perchlorates

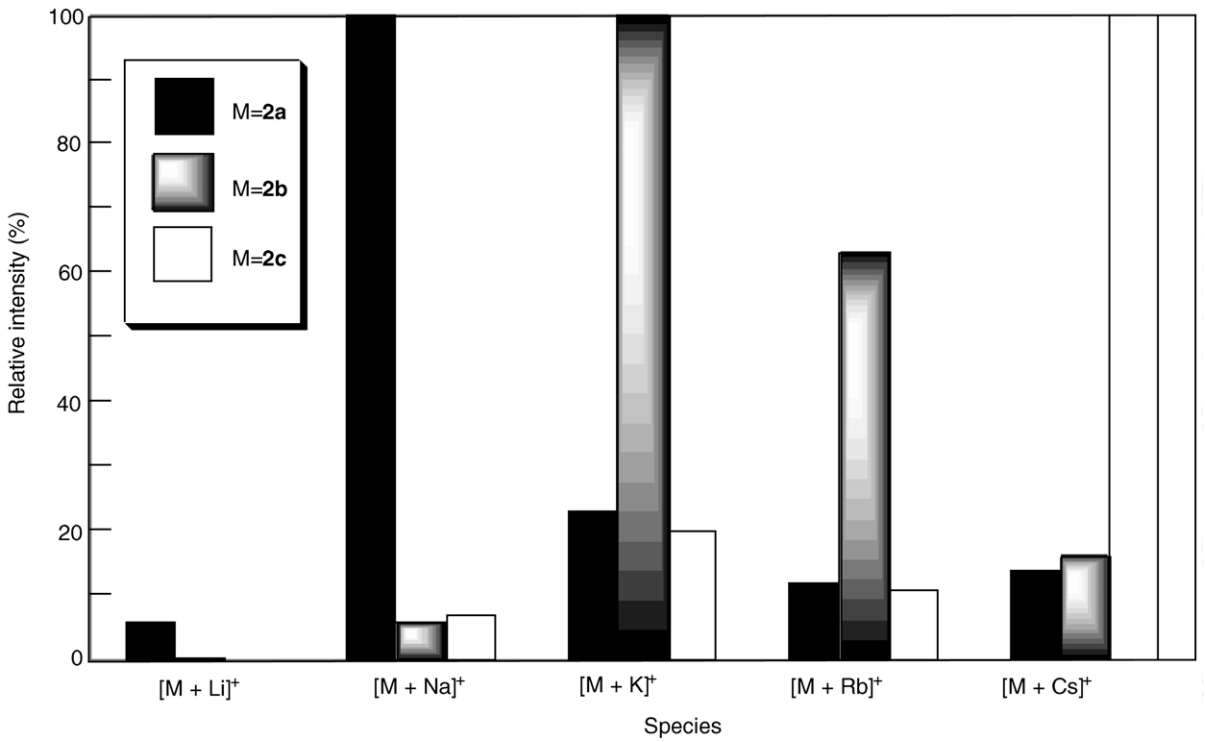


Figure 3. Relative intensity of alkali metal cations complexed with **2a**, **2b**, and **2c** in ESI-MS analysis.

were investigated in a competitive system in CH_3CN-H_2O (4:1, v/v) solution.

As shown in Figure 1, **2b** was completely consumed by complexation so that the molecular ion was not detected at all. Not only **2b** but also both **2a** and **2c** formed exclusively the 1:1 complex with each cation, indicating that these host molecules incorporated the cation by intramolecular sandwich-type complexation. In contrast with **2**, conventional benzo-12-crown-4 (**4**) and benzo-15-crown-5 (**5**) formed both 1:1 and 2:1 (host:guest) complexes with all alkali metal cations. Figure 2 illustrates the spectrum of **5**, as a representative monobenzocrown ether.

Note that bis(benzocrown ether)s **2** showed unique complexing behavior. To stress the selectivity the relative intensity along cations complexed with **2a**, **2b**, and **2c** is illustrated in Figure 3.

Biscrown **2a** showed extraordinarily high Na^+-selectivity. This is apparently due to a strong sandwich-type complexation, since the 12-crown-4 moiety has been well known to exhibit relatively high affinity toward Li^+ compared with other alkali metal cations. Biscrown **2b** showed relatively high K^+-selectivity. It is noteworthy that the crown ether with 15-crown-5 moieties showed the low affinity toward Na^+ as well as Li^+, although **5** shows the highest affinity toward Na^+ among alkali metal cations (Fig. 2). The fact suggests that the formation of intramolecular sandwich-type complexes occurred, preferring to the 1:1 complexation due to size fitting between the cation diameter and cavity diameter. For example, compound **2c** showed exceedingly high Cs^+-selectivity. The arrangement of two crown ethers like **2c** is quite suitable for the intramolecular sandwich-type complexation with Cs^+, since benzo-18-crown-6 (**6**) itself exhibits relatively the low affinity toward Cs^+ and does not form any sandwich-type complexes with any alkali metal cations as shown in Figure 4.

All series of the bis(benzocrown ether)s preferentially and efficiently formed intramolecular sandwich-type complexes with large cations. These results suggest that the bis(benzocrown ether)s make the complexes stable and cation-selective due to the preorganized and fixed structure by the cyclobutane ring as a spacer, which is different from other bis(benzocrown ether)s as mentioned in Section 2.2.3.

2.2.2. Liquid–liquid extraction of alkali metal picrates by bis(benzocrown ether)s. Extraction experiments were carried out in $H_2O-CH_2Cl_2$ systems. In contrast to the data obtained from the ESI-MS analysis, **2a** hardly extracted any cations under the conditions used in this experiment. The low extractability is in accord with its low complexing stability constants for those cations (see Tables 3 and 4). Bis(benzocrown ether) **2b** efficiently extracted larger cations than Na^+, but the selectivity was not so high compared with that expected from the ESI-MS analysis. The efficiency, however, was higher than that of **5**. Compound **2c** also showed high extractability toward larger cations, especially extracting Cs^+ two-times larger than **6**. Thus, the two-phase liquid–liquid extraction evaluated the present ionophores differently from those of ESI-MS analysis in homogeneous media. The liquid–liquid extraction is often affected by the distribution coefficient between the two phases in addition to the complexation constant between the ligand and cation. Since the complexing ability of bis(crown ether)s showed the high selectivity in homogeneous phase as observed in ESI-MS data, the efficient extractability of **2b**

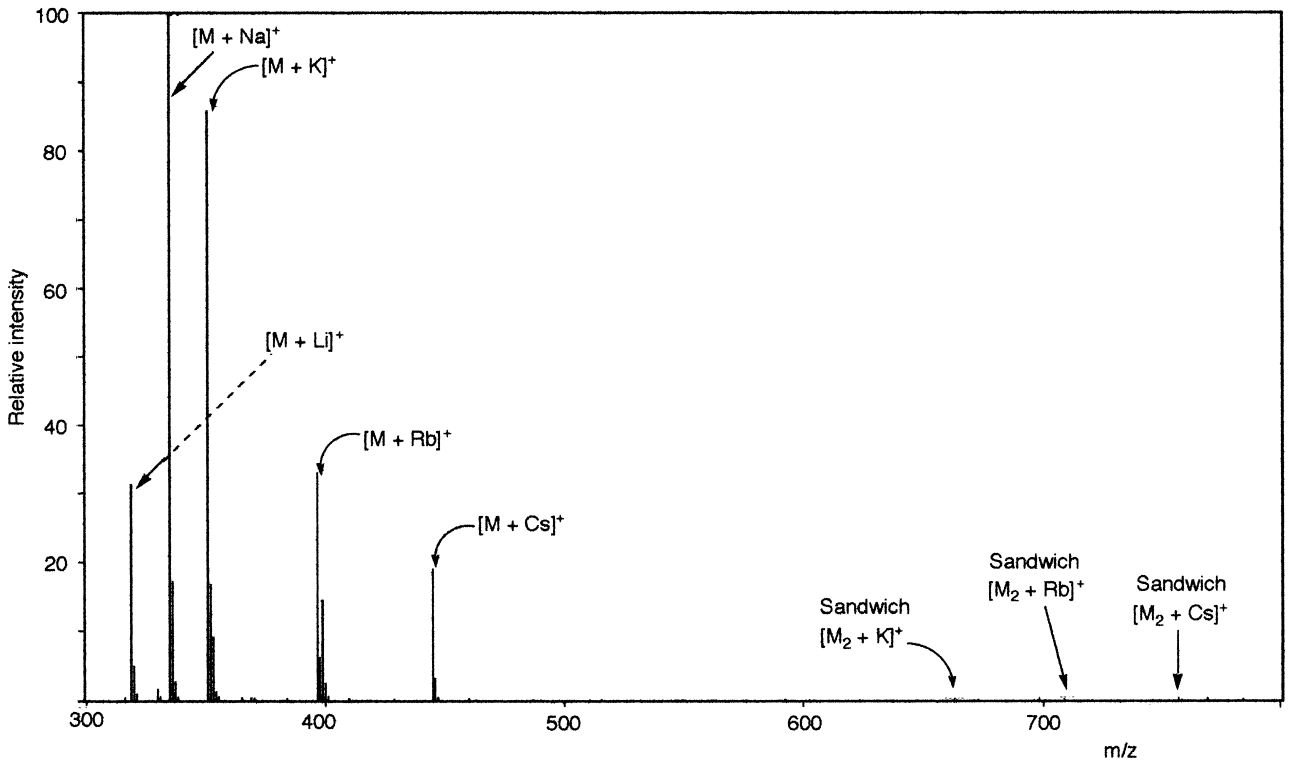
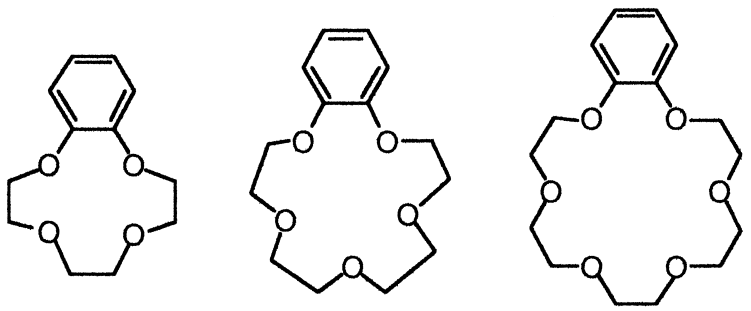


Figure 4. ESI-MS spectrum of **6** in 4:1 (v/v) CH_3CN-H_2O containing an equimolar mixture of $LiClO_4$, $NaClO_4$, $KClO_4$, $RbClO_4$, and $CsClO_4$.

Table 2. Liquid–liquid extraction of metal picrate by crown compounds[a]

Ligand	Percent extraction				
	Li^+	Na^+	K^+	Rb^+	Cs^+
2a[b]	0	1	0	1	1
2b[b]	16	26	73	69	62
2c[b]	1	19	68	60	67
3a[b]	1	1	0	1	1
3b[b]	1	7	17	9	6
3c[b]	1	9	74	49	27
4[b]	1	1	1	1	1
4[c]	1	2	1	1	1
5[b]	2	4	6	5	3
5[c]	1	6	13	8	5
6[b]	1	5	56	38	21
6[c]	2	7	76	54	31

[a] Extraction conditions: Aqueous phase; [MOH]=0.1 M, [picric acid]=5.0×10^{-5} M, 5 mL. Organic phase; CH_2Cl_2, 5 mL.
[b] [ligand]=5.0×10^{-5} M.
[c] [ligand]=1.0×10^{-4} M.



4 **5** **6**

and **2c** for larger cations without selectivity is most likely due to the large distribution coefficients for large cations into CH_2Cl_2.

The extraction efficiency and selectivity of bis(benzocrown ether)s **3a**, **3b**, and **3c** are similar to those of **4**, **5**, and **6**, respectively, suggesting that the 1:1 (cation-crown) complexes are formed (Table 2).

2.2.3. Determination of stability constants (K_a). To assess the binding ability of the bis(benzocrown ether)s **2a–c**, ^1H NMR titration with alkali metal cations was carried out in acetonitrile-d_3 (Table 3) and in acetonitrile-d_3–D_2O (Table 4) at 25 °C.

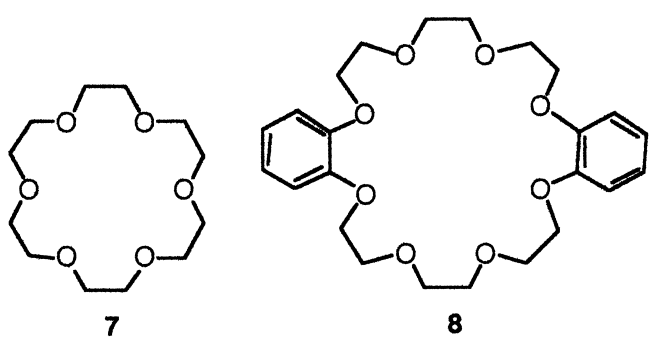
Table 3 shows the stability constants of the bis(benzocrown ether)s and reference compounds with alkali metal cation in acetonitrile-d_3. Biscrown ether **2a** showed higher stability constant toward Na^+ among alkali metal cations, though the value is lower than that of **5**. An extremely high value was obtained for **2b** with K^+ and **2c** with Cs^+. Since these values are too large to accurately assess by a curve fitting method based on the ^1H NMR titration in acetonitrile-d_3, we performed the titration in acetonitrile-d_3–D_2O (4:1 v/v). Biscrown ether **2b** showed high selectivity toward K^+ and the value of **2b** with K^+ was not only large compare with

Table 3. Stability constants of the bis(benzocrown ether)s with alkali metal cation in CD_3CN

Ligand	log K_a		
	Na^+	K^+	Cs^+
2a	3.22	2.40	2.31
2b	3.99	6.51	5.78
2c	4.40	4.53	8.19
5	4.19	2.48	–
6	–	4.84	–

Table 4. Stability constants of the bis(benzocrown ether)s with alkali metal cation in CD_3CN–D_2O (4:1 v/v)

Ligand	log K_a		
	Na^+	K^+	Cs^+
2a	0.78	–	–
2b	2.60	4.63	3.33
2c	3.11	4.21	5.15
5	1.79	1.92	1.75
6	2.60	3.67	2.42
7	–	4.29	–
8	1.04	2.30	2.75



7 **8**

that of **6** with K^+ (Tables 3 and 4) but also that of 18-crown-6 (**7**) with K^+ (Table 4) which is the champion datum in a series of crown ethers containing biscrown compounds[20] and lariat ethers except for Nakatsuji's C-pivot lariat ether with alkali metal cation.[21]

The stability constants in 90% methanolic aqueous solution and the extractability in a $H_2O-CH_2Cl_2$ system for a series of bis(benzo-15-crown ether)s possessing a flexible spacer with potassium cation were reported by Kikukawa and co-workers. According to their data, all bis(benzo-15-crown ether)s show K^+-selectivity and the stability constant of bis(benzo-15-crown-5) possessing triethylene glycol chain spacer (log K=4.64) as well as that possessing octamethylene chain spacer (log K=4.17), which show higher extractability than bis(benzo-15-crown-5) possessing ethylene chain spacer, is lower than that of **6** (log K=4.75). As mentioned above biscrown ether **2b** showed higher stability constant for K^+ than not only **6** but also that of **7**, obviously indicating that complexing ability of **2b** is higher than bis(benzo-15-crown-5) possessing ethylene chain spacer because its extractability for K^+ (53.2%) is lower than that of **6** (54.1%) as well as bis(benzo-15-crown-5) possessing triethylene glycol chain spacer (86.7%).[6] Thus, it was found that the replacement of ethylene spacer by rigid cyclobutane ring spacer results in the efficient sandwich-type complexation structure by fixed *cis*-form of the bis(benzocrown). This 'biscrown effect'[22] is remarkably observed by complexation of **2c** with Cs^+. The stability constant of **2c** is higher than that of any bis(benzocrown ether)s reported by Kikukawa.[6] In acetonitrile-d_3–D_2O (4:1 v/v), the Cs^+-complexing stability of **2c** was higher than that of dibenzo-24-crown-8 (**8**) by about 250 times, which shows the highest Cs^+-affinity in the single looped crown ethers.[5] Thus, it was found that a ligand showing extraordinarily high affinity to Cs^+ is easily obtained by using the cyclobutane ring spacer to bis(benzo-18-crown-6).

3. Conclusion

Bis(benzocrown ether)s arranged at a cyclobutane ring were conveniently synthesized by means of intermolecular [2+2] photocycloaddition of vinylated benzocrown ethers. From the ESI-MS analysis and the comparison of the stability constant, host molecule **2a** having four ethereal oxygens atoms, **2b** having five ethereal oxygens atoms, and **2c** having six ethereal oxygens atoms in the crown ether moiety were found to show excellent Na^+-, K^+-, and Cs^+-selectivity, respectively, due to their sandwich-type complexation.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL α-500 FT NMR spectrometer. HPLC analysis was performed with a Shimadzu LC-6A pump, LC-6A UV detector, and RC-4A data processor. Mass spectra (HRMS) were determined by a JEOL JSM-BU25. UV–vis spectra were recorded by a Hitachi U-3210 spectrophotometer. Electrospray ionization mass spectra (ESI-MS) were obtained on a Perkin–Elmer Sciex API-100 electrospray ionization mass spectrometer under the following conditions: A sample solution was sprayed at a flow rate of 2 μL min^{-1} at the tip of a needle biased by a voltage of 4.5 kV higher than that of a counter electrode. Toluene and benzene were distilled over Na after a prolonged reflux under a nitrogen atmosphere. Guaranteed reagent grade cyclohexane, acetonitrile, and CH_2Cl_2 were distilled before use.

Vinylbenzocrown ether **1a–c** were prepared by the reported method.[23] Reagent grade benzo-12-crown-4 **4**, benzo-15-crown-5 **5**, benzo-18-crown-6 **6**, 18-crown-6 **7**, and dibenzo-24-crown-8 **8** were used without further purification. Commercially available highest grade of alkali metal hydroxides and alkali metal perchlorates were used. Picric acid was purified by recrystallization from acetone. All aqueous solutions were prepared with distilled, deionized water.

4.2. Preparation of bis(benzocrown ether)s 2a–c and 3a–c

Into a 500 mL Pyrex flask with a magnetic stirrer and N_2 inlet was placed a solution of vinylbenzocrown ether **1** (100 mmol) in acetonitrile (10 mL) and nitrogen was bubbled for 15 min. The solution was irradiated by a 400-W high-pressure mercury lamp. The reaction was monitored by HPLC. After irradiation for 9 h, the reaction mixture was evaporated. The residue was purified by silica gel column chromatography with a gradient solution of benzene–acetone to afford the bis-(benzocrown ether)s.

4.2.1. Compound 2a. Isolated yield, 29%; viscous liquid. ^1H NMR ($CDCl_3$); 6.73 (2H, d, J=7.9 Hz), 6.75 (2H, dd, J=7.9, 2.2 Hz), 6.49 (2H, d, J=2.2 Hz,), 4.07–4.06 (4H, m), 3.95–3.93 (4H, m), 3.90–3.87 (2H, m), 3.79–3.77 (4H, m), 3.74–3.71 (12H, m), 2.42–2.36 (2H, m), 2.35–2.30 (2H, m). ^{13}C NMR ($CDCl_3$); 149.71, 148.36, 136.18, 121.99, 118.20, 117.17, 71.55, 71.45, 70.98, 70.86, 69.74, 69.57, 44.79, 24.18. HRMS(EI) calcd for $C_{28}H_{36}O_8$ (M^+): 500.2410. Found, 500.2418.

4.2.2. Compound 2b. Isolated yield, 54%; White solid. Mp 97.1–97.9 °C (acetone–hexane). ^1H NMR ($CDCl_3$); 6.64 (2H, d, 8.3), 6.50 (2H, dd, J=8.3, 1.9 Hz), 6.40 (2H, d, 1.9), 4.04–4.02 (4H, m), 3.90–3.72 (30H, m), 2.44–2.38 (2H, m), 2.34–2.29 (2H, m). ^{13}C NMR ($CDCl_3$); 148.38, 147.18, 134.88, 120.71, 114.85, 113.54, 70.97, 70.92, 70.50, 69.65, 69.55, 69.14, 69.00, 44.90, 24.46. HRMS(EI) calcd for $C_{32}H_{44}O_{10}$ (M^+): 588.2935. Found, 588.2930.

4.2.3. Compound 2c. Isolated yield, 40%; viscous liquid. ^1H NMR ($CDCl_3$); 6.65 (2H, d, 8.3 Hz), 6.52 (2H, d, 8.3 Hz), 6.39 (2H, s), 4.05 (4H, t, 4.6), 3.90–3.85 (6H, m), 3.75–3.67 (32H, m), 2.41–2.38 (2H, m), 2.33–2.29 (2H, m). ^{13}C NMR ($CDCl_3$); 148.16, 146.93, 134.83, 120.61, 114.65, 113.44, 70.67, 69.68, 69.56, 68.97, 68.92, 44.83, 24.47. HRMS(EI) calcd for $C_{36}H_{52}O_{12}$ (M^+): 676.3459. Found, 676.3435.

4.2.4. Compound 3a. Isolated yield, 19%; viscous liquid. ^1H NMR ($CDCl_3$); 6.90 (2H, d, 8.1 Hz), 6.82–6.78 (4H, m),

4.16–4.14 (8H, m), 3.86–3.83 (8H, m), 3.80 (8H, s), 3.42–3.38 (2H, m), 2.26–2.24 (2H, m), 2.08–2.05 (2H, m). ^{13}C NMR ($CDCl_3$); 150.31, 148.68, 139.27, 120.44, 118.03, 116.17, 71.90, 71.43, 71.01, 70.92, 69.81, 69.79, 47.75, 25.62. HRMS(EI) calcd for $C_{28}H_{36}O_8$ (M^+): 500.2410. Found, 500.2405.

4.2.5. Compound 3b. Isolated yield, 15%; White solid. Mp 99.1–100.0 °C (acetone–hexane). ^{1}H NMR ($CDCl_3$); 6.79 (2H, d, J=8.2 Hz), 6.73 (2H, dd, J=8.0, 1.9 Hz), 6.71 (2H, d, J=1.9 Hz), 4.12–4.08 (8H, m), 3.90–3.88 (8H, m), 3.75 (16H, s), 3.39–3.36 (2H, m), 2.24–2.22 (2H, m), 2.06–2.05 (2H, m). ^{13}C NMR ($CDCl_3$); 148.97, 147.42, 137.96, 119.10, 114.10, 112.67, 70.98, 70.53, 70.51, 69.67, 69.61, 69.20, 68.97, 48.15, 25.57. HRMS(EI) calcd for $C_{32}H_{44}O_{10}$ (M^+): 588.2935. Found, 588.2905.

4.2.6. Compound 3c. Isolated yield, 18%; viscous liquid. ^{1}H NMR ($CDCl_3$); 6.81 (2H, d, J=8.6 Hz), 6.74–6.73 (4H, m), 4.14–4.11 (8H, m), 3.92–3.90 (8H, m), 3.77–3.75 (8H, m), 3.72–3.68 (8H, m), 3.63 (8H, s), 3.40–3.34 (2H, m), 2.25–2.23 (2H, m), 2.06–2.04 (2H, m). ^{13}C NMR ($CDCl_3$); 148.79, 147.26, 137.96, 119.12, 114.21, 112.84, 70.73, 70.70, 70.68, 69.67, 69.64, 69.20, 69.05, 48.00, 25.62. HRMS(EI) calcd for $C_{36}H_{52}O_{12}$ (M^+): 676.3459. Found, 676.3430.

4.3. Solvent and additive effects on photodimerization

The yields for photodimerization were measured under a variety of conditions. The 15 mL Pyrex test tubes containing a solution of the precursor olefin with or without additive in a degassed solvent were set around a 400-W high-pressure mercury lamp. After irradiation for the prescribed period, the conversion and the yields of products were determined by HPLC and ^{1}H NMR spectroscopy.

4.4. ESI-MS analysis

The sample solution was 4:1 (v/v) MeCN–H_2O containing the same concentration of the bis(benzocrown ether) and five alkali metal perchlorates (1×10^{-4} mol dm^{-3} each).

4.5. Liquid–liquid extraction of alkali metal picrates

The bis(benzocrown ether)s were used as extractants for alkali metal picrates in a liquid–liquid system together with reference compounds. A CH_2Cl_2 solution of the host compound (5×10^{-5} mol dm^{-3} or 1×10^{-4} mol dm^{-3}, 5 mL) and an aqueous metal picrate solution ([MOH]=0.1 mol dm^{-3}, [picric acid]=1×10^{-5} mol dm^{-3}, 5 mL) were shaken in a 20-mL test tube equipped with a ground glass stopper at room temperature (20–22 °C) for 2 h. After two liquid phase were separated, percent extraction of metal picrates was measured by UV–vis spectroscopy.

4.6. ^{1}H NMR titration of the bis(benzocrown ether)s with alkali metal

A solution of the bis(benzocrown ether)s (1 mmol dm^{-3}) was prepared, and its 500 μL portions were placed in an NMR tube, and the solvent level was marked. A second solution was made in acetonitrile-d_3 with the metal perchlorate. An initial spectrum was recorded, then an appropriate volume of the salt solution was added to the NMR tube and the solvent level was reduced by evaporation to the mark. The spectrum was then recorded again. This procedure was repeated until the salt concentration is reached 10 equiv. to the crownophane. The chemical shifts of the aromatic proton of the bis(benzocrown ether)s before and after each addition of the guest solution were used for calculation of the association constants (K_a). The constants were determined by nonlinear least-squares fitting method of the titration curves for 1:1 complexation, which was monitored by the ESI-MS analysis.

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Facile synthesis of bis(indolyl)methanes using catalytic amount of iodine at room temperature under solvent-free conditions

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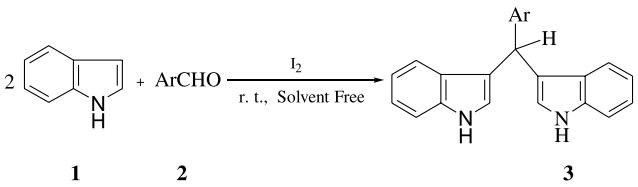
Abstract—Efficient electrophilic substitution reactions of indoles with various aromatic aldehydes were carried out using a catalytic amount of I_2 under solvent-free conditions to afford the corresponding bis(indolyl)methanes in excellent yields.

1. Introduction

Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds.[1] For example, bisindolylalkanes and their derivatives are found in bioactive metabolites of terrestrial and marine origin.[2] Therefore, there is a great deal of interest in the synthesis of this class of compounds. Among the many methods, the synthesis of this class of compounds in the presence of Lewis acids, Brønsted acids or montmorillonite clay K-10 to promote the reaction of indoles with other aromatic or aliphatic aldehydes and ketones have been widely studied.[3–9] More recently, bis(indolyl)methanes were found to be formed in acetonitrile in the presence of other catalysts such as $InCl_3$, $PPh_3{\cdot}HClO_4$ and so on.[10] However, many of these Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required.[11] These problems can be somewhat circumvented by using expensive lithium perchlorate.[12] However, it requires longer reaction times for nitro-substituted aromatic aldehydes, giving the corresponding bis(indolyl)methanes in moderate yields. In this report, we wish to introduce molecular iodine as a mild and highly efficient catalyst for the preparation of bis(indolyl)methanes under solvent-free conditions at room temperature (Scheme 1).



1 2 3

Scheme 1. I_2-catalyzed synthesis of bis(indolyl)methanes in free solvent.

In recent years, molecular iodine has received considerable attention as an inexpensive and easily available catalyst for various organic transformations.[13] Given the large number of similar condensation reactions that have been reported to proceed readily under solvent-free conditions,[14] we proceed to examine the synthesis of bis(indolyl)methanes under solvent-free conditions. The results are shown in Table 1.

2. Results and discussion

In comparison to the reported methods, I_2 in solvent-free conditions was found to be an efficient catalyst in terms of handling, temperature, yields and reaction times. The grinding of solid reagents yields viscous liquid melt phase, which may contain dispersed solid material corresponding to one of the reagents. After the corresponding time, the desired crude product was obtained in very good yields.

As shown in Table 1, this method works with a wide variety of substrates. It is also found that the reaction of **2k** (1 mmol) with **1** (4 mmol) proceeded rapidly in the presence of I_2 at room temperature (by grinding) to give **3k** and **3k′** in 62 and 19%, respectively. The structures of **3a**[15] and **3k** were further confirmed by single crystal X-ray crystallography.[16]

Keywords: Solvent-free; Iodine; Indoles; Aldehydes; Bis(indolyl)methanes.
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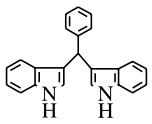
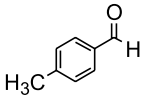
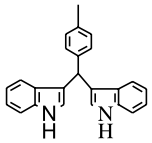
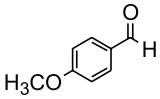
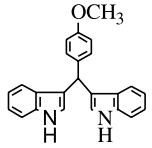
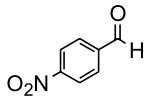
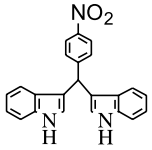
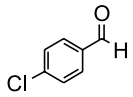
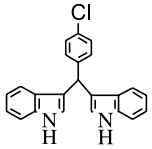
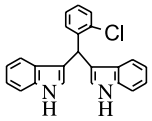
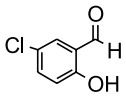
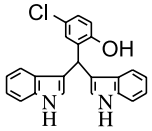
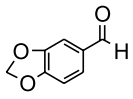
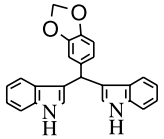
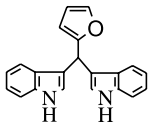
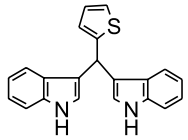
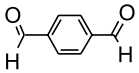
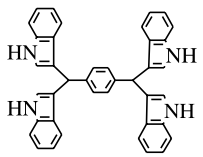
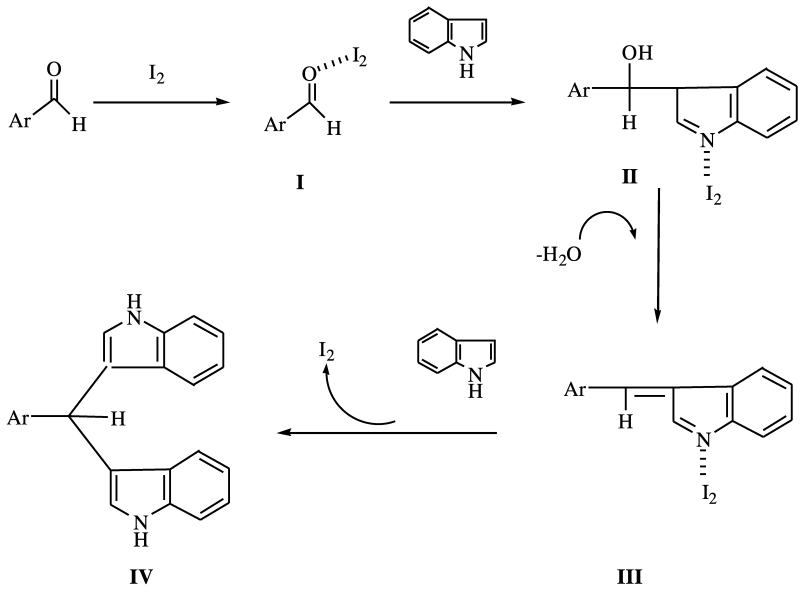
Table 1. The reaction of aromatic aldehyde with indole under solvent-free condition at room temperature[a]

Compdound	Ar–CHO	Products	Time (min)	Yield (%)[b]
2a		**3a** 	10	72
2b		**3b** 	10	83
2c		**3c** 	7	85
2d		**3d** 	7	86
2e		**3e** 	8	91
2f		**3f** 	7	82
2g		**3g** 	9	82
2h		**3h** 	9	90
2i		**3i** 	5	89
2j		**3j** 	9	82
2k		**3k** 	7	62/19[c]

[a] All reactants were ground at room temperature.
[b] Isolation yields.
[c] **3k** and 4-[Bis-(1*H*-indol-3-yl)-methyl]-benzaldehyde (**3k′**) were obtained in 62 and 19%, respectively.



Scheme 2. The probably mechanism for reactions of indoles with various aromatic aldehydes.

According to the literatures,[10a,c,12] we think that iodine catalyzes the reaction as a mild Lewis acid even under solvent-free conditions. As shown in Scheme 2, we give the likely mechanism for the reaction. First, molecular iodine activates the carbonyl group of the aromatic aldehyde to give intermediate **I**, and is followed by indole attack to **I** to give **II** and loss of H_2O from **II** to afford **III** which is activated by iodine. The other indole is added to **III** in the following step to give the TM (**IV**) and molecular iodine, which can catalyze the reaction in a catalytic manner.

3. Conclusions

In summary, we have developed a simple, convenient and efficient synthetic protocol for **3** using a catalytic amount of I_2 under solvent-free conditions at room temperature. The short reaction time coupled with the simplicity of the reaction procedure make this method one of the most efficient methods for the synthesis of this class of compounds (Figs. 1 and 2).

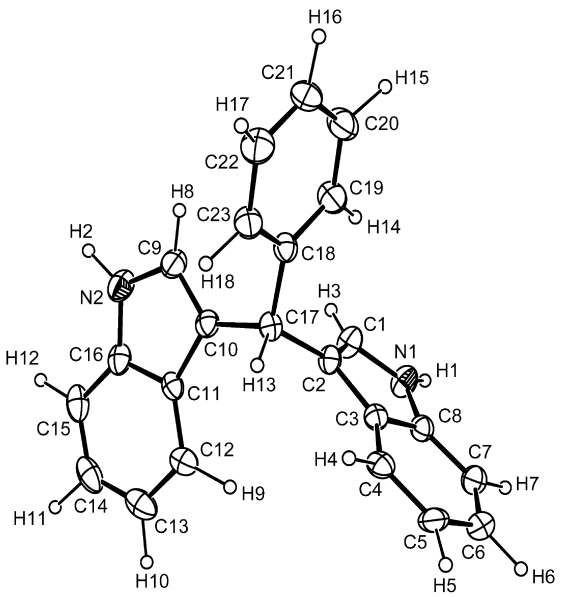


Figure 1. X-ray crystal structure of **3a**.

4. Experimental

4.1. General

Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury MHz spectrometer in $CDCl_3$. IR Spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elemental analyses were performed by a Carlo-Erba EA1110 CNNO-S analyzer. High resolution Mass spectra were obtained using GCT-TOF instrument. X-ray diffraction data were made on a Rigaku Mercury CCD area detector with graphite monochromated Mo Kα radiation.

4.2. Typical experimental procedure

A mixture of benzaldehyde (1 mmol), indole (2 mmol) and I_2 (0.2 mmol) were ground together in a mortar with a pestle at room temperature for several minutes. After completion of the reaction as monitored by TLC, the mixture was treated with $Na_2S_2O_3$ to yield solid **3a**, which was purified by column chromatography (ethyl acetate:petroleum ether=1:9) to afford the pure product (yield: 72%).

4.2.1. 1*H*,1′*H*-3,3′-Phenylmethanediyl-bis-indole, 3a. Colorless needles; mp 150–152 °C (lit,[17] 150–152 °C); IR (KBr): ν 744, 1093, 455, 1600, 1618, 3055, 3412 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (s, 1H, Ar–CH), 6.67 (s, 2H), 7.00 (t, 2H, J=6.8 Hz), 7.15–7.23 (m, 3H), 7.28–7.30 (m, 2H), 7.34–7.40 (m, 6H), 7.94 (br, s, 2H, NH); Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.75; H, 5.56; N, 8.56.

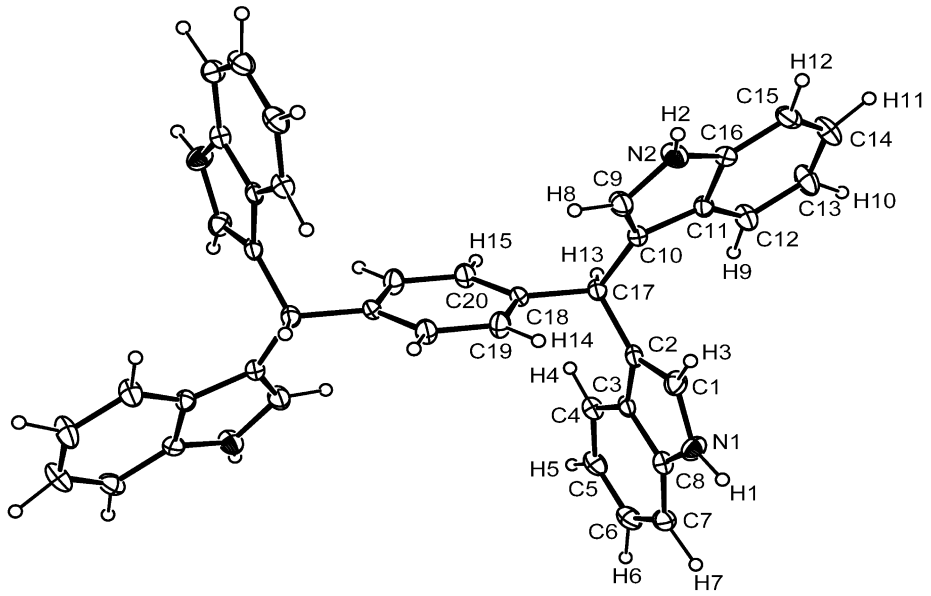


Figure 2. X-ray crystal structure of **3k**.

4.2.2. 3,3′-Bis(indolyl)-4-methylphenylmethane, 3b. Pink solid; mp 94–96 °C (lit,[10] 95–97 °C); IR (KBr): ν 775, 1050, 1215, 1510, 1600, 2930, 3040, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, Ar–CH_3), 5.86 (s, 1H, Ar–CH), 6.68 (s, 2H), 7.02 (t, 2H, J=7.2 Hz), 7.1 (d, 2H, J=7.2 Hz), 7.23–7.27 (m, 6H), 7.4 (d, 2H, J=7.2 Hz), 7.93 (br, s, 2H, NH); Anal. calcd for $C_{24}H_{20}ON_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.37; H, 5.95; N, 8.04.

4.2.3. 1*H*,1′*H*-3,3′-(4-Methoxy-phenylmethanediyl)-bis-indole, 3c. Brown needles; mp 187–189 °C (lit,[10a] 189 °C); IR (KBr): ν 1220, 1244, 1455, 1508, 1609, 2928, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H, CH_3), 5.84 (s, 1H, Ar–CH), 6.66 (s, 2H), 6.82 (d, 2H, J=8.3 Hz), 7.00 (t, 2H, J=7.3 Hz), 7.17 (t, 2H, J=7.3 Hz), 7.19 (s, 2H), 7.35–7.40 (m, 4H), 7.94 (br, s, 2H, NH); Anal. calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.72; H, 5.82; N, 7.98.

4.2.4. 1*H*,1′*H*-3,3′-(4-Nitro-phenylmethanediyl)-bis-indole, 3d. Yellow needles; mp 217–219 °C (lit,[10a] 220–222 °C); IR (KBr): ν 1340, 1456, 1507, 1592, 3052, 3422 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.00 (s, 1H, Ar–CH), 6.70 (s, 2H), 7.00–7.05 (m, 3H), 7.35 (d, 3H, J=8.0 Hz), 7.40 (d, 2H, J=8.0 Hz), 7.52 (d, 2H, J=8.8 Hz), 8.04 (br, s, 2H, NH), 8.15 (d, 2H, J=8.8 Hz); Anal. calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.28; H, 4.51; N, 11.60.

4.2.5. (4-Chloro-phenyl)-(1*H*-indol-3-yl)-methyl]-phenyl-amine, 3e. Pink solid; mp 76–77 °C; IR (KBr): ν 1089, 1455, 1487, 3054, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1H, Ar–CH), 6.66 (s, 2H), 7.02 (t, 2H, J=8.3 Hz), 7.18 (t, 2H, J=7.9 Hz), 7.26–7.38 (m, 8H), 7.98 (br, s, 2H, NH); HRMS [Found: m/z 356.1069(M^+), calcd for $C_{23}H_{17}ClN_2$: M, 356.1080].

4.2.6. (2-Chloro-phenyl)-(1*H*-indol-3-yl)-methyl]-phenyl-amine, 3f. Pink solid; mp 72–74 °C; IR (KBr): ν 1010, 1037, 1093, 1337, 1417, 1455, 1616, 3052, 3412 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 1H, Ar–CH), 6.66 (s, 2H), 7.02 (t, 2H, J=8.0 Hz), 7.11–7.23 (m, 6H), 7.36–7.43 (m, 4H), 7.96 (br, s, 2H, NH); HRMS [Found: m/z 356.1071(M^+), calcd for $C_{23}H_{17}ClN_2$: M, 356.1080].

4.2.7. 2-[Bis-(1*H*-indol-3-yl)-methyl]-4-chloro-phenol, 3g. Yellow needles; mp 78–80 °C; IR (KBr): ν 1039, 1095, 1338, 1416, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.40 (br, s, 1H, OH), 5.96 (s, 1H, Ar–CH), 6.90 (s, 3H), 7.05 (t, 2H, J=7.2 Hz), 7.12–7.14 (m, 2H), 7.23 (t, 2H, J=7.2 Hz), 7.39 (d, 4H, J=8.8 Hz), 8.05 (br, s, 2H, NH); HRMS [Found: m/z 372.1023(M^+), calcd for $C_{23}H_{17}ClN_2O$: M, 372.1029].

4.2.8. Benzo[1,3]dioxol-5-yl-di-indol-3-yl-methane, 3h. Yellow solid; mp 89–91 °C (lit,[10a] 89**–91 °C); IR (KBr): ν 1260, 1450, 1715, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.82 (s, 1H, Ar–CH), 5.92 (s, 2H, CH_2), 6.70 (s, 2H), 6.74 (d, 1H, J=8.2 Hz), 6.84 (d, 2H, J=8.2 Hz), 7.02 (t, 2H, J=7.3 Hz), 7.18 (t, 2H, J=7.3 Hz), 7.36–7.42 (m, 4H), 7.95 (br, s, 2H, NH); HRMS [Found: m/z 366.1355(M^+), calcd for $C_{24}H_{18}N_2O_2$: M, 366.1368].

4.2.9. 3,3′-Bis(indolyl)-4-methylphenylmethane, 3i. Brown solid; mp 322–325 °C (lit,[10a] 325 °C); IR (KBr): ν 1260, 1450, 1715, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.95 (s, 1H, Ar–CH), 6.90 (s, 2H), 7.03–7.50 (m, 11H), 8.00 (br, s, 2H, NH); HRMS [Found: m/z 312.1255(M^+), calcd for $C_{21}H_{16}N_2O$: M, 312.1263].

4.2.10. Diindol-3-yl-[2]thienyl-methane, 3j. Brown solid; mp 151–153 °C (lit,[10a] 149–156 °C); IR (KBr): ν 1260, 1450, 1715, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H, Ar–CH), 6.87 (s, 2H), 6.92–7.48 (m, 11H), 7.98 (br, s, 2H, NH); Anal. calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 76.62; H, 5.04; N, 8.54.

4.2.11. 3k·2AcOEt. Colorless solid; mp 121–123 °C (lit,[10a] 138–140 °C); IR (KBr): ν 1260, 1450, 1715, 3410

(NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 6H, CH_3, J=6.4 Hz), 2.05 (s, 6H, CH_3), 4.09–4.15 (m, 4H, CH_2), 5.84 (s, 2H, Ar–CH), 6.58 (s, 4H), 7.00 (t, 4H, J=7.6 Hz), 7.16 (t, 4H, J=7.6 Hz), 7.32–7.40 (m, 12H), 7.80 (br, s, 4H, NH); Anal. calcd for $C_{48}H_{46}N_4O_4$: C, 77.60; H, 6.24; N, 7.54. Found: C, 77.60; H, 6.42; N, 7.44.

Acknowledgements

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16. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 215713-215714 for compounds **3a** and **3k**·2AcOEt. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (E-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; Fax:+44 1223 336033). Structural parameters for **3k**·2AcOEt: data collection: Rigaku Mercury CCD area detector; radiation: Mo Kα wavelength: λ=0.71070 Å; crystal size: 0.20×0.40×0.05 mm^3; crystal system: triclinic; space group: *P*-1 (#2); unit cell: a=7.1255(9) Å, b=12.1249(5) Å, c=12.5865(5) Å, α=68.89(2)°, β=82.29(2)°, γ=84.44(2)°.
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Ring-opening reaction of methylenecyclopropanes with LiCl, LiBr or NaI in acetic acid

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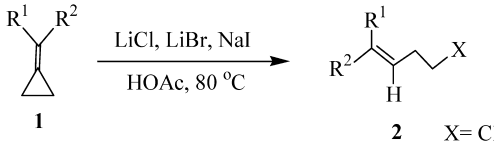
Abstract—The methylenecyclopropanes **1** react with LiCl, LiBr or NaI at 80 °C to give the corresponding *gem*-disubstituted homoallylic halides **2** in good to excellent yields in acetic acid. In some cases, the ring-opening reaction can be completed within 5 min to give the corresponding *gem*-disubstituted homoallylic halides in high yields.

1. Introduction

Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1] Strain in organic molecules often correlates with increased reactivity because the relief of ring strain provides a potent thermodynamic driving force.[2] Recently, Yamamoto reported that the reaction of alkylidenecyclopropanes with HCl or with HBr proceeds very smoothly at 120 °C to produce the corresponding *gem*-disubstituted homoallylic chlorides and bromides in good to excellent yields.[3] However, the reactions were carried out in a well sealed, pressured vial with 4 M hydrogen chloride in 1,4-dioxane or 1 M hydrogen bromide in acetic acid. Obviously, the severe reaction conditions limited its use in organic synthesis. In addition, the preparation of *gem*-disubstituted homoallylic iodides has not been mentioned.

In this paper, we wish to describe a more convenient and useful synthetic method for the preparation of *gem*-disubstituted homoallylic halides including *gem*-disubstituted homoallylic iodides in good yields from the ring-opening reaction of MCPs with LiCl, LiBr, NaI (alkali metal halides) in acetic acid under milder conditions (Scheme 1).



1 **2** X= Cl, Br, I

Scheme 1. The ring-opening reaction of MCPs **1** with LiCl, LiBr, NaI in acetic acid.

2. Results and discussion

Using diphenylmethylenecyclopropane **1a** (0.5 mmol) as a substrate, we first attempted the hydrohalogenation of **1a** using sodium halides (0.75 mmol) in acetic acid (Table 1). We found that using NaCl or NaBr as a hydrohalogenating reagent in acetic acid at 80 °C,[4] only trace of the corresponding homoallylic chloride **2a** or bromide **2b** was formed (Table 1, entries 1 and 2). Using NaI as a hydrohalogenating reagent at 80 °C in acetic acid, the corresponding *gem*-disubstituted homoallylic iodide **2c** was produced in quantitative yield within 10 min, although no reaction occurred at room temperature and only trace of **2c** was formed at 50 °C under the same conditions (Table 1, entries 3–5). This is simply because NaI has higher nucleophilicity than NaCl or NaBr and is soluble in acetic acid at 80 °C. On the other hand, using LiCl or $LiBr{\cdot}H_2O$ as a nucleophile instead of NaCl and NaBr, the ring-opening reaction of **1a** takes place smoothly to give the corresponding *gem*-disubstituted homoallylic chloride **2a** and bromide **2c** in excellent yields within 20 and 60 min, respectively, under identical conditions (Table 1, entries 9 and 10). The other nucleophiles such as NaN_3, KF and NaOAc showed no reactivities to this ring-opening reaction under the same conditions (Table 1, entries 6–8).

Keywords: Methylenecyclopropanes; LiCl; LiBr; NaI; *gem*-Disubstituted homoallylic halides; Ring-opening reaction; Acetic acid.
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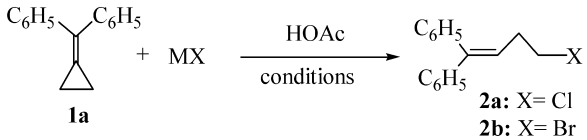
Table 1. The reaction of MCP **1a** with metal halides in acetic acid



1a

2a: X= Cl
2b: X= Br
2c: X= I

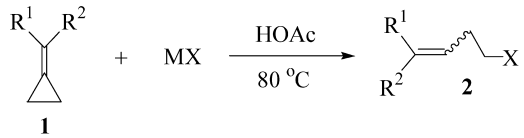
Entry	MX	Temperature (°C)	Time	Yield[a]
1	NaCl	80	48 h	**2a**, trace
2	NaBr	80	48 h	**2b**, trace
3	NaI	15	48 h	**2c**, NR
4	NaI	50	48 h	**2c**, trace
5	NaI	80	10 min	**2c**, 100
6	NaN_3	80	48 h	Trace
7	KF	80	48 h	Trace
8	NaOAc	80	48 h	Trace
9	LiCl	80	60 min	**2a**, 96
10	LiBr·H_2O	80	20 min	**2b**, 98

[a] Isolated yield.

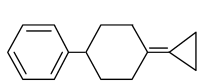
Using various MCPs **1** (0.5 mmol) as the substrates, we carried out the ring-opening reaction of **1** with LiCl, LiBr·H_2O and NaI (0.75 mmol) under the optimized conditions. The results were summarized in Table 2. As shown in Table 2, homoallylic halides **2** were obtained in good to excellent yields (Table 2, entries 1–15). The substituents on the benzene ring significantly affected the reaction. For MCP **1b** having a strongly electron-donating group on the benzene ring, the ring-opening reaction of MCP **1b** could be completed within 5 min in the presence of either LiCl, LiBr or NaI to give the corresponding halides in excellent yields (Table 2, entries 1–3). The electron-withdrawing groups such as F- or Cl- on the benzene ring slowed down the reaction rates. Thus, a prolonged reaction time (1–5 h) was required to complete the reaction for MCPs **1d** and **1e** (Table 2, entries 7–12). For unsymmetric MCP **1f** (R^1=*p*-$MeOC_6H_4$, R^2=C_6H_5), the *gem*-disubstituted homoallylic halides **2p** was obtained as a mixture of *Z*/*E*-isomer (Table 2, entry 13). For aliphatic MCPs **1f-i**, the corresponding homoallylic halides could be obtained under the same conditions for a prolonged reaction time (12 h) in high yields as well (Table 2, entries 14–20). In the case of aliphatic MCP **1g**, the corresponding homoallylic halides were obtained as a mixture of α,β-isomers (Scheme 2).

In conclusion, we disclosed in this paper a more efficient transformation of MCPs **1** to the corresponding *gem*-disubstituted homoallylic chlorides, bromides, and iodides under milder conditions using LiCl, LiBr, and NaI as hydrohalogenating reagents.[5] The reaction was carried out under ambient atmosphere. Inert atmosphere and high pressure reaction vessel are not required. In some cases, the ring-opening reaction can be completed within 5 min to give the corresponding *gem*-disubstituted homoallylic halides in high yields. The rearrangement of cyclopropyl carbinyl cation to a homoallylic cation induced by acetic acid is likely the key step of this ring-opening reaction.[6] The experiments are underway to elucidate the mechanistic details, expand the scope and define the limitations of this reaction.

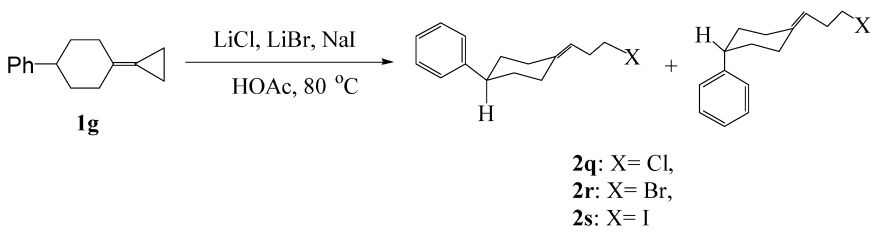
Table 2. The reactions of various MCPs **1** with alkali metal halides in acetic acid



1 **2**

Entry	R^1/R^2	N	MX	Time	Yield[a]
1	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$	**1b**	LiCl	<5 min	**2d**, 99
2	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$	**1b**	LiBr·H_2O	<5 min	**2e**, 100
3	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$	**1b**	NaI	<5 min	**2f**, 100
4	*p*-MeC_6H_4/*p*-MeC_6H_4	**1c**	LiCl	20 min	**2g**, 98
5	*p*-MeC_6H_4/*p*-MeC_6H_4	**1c**	LiBr·H_2O	20 min	**2h**, 96
6	*p*-MeC_6H_4/*p*-MeC_6H_4	**1c**	NaI	10 min	**2i**, 96
7	*p*-FC_6H_4/*p*-FC_6H_4	**1d**	LiCl	5 h	**2j**, 97
8	*p*-FC_6H_4/*p*-FC_6H_4	**1d**	LiBr·H_2O	5 h	**2k**, 92
9	*p*-FC_6H_4/*p*-FC_6H_4	**1d**	NaI	1 h	**2l**, 95
10	*p*-ClC_6H_4/*p*-ClC_6H_4	**1e**	LiCl	4 h	**2m**, 91
11	*p*-ClC_6H_4/*p*-ClC_6H_4	**1e**	LiBr·H_2O	3 h	**2n**, 94
12	*p*-ClC_6H_4/*p*-ClC_6H_4	**1e**	NaI	1 h	**2o**, 98
13	*p*-$MeOC_6H_4$/C_6H_5	**1f**	LiBr·H_2O	20 min	**2p**, 100 (2.0:1)[b]
14		**1g**	LiCl	12 h	**2q**, 100 (1:0.9)[c]
15		**1g**	LiBr·H_2O	12 h	**2r**, 94 (1.47:1)[c]
16			NaI	12 h	**2s**, 89 (4:1)[c]
17	*n*-C_7H_{15}/CH_3	**1h**	LiBr·H_2O	12 h	**2t**, 90 (1.7:1)[b]
18	*n*-C_4H_9/*n*-C_4H_9	**1i**	LiCl	12 h	**2u**, 89
19	*n*-C_4H_9/*n*-C_4H_9	**1i**	LiBr·H_2O	12 h	**2v**, 80
20	*n*-C_4H_9/*n*-C_4H_9	**1i**	NaI	12 h	**2w**, 73

[a] Isolated yield.
[b] *Z*/*E*-mixture.
[c] α/β-mixture.



1g

2q: X= Cl,
2r: X= Br,
2s: X= I

Scheme 2. The ring-opening reaction of aliphatic MCP **1g** with LiCl, LiBr, NaI in acetic acid.

3. Experimental

3.1. General methods

Melting points are uncorrected. ^{1}H NMRs and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI methods, and HRMS was measured on a Finnigan MA+ mass spectrometer. Organic solvents were dried by standard methods when necessary. Commercial reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel. The starting materials (MCPs) **1** were prepared according to the literature.[7]

3.2. General procedure for the reactions of MCPs with alkali metal chlorides, bromides or iodides

MCPs **1** (0.5 mmol) was dissolved in 1.0 mL of acetic acid and then a metal iodide, chloride or bromide (0.75 mmol) was added into the solution. The reaction mixture was heated to 80 °C and was stirred for 5–300 min. The reaction was monitored by TLC plate. After the reaction was completed, it was quenched by the addition of water, the organic compounds were extracted with petroleum ether. The organic layer was washed with saturated aqueous Na_2CO_3, brine, and water, and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography eluenting with hexane/ethyl acetate (5:1) to afford the product **2**.

3.2.1. 4,4-Diphenyl-1-chloro-but-3-ene (2a). This compound was obtained as a colorless oil in 96% yield. IR (neat): ν 3079, 3024, 2956, 1598, 1494, 1444, 1296, 1029 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 2.56 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.55 (t, J=7.2 Hz, 2H, CH_2), 6.12 (t, J=7.2 Hz, 1H, C=CH), 7.23–7.47 (m, 10H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 32.96, 44.42, 124.83, 127.30, 127.33, 127.35, 128.21, 128.39, 129.77, 139.65, 142.15, 144.44; MS (EI) *m/z*: 242 (M^+) (41), 193 (100), 180 (95), 165 (70), 115 (90), 104 (68), 91 (49); HRMS (EI) Calcd for $C_{16}H_{15}Cl$: 242.0862. Found: 242.0829.

3.2.2. 4,4-Diphenyl-1-bromo-but-3-ene (2b). This compound was obtained as a colorless oil in 98% yield. IR (neat): ν 3056, 3024, 1660, 1598, 1494, 1444, 1269 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 2.66 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.41 (t, J=7.2 Hz, 2H, CH_2), 6.08 (t, J=7.2 Hz, 1H, C=CH), 7.15–7.37 (m, 10H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 32.65, 32.84, 125.62, 125.65, 127.23, 127.26, 128.10, 128.27, 129.64, 139.52, 142.02, 144.19; MS (EI) *m/z*: 286 (M^+) (31), 207 (10), 193 (56), 189 (10), 182 (16), 178 (34), 165 (27), 129 (100); HRMS (EI) Calcd for $C_{16}H_{15}Br$: 286.0357. Found: 285.9449.

3.2.3. 4,4-Diphenyl-1-iodo-but-3-ene (2c). This compound was obtained as a colorless oil in 100% yield. IR (neat): ν 3055, 3022, 1598, 1494, 1443, 1239, 759 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 2.67 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.16 (t, J=7.2 Hz, 2H, CH_2), 6.01 (t, J=7.2 Hz, 1H, C=CH), 7.15–7.36 (m, 10H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 5.62, 33.29, 127.22, 127.24, 127.64, 128.11, 129.26, 129.63, 139.54, 142.05, 143.72; MS (EI) *m/z*: 334 (M^+) (20), 207 (75), 191 (16), 178 (23), 129 (100); HRMS (EI) Calcd for $C_{16}H_{15}I$: 334.0218. Found: 334.0194.

3.2.4. 4,4-Bis(4-methoxyphenyl)-1-chloro-but-3-ene (2d). This compound was obtained as a colorless oil in 99% yield. IR (neat): ν 3000, 2956, 1605, 1510, 1287, 1031 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 2.55 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.53 (t, J=7.2 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.94 (t, J=7.2 Hz, 1H, C=CH), 6.77–7.16 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 33.24, 44.80, 55.50, 55.71, 113.74, 113.94, 123.02, 128.73, 131.12, 132.52, 135.46, 143.69, 158.96, 159.24; MS (EI) *m/z*: 302 (M^+) (44), 267 (6), 253 (100), 242 (31), 211 (15), 145 (42), 135 (82); HRMS (EI) Calcd for $C_{18}H_{19}ClO_2$: 302.1074. Found: 302.1118.

3.2.5. 1-[4-Bromo-1-(4-methoxyphenyl)but-1-enyl]-4-methoxybenzene (2e). This compound was obtained as a colorless oil in 100% yield. IR (neat): ν 2920, 2850, 1605, 1509, 1460, 1244, 1172, 1107, 1033 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 2.68 (td, J=6.6, 7.2 Hz, 2H, CH_2), 3.42 (t, J=7.2 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.94 (t, J=6.9 Hz, 1H, C=CH), 6.81 (d, J=8.7 Hz, 2H, ArH), 6.88 (d, J=8.7 Hz, 2H, ArH), 7.09 (d, J=8.7 Hz, 2H, ArH), 7.16 (d, J=8.7 Hz, 2H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 32.90, 33.00, 55.23, 55.27, 113.46, 113.66, 123.67, 128.46, 130.81, 132.07, 135.16, 143.30, 158.76, 158.98; MS (EI) *m/z*: 346 (M^+) (40), 267 (18), 253 (86), 242 (43), 211 (20), 159 (35), 145 (38), 135 (100), 121 (41); HRMS (EI) Calcd for $C_{18}H_{19}BrO_2$: 346.0568. Found: 346.0578.

3.2.6. 4,4-Bis(4-methoxyphenyl)-1-iodo-but-3-ene (2f). This compound was obtained as a colorless oil in 100% yield. IR (neat): ν 2954, 2834, 1606, 1511, 1246, 833 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 2.67 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.18 (t, J=7.2 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.88 (t, J=7.2 Hz, 1H, C=CH), 6.79–7.18 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 5.86, 33.33, 55.08, 55.12, 113.31, 113.46, 125.58, 128.33, 130.68, 131.94, 135.05, 142.66, 158.52,

158.79; MS (EI) *m/z*: 394 (M^+) (8), 267 (28), 227 (9), 205 (13), 159 (19), 121 (23), 84 (100); HRMS (EI) Calcd for $C_{18}H_{19}IO_2$: 394.0430. Found: 394.0446.

3.2.7. 1-[4-Chloro-1-(4-methylphenyl)but-1-enyl]-4-methylbenzene (2g). This compound was obtained as a colorless oil in 98% yield. IR (neat): ν 3023, 2921, 1606, 1511, 1448, 1295, 1110, 1021 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.57 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.54 (t, J=7.2 Hz, 2H, CH_2), 6.03 (t, J=7.2 Hz, 1H, C=CH), 7.03–7.19 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 21.05, 21.21, 32.92, 44.43, 123.62, 127.17, 128.78, 128.94, 129.56, 136.72, 136.78, 136.97, 139.51, 144.12; MS (EI) *m/z*: 270 (M^+) (14), 221 (25), 210 (46), 119 (100), 91 (41); HRMS (EI) Calcd for $C_{18}H_{19}Cl$: 270.1175. Found: 270.1197.

3.2.8. 1-[4-Bromo-1-(4-methylphenyl)but-1-enyl]-4-methylbenzene (2h). This compound was obtained as a colorless oil in 96% yield. IR (neat): ν 3022, 2920, 1609, 1511, 1445, 1267, 1207, 1020 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.66 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.38 (t, J=7.2 Hz, 2H, CH_2), 6.00 (t, J=7.2 Hz, 1H, C=CH), 7.03–7.18 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 21.04, 21.21, 32.77, 32.93, 124.62, 127.15, 128.77, 128.93, 129.52, 136.66, 136.75, 136.95, 139.46, 143.96; MS (EI) *m/z*: 316 (M^+) (73), 221 (100), 205 (42), 143 (97), 129 (55), 105 (60); HRMS (EI) Calcd for $C_{18}H_{19}Br$: 314.0670. Found: 314.0653.

3.2.9. 1-[4-Iodo-1-(4-methylphenyl)but-1-enyl]-4-methylbenzene (2i). This compound was obtained as a colorless oil in 96% yield. IR (neat): ν 3021, 2919, 1609, 1511, 1444, 1239, 1169, 1110, 1020 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.66 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.15 (t, J=7.2 Hz, 2H, CH_2), 5.94 (t, J=7.2 Hz, 1H, C=CH), 7.02–7.18 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 6.78, 21.06, 21.22, 33.39, 126.56, 127.16, 128.77, 128.90, 129.51, 136.71, 136.75, 136.93, 139.50, 143.48; MS (EI) *m/z*: 362 (M^+) (14), 235 (68), 219 (17), 205 (20), 143 (100), 128 (34), 105 (72); HRMS (EI) Calcd for $C_{18}H_{19}I$: 362.0531. Found: 362.0500.

3.2.10. 1-[4-Chloro-1-(4-fluorophenyl)but-1-enyl]-4-fluorobenzene (2j). This compound was obtained as a colorless oil in 97% yield. IR (neat): ν 2958, 2926, 1602, 1508, 1445, 1409, 1297, 1225, 1094, 1015 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.56 (td, J=6.8, 7.2 Hz, 2H, CH_2), 3.57 (t, J=6.8 Hz, 2H, CH_2), 6.04 (t, J=7.2 Hz, 1H, C=CH), 6.92–7.20 (m, 8H, ArH); ^{19}F NMR (282 MHz, TMS, $CDCl_3$): −115.47, −115.02; MS (EI) *m/z*: 278 (M^+) (55), 229 (100), 214 (20), 147 (14), 133 (41), 109 (30); HRMS (EI) Calcd for $C_{16}H_{13}ClF_2$: 278.0674. Found: 278.0664.

3.2.11. 1-[4-Bromo-1-(4-fluorophenyl)but-1-enyl]-4-fluorobenzene (2k). This compound was obtained as a colorless oil in 92% yield. IR (neat): ν 2968, 1602, 1508, 1225, 1158, 1094, 1015 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.67 (td, J=7.2, 7.3 Hz, 2H, CH_2), 3.43 (t, J=7.2 Hz, 2H, CH_2), 6.02 (t, J=7.3 Hz, 1H, C=CH), 6.93–7.20 (m, 8H, ArH); ^{19}F NMR (282 MHz, TMS, $CDCl_3$): −115.47, −115.02; MS (EI) *m/z*: 322 (M^+) (64), 229 (100), 214 (30), 147 (82), 133 (54), 109 (85); HRMS (EI) Calcd for $C_{16}H_{13}BrF_2$: 322.0169. Found: 322.0177.

3.2.12. 1-Fluoro-4-[1-(4-fluorophenyl)-4-iodobut-1-enyl]benzene (2l). This compound was obtained as a colorless oil in 95% yield. IR (neat): ν 3043, 2958, 1601, 1508, 1225, 1158, 1094, 1014 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.67 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.19 (t, J=7.2 Hz, 2H, CH_2), 5.95 (t, J=7.2 Hz, 1H, C=CH), 6.93–7.20 (m, 8H, ArH); ^{19}F NMR (282 MHz, TMS, $CDCl_3$): −115.47, −114.99; ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 5.46, 33.14, 114.89, 115.18, 115.23, 115.51, 127.92, 127.95, 128.78, 128.88, 131.20, 131.31, 135.20, 138.13, 138.85, 141.79, 160.39, 163.66, 163.86; MS (EI) *m/z*: 370 (M^+) (24), 243 (100), 227 (11), 214 (14), 201 (14), 147 (93), 109 (95); HRMS (EI) Calcd for $C_{16}H_{13}F_2I$: 370.0030. Found: 370.0036.

3.2.13. 4,4-Bis(4-chlorophenyl)-1-chloro-but-3-ene (2m). This compound was obtained as a colorless oil in 91% yield. IR (neat): ν 3030, 2956, 2925, 1592, 1492, 1401, 1091 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.57 (td, J=6.6, 6.6 Hz, 2H, CH_2), 3.58 (t, J=6.6 Hz, 2H, CH_2), 6.11 (t, J=6.6 Hz, 1H, C=CH), 7.09–7.38 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 33.03, 44.36, 126.20, 128.64, 128.77, 128.99, 131.31, 133.63, 133.71, 137.77, 140.41, 142.49; MS (EI) *m/z*: 310 (M^+), 275, 261, 226, 191, 163; HRMS (EI) Calcd for $C_{16}H_{13}Cl_3$: 310.0083. Found: 310.0047.

3.2.14. 4,4-Bis-(4-chlorophenyl)-1-bromo-but-3-ene (2n). This compound was obtained as a colorless oil in 95% yield. IR (neat): ν 3030, 2963, 1661, 1590, 1491, 1268, 1091 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.65 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.42 (t, J=6.6 Hz, 2H, CH_2), 6.06 (t, J=7.2 Hz, 1H, C=CH), 7.08–7.37 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 40.42, 41.67, 126.37, 128.26, 128.31, 128.46, 130.96, 131.26, 133.37, 137.39, 140.04, 141.97; MS (EI) *m/z*: 354 (M^+), 261, 250, 235, 226, 202, 191, 163; HRMS (EI) Calcd for $C_{16}H_{13}BrCl_2$: 353.9578. Found: 353.9569.

3.2.15. 4,4-Bis(4-chlorophenyl)-1-iodo-but-3-ene (2o). This compound was obtained as a colorless oil in 98% yield. IR (neat): ν 3030, 2957, 1591, 1491, 1400, 1091 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 2.65 (td, J=7.2, 7.2 Hz, 2H, CH_2), 3.17 (t, J=7.2 Hz, 2H, CH_2), 5.99 (t, J=7.2 Hz, 1H, C=CH), 7.07–7.36 (m, 8H, ArH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 5.20, 33.08, 128.35, 128.49, 128.57, 128.66, 128.75, 130.97, 133.31, 137.46, 140.12, 141.57; MS (EI) *m/z*: 402 (M^+), 275, 250, 204, 163; HRMS (EI) Calcd for $C_{16}H_{13}Cl_2I$: 401.9439. Found: 401.9482.

3.2.16. 1-(4-Bromo-1-phenyl-but-1-enyl)-4-methoxybenzene (2p). This compound was obtained as a colorless oil (*Z*/*E*-mixture, 2:1) in 100% yield. IR (neat): ν 3028, 2958, 2835, 1606, 1575, 1510, 1493, 1443, 1247, 1179, 1034 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): for *Z*- or *E*-**2p**: δ 2.60–2.75 (m, 2H, CH_2), 3.38–3.43 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 5.99 (t, J=7.2 Hz, 1H), 6.78–7.38 (m,

9H, ArH); for *E*- or *Z*-**2p**: δ 2.60–2.75 (m, 2H, CH_2), 3.38–3.43 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.02 (t, *J*=7.2 Hz, 1H), 6.78–7.38 (m, 9H, ArH); MS (EI) *m/z*: 316 (M^+) (77), 277 (3), 237 (15), 223 (100), 208 (10), 191 (10), 178 (17), 165 (19), 129 (42), 121 (24), 115 (37), 91 (28); HRMS (EI) Calcd for $C_{17}H_{17}BrO$: 316.0463. Found: 316.0454.

3.2.17. [4-(3-Chloropropylidene)cyclohexyl]benzene (2q). This compound was obtained as a colorless oil (α/β-mixture, 1:0.9) in 100% yield. IR (neat): ν 3027, 2925, 1603, 1493, 1452, 1292, 1242 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): ^1H NMR (300 MHz, TMS, $CDCl_3$): for α- or β-isomer: δ 1.40–2.40 (m, 9H, CH_2), 2.47–2.56 (m, 1H, CH_2), 2.64–2.75 (m, 1H, CH_2), 3.47–3.58 (m, 2H, CH_2), 5.18 (t, *J*=6.9 Hz, 1H, C═CH), 7.15–7.36 (m, 5H, ArH); for β- or α-isomer: δ 1.40–2.40 (m, 9H, CH_2), 2.47–2.56 (m, 1H, CH_2), 2.64–2.75 (m, 1H, CH_2), 3.47–3.58 (m, 2H, CH_2), 5.54 (t, *J*=6.9 Hz, 1H, C═CH), 7.15–7.36 (m, 5H, ArH); MS (EI) *m/z*: 234 (M^+) (34), 157 (10), 143 (10), 104 (100), 91 (20); HRMS (EI) Calcd for $C_{15}H_{19}Cl$: 234.1175. Found: 234.1168.

3.2.18. [4-(3-Bromopropylidene)cyclohexyl]benzene (2r). This compound was obtained as a colorless oil (α/β-mixture, 1.47:1) in 94% yield. IR (neat): ν 3026, 2925, 1602, 1493, 1452, 1268, 1245, 1206, 1031 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): for α- or β-isomer: δ 1.40–2.40 (m, 9H, CH_2), 2.57–2.71 (m, 2H, CH_2), 3.35–3.44 (m, 2H, CH_2), 5.16 (t, *J*=7.2 Hz, 1H, C═CH), 7.18–7.31 (m, 5H, ArH); for β- or α-isomer: δ 1.40–2.40 (m, 9H, CH_2), 2.57–2.71 (m, 2H, CH_2), 3.35–3.44 (m, 2H, CH_2), 5.54 (d, *J*=4.2 Hz, 1H, C═CH), 7.18–7.31 (m, 5H, ArH); MS (EI) *m/z*: 278 (M^+) (4), 199 (5), 157 (10), 143 (11), 129 (16), 115 (21), 104 (100), 91 (52); HRMS (EI) Calcd for $C_{15}H_{19}Br$: 278.0670. Found: 278.0673.

3.2.19. [4-(3-Iodopropylidene)cyclohexyl]benzene (2s). This compound was obtained as a colorless oil (α/β-mixture, 4:1) in 90% yield. IR (neat): ν 3025, 2924, 1602, 1493, 1451, 1227, 1166 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): for α- or β-isomer: δ 1.42–1.60 (m, 2H, CH_2), 1.80–2.40 (m, 5H, CH_2), 2.58–2.80 (m, 4H, CH_2), 3.05–3.11 (m, 2H, CH_2), 5.13 (t, *J*=7.5 Hz, 1H, C═CH), 7.07–7.18 (m, 5H, ArH); for β- or α-isomer: δ 1.42–1.60 (m, 2H, CH_2), 1.80–2.40 (m, 5H, CH_2), 2.58–2.80 (m, 4H, CH_2), 3.05–3.11 (m, 2H, CH_2), 5.55 (d, *J*=4.2 Hz, 1H, C═CH), 7.07–7.18 (m, 5H, ArH); MS (EI) *m/z*: 326 (M^+) (23), 222 (6), 199 (100), 157 (34), 143 (20), 129 (23), 117 (50), 104 90), 95 (52), 91 (100); HRMS (EI) Calcd for $C_{15}H_{19}I$: 326.0531. Found: 326.0521.

3.2.20. 1-Bromo-4-methyl-undec-3-ene (2t). This compound was obtained as a colorless oil (*Z*/*E*-mixture, 1.7:1) in 90% yield. IR (neat): ν 2957, 2855, 1456, 1378, 1268, 723 cm^{-1}; *Z*- or *E*-**2t**: ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 0.86 (t, *J*=7.2 Hz, 3H, CH_3), 1.26–1.40 (m, 10H, CH_2), 1.61 (s, 3H, CH_3), 1.80–1.96 (m, 2H, CH_2), 2.10–2.20 (m, 2H, CH_2), 3.38 (t, *J*=7.8 Hz, 2H, CH_2), 5.18 (tt, *J*=7.2, 1.0 Hz, 1H, C═CH); *E*- or *Z*-**2t**: ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 0.87 (t, *J*=7.2 Hz, 3H, CH_3), 1.26–1.40 (m, 10H), 1.71 (s, 3H), 1.96–2.20 (m, 2H), 2.55–2.60 (m, 2H), 3.34 (t, *J*=7.8 Hz, 2H), 5.12 (tq, *J*=7.2, 1.0 Hz); MS (EI) *m/z*: 246 (M^+) (25), 162 (51), 125 (16), 95 (35), 83 (72), 55 (100); HRMS (EI) Calcd for $C_{12}H_{23}Br$: 246.0983. Found: 246.0960.

3.2.21. 5-(2-Chloroethylidene)nonane (2u). This compound was obtained as a colorless oil in 89% yield. IR (neat): ν 2957, 2928, 2859, 1465, 1378, 1293, 1138 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 0.85–0.93 (m, 6H, CH_3), 1.27–1.34 (m, 8H, CH_2), 1.97–2.03 (m, 4H, CH_2), 2.48 (dt, *J*=7.2, 7.2 Hz, 2H, CH_2), 3.48 (t, *J*=7.2 Hz, 2H, CH_2), 5.11 (t, *J*=7.2 Hz, CH, C═CH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 14.00, 14.03, 22.46, 22.85, 29.95, 30.30, 30.69, 31.33, 36.54, 44.57, 119.55, 143.31; MS (EI) *m/z*: 202 (M^+) (65), 160 (20), 145 (5), 118 (54), 97 (26), 81 (42), 69 (58), 55 (100); HRMS (EI) Calcd for $C_{12}H_{23}Cl$: 202.1488. Found: 202.1519.

3.2.22. 5-(2-Bromoethylidene)nonane (2v). This compound was obtained as a colorless oil in 80% yield. IR (neat): ν 2957, 2928, 2859, 1465, 1378, 1293, 1138 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 0.88–0.92 (m, 6H, CH_3), 1.30–1.41 (m, 8H, CH_2), 1.96–2.03 (m, 4H, CH_2), 2.57 (dt, *J*=7.2, 7.2 Hz, 2H, CH_2), 3.34 (t, *J*=7.2 Hz, 2H, CH_2), 5.10 (t, *J*=7.2 Hz, CH, C═CH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 13.99, 14.02, 22.45, 22.84, 29.95, 30.28, 30.68, 31.48, 32.93, 36.51, 120.57, 143.21; MS (EI) *m/z*: 246 (M^+) (7), 206 (8), 162 (6), 109 (9), 97 (21), 83 (69), 69 (67), 55 (100) HRMS (EI) Calcd for $C_{12}H_{23}Br$: 246.0983. Found: 246.1002.

3.2.23. 5-(2-Iodoethylidene)nonane (2w). This compound was obtained as a colorless oil in 73% yield. IR (neat): ν 2956, 2927, 2858, 1465, 1378, 1244, 1164 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 0.87–0.93 (m, 6H, CH_3), 1.28–1.35 (m, 8H, CH_2), 1.94–2.01 (m, 4H, CH_2), 2.58 (dt, *J*=7.5, 7.5 Hz, 2H, CH_2), 3.11 (t, *J*=7.5 Hz, 2H, CH_2), 5.06 (t, *J*=7.5 Hz, CH, C═CH); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 6.23, 14.01, 14.03, 22.45, 22.83, 29.97, 30.23, 30.65, 32.15, 36.18, 122.71, 142.74; MS (EI) *m/z*: 294 (M^+) (2), 210 (4), 167 (16), 111 (20), 97 (37), 83 (41), 69 (84), 55 (100); HRMS (EI) Calcd for $C_{11}H_{21}I$: 294.0844. Found: 294.0868.

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Novel multiply hydrogen-bonded heterodimers based on heterocyclic ureas. Folding and stability

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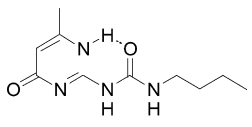
Abstract—A new series of multiply hydrogen-bonded heterodimers have been self-assembled in chloroform-*d*, with ureidopyrimidone derivatives **2** and **3** and 2,7-diamino-1,6-naphthyridine diamide **4** and ureas **5** and **6** as monomers. The self-associating behavior of the compounds and the binding modules of the new heterodimers have been investigated. New tri-center hydrogen bonds have been proposed to explain the stability of the new heterodimers. 2D-NOESY, COSY and temperature variable ^{1}H NMR studies revealed that all the new heterodimers are substantially more stable than the ureidopyrimidone-based quadruply hydrogen-bonded homodimers in chloroform-*d*. As a result, heterodimers **2·4** and **3·4** were assembled quantitatively, while heterodimers **2·5**, **3·5**, **2·6**, and **3·6** were formed in 80–85% yields. It is also revealed that intramolecular hydrogen bonds formed in monomers **5** and **6** reduce the stability of the corresponding heterodimers.

1. Introduction

Intermolecular interactions, particularly hydrogen bonds, are the base of many processes of supramolecular assembly and molecular recognition.[1,2] The strength of these interactions depends mainly on the number of the hydrogen bonds as well as the structural and geometric features of the monomers. With increasing number of the hydrogen bonds, molecular recognition usually becomes more specific and the corresponding supramolecular assemblies become more stable. Nevertheless, intramolecular hydrogen bonds,[3] secondary hydrogen-bonding interactions[4] and prototropic tautomerism[5] can also impose important influence on the binding stability. Systematic investigations of these discrete electronic and structural effects are crucial to control binding selectivity and future design of new binding motifs.

In recent years, quadruply hydrogen-bonded dimeric modules have attracted considerable attention because of their substantially increased stability and selectivity relative to doubly and triply hydrogen-bonded complexes.[3] Among others,[6] the ureidopyrimidone-based AADD (A: proton acceptor, D: proton donor) homodimeric binding motif **1·1**, reported initially by Meijer et al.,[3c] has extensive application in self-assembly of hydrogen bonded supramolecular polymers and oligomers with specific structures or functions[7] and used for regulating the self-assembly of a new series of highly stable donor–acceptor interaction-induced pseudo[2]rotaxanes.[8] We had been interested in developing new non-covalent approaches to dissociating this important homodimeric motif. We envisioned that study in this line would not only lead to the development of new hydrogen bonded assembling modules, but also provide potentially useful principles for regulating the structure and function of ureidopyrimidone-related supramolecular species. In this paper, we report that such kind of highly stable hydrogen-bonded homodimers can be fully or partially dissociated by readily available 2,7-diamino-1,6-naphthyridine amide and urea derivatives, to generate a new series of more robust heterodimers. ^{1}H NMR studies reveal that the stability of the novel heterodimers is remarkably affected by the structures of the 2,7-diamino-1,6-naphthyridine-derived monomers.



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2. Results and discussion

Five compounds **2-6** have been used as monomers to develop new multiply hydrogen-bonded heterodimers. Two new ureidopyrimidone derivatives **2** and **3** have been prepared conveniently in high yields from the reactions of commercially available **7** with the corresponding isocyantes **8a** or **8b** in hot pyridines, as shown in Scheme 1, according to the reported procedures for compounds with similar structures.[3c] Both molecules are substantially more soluble than **1** in organic solvents like chloroform and

Keywords: Self-assembly; Hydrogen bond; Ureidopyrimidone derivatives; Heterodimers.
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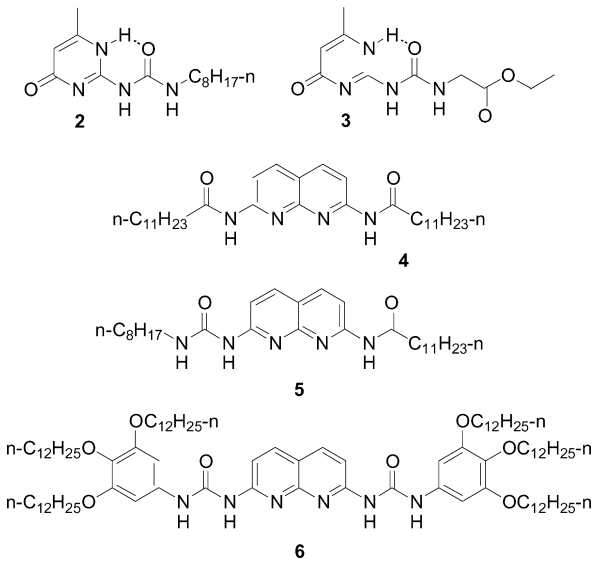
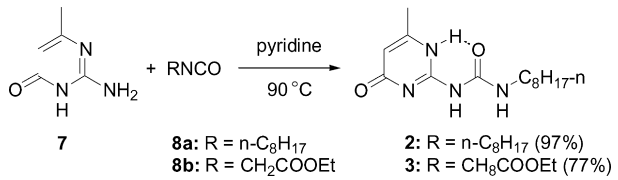
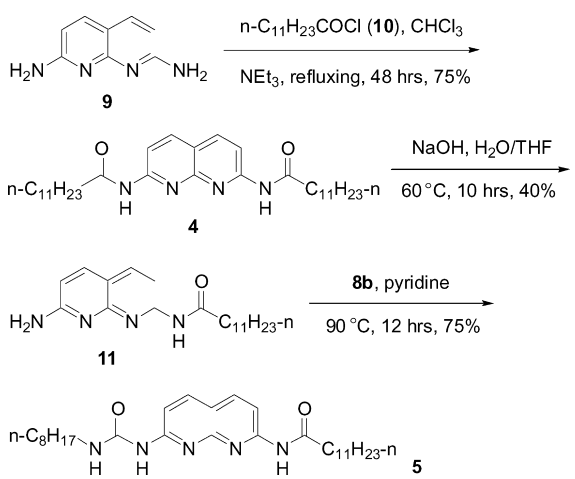


dichloromethane. The synthesis of compounds **4** and **5** is outlined in Scheme 2. Treatment of diamine **9**[3f,9] with excess of lauroyl chloride **10** in refluxing chloroform afforded **4** in good yield. Compound **4** was selectively hydrolyzed, with sodium hydroxide as base, to give amine **11** in 40% yield. The treatment of compound **11** with octyl isocyanate **8b** in hot pyridine led to the formation of compound **5** in 75% yield. Compound **11** could not be prepared directly from the reaction of **9** and **10**, possibly due to the fact that **11** was much more soluble than **9** in chloroform and consequently converted to **4** upon being generated. Compound **6** was prepared following the literature method.[3f] All the compounds have been characterized by ^{1}H NMR and mass spectroscopy and gave right elemental analysis.

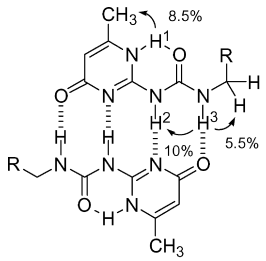


Scheme 1.

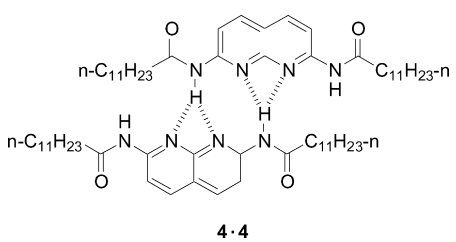


Scheme 2.

^{1}H NMR investigations revealed that compounds **2** and **3** exist exclusively as homodimers **2·2** and **3·3** in $CDCl_3$, respectively. The large downfield chemical shifts observed for NH protons (for **2**: 12.87 (H-1), 12.13 (H-2), 10.76 (H-3) ppm; for **3**: 12.82 (H-1), 12.13 (H-2), 10.72 (H-3) ppm) provided direct evidence for their involvement in strong hydrogen bonding. The assignment of the NH protons and the AADD hydrogen-bonding motif of the homodimers had been determined by the 2D-NOESY and COSY ^{1}H NMR spectra. No other binding modes were observed.[3c] Dilution of the solutions of the compounds in $CDCl_3$ to 1.0×10^{-5} M did not lead to observable dissociation, thus giving a lowest estimate of the binding constants of 1×10^7 M^{-1}. This result is in good agreement with the value obtained for a similar compound.[10] In order to check if the introduction of the ester group to **2** has important effect on the hydrogen bonding motif, quantitative binding studies in the mixed solvent of $CDCl_3$ and DMSO-d_6 (7%, v/v), a strong hydrogen bond acceptor solvent, were performed with the ^{1}H NMR dilution method,[11] which gave the K_{dim}'s to be ca. 780 and 850 M^{-1} for dimers **2·2** and **3·3**, respectively. These values are comparable within the experimental error of the ^{1}H NMR measurements.



The self-association behaviors of compounds **4** and **5** were then investigated in $CDCl_3$ solutions, also by the ^{1}H NMR dilution method. Important upfield chemical shifts ($\Delta\delta_{max}\approx0.11$ ppm) were observed for the NH signal of **4** upon dilution from 0.1 M to 0.4 mM. By fitting the data to a 1:1 binding isotherm, a K_{dim} of ca. 10 M^{-1} was observed for dimer **4·4** with the proposed binding motif.[12]



More complicated changes of chemical shifts of the NH and aromatic proton signals were observed from the ^{1}H NMR dilution experiments of **5**. Representative data are presented in Figure 1. The signals had been assigned based on the 2D-COSY and NOESY experiments (see Scheme 3). All the NH signals were substantially downfield (>9.97 ppm), indicating that these protons were involved in strong hydrogen bonding. Upon dilution from 0.1 M to 0.4 mM, the signals of both NH-1 ($\Delta\delta_{max}\approx1.58$ ppm) and NH-2 ($\Delta\delta_{max}\approx2.74$ ppm) shifted upfield remarkably, indicating

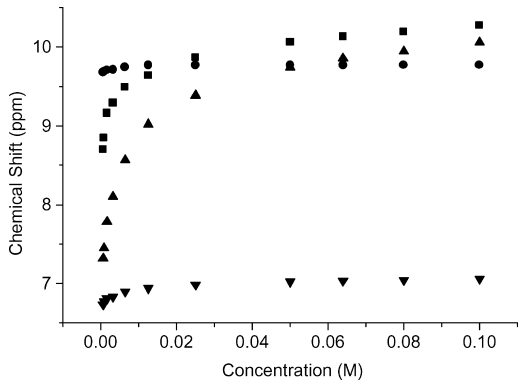
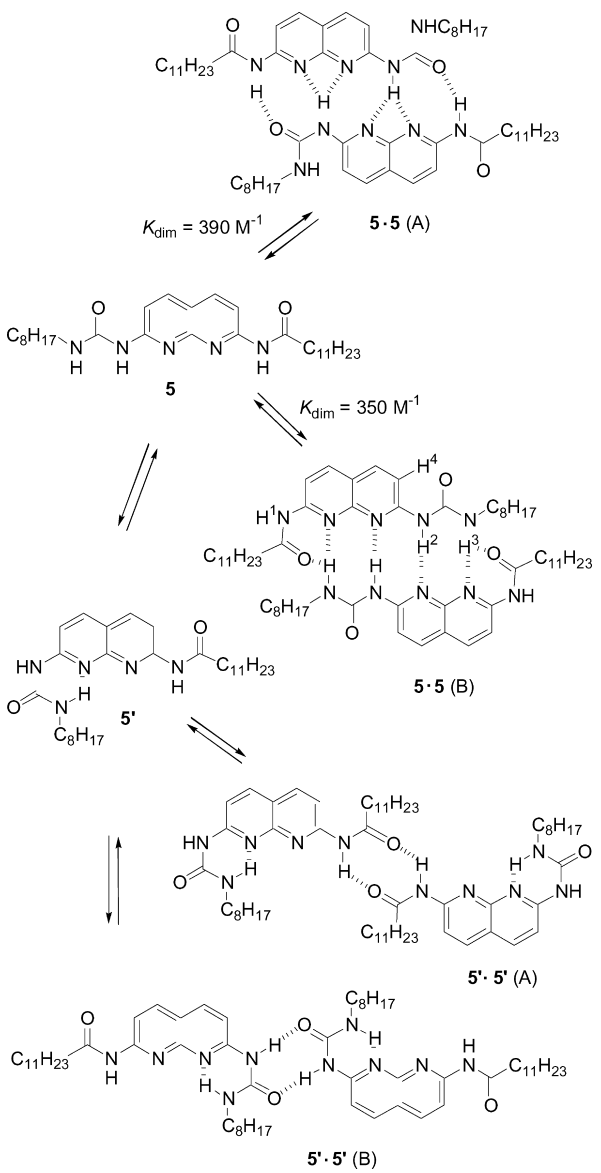


Figure 1. Chemical shift summaries of the dilution study of **5** in $CDCl_3$ from 0.1 M to 0.4 mM at 25 °C: NH-1 (■), NH-2 (▲), NH-3 (●), and H-4 (▼).



Scheme 3.

the formation of intramolecular hydrogen bonds. A fit of the data for NH-1 and NH-2 to a 1:1 binding isotherm gave a comparable K_{dim} of 390 (±40) M^{-1} and 350 (±30) M^{-1}, respectively. Both values are 20 times more than that of doubly hydrogen bonded dimer **4·4** and that of a pyridine-derived urea dimer (K_{dim}=16 M^{-1}),[3f] respectively. Therefore, obviously these binding constants could not be attributed to homodimers **5′·5′** (A) or **5′·5′** (B) (Scheme 3). We propose the formation of two tri-center multiply hydrogen bonded dimers **5·5** (A) and **5·5** (B) (Scheme 3) for the binding constants. Further evidence to support dimer **5·5** came from the fact that H-4 signal of the naphthyridine unit shifted upfield remarkably ($\Delta\delta_{max}$≈0.34 ppm, Figure 1) upon dilution, whereas the signals of other aromatic protons did not exhibit similar concentration dependence ($\Delta\delta_{max}$<0.04 ppm). This observation was consistent with the formation of dimer **5·5** since, in this dimer, H-4 was forced into the anisotropic deshielding area of the urea carbonyl group. The signal of the NH-3 proton was nearly concentration-independent ($\Delta\delta_{max}$≈0.09 ppm), implying that strong hydrogen bonding was always formed for this proton within the concentration range investigated, which could be reasonably attributed to an equilibrium between dimers **5·5** (A) and **5·5** (B) and folded monomer **5′**, which possesses an intramolecular hydrogen bond. Upon dilution, the dimers dissociated gradually into monomer **5′**, leading to upfield chemical shifting of the signals of both NH-1 and NH-2 but not that of NH-3.

Addition of 1 equiv. of **4** to a solution of **2** or **3** in $CDCl_3$ caused the highly stable homodimers **2·2** and **3·3** to fully dissociate and exclusively led to the formation of new complexes **2′·4** and **3′·4**, respectively, as evidenced by ^{1}H NMR spectra.[13] Partial ^{1}H NMR spectra of **2**, **4** and 1:1 mixture solution of **2** and **4** in $CDCl_3$ are presented in Figure 2. The amide proton signal of **4** shifted downfield ($\Delta\delta$ 3.05 ppm) substantially as a result of strong binding to **2**. The self-complementary 4[1*H*]-pyrimidinone conformer **2** isomerized completely to a non-complementary 4[3*H*]-pyrimidinone conformer **2′**. The latter possesses an ADDA quadruple hydrogen bond assay, which is complementary to the ADDA array in compound **4**.[14] The structure of the 4[3*H*]-pyrimidinone skeleton in **2′** was determined by 2D-NOESY technique, which revealed important enhancement of the heterocycle-linked methyl proton signal when irradiating the octyl-linked NH-3 proton. Pronounced intermolecular NOEs were also observed between NH-1 and NH-2 in **2′** and NH in **4**, supporting the complementary binding motif in heterodimer **2′·4**. Upon cooling or heating, all the NH signals moved noticeably, but no further splitting was observed, indicating that no new form of isomeric dimers were generated.

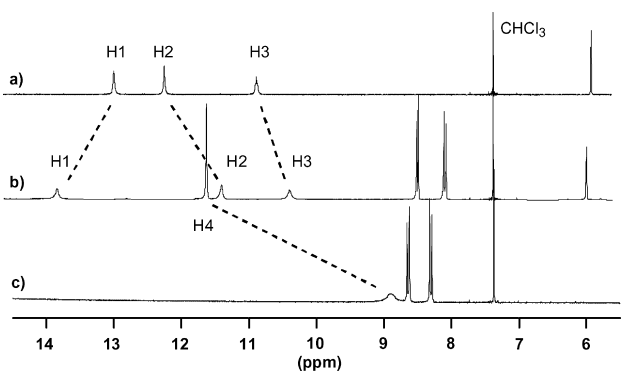
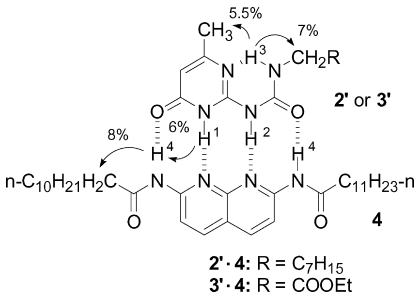


Figure 2. Partial ^{1}H NMR (300 MHz, 10 mM) of (a) **2**, (b) **2**+**4** (1:1), and (c) **4** in $CDCl_3$ at 25 °C.



Obviously it was impossible to determine the binding constant of **2′·4** in pure $CDCl_3$ with the ^1H NMR method, a quantitative binding study was performed in $CDCl_3$/DMSO-d_6 (7%, v/v). Upon dilution of the 1:1 mixture solution of **2** and **4** from 0.1 M to 0.2 mM, the NH signal of **4** moved upfield substantially (Fig. 3). The chemical shift data fit well to a 1:1 binding isotherm, giving a K_{dim}=1.3 (±0.17)×10^4 M^{-1}, which is substantially larger than that of homodimers **2·2** or **3·3**. By using the same principle, K_{dim} for **3′·4** in $CDCl_3$/DMSO-d_6 (7%, v/v) was also obtained to be 1.5 (±0.17)×10^4 M^{-1}, which is comparable to that of **2′·4**.

The binding behavior of **5** to **2** and **3** was then investigated. Adding 1 equiv. of **5** to **2** could also induce homodimer **2·2** to dissociate and generate the new heterodimer **2·5**. However, the dissociation of **2·2** was not exclusive and ca. 15% of **2** still existed as homodimer, as revealed by the ^1H NMR spectrum (Fig. 4(b)). The ratio of the dimers had been determined based on the integrating intensity of NH signals in the two tautomers of **2**. The DAAD tautomer of **2** in the new complex had been referred according to the NOESY experiment and also by comparing it with that of heterodimer **2′·4**. The signals of homodimer **2·2** could be assigned by changing the relative ratio of the two molecules. Very broad signals were exhibited for all the NH protons of **5**, which we attributed to the formation of two isomeric heterodimers **2′·5** (A) and **2′·5** (B) as a result of the unsymmetric structural feature of the two monomers. The fact that homodimer **2·2** exhibited sharp peaks for its NH's indicates that the protomeric isomerization between **2** and **2′** is slow on the NMR time scale. The existence of two isomeric heterodimers A and B had been proved by temperature variable ^1H NMR experiments. For example,

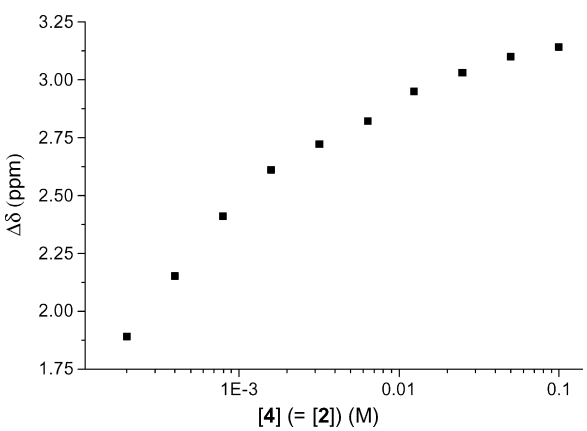


Figure 3. Plot of Δδ of NH signal of **4** upon dilution of the 1:1 mixture solution of **2** and **4** (0.1 M to 0.2 mM) in $CDCl_3$/DMSO-d_6 (7%, v/v) at 25 °C.

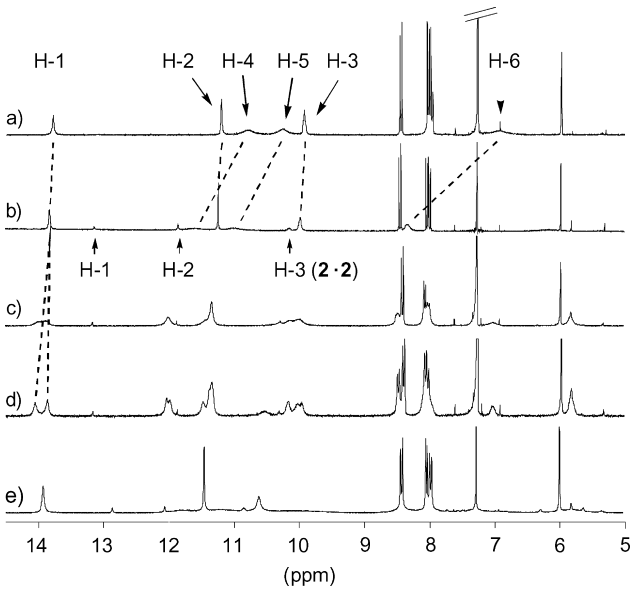
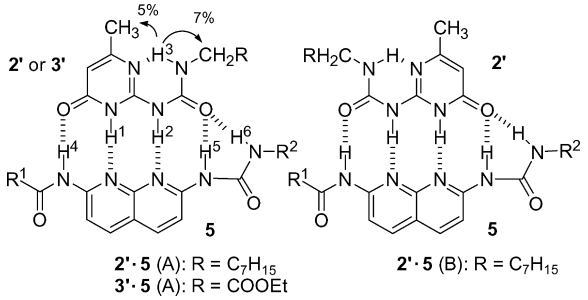


Figure 4. Partial ^1H NMR spectra (300 MHz) of a solution of **3** and **5** (1:1, 4.0 mM) in $CDCl_3$ at 50 °C (a), 25 °C (b), −30 °C (c) and −40 °C (d) and a solution of **3** and **5** (1:1, 4.0 mM) at 25 °C.

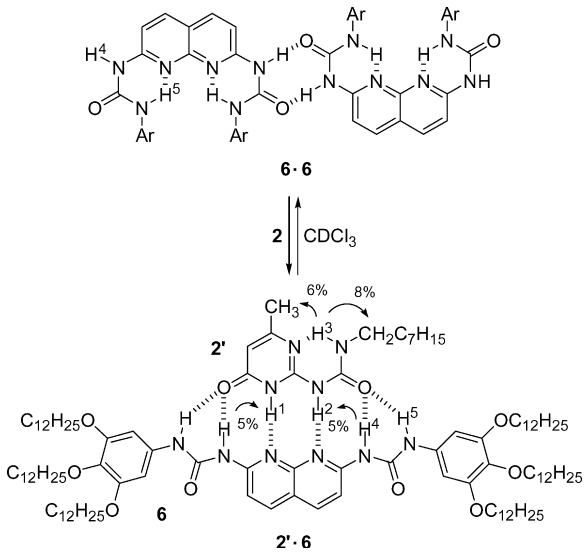
increasing the solution temperature to 50 °C led to pronouncedly sharpening of the NH signals (Fig. 4(a)), suggesting an increased exchange process between dimers A and B, whereas reducing the solution temperature to −40 °C induced the NH-1 to split (Fig. 4(d)), clearly indicating that the two isomers transformed into each other very slowly on the NMR time scale. The value of the corresponding free energy of exchange Δ*G* was determined to be ca. 9.5 kJ/mol based on the coalescence method.[15] Reducing temperature also facilitated the formation of heterodimers. Thus, at −40 °C, ca. 92% (based on the integrating intensity of NH-1) of compound **2** existed in the form of heterodimers (Fig. 4(d)).



Similar ^1H NMR spectral pattern was exhibited for the solution of **3** and **5** in $CDCl_3$ (1:1, Fig. 4(e)), suggesting the formation of heterodimer **3·5** (in ca. 80% yield based on integrating intensity of **3** and **3′**) with the same DAAD-ADDA binding module as that of **2·5**. Adding DMSO-d_6 to the solution of the 1:1 mixtures of **3** and **5** in $CDCl_3$ also promoted the formation of heterodimers (ca. 90% of **3·5** formed in $CDCl_3$/DMSO-d_6 (7%, v/v)). Since the formations of both heterodimers **2·5** and **3·5** were not quantitative and the resolution of the NH signals of compound **5** was very low, the binding constants of these heterodimers in $CDCl_3$/DMSO-d_6 (7%, v/v) could not be determined by ^1H NMR titration or dilution method. Nevertheless, the comparison of the binding behavior of **4** and **5** to **2** or **3** in

$CDCl_3$ reveals that heterodimers **2·4** and **3·4** are obviously more stable than dimers **2·5** and **3·5**. This result can be reasonably ascribed to the larger self-binding ability of **5** relative to **4**.

Previously, Zimmerman et al. had reported that compound **6** folded completely and self-associated through a doubly hydrogen bonded motif with a K_{dim}=95 M^{-1} in $CDCl_3$, as shown in Scheme 4.[3f] To explore if this highly stable folding conformation could be broken to form new heterodimers, ^1H NMR spectroscopic studies were carried out for the solutions of the mixtures of **6** with **2** and **3** in $CDCl_3$. Representative spectra are provided in Figure 5. It was found that ca. 80% of folded **6** were unfolded (based on the integrating intensity of NH-1 of **6** or pyrimidone proton of **2**), to afford the six hydrogen bond-driven heterodimer **2′·6**. This result implies that the stability of dimer **2′·6** is comparable to that of dimer **2′·5** or **3′·5**. Assignments of the peaks and the ADDA binding motif of **2** were achieved



Scheme 4.

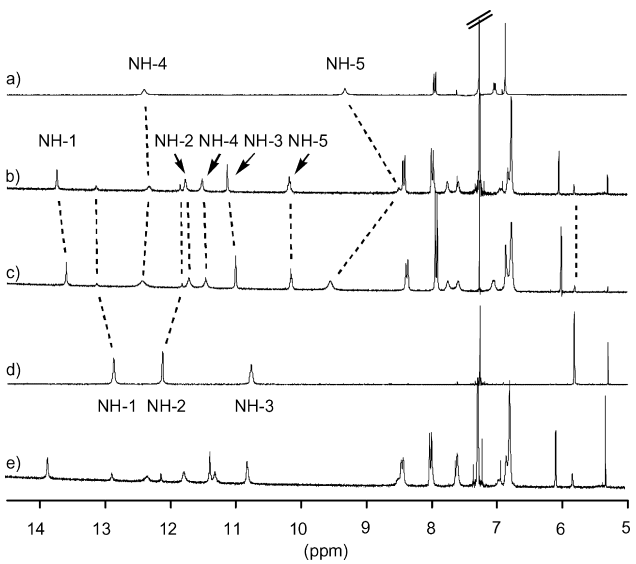


Figure 5. Partial ^1H NMR spectra (300 MHz) in $CDCl_3$ at 25 °C: (a) **6** (4.0 mM), (b) **2**+**6** (1:1, 4.0 mM), (c) **2** (4.0 mM)+**6** (8.0 mM), (d) **2** (4.0 mM), and (e) **3**+**6** (1:1, 4.0 mM).

by 2D-COSY and NOESY techniques (Scheme 4), together with changing the ratio of the monomers (Fig. 5(c)). As observed for the system of **2** and **5**, the remaining homodimer **2·2** also exhibited sharp NH peaks, suggesting that the transformation between the two tautomers of **2** in the two different dimers was slow on the NMR time scale. There are two points that support the formation of the intermolecular hydrogen bonds of NH-5 of **6** with the carbonyl oxygen of **2** in the complex (Scheme 4). First, this peak shifted downfield substantially ($\Delta\delta\approx$0.86 ppm) compared to that in pure **6** at the same concentration. Second, the formation of heterodimer **2′·6** required that the two intramolecular hydrogen bonds in folded **6** were broken, while formation of **2′·5** needed breaking of only one intramolecular hydrogen bond in folded **5**. Nevertheless, dimers **2′·6** and **2′·5** exhibited comparable stability, implying that additional hydrogen bonds, that is, those between NH-5 of **6** and the carbonyl oxygen of **2** were formed. Temperature variable ^1H NMR experiments for the 1:1 solution of **2** and **6** in $CDCl_3$ (4.0 mM, 50 to −40 °C) revealed no new peaks, implying that no new kind of dimers were formed.

Similar ^1H NMR spectral pattern was observed for the system of 1:1 mixtures solution of **3** and **6** (Fig. 5(e)) in $CDCl_3$. The result suggested that the heterodimer **3·6** with the structure similar to that of **2′·6** was also formed (in ca. 82% yield based on ^1H NMR integrating intensity). Attempt to determine the binding constants of both heterodimers in $CDCl_3$/DMSO-d_6 (7%, v/v) with the ^1H NMR dilution method was proved impossible due to rapidly reduced resolution at lowered concentrations.

3. Conclusion

We have reported the self-assembly and characterizations of a new series of multiply hydrogen-bonded heterodimers based on readily available ureidopyrimidones and 2,7-diamino-1,6-naphthyridine amides and ureas. New tri-center hydrogen bonds and exchanging processes between geometrically isomeric dimers have been revealed in the new heterodimers. All the new heterodimers are substantially more stable than the AADD quadruply hydrogen-bonded homodimers reported by Meijer et al. The result demonstrates that the stability of the heterodimers from self-associated heterocyclic monomers is remarkably affected by the number of intermolecular hydrogen bonds formed and the number of intramolecular hydrogen bonds formed in the monomers. Careful consideration of a balance between increasing intermolecular and intramolecular hydrogen bonds are important for future design of new stable hydrogen bonded assemblies.

4. Experimental

4.1. General methods

Melting points are uncorrected. All reactions were carried out under an atmosphere of nitrogen. The ^1H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts

per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures.

4.1.1. 1-(6-Methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl)-3-octyl-urea (2). A suspension of 2-amino-4-hydroxy-6-methylpyrimidine **7** (0.50 g, 0.40 mmol) and octyl isocyanate **8a** (0.62 g, 0.40 mmol) in THF (120 mL) was heated at 90 °C for 48 h. After work-up, the crude product was purified by column chromatography (dichloromethane/methanol 10:1) to afford compound **2** (1.08 g, 97%) as a white solid. Mp 171–173 °C. ^{1}H NMR: δ 0.86 (t, J=6.6 Hz, 3H), 1.25–1.30 (m, 10H), 1.54–1.61 (m, 2H), 2.22 (s, 3H), 3.20–3.26 (m, 2H), 5.81 (s, 1H), 10.13 (s, 1H, NH), 11.85 (s, 1H, NH), 13.14 (s, 1H, NH). MS (EI) *m/z*: 280 [M$^+$]. Anal. calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.84; H, 8.60; N, 19.97.

4.1.2. [3-(6-Methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl)-ureido]-acetic acid ethyl ester (3). A mixture of compound **7** (0.50 g, 4.00 mmol) and ethyl 2-isocyanoglycinate **8b**[16] (0.50 g, 3.91 mmol) in dried pyridine (20 mL) was stirred at 90 °C for 12 h. Then, the solvent was removed under reduced pressure. The resulting residue was washed with ether thoroughly to give a white solid, which was subjected to flash chromatography (dichloromethane/methanol, 10:1) to give compound **3** as a white solid (0.77 g, 78%). Mp 197–199 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J=7.6 Hz, 3H), 2.22 (s, 3H), 3.99 (d, J=7.6 Hz, 2H), 4.12–4.25 (m, 2H), 5.82 (s, 1H), 10.76 (s, 1H), 12.13 (s, 1H), 12.87 (s, 1H). MS (EI) *m/z*: 254 [M$^+$]. Anal. calcd for $C_{10}H_{14}N_4O_4$: C 47.24, H 5.55, N 22.03. Found: C 47.17, H 5.50, N 22.26.

4.1.3. Dodecanoic acid (7-dodecanoylamino-[1,8]naphthyridin-2-yl)-amide (4). To a stirred suspension of 2,7-diamino-1,8-naphthyridine **9** (1.60 g, 10.0 mmol) in chloroform (200 mL) were added triethylamine (5 mL), *N*,*N*′-dimethyl-4-aminopyridine (DMAP, 61 mg, 5%), and lauroyl chloride **10** (5.48 g, 25.0 mmol), respectively. The mixture was heated under reflux for 72 h. Upon cooling to room temperature, the solid was filtrated off and washed with chloroform (50 mL). The combined organic phase was washed with dilute aqueous hydrochloride solution (1 N, 2×50 mL), aqueous sodium carbonate solution (1 N, 2×50 mL), water (30 mL), brine (50 mL), and dried over magnesium sulfate. After the solvent was removed in vacuo, the resulting residue was purified by column chromatography (dichloromethane/ethyl acetate 5:1). The title compound was obtained as a colorless solid in 75% yield. Mp 130–132 °C; ^{1}H NMR ($CDCl_3$): δ 0.89 (m, 3H), 1.42–1.20 (m, 16H), 1.75 (m, 4H), 2.43 (t, J=6.8 Hz, 4H), 8.15 (d, J=6.1 Hz, 2H), 8.17 (s, 2H), 8.42 (d, J=6.1 Hz, 2H). MS (FAB) *m/z*: 525 [M$^+$ +H]. Anal. calcd for $C_{32}H_{52}N_4O_2$: C 73.24, H 9.99, N 10.68. Found: C 73.15, H 10.07, N 10.75.

4.1.4. Dodecanoic acid (7-amino-[1,8]naphthyridin-2-yl)-amide (11). To a stirred solution of compound **4** (0.80 g, 1.60 mmol) in tetrahydrofuran (80 mL) was added sodium hydroxide (64.0 mg, 1.60 mmol). The mixture was heated under reflux for 6 h. Then, the solvent was removed under reduced pressure. The resulting residue was triturated with dichloromethane (400 mL) and the organic phase was washed with water (50 mL×2), saturated brine solution (50 mL), and dried over sodium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (dichloromethane/ethyl acetate 5:1), to afford compound **11** (0.23 g, 40%) as a white solid and un-reacted compound **4** (0.32 g, 40%). Compound **11**. Mp 140–141 °C. ^{1}H NMR: δ 0.87 (t, J=6.3 Hz, 3H), 1.25–1.37 (m, 10H), 1.68–1.77 (m, 2H), 2.45 (t, J=7.5 Hz, 2H), 5.33 (s, 2H, NH_2), 6.66 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 8.20 (d, J=8.7 Hz, 1H), 8.28 (s, 1H, NH). MS (EI) *m/z*: 342 [M$^+$]. Anal. calcd for $C_{20}H_{30}N_4O$: C, 70.14; H, 8.82; N, 16.36. Found: C, 69.95; H, 8.91; N, 16.15.

4.1.5. Dodecanoic acid [7-(3-octyl-ureido)-[1,8]naphthyridin-2-yl]-amide (5). A suspension of compounds **11** (0.14 g, 0.40 mmol) and **8a** (0.12 g, 0.80 mmol) in tetrahydrofuran (50 mL) was heated under reflux for 6 h. The solvent was then removed under reduced pressure. The resulting residue was washed with ether thoroughly and then purified by column chromatography (dichloromethane/ethyl acetate 5:1), to afford compound **5** (0.20 g, 98%) as a white solid. Mp 166–167 °C. ^{1}H NMR: δ 0.83–0.89 (m, 6H), 1.24–1.35 (m, 24H), 1.60–1.76 (m, 6H), 2.45 (t, J=7.8 Hz, 2H), 3.35–3.40 (m, 2H), 6.96 (d, J=8.7 Hz, 1H), 7.93 (d, J=8.7 Hz, 1H), 8.04 (d, J=8.7 Hz, 1H), 8.38 (d, J=8.7 Hz, 1H), 8.77(s, 1H, NH), 9.12 (s, 1H, NH), 9.75 (s, 1H, NH). MS (EI) *m/z*: 497 [M$^+$]. Anal. calcd for $C_{29}H_{47}N_5O_2$: C, 69.98; H, 9.52; N, 14.07. Found: C, 70.02; H, 9.63; N, 14.01.

4.1.6. 1-(3,4,5-Tris-dodecyloxy-phenyl)-3-{7-[3-(3,4,5-tris-dodecyloxy-phenyl)-ureido]-[1,8]naphthyridin-2-yl}-urea (6). A solution of 3,4,5-tris-dodecyloxy-benzoyl azide[3f,17] (1.0 g, 1.33 mmol) in 20 mL of toluene was heated at 100 °C for 5 h. The solution was cooled and the solvent was removed under reduced pressure to afford the corresponding isocyanate, which was used in the next step without further purification. The above isocyanate (0.50 g, 0.75 mmol), naphthyridine **9** (47 mg, 0.35 mmol), and triethylamine (1 mL) were added to DMF (5 mL) with stirring at room temperature. The mixture was heated at 90 °C for 12 h. The solvent was then distilled under reduced pressure and the residue was triturated with chloroform (100 mL). After work-up, the crude product was purified by column chromatography (dichloromethane/methanol 20:1) to afford compound **6** (0.21 g, 40%) as a yellow powder. Mp >225 °C [223 °C[3f]]. ^{1}H NMR ($CDCl_3$): δ 0.80–0.83 (m, 18H), 1.30–1.33 (m, 104H), 1.48–1.51 (m, 4H), 1.68–1.72 (m, 12H), 3.68 (t, J=5.5 Hz, 8H), 3.92 (t, J=6.5 Hz, 4H), 6.89 (s, 4H), 7.08 (d, J=8.0 Hz, 2H), 7.97 (d, J=8.0 Hz, 2H), 9.82 (s, 2H), 12.50 (s, 2H). MS (maldi-tof) *m/z*: 1506 [M$^+$+H].

4.2. Binding studies

All ^{1}H NMR binding studies were carried out at 25 °C. Chloroform-*d* used in binding studies was passed through a short column of dry, activated basic alumina prior to use. DMSO-d_6 was used as provided without further purification. Volumetric flasks and syringes used in preparing solutions

were washed with dried dichloromethane and dried in vacuum before use. Samples (usually 0.6 mL) were prepared from stock solutions, transferred to the NMR tubes and diluted accordingly with syringes. For one series, usually 10–20 samples were prepared and binding constants reported are the average of two or three experiments, which were obtained by fitting chemical shift change data to 1:1 binding isotherms with standard non-linear curve-fitting procedures.[11] The non-linear equations were derived from mass-balance equations, the relationship between the concentrations of free and complexed sample and the weighted chemical shifts under the condition of rapid exchange.[11]

Acknowledgements

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12. A K_{dim} of less than 5 M^{-1} had been reported for a molecule with similar structure, see Ref. 3f.
13. Complex **2′·4** had been mentioned, without detailed characterization or quantitative binding study, in a previous paper (Ref. 8).
14. An example of complexation-induced isomerization has been reported for 3*H*-pyrido-(2,3-*d*)pyrimidin-4-one-2-urea derivatives, see Ref. 3d.
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An auxiliary induced asymmetric synthesis of functionalized cyclobutanes by means of catalytic (2+2)-cycloaddition reaction

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Abstract—A new entry to optically active hydroxycyclobutanes is described. Treatment of silyl enol ether and (−)-8-phenylmenthyl acrylate in the presence of a catalytic amount of $EtAlCl_2$ affords enantiomerically enriched multi-substituted cyclobutane compounds in a good yield and diastereofacial selectivity.

1. Introduction

Previous work in our laboratory has demonstrated $EtAlCl_2$ catalyzed (2+2)-cycloaddition of silyl enol ether with α,β-unsaturated ester.[1] This process concisely provides siloxycyclobutane carboxylate in a high yield with an excellent stereoselectivity. Further studies revealed the reaction proceeds via a stepwise pathway, like a sequential Michael addition and aldol reaction. Chiral substances possessing a hydroxycyclobutane skeleton are found often in nature (Fig. 1)[2] and serve as key intermediates[3] in routes to biologically and medicinally important synthetic targets. However, stereocontrolled construction of the multi-substituted cyclobutanes remains a difficult task in preparative organic chemistry.[4–9] Recently we have demonstrated that chiral auxiliary such as phenylmenthol effectively induces new asymmetric centers with excellent diastereoselectivity in case of the intramolecular Michael–aldol reaction using a stoichiometric amount of trimethylsilyl iodide and hexamethyldisilazane.[5] Here we wish to report asymmetric catalytic intermolecular (2+2)-cycloaddition with 8-phenylmenthyl acrylate to afford enantiomerically enriched cyclobutanes.

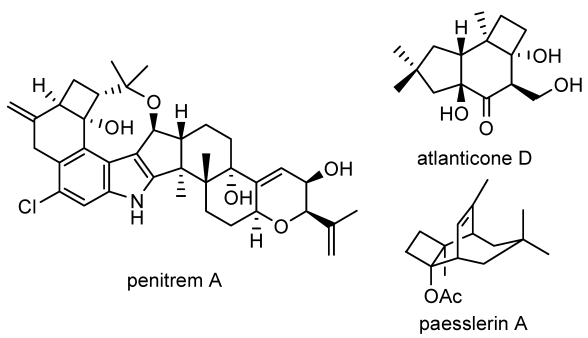

Figure 1. Examples of natural substances possessing functionalized cyclobutane ring.

2. Results and discussions

2.1. Asymmetric (2+2)-cycloaddition

Based on the results of our previous studies,[1] reaction was conducted using 1 equiv. of (−)-8-phenylmenthyl acrylate (**2a**) and 1.2 equiv. of silyl enol ether **1** in the presence of 20 mol% of $EtAlCl_2$ catalyst at −78 °C in CH_2Cl_2 (Scheme 1). Theoretically, eight disatereomeric isomers could be produced by this reaction since three stereogenic centers are generated on cyclobutane ring. The results of the (2+2)-cycloaddtion are summarized in Table 1. In the reaction of *t*-butyldimethylsiloxy-1-cyclohexene (**1a**) with **2a**, production of two diastereomers *trans*-**3a** and *cis*-**3a** in 51 and 33% yield, respectively, was observed (entry 1). These diastereomeic products can be separated by silica gel chromatography. Both *trans*-**3a** and *cis*-**3a** were analytically pure stereoisomeric compounds in ^1H and ^{13}C NMR spectroscopies. Except for siloxyethylene **1i** (entry 9), the resulting cyclobutane adducts were obtained in moderate to high yield from cyclic and acyclic substrates possessing TBS or TIPS moiety. However, only small amounts of cycloadducts were observed in the reaction of less stable TES enol ether **1c** (entry 3). The low yield of cycloadducts **3** was originated from decomposition of silyl enol ether into the corresponding ketone or dimeric aldol-adduct **4** (entries

Keywords: Hydroxycyclobutanes; (2+2)-Cycloadditions; Stereoselectivity; Chiral auxiliary; Asymmetric induction.
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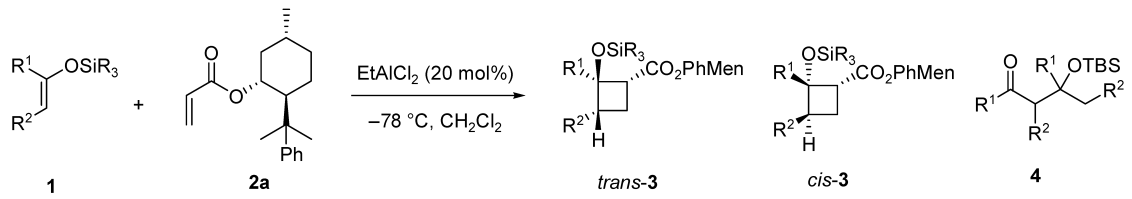


Scheme 1.

3, 4, 5 and 9). Interestingly, *trans*-**3** was exclusively furnished in an excellent yield using TBS enol ethers **1f** or **1k** as a substrate (entries 6 and 11).

To our surprise, it was observed a TIPS enol ether gives cyclobutane **3** with the higher *cis*-selectivity compared with the corresponding TBS enol ether (entry 1 vs. 2, 4 vs. 5, or 6 vs. 7). The selectivity in this asymmetric reaction is a complementary result against the one using achiral substrates.[1] We have reported that the *trans*-selectivity is enhanced in the reaction with achiral acrylate when more sterically bulky silyl enol ethers are employed as substrates. It has been proved no decomposition nor isomerization of cyclobutane products occurs under the (2+2)-cycloaddition conditions and work-up process. Although the detailed conformation of the transition state in this (2+2)-cycloaddition remains to be clarified, we assume an additional steric and/or stereoelectronic effect between triisopropylsilyl group and phenylmenthyl moiety causes the preferred production of *cis*-isomer.

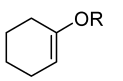
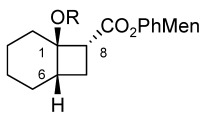
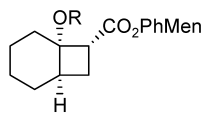
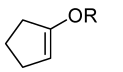
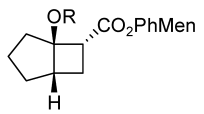
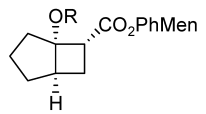
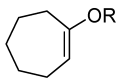
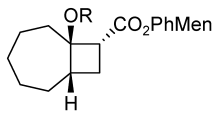
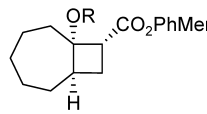
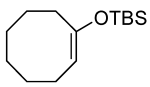
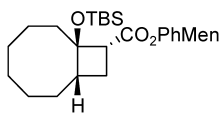
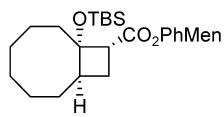
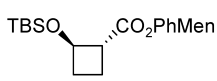
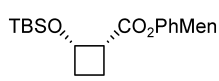
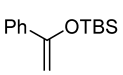
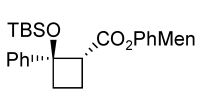
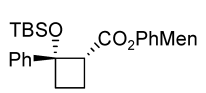
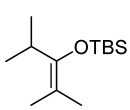
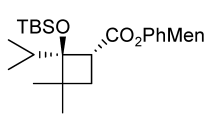
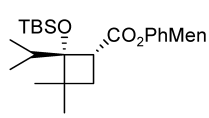
Phenylmenthyl methacrylate (**2b**) also affords (2+2)-adduct *trans*-**3l** in 42% yield along with *cis*-**3l** (3% yield) by the reaction with **1f** (Scheme 2). On the contrary, crotonate **2c** furnished cycloadducts in only 6% yield as a mixture of two diastereomers even using 100 mol% of a Lewis acid at the elevated temperature.

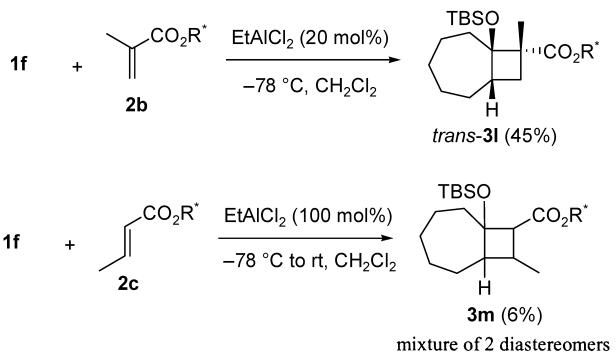
2.2. Stereochemical study of (2+2)-cycloaddition product

The absolute configuration of *trans*-**3a**, whose single crystals (colorless prisms) were prepared from a mixed solvent system of AcOH and MeOH, was determined by X-ray crystallography (Fig. 2). It reveals that *trans*-**3a** has the (1*R*,6*S*,8*R*)-bicyclo[4.2.0]octane skeleton.

The stereochemistry of *cis*-**3a** was determined by chemical transformation as shown in Scheme 3. Both diastereomers *trans*- and *cis*-**3a** were, separately, reduced with DIBAL-H into alcohols *trans*- and *cis*-**5a**, respectively. Since those

Table 1. Asymmetric (2+2)-cycloaddion reaction

Entry	Silyl enol ether		Product			
			trans-**3**	Yield (de) (%)	*cis*-**3**	Yield (de) (%)
1		**1a** (R=TBS)		51 (>99)		33 (>99)
2		**1b** (R=TIPS)		23 (>99)		41 (>99)
3		**1c** (R=TES)		5 (>99)		1 (>99)
4		**1d** (R=TBS)		28 (>99)		5 (>99)
5		**1e** (R=TIPS)		26 (>99)		16 (>99)
6		**1f** (R=TBS)		89 (>99)		0 (—)
7		**1g** (R=TIPS)		54 (>99)		16 (>99)
8		**1h**		74 (>99)		10 (>99)
9		**1i**		0 (—)		0 (—)
10		**1j**		62 (>99)		25 (>99)
11		**1k**		91 (>99)		0 (—)



Scheme 2. R*=8-phenylmenthyl.

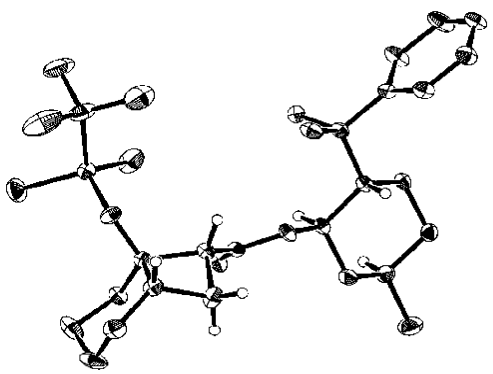
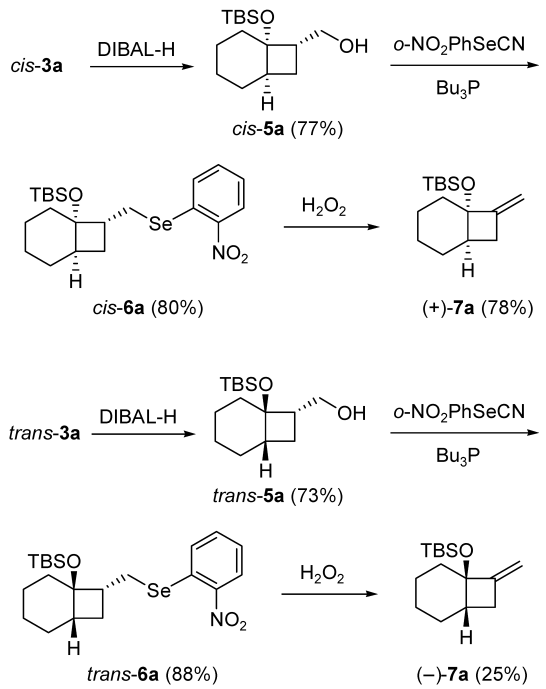


Figure 2. ORTEP drawing of *trans*-**3a**.



Scheme 3.

spectral data are not identical, the stereochemistry of cyclobutane skeleton of *cis*-**3a** corresponds to (1*R*,6*S*,8*S*) or its enantiomeric (1*S*,6*R*,8*R*). In order to remove the chirality at C(8) position, *cis*-**5a** was conducted to Grieco's dehydration reaction.[10] Namely, by treatment with *o*-nitrophenylselenyl cyanide in the presence of tributylphosphine *cis*-**5a** was transformed into selenoether *cis*-**6a**. Exposure of *cis*-**6a** under the oxidation conditions furnished *exo*-olefine (+)-**7a**, whose specific rotation ($[\alpha]_D$ in $CHCl_3$) is +10.4. In accordance with the above procedure, *trans*-**5a** was converted into (−)-**7a** ($[\alpha]_D$=−9.8 in $CHCl_3$), whose spectral data except for chiroptical sense were consistent with (+)-**7a**. Consequently, it has been made clear that *cis*-**3a** possesses the (1*S*,6*R*,8*R*)-bicyclo[4.2.0]octane framework.

The above stereochemical studies reveal that *trans*-**3a** and *cis*-**3a** possess the same (*R*)-configuration at the α-carbon of ester function. Thus, silyl enol ether **1a** would selectively approach to the enoate moiety from one side with complete diastereofacial recognition; the diastereofacial selection favoring **3a** is controlled by π-stacking interaction of the aromatic ring of phenylmenthol moiety (Fig. 3).[11] When TBS enol ether **3a** was reacted with phenylisomenthyl acrylate (**2d**),[12] which would not be expected for good conformational fixation by π-stacking interaction, under the same conditions, non-selective formation of four considerable diastereomers was observed (Scheme 4). It has been, thus, made clear that 8-phenylmenthyl moiety works as an effective chiral auxiliary in the $EtAlCl_2$ catalyzed (2+2)-cycloaddition of silyl enol ether with α,β-unsaturated ester.

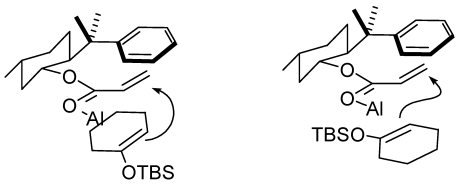
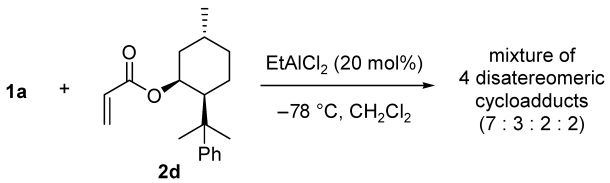


Figure 3. Proposed transition state models for the production of *trans*-**3a** (left) and *cis*-**3a** (right).



Scheme 4.

For the bicyclic compounds, *trans*- and *cis*-**3b**–**h**,**l**, their relative configurations around the cyclobutane ring were assigned based on analogy in ^1H and ^{13}C NMR spectroscopies. On the other hand, the relative stereochemistries of *trans*-**3j**, *cis*-**3j** and *trans*-**3k** were confirmed by NOESY experiment after transformation into the corresponding alcohols *trans*-**5j**, *cis*-**5j** and *trans*-**5k**, respectively (Fig. 4). The absolute configuration of all the product was presumed based on the mechanism described as above.

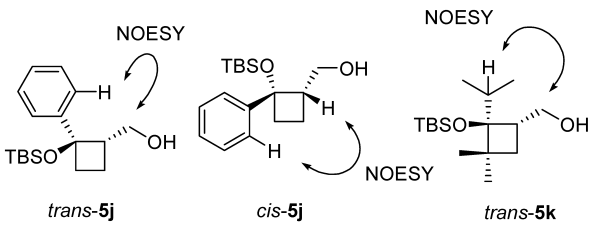


Figure 4.

3. Conclusion

In summary, we have developed a versatile, convenient and stereoselective method for the formation of optically active hydroxycyclobutanes using $EtAlCl_2$ catalyzed (2+2)-cycloaddition reaction. The reaction provides optically active multi-substituted cyclobutane compounds from readily available silyl enol ethers and 8-phenylmenthyl acrylate. The relative and absolute stereochemistries of cyclobutane products were assigned on the basis of X-ray crystallographic analysis and their chemical transformation.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere. Anhydrous THF and CH_2Cl_2 were purchased from the Kanto Chemical Co., Inc. Unless otherwise described, other materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried over $MgSO_4$ or Na_2SO_4, filtered and concentrated under reduced pressure using an evaporator. Column chromatography was performed on Merck silica gel 60 N (230–400 mesh), and flash column chromatography was performed on Cica silica gel 60 (spherical/40–100 μm). Reactions and chromatography fractions were analysed employing precoated silica gel plate (Merck silica gel $60F_{254}$). All melting points were determined on Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured on JASCO IR Report-100 spectrophotometer or Shimadzu FTIR-8300 spectrometer. The ^1H and ^{13}C NMR spectra were recorded at Varian Gemini 2000 (300 and 75 MHz), JEOL AL 400 (400 and 100 MHz) as $CDCl_3$ solutions, respectively, and were reported in ppm downfield from TMS (δ=0) for the ^1H NMR and relative to the central $CDCl_3$ resonance (δ=77.00) for the ^{13}C NMR. Mass spectra were recorded on JEOL DX-303 or AX-500 spectrometer. Elemental analyses were performed on Yanagimoto MT-3 or YANACO CHN CORDER MT-6, and the results (C, H) were within±0.4% of theoretical values.

4.2. General procedure for (2+2)-cycloaddition reaction

To a solution of phenylmenthyl ester **2** (0.23 mmol) and silyl enol ether **1** (0.28 mmol) in CH_2Cl_2 (2 mL) was slowly added $EtAlCl_2$ (0. 46 μmol; 0.9 M solution in hexane) at −78 °C. After being stirred for 50 min, the resulting mixture was quenched with sat. $NaHCO_3$, and then was extracted with Et_2O three times. The organic layer was washed with brine, dried and concentrated. The residue was purified by column chromatography on silica gel with 2% Et_2O/hexane to give **3**.

4.2.1. (1*R*,6*S*,8*R*)-1-(*tert*-Butyldimethylsiloxy)-8-[(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]bicyclo[4.2.0]octane (*trans*-3a). Colorless prisms, mp 108–110 °C (from AcOEt–MeOH); $[\alpha]_D^{27}$ (*c* 0.94, $CHCl_3$) −36.6; IR (KBr) 2927, 2856, 1717, 1249, 1184, 1101, 836, 768, 699, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 4H), 7.21–7.12 (m, 1H), 4.83 (ddd, 1H, *J*=4.4, 10.7, 10.7 Hz), 2.77 (dd, 1H, *J*=8.8, 9.9 Hz), 2.18–1.82 (m, 3H), 1.76–1.16 (m, 10H), 1.32 (s, 3H), 1.22 (s, 3H), 1.08–0.72 (m, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.4, 128.0, 125.6, 125.2, 76.4, 74.3, 50.2, 41.9, 40.5, 39.9, 34.5, 32.1, 31.3, 27.2, 26.8, 26.0, 25.6, 23.4, 21.7, 21.4, 20.3, 19.2, 17.9, −2.92, −2.98; LRMS *m/z* 441 (M^+−57). Anal. calcd for $C_{31}H_{50}O_3Si$: C, 74.64; H, 10.10, found C, 74.60; H, 10.02.

4.2.2. (1*S*,6*R*,8*R*)-1-(*tert*-Butyldimethylsiloxy)-8-[(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]bicyclo[4.2.0]octane (*cis*-3a). Colorless oil; $[\alpha]_D^{28}$ (*c* 0.94, $CHCl_3$) −6.1; IR (neat) 2928, 2855, 1718, 1472, 1250, 1082, 835, 733, 699, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.21 (m, 4H), 7.19–7.11 (m, 1H), 4.86 (ddd, 1H, *J*=4.4, 10.7, 10.7 Hz), 2.73 (dd, 1H, *J*=7.6, 7.6 Hz), 2.20 (m, 1H), 2.08–1.81 (m, 4H), 1.63–0.74 (m, 17H), 1.34 (s, 3H), 1.22 (s, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.079 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.7, 127.9, 125.6, 125.1, 79.1, 74.0, 50.4, 46.9, 42.1, 39.9, 36.1, 34.5, 31.2, 28.9, 27.0, 26.8, 26.2, 25.9, 24.3, 22.8, 22.3, 21.6, 18.1, −2.28, −2.51; LRMS *m/z* 498 (M^+); HRMS calcd for $C_{31}H_{50}O_3Si$ 498.3529, found 498.3529.

4.2.3. (1*R*,6*S*,8*R*)-1-Triisopropylsiloxy-8-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[4.2.0]octane (*trans*-3b). Colorless prisms, mp 54–55 °C (from AcOEt–MeOH); $[\alpha]_D^{28}$ (*c* 0.50, $CHCl_3$) −38.0; IR (KBr) 2943, 2924, 2866, 1732, 1207, 1184, 1138, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.23 (m, 4H), 7.15–7.11 (m, 1H), 4.82 (ddd, 1H, *J*=10.7, 10.7, 4.4 Hz), 2.60 (dd, 1H, *J*=9.4, 9.4 Hz), 2.16–2.08 (m, 1H), 2.05–1.93 (m, 1H), 1.90–1.84 (m, 1H), 1.80–1.73 (m, 1H), 1.60–0.80 (m, 18H), 1.31 (s, 3H), 1.20 (s, 3H), 1.08–0.94 (m, 18H), 0.87–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 151.3, 127.8, 125.4, 125.0, 76.0, 74.3, 50.8, 50.3, 42.0, 41.0, 40.0, 34.6, 32.9, 31.4, 27.1, 27.0, 26.4, 23.5, 21.9, 21.6, 20.6, 19.1, 18.4, 13.3; LRMS *m/z* 540 (M^+). Anal. calcd for $C_{34}H_{56}O_3Si$: C, 75.50; H, 10.44, found C, 75.40; H, 10.37.

4.2.4. (1*S*,6*R*,8*R*)-1-Triisopropylsiloxy-8-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl] bicyclo[4.2.0]octane (*cis*-3b). Colorless oil; $[\alpha]_D^{28}$ (*c* 0.53, $CHCl_3$) −1.0; IR (neat) 2943, 2866, 1724, 1462, 1242, 1115, 1088, 413 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 4H), 7.15–7.11 (m, 1H), 4.85 (ddd, 1H, *J*=10.7, 10.7, 4.4 Hz), 2.78 (dd, 1H, *J*=8.5, 8.5 Hz), 2.24–2.17 (m, 1H), 2.04–1.96 (m, 4H), 1.69–0.81 (m, 17H), 1.30 (s, 3H), 1.22 (s, 3H), 1.05 (d, 18H, *J*=7.6 Hz), 0.90–0.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.5, 127.8, 125.4, 125.0, 80.7, 73.7, 50.4, 45.2, 42.2, 40.0, 35.3, 34.6, 31.3, 30.6, 27.1, 26.9, 26.8, 26.3, 23.5, 22.8, 21.8, 18.6, 18.2; LRMS *m/z* 540 (M^+). Anal. calcd for $C_{34}H_{56}O_3Si$: C, 75.50; H, 10.44, found C, 75.52; H, 10.39.

4.2.5. (1*R*,6*S*,8*R*)-1-Triethylsiloxy-8-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[4.2.0]octane (*trans*-3c). Pale yellow oil; $[\alpha]_D^{27}$ (*c* 0.54, $CHCl_3$) −47.1; IR (neat) 2953, 2928, 2874, 1715, 1238, 1186, 1101, 1078, 1018, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 4H), 7.17–7.12 (m, 1H), 4.80 (ddd, 1H, *J*=10.7, 10.7, 4.1 Hz), 2.59 (dd, 1H,

J=9.4, 9.4 Hz), 2.19–2.08 (m, 1H), 2.00–1.85 (m, 2H), 1.71–1.64 (m, 1H), 1.61–0.75 (m, 15H), 1.34 (s, 3H), 1.22 (s, 3H), 0.97 (t, 9H J=7.8 Hz), 0.64 (q, 6H, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 151.2, 127.8, 125.4, 125.0, 76.3, 74.5, 50.5, 50.4, 42.0, 40.7, 40.1, 34.6, 32.4, 31.4, 28.0, 27.1, 25.7, 23.5, 21.9, 21.5, 20.5, 19.1, 7.1, 6.2; LRMS m/z 498 (M^+); HRMS calcd for $C_{34}H_{56}O_3Si$, 498.3529, found 498.3564.

4.2.6. (1*S*,6*R*,8*R*)-1-Triethylsiloxy-8-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[4.2.0]octane (*cis*-3c). Colorless oil; $[\alpha]_D^{27}$ (c 0.58, $CHCl_3$) −3.1; IR (neat) 2951, 2936, 2874, 1715, 1182, 1161, 1084, 741, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 4H), 7.15–7.09 (m, 1H), 4.88 (ddd, 1H, J=4.0, 10.6, 10.6 Hz), 2.72 (dd, 1H, J=7.0, 7.0 Hz), 2.24–2.20 (m, 1H), 2.03–1.92 (m, 4H), 1.90–1.73 (m, 3H), 1.66–0.82 (m, 16H), 1.33 (s, 3H), 1.22 (s, 3H), 0.93 (t, 9H J=7.6 Hz), 0.65–0.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 151.5, 127.8, 125.4, 125.0, 78.4, 74.0, 50.5, 48.3, 42.1, 40.7, 40.0, 36.4, 34.7, 31.4, 28.0, 27.0, 26.4, 23.0, 22.7, 22.2, 21.8, 7.2, 6.6; LRMS m/z 498 (M^+); HRMS calcd for $C_{34}H_{56}O_3Si$, 498.3529, found 498.3518.

4.2.7. (1*R*,5*S*,7*R*)-1-*tert*-Butyldimethylsiloxy-7-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[3.2.0]heptane (*trans*-3d). Pale yellow oil; $[\alpha]_D^{29}$ (c 0.66, $CHCl_3$) −33.5; IR (neat) 2953, 2928, 2855, 1717, 1258, 1225, 1096, 837, 775, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.20 (m, 4H), 7.18–7.10 (m, 1H), 4.83 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.93 (dd, 1H, J=10.1, 10.1 Hz), 2.44–2.36 (m, 1H), 2.05–1.88 (m, 4H), 1.82–1.65 (m, 5H), 1.60–0.70 (m, 10H), 1.33 (s, 3H), 1.23 (s, 3H), 0.86 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 151.1, 127.8, 125.4, 125.1, 86.7, 74.5, 50.5, 49.0, 44.4, 42.0, 40.1, 37.6, 34.6, 31.4, 31.4, 27.9, 27.0, 25.8, 24.8, 21.9, 20.0, 17.9, −2.88, −2.95; LRMS m/z 484 (M^+). Anal. calcd for $C_{30}H_{48}O_3Si$: C, 74.33; H, 9.98, found C, 74.32; H, 9.83.

4.2.8. (1*S*,5*R*,7*R*)-1-*tert*-Butyldimethylsiloxy-7-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[3.2.0]heptane (*cis*-3d). Pale yellow oil; $[\alpha]_D^{29}$ (c 0.34, $CHCl_3$) −13.7; IR (neat) 2951, 2930, 2856, 1732, 1173, 1161, 1097, 905, 835, 775, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 4H), 7.18–7.10 (m, 1H), 4.78 (ddd, 1H, J=4.1, 10.5, 10.5 Hz), 2.77 (dd, 1H, J=8.3, 8.3 Hz), 2.54–2.46 (m, 1H), 2.45–2.34 (m, 1H), 2.18–2.08 (m, 1H), 1.87–1.75 (m, 5H), 1.60–0.70 (m, 12H), 1.38 (s, 3H), 1.25 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.5, 127.8, 125.5, 125.0, 86.2, 74.9, 50.6, 48.3, 43.1, 42.0, 41.6, 40.4, 34.7, 31.5, 31.3, 29.5, 27.2, 25.9, 24.0, 21.8, 21.8, 18.2, −2.47, −2.87; LRMS m/z 484 (M^+); HRMS calcd for $C_{30}H_{48}O_3Si$, 484.3373, found 484.3403.

4.2.9. (1*R*,5*S*,7*R*)-1-Triisopropylsiloxy-7-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[3.2.0]heptane (*trans*-3e). Pale yellow oil; $[\alpha]_D^{29}$ (c 1.83, $CHCl_3$) −30.5; IR (neat) 2951, 2889, 2866, 1719, 1223, 1194, 1121, 1105, 881, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (m, 4H), 7.18–7.10 (m, 1H), 4.84 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.98 (dd, 1H, J=10.0, 10.0 Hz), 2.46–2.36 (m, 1H), 2.11–1.86 (m, 3H), 1.81–1.66 (m, 4H), 1.60–0.75 (m, 12H), 1.32 (s, 3H), 1.22 (s, 3H), 1.06 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 151.2, 127.8, 125.4, 125.0, 86.7, 74.5, 50.5, 49.6, 44.8, 42.0, 40.1, 37.8, 34.6, 31.6, 31.4, 27.7, 25.9, 24.5, 21.9, 19.8, 18.3, 13.2; LRMS m/z 526 (M^+). Anal. calcd for $C_{33}H_{54}O_3Si$: C, 75.23; H, 10.33, found C, 75.42; H, 10.27.

4.2.10. (1*S*,5*R*,7*R*)-1-Triisopropylsiloxy-7-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[3.2.0]heptane (*cis*-3e). Colorless oil; $[\alpha]_D^{28}$ (c 1.01, $CHCl_3$) −11.1; IR (neat) 2947, 2866, 1732, 1231, 1163, 1103, 883, 700, 681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 4H), 7.16–7.08 (m, 1H), 4.84 (ddd, 1H, J=10.6, 10.6, 4.1 Hz), 2.75 (dd, 1H, J=8.5, 8.5 Hz), 2.48–2.38 (m, 1H), 2.35–2.20 (m, 1H), 2.11–2.02 (m, 1H), 2.00–1.90 (m, 1H), 1.90–1.67 (m, 4H), 1.67–0.74 (m, 12H), 1.34 (s, 3H), 1.22 (s, 3H), 1.05 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.4, 127.8, 125.4, 125.0, 86.6, 74.5, 50.6, 48.7, 43.8, 42.0, 41.6, 40.2, 34.6, 31.3, 28.2, 27.1, 25.2, 24.3, 22.0, 21.8, 18.4, 18.3, 13.5; LRMS m/z 526 (M^+); HRMS calcd for $C_{33}H_{54}O_3Si$, 526.3842, found 526.3888.

4.2.11. (1*R*,7*S*,9*R*)-1-*tert*-Butyldimethylsiloxy-9-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[5.2.0]nonane (*trans*-3f). Colorless prisms, mp 86–88 °C (from AcOEt–MeOH); $[\alpha]_D^{28}$ (c 0.54, $CHCl_3$) −31.4; IR (KBr) 2924, 2855, 1728, 1254, 1150, 1126, 1065, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.24 (m, 4H), 7.15–7.13 (m, 1H), 4.83 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.73 (dd, 1H, J=9.8, 9.8 Hz), 2.14 (m, 1H), 1.99 (m, 1H), 1.91–1.84 (m, 2H), 1.79–0.81 (m, 20H), 1.30 (s, 3H), 1.20 (s, 3H), 0.90 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.2, 127.8, 125.3, 125.0, 82.3, 74.4, 74.1, 50.3, 48.7, 46.7, 40.0, 34.7, 32.7, 31.4, 26.9, 26.7, 26.5, 26.1, 25.9, 23.7, 22.5, 22.0, 21.8, 18.2, −2.67, −2.84; LRMS m/z 455 (M^+−57). Anal. calcd for $C_{32}H_{52}O_3Si$: C, 74.94; H, 10.22, found C, 75.00; H, 10.11.

4.2.12. (1*R*,7*S*,9*R*)-1-Triisopropylsiloxy-9-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[5.2.0]nonane (*trans*-3g). Colorless needles, mp 87–88 °C (from AcOEt–MeOH); $[\alpha]_D^{28}$ (c 0.44, $CHCl_3$) −27.9; IR (KBr) 2926, 2866, 1728, 1460, 1252, 1225, 1205, 1192, 1130, 772, 700, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.23 (m, 4H), 7.15–7.10 (m, 1H), 4.84 (ddd, 1H, J=4.1, 10.5, 10.5 Hz), 2.76 (dd, 1H, J=10.0, 10.0 Hz), 2.25–2.17 (m, 1H), 2.04–1.97 (m, 1H), 1.90–0.81 (m, 22H), 1.29 (s, 3H), 1.19 (s, 3H), 1.10 (s, 18H), 0.88–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 151.3, 127.8, 125.3, 125.0, 82.3, 74.2, 50.3, 49.4, 47.1, 41.9, 40.0, 36.3, 34.6, 34.3, 33.6, 32.2, 31.4, 26.9, 26.7, 26.5, 23.7, 22.1, 21.9, 18.5, 13.4; LRMS m/z 554 (M^+). Anal. calcd for $C_{32}H_{52}O_3Si$: C, 74.94; H, 10.22, found C, 75.00; H, 10.11.

4.2.13. (1*S*,7*R*,9*R*)-1-Triisopropylsiloxy-9-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[5.2.0]nonane (*cis*-3g). Colorless oil; $[\alpha]_D^{28}$ (c 0.87, $CHCl_3$) −9.0; IR (neat) 2924, 2866, 1722, 1454, 1240, 1092, 762, 700, 677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 4H), 7.15–7.10 (m, 1H), 4.84 (ddd, 1H,

J=4.4, 10.5, 10.5 Hz), 2.87 (dd, 1H, J=8.8, 8.8 Hz), 2.41 (br, 1H), 2.12 (dd, 1H, J=10.5, 20.0 Hz), 2.04–1.94 (m, 1H), 1.92–1.85 (m, 1H), 1.80–1.71 (m, 1H), 1.70–0.80 (m, 19H), 1.32 (s, 3H), 1.20 (s, 3H), 1.05 (s, 18H), 0.86–0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.5, 127.8, 125.4, 125.0, 84.3, 73.9, 50.5, 46.6, 45.9, 42.1, 40.9, 40.0, 34.6, 31.8, 31.3, 30.2, 26.9, 26.8, 26.6, 25.6, 24.9, 21.8, 21.5, 18.6, 13.8; LRMS m/z 554 (M^+); HRMS calcd for $C_{32}H_{52}O_3Si$, 554.4155, found 554.4156.

4.2.14. (1*R*,8*S*,10*R*)-1-*tert*-Butyldimethylsiloxy-9-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[6.2.0]decane (*trans*-3h). Colorless oil; $[\alpha]_D^{27}$ (c 0.76, $CHCl_3$) −14.2; IR (neat) 2927, 2855, 1713, 1240, 1165, 1136, 1005, 833, 812, 766, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.22 (m, 4H), 7.16–7.10 (m, 1H), 4.84 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.85 (dd, 1H, J=10.0, 10.0 Hz), 2.03–1.78 (m, 3H), 1.68–0.80 (m, 23H), 1.29 (s, 3H), 1.20 (s, 3H), 0.91 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 151.2, 127.8, 125.3, 125.1, 81.7, 74.2, 50.3, 49.8, 46.5, 42.0, 40.0, 34.6, 31.4, 30.5, 28.9, 27.1, 26.9, 26.8, 26.7, 26.1, 24.9, 24.3, 24.1, 21.9, 21.4, 18.5, −2.34, −2.75; LRMS m/z 526 (M^+); HRMS calcd for $C_{33}H_{54}O_3Si$: 526.3842, found 526.3854.

4.2.15. (1*S*,8*R*,10*R*)-1-*tert*-Butyldimethylsiloxy-9-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[6.2.0]decane (*cis*-3h). Colorless oil; $[\alpha]_D^{26}$ (c 0.28, $CHCl_3$)+22.2; IR (neat) 2926, 2855, 1722, 1445, 1259, 1165, 1094, 1022, 835, 810, 764, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.19 (m, 4H), 7.15–7.09 (m, 1H), 4.91 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.39 (dd, 1H, J=9.5, 9.5 Hz), 2.03–1.89 (m, 2H), 1.83–0.82 (m, 24H), 1.31 (s, 3H), 1.19 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$);δ 171.6, 151.3, 127.8, 125.3, 125.0, 81.2, 73.8, 50.6, 49.3, 47.2, 42.6, 39.8, 34.5, 31.9, 31.4, 29.1, 27.1, 26.7, 26.1, 26.0, 25.3, 24.9, 24.4, 24.3, 22.0, 21.0, 18.5, −2.10, −2.42; LRMS m/z 526 (M^+); HRMS calcd for $C_{33}H_{54}O_3Si$: 526.3842, found 526.3854.

4.2.16. (1*R*,2*R*)-1-*tert*-Butyldimethylsiloxy-2-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]-1-phenylcyclobutane (*trans*-3j). Colorless oil; $[\alpha]_D^{27}$ (c 1.17, $CHCl_3$) −48.0; IR (neat) 2928, 2856, 1715, 1256, 1005, 833, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.30–7.15 (m, 7H), 7.15–7.09 (m, 1H), 4.49 (ddd, 1H, J=4.4, 10.6, 10.6 Hz), 3.22 (dd, 1H, J=9.4, 9.4 Hz), 2.64–2.56 (m, 1H), 2.25 (q, 4H, J=10.6 Hz), 1.79–1.62 (m, 3H), 1.47–1.35 (m, 2H), 1.24 (s, 3H), 1.11 (s, 3H), 0.90 (s, 9H), 0.94–0.55 (m, 7H), 0.15 (q, 1H, J=12.0 Hz), −0.02 (s, 3H), −0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 151.3, 142.2, 127.7, 127.6, 127.3, 126.3, 125.3, 125.0, 80.6, 73.9, 55.3, 50.1, 40.5, 39.9, 34.4, 33.9, 31.0, 26.8, 26.3, 25.9, 21.6, 18.1, 15.4, −2.83, −2.93; LRMS m/z 520 (M^+). Anal. calcd for $C_{32}H_{48}O_3Si$: C, 76.10; H, 9.29, found C, 75.89; H, 8.97.

4.2.17. (1*S*,2*R*)-1-*tert*-Butyldimethylsiloxy-2-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]-1-phenylcyclobutane (*cis*-3j). Colorless oil; $[\alpha]_D^{27}$ (c 1.17, $CHCl_3$) −37.3; IR (neat) 2928, 2856, 1722, 1229, 1124, 980, 835, 764, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.52 (m, 2H), 7.35–7.18 (m, 7H), 7.13–7.05 (m, 1H), 4.92 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.95 (dd, 1H, J=7.8, 7.8 Hz), 2.67–2.55 (m, 1H), 2.32 (ddd, 1H, J=5.4, 10.7, 10.7 Hz), 2.14–1.96 (m, 3H), 1.63–0.70 (m, 10H), 1.35 (s, 3H), 1.23 (s, 3H), 0.80 (s, 9H), −0.13 (s, 3H), −0.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.4, 145.7, 127.9, 127.8, 127.2, 126.4, 125.4, 125.0, 80.7, 74.5, 53.3, 50.4, 42.3, 40.1, 34.6, 31.9, 31.4, 27.3, 27.0, 26.0, 21.8, 18.2, 17.7, −2.94, −3.37; LRMS m/z 520 (M^+); HRMS calcd for $C_{32}H_{48}O_3Si$, 520.3373, found 520.3378.

4.2.18. (1*S*,4*R*)-1-*tert*-Butyldimethylsiloxy-1-isopropyl-2,2-dimethyl-4-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]cyclobutane (*trans*-3k). Colorless oil; $[\alpha]_D^{26}$ (c 0.85, $CHCl_3$) −7.4; IR (neat) 2959, 2928, 2856, 1715, 1254, 1070, 764, 700, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 4H), 7.16–7.11 (m, 1H), 4.85 (ddd, 1H, J=4.4, 10.7, 10.7 Hz), 2.78 (dd, 1H, J=6.4, 10.0 Hz), 2.31–2.20 (m, 1H), 2.05–1.95 (m, 1H), 1.94–1.84 (m, 1H), 1.62–0.78 (m, 17H), 1.32 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.93 (s, 9H,), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 151.3, 127.9, 125.4, 125.2, 74.3, 50.3, 47.4, 42.9, 41.4, 39.9, 34.5, 32.6, 31.4, 26.9, 26.2, 24.7, 21.8, 19.1, 17.7, 17.5, −2.28, −2.51; LRMS m/z 457 (M^+−57); HRMS calcd for $C_{32}H_{48}O_3Si$: 457.3138, found 457.3156.

4.2.19. (1*R*,7*S*,9*R*)-1-(*tert*-Butyldimethylsiloxy)-9-methyl-9-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]bicyclo[5.2.0]nonane (*trans*-3l). Colorless oil; $[\alpha]_D^{27}$ (c 0.47, $CHCl_3$) −4.5; IR (neat) 2926, 2855, 1715, 1456, 1076, 835, 773, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 4H), 7.17–7.11 (m, 1H), 4.79 (ddd, 1H, J=4.1, 10.6, 10.6 Hz), 2.43–2.30 (m, 1H), 2.05–1.93 (m, 2H), 1.81–0.72 (m, 21H), 1.32 (s, 3H), 1.29 (s, 3H), 1.20 (s, 3H), 0.89 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 151.1, 127.9, 125.4, 1251, 83.6, 75.1, 50.7, 50.3, 43.8, 41.8, 40.2, 34.7, 31.5, 31.4, 29.0, 28.2, 27.3, 26.2, 24.9, 23.4, 21.9, 21.9, 21.8, 18.8, 0.09, −1.63, −1.72; LRMS m/z 526 (M^+); HRMS calcd for $C_{33}H_{54}O_3Si$, 526.3842, found 526.3861.

4.3. X-ray crystallography[13]

Prismatic crystals of *trans*-**3a** suitable for X-ray crystallography were grown by slow crystallization from AcOH–MeOH. A Colorless prism crystal of *trans*-**3a** having approximate dimensions of 0.20×0.20×0.20 mm was mounted on a glass fiber. All measurements were made on a Rigaku/MSC Mercury CCD diffractometer with graphite monochromated Mo Ka radiation. The data were collected at a temperature of −100±1 °C to a maximum 2θ value of 55.0°. The structure was solved using the programs in teXsan; the compound *trans*-**3a** belongs to the monoclinic space group $P2_1$ (#4) with a=10.168(2) Å, b=11.027(2) Å, c=13.583(3) Å, β=91.139(4)°, V=1522.6(5) Å^3, Z=2, and D=1.088 g/cm^3. R=0.034, and R_w=0.036 for 3644 unique reflections. GOF=0.92.

4.4. General procedure for reduction of ester 3 into alcohol 5

To a solution of **3** (1.0 equiv.) in CH_2Cl_2 (0.1 M) was

gradually added DIBAL-H (7.0 equiv., 1 M hexane solution) at −78 °C. The mixture was stirred for 70 min at the same temperature, and then was quenched with MeOH. The resulting mixture was filtered through Celite® and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (12% AcOEt/hexane) to afford alcohol **5**.

4.4.1. (1*R*,6*S*,8*S*)-1-*tert*-Butyldimethylsiloxy-8-hydroxymethylbicyclo[4.2.0]octane (*trans*-5a). *Compound trans*-**5a** was obtained from *trans*-**3a** (252 mg, 0.51 mmol) in 73% yield (100 mg). Colorless needles, mp 72–73 °C (from AcOEt–hexane); $[\alpha]_D^{28}$ (*c* 0.27, $CHCl_3$) −32.9; IR ($CHCl_3$) 3683, 3607, 3032, 3013, 1234, 1200, 802, 706, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78–3.73 (m, 1H), 3.60–3.54 (m, 1H), 2.30–2.17 (m, 2H), 1.73–1.22 (m, 9H), 1.08 (d, 1H, *J*=10.2 Hz), 1.03 (d, 1H, *J*=10.5 Hz), 0.85 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.5, 62.9, 48.6, 40.8, 31.1, 25.8, 23.7, 21.8, 20.4, 18.0, −2.36, −2.40; LRMS *m*/*z* 213 (M^+−57). Anal. calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18, found C, 66.43; H, 10.84.

4.4.2. (1*S*,6*R*,8*S*)-1-*tert*-Butyldimethylsiloxy-8-hydroxymethylbicyclo[4.2.0]octane (*cis*-5a). *Compound cis*-**5a** was obtained from *cis*-**3a** (35 mg, 0.070 mmol) in 77% yield (13 mg). Colorless oil; $[\alpha]_D^{27}$ (*c* 0.49, $CHCl_3$)+6.1; IR (neat) 3354, 2930, 2856, 1462, 1252, 1180, 1076, 881, 835, 772, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92–3.86 (m, 1H), 3.68–3.59 (m, 1H), 2.53–2.40 (m, 2H), 2.37–2.25 (m, 1H), 1.88–1.81 (m, 1H), 1.76–1.66 (m, 2H), 1.52–1.34 (m, 7H), 0.89 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.9, 45.7, 40.0, 37.6, 25.9, 25.6, 21.4, 21.1, 20.0, 18.1, −2.24, −2.40; LRMS *m*/*z* 213 (M^+−57); HRMS *m*/*z* calcd for $C_{15}H_{30}O_2Si$ (M^+−57): 213.1311, found 213.1321.

4.4.3. (1*R*,2*S*)-1-*tert*-Butyldimethylsiloxy-2-hydroxymethyl-1-phenylcyclobutane (*trans*-5j). *Compound trans*-**5j** was obtained from *trans*-**3j** (63 mg, 0.12 mmol) in 83% yield (29 mg). Colorless oil; $[\alpha]_D^{28}$ (*c* 1.17, $CHCl_3$) −24.6; IR (neat) 3329 2953, 2930, 2856, 1254, 775, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.39–7.33 (m, 2H), 7.29–7.26 (m, 1H), 3.21 (ddd, 1H, *J*=6.3, 6.8, 11.4 Hz), 3.13 (ddd, 1H, *J*=5.8, 6.1, 11.6 Hz), 2.85–2.76 (m, 1H), 2.70 (ddd, 1H, *J*=2.7, 8.7, 11.6 Hz), 2.38–2.28 (m, 1H), 2.03–1.93 (m, 1H), 1.48–1.36 (m, 1H), 0.91 (s, 9H), 0.75 (dd, 1H, *J*=5.8, 6.3 Hz), −0.01 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 128.1, 127.2, 126.2, 79.4, 63.3, 52.2, 33.3, 25.9, 18.0, 16.4, −2.86, −2.97; LRMS *m*/*z* 292 (M^+); HRMS calcd for $C_{17}H_{28}O_2Si$, 292.1859, found 292.1883.

4.4.4. (1*S*,2*S*)-1-*tert*-Butyldimethylsiloxy-2-hydroxymethyl-1-phenylcyclobutane (*cis*-5j). *Compound cis*-**5j** was obtained from *cis*-**3j** (26 mg, 0.050 mmol) in 66% yield (10 mg). Colorless oil; $[\alpha]_D^{27}$ (*c* 0.39, $CHCl_3$) −2.9; IR (neat) 3420, 2953, 2930, 2856, 1252, 1126, 835, 777, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2H), 7.39–7.34 (m, 2H), 7.30–7.25 (m, 1H), 4.15 (ddd, 1H, *J*=3.2, 11.2, 11.2 Hz), 3.79 (ddd, 1H, *J*=4.6, 9.8, 11.5 Hz), 3.22 (dd, 1H, *J*=3.2, 9.8 Hz), 2.88–2.80 (m, 1H), 2.70–2.60 (m, 1H), 2.49–2.39 (m, 1H), 1.73–1.62 (m, 1H), 1.55–1.46 (m, 1H), 0.87 (s, 9H), −0.01 (s, 3H), −0.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 128.2, 127.3, 126.3, 79.7, 64.3, 50.2, 31.9, 25.8, 17.9, 14.9, −3.14, −3.69; LRMS *m*/*z* 292 (M^+); HRMS calcd for $C_{17}H_{28}O_2Si$, 292.1859, found 292.1871.

4.4.5. (1*S*,4*S*)-1-*tert*-Butyldimethylsiloxy-4-hydroxymethyl-1-isopropyl-2,2-dimethylcyclobutane (*trans*-5k). *Compound trans*-**5k** was obtained from *trans*-**3k** (65 mg, 0.13 mmol) in 61% yield (22 mg). Colorless needles, mp 60–61 °C (from AcOEt–hexane); $[\alpha]_D^{26}$ (*c* 0.78, $CHCl_3$)+6.4; IR (neat) 3317, 2934, 2860, 1462, 1256, 1067, 862, 835, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09–3.96 (m, 1H), 3.71 (dd, 1H, *J*=10.3, 10.3 Hz), 2.49–2.37 (m, 1H), 2.01–1.84 (m, 2H), 1.32 (dd, 1H, *J*=4.4, 11.7 Hz), 1.17 (s, 3H), 1.03 (s, 3H), 0.94 (s, 9H), 0.85 (d, 6H, *J*=7.1 Hz), 0.23 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.4, 64.4 45.5, 42.2, 34.0, 31.0, 26.8, 26.3, 25.8, 19.2, 17.3, −1.58, −1.85; LRMS *m*/*z* 228 (M^+−58); HRMS calcd for $C_{13}H_{28}OSi$: 228.1909, found 228.1889.

4.5. Transformation into *exo*-olefin 7a

4.5.1. (1*S*,6*R*,8*R*)-1-*tert*-Butyldimethylsiloxy-8-*o*-nitrophenylselanylmethylbicyclo[4.2.0]octane (*cis*-6a). To a solution of *cis*-**5a** (74 mg, 0.27 mmol) and *o*-nitrophenylselenocyanide (75 mg, 0.33 mmol) in THF (4.0 mL) was slowly added tributylphosphine (85 μL, 0.34 mmol) at ambient temperature, and the resulting solution was stirred for 22.5 h at 50–55 °C. After removal of solvent, the residue was purified by column chromatography on silica gel with 2% AcOEt/hexane to give *cis*-**6a** (100 mg, 80%) as yellowish prisms, mp 63–65 °C (from AcOEt–hexane); $[\alpha]_D^{28}$ (*c* 0.37, $CHCl_3$) −1.6; IR (KBr) 2928, 2855, 1512, 1329, 1304, 1067, 835, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30–8.25 (m, 1H), 7.56–7.46 (m, 2H), 7.31–7.25 (m, 1H), 3.22 (dd, 1H, *J*=5.5, 11.2 Hz), 2.98 (dd, 1H, *J*=10.6, 10.6 Hz), 2.52–2.33 (m, 2H), 1.84–1.21 (m, 10H), 0.93 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 133.3, 129.1, 126.3, 125.0, 76.6, 41.6, 40.1, 36.7, 27.7, 27.2, 26.7, 26.0, 22.3, 22.1, 18.4, −2.23; LRMS *m*/*z* 398 (M^+−57). Anal. calcd for $C_{21}H_{33}NO_3SeSi$: C, 55.49; H, 7.32; N, 3.08, found C, 55.67; H, 7.15; N, 2.92.

4.5.2. (1*S*,6*R*)-1-*tert*-Butyldimethylsiloxy-8-methylidenebicyclo[4.2.0]octane ((+)-7a). To a solution of *cis*-**6a** (72 mg, 0.16 mmol) in THF (3.2 mL) was added H_2O_2 (31% v/v; 300 μL) at 0 °C, and the mixture was stirred for 17.5 h at ambient temperature. The resulting mixture was extracted with Et_2O twice, dried, and concentrated. The residue was chromatographed on silica gel (hexane) to furnish (+)-**7a** (31 mg, 78%) as colorless oil, $[\alpha]_D^{27}$ (*c* 1.75, $CHCl_3$)+10.4; IR (neat) 2930, 2856, 1680, 1252, 1142, 1088, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91–4.86 (m, 1H), 4.69–4.63 (m, 1H), 2.42–2.25 (m, 2H), 2.20–2.10 (m, 1H), 1.78–1.18 (m, 8H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 101.2 77.6, 39.9, 35.8, 28.5 25.8, 24.2, 21.3 20.8 18.2, −2.40, −2.44; LRMS *m*/*z* 252 (M^+); HRMS *m*/*z* calcd for $C_{15}H_{28}OSi$ (M^+): 252.1909, found 252.1916.

4.5.3. (1*R*,6*S*,8*R*)-1-*tert*-Butyldimethylsiloxy-8-*o*-nitrophenylselenylmethylbicyclo[4.2.0]octane (*trans*-6a). To

a solution of *trans*-**5a** (95 mg, 0.35 mmol) and *o*-nitrophenylselenocyanide (96 mg, 0.42 mmol) in THF (4.0 mL) was slowly added tributylphosphine (105 μL, 0.42 mmol) at ambient temperature, and the resulting solution was stirred for 17 h at the same temperature and additional 5.5 h at 50 °C. After removal of solvent, the residue was purified by column chromatography on silica gel with 2% AcOEt/hexane to give *trans*-**6a**. (140 mg, 88%) as yellowish prisms, mp 91–93 °C (from AcOEt–hexane); $[\alpha]_D^{28}$ (*c* 0.36, $CHCl_3$) −54.8; IR (KBr) 2928, 2855, 1508, 1333, 1252, 1094, 773, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, *J*=7.8 Hz), 7.52–7.48 (m, 2H), 7.33–7.27 (m, 1H), 3.10 (dd, 1H, *J*=5.9, 11.0 Hz), 2.84 (dd, 1H, *J*=9.8, 9.8 Hz), 2.38–2.27 (m, 1H), 2.26–2.16 (m, 1H), 1.84 (dd, 1H, *J*=8.5, 8.5 Hz), 1.76–1.20 (m, 8H), 1.15 (d, 1H, *J*=10.3 Hz), 1.09 (d, 1H, *J*=10.5 Hz), 0.89 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 133.4, 128.9, 126.4, 125.1, 75.8, 44.7, 40.6, 31.1, 26.0, 25.8, 23.8, 23.6, 21.8, 20.4, 18.0, −2.24, −2.34; LRMS *m/z* 398 (M^+−57). Anal. calcd for $C_{21}H_{33}NO_3SeSi$: C, 55.49; H, 7.32; N, 3.08, found C, 55.34; H, 7.10; N, 2.92.

4.5.4. (1*R*,6*S*)-1-*tert*-Butyldimethylsiloxy-8-methylidene-bicyclo[4.2.0]octane ((−)-7a). To a solution of *trans*-**6a** (118 mg, 0.26 mmol) in THF (5.2 mL) was added H_2O_2 (31% v/v; 430 μL) at 0 °C, and the mixture was stirred for 21 h at ambient temperature. The resulting mixture was extracted with Et_2O twice, dried, and concentrated. The residue was chromatographed on silica gel (hexane) to furnish (−)-**7a** (16 mg, 25%) as colorless oil, $[\alpha]_D^{26}$ (*c* 0.75, $CHCl_3$) −9.8. All spectral data were identical with (+)-**7**.

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Tetrahedron

Improved synthesis of 6-amino-6-deoxy-D-galactono-1,6-lactam and D-mannono-1,6-lactam from corresponding unprotected D-hexono-1,4-lactones

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Abstract—Regioselective bromination of unprotected D-galactono-1,4-lactone and D-mannono-1,4-lactone with PPh_3/CBr_4 led to 6-bromo-6-deoxy derivatives. These intermediates were treated with LiN_3 and hydrogenated to give 6-amino-6-deoxy-D-galactono-1,6-lactam (**8**) and 6-amino-6-deoxy-D-mannono-1,6-lactam (**13**) in 74 and 67% overall yield, respectively.

1. Introduction

The discovery of the glycosidase inhibitor activity of the natural product nojirimycin **1** initiated the synthesis of various polyhydroxylated piperidine and pyrrolidine derivatives (azasugars).[1] This group of inhibitors is potentially useful for treating metabolic disorders such as diabetes,[2] cancer[3] and AIDS.[4] Seven-member azasugars (polyhydroxyazepanes **2**, **3**, **4**) have also shown to possess potent inhibitory activities.[5] (Fig. 1) The hydroxyl groups, in azepanes, adopt different spatial disposition due to the flexibility of the seven-member ring, therefore increasing the formation of hydrogen bonds to make contact with the enzyme.

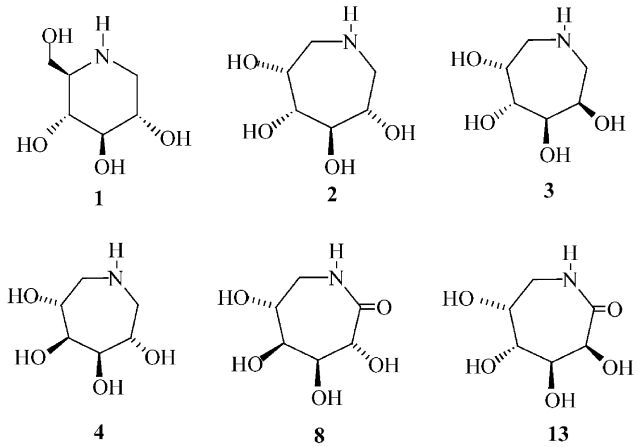

Figure 1. Examples of azasugars.

However, only a few reports have appeared on the synthesis of seven-member iminosugars. In some of those reported they have been obtained in admixture with their corresponding six-member ring derivatives, requiring separation.[6]

The use of protected D-galactono-1,4-lactone and D-mannono-1,4-lactone for preparing the corresponding lactams **8**[7] and **13**[8] has been described. The title compounds were obtained in 54 and 27% overall yield, respectively.

In the continuation of our interest in the synthesis of azasugars,[9] we now describe a direct and improved synthetic route to 6-amino-6-deoxy-D-1,6-galactonolactam (**8**) and 6-amino-6-deoxy-D-mannono-1,6-lactam (**13**) from unprotected D-galactono-1,4-lactone and D-mannono-1,4-lactone, in three steps.

2. Results and discussion

The selective bromination of the primary hydroxyl group in D-galactono-1,4-lactone (**5**) using triphenylphosphine (PPh_3)-carbon tetra-bromide (CBr_4) in pyridine gave the 6-bromo-6-deoxy-D-galactono-1,4-lactone (**6**) in 82% yield as the key starting material for the synthesis of lactam **8**. The introduction of an azide function at the C-6 position was achieved using lithium azide (LiN_3) to give 6-azido-6-deoxy-D-galactono-1,4-lactone (**7**) in 91% yield. A one-pot procedure for the azidation of (**5**), was attempted: either by using a mixture of PPh_3-CBr_4 and lithium azide in (DMF)

Keywords: D-galactono-1,4-lactone; D-mannono-1,4-lactone; 6-Bromo-6-deoxy-D-hexono-1,4-lactones; Seven-member azasugars; 6-Amino-6-deoxy-D-galactono; D-mannono-1,6-lactams.
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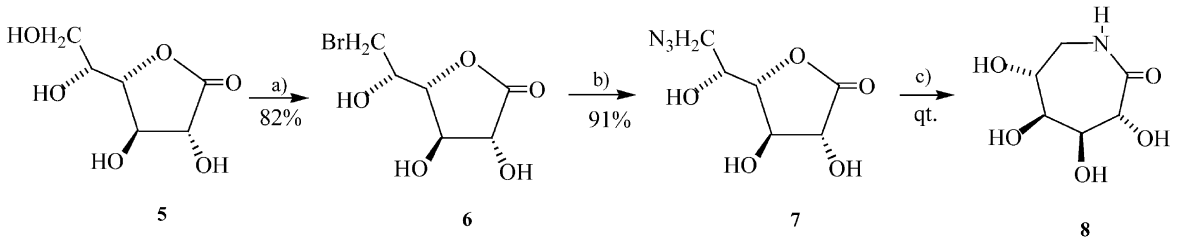


Scheme 1. Conditions: (a) PPh_3, CBr_4; (b) LiN_3; (c) H_2, Pd/C.

to give compound **7** but in only 11% yield, or by using Mitsunobu reaction (PPh_3-diethyl azodicarboxylate-diphenylphosphoryl azide in DMF) to give **7** in 40% yield.

Catalytic hydrogenation of **7** over palladium on charcoal (10%), at room temperature, produced quantitatively the desired 6-amino-6-deoxy-D-galactono-1,6-lactam (**8**) (Scheme 1).

D-mannono-1,4-lactone was used as the key starting material for the synthesis of lactam **13** (Scheme 2). For synthesis of D-mannono-1,4-lactone (**10**), which was not commercially available, we have used two procedures. First, we have hydrogenated the double bound of D-isoascorbic acid as describe in literature[8] but the yield of this reaction was lower than 50%. In a second time oxidation, of D-mannose (**9**), using bromine and barium carbonate in water[10] afforded a mixture of D-mannono-1,4-lactone (**10**) and D-mannono-1,5-lactone. Isolation of compound **10** was very difficult and lead to substantially lower yield.

However, when sodium hydrogencarbonate was used instead of barium carbonate, D-mannono-1,4-lactone (**10**) was isolated in quantitative yield.

Treatment of D-mannono-1,4-lactone (**10**) with PPh_3–CBr_4 in pyridine gave the 6-bromo-6-deoxy-D-mannono-1,4-lactone (**11**) in 69% yield. The reaction of the brominated derivative **11** with LiN_3 afforded the 6-azido-6-deoxy-D-mannono-1,4-lactone (**12**) in 98% yield. Hydrogenation of **12** with H_2–Pd/C produced quantitatively 6-amino-6-deoxy-D-mannono-1,6-lactam (**13**) (Scheme 2).

Overall yields for the transformation of unprotected D-galactono and D-mannono-1,4-lactones into corresponding 6-amino-6-deoxy-D-hexono-1,6-lactams are 74 and 67%, respectively.

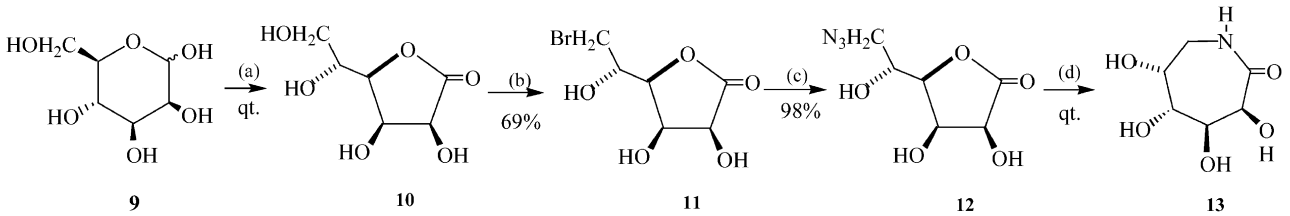
3. Experimental

3.1. General

Melting points were determined on a Buchi 535 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp (λ=589 nm) at 24 °C. ^1H and ^{13}C NMR spectra were recorded in D_2O, in MeOD or in DMSO-d_6. Me_4Si was used as an internal standard on a Bruker 300 MHz spectrometer.

Thin-layer chromatography (TLC) was performed on E. Merck glass plates silica gel sheets (SilicaGel F_{254}) and visualised under UV light and/or stained with phosphomolybdic acid-aqueous H_2SO_4 solution. Column chromatography was carried out on silica gel (E. Merck 230–400 mesh). All solvents were distilled before use.

3.1.1. 6-Bromo-6-deoxy-D-galactono-1,4-lactone (6). To a solution of D-galactono-1,4-lactone (**5**) (10 g, 56.2 mmol) in pyridine (200 mL) was added triphenylphosphine (30 g, 2 equiv.) and carbon tetra-bromide (3×6 g, 1 equiv.) at 20 min intervals. The mixture was stirred, under an inert atmosphere, at room temperature for 18 h. Methanol was added and the solution was kept for 10 min at room temperature and concentrated in vacuo. The toluene (50 mL) was added to the crude material. After concentration, the residue was diluted with water and washed with CH_2Cl_2. The water extracts were concentrated in vacuo and the obtained residue was chromatographed on silica gel. Elution with EtOAc–hexanes (9:1) to give **6** (11.2 g, 82%) as white solid: R_f 0.6 (EtOAc–MeOH 9:1); mp 126–127 °C; $[\alpha]_D^{24}$ −100 (*c* 1.0, H_2O). Anal. calcd % for $C_6H_9BrO_5$: C, 29.90; H, 3.76; Br, 33.15. Found % C, 30.4; H, 3.70; Br 33.02; ^1H NMR (300 MHz, MeOD) δ 4.42 (d, 1H, *J*=8.4 Hz), 4.32 (m, 2H), 3.98 (m, 1H), 3.62 (dd, 1H, *J*=6.9, 10.3 Hz), 3.50 (dd, 1H, *J*=6.7, 10.2 Hz). ^{13}C NMR (75 MHz, MeOD) δ 174.9, 80.3, 74.7, 73.8, 69.0, 32.5.



Scheme 2. Conditions: (a) Br_2, H_2O, $NaHCO_3$; (b) PPh_3, CBr_4; (c) LiN_3; (d) H_2, Pd/C.

3.1.2. 6-Azido-6-deoxy-D-galactono-1,4-lactone (7). A stirred solution of 6-bromo-6-deoxy-D-galactono-1,4-lactone (**6**) (1 g, 4.15 mmol) in DMF (10 mL) was treated with lithium azide (20% in H_2O) (12 mL, 1.3 equiv.) and set aside at 80 °C for 1 h. The mixture was poured into ice-water (15 mL) and the product extracted with ethyl acetate. The organic layer was concentrated in vacuo and the obtained residue was chromatographed on silica gel. Elution with EtOAc–hexanes (7:3) to give **7** (0.74 g, 91%) as yellow oil: R_f 0.7 (EtOAc–MeOH 9:1); $[\alpha]_D^{24}$ −65 (*c* 1.0, MeOH). Lit.[7] $[\alpha]_D^{23}$ −70.6 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 4.40 (d, 1H, *J*=8.8 Hz), 4.27 (dd, 1H, *J*=8.2, 8.8 Hz), 4.11 (dd, 1H, *J*=2.8, 8.1 Hz), 3.91 (m, 1H), 3.51 (dd, 1H, *J*=7.7, 12.7 Hz), 3.41 (dd, 1H, *J*=5.0, 12.7 Hz); ^{13}C NMR (75 MHz, MeOD) δ 175.0, 80.8, 74.6, 73.6, 68.5, 53.4.

3.1.3. 6-Amino-6-deoxy-D-galactono-1,6-lactam (8). A solution of compound **7** (0.35 g, 1.72 mmol) in ethanol (8 mL) was treated with palladium on charcoal (10%, 0.035 g) and then hydrogenated for 18 h at room temperature. The mixture was filtered through a layer of celite and the filtrate was concentrated in vacuo to give **8** as white solid: R_f 0.4 (EtOAc–MeOH 3:2); mp 168–170 °C; $[\alpha]_D^{24}$ −13 (*c* 1.0, H_2O). Lit.[7] $[\alpha]_D^{25}$ −16.3 (*c* 1.0, H_2O); mp 175–176 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.43 (d, 1H, *J*=9.3 Hz), 3.91 (m, 1H), 3.71 (m, 2H), 3.50 (dd, 1H, *J*=4.6, 15.8 Hz), 3.21 (dd, 1H, *J*=2.9, 15.8 Hz); ^{13}C NMR (75 MHz, D_2O) δ 176.4, 73.3, 69.1, 40.6.

3.1.4. D-mannono-1,4-lactone (10). To a solution of D-mannose (**9**) (5 g, 2.8 mmol) and sodium hydrogencarbonate (3.35 g, 4 mmol) in distilled water (50 mL) cooled at 0 °C, bromine (3×1 mL, 58.5 mmol) was added at 20 min intervals. The reaction mixture was stirred at this temperature for 1 h and then for 4 days at room temperature. Sodium thiosulfate was added to destroy the excess of bromine and the solvent was removed in vacuo to give a white solid. The obtained solid was chromatographed on silica gel. Elution with EtOAc–MeOH (9:1) and recrystallized from 2-propanol to give quantitatively compound **10** as white solid: R_f 0.5 (EtOAc–MeOH 7:3); mp 145–146 °C; $[\alpha]_D^{24}$ +53 (*c* 1.0, H_2O). Lit.[11] mp 151 °C; $[\alpha]_D^{20}$ +51.2 (*c* 2, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.55 (d, 1H, *J*=4.6 Hz), 4.50 (dd, 1H, *J*=2.7, 4.6 Hz), 4.31 (dd, 1H, *J*=8.9, 2.8 Hz), 3.96 (m, 1H), 3.80 (dd, 1H, *J*=2.8, 11.7 Hz), 3.67 (dd, 1H, *J*=5.1, 11.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.1, 78.6, 71.2, 69.8, 68.5, 63.2.

3.1.5. 6-Bromo-6-deoxy-D-mannono-1,4-lactone (11). Reaction of **10** (2.15 g, 12 mmol) with triphenylphosphine and carbon tetra-bromide in pyridine, as in case of **5** gave **11** (2 g, 69%) as white solid: R_f 0.44 (EtOAc–MeOH 9:1); mp 136–137 °C; $[\alpha]_D^{24}$ +55 (*c* 1.0, H_2O). Lit.[12] mp 136–139 °C; $[\alpha]_D^{20}$ +54.7 (*c* 1.1, H_2O). ^{1}H NMR (300 MHz, MeOD) δ 4.61 (d, 1H, *J*=4.6 Hz), 4.47 (dd, 1H, *J*=2.7, 4.6 Hz), 4.32 (dd, 1H, *J*=2.7, 9.0 Hz), 4.13 (m, 1H), 3.75 (dd, 1H, *J*=2.8, 11.6 Hz), 3.63 (dd, 1H, *J*=5.1, 11.6 Hz). ^{13}C NMR (75 MHz, MeOD) δ 177.3, 80.6, 71.8, 70.1, 67.5, 37.4.

3.1.6. 6-Azido-6-deoxy-D-mannono-1,4-lactone (12). Reaction of **11** (0.7 g, 2.9 mmol) in DMF with lithium azide, as in case of **6** gave **12** (0.58 g, 98%) as yellow oil: R_f 0.6 (EtOAc–MeOH 9:1); $[\alpha]_D^{24}$ +20 (*c* 1.0, MeOH). Anal. calcd % for $C_6H_9N_3O_5$: C, 35.47; H, 4.47. Found % C, 35.42; H, 4.42; ^{1}H NMR (300 MHz, MeOD) δ 4.68 (d, 1H, *J*=4.5 Hz), 4.57 (dd, 1H, *J*=2.7, 4.4 Hz), 4.52 (dd, 1H, *J*=2.7, 8.9 Hz), 4.15 (m, 1H), 3.55 (dd, 1H, *J*=2.2, 12.8 Hz), 3.39 (dd, 1H, *J*=4.9, 12.8 Hz). ^{13}C NMR (75 MHz, MeOD) δ 176.6, 79.2, 71.3, 69.6, 67.4, 54.2.

3.1.7. 6-Amino-6-deoxy-D-mannono-1,6-lactam (13). Compound **12** (0.3 g, 1.48 mmol) in ethanol was treated with palladium on charcoal and then hydrogenated for 18 h, as in case of **7**, to give **13**, in quantitative yield, as white solid: R_f 0.4 (EtOAc–MeOH 3:2); mp 150–152 °C; $[\alpha]_D^{24}$ +47 (*c* 1.0, H_2O). Anal. calcd % for $C_6H_{11}NO_5$: C, 40.68; H, 6.26. Found % C, 40.60; H, 6.12; ^{1}H NMR (300 MHz, D_2O) δ 4.71 (d, 1H, *J*=5.6 Hz), 3.98 (m, 2H), 3.74 (m, 1H), 3.52 (dd, 1H, *J*=6.8, 13.4 Hz), 2.84 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 175.9, 75.1, 72.2, 75.1, 68.8, 67.4, 39.7.

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Aza-Baylis–Hillman reactions of diisopropyl azodicarboxylate or diethyl azodicarboxylate with acrylates and acrylonitrile

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Abstract—It has been found that in the Baylis–Hillman reactions of DIAD or DEAD with acrylates or acrylonitrile, the Lewis base and solvent can significantly affect the reaction rate. Using DABCO as Lewis base in DMF or THF, the corresponding aza-Baylis–Hillman adducts **2** or **3** can be obtained in moderate to good yields.

1. Introduction

Since Baylis and Hillman first reported the reactions of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of a strong Lewis base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1972,[1] the Baylis–Hillman reaction has made great progress,[2] advancing to a catalytic asymmetric version.[3] However, in this very simple and useful reaction, only aldehydes (RCHO),[1–3] *N*-arylidene-4-methylbenzenesulfonamides (ArCH=NTs),[4] and *N*-arylidenediphenylphosphinamides [ArCH=NP(O)Ph_2][5] are in general used as the substrates for the reaction with α,β-unsaturated ketones, nitriles or esters. In 1998, Kamimura and co-workers reported a facile preparation of α-hydrazino-α,β-unsaturated ketones via aza-Baylis–Hillman reaction of diethyl azodicarboxylate (DEAD) or di-*tert*-butyl azodicarboxylate with α,β-unsaturated ketones catalyzed by DABCO.[6] In that paper, they mentioned that no reaction occurred in the aza-Baylis–Hillman reaction of DEAD with methyl acrylate under the same conditions.[6] During our comprehensive investigations on the aza-Baylis–Hillman reaction,[4,5] we found that the aza-Baylis–Hillman reaction of DEAD with methyl acrylate indeed produced a polymeric compound, but the corresponding aza-Baylis–Hillman adducts can be garnered in moderate to high yields if either DIAD is used as a substrate or other acrylates are used as the Michael acceptors. Herein, we report the aza-Baylis–Hillman reaction of diisopropyl azodicarboxylate (DIAD) and DEAD with various acrylates and acrylonitrile in the presence of an array of Lewis bases.[5]

2. Results and discussion

At first, we systematically examined the promoters and solvents for the aza-Baylis–Hillman reaction of DIAD with methyl vinyl ketone (MVK) (Table 1) to search for the optimal conditions.[7] We found that the Lewis bases and solvents played very important roles for this reaction. Phosphane Lewis bases such as triphenylphosphine (PPh_3) showed no catalytic activity for this reaction (Table 1, entry 5). Nitrogen Lewis bases such as DABCO, 4-*N*,*N*-dimethylpyridine (DMAP), triethylamine (Et_3N) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) could serve as effective promoters to give the corresponding adduct **1** in moderate to high yields (Table 1, entries 1–4 and 6–9). DMF or THF is the solvent of choice. Lewis base DABCO gave the best result in DMF (Table 1, entry 1). In all these cases, the normal aza-Baylis–Hillman adduct **1** was formed exclusively.

The reaction was further investigated using DABCO as a Lewis base and phenyl acrylate as a Michael acceptor[8] and it was found that the corresponding aza-Baylis–Hillman adduct **2a** was obtained in good yield. Its structure was determined by spectroscopic data and microanalysis.

We then examined the solvent effect in this type of aza-Baylis–Hillman reaction at room temperature. The results are summarized in Table 2. In THF or DMF, adduct **2a** was obtained in 71 and 81% yield (Table 2, entries 1 and 2), respectively. On the other hand, MeCN or dichloromethane gave lower yields of 58 and 62% (Table 2, entries 3 and 4),

Keywords: Diisopropyl azodicarboxylate; Diethyl azodicarboxylate; Lewis base DABCO; Aza-Baylis–Hillman reaction.
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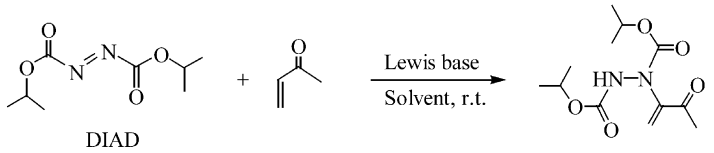
Table 1. The effects of Lewis base and solvent in the aza-Baylis–Hillman reaction of DIAD with MVK

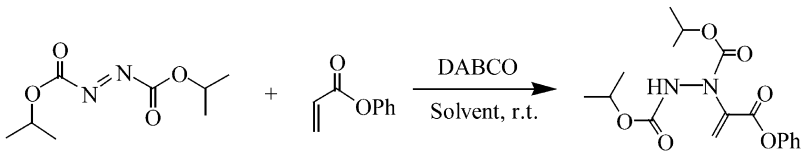


DIAD **1**

Entry	Lewis base	Solvent	Time (h)	Yield (%)[a] (**1**)
1	DABCO	THF	12	94
2	DABCO	DMF	12	63
3	DMAP	THF	12	68
4	Et_3N	THF	12	54
5	PPh_3	DMF	12	NR
6	DBU	DMF	4	74
7	DBU	MeCN	4	49
8	DBU	THF	4	51
9	DBU	CH_2Cl_2	4	34

[a] Isolated yields.

Table 2. The solvent effects in the aza-Baylis–Hillman reaction of DIAD with phenyl acrylate catalyzed by DABCO



2a

Entry	Solvent	Time (h)	Yield (%)[a] (**2a**)
1	THF	12	71
2	DMF	12	81
3	MeCN	12	58
4	CH_2Cl_2	12	62

[a] Isolated yields.

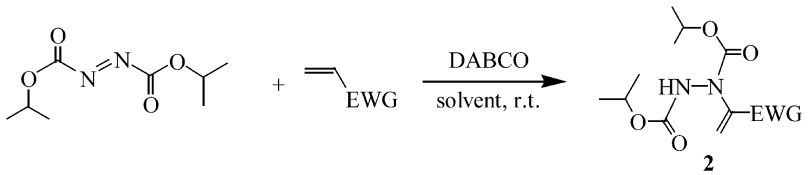
respectively. The best reaction condition for this type of aza-Baylis–Hillman reaction therefore is to carry out the reaction in THF or DMF using DABCO as a Lewis base promoter.

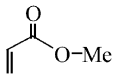
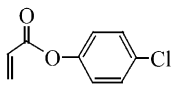
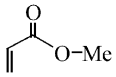
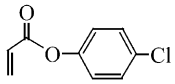
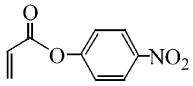
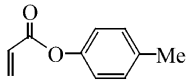
Under the optimized reaction conditions, we then extended the aza-Baylis–Hillman reactions of DIAD to other acrylates in THF or DMF. The results are summarized in Table 3. Using methyl acrylate as a Michael acceptor, we found that the corresponding aza-Baylis–Hillman adduct **2b** was formed in 24% in THF and 57% in DMF, respectively (Table 3, entries 1 and 3). Thus, if using DIAD as the substrate, the aza-Baylis–Hillman reaction with methyl acrylate can take place to give the corresponding aza-Baylis–Hillman adduct in moderate yield. For other phenyl acrylates such as *p*-chlorophenyl acrylate, *p*-nitrophenyl acrylate, and *p*-methylphenyl acrylate, the corresponding aza-Baylis–Hillman products **2c**, **2e**, **2f** were produced in good to high yields in DMF as well (Table 3, entries 5–7). For acrylonitrile, the corresponding adduct **2d** was also obtained in moderate yield (Table 3, entry 4). Their structures were determined by ^1H, ^{13}C NMR spectroscopic data, and HRMS or microanalyses. The relative configurations of C(O)–NHN and C(O)–NCN were disclosed by X-ray diffraction of **2f**.[9] The ORTEP draw of **2f** is shown in Figure 1 (its X-ray crystal data have been summarized in Section 3).

Additional work on the aza-Baylis–Hillman reaction of DEAD with acrylates or acrylonitrile was carried out under the optimized reaction conditions. The results are summarized in Table 4. As can be seen from Table 4, results similar to those from DIAD were obtained, although in the case of the reaction of DEAD with methyl acrylate only trace amount of adduct **3a** was obtained among polymeric materials (Table 3, entry 1). In contrast, using various phenyl acrylates as the Michael acceptors, the corresponding aza-Baylis–Hillman adducts **3c–f** were obtained in good to high yields under the same conditions (Table 3, entries 3–6). For acrylonitrile, the corresponding aza-Baylis–Hillman adduct **3b** was formed in moderate yield as well (Table 3, entry 2).

It should be emphasized here that only using dialkyl azocarboxylates such as DEAD or DIAD as the substrate, this type of aza-Baylis–Hillman reaction can take place. For other azo-compounds, for example, diphenyl azocarboxylate, 2,2′-azobisisobutyronitrile (AIBN), azobenzene, no reaction occurred under the same conditions (Scheme 1). It appears that a relatively stronger

Table 3. The aza-Baylis–Hillman reaction of DIAD with acrylates and acrylonitrile catalyzed by DABCO in THF and DMF



Entry	EWG	Solvent	Time (h)	Yield (%)[a] (**2**)
1		THF	12	**2b**, 24
2		THF	12	**2c**, 32
3		DMF	12	**2b**, 57
4		DMF	12	**2d**, 40
5		DMF	12	**2c**, 67
6		DMF	12	**2e**, 61
7		DMF	12	**2f**, 91

[a] Isolated yields.

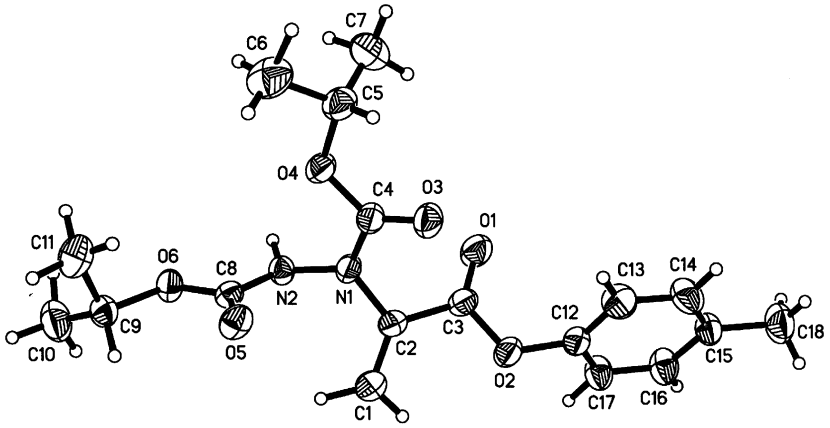


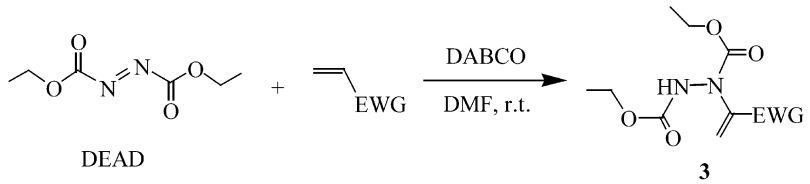
Figure 1. The ORTEP draw of **2f**.

electron-withdrawing group in the electrophile is required to initiate the nucleophilic attack of a zwitterionic species generated from Lewis base with α,β-unsaturated ketones or esters according to the typical reaction mechanism of Baylis–Hillman reaction.[2]

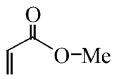
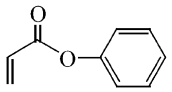
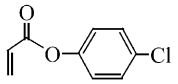
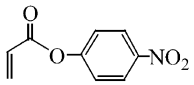
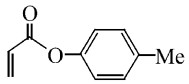
The plausible mechanism was described in Scheme 2.[2] The generated ammonium enolate **A** added to the N=N double bond to give the zwitterionic species **B** in *anti*-configuration[10] which underwent E2-elimination or intramolecular proton transfer and E1cb elimination from intermediated **C** to give the aza-Baylis–Hillman adduct and regenerate the nucleophilic promoter (Scheme 2).

In conclusion, we have found that the aza-Baylis–Hillman reaction of DIAD or DEAD with acrylates or acrylonitrile can take place in the presence of DABCO in DMF. For various phenyl acrylates, the corresponding

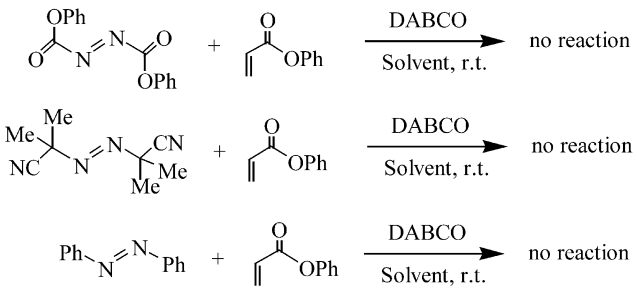
Table 4. The aza-Baylis–Hillman reaction of DEAD with acrylates and acrylonitrile in DMF catalyzed by DABCO



DEAD **3**

Entry	EWG	Time (h)	Yield (%)[a] (**3**)
1		12	**3a**, Trace
2		12	**3b**, 31
3		12	**3c**, 86
4		12	**3d**, 70
5		12	**3e**, 95
6		12	**3f**, 90

[a] Isolated yields.



Scheme 1.

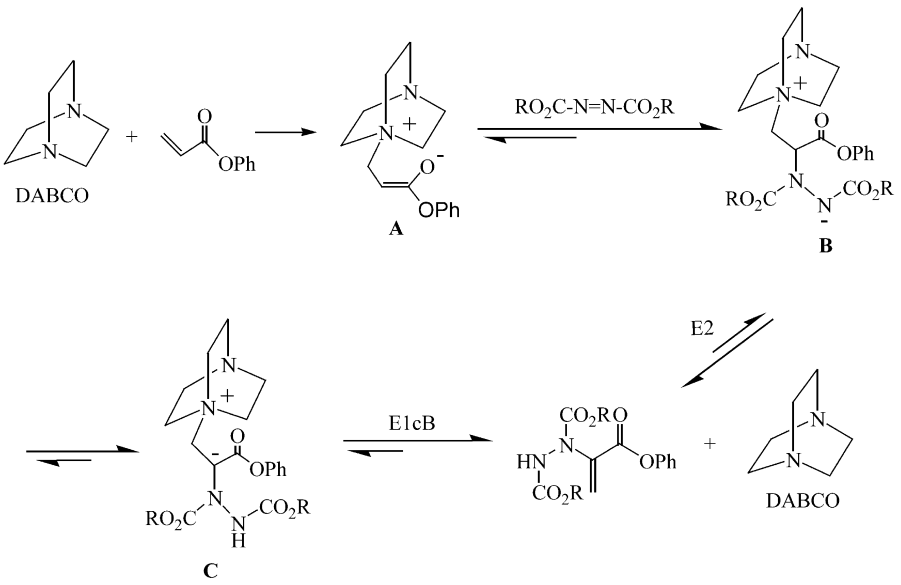
aza-Baylis–Hillman adducts **2** or **3** can be obtained in good to high yields. This finding can expand the scope and limitations of the previous literature of this type of aza-Baylis–Hillman reaction[7] and provide the corresponding α-hydrazino-α,β-unsaturated esters under mild conditions. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose its scope and limitations. Work in this direction is currently in progress.

3. Experimental

3.1. General

MPs were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ solution with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Mass spectra were recorded with a HP-5989 instrument. Some of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure. DIAD and DEAD were purchased from Aldrich. Co.

3.1.1. Typical reaction procedure of DIAD with phenyl acrylate at room temperature. To a Schlenk tube with DABCO (6 mg, 0.05 mmol) in DMF (0.5 mL) was added DIAD (101 mg, 99 μL, 0.50 mmol) and phenyl acrylate (74 mg, 0.50 mmol) and the reaction mixture was stirred for 12 h at room temperature (20 °C). The reaction mixture was washed with water (3×10 mL) and extracted with dichloromethane (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent removed under reduced pressure and the residue purified by silica gel column chromatography (eluent: EtOAc/petroleum=1:2) to give aza-Baylis–Hillman adduct **2a** (141 mg, yield 81%) as a white solid; mp 108–110 °C; IR (CH_2Cl_2) ν 1748 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.28–1.36 (12H, m, CH_3), 4.97–5.06 (2H, m, CH), 6.19 (1H, br. s, =CH), 6.44 (1H, br. s, =CH), 6.92 (1H, br. s, NH), 7.14–7.16 (2H, m, ArH), 7.24–7.30 (1H, m, ArH), 7.39–7.44 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.40, 21.47, 21.61, 21.67, 69.86, 71.17, 121.09, 121.36, 125.84, 129.22, 137.98, 150.26, 153.94, 155.59, 161.80; MS (EI) *m/e* 267 (M^+−83, 0.01), 264 (M^+−86, 5.72), 222



Scheme 2.

(M^+-128, 26.19), 173 (M^+-177, 28.93), 94 (M^+-256, 100), 43 (M^+-307, 66.87). Anal. calcd for $C_{17}H_{22}N_2O_6$ requires C, 58.27; H, 6.33; N, 8.00%. Found: C, 58.18; H, 6.29; N, 7.81%.

3.1.2. Aza-Baylis–Hillman adduct 1 (86 mg, yield 63%). A colorless oil; IR (CH_2Cl_2) ν 1717 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.19–1.29 (12H, m, CH_3), 2.33 (3H, s, CH_3), 4.87–4.97 (2H, m, CH), 5.91 (1H, br. s, ═CH), 5.96 (1H, br. s, ═CH), 7.25 (1H, br. s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.39, 21.51, 21.66, 21.76, 25.77, 69.69, 71.05, 118.76, 146.19, 155.52, 162.46, 195.13; MS (EI) *m/e* 273 (M^++1, 1.75), 171 (M^+-101, 7.36), 144 (M^+-128, 16.35), 100 (M^+-172, 15.02), 43 (M^+-229, 100); HRMS calcd for $C_{12}H_{20}N_2O_5$: 272.1372. Found: 272.1355.

3.1.3. Aza-Baylis–Hillman adduct 2b (82 mg, yield 57%). A colorless oil; IR (CH_2Cl_2) ν 1717 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.24–1.35 (12H, m, CH_3), 3.81 (3H, s, OCH_3), 4.92–5.07 (2H, m, CH), 5.98 (1H, br. s, ═CH), 6.17 (1H, br. s, ═CH), 7.16 (1H, br. s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.51, 21.59, 21.66, 21.76, 52.37, 69.87, 71.06, 122.73, 138.13, 154.14, 155.59, 163.92; MS (EI) *m/e* 289 (M^++1, 0.65), 205 (M^+-83, 8.72), 160 (M^+-128, 7.53), 116 (M^+-172, 9.96), 43 (M^+-245, 100); HRMS calcd for $C_{12}H_{20}N_2O_6$: 288.1321. Found: 288.1304.

3.1.4. Aza-Baylis–Hillman adduct 2c (128 mg, yield 67%). A white solid; mp 100–102 °C; IR (CH_2Cl_2) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.29–1.34 (12H, m, CH_3), 4.99–5.09 (2H, m, CH), 6.17 (1H, br. s, ═CH), 6.39 (1H, br. s, ═CH), 7.10–7.16 (2H, m, ArH), 7.27 (1H, br. s, NH), 7.35–7.41 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.69, 21.76, 22.48, 22.61, 70.06, 71.36, 122.61, 122.89, 129.27, 131.28, 137.87, 148.82, 153.93, 155.65, 161.67; MS (EI) *m/e* 385 (M^++1, 0.53), 298 (M^+-86, 2.23), 215 (M^+-169, 29.21), 173 (M^+-211, 51.81), 128 (M^+-256, 100), 43 (M^+-341, 52.22). Anal. calcd for $C_{17}H_{21}N_2O_6Cl$ requires C, 53.06; H, 5.50; N, 7.28%. Found: C, 53.18; H, 5.55; N, 7.15%.

3.1.5. Aza-Baylis–Hillman adduct 2d (51 mg, yield 40%). A colorless oil; IR (CH_2Cl_2) ν 1747 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.26–1.37 (12H, m, CH_3), 4.94–5.08 (2H, m, CH), 5.69 (1H, br, NH), 5.93 (1H, br, ═CH), 7.02 (1H, br, ═CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.55, 21.63, 21.73, 25.44, 67.78, 70.54, 114.09, 118.57, 121.70, 152.26, 155.33; MS (EI) *m/e* 255 (M^+, 1.98), 154 (M^+-101, 8.91), 127 (M^+-128, 25.74), 83 (M^+-172, 15.84), 43 (M^+-212, 100); HRMS calcd for $C_{11}H_{17}N_3O_4$: 255.1219. Found: 255.1185.

3.1.6. Aza-Baylis–Hillman adduct 2e (120 mg, yield 61%). A colorless oil; IR (CH_2Cl_2) ν 1743 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.24–1.33 (12H, m, CH_3), 4.98–5.05 (2H, m, CH), 6.16 (1H, br. s, NH), 6.40 (1H, br. s, ═CH), 6.59 (1H, br. s, ═CH), 7.35–7.38 (2H, m, ArH), 8.27–8.33 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.50, 21.60, 21.70, 21.77, 70.54, 71.85, 115.48, 122.22, 125.09, 125.95, 129.51, 145.37, 155.01, 161.05, 162.66; MS (EI) *m/e* 397 (M^++2, 0.68), 396 (M^++1, 3.16), 309 (M^+-86, 3.66), 267 (M^+-128, 18.81), 140 (M^+-255, 14.08), 43 (M^+-352, 100); HRMS calcd for $C_{17}H_{21}N_3O_8+Na^+$: 418.1226. Found: 418.1221.

3.1.7. Aza-Baylis–Hillman adduct 2f (166 mg, yield 91%). A white solid; mp 104–105 °C; IR (CH_2Cl_2) ν 1751 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.24–1.30 (12H, m, CH_3), 2.35 (3H, s, CH_3), 4.97–5.02 (2H, m, CH), 6.17 (1H, br. s, ═CH), 6.31 (1H, br. s, ═CH), 6.90 (1H, br. s, NH), 7.00–7.03 (2H, m, ArH), 7.18–7.21 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.61, 21.51, 21.65, 21.71, 21.78, 69.89, 71.18, 120.77, 129.68, 129.74, 135.50, 138.04, 148.06, 154.01, 155.62, 162.02; MS (EI) *m/e* 365 (M^++1, 0.31), 278 (M^+-86, 2.35), 215 (M^+-149, 20.31), 173 (M^+-191, 32.71), 108 (M^+-256, 100). Anal. calcd for $C_{18}H_{24}N_2O_6$ requires C, 59.33; H, 6.64; N, 7.69%. Found: C, 59.38; H, 6.84; N, 7.63%.

The aza-Baylis–Hillman reaction of DEAD with acrylates or acrylonitrile was carried out in the same manner as that described above.

3.1.8. Aza-Baylis–Hillman adduct 3b (35 mg, yield 31%). A colorless oil; IR (CH_2Cl_2) ν 1740 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.25–1.39 (6H, m, CH_3), 4.20–4.41 (4H, m, CH_2), 5.73 (1H, s, NH), 5.99 (1H, br. s, ═CH), 6.82 (1H, br. s, ═CH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.15, 14.29, 62.90, 64.21, 114.02, 121.54, 125.45, 152.77, 155.53; MS (EI) *m/e* 228 (M^++1, 100), 184 (M^+−43, 49.00), 156 (M^+−71, 51.14), 129 (M^+−98, 26.58); HRMS calcd for $C_7H_8N_3O_3$ [M^+−OEt]: 182.0566. Found: 182.0528.

3.1.9. Aza-Baylis–Hillman adduct 3c (138 mg, yield 86%). A white solid; mp 100–103 °C; IR (CH_2Cl_2) ν 1748 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.26–1.33 (6H, m, CH_3), 4.21–4.30 (4H, m, CH_2), 6.23 (1H, br. s, ═CH), 6.49 (1H, br. s, ═CH), 7.02 (1H, br. s, NH), 7.13–7.16 (2H, m, ArH), 7.24–7.30 (1H, m, ArH), 7.38–7.45 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.24, 14.30, 62.22, 63.32, 121.21, 124.69, 126.06, 129.40, 137.77, 150.33, 154.60, 155.95, 161.86; MS (EI) *m/e* 323 (M^++1, 0.03), 229 (M^+−93, 100), 157 (M^+−165, 24.15), 129 (M^+−193, 60.31), 101 (M^+−221, 66.81). Anal. calcd for $C_{15}H_{18}N_2O_6$ requires C, 55.89; H, 5.63; N, 8.69%. Found: C, 55.62; H, 5.50; N, 8.60%.

3.1.10. Aza-Baylis–Hillman adduct 3d (125 mg, yield 70%). A white solid; mp 68–70 °C; IR (CH_2Cl_2) ν 1747 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.24–1.33 (6H, m, CH_3), 4.21–4.29 (4H, m, CH_2), 6.21 (1H, br. s, ═CH), 6.44 (1H, br. s, ═CH), 7.02 (1H, br. s, NH), 7.04–7.19 (2H, m, ArH), 7.33–7.39 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.20, 14.26, 62.22, 63.33, 122.61, 122.89, 129.40, 131.37, 137.53, 148.73, 154.45, 155.93, 161.60; MS (EI) *m/e* 311 (M^+−45, 1.43), 229 (M^+−127, 100), 129 (M^+−227, 68.48), 101 (M^+−255, 68.31). Anal. calcd for $C_{15}H_{17}N_2O_6Cl$ requires C, 50.50; H, 4.80; N, 7.85%. Found: C, 50.61; H, 4.72; N, 7.86%.

3.1.11. Aza-Baylis–Hillman adduct 3e (174 mg, yield 95%). An orange oil; IR (CH_2Cl_2) ν 1752 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.24–1.36 (6H, m, CH_3), 4.23–4.33 (4H, m, CH_2), 6.23 (1H, br. s, ═CH), 6.44 (1H, br. s, ═CH), 6.99 (1H, br. s, NH), 7.35 (2H, d, J=9.0 Hz, ArH), 8.31 (2H, d, J=9.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.52, 14.58, 62.63, 63.78, 122.57, 125.43, 137.80, 145.65, 154.68, 155.34, 156.28, 156.31, 161.30; MS (EI) *m/e* 295 (M^+−72, 6.50), 183 (M^+−184, 15.22), 139 (M^+−228, 100), 109 (M^+−358, 53.82), 65 (M^+−302, 82.12); HRMS calcd for $C_{15}H_{17}N_3O_8$+Na^+: 390.0913. Found: 390.0908.

3.1.12. Aza-Baylis–Hillman adduct 3f (151 mg, yield 90%). A white solid; mp 76–78 °C; IR (CH_2Cl_2) ν 1747 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.24–1.32 (6H, m, CH_3), 2.35 (3H, s, CH_3), 4.20–4.28 (4H, m, CH_2), 6.21 (1H, br. s, ═CH), 6.46 (1H, br. s, ═CH), 6.99–7.03 (2H, m, ArH), 7.03–7.06 (1H, br. s, NH), 7.18–7.21 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.58, 14.64, 21.08, 62.51, 63.61, 121.20, 130.18, 130.20, 136.03, 148.42, 154.98, 156.29, 156.31, 162.38; MS (EI) *m/e* 337 (M^++1, 0.81), 229 (M^+−107, 100), 129 (M^+−207, 46.79), 101 (M^+−235, 43.41). Anal. calcd for $C_{16}H_{20}N_2O_6$ requires C, 57.13; H, 5.99; N, 8.33%. Found: C, 57.25; H, 6.03; N, 8.36%.

3.2. Crystallography

A suitable single crystal was mounted at the top of a glass capillary. Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radition λ=0.71069 Å using the ω–2θ technique at 20 °C. The data were collected for Lorentz polarization effects. The structure was solved by direct methods and expanded using Fourier techniques.[11] The non-hydrogen atoms were refined anisotropically by full-matrix least squares. All hydrogen atoms were included in calculated position. All calculations were performed using the TEXSAN crystallographic software package. Its crystal structure has been deposited at the Cambridge Crystallographic Data Center and has been allocated the deposition number: CCDC 215759.

Crystal data of **2f**: empirical formula: $C_{18}H_{24}N_2O_6$; formula weight: 364.39; crystal color, habit: colorless, prismatic; crystal dimensions: 0.451×0.390×0.123 mm^3; crystal system: monoclinic; lattice type: primitive; lattice parameters: a=11.2800(9) Å, b=9.2104(8) Å, c=19.2985(16) Å, α=90°, β=98.879°, γ=90°, V=1981.0(3) $Å^3$; space group: $P2(1)/c$; Z=4; D_{calc}=1.222 g/cm^3; F_{000}=776; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0449, 0.0805.

Acknowledgements

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7. The aza-Baylis–Hillman reaction of DIAD with MVK has not been reported previously.
8. Using phenyl acrylate as a Michael acceptor, the aza-Baylis–Hillman adduct **2a** is easily detected by TLC.
9. The C–N bond in amides has the double bond character. The geometric stereoisomer can be formed in some cases. Please see: (a) Fernandez, A. H.; Alvarez, R. M.; Abajo, T. M. *Synthesis* **1996**, 1299–1301. (b) Booth, B. L.; Noori, G. F. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2894. (c) Powell, J. E.; Osuch, C.; Burkholder, H. R.; Kulprathipanja, S.; Miller, J. H.; Stadtherr, L. G.; Baughman, R. G. *J. Org. Chem.* **1978**, *43*, 3166–3169, In this type of aza-Baylis–Hillman reaction, we found that the products **2** and **3** were formed stereospecifically.
10. The steric repulsion between two CO_2R groups causes that the *anti*-configuration is thermodynamically more favorable.
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Asymmetric aldol reactions using catalytic D(+)-proline: a new, economic and practical approach to a commonly employed C1–C6 keto-acid synthon of the epothilones

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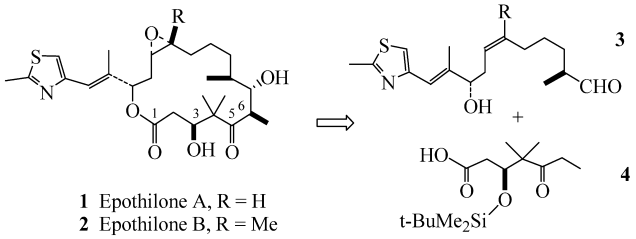
Abstract—A new approach to ketoacid **4**, a common C1–C6 fragment used in the total synthesis of epothilones was initiated by direct aldol reaction of acetone with a pivaldehyde-like substance **5**, catalyzed with D-proline, leading to a 2,6-diketoalcohol with better than 99% ee. Further intramolecular closure of the diketone **8** followed by oxidation of the silyl protected hydroxycyclohexenone **14** led to the desired product **4**. None of the steps have been optimized, yet the overall yield for the four-step process is 31%. The use of commercially available D-proline to construct the chiral center of **4** under very mild reaction conditions provided an economical and practical method for its construction.

1. Introduction

Since their discovery in 1993,[1] epothilones A–D have evoked a strong interest from the scientific community because of their taxotere-like anticancer activity.[2] One of the common strategies for total synthesis of epothilones includes construction of a C1–C6 fragment, for example, a ketoacid **4**, which undergoes aldol condensation with an aldehyde to set important stereochemical features of the epothilone architecture (Scheme 1).[3–8]

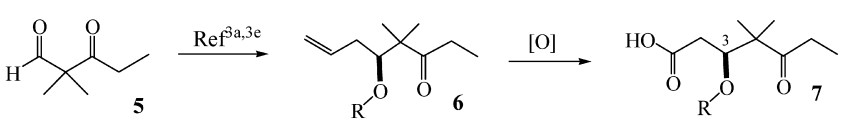


1 Epothilone A, R = H
2 Epothilone B, R = Me

Scheme 1.

The key for preparation of the C1–C6 fragment is to introduce a hydroxyl group at the C-3 position in an optically pure form. Nicolaou et al. has used Brown's allyl isopinocampheyl borane reagent [(+)-Ipc_2B(allyl)] to react with ketoaldehyde **5** to provide enantiomerically pure homoallyl alcohol (ee>98%), which was then oxidized to an alcohol derivative, ketoacid **7** (Scheme 2).[3a,e]

Wessjohann et al. obtained the alcohol **7** (92% de, R=*t*-$BuMe_2Si$) by a chromium-Reformatsky reaction of a chiral *N*-bromoacyloxazolidinone with the ketoaldehyde **5**, wherein the amide portion of the alcohol was hydrolyzed to ketoacid.[8] We found that the aldol reaction of chiral *N*-methylthioacetyloxazolidinones with the ketoaldehyde **5** can furnish the alcohol **7**, but the enantioselectivity is reversed if the boron reagents for forming the boron-enolate were different. With dibutylboron triflate the desired *S*-isomer was obtained in 54% de.[9] DeBrabander et al. reported that aldol reaction of acetylbornanesultam with the ketoaldehyde **5** can afford the alcohol **7** (R=*t*-$BuMe_2Si$) with 88% de.[10] Recently Altmann et al.[7] scaled up



Scheme 2.

Keywords: Epothilone; C1–C6 Keto-acid synthon; Asymmetric aldol reaction; Proline.
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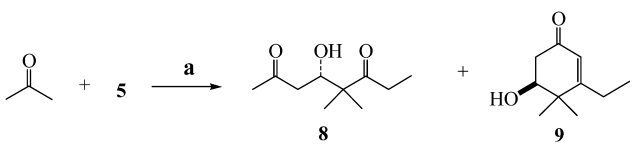
DeBrabander's synthesis, and determined the sign of optical rotation for *S*-ketoacid **4** should be negative instead of positive as reported by Nicolaou and DeBrabander's group, which was also confirmed by Avery.[11] Besides the above asymmetric aldol reactions, Kalesse et al. has made use of Sharpless's asymmetric epoxidation to establish the chiral center at the hydroxyl carbon (C-3), and furnished the ketoacid **7** by at least 13 steps from a chiral epoxide.[3] In addition, optical resolution has been used to prepare the ketoacid **7**. Shioji et al. reported that the corresponding racemic ketoacid *tert*-butyl ester of **7** can be resolved to its optical pure *S*-isomer by lipase.[12] Liu et al. treated a racemic terminal epoxide of a vinyl ketone with Jacobson's hydrolytic kinetic resolution to afford its required enantiomer, which was transferred to ketoacid **7** by carbomethoxylation and hydrolysis.[6] Here we report that the key C-3 chiral center connected with **4** could be introduced by the direct aldol condensation of ketoaldehyde **5** with acetone catalyzed by D-proline. Processing of the terminal methylketone group to a carboxylic acid was achieved in an unexpected fashion as outlined below.

2. Results and discussion

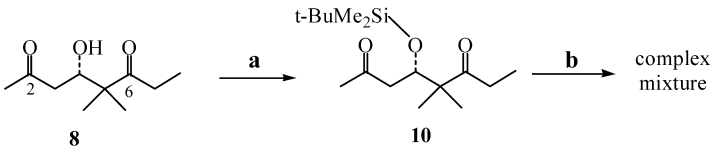
In 2000, List et al. found that the reaction of acetone with branched aldehydes such as isobuytraldehyde in the presence of L-proline can give very high yields and very high enantioselectivities of aldol products.[13] If List's conditions were used to construct the key C-3 chiral center such as **7**, it could provide an outstanding method for preparation of ketoacid **5**. We found that the 24 h reaction of D-proline (35 mol%) in DMSO/acetone with ketoaldehyde **5**[14] furnished aldol product **8** in 75% yield and with better than 99% ee (Mosher ester analysis). In addition, 1.9% of intramolecular cyclization product **9** was obtained from **8** (Scheme 3).



Scheme 3. (a) 0.35 equiv. D-proline, DMSO–acetone 4:1, rt, 24 h, 75% yield and >99% ee for **8**, 1.9% yield for **9**.

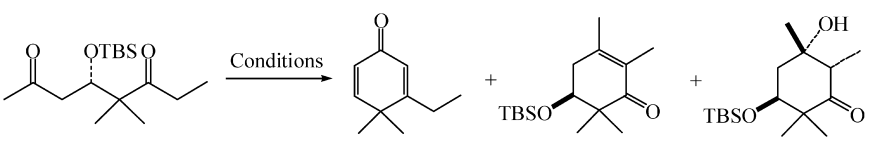
Silylation of **8** with *tert*-butyldimethylsilyl triflate (TBSOTf) afforded protected product **10** in 90% yield. Transformation of the methyl ketone group of **10** by selective bromoform reaction would be the most expedient synthetic route to ketoacid **4**. Unfortunately, attempted bromoform or iodoform reaction of **10** gave only complex mixtures when **10** was halogenated under basic conditions (Scheme 4). This is not surprising given the availability of 7 carbonyl α-protons in **10**, for which multiple reaction pathways can be envisioned for **10** under strongly basic conditions. Alternatively, low temperature kinetic enolization of the C1 methyl ketone of **7** or **9** providing an easily oxidizable silyl enol ether is an approach currently being investigated.

Nonetheless, it was recognized that the intramolecular aldol product, hydroxycyclohexenone **9**, could be transformed to ketoacid **4** by oxidative cleavage after its protection with various groups. For this study, the *tert*-butyldimethylsilyl moiety was used affording **10**. Results of intramolecular aldol reaction of **10** are shown in Table 1. When NaOH was reacted with **10** in H_2O/ethanol (1:1), the major product **12** was produced in 50% yield from attack of the $\Delta^{6,7}$ enolate on the C-2 ketone followed by β-elimination. Also produced in 25% yield was the dienone **11**, resulting from attack of the $\Delta^{1,2}$ enolate on the C-6 ketone followed by two β-eliminations. Product distributions in the reaction of **10** with amine bases such as pyrrolidine or proline were dependent on solvent effects. For example, reaction of **10** with 1 equiv. of pyrrolidine in THF gave 56% of the aldol adduct **13** in addition to 23% of dienone **11**. The



Scheme 4. (a) TBSOTf, DIPEA, CH_2Cl_2, −78 °C to rt, 2.5 h, 90% yield; (b) Br_2, NaOH, dioxane, H_2O, 0 °C.

Table 1. Products for intramolecular aldol condensation of **10** under different conditions



Entry	Conditions	**11** (%)	**12** (%)	**13** (%)
1	4 equiv. NaOH/H_2O/ethanol, 0 °C, 1 h	25	50	0
2	1 equiv. Pyrrolidine/THF, rt, 72 h	23	0	56
3	1 equiv. Pyrrolidine/CH_3CN, rt, 72 h	68	9.1	0
4	0.5 equiv. DL-Proline/DMF, 65 °C, 2 h	53	32	0

configuration of **13** was determined by the 2D-NMR NOESY spectrum.

On the other hand, the same reaction conducted in acetonitrile led to 68% of dienone **11** and only 9.1% of enone **12**. The β-silyloxy group in cyclohexenones readily undergoes elimination as reported by Corey et al.[15] in the related cyclopentanones. Clearly, ethyl substituted products (3-ethyl) produced in basic equilibria are capable of dual β-eliminations because the *gem*-dimethyl moiety does not interfere with the second elimination. Those products (2,3-dimethyl) from the other mode of aldol reaction can only readily eliminate HOH, and not the silyloxy group. In acetonitrile, elimination is faster than in THF, as evidenced by the high yield of the aldol intermediate **13** in THF but not acetonitrile.

With racemic proline in DMF at 65 °C for 2 h (entry 4), dienone **11** was the major product produced in 53% yield, while the remaining isolable material was the 2,3-dimethyl enone **12** (23% yield). Certainly the elevated temperature, zwitterionic proline and polar solvent were effective in solvolyzing aldol adducts thus producing the thermodynamic endpoint, dienone **11**, over other more sensitive intermediates leading to **11**. From the other manifold, aldol adduct **12** could not undergo the second elimination due to the gem-dimethyl group.

We reasoned that because the hydroxyl group is a poorer leaving group than a silyloxy group, that intramolecular aldol reaction of hydroxydiketone **8** in the presence of pyrrolidine could provide enhanced selectivity for 5β-hydroxy-2-eneone **9**, and suppress formation of undesired **11**. Thus, upon treatment of the diketo-alcohol **8** with pyrrolidine in dichloromethane at ambient temperature, compound **9** was produced in 76% yield and 41% of **8** was recovered.[16] Now, protection of **9** as the TBDMS silyl ether could be readily achieved in 81% unoptimized yield using the Corey method[15] with TBSCl and imidazole. On the other hand, with TBSOTf as the silylating agent, a variety of amine bases lead to dual elimination product **11**: DIPEA, 2,6-lutidine or pyridine. Finally, the double bond of **14** could be smoothly cleaved to the desired ketoacid **4** in 67% yield by the Sharpless method[17] employing $NaIO_4$ and $RuCl_3$ in $CCl_4/CH_3CN/H_2O$ (1:1:1.6) (Scheme 5). The keto-acid thus obtained (**4**) had a negative sign of optical rotation ($[\alpha]_D^{25}=-15.8$ (*c* 4.7, $CHCl_3$); while **4** prepared by a literature method[7,10] showed $[\alpha]_D^{25}=-15$ (*c* 0.56, $CHCl_3$). Further, **4** had an identical ^1H and ^{13}C NMR spectra compared to literature values.[2e,7] This result confirmed that the absolute configuration at the chiral center of **8** was 3*S*.

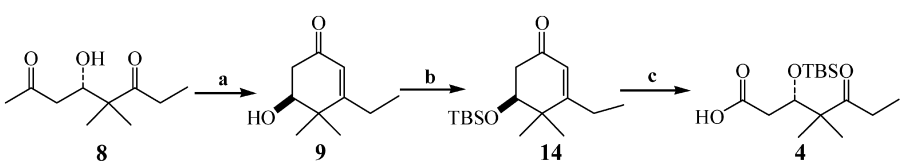
In summary, we have developed a new approach to ketoacid **4**, a common C1–C6 fragment for total synthesis of epothilones initiated by direct aldol reaction of acetone with a pivaldehyde-like substance **5**, catalyzed with D-proline, leading to a diketoalcohol with better than 99% ee. Further intramolecular closure of the diketone **8** followed by oxidation of the silyl protected hydroxycyclohexenone **14** led to the desired product. None of the steps have been optimized, yet the overall yield for the four-step process is 31%. The use of commercially available D-proline to construct the chiral center of **4** under very mild reaction conditions provided an economical and practical method for its construction.

3. Experimental

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Where necessary, chemicals were purified according to reported procedures.[18] For example, tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use and could be stored over 4A molecular sieves to ensure the lowest levels of water. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with a 254 nm UV light. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040–0.063 mm, 230–400 mesh ASTM). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 at 400 and 100 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded on a Bruker BioApex FTMS system. Optical rotations were determined on a Rudolph Autopol IV polarimeter. All mps were uncorrected.

3.1. General

3.1.1. (−)-4*S*-4-Hydroxy-5,5-dimethyl-2,6-octanedione (8). A mixture of D-proline (2.0 g, 0.35 mmol) in anhydrous acetone (50 mL) and anhydrous DMSO (200 mL) was stirred at room temperature for 15 min. At this time, the aldehyde **5** was added and the mixture stirred at room temperature for 24 h. Saturated aqueous ammonium chloride (250 mL) was added and the reaction mixture was extracted with ethyl acetate (3×200 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The residue was subjected to flash chromatography (silica gel, EtOAc–hexanes 1:1) providing **8** (7.0 g, 75%) and **9** (160 mg, 1.9%) as colorless oils; for **8**. R_f=0.53 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{25}=-48.8$ (*c*=1.2, $CHCl_3$); IR (thin film) ν_{max} 3493, 2975, 2940, 2857, 1704, 1701, 1469, 1366, 1099, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (m,



Scheme 5. (a) 0.1 equiv. pyrrolidine, CH_2Cl_2, rt, 3 h, 76% yield; (b) TBSCl, imidazole, DMF, rt, 72 h, 81%; (c) 0.03 equiv. $RuCl_3$, 5.5 equiv. $NaIO_4$, CCl_4–CH_3CN–H_2O 1:1:1.6, 1 h, 67%.

1H, C*H*OH), 3.46 (s, 1H, O*H*), 2.35–2.28 (m, 4H, CHCH_2CO, CH_3CH_2CO), 1.95 (s, 3H, CH_3CO), 0.90, 0.87 (2s, 6H, C(CH_3)$_2$), 0.76 (t, J=6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 209.0, 71.7, 51.0, 45.1, 31.0, 30.4, 20.8, 19.5, 7.5; ESI$^+$ HRMS m/z 209.1108, M+Na$^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1154.

3.1.2. (−)-5*S*-3-Ethyl-4,4-dimethyl-5-hydroxycyclohex-2-enone (9). To the solution of **8** (2.90 g, 15.6 mmol) in dichloromethane (10 mL) at room temperature was added pyrrolidine (0.11 g, 1.56 mmol). The solution was stirred at room temperature for 3 h and then concentrated on the rotary evaporator at room temperature. The residue was purified by flash chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product **9** as a colorless oil (1.16 g, 76% based on converted **8**) along with recovered **8** (1.20 g or 41%). R_f=0.32 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{25}$=−17.8 (c=0.70, $CHCl_3$); IR (thin film) ν_{max} 3430, 2971, 2938, 2881, 1666, 1647, 1610, 1468, 1417, 1362, 1283, 1047, 863 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (s, 1H, C*H*=C), 4.16 (s, 1H, O*H*), 3.70–3.60 (m, 1H, C*H*OH), 2.47–2.29 (m, 2H, HOCHCH_2), 2.10 (q, 2H, J=6.8 Hz, CH_2CH_3), 1.01, 0.96 (2s, 6H, C(CH_3)$_2$), 0.89 (t, J=6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 173.5, 122.8, 73.7, 42.4, 41.1, 24.7, 23.9, 20.3, 11.3; ESI$^+$ HRMS m/z 151.1104, M−H_2O+H$^+$ calcd for $C_{10}H_{15}O$ 151.1123.

3.1.3. (−)-5*S*-3-Ethyl-4,4-dimethyl-5-(*tert*-butyldimethylsilyl)oxycyclohex-2-enone (14). To a solution of *tert*-butyldimethylsilylchloride (0.247 g, 1.65 mmol) at 0 °C was added a solution of **9** (0.180 g, 1.07 mmol) and imidazole (0.146 g, 2.14 mmol) in DMF (0.8 mL). The ice bath was removed and the solution was stirred at room temperature for 72 h until all of the starting material had disappeared by TLC. The mixture was directly subjected to flash chromatography to give **14** as a colorless oil (0.255 mg, 81%). R_f=0.88 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{25}$=−7.7 (c=0.58, $CHCl_3$); IR (thin film) ν_{max} 2957, 2931, 2884, 2857, 1673, 1614, 1471, 1256, 110, 1079, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 1H, C*H*=C), 3.65 (dd, 1H, J=9.6, 4.4 Hz, 1H, C*H*OH), 2.39 (dd, J=16.4, 4.4 Hz, 1H, HOCHCH_2), 2.08 (dd, J=16.4, 9.6 Hz, 1H, HOCHCH_2), 2.10 (q, 2H, J=6.0 Hz, CH_2CH_3), 0.98, 0.0.93 (2s, 6H, C(CH_3)$_2$), 0.89 (t, J=6.0 Hz, 3H, CH_2CH_3), 0.70 (s, 9H, SiC(CH_3)$_3$), −0.11, −0.12 (2s, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 172.2, 123.2, 74.7, 43.2, 41.7, 25.5, 24.8, 23.7, 20.5, 17.7, 11.6, −3.7, −4.4; ESI$^+$ HRMS m/z, 283.2106, M+H$^+$ calcd for $C_{16}H_{31}O_2Si$ 283.2093.

3.1.4. (−)-4*S*-4-(*tert*-Butyldimethylsilyl)oxy-5,5-dimethyl-2,6-octanedione (10). To the solution of **8** (5.58 g, 30 mmol) and *N*,*N*-diisopropylethylamine (6.19 g, 48 mmol) in dichloromethane (200 mL) at −78 °C was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (11.9 g, 45 mmol). The solution was slowly warmed to room temperature and stirred for about 2 h until the starting material disappeared. The reaction was quenched with aqueous ammonium chloride and extracted with ethyl acetate. The organic solution was dried over anhydrous sodium sulfate and evaporated. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexanes) to give **10** as a colorless oil (8.1 g, 90%). R_f=0.79 (silica gel, 25% ethyl acetate in hexane); $[\alpha]_D^{25}$=−47.5 (c 1.67, $CHCl_3$); IR (thin film) ν_{max} 2956, 2934, 2886, 2857, 1716, 1471, 1362, 1254, 1091, 1024, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32–4.45 (m, 1H, SiOC*H*CH_2), 2.52–2.25 (m, 4H, SiOCHCH_2, CH_2CH_3), 1.99 (s, 3H, COCH_3), 0.94, 0.95 (2s, 6H, C(CH_3)$_2$), 0.84 (t, 3H, J=7.2 Hz, CH_2CH_3), 0.70 (s, 9H, SiC(CH_3)$_3$), −0.05, −0.18 (2s, 6H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 206.2, 71.9, 52.4, 48.2, 31.8, 30.7, 25.9, 21.4, 20.4, 18.0, 7.6, −3.6, −4.4; ESI$^+$ HRMS m/z 323.2017, M+Na$^+$ calcd for $C_{16}H_{32}O_3NaSi$ 323.2018.

3.1.5. 3-Ethyl-4,4-dimethylcyclohex-2,5-dienone (11) and (+)-3*S*,5*S*,6*S*-3-(*tert*-butyldimethylsilyl)oxy-5-hydroxy-2,2,5,6-tetramethylcyclohexanone (13). To the solution of **10** (0.30 g, 1 mmol) in THF (1 mL) at room temperature was added pyrrolidine (0.071 g, 1 mmol). The solution was stirred at room temperature for 72 h. Saturated aqueous ammonium chloride was added and extracted with ethyl acetate. The organic phase was dried, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes) to give **13** (0.084 g, 56%) as a white solid and **11** (0.065 g, 23%) as colorless oil; **11**. R_f=0.52 (silica gel, 25% ethyl acetate in hexane); IR (thin film) ν_{max} 2971, 2936, 2879, 1666, 1625, 1603, 1486, 1294, 1138, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85, 6.12 (2d, J=8 Hz, 2H, C*H*=C*H*), 6.08 (s, 1H, C*H*=C), 2.28 (q, J=6.2 Hz, 2H, CH_2CH_3), 1.18 (s, 6H, C(CH_3)$_2$), 1.15 (t, J=6.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 170.5, 158.4, 126.5, 124.3, 40.6, 26.1, 24.2, 12.1; ESI$^+$ HRMS m/z 151.1122, M+H$^+$ calcd for $C_{10}H_{15}O$ 151.1123. **13**. R_f=0.53 (silica gel, 25% ethyl acetate in hexane); mp 93.2 °C; $[\alpha]_D^{25}$=+132 (c 0.41, $CHCl_3$); IR (thin film) ν_{max} 3499, 2933, 2887, 2857, 1703, 1463, 1378, 1255, 1093, 1061, 1030, 982, 867, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, J=9.6, 6.4 Hz, 1H, SiOC*H*CH_2), 2.68 (q, J=6.4 Hz, 1H, C*H*CH_3), 1.92–1.99 (m, 2H, SiOCHCH_2), 1.65 (s, 1H, O*H*), 1.31, 1.08, 1.06 (3s, 9H, CCH_3, C(CH_3)$_2$), 1.02 (d, J=6.4 Hz, 3H, CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.070, 0.041 (2s, 6H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 73.0, 72.5, 51.0, 48.2, 44.7, 28.9, 25.8, 21.8, 19.3, 18.0, 7.4, −4.1, −5.0; ESI$^+$ HRMS m/z 323.2020, M+Na$^+$ calcd for $C_{16}H_{32}O_3NaSi$ 323.2018.

3.1.6. (+)-5*S*-2,3,6,6-Tetramethyl-5-(*tert*-butyldimethylsilyl)oxy-cyclohex-2-enone (12). To the solution of **4** (0.30 g, 1 mmol) in ethanol (20 mL) and H_2O (18 mL) NaOH (0.16 g, 4 mmol in 2 mL of water) was added at 0 °C. The reaction mixture was stirred at above temperature for 2 h and extracted with ethyl acetate. The organic phase was dried, filtered and evaporated in reduced pressure. The residue was purified by flash chromatography to give **12** (0.141 mg, 50%) and **11** (0.038 g, 25%) as colorless oil. R_f=0.61 (silica gel, 25% ethyl acetate in hexane); $[\alpha]_D^{25}$=+57.8 (c 0.64, $CHCl_3$); IR (thin film) ν_{max} 2955, 2930, 2892, 2857, 1667, 1641, 1471, 1379, 1255, 1102, 1069, 873, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70–3.60 (m, 1H, SiOC*H*CH_2), 2.30–2.40 (m, 2H, SiOCHCH_2), 1.83, 1.67, 1.05, 1.03 (4s, 12H, CH_3C=CCH_3, C(CH_3)$_2$), 0.82 (s, 9H, SiC(CH_3)$_3$), 0.0029–0.020 (m, 6H,

$Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 148.8, 129.4, 73.8, 47.2, 39.2, 25.9, 22.1, 21.4, 18.4, 18.1, 11.5, −4.1, −4.8; ESI^+ HRMS *m/z* 151.1122, M−TBSOH+H^+ calcd for $C_{10}H_{15}O$ 151.1123.

3.1.7. (−)-3*S*-3-(*tert*-Butyldimethylsilyl)oxy-4,4-dimethyl-5-oxo-heptanoic acid (4). Sodium periodate (1.18 g, 5.5 mmol) was added into the solution of enone **14** (282 mg, 1.0 mmol) in CCl_4 (1.8 mL) and CH_3CN (1.8 mL). Under vigorous magnetic stirring, $RuCl_3$ (2.9 mL, 9.28 mM in distilled H_2O, 0.027 mmol) was added and stirring was continued for about 1 h until the starting material had disappeared by TLC. Water was gradually added until the separated $NaIO_3$ dissolved and the mixture was then extracted with ethyl acetate (3×5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent was then rotary evaporated. The residue was subjected to flash chromatography (silica gel, 50% ethyl acetate in hexanes) to give **4** (0.202 g, 67%) as a colorless oil. $[\alpha]_D^{25}=-15.8$ (*c* 4.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H, COO*H*), 4.45 (dd, 1H, *J*=6.8, 3.6 Hz, SiOC*H*), 2.62–2.42 (m, 3H, CH_2CH_{-3}, CH_2COOH), 2.34, 2.30 (dd, *J*=6.8, 16 Hz, $SiOCHCH_2$), 1.12, 1.06 (2s, 6H, $2CH_3$), 0.98 (t, 3H, *J*=7.2 Hz, CH_2CH_{-3}), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.036, 0.017 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 178.5, 73.7, 52.7, 39.5, 31.9, 26.1, 21.1, 20.7, 18.3, 7.9, −4.2, −4.7.

3.2. Synthesis of Mosher ester

Into a flask **8** (37.2 mmg, 0.2 mmol), *R*-(+)-α-methoxy-α-trifluromethylphenylacetic acid (MPTA, 56.2 mg, 0.24 mmol), DCC (53.6 mg, 0.26 mmol), DMAP (6.1 mg, 0.05 mmol) and dichloromethane (5 mL) were added in order. The mixture was stirred at room temperature for 24 h and directly subjected to flash chromatography (silica gel, 40% ethyl acetate in hexanes) to give the Mosher ester (22 mg, 30% for **8** and 45 mg, 56% for racemic **8**).

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Highly diastereoselective conjugate additions of monoorganocopper reagents to chiral imides

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Abstract—Stereoselective conjugate additions to chiral *N*-enoyl amides employing various monoorganocuprate reagents, Li[RCuI], are described. The presence of TMSI in the addition of Li[RCuI] in THF provided the highest stereoselectivities. Reversed major diastereomeric ratios were obtained employing Li[RCuI] in ether or conventional copper-promoted Grignard reagents. The results presented support the favored *anti-s-cis* conformation of the substrates using Li[RCuI]/TMSI in THF, while the copper-promoted Grignard reagents or the Li[RCuI] reagents in ether favor the opposite *syn-s-cis* conformation. Influence of lithium ions on the stereoselective conjugate addition of the monoorganocuprate reagent, Li[BuCuI], has been investigated and two different mechanistic pathways are presented. The results show that iodotrimethylsilane (TMSI) is crucial for the asymmetric conjugate addition of the copper reagent, but only in THF or when 12-crown-4 is used. The reaction is thought not to involve any halosilane in any critical steps in the organocopper mechanisms conducted in ether. The $(CuI)_4(SMe_2)_3$ complex precursor plays an instrumental role for the conjugate addition using monoorganocopper reagents.

1. Introduction

Organocopper reagents are among the most versatile reagents available for conjugate addition reactions.[1] Applications of organocopper chemistry began nearly four decades ago when House[2] demonstrated the very useful Gilman reagents, LiR_2Cu, in conjugate addition reactions. However, the major disadvantage with the LiR_2Cu type reagent is that one has to employ at least 2 equiv. of the lithium reagent for each equivalent of copper(I) source, which would become a serious dilemma if indispensable R groups are employed. The monoorganocopper reagents, depicted either as RCu·LiX or Li[RCuX],[2b] possess an excellent economy of group transfer. However, their inherent lower solubility and reactivity have limited their widespread use as reliable reagents in conjugate addition reactions. These problems can sometimes be solved by taking advantage of Lewis acids[3] or non-transferable ligands,[4] in the conjugate addition process. Chlorotrimethylsilane (TMSCl) is probably the most common additive employed with Gilman type reagents.[5]

Several contradicting theories have appeared regarding the precise role of TMSCl in the addition of LiR_2CuLi,[5f–u] but it seems most likely that TMSCl is favoring a rate limiting silylation of an intermediate copper π-complex.[5d,e] This mechanistic insight regarding the organocuprate in conjugate addition was supported by determination of kinetic isotope effects for $Li[Bu_2Cu]$ promoted by TMSCl to enones in ether and THF.[5v] Because of the uncertainty of many variables in the organocopper reactions (e.g. cuprate structures, solvent, additives, reaction conditions, substrate as well as the cuprate cluster at each stage of the reaction pathway), a detailed mechanistic explanation has not yet emerged. Nor could an α-cuprioketone be neglected as a favored reaction intermediate.[6] It is generally accepted that the initial lithium–carbonyl coordination is a critical initial feature in the conjugate addition in the absence of additives, which also seems to be a sufficient activator for highly reactive α,β-unsaturated systems. On the other hand, butylcopper prepared from BuLi and CuI in ether, washed free from LiI at −78 °C, has been reported to undergo conjugate addition to a chiral enoate in the presence of iodotrimethylsilane (TMSI).[7c] Thus, in absence of lithium, there is evidence that powerful electrophiles, e.g. trimethylsilyl triflate[7d] and TMSI,[7] can promote the conjugate addition of butylcopper.

Chiral 2-oxazolidinones[8] have also been used as efficient chiral auxiliaries for copper-promoted asymmetric conjugate additions of Grignard reagents[9] and zirconium reagents.[10] Recently, we reported stereoselectivities as high as 96% diastereomeric excess (de) employing TMSI as an additive using Li[RCuI] in asymmetric conjugate

Keywords: Organocopper; Conjugate addition; 1,4-Addition; TMSI; Asymmetric addition.
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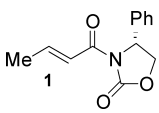
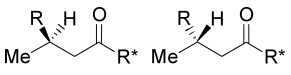
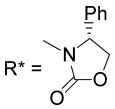
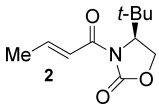
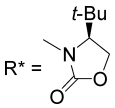
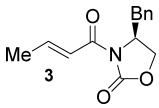
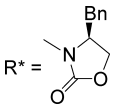
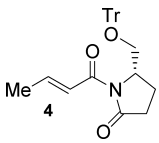
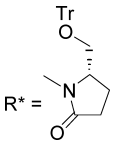
Table 1. Asymmetric conjugate additions to various *N*-crotonyl substituted chiral auxiliaries (**1**–**4**)

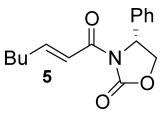
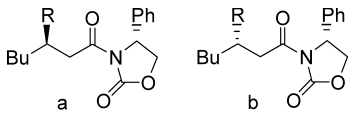
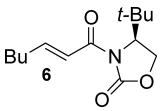
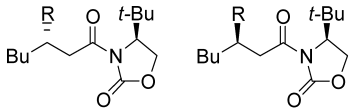
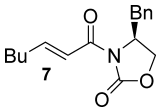
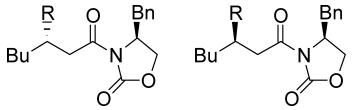
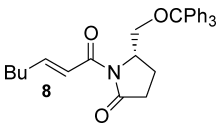
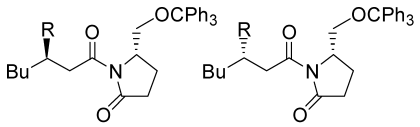
Substrate	Entry	Cu(I)[a]	Reagent	Additives(s)[b]	Ratio(a:b)	Yield[c]	Product (a:b)	Reference
	1	A	Li[BuCuI]/THF	TMSI	**15**; R=Bu; 98:2 (**15***S*:**15***R*)	83		9f,g
	2	A	Li[BuCuI]/THF	-	**15**; R=Bu; 24:76 (**15***S*:**15***R*)	60(30)		9g
	3	A	Li[BuCuI]/THF	TMSCI	**15**; R=Bu; 14:86 (**15***S*:**15***R*)	12(85)		9g
	4	A	Li[BuCuI]/Et_2O	TMSI	**15**; R=Bu; 6:94 (**15***S*:**15***R*)	90		9g
	5	A	Li[BuCuI]/Et_2O	-	**15**; R=Bu; 6:94 (**15***S*:**15***R*)	90		9g
	6	A	Li[BuCuI]/Et_2O (2 h)	TMSI	**15**; R=Bu; 6:94 (**15***S*:**15***R*)	75(20)		9g
	7	A	Li[BuCuI]/Et_2O (2 h)	-	**15**; R=Bu; 6:94 (**15***S*:**15***R*)	75(20)		9g
	8	A	Li[BuCuI]/Et_2O	TMSI/12 4[d]	**15**; R=Bu; 72:28 (**15***S*:**15***R*)	80		9g
	9	A	Li[BuCuI]/Et_2O	TMSI/12 4[e]	**15**; R=Bu; 96:4 (**15***S*:**15***R*)	80		9g
	10	A	Li[BuCuI]/Et_2O	12 4[e]	**15**; R=Bu; -	0(90)		9g
	11	A	Li[BuCuI]/THF	$MgBr_2$[f]	**15**; R=Bu; 9:91 (**15***S*:**15***R*)	77		9f
	12	B[g]	Li[BuCuI]/THF	TMSI	**15**; R=Bu; 90:10 (**15***S*:**15***R*)	50(45)		9g
	13	B	Li[BuCuI]/THF	-	**15**; R=Bu; 44:56 (**15***S*:**15***R*)	12(85)		9g
	14	B	Li[BuCuI]/THF	TMSI	**15**; R=Bu; -	0(95)		9g
	15	A	Li[BuCuI]LiI/THF	TMSCI	15; R=Bu; 69:31 (**15***S*:**15***R*)	55(40)		9g
	16	A	Li[BuCuI]LiI/Et_2O	TMSCI	**15**; R=Bu; 45:55 (**15***S*:**15***R*)	85		9g
	17	A	Li[PuCuI]/THF	TMSI	**16**; R=Ph; 96:4 (**16***R*:**16***S*)	83		9f
	18	A	Li[PuCuI]/THF	-	**16**; R=Ph; 10:90 (**16***R*:**16***S*)	81		
	19	A	PhMgCI/CuI[h]/THF	-	**16**; R=Ph; 5:95 (**16***R*:**16***S*)	74		9f
	20	A	PhMgCI/CuI[h]/THF	TMSI	**16**; R=Ph; 5:95 (**16***R*:**16***S*)	51(40)		9f
	21	A	Li[BuCuI]/THF	TMSI	**17**; R=Bu; 93:7 (**17***R*:**17***S*)	80		
	22	A[i]	Li[BuCuI]/THF	TMSI	**17**; R=Bu; 93:7 (**17***R*:**17***S*)	77		
	23	A	BuMgBr/CuI[h]/THF	-	**17**; R=Bu; 9:91 (**17***R*:**17***S*)	75		
	24	A	Li[PuCuI]/THF	TMSI	**18**; R=Ph; 95:5 (**18***S*:**18***R*)	75		
	25	A	Li[BuCuI]/THF	TMSI	**19**; R=Bu; 85:15 (**19***R*:**19***S*)	98		9f
	26	A	Li[BuCuI]/THF	BF_3OEt_2	**19**; R=Bu; 80:20 (**19***R*:**19***S*)	14(85)		
	27	A	Li[BuCuI]/THF	$MgBr_2$[f]	**19**; R=Bu; 50:50 (**19***R*:**19***S*)	71		9f
	28	A	Li[PuCuI]/THF	TMSI	**20**; R=Ph; 87:13 (**20***S*:**20***R*)	86		9f
	29	A	PhMgCI/CuI[h]	-	**20**; R=Ph; 45:55 (**20***S*:**20***R*)	80		9f
	30	A	Li[*t*-BuCuI]/THF	TMSI	**21**; R=*t*-Bu; 87:13 (**21***S*:**21***R*)[j]	85		9f
	31	A	Li[BuCuI]/THF	TMSI	**22**; R=Bu; 94:6 (**22***S*:**22***R*)	97		7d
	32	A	Li[BuCuI]/LiI[k]/THF	TMSI	**22**; R=Bu; 93:7 (**22***S*:**22***R*)	97		
	33	A	Li[BuCuI]/THF	BF_3OEt_2	**22**; R=Bu; -	0(95)		
	34	A	BuMgBr/CuI[h]/THF	TMSI	**22**; R=Bu; 4:96 (**22***S*:**22***R*)	92		
	35	A	BuMgBr/CuI[l]/THF	TMSI	**22**; R=Bu; 7:93 (**22***S*:**22***R*)	47(50)		
	36	A	Li[PuCuI]/THF	TMSI	**23**; R=Ph; 96:4 (**23***R*:**23***S*)	94		7d
	37	A	Li[*t*-BuCuI]/THF	TMSI	**24**; R=*t*-Bu; 89:11 (**24***R*:**24***S*)	90[m]		
	38	A	Li[Bu_2Cu]LiI/Et_2O	TMSCI	**22**; R=Bu; 45:55 (**22***S*:**22***R*)	63		
	39	A	Li[Bu_2Cu]LiI/THF	TMSCI	**22**; R=Bu; 15:85 (**22***S*:**22***R*)	15		
	40	A	Li[Ph_2Cu]LiI/THF	TMSCI	**22**; R=Ph; 10:90 (**22***S*:**22***R*)	94		

[a] 1.4–1.5 equiv. of 'RCu' vs substrate. Reactions quenched after 4 h at −78 °C. A=CuI purified via DMS and used as the $(CuI)_4(DMS)_3$ complex. B=99.999% purity grade CuI.
[b] 1.0 equiv. additive vs copper reagent.
[c] Based on isolated and purified material (a+b). Recovered substrate in brackets.
[d] 1.0 equiv. 12-crown-4 vs lithium.
[e] 2.0 equiv. 12-crown-4 vs lithium.
[f] Precomplexed $MgBr_2{\cdot}OEt_2$ (1 equiv.) and imide **3** at +20 °C.
[g] 0.75 equiv. DMS added to CuI.
[h] CuI·0.75DMS (1 equiv.) vs RMgBr.
[i] $(CuI)_4(i\text{-}Pr_2S)_3$ complex.
[j] *R*/*S* assignments based on X-ray structure of **21a**(**21***S*).
[k] 9 equiv. LiI added.
[l] 10 mol% CuI·0.75DMS vs BuMgBr.
[m] *R*/*S* assignments based on analogy.

additions to enantiomerically pure *N*-enoyl 2-oxazolidinones.[9f,g] We also described the efficiency of $MgBr_2$ as an additive to alter the availability of the possible π-faces in asymmetric conjugate addition reactions to these substrates. In an associated study, we reported the influence of dimethyl sulfide (DMS) as a key component for obtaining outstanding yields and high levels of stereoselectivity in the 1,4-addition of monosilylcopper reagents.[11]

We now report a wide variety of copper-promoted asymmetric conjugate addition reactions utilizing a number of chiral *N*-enoyl substituted amides. Several auxiliaries have been scrutinized in order to expand the scope of the asymmetric conjugate additions employing the Li[RCuI]/TMSI system. The monoorganocopper reagent prepared from the CuI·0.75DMS precursor complex is extraordinarily useful in conjugate addition reactions. DMS remaining from purified CuI, plays a decisive role in obtaining very high yields and surprisingly high levels of stereoselectivity. Due to the drastic solvent dependence on the conjugate addition of Li[RCuI], two significantly different mechanistic models are presented.

Table 2. Asymmetric conjugate additions to various *N*-heptenoyl substituted chiral auxiliaries (**5**–**8**)

Entry	Reagent(s)[a] (RCu)	Substrate product(s) (a:b)	Product(s) (a:b)	Ratio (**a**:**b**)	Yield[b]	Reference
41	Li[PhCuI]/TMSI			**25**; R=Ph; 97:3 (**25***R*:**25***S*)	83	9f
42	Li[PhCuI]/TMSI			**15**; R=Me; 91:9 (**15***R*:**15***S*)	84	9f
43	Li[PhCuI]/TMSI			**26**; R=Ph; 91:9 (**26***S*:**26***R*)	90	
44	Li[MeCuI]/TMSI			**17**; R=Me; 93:7 (**17***S*:**17***R*)	71	
45	Li[PhCuI]/TMSI			**27**; R=Ph; 88:12 (**27***S*:**27**R	87	9f
46	Li[MeCuI]/TMSI			**19**; R=Me; 82:18 (**19***S*:**19***R*)	86	9f
47	Li[Me_2CuI]/TMSI			**19**; R=Me; -	0(80)	
48	Li[MeCuI]/TMSI			**22**; R=Me; 97:3 (**22***R*:**22***S*)	91	7d
49	Li[MeCuI]/BF_3OEt_2			**22**; R=Me; -	0(95)	
50	Li[PhCuI]/TMSI			**28**; R=Ph; 94:6 (**28***R*:**28***S*)	92	7d

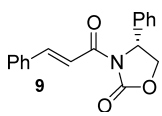
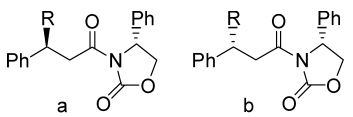
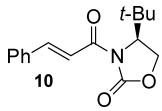
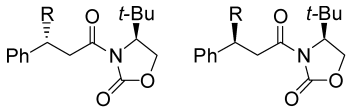
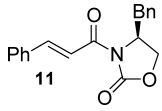
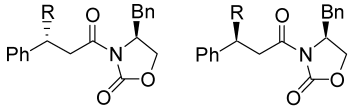
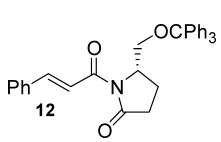
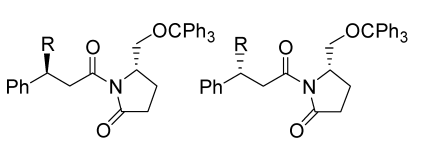
[a] 1.4–1.5 equiv. of 'RCu' vs substrate. 'RCu'/additive ratio=1:1. Solvent: THF. Reactions quenched after 4 h at −78 °C. Purified CuI used as the CuI·0.75DMS complex.
[b] Based on purified and isolated material (a+b). Recovered substrate in brackets.

2. Results and discussion

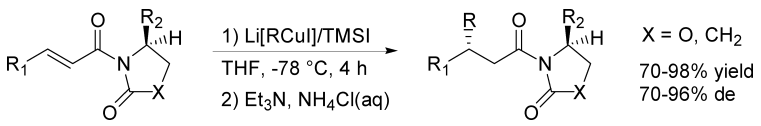
This study focuses on conjugate additions of organocopper reagents to various optically active *N*-enoyl 2-oxazolidinones and 2-pyrrolidinones. The TMSI promoted conjugate addition of Li[RCuI] has been used with considerable success to many α,β-unsaturated systems, and we now show the versatility of this protocol when using a number of chiral starting materials. The TMSI-promoted addition of Li[RCuI] was compared in terms of yield and diastereomeric ratio to a number of very common organocopper reagents (e.g., R_2CuLi/TMSCl, RMgX/CuI, or RCu/BF_3) in asymmetric conjugate addition (Tables 1–3). Employing the monoorganocuprate reagent, Li[RCuI], in the presence of TMSI was undoubtedly the most successful system, giving highest yields and highest diastereomeric ratios (Scheme 1).

The lithium monoorganocuprate reagents, Li[RCuI], were prepared from 1 equiv. of the appropriate organolithium

Table 3. Asymmetric conjugate additions to various *N*-cinnamoyl substituted chiral auxiliaries (**9**–**12**)

Entry	Reagent(s)[a] (RCu)	Substrate	Product(s) (a:b)	Ratio (**a:b**)	Yield[b]	Reference
51	Li[MeCuI]/TMSI			**16**; R=Me; 92:8 (**16***S*:**16***R*)	80	9f
52	Li[MeCuI]/TMSI			**25**; R=Bu; 92:8 (**25***S*:**25***R*)	96	9f
53	Li[MeCuI]/TMSI			**18**; R=Me; 95:5 (**18***R*:**18***S*)	80	
54	Li[MeCuI]/TMSI			**26**; R=Bu; 91:9 (**26***R*:**26***S*)	83	
55	Li[MeCuI]/TMSI			**27**; R=Bu; 90:10 (**27***R*:**27***S*)	91	9f
56	Li[MeCuI]/TMSI			**20**; R=Me; 89:14 (**20***R*:**20***S*)	83	9f
57	$LiMe_2Cu$/TMSCl			**20**; R=Me; -	0(80)	
58	$LiMe_2Cu$/TMSCl[c]			**20**; R=Me; -	20(70)	
59	Li[MeCuI]/TMSI			**23**; R=Me; 94:6 (**23***S*:**23***R*)	99	7d
60	Li[BuCuI]/TMSI			**28**; R=Bu; 96:4 (**28***S*:**28***R*)	93	7d
61	Li[BuCuI]/TMSOTf			**28**; R=Bu; 92:8 (**28***S*:**28***R*)	93	7d
62	Li[BuCuI]/TMSI[d]			**28**; R=Bu; 91:9 (**28***S*:**28***R*)	59(35)	

[a] 2.0 equiv. of 'RCu' vs substrate. 'RCu'/additive ratio=1:1. Solvent: THF. Reactions quenched after 4 h at −78 °C. Purified CuI used as the CuI·0.75DMS complex.
[b] Based on purified and isolated material (a+b). Recovered substrate in brackets.
[c] Ether as solvent.
[d] 1.4 equiv. Li[BuCuI]/TMSI vs **12**.



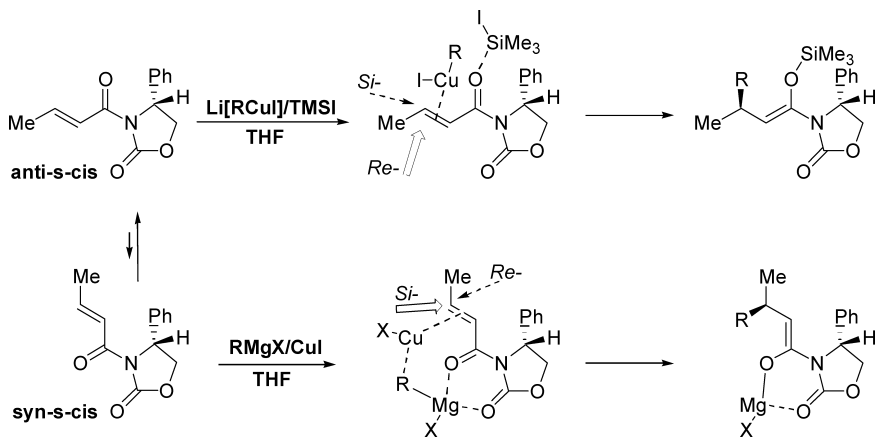
Scheme 1.

reagent and 1.1 equiv. of DMS purified CuI.[12] The initial CuI–DMS complex isolated is unstable, but after removal of DMS under reduced pressure, the final stoichiometry {[CuI]$_4$[DMS]$_3$}, remains essentially the same.[13] The CuI purified via DMS is the Cu(I) precursor of choice because of the high yields as well as high stereoselectivities in the conjugate additions to chiral crotonates (Table 1). Thus, employing phenylglycine-derived imide (**1**) in a conjugate addition reaction of Li[BuCuI]/TMSI, obtained from BuLi and CuI·0.75DMS, gave 96% de of product **15***S* (entry 1). It was instrumental to use the purified CuI·0.75DMS complex[14] instead of the high purity grade CuI, with or without the presence of DMS. Entries 12–14 demonstrate the effect of DMS, either by precomplexation[15a] or subsequent addition,[15b] on the solubility and reactivity of the copper reagent. Efforts to alter the stereoselectivity utilizing the bulkier diisopropyl sulfide ligand,[16] CuI·0.75S (*i*-Pr)$_2$,[17] resulted in a stereoselectivity of product **17** identical to that found using the CuI·0.75DMS complex (entries 21, 22).

Typically, 1.4 equiv. of the Li[RCuI]/TMSI reagent system was employed, but for the less reactive cinnamates 2 equiv. of the copper reagent generally was necessary (Table 3). The diasteromeric ratios of the products were measured on clearly resolved ^{1}H NMR signals of the crude reaction products. The absolute configuration at the β-carbon was established by optical rotation of the optically active carboxylic acids[18] or alcohols[19] obtained after chemical removal of the chiral auxiliaries. Phenylglycine- and pyrrolidinone-derived auxilaries were the most efficient for the conjugate additions employing the Li[RCuI]/TMSI as reagent systems. The phenylglycine-derived oxazolidinone has previously been found to be an excellent auxiliary for conjugate additions of copper-promoted Grignard reagents[9a] and zirconium reagents.[10] In comparison, the *tert*-leucine- and valine-derived[9f] oxazolidinone auxiliaries were found to yield slightly lower stereoselectivities (~90% de) while the phenylalanine-derived auxiliary gave modest selectivities (~70% de) under identical reaction conditions.

The presence of TMSI is crucial for high stereoselectivity and yield, but only in THF. Avoiding TMSI in the addition of Li[BuCuI] in THF not only decreased the rate of the reaction, but also provided excess of diastereomer **15***R* (entry 2). This same major diasteromer was obtained in much greater excess and yield in ether (entry 4). As the initial metal-carbonyl interaction seems stronger in ether compared to THF, the imide is allowed to more readily undergo a conjugate addition via the proposed metal chelated *syn-s-cis* conformation rather than the *anti-s-cis* conformer (Scheme 2).[9f]

Absence of TMSI during the conjugate addition of Li[BuCuI] seems to favor the substrate reacting in a *syn*-carbonyl *s-cis* conformation, where a weak chelation effect of the lithium cation may play a role in providing excess of the opposite diastereomer (**15***R*). Addition of scavenger chelating agents to the organocopper reagent such as $MgBr_2$ or LiI (entry 32) did not initially appear to affect the de or the yield for the TMSI-activated additions of Li[RCuI].[9f] The 'forced' complexation between $MgBr_2$·OEt_2 and substrates, on the other hand, has a remarkable effect on the conjugate addition of Li[BuCuI] (entries 11, 27). The precomplexed $MgBr_2$/imide and the Grignard reagents seem to react with the imide adopting the *syn-s-cis* conformation. Thus, conducting the 1,4-addition reactions employing the copper reagents in the presence of magnesium, either in the form of a Grignard reagent or as a 'forced' precomplexed $MgBr_2$·OEt_2/imide, provided excess of the opposite major diastereomer than the Li[RCuI]/TMSI reagent system in THF. The Li[RCuI]/TMSI reagents provide higher levels of stereoselectivity than the corresponding copper-promoted Grignard reagents. This is particularly the case for the phenylalanine-derived auxiliary (**3**), where a nearly complete loss of stereoselectivity was obtained using a copper-promoted addition of PhMgCl (entry 29) while the conjugate addition of Li[PhCuI]/TMSI provided 74% de of diastereomer **20***S* (entry 28). The copper-promoted Grignard reagent additions were faster than the corresponding



Scheme 2.

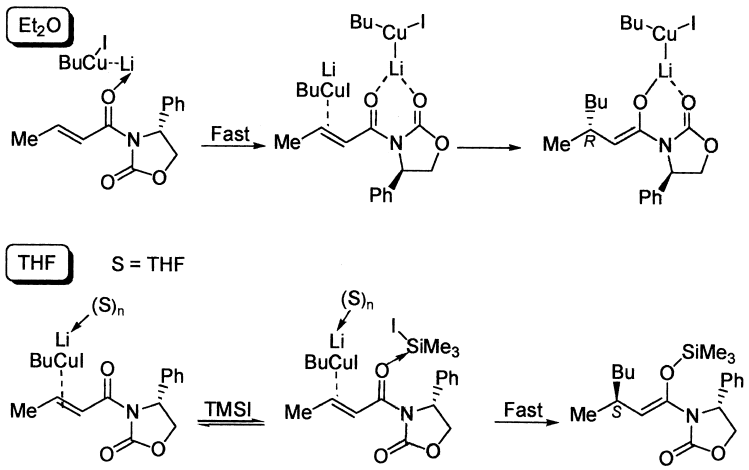
additions employing Li[RCuI]/TMSI in THF. Thus, quenching a Li[PhCuI]/TMSI reaction at −78 °C after 2 h confirmed 50% consumption of substrate **1** whereas the addition of PhMgCl/CuI was complete within 2 h at −78 °C. A relatively slow reaction at −78 °C is most likely a crucial factor in obtaining high stereoselectivity. In comparison, the TMSI-promoted conjugate additions of Li[MeCuI] at −78 °C to imides **5** and **9** provided 82–84% de of products **15** and **16**, whereas the analogous MeMgBr/CuBr addition to the same cinnamate **9** has been reported to give only 48% de.[9a] The same major stereoisomer was obtained when TMSI (entry 25) was replaced with $BF_3{\cdot}OEt_2$ (entry 26), but the yield was only 14% under identical reaction conditions (4 h, −78 °C). Thus, the Li[PhCuI]/TMSI system is far more efficient in conjugate addition reactions than the copper-promoted Grignard reagents or Li[RCuI]/BF_3 in terms of yield and stereoselectivity to the imides (entry 33).

Two significantly distinct solvent-dependent reaction pathways were observed for the conjugate addition of Li[BuCuI]/TMSI to *N*-crotonyl-2-oxazolidinone (**1**). Conducting the addition to (**1**) in THF afforded 96% de of product **15***S* (entry 1). On the other hand, conducting the conjugate addition in ether and employing the same copper reagent (entry 4) gave 88% de of the opposite diastereomer (**15***R*) in 90% yield. Due to the dramatic switch in diastereomeric ratio, several mechanistic questions for the iodosilane promoted conjugate addition of the monoorganocuprate reagents become apparent. The lithium ion is proposed to initially coordinate one or both carbonyl groups in the imide when conducting the reaction in ether, while a rapid silylation by TMSI of the copper π-complex is more likely the case when the reaction is conducted in THF.

Much to our surprise, we found that the presence of TMSI for the addition of Li[BuCuI] to **1** in ether was unnecessary (entry 5).[9g] The results, such as reaction rates, chemical yields and stereoselectivities, were identical whether or not TMSI was present in the conjugate addition of Li[BuCuI] to **1** in ether (entry 6). By interrupting the Li[BuCuI] addition reactions after 2 h instead of the standard 4 h reaction time, an identical chemical yield as well as stereoselectivity of **15***R* was obtained with or without the presence of TMSI (entry 7). Employing 1 equiv. of 12-crown-4 relative to Li[BuCuI]/TMSI in ether increased the influence of the iodosilane as the silylating agent due to the crown ether–lithium complexation (entry 8). Increasing the amount of crown ether to 2 equiv. resulted in an increased stereoselectivity in favor of product **15***S* (entry 9). 12-Crown-4 Gilman type reagents have been characterized by crystallography, where it was shown that each lithium ion is coordinated to two 12-crown-4 molecules.[20] Although the iodosilane is considered highly electrophilic,[21] we propose that the lithium–carbonyl coordination in ether is kinetically favored over the TMSI-carbonyl interaction. Our results reported show that TMSI appears to coordinate very favorably to the carbonyl group in THF or in the presence of 12-crown-4.[22] When Li[BuCuI] is added to **1** in the absence of TMSI, either in THF (entry 2) or in the presence of 2 equiv. of 12-crown-4 (entry 10), the initial lithium carbonyl interaction decreases, as shown by the significant drop in yield.

Scheme 3 depicts the different proposed mechanisms of the conjugate addition reaction conducted in THF relative to ether that rationalize the dramatic change in stereoselectivity. TMSI is proposed to rapidly silylate an initial copper π-complex in THF, thus allowing the copper reagent to add to **1** via the most available π-face of the *s-cis* enone with the imide carbonyls adopting an *anti* non-chelated conformation. The rapid silylation of an initial copper π-complex has not only been proposed for the Me_2CuLi/TMSCl[5d,e,v] combination but also for Li[BuCuI]/TMSI in additions to cyclohexenone,[23] a process which is reported here to be favored only in THF.[24] However, in ether, a lithium species is believed to chelate the carbonyl groups preceding the formation of the copper π-complex,[25,26] therefore allowing the addition to occur with the most available π-face of the imide in an *s-cis* conformation, yielding excess of the other diastereomer (**15***R*). Although since formation of an α-cuprioketone[27] has been reported for Gilman type reagents as a favored intermediate, it can not be neglected as one possible intermediate also for the Li[BuCuI] reagent. The nature of the monoorganocopper species forming the π-complex[28] depicted is unknown, but there is the possibility for dimer[29] and higher oligomer[30] formations. Employing 1 equiv. TMSCl relative to lithium has a retarding effect on the conjugate addition of Li[BuCuI] (entry 3). Compared to the more electrophilic TMSI (a softer iodide), TMSCl (a harder chloride) is proposed to inhibit the reactivity of the Li[BuCuI] reagent, observed as a considerable drop in yield, either via a chlorine–copper or chlorine–lithium interaction. The rate of the conjugate addition was higher in the absence of TMSCl (entry 2). As expected, employing 1 equiv. of TMSCl in combination with the more reactive Gilman reagent, Li[Bu_2Cu]LiI showed a moderate solvent dependence; a slower reaction was observed in THF[31] (entry 15) relative to ether (entry 16). Conjugate addition of Li[PhCuI] to **1** in ether (entry 18) provided 80% de of **16***S* while the TMSI promoted reaction of Li[PhCuI] in THF (entry 17) provided 92% de of **16***R*.

Koga's glutamic acid derived auxiliary (**4**)[18] was compared to the 2-oxazolidinones under the same reaction conditions. Due to the presence of a large trityl group, the Li[RCuI]/TMSI system provided high stereoselectivities comparable to those of the phenylglycine-derived auxiliary (**1**). The TMSCl promoted conjugate addition of the Gilman reagent, Li[Bu_2Cu]LiI, to substrate **4** gave on the other hand a lower stereoselectivity (entry 39). A noteworthy improvement of the yield was obtained (63%) once the solvent was changed from THF to ether (entry 38), but the stereoselectivity was very low. A significant improvement of both yield and stereoselectivity was obtained using the less reactive Li[Ph_2CuI]LiI reagent in the presence of TMSCl (entry 40). Thus, the Li[RCuI]/TMSI combination is far more efficient to the imides than the TMSCl promoted additions of Gilman reagents. The presence of TMSI also facilitated the conjugate addition of the *tert*-butyl group using Li[*t*-BuCuI] in THF (entries 30, 37). The copper-promoted conjugate additions of RMgBr give no advantage in the presence of TMSI (entries 34, 35). Additionally, entries 19 and 20 illustrate a lower yield obtained in the presence of TMSI, which suggests that the Grignard reagents are incompatible with TMSI.



Scheme 3. Proposed influence of the lithium ion in ether vs THF.

Conjugate additions of various copper reagents to the *N*-heptenoyl-derived auxilaries are collected in Table 2. The efficiency of the auxiliaries follows essentially the same order as the *N*-crotonyl-derived auxilaries previously discussed. Although the MeCu/LiI and PhCu/LiI reagents are less reactive than BuCu/LiI, the Li[MeCuI]/TMSI combination underwent a smooth conjugate addition at −78 °C to imides **5**–**8**. Similarly, the Li[PhCuI]/TMSI system gave high yields to the same imides. In sharp contrast, organocopper combinations such as $LiMe_2Cu$/TMSCl (entry 47) or Li[MeCuI]/BF_3 (entry 49) proved to be completely insufficient in conjugate additions to imides **7** and **8**.

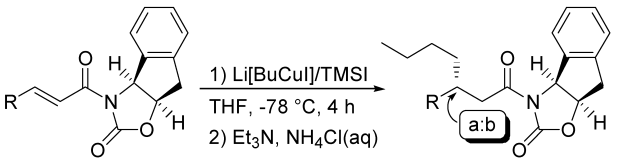
The conjugate additions to the various *N*-cinnamoyl-derived auxiliaries are collected in Table 3. As the *N*-cinnamoyl derivative is slightly less reactive than the *N*-crotonyl and the *N*-heptenoyl analog, a complete consumption of the starting material was achieved by employing two equiv. of the Li[RCuI]/TMSI reagent. Very efficient conjugate additions of MeCu at −78 °C to cinnamates **9**–**12** were obtained employing 2 equiv. of the Li[MeCuI]/TMSI combination. The Li[Me_2Cu]/TMSCl mixture with **11**, in ether or THF, gave a very low yield of product (entries 57, 58). Conducting the conjugate addition of Li[BuCuI] in THF using TMSOTf[7d] (entry 61) instead of TMSI (entry 60), provided a slightly reduced de of product **28***S*.

As a final point, due to the ability for the free rotation of the phenyl group in the phenylglycine-derived auxiliary, we also paid attention to the corresponding indanol auxiliary (Scheme 4).[32] Although the indanol auxiliaries are more rigid and might be expected to give higher stereoselectivities in the conjugate addition of Li[BuCuI]/TMSI, our results show that the indanol auxiliary did not give any advantage over the phenylglycine-derived auxiliary.

3. Conclusions

In this paper we show that the Li[RCuI]/TMSI system is a very efficient reagent in asymmetric conjugate additions to chiral imides. The Li[RCuI] reagent is a versatile reaction system that provides a more economical use of the 'R' group compared with the Gilman type reagents. The presence of TMSI during the conjugate additions of Li[RCuI] in THF gave diastereomeric ratios that were inverted in relationship to conjugate additions conducted with copper-promoted Grignard reagents,[9] copper-promoted zirconium reagents[10] or monosilylcopper reagents Li[$PhMe_2SiCuI$].[11,33] Similarly, Li[RCuI]/TMSI provided an excess of the opposite diastereomer compared to the TMSCl-promoted addition of Li[R_2Cu]LiI. The differentiation between the two possible *Si*- and *Re*-diastereofacial π-faces is likely caused by a chelating counter cation effect, which allows the substrate to react in a different favored conformation. The TMSI-promoted additions of monoorganocuprate reagents seem to undergo an initial copper π-complex formation followed by an alkyl/aryl transfer via the more stable non-chelated *anti-s-cis* conformation.[9f] We have also demonstrated the importance of using the DMS-purified CuI complex, (CuI·0.75DMS), in order to obtain high yields as well as high stereoselectivities in the conjugate addition of Li[RCuI]/TMSI.

Our results also show that the TMSI system is crucial for the asymmetric conjugate addition of the copper reagent, but only in THF or in the presence of 12-crown-4. The reaction is proposed not to involve any halosilane in the critical steps in the conjugate addition conducted in ether. Although the mechanistic details of the organocopper reactions are very elusive, a qualitative pattern using the Li[RCuI] is emerging. Further synthetic developments will be reported in due course.



Scheme 4. 1,4-Additions using the indanol auxiliary.

4. Experimental

4.1. General

All organocopper reactions were conducted under inert atmosphere and in septum capped oven-dried glassware. All new compounds were fully characterized using ^{1}H and ^{13}C NMR, IR and HRMS. Chemical yields are based on purified material (>98% by ^{1}H NMR spectroscopy). ^{1}H (500 MHz) and ^{13}C (125 MHz, standard: $^{13}CDCl_3$, δ=77.23 ppm) NMR spectra were recorded on a Varian 500-MHz instrument using TMS as internal standard (δ=0 ppm). Coupling patterns are abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; se, sextet; qu, quintet; m, multiplet; *J*, coupling. Proton assignments were obtained from COSY and DEPT spectra. Mass spectra were recorded using a VG-ZAB or a VG 7070 instrument. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR instrument. Optical rotations were measured using a Rudolf Autopol III Polarimeter. Elemental analysis was performed by Numega in San Diego. Flash chromatography was conducted using silica gel (Whatman, 60 Å, 230–400 mesh).

4.2. Chemicals

The CuI·0.75DMS complex was prepared from commercially available CuI and DMS according to the procedure described by House.[12] Ether and tetrahydrofuran (THF) were distilled from sodium–benzophenone ketyl and collected when the indicator became deep blue. Triethylamine (Et_3N) was distilled from CaH_2 under argon. BuLi (2.5 or 1.6 M in hexanes), *t*-BuLi (1.7 M in pentane), PhLi (1.8 M cyclohexane/ether) and MeLi (1.4 M in Et_2O) were purchased from Aldrich. Iodotrimetylsilane (TMSI) stabilized with copper chips was purchased from Aldrich and stored septum capped in freezer.

4.3. Preparation of imides 1–14 utilizing BuLi/THF/RCOCl[34]

Typically, butyllithium (1.6 M in hexane, 1.92 mL, 3.08 mmol) was added to a solution of the amide (2.80 mmol) in THF (10 mL) at −78 °C under argon. The resulting mixture was stirred for 45 min and a solution of the corresponding acyl chloride (3.36 mmol, 1.2 equiv.) in THF (5 mL) was added at −78 °C. The reaction mixture was stirred for an additional 30 min and then warmed to ambient temperature. Saturated aqueous ammonium chloride (1 mL) was added to the mixture and then diluted with water (30 mL). After extraction with ether (3×30 mL), the combined organics were dried over $MgSO_4$, filtered and evaporated. The crude product was subsequently purified using chromatography on a silica gel column.

4.4. Typical procedure for TMSI promoted conjugate additions. Preparation of compounds 15–30. Determination of absolute stereochemistry

Appropriate organolithium reagent (1.4–2.0 mmol, 1.25 equiv.) was slowly added to rapidly stirred slurry of CuI·0.75DMS (1.3 equiv.) at −78 °C in THF (10 mL). The resulting dark brown slurry was stirred 20 min at −78 °C, and TMSI (1.25 equiv.) was added drop wise via a gas-tight micro syringe. After 5 min, the appropriate substrate (1 equiv.) dissolved in THF (7–10 mL) was added via the reaction flask wall at −78 °C using a gas-tight syringe. The reaction mixture was stirred for 4 h at −78 °C and dry triethylamine (0.75 mL) was added.[35] After stirring an additional hour at −78 °C, a saturated solution of NH_4Cl/NH_3 (pH ~10) was added (5 mL). After increasing the temperature to +20 °C and removal of septum, the resulting mixture was stirred until a homogenous deep blue solution was obtained. The mixture was then poured out in mixture of ether (25 mL) and water (25 mL) and transferred to a separation funnel. The aqueous phase was extracted with ether (3×25 mL) and the combined organic layers dried over $MgSO_4$. After removal of the solvent, the crude material was dried and the diastereomeric ratio was analyzed using ^{1}H NMR spectroscopy. After purification of the crude product using flash-chromatography (silica gel), the chiral auxilary was disconnected using either KOH in MeOH[18] (pyrrolidinone derivatives) or $LiBH_4$ in ether[19] (oxazolidinone derivatives) to give optically active β-substitued carboxylic acids or corresponding alcohols.

4.5. Conjugate addition of Li[BuCuI] to a homogenous $MgBr_2$–imide complex

$MgBr_2{\cdot}OEt_2$ (0.493 mmol) was added under argon to a stirred solution of imide **1** (0.493 mmol) in anhydrous THF (7 mL) at +20 °C. After 5 min, the homogenous $MgBr_2$-imide complex was added via syringe under argon to Li[BuCuI] at −78 °C, prepared from BuLi (2.5 equiv., 1.23 mmol) and CuI·0.75DMS (1.23 mmol) in anhydrous THF (10 mL). The reaction mixture was next stirred under argon for 4 h at −78 °C. Subsequently, the copper reagent was quenched with a saturated solution of NH_4Cl/NH_3 (pH ~10, 5 mL). After increasing the temperature to +20 °C, the resulting mixture was stirred until a homogenous deep blue solution was obtained. The solution was then poured out in mixture of ether (25 mL) and water (25 mL). The aqueous phase was extracted with ether (3×25 mL) and the combined organic layers dried over $MgSO_4$. After removal of the solvent, the crude material was dried and the diasteromeric ratio was analyzed using ^{1}H NMR spectroscopy (94%). Purification using flash chromatography provided 110 mg (77%) of imide **15** in 94% de (**15***R*).

4.5.1. *N*-(2′*E*-Butenoyl)-4*R*-phenyl-1,3-oxazolidin-2-one (1).[9a] Flash chromatography (30% Et_2O in hexanes; R_f 0.40) yielded 76% (438 mg) of **1** as a white solid; mp 76–78 °C; $[\alpha]_D^{20}$ −110.8° (*c* 0.85, $CHCl_3$) {lit.[9a] mp 77–79 °C; $[\alpha]_D^{22}$ +111.8° for the *S*-enantiomer, (*c* 1.08 $CHCl_3$)}; ^{1}H NMR δ 7.40 (m, Ar–*H*, 2H), 7.34–7.29 (m, Ar–*H*, 3H), 7.28 (dq, COC*H*=CH, 'partly hidden,' *J*=15.3, 1.6 Hz, 1H), 7.09 (dq, COCH=C*H*, *J*=15.3, 7.0 Hz, 1H), 5.48 (dd, NC*H*, *J*=8.7, 3.9 Hz, 1H), 4.69 (dd, OCH_2, *J*=8.8, 8.8 Hz, 1H), 4.27 (dd, OCH_2, *J*=8.9, 3.9 Hz, 1H), 1.93 (dd, CH_3CH=CH, *J*=7.0, 1.7 Hz, 1H); ^{13}C NMR δ 176.5, 164.8, 147.5, 139.4, 129.4, 128.9, 126.2, 122.0, 70.1, 57.9, 18.6; FTIR (film, cm^{-1}) 1780, 1686, 1637; HRMS (EI) calcd for $[C_{13}H_{13}NO_3]$ 231.0895, found 231.0900.

4.5.2. *N*-(2′*E*-Butanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (2).[9e] Flash chromatography (30% Et_2O in pentane, R_f 0.50) yielded 70% (600 mg) of **2** as a clear oil; $[\alpha]_D^{20}$ +93.1°

(c 1.45, $CHCl_3$); ^{1}H NMR δ 7.28 (dt, COC*H*=CH, J=15.3, 1.5 Hz, 1H), 7.15 (dt, COCH=C*H*, J=15.3, 7.0 Hz, 1H), 4.53 (dd, NC*H*, J=7.4, 1.5 Hz, 1H), 4.28 (dd, OCH_2, J=9.2, 1.4 Hz, 1H), 4.24 (dd, OCH_2, J=9.2, 7.6 Hz, 1H), 1.96 (dd, CH_3CH, J=7.0, 1.5 Hz, 3H), 0.94 (s, t-Bu, 9H); ^{13}C NMR δ 165.5, 154.9, 147.0, 122.2, 65.4, 61.0, 36.1, 26.8, 18.7; FTIR (film, cm^{-1}) 1778, 1700, 1634; HRMS (EI) calcd for $[C_{11}H_{18}NO_3]^+$ 212.1287 (MH^+), found 212.1282.

4.5.3. *N*-(2′*E*-Butenoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (3).[34] Flash chromatography (50% Et_2O in pentane; R_f 0.50) yielded 91% (880 mg) of **3** as a white solid, mp 83.3–83.9 °C; $[\alpha]_D^{20}$ +70.1° (c 0.85, $CHCl_3$) {lit.[34] mp 85.0–86.0 °C; $[\alpha]_D$ +77.9°, (c 2.00, $CHCl_3$)}; ^{1}H NMR δ 7.36–7.31 (m, Ar–*H*, 2H), 7.30–7.17 (m, Ar–*H* and olefinic, 5H), 4.73 (m, NC*H*, 1H), 4.21 (dd, CH_2O, J=9.0, 7.7 Hz, 1H), 4.18 (dd, CH_2O, J=9.0, 2.9 Hz, 1H), 3.33 (dd, CH_2Ph, J=13.4, 3.2 Hz, 1H), 2.80 (dd, CH_2Ph, J=13.4, 9.5 Hz, 1H), 1.98 (d, CH_3CH, J=5.6 Hz, 3H); ^{13}C NMR δ 165.2, 153.7, 147.2, 135.6, 129.7, 129.2, 127.5, 122.1, 66.3, 55.5, 38.1, 18.8; FTIR (KBr, cm^{-1}) 1778, 1690, 1636; HRMS (EI) calcd for $[C_{14}H_{15}NO_3]$ 245.1052, found 245.1054.

4.5.4. *N*-(2′*E*-Butenoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (4).[18,36] Flash chromatography (40% EtOAc in hexane; R_f 0.4) yielded 82% of **4** as a colorless solid, mp 115–116 °C; $[\alpha]_D^{20}$ −85.1° (c 1.20, $CHCl_3$) {lit.[18,36] mp 116–117 °C; $[\alpha]_D^{20}$ −86.2° ($CHCl_3$)}; ^{1}H NMR δ 7.31–7.26 (m, Ar–*H*, 6H), 7.22 (dq, C*H*–CO, J=15.2, 1.7 Hz, 1H), 7.22–7.17 (m, Ar–*H*, 6H), 7.17–7.12 (m, Ar–*H*, 3H), 7.02 (dq, C*H*–CH_3, J=15.2, 6.8 Hz, 1H), 4.46 (m, N–C*H*, 1H), 3.50 (dd, CH_2O, J=9.8, 4.0 Hz, 1H), 3.07 (dd, CH_2O, J=9.8, 2.8 Hz, 1H), 2.89 (ddd, α-CH_2, J=17.8, 10.0, 10.3 Hz, 1H), 2.42 (ddd, α-CH_2, J=17.8, 9.9, 1.7 Hz, 1H), 2.06–1.97 (m, CH_2CH_2, 2H), 1.90 (dd, CH_3, J=7.0, 1.7 Hz, 3H); ^{13}C NMR δ 176.6, 165.8, 145.6, 143.7, 128.6, 127.9, 127.1, 124.1, 87.0, 64.2, 56.8, 33.4, 21.2, 18.5; FTIR (KBr, cm^{-1}) 1732, 1678, 1634; HRMS (DCI/NH_3) calcd for $[C_{28}H_{28}NO_3]^+$ 426.2069 (MH^+), found 426.2074.

4.5.5. *N*-(2′*E*-Heptenoyl)-4*R*-phenyl-1,3-oxazolidin-2-one (5). Flash chromatography (20% EtOAc in petroleum ether; R_f 0.50) yielded 72% (525 mg) of **5** as a white solid; mp 71–73 °C; $[\alpha]_D^{20}$ −118.7° (c 1.63, $CHCl_3$); ^{1}H NMR δ 7.40–7.35 (m, Ar–*H*, 2H), 7.34–7.29 (m, Ar–*H*, 3H), 7.25 (dt, COC*H*=CH, J=15.3, 1.5 Hz, 1H), 7.09 (dt, COCH=C*H*, J=15.3, 7.0 Hz, 1H), 5.48 (dd, NC*H*, J=8.8, 3.9 Hz, 1H), 4.69 (dd, OCH_2, J=8.8, 8.8 Hz, 1H), 4.27 (dd, OCH_2, J=8.8, 3.9 Hz, 1H), 2.26 (m, CH_2CH=CH, 2H), 1.44 (qu, CH_2, J=7.2 Hz, 2H), 1.34 (se, CH_2CH$_3$, J=7.2 Hz, 2H), 0.9 (t, CH_3, J=7.2 Hz, 3H); ^{13}C NMR δ 165.0, 154.0, 152.6, 139.4, 129.4, 128.9, 126.2, 120.4, 70.1, 57.9, 32.5, 30.3, 22.4, 13.9; FTIR (film, cm^{-1}) 1780, 1686, 1636; HRMS (EI) calcd for $[C_{16}H_{19}NO_3]$ 273.1365, found 273.1357. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.46; H, 6.84; N, 4.91.

4.5.6. *N*-(2′*E*-Heptanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (6). Flash chromatography (50% Et_2O in pentane, R_f 0.50) yielded 88% (395 mg) of **6** as a clear syrup; $[\alpha]_D^{20}$ +76.7° (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.26 (dt, C*H*=CHCH$_2$, J=15.4, 1.5 Hz, 1H), 7.14 (dt, CH=C*H*CH$_2$, J=15.4, 7.0 Hz, 1H), 4.51 (dd, NC*H*, J=7.6, 1.8 Hz, 1H), 4.29 (dd, OCH_2, J=9.2, 1.8 Hz, 1H), 4.24 (dd, OCH_2, J=9.2, 7.6 Hz, 1H), 2.28 (m, CH=CHCH_2, 2H), 1.48 (qu, CH_2, 2H), 1.36 (se, CH_2CH$_3$, J=7.6 Hz, 2H), 0.94 (s, t-Bu, 9H), 0.92 (t, CH_3CH$_2$, J=7.2 Hz, 3H); ^{13}C NMR δ 165.7, 154.9, 152.0, 120.6, 65.4, 61.0, 36.1, 32.6, 30.4, 25.8, 22.5, 14.0; FTIR (film, cm^{-1}) 1778, 1688, 1634; HRMS (EI) calcd for $[C_{14}H_{23}NO_3]$ 253.1678, found 253.1679.

4.5.7. *N*-(2′*E*-Heptenoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (7). Flash chromatography (30% Et_2O in pentane; R_f 0.35) yielded 70% (817 mg) of **7** as a white solid; mp 58–60 °C; $[\alpha]_D^{20}$ +90.38° (c 1.31, $CHCl_3$); ^{1}H NMR δ 7.36–7.31 (m, Ar–*H* and olefinic, 2H), 7.29–7.17 (m, Ar–*H* and olefinic, 5H), 4.73 (m, N–C*H*, 1H), 4.21 (dd, CH_2O, J=9.0, 8.1 Hz, 1H), 4.16 (dd, CH_2O, J=9.0, 3.1 Hz, 1H), 3.34 (dd, CH_2Ph, J=13.4, 3.3 Hz, 1H), 2.86 (dd, CH_2Ph, J=13.4, 9.5 Hz, 1H), 2.31 (dt, CH_2–CH=CH, J=7.0, 6.5 Hz, 2H), 1.50 (m, CH_2CH$_2$, 2H), 1.38 (m, CH_2CH$_3$, 2H), 0.92 (t, CH_3CH$_2$, J=7.5 Hz, 3H); ^{13}C NMR δ 165.4, 153.7, 152.2, 135.6, 129.7, 129.2, 127.5, 120.6, 66.3, 55.6, 38.2, 32.6, 30.4, 22.5, 14.0; FTIR (KBr, cm^{-1}) 1778, 1678, 1631; HRMS (EI) calcd for $[C_{17}H_{21}NO_3]$ 287.1521, found 287.1528. Anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.40; H, 7.26; N, 4.53.

4.5.8. *N*-(2′*E*-Heptenoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (8).[18] Flash chromatography (30% Et_2O in pentane; R_f 0.4) yielded 72% (0.94 g) of **8** as a light yellow oil; $[\alpha]_D^{20}$ −66.2° (c 1.13, $CHCl_3$) {lit.[18] $[\alpha]_D^{20}$ −64.5° ($CHCl_3$)}; ^{1}H NMR δ 7.38–7.34 (m, Ar–*H*, 6H), 7.33 (dt, C*H*–CO, J=15.4, 1.4 Hz, 1H), 7.27–7.22 (m, Ar–*H*, 6H), 7.21–7.16 (m, Ar–*H*, 3H), 7.10 (dt, CH_2C*H*=CHCO, J=15.4, 7.0 Hz, 1H), 4.51 (m, N–C*H*, 1H), 3.56 (dd, CH_2O, J=9.8, 4.0 Hz, 1H), 3.14 (dd, CH_2O, J=9.8, 2.7 Hz, 1H), 2.94 (ddd, α-CH_2, J=17.8, 10.0, 10.0 Hz, 1H), 2.46 (ddd, α-CH_2, J=17.8, 9.9, 2.0 Hz, 1H), 2.29 (dq, CH_2CH=CH, J=7.0, 1.3 Hz, 2H), 2.07–1.96 (m, CH_2-ring, 1H), 1.96–1.89 (m, CH_2-ring, 1H), 1.53–1.44 (m, CH_2-chain, 2H), 1.43–1.33 (m, CH_2-chain, 2H), 0.92 (t, CH_3CH$_2$, J=7.3 Hz, 3H); ^{13}C NMR δ 176.4, 166.2, 150.9, 143.7, 128.8, 127.1, 127.3, 122.7, 87.2, 64.4, 57.0, 33.6, 32.6, 30.6, 22.5, 21.3, 14.1; FTIR (neat, cm^{-1}) 1733, 1675, 1634; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{31}H_{33}NO_3Na]^+$ 490.2358, found 490.2379.

4.5.9. *N*-(3′-Phenyl-2′*E*-propenoyl-)-4*R*-phenyl-1,3-oxazolidin-2-one (9).[9a] Flash chromatography (15% EtOAc in petroleum ether; R_f 0.40) yielded 88% (642 mg) of **9** as a white solid. Recrystallization (EtOAc/Hexanes) afforded **9** as white crystals; mp 169–170 °C; $[\alpha]_D^{20}$ −3.9° (c 0.85, $CHCl_3$) {lit.[9a] mp 169–171 °C; $[\alpha]_D^{22}$ +3.4° for the *S*-enantiomer, (c 0.74, $CHCl_3$)}; ^{1}H NMR δ 7.93 (d, PhC*H*, J=15.5 Hz, 1H), 7.78 (d, PhCHC*H*, J=15.5 Hz, 1H), 7.61–7.57 (m, Ar–*H*, 2H), 7.42–7.37 (2m, Ar–*H*, 5H), 7.37–7.32 (2m, Ar–*H*, 3H), 5.56 (dd, NC*H*, J=8.7, 3.8 Hz, 1H), 4.74 (dd, OCH_2, J=8.7, 8.7 Hz, 1H), 4.32 (dd, OCH_2, J=8.7, 3.8 Hz, 1H); ^{13}C NMR δ 165.0, 154.0, 146.9, 139.2, 134.7, 130.9, 129.4, 129.1, 128.9, 128.9, 126.2, 117.1, 70.2, 58.1; FTIR (film, cm^{-1}) 1778, 1684, 1622; HRMS (EI) calcd for $[C_{18}H_{15}NO_3]$ 293.1052, found 293.1042.

4.5.10. *N*-(3′-Phenyl-2′*E*-Propanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (10).[37] Flash chromatography (50% Et_2O in pentane; R_f 0.50) yielded 85% (437 mg) of **10** as a clear syrup; $[\alpha]_D^{20}$ +115.5° (*c* 1.50, CH_2Cl_2), {lit.[37] mp 99–100 °C; $[\alpha]_D^{25}$ +115.4, (*c* 0.5, CH_2Cl_2)}; ^{1}H NMR δ 7.95 (d, olefinic, *J*=15.6 Hz, 1H), 7.85 (d, olefinic, *J*=15.6 Hz, 1H), 7.62 (m, Ar–*H*, 2H), 7.39 (m, Ar–*H*, 3H), 4.59 (dd, NC*H*, *J*=7.4, 1.9 Hz, 1H), 4.33 (dd, OCH_2, *J*=9.2, 1.8 Hz, 1H), 4.28 (dd, OCH_2, *J*=9.2, 7.4 Hz, 1H), 0.98 (s, *t*-Bu, 9H); ^{13}C NMR δ 165.8, 155.0, 146.6, 134.9, 130.8, 129.1, 128.8, 117.4, 65.5, 61.2, 36.2, 25.9; FTIR (film, cm^{-1}) 1776, 1683, 1624; HRMS (EI) calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1374. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.60; H, 7.35; N, 4.90.

4.5.11. *N*-(3′-Phenyl-2′*E*-propenoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (11).[38] Flash chromatography (40% Et_2O in pentane; R_f 0.30) yielded 88% (1.22 g) of **11** as a white solid, mp 122–124 °C; $[\alpha]_D^{20}$ +44.6° (*c* 1.0, $CHCl_3$) {lit.[38] mp 121 °C; $[\alpha]_D^{20}$ +45.6 (*c* 1.1 $CHCl_3$)}; ^{1}H NMR δ 7.92 (2d, olefinic, *J*=15.0 Hz, 2H), 7.64 (m, Ar–*H*, 2H), 7.41 (m, Ar–*H*, 3H), 7.34 (t, Ar–*H*, *J*=7.2 Hz, 2H), 7.29 (d, Ar–*H*, *J*=7.2 Hz, 1H), 7.25 (m, Ar–*H*, 2H), 4.81 (m, NC*H*, 1H), 4.26 (dd, CH_2O, *J*=7.2, 7.2 Hz, 1H), 4.21 (dd, CH_2O, *J*=7.2, 2.1 Hz, 1H), 3.38 (dd, CH_2Ph, *J*=12.4, 2.9 Hz, 1H), 2.86 (dd, CH_2Ph, *J*=12.4, 8.3 Hz, 1H); ^{13}C NMR δ 165.4, 153.7, 146.6, 135.6, 134.8, 130.9, 129.7, 129.2, 129.1, 128.9, 127.5, 117.2, 66.4, 55.6, 38.1; FTIR (film, cm^{-1}) 1777, 1678, 1621; HRMS (EI) calcd for [$C_{19}H_{17}NO_3$] 307.1208, found 307.1201.

4.5.12. *N*-(3′-Phenyl-2′*E*-propenoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (12).[18] Flash chromatography (30% Et_2O in pentane; R_f 0.26) yielded 96% of **12** as a colorless oil that solidified upon standing, mp 81–83 °C; $[\alpha]_D^{20}$ −2.3° (*c* 1.3, $CHCl_3$) {lit.[18] oil; $[\alpha]_D$ −1.6° (*c* 9.86 $CHCl_3$)}; ^{1}H NMR δ 7.92 (d, PhC*H*–, *J*=15.8 Hz, 1H), 7.71 (d, PhCH=C*H*, *J*=15.8 Hz, 1H), 7.58–7.54 (m, Ar–*H*, 2H), 7.35–7.26 (m, Ar–*H*, 9H), 7.22–7.10 (m, Ar–*H*, 9H), 4.53 (m, N–C*H*, 1H), 3.55 (dd, CH_2O, *J*=9.8, 3.9 Hz, 1H), 3.13 (dd, CH_2O, *J*=9.8, 2.7 Hz, 1H), 2.94 (ddd, α-CH_2, *J*=17.8, 10.6, 10.0 Hz, 1H), 2.47 (ddd, α-CH_2, *J*=17.8, 9.9, 2.0 Hz, 1H), 2.05 (m, CH_2CH_2, 1H), 1.95 (m, CH_2CH_2, 1H); ^{13}C NMR δ 176.5, 165.9, 145.4, 143.7, 135.2, 130.3, 128.8, 128.6, 128.5, 127.9, 127.1, 119.5, 87.3, 64.4, 57.1, 33.6, 21.3; FTIR (KBr, cm^{-1}) 1730, 1670, 1617; HRMS (FAB DCM/NBA/NaCl) calcd for [$C_{33}H_{29}NO_3Na$]$^+$ 510.2045, found 510.2033.

4.5.13. *N*-(2′*E*-Butenoyl)-(4*S*,5*R*)-indano[1,2-*d*]oxazolidin-2-one (13).[32] Flash chromatography (50% ether in pentane, R_f 0.50 on silica gel) yielded 94% of **13** as a clear solid; mp 116–117 °C. ^{1}H NMR δ 7.67 (d, Ar–*H*, *J*=7.6 Hz, 1H), 7.34 (dd, Ar–*H*, *J*=7.6 Hz, 1H), 7.30–7.20 (m, olefinic and Ar–*H*, 4H), 5.98 (d, NC*H*, *J*=6.8 Hz, 1H), 5.29 (m, OC*H*, 1H), 3.39 (m, ArCH_2, 2H), 1.97 (d, CH_3, *J*=4.7 Hz, 3H); ^{13}C NMR δ 166.0, 153.7, 147.6, 140.1, 139.9, 130.5, 128.8, 128.1, 125.8, 122.5, 78.7, 63.9, 38.7, 19.2; FTIR (CH_2Cl_2, cm^{-1}) 1774.2, 1682.7, 1636.4; HRMS (EI) calc for [$C_{14}H_{13}NO_3$] 243.0895, found 243.0896.

4.5.14. *N*-(3′-Phenyl-2′*E*-propenoyl)-(4*S*,5*R*)-indano[1,2-*d*]-oxazolidin-2-one (14).[37] Flash chromatography (50% ether in pentane, R_f 0.50 on silica gel) yielded 51% of **14** as a clear solid; mp 195–196 °C; $[\alpha]_D^{20}$ +292° (*c* 0.65, CH_2Cl_2) {lit.[37] mp 185–188 °C; $[\alpha]_D^{25}$ −280° for the 4*R*,5*S* isomer (*c* 1.0 CH_2Cl_2)}; ^{1}H NMR δ 7.95 (d, olefinic, *J*=15.7 Hz, 1H), 7.92 (d, olefinic, *J*=15.7 Hz, 1H), 7.73 (d, Ar–*H*, *J*=7.7 Hz, 1H), 7.64–7.61 (m, Ar–*H*, 2H), 7.41–7.27 (m, Ar–*H*, 6H), 6.07 (d, NC*H*, *J*=6.9 Hz, 1H), 5.35–5.31 (m, OC*H*, 1H), 3.42 (m, CH_2, 2H); ^{13}C NMR δ 165.6, 153.1, 146.5, 139.5, 139.2, 134.6, 130.7, 129.9, 128.9, 128.7, 128.2, 127.5, 125.2, 117.0, 78.1, 63.4, 38.0; FTIR (film, cm^{-1}) 1774, 1675, 1621; MS: m/z=328 (M+Na^+, 100%).

4.5.15. *N*-(3′*R*-Methylheptanoyl)-4*S*-phenyl-1,3-oxazolidin-2-one (15*R*). Obtained from the reaction using imide **5** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (20% EtOAc in petroleum ether; R_f 0.40) to give 84% (82% de) of **15***R* as a white solid; mp 46–49 °C; ^{1}H NMR δ 7.40–7.35 (m, Ar–*H*, 2H), 7.35–7.32 (m, Ar–*H*, 1H), 7.32–7.28 (m, Ar–*H*, 2H), 5.44 (dd, NC*H*, *J*=8.8, 3.8 Hz, 1H), 4.68 (dd, OCH_2, *J*=8.9, 8.8 Hz, 1H), 4.27 (dd, OCH_2, *J*=8.9, 3.8 Hz, 1H), 2.99 (dd, COCH_2, *J*=16.0, 5.4 Hz, 1H), 2.68 (dd, COCH_2, *J*=16.0, 8.6 Hz, 1H), 1.99 (m, methine, 1H), 1.32–1.13 (m, 3× CH_2, 6H), 0.85 (d, CH_3CH, 'partly hidden,' *J*=6.6 Hz, 3H), 0.84 (t, CH_3CH_2, 'partly hidden,' *J*=6.7 Hz, 3H); ^{13}C NMR δ 172.6, 153.9, 139.5, 129.4, 128.9, 126.2, 70.0, 57.8, 42.8, 36.8, 29.9, 29.3, 23.0, 19.8, 14.2; FTIR (film, cm^{-1}) 1782, 1702; HRMS (EI) calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1689.

4.5.16. *N*-(3′*S*-Methylheptanoyl)-4*S*-phenyl-1,3-oxazolidin-2-one (15*S*). Obtained from the reaction using imide **1** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.40) to give 83% (96% de) of **15***S* as a white solid; mp 58–60 °C; ^{1}H NMR δ 7.40–7.35 (m, Ar–*H*, 2H), 7.35–7.32 (m, Ar–*H*, 1H), 7.32–7.28 (m, Ar–*H*, 2H), 5.43 (dd, NC*H*, *J*=8.8, 3.8 Hz, 1H), 4.68 (dd, OCH_2, *J*=8.8, 8.8 Hz, 1H), 4.26 (dd, OCH_2, *J*=8.8, 3.8 Hz, 1H), 2.84 (d, COCH_2, *J*=7.0 Hz, 2H), 1.98 (m, methine, 1H), 1.31–1.09 (m, 3× CH_2, 6H), 0.87 (d, CH_3CH, *J*=6.6 Hz, 3H), 0.85 (t, CH_3CH_2, *J*=7.0 Hz, 3H); ^{13}C NMR δ 172.6, 153.9, 139.5, 129.4, 128.9, 126.1, 70.0, 57.8, 42.8, 36.5, 30.0, 29.4, 23.0, 19.9, 14.3; FTIR (film, cm^{-1}) 1782, 1702; HRMS (EI) calcd for [$C_{17}H_{24}NO_3$]$^+$ (MH^+) 290.1756, found 290.1764.

4.5.17. *N*-(3′*R*-Phenylbutanoyl)-4*S*-phenyl-1,3-oxazolidin-2-one (16*R*). Obtained from the reaction using imide **1** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.35) to give 83% of **16***R* (92% de) as a white solid; mp 138–142 °C; ^{1}H NMR δ 7.37–7.15 (4m, Ar–*H*, 10H), 5.28 (dd, NC*H*, *J*=8.7, 3.4 Hz, 1H), 4.52 (dd, OCH_2, *J*=8.8, 8.7 Hz, 1H), 4.19 (dd, OCH_2, *J*=8.8, 3.4 Hz, 1H), 3.38 (dd, COCH_2, *J*=16.0, 8.0 Hz, 1H), 3.32 (se, methine, *J*=7.0 Hz, 1H), 3.13 (dd, COCH_2, *J*=16.0, 6.1 Hz, 1H), 1.25 (d, CH_3CH, *J*=6.8 Hz, 3H); ^{13}C NMR δ 171.5, 153.9, 145.8, 139.3, 129.3, 128.8, 128.6, 127.2, 126.5, 126.1, 70.1, 57.7, 43.4, 36.1, 22.4; FTIR (film, cm^{-1}) 1782, 1707; HRMS (EI) calcd for [$C_{19}H_{19}NO_3$] 309.1365, found 309.1358.

4.5.18. *N*-(3′*S*-Phenylbutanoyl)-4*S*-phenyl-1,3-oxazolidin-2-one (16*S*). Obtained from the reaction using

cinnamate **9** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.30) to give 80% of **16*S*** (84% de) as a white solid; ^1H NMR δ 7.40–7.15 (m, Ar–*H*, 8H), 7.10–7.04 (m, Ar–*H*, 2H), 5.38 (dd, NC*H*, *J*=8.8, 3.9 Hz, 1H), 4.62 (dd, OCH_2, *J*=8.8, 8.8 Hz, 1H), 4.17 (dd, OCH_2, *J*=8.8, 3.9 Hz, 1H), 3.47 (dd, COCH_2, *J*=15.9, 6.7 Hz, 1H), 3.32 (m, methine, 1H), 3.05 (dd, COCH_2, *J*=15.9, 7.9 Hz, 1H), 1.25 (d, CH_3CH, *J*=7.0 Hz, 3H); ^{13}C NMR δ 171.6, 153.8, 145.7, 139.0, 129.3, 128.6, 128.6, 127.1, 126.5, 125.8, 70.0, 57.7, 43.3, 36.2, 21.9; FTIR (film, cm^{-1}) 1780, 1702. HRMS (EI) calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1371.

4.5.19. *N*-(3′*R*-Methylheptanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (17*R*). Obtained from the reaction using imide **2** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (10% Et_2O in pentane; R_f 0.50) to give 80% (86% de) of **17*R*** as a clear oil; ^1H NMR δ 4.45 (dd, NC*H*, *J*=7.6, 1.6 Hz, 1H), 4.27 (dd, OCH_2, *J*=9.3, 1.6 Hz, 1H), 4.24 (dd, OCH_2, *J*=9.3, 7.7 Hz, 1H), 2.87 (dd, COCH_2, *J*=16.4, 7.7 Hz, 1H), 2.81 (dd, COCH_2, *J*=16.4, 5.9 Hz, 1H) 2.04 (m, methine, 1H), 1.43–1.16 (m, 3× CH_2, 6H), 0.98 (d, CH_3CH, *J*=6.7 Hz, 3H), 0.93 (s, *t*-Bu, 9H), 0.89 (t, CH_3CH$_2$, *J*=6.8 Hz, 3H); ^{13}C NMR δ 173.1, 154.9, 65.4, 61.1, 42.7, 36.6, 35.9, 30.0, 29.4, 25.9, 23.0, 20.0, 14.3; FTIR (film, cm^{-1}) 1780, 1703; HRMS (EI) calcd for $[C_{15}H_{28}NO_3]^+$ (MH^+) 270.2069, found 270.2068.

4.5.20. *N*-(3′*S*-Methylheptanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (17*S*). Obtained from the reaction using imide **6** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (10% Et_2O in pentane; R_f 0.50) to give 71% (86% de) of **17*S*** as a clear oil; ^1H NMR δ 4.45 (dd, NC*H*, *J*=7.5, 1.6 Hz, 1H), 4.28 (dd, OCH_2, *J*=9.2, 1.7 Hz, 1H), 4.22 (dd, OCH_2, *J*=9.2, 7.6 Hz, 1H), 3.00 (dd, COCH_2, *J*=16.0, 5.5 Hz, 1H), 2.66 (dd, COCH_2, *J*=16.0, 8.1 Hz, 1H) 2.07 (m, methine, 1H), 1.43–1.19 (m, 3× CH_2, 6H), 0.96 (d, CH_3CH, *J*=6.7 Hz, 3H), 0.94 (s, *t*-Bu, 9H), 0.89 (t, CH_3CH$_2$, *J*=7.1 Hz, 3H); ^{13}C NMR δ 173.1, 154.9, 65.5, 61.1, 42.7, 36.8, 36.0, 30.1, 29.3, 25.9, 23.1, 19.9, 14.3; FTIR (film, cm^{-1}) 1781, 1705; HRMS (EI) calcd for $[C_{15}H_{28}NO_3]^+$ 270.2069, found 270.2064.

4.5.21. *N*-(3′*R*-Phenylbutanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (18*R*). Obtained from the reaction using imide **10** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.40) to give 80% (90% de) of **18*R*** as a white solid; mp 72.6–73.7 °C; ^1H NMR δ 7.30–7.24 (m, Ar–*H*, 4H), 7.20–7.15 (m, Ar–*H*, 1H), 4.37 (dd, NC*H*, *J*=7.6, 1.7 Hz, 1H), 4.23 (dd, OCH_2, *J*=9.3, 1.7 Hz, 1H), 4.18 (dd, OCH_2, *J*=9.3, 7.6 Hz, 1H), 3.53 (dd, COCH_2, *J*=16.1, 7.6 Hz, 1H), 3.40 (se, methine, *J*=7.0 Hz, 1H), 3.10 (dd, COCH_2, *J*=16.1, 7.1 Hz, 1H), 1.33 (d, CH_3CH, *J*=7.1 Hz, 3H), 0.75 (s, *t*-Bu, 9H); ^{13}C NMR δ 172.1, 154.8, 145.9, 128.6, 127.2, 126.5, 65.4, 61.0, 43.1, 36.5, 35.7, 25.6, 22.5; FTIR (film, cm^{-1}) 1779, 1706; HRMS (EI) calcd for $[C_{17}H_{23}NO_3]$ 289.1678, found 289.1689.

4.5.22. *N*-(3′*S*-Phenylbutanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (18*S*). Obtained from the reaction using imide **2** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.45) to give 75% (90% de) of **18*S*** as a white solid; ^1H NMR δ 7.31–7.21 (m, Ar–*H*, 4H), 7.20–7.16 (m, Ar–*H*, 1H), 4.30 (NC*H*, *J*=7.7, 1.0 Hz, 1H), 4.19 (dd, OCH_2, *J*=9.0, 1.3 Hz, 1H), 4.02 (dd, OCH_2, *J*=9.0, 7.8 Hz, 1H), 3.40 (m, methine, 'partly hidden,' 1H), 3.37 (dd, COCH_2, 'partly hidden,' 1H), 3.17 (dd, COCH_2, *J*=15.3, 5.7 Hz, 1H), 1.34 (d, CH_3CH, *J*=6.7 Hz, 3H), 0.88 (s, *t*-Bu, 9H); ^{13}C NMR δ 172.2, 154.9, 145.8, 128.7, 127.3, 126.6, 65.5, 61.2, 43.2, 36.6, 35.9, 25.8, 22.6; FTIR (film, cm^{-1}) 1779, 1704; HRMS (EI) calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1673.

4.5.23. *N*-(3′*R*-Methylheptanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (19*R*). Obtained from the reaction using imide **3** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.50) to give 98% (70% de) of **19*R*** as a clear oil; ^1H NMR δ 7.37–7.33 (m, Ar–*H*, 2H), 7.32–7.27 (m, Ar–*H*, 1H), 7.25–7.22 (m, Ar–*H*, 2H), 4.71 (m, NC*H*, 1H), 4.21 (dd, OCH_2, *J*=9.0, 7.0 Hz, 1H), 4.17 (dd, OCH_2, *J*=9.0, 2.5 Hz, 1H), 3.34 (dd, PhCH_2, *J*=12.0, 3.0 Hz, 1H), 2.92 (dd, COCH_2, *J*=15.5, 4.5 Hz, 1H), 2.84 (dd, COCH_2, *J*=15.5, 6.0 Hz, 1H), 2.78 (dd, PhCH_2, *J*=12.0, 9.0 Hz, 1H), 2.10 (m, methine, 1H), 1.46–1.20 (m, 3× CH_2, 6H), 1.02 (d, CH_3CH, *J*=6.0 Hz, 3H), 0.92 (t, CH_3CH$_2$, *J*=6.5 Hz, 3H); ^{13}C NMR δ 173.1, 153.6, 135.6, 129.6, 129.2, 127.5, 66.3, 55.4, 42.7, 38.2, 36.7, 29.9, 29.4, 23.0, 20.00, 14.3; FTIR (film, cm^{-1}) 1780, 1700; HRMS (EI) calcd for $[C_{18}H_{26}NO_3]^+$ (MH^+) 304.1913, found 304.1921.

4.5.24. *N*-(3′*S*-Methylheptanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (19*S*). Obtained from the reaction using imide **7** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.25) to give 86% (65% de) of **19*S*** as slight yellow syrup; ^1H NMR δ 7.35–7.30 (m, Ar–*H*, 2H), 7.29–7.24 (m, Ar–*H*, 1H), 7.21 (m, Ar–*H*, 1H), 4.18 (dd, OCH_2, *J*=9.0, 7.6 Hz, 1H), 4.14 (dd, OCH_2, *J*=9.0, 3.0 Hz, 1H), 3.31 (dd, PhCH_2, *J*=13.4, 3.3 Hz, 1H), 2.98 (dd, COCH_2, *J*=16.1, 5.5 Hz, 1H), 2.74 (dd, PhCH_2, 'partly hidden,' *J*=13.4, 9.6 Hz, 1H), 2.72 (dd, COCH_2, *J*=16.1, 8.3 Hz, 1H), 2.08 (m, methine, 1H), 1.44–1.19 (m, 3× CH$_2$, 6H), 0.98 (d, CH_3CH, *J*=6.6 Hz, 3H), 0.90 (t, CH_3CH2, *J*=6.8 Hz, 3H); ^{13}C NMR δ 173.0, 153.6, 135.6, 129.6, 129.1, 127.5, 66.3, 55.4, 42.7, 38.2, 36.8, 29.8, 29.3, 23.0, 19.9, 14.2; FTIR (film, cm^{-1}) 1780, 1699; HRMS (EI) calcd for $[C_{18}H_{25}NO_3]$ 303.1834, found 303.1832.

4.5.25. *N*-(3′*R*-Phenylbutanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (20*R*). Obtained from the reaction using imide **11** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.40) to give 83% (72% de) of **20*R*** as a white solid; ^1H NMR δ 7.33–7.14 (m, Ar–*H*, 8H), 7.08–7.05 (m, Ar–*H*, 2H), 4.64 (m, NC*H*, 1H), 4.15 (dd, OCH_2, *J*=9.0, 7.9 Hz, 1H), 4.10 (dd, OCH_2, *J*=9.0, 3.0 Hz, 1H), 3.50–3.38 (m, COCH_2 and methine, 2H), 3.11–3.04 (m, COCH_2 and CH_2Ph, 2H), 2.59 (dd, CH_2Ph, *J*=13.6, 9.4 Hz, 1H), 1.35 (t, CH_3CH, *J*=6.8 Hz, 3H); ^{13}C NMR δ 172.2, 153.6, 145.9, 135.4, 129.6, 129.1, 128.7, 127.5, 127.3, 126.6, 66.2, 55.2, 43.4, 37.8, 36.2, 22.2; FTIR (film, cm^{-1}) 1781, 1700; HRMS (EI) calcd for $[C_{20}H_{21}NO_3]$ 323.1521, found 323.1524.

4.5.26. *N*-(3′*S*-Phenylbutanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (20*S*). Obtained from the reaction using crotonate **3** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.40) to give 86% (74% de) of **20***S* as white crystals; mp 113–115 °C; ^{1}H NMR δ 7.35–7.17 (m, Ar–*H*, 10H), 4.55 (m, NC*H*, 1H), 4.10 (dd, OCH_2, *J*=9.0, 2.7 Hz, 1H), 4.05 (dd, OCH_2, *J*=9.0, 7.8 Hz, 1H), 3.42 (m, methine, 'partly hidden,' 1H), 3.37 (m, COCH_2, 'partly hidden,' 1H), 3.25 (dd, CH_2Ph, *J*=13.4, 3.3 Hz, 1H), 3.18 (dd, COCH_2, *J*=15.8, 5.9 Hz, 1H), 2.70 (dd, CH_2Ph, *J*=13.4, 9.8 Hz, 1H), 1.38 (d, CH_3CH, *J*=6.8 Hz, 3H); ^{13}C NMR δ 172.1, 153.6, 145.9, 135.5, 129.6, 129.2, 128.7, 127.5, 127.2, 126.6, 66.3, 55.4, 43.5, 38.1, 36.4, 22.4; FTIR (film, cm^{-1}) 1781, 1704; HRMS (EI) calcd for $C_{20}H_{21}NO_3$ 323.1521, found 323.1532.

4.5.27. *N*-(4′,4′-Dimethyl-3′*S*-methylpentanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (21*S*). Obtained from the reaction using imide **3** and *t*-BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.45) to give 85% (74% de) of **21***S* as a white solid; mp 126–127 °C; ^{1}H NMR δ 7.36–7.31 (m, Ar–*H*, 2H), 7.29–7.26 (m, Ar–*H*, 1H), 7.23–7.20 (m, Ar–*H*, 2H), 4.68 (m, NC*H*, 1H), 4.18 (dd, OCH_2, *J*=9.0, 7.7 Hz, 1H), 4.15 (dd, OCH_2, *J*=9.0, 3.0 Hz, 1H), 3.33 (dd, PhCH_2, *J*=13.4, 3.3 Hz, 1H), 3.02 (dd, COCH_2, *J*=16.2, 3.1 Hz, 1H), 2.78 (dd, COCH_2, *J*=16.2, 10.2 Hz, 1H), 2.76 (m, PhCH_2, 'partly hidden,' 1H), 2.02–1.92 (m, methine, 1H), 0.94 (d, CH_3CH, *J*=6.8 Hz, 3H), 0.91 (s, *t*-Bu, 9H); ^{13}C NMR δ 174.0, 153.6, 135.6, 129.6, 129.2, 127.5, 66.3, 55.6, 39.3, 38.4, 38.3, 33.1, 27.4, 15.3; FTIR (film, cm^{-1}) 1779, 1645; HRMS (EI) calcd for $C_{18}H_{25}NO_3$ 303.1834, found 303.1845. Anal. calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.10; H, 8.07; N, 4.23.

4.5.28. *N*-(3′*R*-Methylheptanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (22*R*). Obtained from the reaction using imide **8** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (20% Et_2O in pentane; R_f 0.30) to give 91% (93% de) of **22***R* as a colorless syrup; ^{1}H NMR δ 7.31–7.26 (m, Ar–*H*, 6H), 7.24–7.13 (m, Ar–*H*, 9H), 4.41 (m, N–C*H*, 1H), 3.47 (dd, CH_2O, *J*=9.0, 3.6 Hz, 1H), 3.09 (dd, CH_2O, *J*=9.0, 1.8 Hz, 1H), 2.87 (m, α-CH_2CH$_2$ 'partly hidden,' 1H), 2.83 (dd, CH_2CH, *J*=15.0, 4.5 Hz, 1H), 2.67 (dd, CH_2CH, *J*=15.0, 6.5 Hz, 1H), 2.39 (ddd, α-CH_2CH$_2$, *J*=17.5, 10.0, 1.0 Hz, 1H), 1.99 (m, CH_2CH$_2$-ring, 1H), 1.93 (m, C*H*CH$_2$, 1H), 1.85 (m, CH_2CH$_2$-ring, 1H), 1.35–1.10 (m, 3× CH_2, 6H), 0.84 (d, CH_3–CH, *J*=6.0 Hz, 3H), 0.77 (t, CH_3CH$_2$, *J*=6.0 Hz, 3H); ^{13}C NMR δ 176.4, 173.7, 143.9, 128.8, 128.1, 127.4, 87.2, 64.2, 56.8, 44.4, 37.0, 33.5, 29.52, 29.49, 23.1, 21.5, 20.0, 14.3; FTIR (film, cm^{-1}) 1733, 1690; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{32}H_{37}NO_3Na]^+$ 506.2671, found 506.2660.

4.5.29. *N*-(3′*S*-Methylheptanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (22*S*). Obtained from the reaction of crotonate **4** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (20% Et_2O in pentane; R_f 0.30) to give 95% (88% de) of **22***S* as a colorless syrup; ^{1}H NMR δ 7.27–7.23 (m, Ar–*H*, 6H), 7.19–7.09 (m, Ar–*H*, 9H), 4.37 (m, N–C*H*, 1H), 3.45 (dd, CH_2O, *J*=9.2, 3.4 Hz, 1H), 3.04 (dd, CH_2O, *J*=9.2, 1.9 Hz, 1H), 2.85 (dd, CH_2CH, *J*=16.5, 4.8 Hz, 1H), 2.81 (m, α-CH_2CH$_2$ 'partly hidden,' 1H), 2.60 (dd, CH_2CH, *J*=16.5, 7.4 Hz, 1H), 2.35 (ddd, α-CH_2CH$_2$, *J*=17.5, 9.8, 1.6 Hz, 1H), 1.97 (m, CH_2CH$_2$-ring, 1H), 1.89 (m, C*H*CH$_2$, 1H), 1.81 (m, CH_2CH$_2$-ring, 1H), 1.28–1.06 (m, 3× CH_2, 6H), 0.84 (d, CH_3–CH, *J*=5.8 Hz, 3H), 0.77 (t, CH_3CH$_2$, *J*=5.8 Hz, 3H); ^{13}C NMR δ 176.4, 173.7, 143.9, 128.8, 128.1, 127.3, 87.2, 64.2, 56.9, 44.4, 36.9, 33.5, 29.4, 29.4, 23.1, 21.5, 20.2, 14.3; FTIR (film, cm^{-1}) 1733, 1690; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{32}H_{37}NO_3Na]^+$ 506.2671, found 506.2694.

4.5.30. *N*-(3′*R*-Phenylbutanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (23*R*). Obtained from the reaction using crotonate **4** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane, R_f 0.25) in 94% (80% de). Partly separation of the diastereomers yielded 90% of **23***R* (93% de) as a white solid; ^{1}H NMR δ 7.30–7.07 (3m, Ar–*H*, 20H), 4.29 (m, N–C*H*, 1H), 3.46 (dd, CH_2O, *J*=9.7, 3.2 Hz, 1H), 3.34 (dd, CH_2CH *J*=16.1, 6.5 Hz, 1H), 3.25 (qdd, Ph–C*H*, *J*=6.5 Hz, 1H), 3.06 (dd, CH_2O, *J*=9.7, 2.4 Hz, 1H), 3.00 (dd, CH_2CH *J*=16.1, 6.5 Hz, 1H), 2.82 (ddd, α-CH_2, *J*=18.0, 11.3, 9.2 Hz, 1H), 2.32 (ddd, α-CH_2, *J*=18.0, 9.2, 1.7 Hz, 1H), 1.89, 1.83 (m, CH$_2$CH_2, 1H each), 1.25 (d, CH_3–CH, *J*=6.8 Hz, 3H); ^{13}C NMR δ 176.5, 172.7, 146.5, 143.9, 128.8, 128.6, 128.1, 127.4, 127.3, 126.4, 87.2, 64.2, 56.9, 45.2, 35.9, 33.4, 22.5, 21.4; FTIR (KBr, cm^{-1}) 1732, 1694; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{34}H_{33}NO_3Na]^+$ 526.2358, found 526.2380.

4.5.31. *N*-(3′*S*-Phenylbutanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (23*S*). Obtained from the reaction using cinnamate **12** and MeCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane, R_f 0.20) in 99% (93% de). Partly separation of the diastereomers yielded 94% of **23***S* (98% de) as a white solid; ^{1}H NMR δ 7.27–7.08 (3m, Ar–*H*, 20H), 4.37 (m, N–C*H*, 1H), 3.37 (dd, CH_2O, *J*=9.8, 4.0 Hz, 1H), 3.26 (m, Ph–C*H*, 1H), 3.19 (dd, CH_2CH *J*=16.4, 5.3 Hz, 1H), 3.10 (dd, CH_2CH, *J*=16.4, 8.4 Hz, 1H), 3.06 (dd, CH_2O, *J*=9.8, 2.2 Hz, 1H), 2.81 (ddd, α-CH_2-ring, *J*=16.8, 10.8, 8.4 Hz, 1H), 2.37 (ddd, α-CH_2-ring, *J*=16.8, 8.4, 1.2 Hz, 1H), 1.98, 1.82 (m, CH_2CH$_2$, 1H each), 1.21 (d, CH_3–CH, *J*=6.8 Hz, 3H); ^{13}C NMR δ 176.4, 172.8, 146.6, 143.8, 128.8, 128.7, 127.1, 127.3, 127.2, 126.4, 87.2, 64.0, 56.9, 45.2, 35.8, 33.4, 22.2, 21.5; FTIR (KBr, cm^{-1}) 1735, 1692; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{34}H_{33}NO_3Na]^+$ 526.2358, found 526.2360.

4.5.32. *N*-(4′,4′-Dimethyl-3′*R*-methylpentanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (24*R*). Obtained from the reaction using crotonate **4** and *t*-BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.45) to give 90% (77% de) of **24***R* as a white solid; ^{1}H NMR δ 7.39–7.34 (m, Ar–*H*, 6H), 7.32–7.20 (m, Ar–*H*, 9H), 4.48 (m, N–C*H*, 1H), 3.57 (dd, CH_2O, *J*=9.0, 3.2 Hz, 1H), 3.14 (dd, CH_2O, *J*=9.0, 1.9 Hz, 1H), 3.10 (dd, CH_2CH, *J*=16.1, 2.5 Hz, 1H), 2.95 (ddd, α-CH_2CH$_2$, *J*=17.5, 10.4, 10.4 Hz, 1H), 2.67 (dd, CH_2CH, *J*=16.1, 10.0 Hz, 1H), 2.43 (ddd, α-CH_2CH$_2$, *J*=17.5, 9.5, 0.9 Hz, 1H), 2.07 (m, CH_2-ring, 1H), 1.92 (m, CH_2-ring,

1H), 1.88 (m, C*H*CH_2, 'partly hidden,' 1H), 0.90 (s, *t*-Bu, 9H), 0.88 (d, CH_3CH, *J*=6.0 Hz, 3H); ^{13}C NMR δ 176.4, 174.6, 143.9, 128.8, 128.1, 127.4, 87.2, 64.3, 57.0, 40.1, 38.7, 33.6, 33.1, 27.5, 21.5, 15.4; FTIR ($CHCl_3$, cm^{-1}) 1733, 1690.

4.5.33. *N*-(3′*R*-Phenylheptanoyl)-4*S*-phenyl-1,3-oxazolidin-2-one (25*R*). Obtained from the reaction using imide **5** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (20% EtOAc in petroleum ether; R_f 0.35) to give 83% (94% de) of **25***R* as a white solid; mp 102–104 °C; ^{1}H NMR δ 7.37–7.29 (m, Ar–*H*, 3H), 7.27–7.21 (m, Ar–*H*, 4H), 7.19–7.14 (m, Ar–*H*, 3H), 5.24 (dd, NC*H*, *J*=8.5, 3.4 Hz, 1H), 4.49 (dd, OCH_2, *J*=8.8, 8.8 Hz, 1H), 4.19 (dd, OCH_2, *J*=8.8, 3.4 Hz, 1H), 3.44 (dd, COCH_2, *J*=17.7, 10.5 Hz, 1H), 3.14 (dd, COCH_2, 'partly hidden,' *J*=17.7, 5.4 Hz, 1H), 3.13 (m, methine, 'partly hidden,' 1H), 1.60 (m, CH_2, 2H), 1.24–1.10 (m, 2×CH_2, 4H), 0.78 (t, CH_3CH$_2$, *J*=7.2 Hz, 3H); ^{13}C NMR δ 171.7, 153.9, 144.4, 139.3, 129.3, 128.8, 128.5, 127.9, 126.5, 126.1, 70.1, 57.8, 42.3, 41.9, 36.4, 29.7, 22.8, 14.1; FTIR (film, cm^{-1}) 1781, 1706; HRMS (EI) calcd for [$C_{22}H_{25}NO_3$] 351.1834, found 351.1821.

4.5.34. *N*-(3′*S*-Phenylheptanoyl)-4*S*-phenyl-1,3-oxazolidin-2-one (25*S*). Obtained from the reaction using imide **9** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (20% EtOAc in petroleum ether; R_f 0.45) to give 96% (83% de) of **25***S* as a white solid; mp 95–98 °C; ^{1}H NMR δ 7.26–7.14 (m, Ar–*H*, 8H), 6.98–6.95 (m, Ar–*H*, 2H), 5.36 (dd, NC*H*, *J*=8.8, 4.2 Hz, 1H), 4.62 (dd, OCH_2, *J*=8.8, 8.8 Hz, 1H), 4.16 (dd, OCH_2, *J*=8.8, 4.2 Hz, 1H), 3.53 (dd, COCH_2, *J*=15.4, 7.3 Hz, 1H), 3.14 (qu, methine, *J*=7.0 Hz, 1H), 3.07 (dd, COCH_2, *J*=15.4, 6.9 Hz, 1H), 1.60 (m, CH_2, 2H), 1.26–1.02 (m, 2×CH_2, 4H), 0.79 (t, CH_3CH$_2$, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 153.8, 144.2, 138.9, 129.3, 128.69, 128.57, 127.9, 126.5, 125.7, 70.0, 57.8, 42.12, 42.10, 36.2, 29.8, 22.8, 14.1; FTIR (film, cm^{-1}) 1782, 1702; HRMS (EI) calcd for [$C_{22}H_{25}NO_3$] 351.1834, found 351.1848.

4.5.35. *N*-(3′*R*-Phenylheptanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (26*R*). Obtained from the reaction using imide **10** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.40) to give 83% (82% de) of **26***R* as a white solid; mp 68–71 °C; ^{1}H NMR δ 7.30–7.13 (m, Ar–*H*, 5H), 4.33 (dd, NC*H*, *J*=7.6, 1.7 Hz, 1H), 4.21 (dd, OCH_2, *J*=9.2, 1.7 Hz, 1H), 4.15 (dd, OCH_2, *J*=9.2, 7.6 Hz, 1H), 3.58 (dd, COCH_2, *J*=16.1, 8.8 Hz, 1H), 3.20 (m, methine, 1H), 3.03 (dd, COCH_2, *J*=16.1, 6.1 Hz, 1H), 1.65 (m, CH_2, 2H), 1.35–1.07 (m, 2×CH_2, 4H), 0.83 (t, CH_3CH$_2$, *J*=7.3 Hz, 3H), 0.68 (s, *t*-Bu, 9H); ^{13}C NMR δ 172.3, 154.8, 144.4, 128.5, 128.0, 126.5, 65.3, 61.0, 42.3, 41.7, 36.6, 35.6, 29.8, 25.5, 22.8, 14.1; FTIR (film, cm^{-1}) 1778, 1706; HRMS (EI) calcd for [$C_{20}H_{29}NO_3$] 331.2147, found 331.2155.

4.5.36. *N*-(3′*S*-Phenylheptanoyl)-4*S*-*tert*-butyl-1,3-oxazolidin-2-one (26*S*). Obtained from the reaction using imide **6** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.40) to give 90% (82% de) of **26***S* as a clear syrup; ^{1}H NMR δ 7.29–7.23 (m, Ar–*H*, 2H), 7.23–7.15 (m, Ar–*H*, 3H), 4.23 (dd, NC*H*, *J*=7.7, 1.4 Hz, 1H), 4.15 (dd, OCH_2, *J*=9.2, 1.5 Hz, 1H), 3.93 (dd, OCH_2, *J*=9.2, 7.7 Hz, 1H), 3.41 (dd, COCH_2, *J*=15.5, 8.8 Hz, 1H), 3.21 (m, methine, 1H), 3.15 (dd, COCH_2, *J*=15.5, 5.6 Hz, 1H), 1.73–1.60 (m, CH_2, 2H), 1.34–1.06 (m, 2×CH_2, 4H), 0.85 (s, *t*-Bu, 9H), 0.83 (t, CH_3CH$_2$, *J*=7.3 Hz, 3H); ^{13}C NMR δ 172.3, 154.9, 144.3, 128.5, 128.0, 126.6, 65.4, 61.3, 42.4, 41.9, 36.6, 35.8, 29.7, 25.8, 22.8, 14.1; FTIR (film, cm^{-1}) 1774, 1702; HRMS (EI) calcd for [$C_{20}H_{29}NO_3$] 331.2147, found 331.2150.

4.5.37. *N*-(3′R-Phenylheptanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (27*R*). Obtained from the reaction using cinnamate **11** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexane; R_f 0.40) to give 91% (85% de) of **27***R*. Partly separation of the diastereomers gave 88% (89% de) of **27***R* as a white solid; ^{1}H NMR δ 7.35–7.15 (m, Ar–*H*, 8H), 7.01 (dd, Ar–*H*, *J*=7.9, 1.7 Hz, 2H), 4.58 (m, N–C*H*, 1H), 4.12 (dd, CH_2O, *J*=8.5, 8.5 Hz, 1H), 4.06 (dd, CH_2O, *J*=8.5, 3.0 Hz, 1H), 3.50 (dd, CH_2CH, *J*=16.1, 8.5 Hz, 1H), 3.24 (m, C*H*CH$_2$, 1H), 3.09 (dd, CH_2CH, *J*=16.1, 6.1 Hz, 1H), 2.98 (dd, CH_2Ph, *J*=13.6, 3.2 Hz, 1H), 2.50 (dd, CH_2Ph, *J*=13.6, 9.3 Hz, 1H), 1.74–1.62 (m, alkyl-CH_2, 2H), 1.35–1.09 (m, alkyl-CH_2, 4H), 0.83 (t, CH_3CH$_2$, *J*=7.1 Hz, 3H); ^{13}C NMR δ 172.3, 153.6, 144.4, 135.3, 129.6, 129.1, 128.6, 128.0, 127.4, 126.6, 66.1, 55.1, 42.1, 42.1, 37.7, 36.4, 29.8, 22.8, 14.2; FTIR (film, cm^{-1}) 1781, 1700; HRMS (EI) calcd for $C_{23}H_{27}NO_3$ 365.1991, found 365.1996.

4.5.38. *N*-(3′*S*-Phenylheptanoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (27*S*). Obtained from the reaction of imide **7** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in hexanes; R_f 0.35) to give 87% (75% de) of **27***S* as colorless syrup; ^{1}H NMR δ 7.33–7.21 (m, Ar–*H*, 7H), 7.20–7.14 (m, Ar–*H*, 3H), 4.47 (m, N–C*H*, 1H), 4.05 (dd, CH_2O, *J*=9.0, 2.6 Hz, 1H), 3.96 (dd, CH_2O, *J*=9.0, 9.0 Hz, 1H), 3.38 (dd, CH_2CH, *J*=15.3, 7.9 Hz, 1H), 3.24 (m, C*H*CH$_2$, 'partly hidden,' 1H), 3.22–3.18 (m, CH_2Ph and CH_2CH, 'partly hidden,' 2H), 2.65 (dd, CH_2Ph, *J*=13.4, 9.9 Hz, 1H), 1.76–1.63 (m, CH_2CH, 2H), 1.38–1.09 (2m, alkyl chain, 4H), 0.84 (t, CH_3CH$_2$, *J*=7.3 Hz, 3H); ^{13}C NMR δ 172.2, 153.6, 144.4, 135.6, 129.6, 129.1, 128.5, 127.9, 127.5, 126.6, 66.3, 55.4, 42.3, 42.1, 38.0, 36.5, 29.8, 22.8, 14.1; FTIR (film, cm^{-1}) 1781, 1699; HRMS (EI) calcd for [$C_{23}H_{27}NO_3$] 365.1991, found 365.1988.

4.5.39. *N*-(3′*R*-Phenylheptanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (28*R*). Obtained from the reaction using imide **8** and PhCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.35 on silica gel) to give 92% (89% de) of **28***R* as a colorless syrup; ^{1}H NMR δ 7.30–7.06 (m, Ar–*H*, 20H), 4.22 (N–C*H*, 1H), 3.42 (dd, CH_2O, *J*=9.8, 4.0 Hz, 1H), 3.37 (dd, CH_2CH, *J*=16.1, 8.1 Hz, 1H), 3.07 (m, C*H*–Ph, 'partly hidden,' 1H), 3.04 (dd, CH_2O, *J*=9.8, 2.7 Hz, 'partly hidden,' 1H), 3.01 (dd, CH_2CH, *J*=16.1, 5.6 Hz, 1H), 2.78 (ddd, α-CH_2CH$_2$, *J*=17.9, 11.0, 10.1 Hz, 1H), 2.34 (ddd, α-CH_2CH$_2$, *J*=17.9, 9.3, 2.4 Hz, 1H), 1.80 (m, CH_2CH$_2$-ring, 2H), 1.60 (m, CH_2CH$_2$-chain, 2H), 1.27–1.10 (m, CH_2CH$_2$-chain, 'partly hidden,' 2H), 1.14–0.99 (2m, CH_2CH$_2$-chain, 1H each), 0.76 (t, CH_3CH$_2$, *J*=7.1 Hz,

3H); ^{13}C NMR δ 176.4, 172.8, 145.0, 143.9, 128.8, 128.4, 128.1, 128.0, 127.3, 126.3, 87.2, 64.2, 56.9, 44.0, 41.7, 36.5, 33.3, 29.9, 22.8, 21.3, 14.2; FTIR (film, cm^{-1}) 1734, 1692; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{34}H_{39}NO_3Na]^+$ 568.2828, found 568.2855.

4.5.40. *N*-(3′*S*-Phenylheptanoyl)-5*S*-triphenylmethoxymethyl-2-pyrrolidinone (28*S*). Obtained from the reaction using cinnamate **12** and BuCu(LiI)TMSI. The crude product was purified using flash chromatography (30% Et_2O in pentane; R_f 0.35 on silica gel) to give 93% (93% de) of **28*S*** as a colorless syrup; ^{1}H NMR δ 7.24–7.06 (m, Ar–*H*, 20H), 4.31 (m, N–C*H*, 1H), 3.29 (dd, CH_2O, *J*=9.8, 4.1 Hz, 1H), 3.21 (dd, CH_2CH, *J*=16.4, 7.4 Hz, 1H), 3.15 (dd, CH_2CH, *J*=16.4, 6.6 Hz, 1H), 3.08 (m, C*H*–Ph, 1H), 2.99 (dd, CH_2O, *J*=9.8, 2.5 Hz, 1H), 2.74 (ddd, α-CH_2CH$_2$, *J*=18.1, 11.1, 9.9 Hz, 1H), 2.34 (ddd, α-CH_2CH$_2$, *J*=18.1, 9.9, 1.4 Hz, 1H), 1.94 (m, CH_2-ring, 1H), 1.78 (m, CH_2-ring, 1H), 1.64–1.48 (2m, CH_2, 1H each), 1.90–1.20 (m, 2×CH_2, 4H), 0.74 (t, CH_3CH$_2$, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 172.9, 145.0, 143.8, 128.7, 128.5, 128.0, 127.9, 127.3, 126.3, 87.2, 63.9, 56.9, 44.0, 41.5, 36.4, 33.3, 29.8, 22.8, 21.5, 14.2; FTIR FTIR (film, cm^{-1}) 1734, 1693; HRMS (FAB DCM/NBA/NaCl) calcd for $[C_{34}H_{39}NO_3Na]^+$ 568.2828, found 568.2833.

4.5.41. *N*-(3′*R*-Phenylheptanoyl)-(4*S*,5*R*)-indano[1,2-*d*]-oxazolidin-2-one (29). Obtained from the reaction using imide **14** and BuCu(LiI) TMSI. Crude product was purified using flash chromatography (30% ether in pentane, R_f 0.30 on silica gel) to give 86% (95% de) of **29** as a clear oil. ^{1}H NMR δ 7.31–7.10 (m, Ar–*H*, 9H), 5.87 (d, NC*H*, *J*= 7.0 Hz, 1H), 5.23 (m, OC*H*, 1H), 3.41 (dd, COCH_2, *J*=16.0, 7.9 Hz, 1H), 3.34 (m, ArCH_2, 2H), 3.25 (m, ArC*H*, 1H), 3.15 (dd, COCH_2, *J*=16.0, 6.6 Hz, 1H), 1.69 (m, CH_2, 2H), 1.36–1.08 (m, 2×CH$_2$, 4H), 0.84 (t, CH_3CH$_2$, *J*=7.3 Hz, 3H); ^{13}C NMR δ 172.6, 153.1, 144.4, 139.4, 139.2, 129.8, 128.5, 128.3, 127.9, 127.2, 126.5, 125.2, 78.2, 63.1, 42.1, 41.9, 38.1, 36.2, 29.8, 22.8, 14.1; FTIR (film, cm^{-1}) 1782, 1698; HRMS (DEI) calc for $[C_{23}H_{25}NO_3]$ 363.1834, found 363.1842.

4.5.42. *N*-(3′*R*-Methylheptanoyl)-(4*S*,5*R*)-indano[1,2-*d*]-oxazolidin-2-one (30). Obtained from the reaction using imide **13** and BuCu(LiI) TMSI. The crude product was purified using flash chromatography (30% ether in pentane, R_f 0.40 on silica gel) to give 87% (90% de) of **30** as a clear oil; ^{1}H NMR δ 7.63 (d, Ar–*H*, *J*=7.7 Hz, 1H), 7.34 (m, Ar–*H*, 1H), 7.26 (m, Ar–*H*, 2H), 5.95 (d, NC*H*, *J*=6.9 Hz), 5.26, (m, OC*H*, 1H), 3.38 (m, ArCH_2, 2H), 2.86 (dd, COCH_2, *J*=17.9, 6.5 Hz, 1H), 2.83 (dd, COCH_2, *J*=17.9, 7.3 Hz, 1H), 2.08 (m, CH3C*H*, 1H), 1.42–1.18 (m, alkyl, 6H), 0.97 (d, CH_3CH, *J*=6.7 Hz, 3H), 0.89 (t, CH_3CH$_2$, *J*=6.7 Hz, 3H); ^{13}C NMR δ 173.5, 153.2, 139.7, 139.5, 130.0, 128.3, 127.4, 125.4, 78.1, 63.2, 42.5, 38.2, 36.6, 30.0, 29.3, 23.0, 19.9, 14.3; FTIR (film, cm^{-1}) 1781, 1698; HRMS (DEI) calc for $[C_{18}H_{23}NO_3]$ 301.1678, found 301.1675.

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Synthesis of enantiomeric-pure cyclohexenyl nucleoside building blocks for oligonucleotide synthesis

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Abstract—Lipases were used for the resolution of (±) (4a*R*, 7*R*, 8a*S*)-2-phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxine. This separation was carried out on preparative scale and used for the synthesis of eight phosphoramidites of cyclohexenyl nucleosides (D- and L-series).

1. Introduction

Since nucleic acids with a six-membered carbohydrate moiety in the backbone are potentially more preorganized than furanose-type nucleic acids, they might have an entropic advantage during hybridization and, hence, could form more stable duplexes.[1] This is exemplified with hexitol nucleic acids (HNA)[2] and with altritol nucleic acids (ANA)[3] that demonstrate strong self-complementary hybridization and hybridization with ribonucleic acids (RNA). Their carbocyclic congeners, cyclohexane nucleic acids (CNA), also hybridize with natural nucleic acids.[4] Hexitol nucleic acids, however, have the disadvantage that they are poorly recognized by nucleic acids metabolizing enzymes which might be ascribed to their rigidity.[5] Therefore, we developed nucleosides and oligonucleotides based on a cyclohexene system. These nucleosides are more flexible than the anhydrohexitol nucleosides and are better mimics of a furanose nucleoside.[6] D-Cyclohexenyl guanine (Cycl-G) has been evaluated against a whole range of herpes viruses and its activity was comparable with those of acyclovir (ACV) and ganciclovir (GCV).[7] (±)Cyclohexenyl cytosine is a potent anti-VZV compound.[8] Cyclohexenyl adenine (Cycl-A) has been incorporated into oligonucleotides.[9] Compared to a single stranded DNA oligomer, the affinity of these cyclohexene nucleic acids (CeNAs) for complementary DNA sequences diminished slightly, while an increase was noticed for RNA complements. Moreover, a CeNA/RNA duplex could be recognized by RNase H, resulting in RNA strand cleavage in serum.[9,10]

However, the difficulty to synthesize chiral cyclohexene derivatives in high enantiomeric excess and in bulk quantities has hampered the further study of cyclohexenyl nucleosides and their oligonucleotides. It has been recognized that D- and L-nucleotides have different properties, exemplified by the findings that D-CNAs hybridize with natural nucleic acids and are RNA-selective while L-CNA hybridize either very weakly or not at all with natural nucleic acids.[4] Recently, a novel and facile method to prepare D- and L-cyclohexenyl nucleosides has been reported.[11] The resolution of these analogues via the formation of diastereomeric esters with (*R*)-(−)-methylmandelic acid is, however, a multistep and tedious work (difficult chromatographic separation), and expensive on large scale.

Therefore we developed a method for the separation of the enantiomers of a racemic intermediate of the synthetic scheme leading to cyclohexenyl nucleosides via an enzyme-catalyzed resolution strategy.[12] This method enables synthesis of the cyclohexenyl nucleosides with all four nucleobases. Further derivatization into their phosphoramidite derivatives afforded suitable building blocks for DNA synthesis as depicted in Figure 1. Here we defined the compounds or their derivatives as an 'a'-type or 'b'-type depending on the type of enantiomer that is considered. The 'a'-type has the 1′*S*, 4′*R*, 5′*S* configuration, overall resembling the D-anhydrohexitol series, while the 'b'-type has the mirror configuration with 1′*R*, 4′*S*, 5′*R* (Fig. 2).

Keywords: Cyclohexenyl nucleosides; Enzymatic resolution; Phosphoramidite; Mitsunobu reaction.
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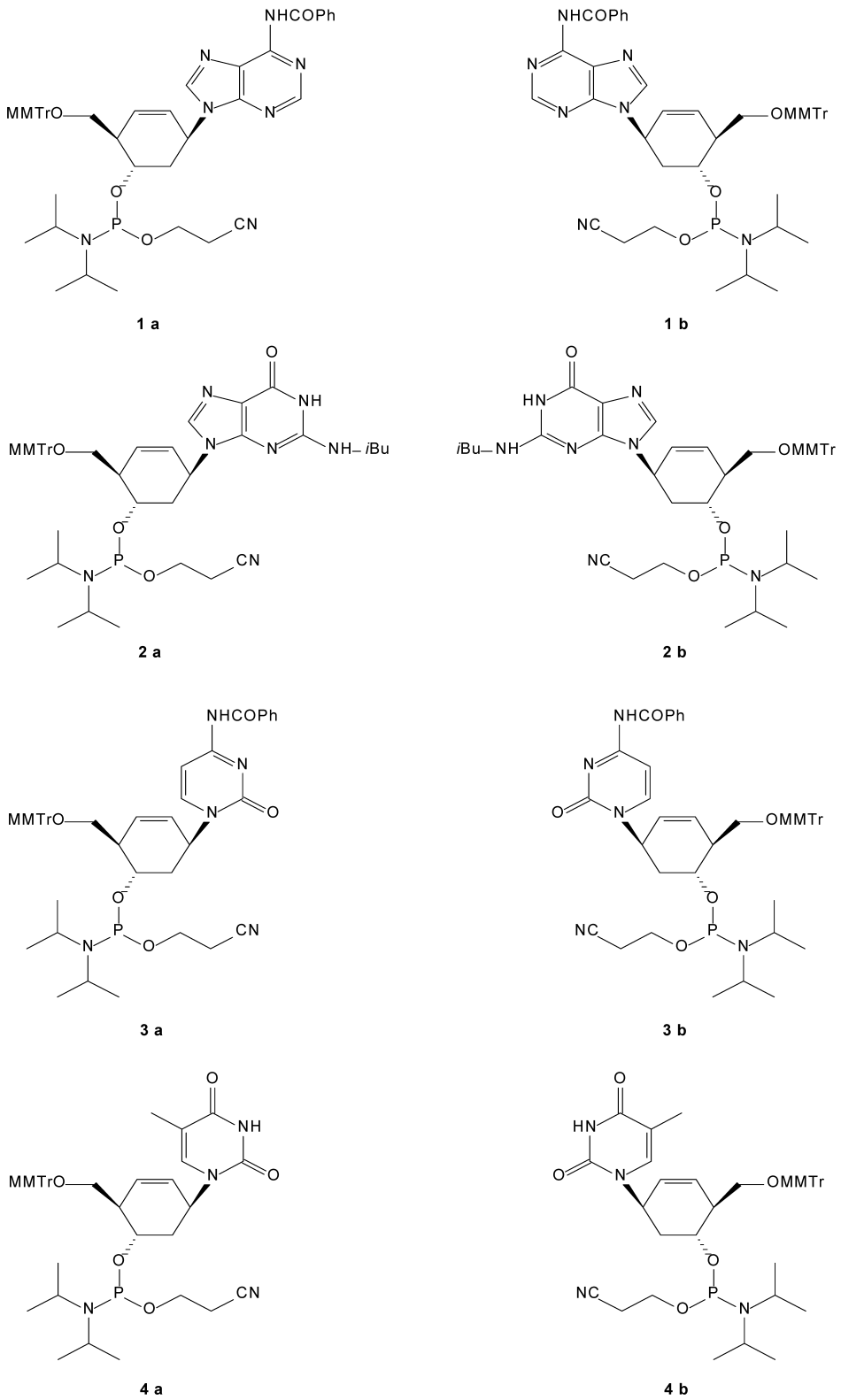


Figure 1. Cyclohexenyl nucleoside building blocks for DNA synthesis.

2. Results and discussion

2.1. Enzymatic resolution of the racemic intermediate 5

For the synthesis of cyclohexenyl nucleosides, racemic compound **5** is the key intermediate for the subsequent introduction of nucleobases. Several methods for resolving **5** could be envisaged, i.e. kinetic resolution using Sharpless epoxidation,[13] enzymatic resolution[14] or formation of diastereomeric esters.[5] The previous study on enzymatic resolution of **5** using vinyl acetate and Lipase PS (Amano) was not successful,[11] and gave only 33% of enantiomeric excess. We started our study with transesterification by screening three different lipases, Novozyme® 435, CRL

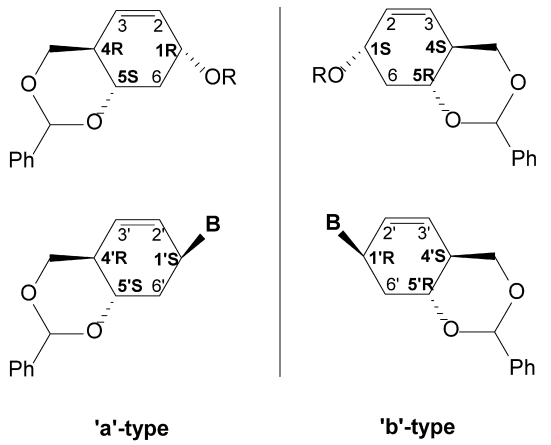


Figure 2. Nomenclature used for cyclohexenyl compounds in this manuscript.

(*Candida rugosa lipase*) and PCL (*Pseudomonas cepacia lipase*). Novozyme® 435 is a member of the lipases of *Candida antarctica B*, and is particularly useful in the synthesis of esters and amides, and has a broad substrate specificity (Fig. 3).[12]

The transesterification reactions were carried out using a test amount of *rac*-**5** (70 mg) and vinyl propionate (VP) (5 equiv.) catalysed by 14% (w/w) of enzymes at room temperature to give enantiomeric pure product *ent*-**6b** and enantiomeric pure substrate *ent*-**5a** (Table 1, Fig. 3). Vinyl propionate was used as organic solvent in individual reactions. We also examined toluene as organic solvent in each reaction (data not shown here), but found that toluene could neither improve the selectivity nor accelerate the reaction. Although none of the evaluated enzymes were synthetically useful, use of Novozyme® 435 showed the best selectivity (E=14).

We further investigated the Novozyme® 435-catalyzed transesterification of *rac*-**5** with formation of *ent*-**7b** and *ent*-**5a** with different acetyl donors (Table 1). Vinyl acetate (VA) and isopropenyl acetate (IPA) were respectively used both as acetyl donor and as organic solvent. A moderate selectivity as expressed in an E value of 22 was obtained with isopropenyl acetate. Under these circumstances, the reaction reached a point of conversion of 49% within 20 h.

Having obtained improved results by using Novozyme® 435 and isopropenyl acetate, we tried to increase the enantioselectivity by further changing the reaction conditions (Table 1). We did not examine a temperature effect on selectivity since testing-scale reactions would not generate much heat which otherwise might have significant influence on temperature. Toluene, octane, chloroform and

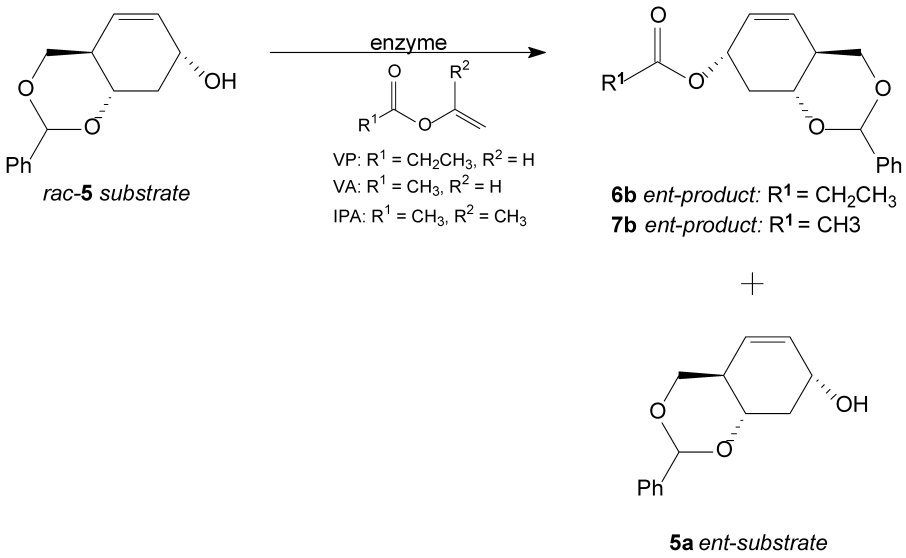


Figure 3. Transesterification of *rac*-**5** with different enzymes.

Table 1. Transesterification of *rac*-**5** with vinyl propionate in the presence of different enzymes, with different acetyl donors and under various conditions using Novozyme® 435 and isopropenyl acetate

Reagents	Enzymes	Conditions solvent /additive	Conversion (%)	Time (h)	e.e.$_s$ (%)	e.e.$_p$ (%)	E
Vinyl propionate	Novozyme® 435	–/–	30	3	37	82	14
Vinyl propionate	CRL	–/–	49	27	51	35	3
Vinyl propionate	PCL	–/–	45	27	40	46	4
Vinyl acetate	Novozyme® 435	–/–	66	43	79	39	5
Isopropenyl acetate	Novozyme® 435	–/–	49	20	93	74	22
Isopropenyl acetate	Novozyme® 435	*Toluene*/–	64	43	65	47	7
Isopropenyl acetate	Novozyme® 435	*Octane*/–	59	20	62	29	3
Isopropenyl acetate	Novozyme® 435	*$CHCl_3$*/–	41	24	69	86	28
Isopropenyl acetate	Novozyme® 435	*CH_2Cl_2*/–	49	20	95	84	50
Isopropenyl acetate	Novozyme® 435	*CH_2Cl_2/Et_3N*	71	20	>99	49	19
Isopropenyl acetate	Novozyme® 435	–/*Et_3N*	60	20	95	70	20

dichloromethane were examined as organic solvent for the transesterification reactions. Both the reactions using chloroform and dichloromethane as organic solvent exhibited good (E=28) to excellent (E=50) selectivity. Attempts were tried to add some additives such as triethylamine, which might change the pH environment and thus the enzymatic activity, which could lead to further improvement of selectivity. The results shown in Table 1, however, revealed that triethylamine enhanced the reaction rate but had negative effect on the selectivity. A test reaction with vinyl butyrate (data not shown here) using the same conditions afforded the highest selectivity (E=127) but with a relatively slow reaction rate (52% conversion, 39 h), which is not favored for economical and practical reasons.

We also investigated the enzyme-catalyzed (PLE, CRL, CAL-B) hydrolysis of *rac*-**7**, which gave the product *ent*-**5a** and the substrate *ent*-**7b** (Fig. 4, Table 2).

None of the enzyme-catalyzed hydrolysis reactions showed useful selectivity as well as good enzymatic activity. The PLE-catalyzed hydrolysis of the racemic ester **7** at room temperature in a 0.1 M phosphate buffer (pH 8.0) in the presence of 10% (v/v) acetone proceeded somewhat faster than in the presence of 10% (v/v) *t*-BuOH, but did not improve the selectivity. CRL-catalyzed hydrolysis exceptionally gave *ent*-**5b** as the product and *ent*-**7a** as the residual substrate, which indicates that the enzyme may favor the 'b-type' configuration of the racemic substrate. This phenomenon was also observed for the hydrolysis of *rac*-**6** and *rac*-**8**. We then turned our attention to the hydrolysis of different racemic esters *rac*-**6**, *rac*-**8** (Fig. 4, Table 2). As seen from the table, the hydrolysis reaction was best conducted by PLE-catalysed hydrolysis of *rac*-**8** in a 0.1 M phosphate buffer solution at pH 8.0 in the presence of 10% (v/v) *t*-BuOH affording *ent*-**5a** and *ent*-**8b** with a selectivity of (E=45). The resolution might be further optimized by changing cosolvent, i.e. acetone or *t*-BuOMe. However, all enzyme-catalyzed hydrolysis reactions had a much lower reaction rate than transesterifications. This could be explained as the former reaction was carried out in heterogeneous phases.

In view of the obtained results, enzyme-catalyzed transesterification was finally adopted for the separation of the racemic intermediate **5** considering both economical and practical aspects.

2.2. Separation and purification of enantiomers of rac-5

The overall procedure for separation and purification of racemic **5** is shown in Figure 5. The transesterification was carried out with 14% (w/w) of Novozyme® 435 catalyzed acylation of racemic substrate *rac*-**5** using 5 equiv. of isopropenyl acetate as the acetyl donor in 50 volumes of dichloromethane at room temperature. Chiral high performance liquid chromatography (HPLC)[11] was used to follow the reaction to determine the end point. The reaction was

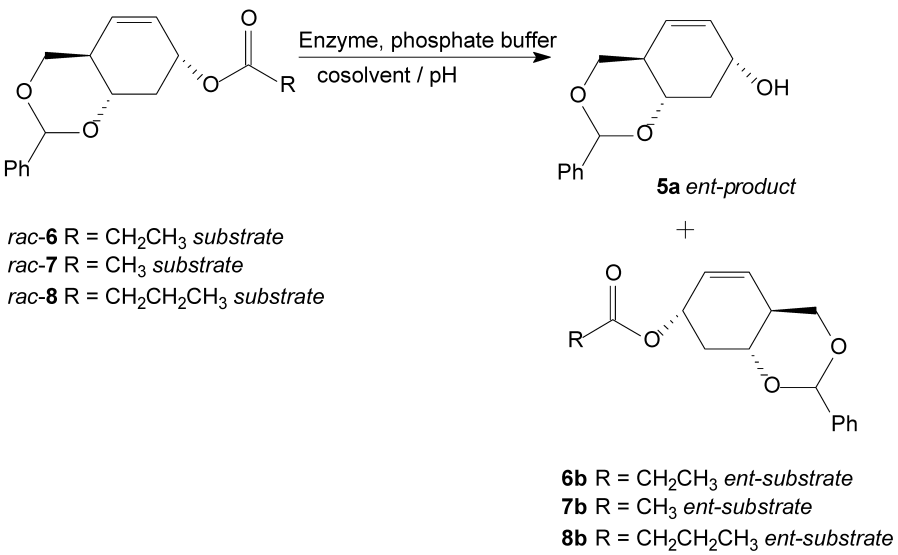


Figure 4. Hydrolysis of different racemic esters *rac*-**6** *rac*-**7** and *rac*-**8**.

Table 2. Hydrolysis of *rac*-**6**, *rac*-**7** and *rac*-**8** with different enzymes

Substrates (R=)	Enzymes	Conditions cosolvent/pH	Conversion (%)	Time (h)	e.e.$_s$ (%)	e.e.$_p$ (%)	E
$-CH_3$	PLE	*t*-BuOH/8.0	11	22	<1	30	2
$-CH_3$	PLE	Acetone/8.0	44	24	27	46	4
$-CH_2CH_3$	PLE	*t*-BuOH/8.0	35	17	40	68	8
$-CH_2CH_2CH_3$	PLE	*t*-BuOH/8.0	13	10	9	95	45
$-CH_3$	CRL*	*t*-BuOH/7.5	17	24	26	65	6
$-CH_2CH_3$	CRL*	*t*-BuOH/7.5	85	24	30	2	1
$-CH_2CH_2CH_3$	CRL*	*t*-BuOH/7.5	27	4	24	11	2
$-CH_3$	CAL-B	*t*-BuOH/7.5	21	25	10	16	1
$-CH_2CH_2CH_3$	CAL-B	*t*-BuOH/7.5	21	30	15	63	4

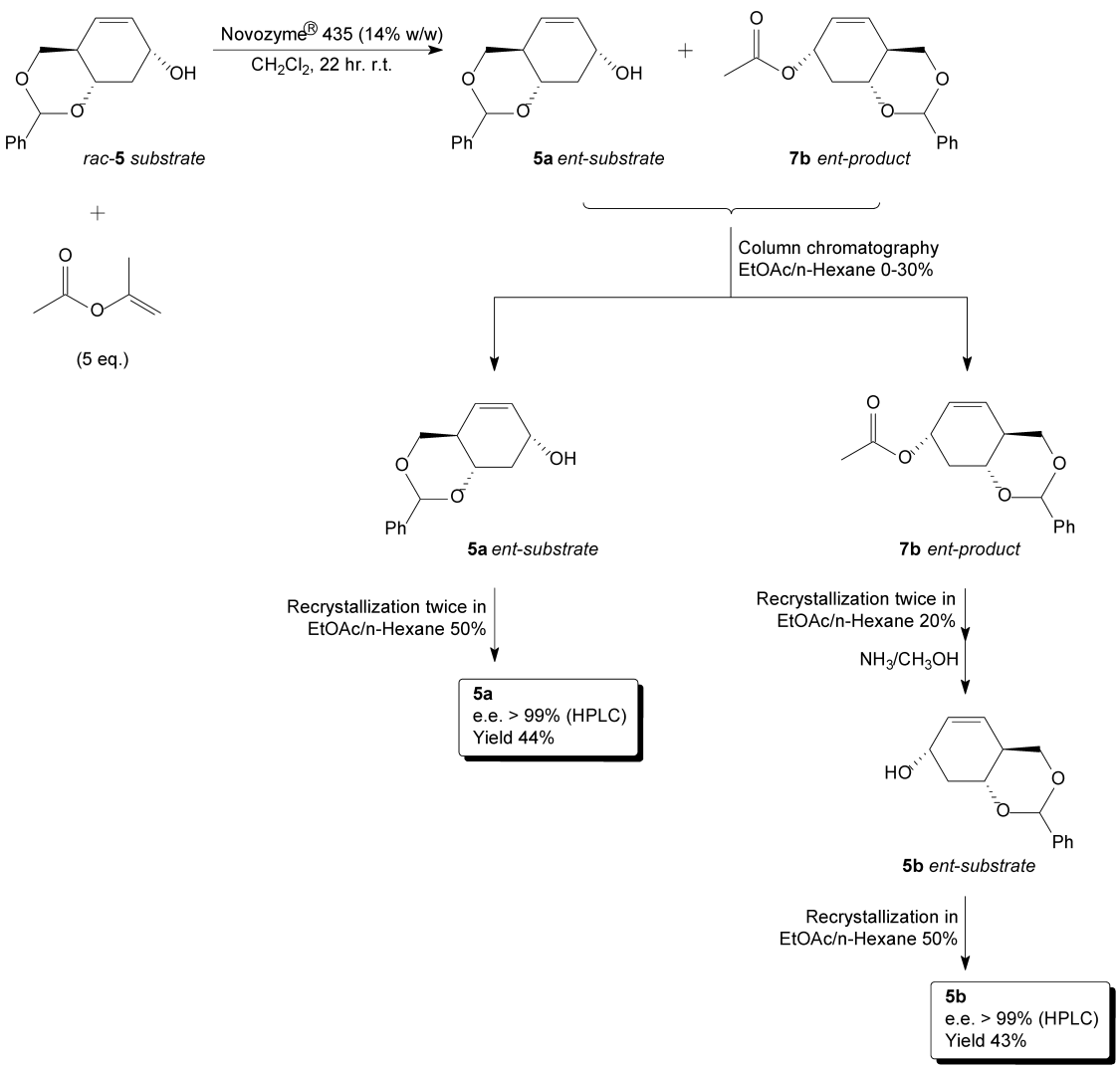


Figure 5. Procedure for separation and purification of enantiomers of **5**.

stopped after 22 h (52% conversion) and optically pure substrate **5a** (e.e.$_s$>97%) and product **7b** (e.e.$_p$>85%) were obtained, which were subsequently separated easily by column chromatography.

Following two recrystallizations from 50% of ethyl acetate in *n*-hexane, a colorless needle crystal of the enantiomeric pure **5a** with an enantiomeric excess value (e.e.) of over 99% was obtained in an overall yield of 44% (calculation based on *rac*-**5**). The absolute configuration was established via comparison of its guanine nucleoside derivative with an authentic sample which was described in the literature.[11] High optical purity (e.e.>97%) for the isolated product of *ent*-**7b** was achieved by recrystallizing twice from 20% ethyl acetate in *n*-hexane. Subsequently *ent*-**7b** was further treated with saturated ammonia/methanol solution to afford *ent*-**5b**. Likewise, recrystallized from 50% of ethyl acetate in *n*-hexane, **5b** was afforded as a colorless needle with e.e. value of over 99% in an overall yield of 43%.

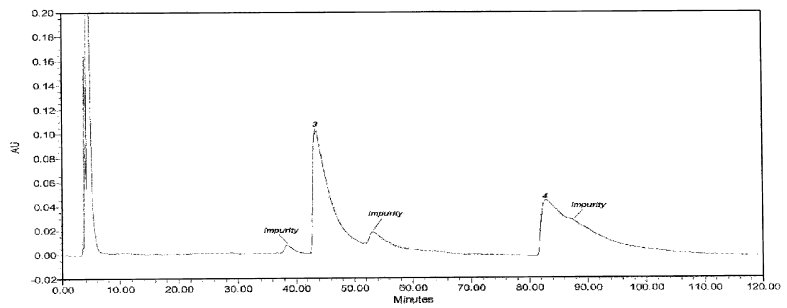
Figure 6 shows the enzymatic separation of the racemic mixture of **5** by chiral chromatography. A 1:1 mixture of **5a** and **5b** is shown in (A), while (B) and (C) show the results for enzyme-catalyzed hydrolysis and transesterification with a selectivity of (E=2) and (E=50), respectively. The identification of the obtained optically pure **5a** and **5b** are shown in (D) and (E), respectively.

In general, compared with enzyme-catalyzed hydrolysis and other described chemical methods, Novozyme® 435-catalyzed transesterification is the most facile approach to achieve the highest selectivity with economical and practical advantages.

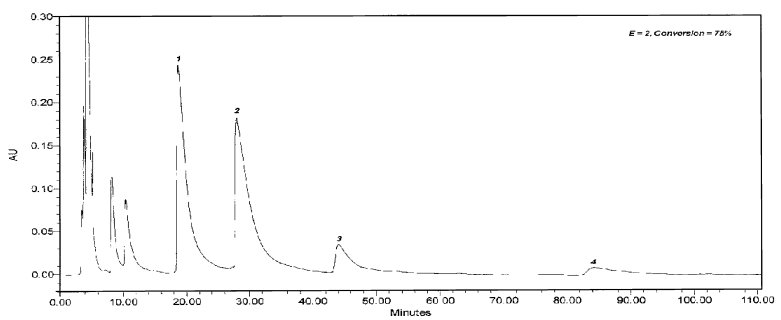
2.3. Synthesis of cyclohexenyl nucleoside building blocks

For investigation of the properties of cyclohexenyl containing nucleic acids, the enantiomeric pure protected phosphoramidite nucleosides of the four natural nucleobases were synthesized independently. The synthesis started with the previously separated enantiomerically pure (e.e.>99%) cyclohexene precursors **5a** and **5b**. The purine base moieties (adenine or 2-amino-6-chloropurine) were introduced via a direct nucleophilic displacement strategy using the Mitsunobu condensation reaction,[15] to give nucleosides **9a**,**b** (yield of 45%) and **10a**,**b** (yield of 37%)[7,11] (Fig. 7). The adenine base of **9a**,**b** was thereafter protected by the benzoyl protecting group, followed by removal of the

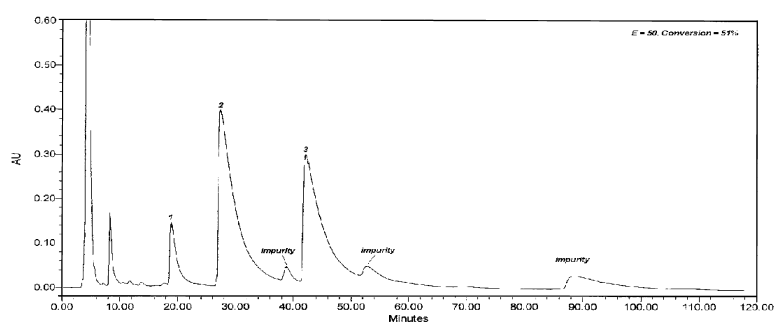
Panel A



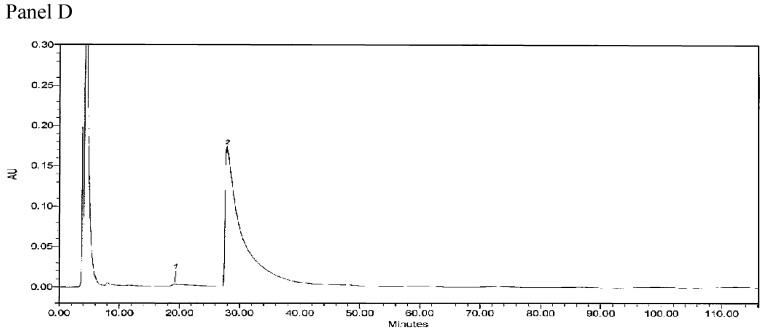
Panel B



Panel C



Panel D



Panel E

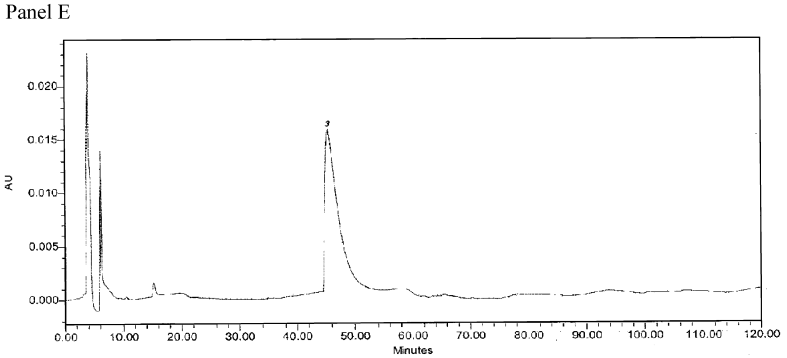


Figure 6 (*legend opposite*)

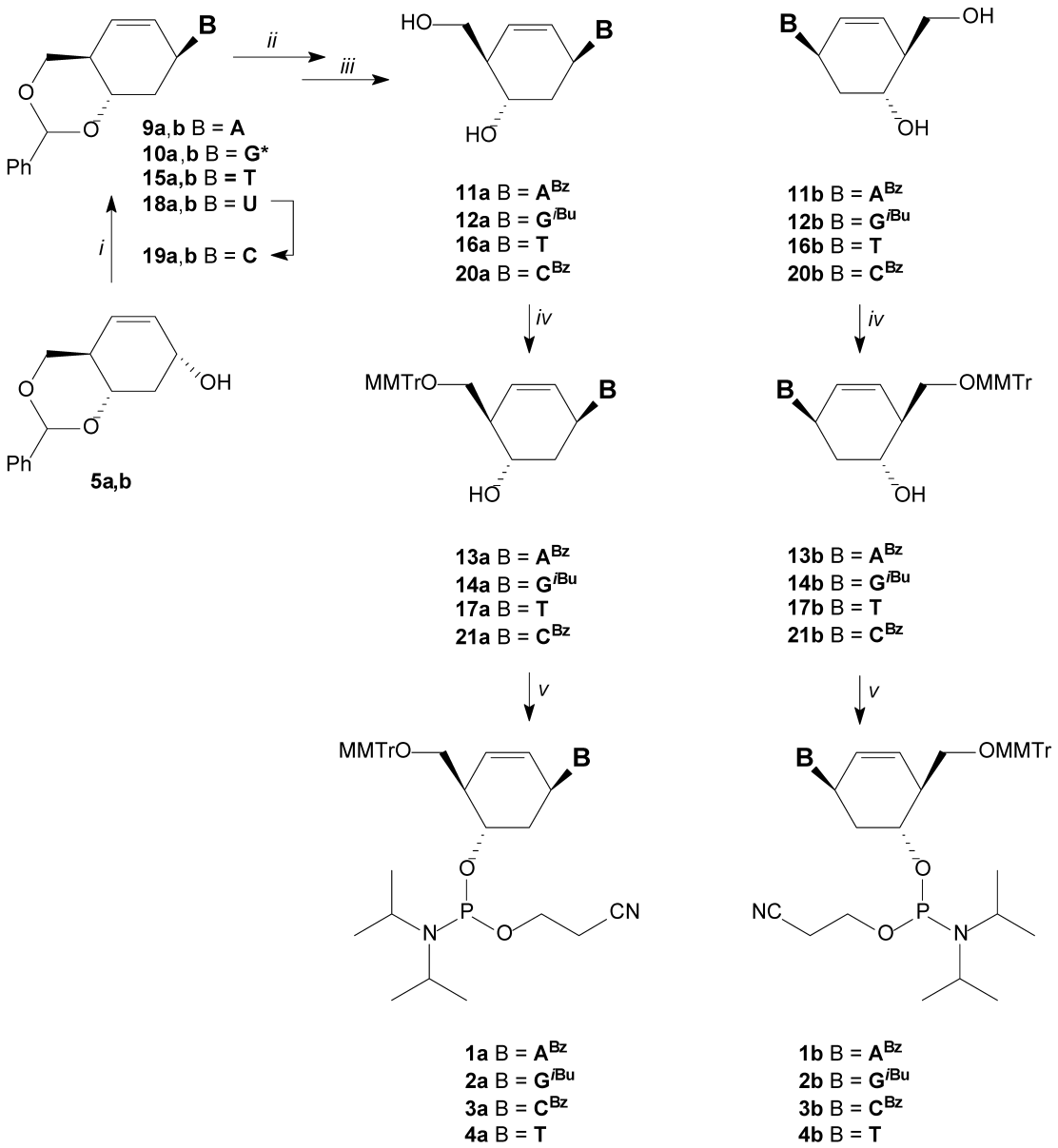


Figure 7. Synthesis for phosphoramidite building blocks **1**–**4** (a- and b-series). (i) Mitsunobu reaction; (ii) BzCl, pyridine for A and C; for G: first TFA/H_2O (80%), then TMS-Cl, isobutyric anhydride, pyridine, 0 °C rt for G; (iii) TFA/H_2O (80%), 40 h; (iv) MMTrCl, pyridine, rt; (v) $(iPr)_2N(CE)PCl$, $(iPr)_2NEt$, CH_2Cl_2.

benzylidene protecting group using 80% TFA/H_2O solution at room temperature for 2 days to give **11a**,**b** in 48% yield. The congeners **10a**,**b** on the other hand were first treated with 80% TFA/H_2O solution for 40 h, followed by protection of the 2-NH_2 position with the isobutyryl group via a transient protection approach to afford **12a**,**b** in 32% yield.[16] The monomethoxytritylation of **11a**,**b** and **12a**,**b** at the primary hydroxyl groups (4′-CH_2OH) was less straightforward. The bis-tritylated product as well as the mono-tritylated product at the secondary alcohol (5′-OH) group were likewise obtained in a total yield of 20–30%. These side reactions could be avoided by starting the reaction at 0 °C and gradually raising the temperature to room temperature with careful control of the reaction time by monitoring with TLC. The secondary hydroxyl groups (5′-OH) of **13a**,**b** and **14a**,**b** were further reacted with 2-cyanoethyl-*N*,*N*-diisopropylchlorophosphoramidite to yield enantiomeric pure **1a**,**b** and **2a**,**b** (yield of 86–92% and 66–74%, respectively), as the nucleotide building blocks.

Figure 6. Enzymatic resolution of the racemic mixture of **5**. (A) Chromatogram for the racemic mixture of **5**. Chromatographic conditions: Chiralpak AD (250×4.6 mm) Mobile phase: *n*-hexane/EtOH 98:2, Detection: UV_{220} nm; Flow rate: 1.0 mL/min; Injection volume: 10 μL. Peak 3=**5a**, peak 4=**5b**. (B) Analysis of the PLE-catalyzed hydrolysis reaction of *rac*-**8**. Chromatographic conditions: see (A). Peak 1=**8a**, peak 2=**8b**, peak 3=**5a**, peak 4=**5b**. (C) Analysis of the Novozyme®-catalyzed transesterification of *rac*-**5**.Chromatographic conditions: see (A). Peak 1=**6a**, peak 2=**6b**, peak 3=**5a**. (D) Analysis of **6b** obtained following column chromatography of the Novozyme®-catalyzed transesterification reaction of *rac*-**5**. Chromatographic conditions: see (A). Peak 1=**6a**, peak 2=**6b**. (E) Analysis of **5a** obtained following column chromatography of the Novozyme®-catalyzed transesterification reaction of *rac*-**5**. Chromatographic conditions: see (A). Peak 3=**5a**.

Alkylation of pyrimidine bases (cytosine and thymine) is more problematic than that of purines. The thymine base could be directly coupled to the sugar part by the Mitsunobu procedure. When the benzylidene protecting groups were removed the unprotected thymine nucleoside analogues **16a** and **16b** (overall yield of 16%) were obtained which were monotritylated at the primary hydroxyl group to afford **17a** and **17b** (yield of 59%). The secondary hydroxyl groups (5′-OH) were then phosphitylated to obtain the phosphoramidites, **4a** and **4b** (81–85% yield). The cytosine nucleoside **19a**,**b** (overall yield 41%) could be obtained starting from the uracil congener **18a**,**b**.[17] Following protection of the cytosine base with a benzoyl group, the benzylidene group was removed in acidic medium, to obtain the cyclohexenyl cytosine nucleosides **20a**,**b** (yield of 16–21%). Finally, following the tritylation at 4′-OH, compounds **21a**,**b** was converted to the protected phosphoramidite building block **3a**,**b** (yield of 77–87%).

The identification of the protected cyclohexenyl nucleosides and their enantiomers are exemplified with compounds **11a** and **11b**. Their structures were deduced from ^{1}H NMR analysis. Table 3 shows the chemical shifts and coupling constants for all protons. The β-conformation was previously confirmed by ^{1}H NMR analysis of its racemic unprotected congener.[6] Here the small value of the coupling constant between H-2′ and H-1′ ($J_{2'\text{-}1'}$=2.4 Hz) might also indicate that the base moiety occupies the axial position. The two enantiomers of the compound **11** give similar spectroscopic data.

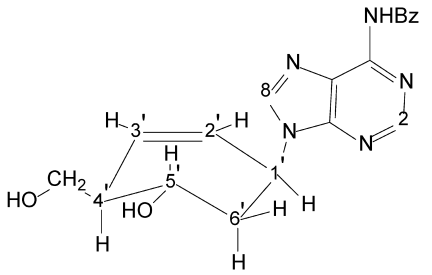
3. Conclusion

In summary, enzymatic resolution of the racemic **5** by employing a transesterification reaction with Novozyme® 435 allows the isolation of optically pure enantiomers in preparative scale. In comparison with other chemical methods,[11] the developed method is highly efficient, easy to perform and economical for multigram preparations. The different enantiomeric series of nucleoside phosphoramidite derivatives with the four natural nucleobases were synthesized as building blocks and they will be used for the synthesis of the corresponding nucleic acids analogues (CeNA).[9]

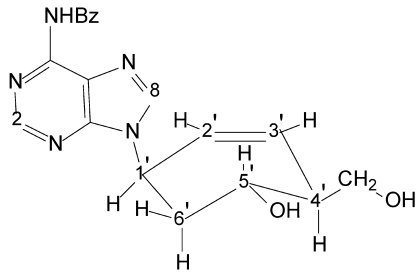
4. Experimental

All solvents used for reactions are analytical grade or freshly distilled. 1,4-Dioxane was refluxed on sodium/benzophenone and distilled. Anhydrous pyridine was refluxed on potassium hydroxide and distilled. PLE (40 KU/306 mg, suspension in 3.2 M $(NH_4)_2SO_4$) solution was purchased from Roche Diagnostics. CRL (26 U/mg), PCL (40 U/mg) were purchased from Fluka. CAL-B

Table 3. ^{1}H NMR chemical shifts (δ) and coupling constants (*J*) of **11a** and **11b**



11a



11b

Proton	Coupled to proton	**11a**		**11b**	
		δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)
1′(m)		5.47		5.45	
2′(ddd)	4′	5.93	1.7	5.94	1.5
	1′		2.4		2.4
	3′		10.0		9.9
3′(dd)	4′	6.13	2.5	6.07	2.7
	2′		10.0		9.9
4′(m)		2.50		2.50	
5′(m)	6′eq	3.81	2.9	3.80	2.9
	4′		5.7		5.7
	6′ax		9.6		9.6
5′-OH (d)	5′	4.74	4.4	4.75	–
6′(m)		2.03–2.37		2.01–2.41	
$HOCH_{2a}$-(m)	4′	3.53	5.1	3.54	5.1
	$HOCH_{2b}$–		10.3		10.3
$HOCH_{2b}$-(m)	4′	3.61	5.4	3.60	5.3
	$HOCH_{2a}$–		10.6		10.6
–OH (t)	$HOCH_2$–	4.68	5.4	4.68	–
2 (s)		8.21		8.24	
8 (s)		7.97		7.91	
Bz		7.26–7.60		7.25–7.57	

(Chirazyme® L-2, lyo, 120 U/mg) was purchased from Boehringer Mannheim. Novozyme® 435 (10 U/mg) was donated by Novo-Nordisk A/S. Enzymatic reactions were run at room temperature. Enantiomer compositions were determined by chiral HPLC analysis with a Chiralpak AD column (250×4.6 mm) on a Waters 6000 controller liquid chromatograph equipped with a Waters 2487 UV detector. ^{1}H NMR was determined with a 200 MHz Varian Gemini spectrometer with tetramethylsilane (TMS) as internal standard for ^{1}H NMR spectra and the same apparatus was used for ^{13}C NMR determination with DMSO-d_6 (39.6 ppm) or $CDCl_3$ (76.9 ppm) as internal standard for the ^{13}C NMR spectra (s=singlet, d=doublet, dd=double doublet, t=triplet, br s=broad singlet, br d=broad doublet, m=multiplet). ^{31}P NMR spectra was obtained as 85% H_3PO_4 as external standard. Exact mass measurements were performed on a quadrupole time-of-flight mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) equipped with a standard electrospray-ionization (ESI) interface; samples were infused in *i*-PrOH/H_2O 1:1 at 3 μL/min column chromatography was performed on ICN silica gel 63–200 μm, 60 Å. Precoated aluminium sheets (Fluka Silica gel/TLC-cards, 254 nm) were used for TLC; the spots were examined with UV.

Chiral HPLC analysis for determination of enantiomer composition: Mobile phase: *n*-hexane/EtOH 98:2, flow rate: 1 mL/min, UV wavelength: 220 nm, t_R (1)=18.7, t_R (2)=28.1, t_R (3)=43.8, t_R (4)=83.5 min.

4.1. Transesterification reactions of *rac*-5

The selectivity of the reaction is expressed as the enantiomeric ratio (*E*), which mathematically links to the conversion (*c*) of the reaction,[18] and the optical purities of substrate (e.e.$_s$) and product (e.e.$_p$). The dependence of the selectivity and the conversion of the reaction is:

for the product

$$E = \frac{\ln[1 - c(1 + \text{e.e.}_p)]}{\ln[1 - c(1 - \text{e.e.}_p)]}$$

for the substrate

$$E = \frac{\ln[(1 - c)(1 - \text{e.e.}_s)]}{\ln[(1 - c)(1 + \text{e.e.}_s)]}$$

where *c*, conversion; e.e., enantiomeric excess of substrate (S) or product (P); *E*, enantiomeric ratio.

The following equation is recommended instead because only values for the optical purities of substrate and the product need to be measured.[19]

$$E = \ln\left(\frac{1 - \text{e.e.}_s}{1 + \frac{\text{e.e.}_s}{\text{e.e.}_p}}\right) / \ln\left(\frac{1 + \text{e.e.}_s}{1 + \frac{\text{e.e.}_s}{\text{e.e.}_p}}\right)$$

With Novozyme® 435. *rac*-**5**[11] (70 mg, 0.30 mmol) and vinyl propionate (5 mL, 46.8 mmol) were mixed. Subsequently, Novozyme® 435 (10 mg, 100U) was added and the reaction mixture was stirred at room temperature. The reaction was stopped at 3 h (30% conversion) by filtration. Chiral HPLC analysis of a sample from the filtrate showed the presence of **6b** *ent*-product with 82% e.e. and of **5a** *ent*-substrate with 37% e.e.

With CRL. The reaction was carried out with *rac*-**5** (70 mg, 0.30 mmol) and vinyl propionate (5 mL, 46.8 mmol). CRL (10 mg, 260U) was added under the above conditions. The reaction was stopped at 27 h (49% conversion) by filtration. Chiral HPLC analysis of a sample from the filtrate showed the presence of **6b** *ent*-product with 35% e.e. and of **5a** *ent*-substrate with 51% e.e.

With PCL. The reaction was carried out with *rac*-**5** (70 mg, 0.30 mmol) and vinyl propionate (5 mL, 46.8 mmol). PCL (10 mg, 400U) was added under the above conditions. The reaction was stopped at 27 h (45% conversion) by filtration. Chiral HPLC analysis of a sample from the filtrate showed the presence of **6b** *ent*-product with 46% e.e. and of **5a** *ent*-substrate with 40% e.e.

With vinyl acetate. *rac*-**5** (70 mg, 0.30 mmol) was dissolved in vinyl acetate (5 mL, 54 mmol) and Novozyme® 435 (10 mg, 100U) was subsequently added at room temperature. The reaction was stopped at 43 h (66% conversion) by filtration. Chiral HPLC analysis of a sample from the mixture showed the presence of **7b** *ent*-product with 39% e.e. and of **5a** *ent*-substrate with 79% e.e.

With isopropenyl acetate. *rac*-**5** (70 mg, 0.30 mmol) with isopropenyl acetate (145 mg, 1.5 mmol) and Novozyme® 435 (10 mg, 100U) was added under the above conditions. The reaction was stopped at 20 h (49% conversion) by gel filtration. HPLC analysis of a sample from the filtration showed the presence of **7b** *ent*-product with 74% e.e. and **5a** *ent*-substrate with 93% e.e.

The procedures for transesterification of *rac*-**5** with various solvents and additives are given here exemplified by using CH_2Cl_2 and CH_2Cl_2/Et_3N.

With CH_2Cl_2. *rac*-**5** (70 mg, 0.30 mmol) and isopropenyl acetate (145 mg, 1.5 mmol) were dissolved in CH_2Cl_2 (5 mL). Subsequently, Novozyme® 435 (10 mg, 100U) was added and the reaction mixture was stirred at room temperature. The reaction was stopped at 20 h (49% conversion) by filtration. Chiral HPLC analysis of a sample from the mixture showed the presence of **7b** *ent*-product with 84% e.e. and of **5a** *ent*-substrate with 95% e.e.

With CH_2Cl_2/Et_3N. *rac*-**5** (70 mg, 0.30 mmol), isopropenyl acetate (145 mg, 1.5 mmol) and Et_3N (10.6 μL, 75 μmol) were dissolved in CH_2Cl_2 (5 mL). Subsequently, Novozyme® 435 (10 mg, 100U) was added and the reaction mixture was stirred at room temperature. The reaction was stopped at 20 h (71% conversion) by filtration. Chiral HPLC analysis of a sample from the mixture showed the presence of **7b** *ent*-product with 49% e.e. and of **5a** *ent*-substrate with >99% e.e.

4.1.1. (±)-(4a*R*,7*R*,8a*S*)-2-Phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7-yl acetate (*rac*-7). To a mixture of *rac*-**5** (0.72 g, 3.1 mmol) in pyridine (10 mL), acetyl chloride (0.35 mL, 4.9 mmol) was added at 0 °C and the mixture was stirred at room temperature for 6 h. The reaction was poured into saturated aqueous $NaHCO_3$ and stirred for half-an-hour. The mixture was extracted with CH_2Cl_2 and the organic layer was separated, dried over

anhydrous Na_2SO_4 and co-evaporated with toluene in vacuo. The crude was purified by column chromatography (EtOAc/*n*-hexane, 0–30%) to afford 0.78 g of *rac*-**7** (yield 94%).

^{1}H NMR ($CDCl_3$) δ 1.88–1.99 (m, 1H, H-8), 2.09 (s, 3H, $-CH_3$), 2.48–2.69 (m, 2H, H-8, H-4a), 3.59–3.80 (m, 2H, 4-CH_2O-), 4.28 (dd, 1H, J=10.8, 4.6 Hz, H-7), 5.50–5.72 (m, 3H, H-8a, H-5, H-6), 5.62 (s, 1H, 2-CHPh), 7.27–7.51 (m, 5H, aromatic-H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.8 ($-CH_3$), 33.9 (C-8), 39.5 (C-4a), 69.5 (C-7), 70.1 (4-CH_2O-), 76.1 (C-8a), 101.8 (2-CHPh), 125.9, 126.7, 128.1, 128.4, 128.7, 137.8 (aromatic-C) 170.3 ($-OCO-$) ppm. LISMS (CH_3OH/H_2O) 275.1 $(M+H)^+$.

4.1.2. (±)-(4a*R*,7*R*,8a*S*)-2-Phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7-yl propionate (rac-6). *rac*-**5** (0.72 g, 3.1 mmol) in pyridine (10 mL) was reacted with propionyl chloride (0.39 mL, 4.5 mmol) using the previous procedure to afford 0.78 g (yield 90%) of *rac*-**6** as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, $-CH_2CH_3$), 1.82–1.94 (m, 1H, H-8), 2.28 (q, 2H, $-CH_2CH_3$), 2.21–2.47 (m, 2H, H-8, H-4a), 3.59–3.92 (m, 2H, 4-CH_2O-), 4.54 (dd, 1H, J=10.7, 4.2 Hz, H-7), 5.53–5.61 (m, 3H, H-8a, H-5, H-6), 5.59 (s, 1H, 2-CHPh), 7.39–7.51 (m, 5H, aromatic-H) ppm; ^{13}C NMR ($CDCl_3$) δ 9.04 ($-CH_2CH_3$), 27.6 ($-CH_2CH_3$), 32.4 (C-8), 39.8 (C-4a), 68.0 (C-7), 70.1 (4-CH_2O-), 76.1 (C-8a), 102.1 (2-CHPh), 125.9, 126.7, 128.1, 128.4, 128.7, 138.3 (aromatic-C), 170.4 ($-OCO-$) ppm. LISMS (CH_3OH/H_2O) 289.1 $(M+H)^+$.

4.1.3. (±)-(4a*R*,7*R*,8a*S*)-2-Phenyl-4a,7,8,8a-tetrahydro-4*H*-1,3-benzodioxin-7-yl-butyrate (rac-8). *rac*-**5** (0.70 g, 3.0 mmol) and 30 mg of DMAP in pyridine (10 mL) reacted with butyric anhydride (0.74 mL, 4.5 mmol) using above procedure to afford 0.83 g (yield 91%) of *rac*-**8** as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, $-CH_2CH_2CH_3$), 1.61 (m, 2H, $-CH_2CH_2CH_3$), 1.80–1.95 (m, 1H, H-8), 2.22–2.47 (m, 4H, H-8, $-CH_2CH_2CH_3$, H-4a), 3.80–3.95 (m, 2H, 4-CH_2O-), 4.54 (m, 1H, H-7), 5.53–5.61 (m, 3H, H-8a, H-5, H-6), 5.59 (s, 1H, 2-CHPh), 7.39–7.53 (m, 5H, aromatic-H) ppm; ^{13}C NMR ($CDCl_3$) δ 10.5 ($-CH_2CH_2CH_3$), 18.4 ($-CH_2CH_2CH_3$), 32.4 (C-8), 36.1 ($-CH_2CH_2CH_3$), 41.4 (C-4a), 67.9 (C-7), 69.1 (4-CH_2O-), 75.8 (C-8a), 102.7 (2-CHPh), 125.8, 126.7, 127.6, 128.6, 131.7, 138.8 (aromatic-C) 172.4 ($-OCO-$) ppm. LISMS (CH_3OH/H_2O) 302.2 $(M+H)^+$.

4.2. Resolution of *rac*-7

With PLE. The ester *rac*-**7** (200 mg, 0.73 mmol) dissolved in (a) *t*-BuOH (4 mL) or (b) acetone (4 mL) was added to the phosphate buffer solution (36 mL, pH 8.0, adjusted by 1 N HCl). Subsequently, PLE (0.1 mL, 130U) was added and the mixture was efficiently stirred at room temperature while the pH value was held constant at 8.0 by the addition of 1 M NaOH solution with a pH-stat autotitrator. The reaction was stopped after 22 h (11% conversion) and 24 h (44% conversion), respectively, and the mixture was extracted continuously with CH_2Cl_2 (50 mL) for 17 h (Soxlet apparatus). The organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Chiral HPLC analysis of a sample of the residue showed the presence of **5a** *ent*-product with 30% e.e. and of **7b** *ent*-substrate with <1% e.e. for (a); and of **5a** *ent*-product with 46% e.e. and of **7b** *ent*-substrate with 27% e.e. for (b).

With CRL. The hydrolysis was carried out with *rac*-**7** (200 mg, 0.73 mmol), *t*-BuOH (4 mL) and CRL (5 mg, 130U) in aqueous phosphate buffer solution (36 mL, pH 8.0, adjusted by 1 N HCl). Work-up was done as described above after 24 h (17% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5b** *ent*-product with 65% e.e. and of **7a** *ent*-substrate with 26% e.e.

With CAL-B. The hydrolysis was carried out with *rac*-**7** (200 mg, 0.73 mmol), *t*-BuOH (4 mL) and CAL-B (20 mg, 2.4 KU) in phosphate buffer solution (36 mL, pH 7.5, adjusted by 1 N HCl). Work-up as described above after 25 h (21% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5a** *ent*-product with 16% e.e. and of **7b** *ent*-substrate with 10% e.e.

4.3. Resolution of *rac*-6

With PLE. The hydrolysis was carried out with *rac*-**6** (200 mg, 0.69 mmol), *t*-BuOH (4 mL) and PLE (0.1 mL, 130U) in phosphate buffer solution (36 mL, pH 7.5, adjusted by 1 N HCl). Work-up after 17 h (35% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5a** *ent*-product with 68% e.e. and of **6b** *ent*-substrate with 40% e.e.

With CRL. The hydrolysis was carried out with *rac*-**6** (200 mg, 0.69 mmol), *t*-BuOH (4 mL) and CRL (5 mg, 130U) in aqueous phosphate buffer solution (36 mL, pH 7.5, adjusted by 1 N HCl). Work-up after 24 h (85% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5b** *ent*-product with 2% e.e. and of **6a** *ent*-substrate with 30% e.e.

4.4. Resolution of *rac*-8

With PLE. The hydrolysis was carried out with *rac*-**8** (200 mg, 0.66 mmol), *t*-BuOH (4 mL) and PLE (0.1 mL, 130U) in aqueous phosphate buffer solution (36 mL, pH 7.5, adjusted by 1 N HCl). Work-up after 10 h (13% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5a** *ent*-product with 95% e.e. and of **8b** *ent*-substrate with 9% e.e.

With CRL. The hydrolysis was carried out with *rac*-**8** (200 mg, 0.66 mmol), *t*-BuOH (4 mL) and CRL (5 mg, 130U) in aqueous phosphate buffer solution (36 mL, pH 7.5, adjusted by 1 N HCl). Work-up after 4 h (27% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5b** *ent*-product with 11% e.e. and of **8a** *ent*-substrate with 24% e.e.

With CAL-B. The hydrolysis was carried out with *rac*-**8** (200 mg, 0.66 mmol), *t*-BuOH (4 mL) and CAL-B (20 mg, 2.4 KU) in aqueous phosphate buffer solution (36 mL, pH

7.5, adjusted by 1 N HCl). Work-up after 30 h (21% conversion). Chiral HPLC analysis of a sample of the residue showed the presence of **5a** *ent*-product with 63% e.e. and of **8b** *ent*-substrate with 15% e.e.

4.5. Isolation of enantiomerically pure cyclohexene precursor

The precursor *rac*-**5** (14.0 g, 60.2 mmol) and isopropenyl acetate (32.8 mL, 301 mmol) were dissolved in dichloromethane (700 mL). Subsequently, Novozyme® 435 (2 g, 20 KU) was added and the reaction mixture was stirred at room temperature. The reaction was stopped at 22 h (52% conversion) by filtration. The filtrate was concentrated in vacuo and submitted to column chromatography (EtOAc/*n*-hexane, 0–30%). The first portion of eluent was concentrated to afford a white solid which was twice recrystallized from 20% EtOAc in *n*-hexane giving a white needle crystal of **6b** *ent*-product (8.07 g, 98% e.e.). Following treatment with 50 mL of a saturated ammonia/methanol solution at room temperature for 14 h, the reaction mixture was concentrated and co-evaporated with methanol to afford a pale-yellow oil which was purified by column chromatography (EtOAc/*n*-hexane, 50:50, R_f=0.5). A white solid was obtained and recrystallized twice from 50% EtOAc in *n*-hexane twice affording a white needle crystal of **5b** (6.1 g, yield 89%) with enantiomeric excess (e.e.) >99% (overall yield 43% starting from *rac*-**5**). The second fraction from the first chromatographic purification was concentrated and thereafter crystallized twice from 50% EtOAc in *n*-hexane to afford a white needle crystal of **5a** (6.2 g, yield 44%) with enantiomeric excess (e.e.) >99%.

4.6. Synthesis of cyclohexenyl nucleoside building blocks

For all reactions, analytical grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried glassware (100 °C) under a nitrogen atmosphere.

Compound **9a**,**b** were synthesized using the procedure for preparation of the racemic isomer as described in literature.[7] Compound **10a**,**b** were prepared using the synthetic method for racemic Cycl-G.[11] The other isomers **18a**,**b**, **19a**,**b** and **15a**,**b** were obtained analogously to the preparation of their racemic isomers.[20]

4.6.1. N^6-Benzoyl-9-[(1′*S*,4′*R*,5′*S*)-5′-hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclo-hexenyl]adenine (13a). To a solution of **9a** (590 mg, 1.71 mmol) in pyridine (10 mL) at 0 °C was added benzoyl chloride (0.52 mL, 5.13 mmol) and kept at room temperature overnight. The reaction mixture was cooled to 0 °C, and saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with H_2O (20 mL), concentrated, and co-evaporation with toluene. The residue was treated with saturated ammonia/methanol solution (25 mL) for 5 min. Following evaporation of the solvent and co-evaporation with methanol, the residue was further treated with 80% CF_3COOH in water for 40 h. The reaction mixture was concentrated and co-evaporated with toluene and methanol three times. The crude was purified by silica gel column chromatography (CH_3OH/CH_2Cl_2, 0–10%, R_f=0.3) to give **11a** (430 mg, 1.18 mmol, yield 70%). To a solution of the obtained **11a** (co-evaporated three times with freshly dried pyridine) in dry pyridine (5 mL) at 0 °C under nitrogen was added monomethoxytrityl chloride (436 mg, 1.41 mmol) in portions. After the mixture was stirred at 0 °C for 1 h, the temperature was raised to room temperature. The reaction mixture was treated with CH_3OH (5 mL) at 0 °C after 22 h reaction. After the mixture was stirred at room temperature for 0.5 h, the resulting mixture was concentrated. The residue was co-evaporated with toluene and methanol, and chromatographed on silica gel (CH_3OH/CH_2Cl_2, 0–2%, Et_3N 1%) to give **13a** (470 mg, 0.74 mmol, 63% yield, overall yield of 43%) as a white foam.

^{1}H NMR ($CDCl_3$) δ 2.03–2.40 (m, 2H, H-6′, 6″), 2.55 (m, 1H, H-4′), 3.04 (br s, 1H, 5′-OH), 3.26 (t, 1H, *J*=8.6 Hz, $-OCH_2-$), 3.57 (dd, 1H, *J*=4.4, 9.2 Hz, $-OCH_2-$), 3.81 (br s, 4H, $-OCH_3$, H-5′), 5.47 (m, 1H, H-1′), 5.93 (br s, 2H, H-2′, H-3′), 6.87 (d, 2H, *J*=9.2 Hz, aromatic H), 7.26–7.61 (m, 15H, aromatic H), 7.91 (s, 1H, H-8), 8.05 (d, 2H, aromatic H), 8.81 (s, 1H, H-2), 9.12 (br s, 1H, 6-N*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 35.7 (C-6′), 44.4 (C-4′), 49.6 (C-1′), 55.2 ($-OCH_3$), 65.9 ($-OCH_2-$), 66.7 (C-5′), 87.4 ($-OC^{TrMM}$), 123.9 (C-2′), 113.3, 127.3, 128.0, 128.1, 128.3, 128.9, 130.3, 132.7, 135.0, 143.9, 158.9, (aromatic C), 133.9 (C-3′), 141.9 (C-8), 149.6 (C-2), 151.7 (C-6), 152.6 (C-4), 164.8 ($-NHC{=}O$) ppm. HRMS calcd for $C_{39}H_{36}N_5O_4$ $(M+H)^+$: 638.2767, found 638.2770.

4.6.2. N^6-Benzoyl-9-[(1′*R*,4′*S*,5′*R*)-5′-hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]adenine (13b). Starting from 770 mg (2.2 mmol) of **9b**, an amount of 618 mg (0.96 mmol, overall yield of 44%) of **13b** was obtained. Spectroscopic data are the same as for **13a**.

4.6.3. N^2-Isobutyryl-9-[(1′*S*,4′*R*,5′*S*)-5′-hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]guanine (14a). To a solution of **10a** (460 mg, 1.66 mmol) in dry pyridine (12 mL) at 0 °C under nitrogen was added dropwise trimethylsilyl chloride (1.06 mL, 8.29 mmol). After the mixture was stirred for 1 h, isobutyric anhydride (0.83 mL, 4.98 mmol) was added slowly. The mixture was stirred at 0 °C for 1 h, warmed to room temperature and kept stirring for an additional 14 h. The reaction mixture was then cooled in an ice-water bath and quenched with water (12 mL). The resulting mixture was stirred at room temperature for 15 min and concentrated. The residue was purified by column chromatography (CH_3OH/CH_2Cl_2, 5–20%, R_f=0.4) to afford **12a** (730 mg, 2.10 mmol, yield 63%). Following the monomethoxytritylation procedure as for preparation of **13a**, using 972 mg (3.15 mmol) of monomethoxytrityl chloride in 15 mL pyridine, **14a** was obtained (380 mg, 0.61 mmol, 29% yield, overall yield of 37%) as a pale yellow foam.

^{1}H NMR ($CDCl_3$) δ 1.20 (dd, 6H, *J*=4.9, 6.8 Hz, $-CH(CH_3)_2$), 2.01–2.25 (m, 2H, H-6′, 6″), 2.50 (m, 2H, H-4′, 2-N*H*CO–), 3.21 (m, 2H, $-OCH_2-$, 5′-O*H*), 3.50 (dd, 1H, *J*=4.6, 9.3 Hz, $-OCH_2-$), 3.80 (s, 3H, $-OCH_3$), 3.90 (m, 1H, H-5′), 5.07 (m, 1H, H-1′), 5.85 (br s, 2H, H-2′, H-3′), 6.85 (d, 2H, *J*=8.8 Hz, aromatic H), 7.23–7.46 (m, 12H, aromatic H), 7.51 (s, 1H, H-8), 8.47 (br s, 1H, 1-N*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 18.8 ($-CH(CH_3)_2$), 35.7 (C-6′), 36.3

Table 4. Analytical data for the phosphoramidites

	mmol of starting material	Yield (%)	R_f	HRMS $(M+H)^+$		^{31}P NMR
			n-Hexane/acetone/TEA (49:49:2)	Calcd	Found	
1a	0.72	86	0.46	838.3846 For $C_{48}H_{53}N_7O_5P$	838.3859	148.357, 148.393
1b	0.90	92	0.46	838.3846 For $C_{48}H_{53}N_7O_5P$	838.3840	148.308, 148.345
2a	0.57	66	0.38	820.3951 For $C_{45}H_{55}N_7O_6P$	820.3944	146.115, 147.142
2b	0.62	74	0.38	820.3951 For $C_{45}H_{55}N_7O_6P$	820.3953	146.085, 147.148
3a	0.40	87	0.51	814.3733 For $C_{47}H_{53}N_5O_6P$	814.3759	148.314, 148.465
3b	0.73	77	0.51	814.3733 For $C_{47}H_{53}N_5O_6P$	814.3732	148.314, 148.459
4a	0.77	85	0.51	725.3467 For $C_{41}H_{50}N_4O_6P$	725.3472	147.632, 148.127
4b	1.01	81	0.51	725.3467 For $C_{41}H_{50}N_4O_6P$	725.3455	147.644, 148.163

(−*C*H(CH$_3$)$_2$), 44.3 (C-4′), 49.4 (C-1′), 55.2 (−O*C*H$_3$), 65.6 (−O*C*H$_2$−), 66.4 (C-5′), 87.2 (−O*C*^{TrMM}), 121.6 (C-5), 124.3 (C-2′), 113.3, 127.2, 128.1, 128.3, 130.3, 135.1, 144.1, 158.9 (aromatic C), 133.4 (C-3′), 138.0 (C-8), 147.2 (C-2), 147.8 (C-4), 155.8 (C-6), 178.6 (−NH*C*=O) ppm. HRMS calcd for $C_{36}H_{38}N_5O_5$ $(M+H)^+$: 620.2872, found 620.2869.

4.6.4. N^2-Isobutyryl-9-[(1′*R*,4′*S*,5′*R*)-5′-hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]guanine (14b). Starting from 600 mg (2.16 mmol) of **10b**, an amount of 420 mg (0.68 mmol, overall yield of 31%) of **14b** was obtained. Spectroscopic data are the same as for **14a**.

4.6.5. 1-[(1′*S*,4′*R*,5′*S*)-5′-Hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]-thymine (17a). 15a (750 mg, 2.21 mmol) was treated with 80% CF_3COOH in H_2O for 40 h. After evaporation and co-evaporation with toluene and methanol, the residue was purified by column chromatography (CH_3OH/CH_2Cl_2, 0–10%, R_f=0.25) to give **16a** (334 mg, 1.32 mmol, yield 60%). Following the procedure used for preparation of **13a**, using 778 mg (2.52 mmol) of monomethoxytrityl chloride in 15 mL pyridine, **17a** was obtained (410 mg, 0.78 mmol, 59% yield, overall yield of 35%) as a white foam.

^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H, −C*H*$_3$), 1.95–2.00 (m, 2H, H-6′, 6″), 2.43 (m, 1H, H-4′), 2.73 (d, 1H, 5′-OH), 3.19 (m, 1H, −OC*H*$_2$−), 3.51 (dd, 1H, *J*=4.4, 9.5 Hz, −OC*H*$_2$−), 3.80 (br s, 4H, −OC*H*$_3$, H-5′), 5.26 (m, 1H, H-1′), 5.62 (m, 1H, H-2′), 5.91 (m, 1H, H-3′), 6.86 (d, 2H, *J*=8.8 Hz, aromatic H), 6.97 (s, 1H, H-6), 7.22–7.46 (m, 12H, aromatic H), 8.41 (br s, 1H, 3-N*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 12.3 (−*C*H$_3$), 35.1 (C-6′), 44.0 (C-4′), 50.5 (C-1′), 55.2 (−O*C*H$_3$), 65.4 (−O*C*H$_2$−), 66.3 (C-5′), 87.3 (−O*C*^{TrMM}), 110.1 (C-5), 124.9 (C-2′), 113.3, 127.3, 128.1, 128.3, 130.3, 135.1, 144.1, 158.8 (aromatic C), 134.4 (C-3′), 137.4 (C-6), 150.7 (C-2), 163.6 (C-4) ppm. HRMS calcd for $C_{32}H_{32}N_2O_5Na$ $(M+Na)^+$: 547.2208, found 547.2212.

4.6.6. 1-[(1′*R*,4′*S*,5′*R*)-5′-Hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]-thymine (17b). Starting from 875 mg (2.57 mmol) of **15b**, an amount of 540 mg (1.03 mmol, overall yield 40%) of **17b** was obtained. Spectroscopic data are the same as for **17a**.

4.6.7. N^4-Benzoyl-1-[(1′*S*,4′*R*,5′*S*)-5′-hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]cytosine (21a). To a solution of **19a** (660 g, 2.04 mmol) in pyridine (10 mL) at 0 °C was added benzoyl chloride (0.72 mL, 6.12 mmol) and the mixture was kept at room temperature overnight. The reaction mixture was cooled to 0 °C, and saturated aqueous $NaHCO_3$ (5 mL) was added and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with H_2O (15 mL), concentrated, and co-evaporated with toluene. The residue was treated with saturated ammonia/methanol solution (25 mL) for 5 min. Following evaporation of the solvent and co-evaporation with methanol, the residue was further treated with 80% CF_3COOH in H_2O for 40 h. The reaction mixture was concentrated and co-evaporated with toluene and methanol three times. The crude was purified by silica gel column chromatography (CH_3OH/CH_2Cl_2, 0–10%, R_f=0.45) to give **20a** (560 mg, 1.64 mmol, yield 76%). Tritylation according to the preparation of **13a**, using 608 mg (6.30 mmol) of monomethoxytrityl chloride in 15 mL pyridine, afforded **21a** (320 mg, 0.52 mmol, 32% yield, overall yield of 26%) as a white foam.

^{1}H NMR ($CDCl_3$) δ 1.98–2.11 (m, 2H, H-6′, 6″), 2.29 (m, 1H, H-4′), 2.36 (br, 1H, 5′-OH), 3.10 (m, 1H, −OCH_2−), 3.73 (m, 1H, −OCH_2−), 3.79 (s, 3H, −OCH_3), 4.14 (m, 1H, H-5′), 5.41 (m, 1H, H-1′), 5.68 (m, 1H, H-2′), 6.05 (m, 1H, H-3′), 6.83 (d, 2H, *J*=8.8 Hz, aromatic H), 7.20–7.52 (m, 18H, aromatic H, H-5), 7.98 (d, 1H, H-6), 8.65 (br s, 1H, 4-NH) ppm; ^{13}C NMR ($CDCl_3$) δ 35.5 (C-6′), 44.8 (C-4′), 53.3 (C-1′), 55.2 (−O*C*H$_3$), 63.3 (−O*C*H$_2$−), 64.0 (C-5′), 87.0 (−O*C*^{TrMM}), 95.8 (C-5), 123.6 (C-2′), 113.3, 127.2, 128.1, 128.8, 130.2, 135.9, 138.0, 144.1, 158.7 (aromatic C), 132.8 (C-3′), 147.1 (C-6), 156.0 (C-2), 162.1 (C-4), 167.5 (−NH*C*=O) ppm. HRMS calcd for $C_{38}H_{36}N_3O_5$ $(M+H)^+$: 614.2654, found 614.2647.

4.6.8. N^4-Benzoyl-1-[(1′*R*,4′*S*,5′*R*)-5′-hydroxy-4′-(monomethoxytrityl)oxymethyl-2′-cyclohexenyl]cytosine (21b). Starting from 920 mg (2.84 mmol) of **19b**, an amount of

540 mg (1.58 mmol, overall yield of 31%) of **21b** was obtained. Spectroscopic data are the same as for **21a**.

4.7. Synthesis of the amidite building blocks (1a, 1b, 2a, 2b, 3a, 3b, 4a and 4b)

4.7.1. General procedure for phosphoramidite synthesis. The phosphitylation reaction was carried out on 0.4–1 mmol of the monomethoxytritylated derivative (**13a**,**b**, **14a**,**b**, **17a**,**b** and **21a**,**b**, respectively) in 5–10 mL dichloromethane using freshly distilled diisopropylethylamine (3 equiv.) and 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (1.5 equiv.) under argon. The reaction mixture was stirred at room temperature for 60 min when TLC indicated complete reaction. Water (3 mL) was added, the solution was stirred for 10 min and partitioned between CH_2Cl_2 (50 mL) and aqueous $NaHCO_3$ (30 mL). The organic phase was washed with aqueous NaCl (3×30 mL) and the aqueous phases were back extracted with CH_2Cl_2 (30 mL). Evaporation of the organics left an oil which was flash purified on 45 g of silica gel (hexane/acetone/TEA, 49:49:2) to afford the product as a foam after co-evaporation with dichloromethane. Dissolution in 3 mL of dichloromethane and double precipitation in 160 mL cold (−60 °C) hexane afforded the desired product as a white powder. The obtained material was dried in vacuo and stored under nitrogen at −20 °C until use for oligonucleotide synthesis.

Yields, starting quantity, R_f values, mass analysis and ^{31}P NMR data are given in Table 4.

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A stereoselective total synthesis of (+)-α-herbertenol

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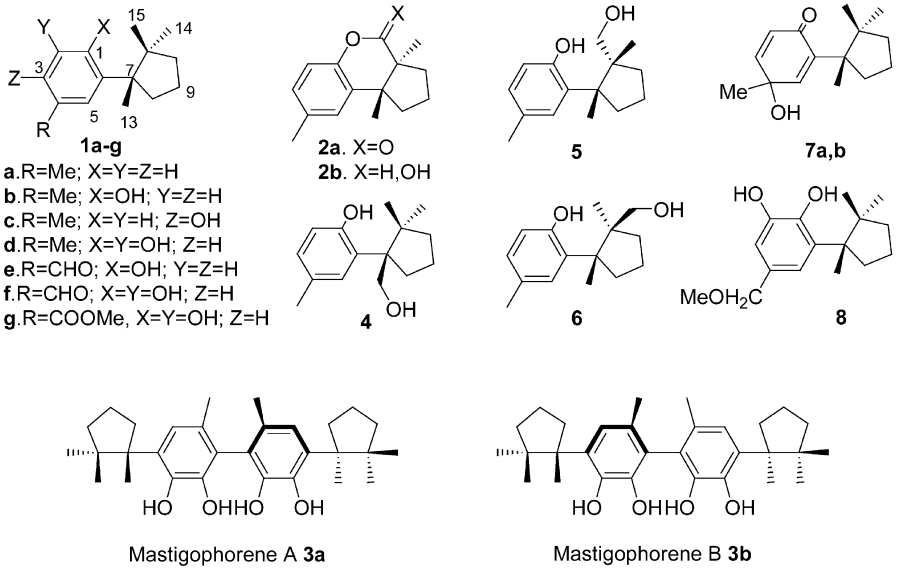
Abstract—A stereoselective total synthesis of (+)-α-herbertenol starting from the allyl alcohol **12**, readily available in three steps from the monoterpene (*R*)-limonene, is described. Claisen rearrangement of the aryl allyl ether **10** and concomitant cyclisation furnished a 5:3 mixture of the tricyclic compounds **13** and **14**. Degradation of the isopropenyl group followed by cleavage of the central ring and functional group manipulation transformed **13** into (+)-α-herbertenol (**1b**).

1. Introduction

Herbertanes are a small group of sesquiterpenes, which are considered as chemical markers for the liverworts belonging to the genus *Herbertus*.[1a] Isolation of the first members of the herbertane group herbertene **1a**, α-herbertenol **1b**, β-herbertenol **1c**, herbertenediol **1d**, herbertenal **1e** and herbertenolide **2a** from *Herberta adunca* was reported earlier by Matsuo and co-workers.[1b] Subsequently,[1c] Rycroft et al. reported the isolation of the aldehyde **1f** and the ester **1g** from *Herbertus aduncus*. The phenolic herbertanes, for example, **1b**–**d** have been shown to possess interesting biological properties such as growth inhibiting activity, antifungal, antilipid peroxidation and neurotropic activities.[1,2] The dimeric herbertanes mastigophorenes A and B **3a** and **3b**, isolated[3] along with their isomers mastigophorenes C and D and herbertenols from the liverwort *Mastigophora diclados*, were shown to stimulate nerve growth. Recently,[1a] Asakawa and co-workers reported the isolation of seven new members of the herbertane group herbertenelactol **2b**, 1,13-herbertenediol **4**, 1,14-herbertenediol **5**, 1,15-herbertenediol **6**, herbertenones A and B **7a**,**b** and 12-methoxy-herbertenediol **8** along with dimeric herbertanes mastigophorenes A–C, from the Japanese liverwort *Herberta sakuraii*.

The presence of two vicinal quaternary carbons on a cyclopentane moiety and associated biological activities



Keywords: Herbertenediol; Mastigophorenes; Cyclopentane.
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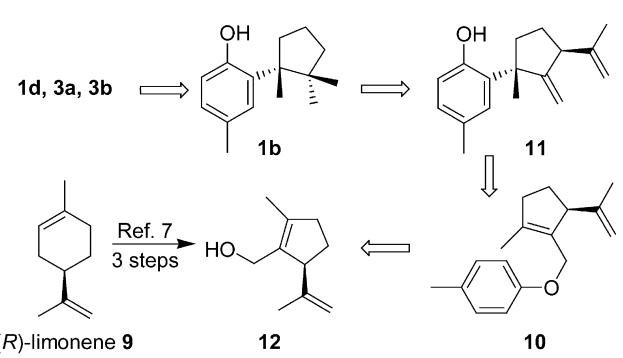
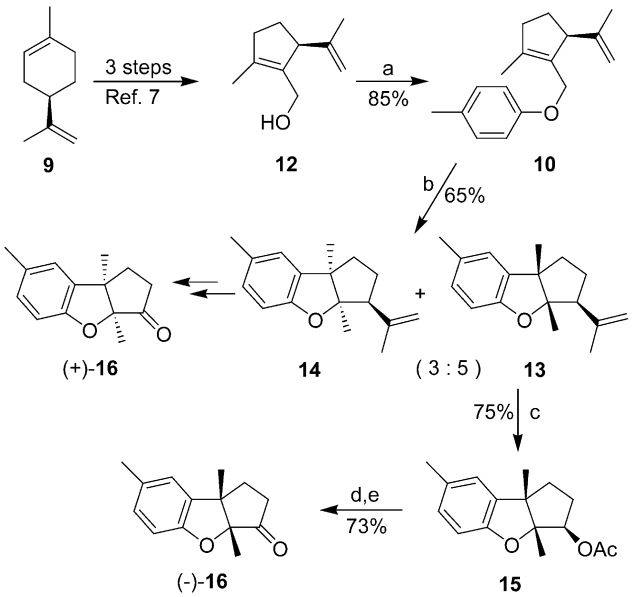
made mastigophorenes and herbertenols interesting synthetic targets of current interest. Until recently, unlike the parent hydrocarbon, the phenolic herbertanes have received very little attention from synthetic chemists despite their interesting biological properties. However, the scenario has been changed and significant synthetic activity is reported since 1999.[2,4–6] The first enantioselective synthesis of (−)-α-herbertenol **1b** was reported[5a] by Abad and co-workers in 1999. The first synthesis of mastigophorenes A and B **3a** and **3b** was achieved[5b] in 1999 via the phenolic coupling of natural herbertenediol **1d**. Almost at the same time,[5c] Meyers and Degnan reported an enantioselective synthesis of herbertenediol (−)-**1d** and its conversion to mastigophorenes A and B (−)-**3a** and (−)-**3b**. In 2001, Fukuyama and co-workers reported[5f] the enantioselective synthesis of (−)-α-herbertenol **1b** and its conversion to (−)-herbertenediol **1d** and mastigophorenes **3a** and **3b**. Recently, Kita and co-workers have developed[6a] an enantioselective synthesis of herbertenediol **1d** via rearrangement of an epoxytosylate, and later extended[6b] the methodology for the synthesis of α-herbertenol **1b**. Herein we wish to report a stereoselective total synthesis of (+)-α-herbertenol starting from the readily and abundantly available monoterpene (*R*)-limonene **9** employing Claisen rearrangement as the key reaction for the generation of the chiral quaternary carbon atom.

It was contemplated that Claisen rearrangement of the aryl ether **10** generates methylenecyclopentane **11** containing the requisite chiral quaternary carbon atom, which can be further elaborated into α-herbertenol **1b** (Scheme 1). Visualising the isopropenyl group as a masked hydroxy group, the allyl alcohol **12** was chosen as the appropriate chiral starting material, which could be readily obtained[7] from the abundantly available monoterpene (*R*)-limonene **9**.

The synthetic sequence is depicted in Schemes 2 and 3. To begin with, the allyl alcohol **12** was prepared from *R*-limonene in three steps,[7] viz. chemoselective ozonolysis of the ring olefin followed by intramolecular aldol condensation and regioselective reduction. The allyl alcohol **12** was then coupled with *p*-cresol under Mitsunobu conditions.[8] Thus, reaction of the allyl alcohol **12** with *p*-cresol in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) furnished the ether **10** in 85% yield. Thermal activation of the ether **10** in *N*,*N*-dimethylaniline in a sealed tube at 180 °C generated, instead of the phenol **11**, a ≈5:3 mixture of the cyclised products **13** and **14**, in 65% yield, which were separated by silica gel and

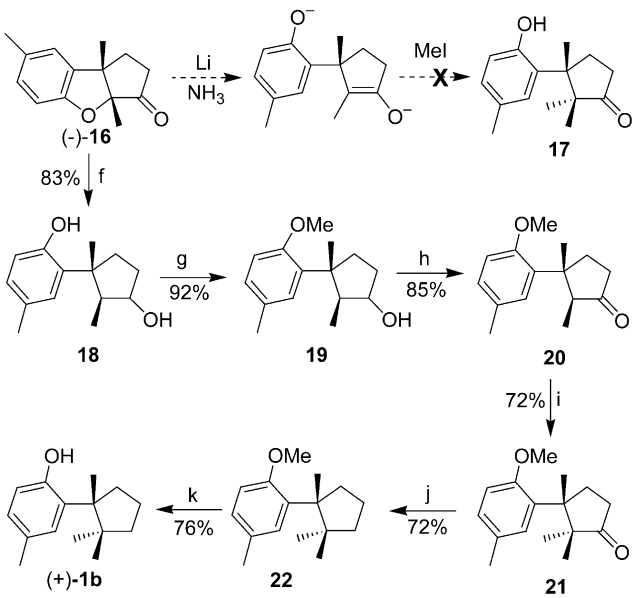


Scheme 1.



Scheme 2. Reagents, conditions and yields: (a) *p*-cresol, PPh_3, DIAD, THF, room temperature, 10 h, 85%; (b) $PhNMe_2$, sealed tube, 180 °C, 72 h, 65%; (c) O_3/O_2, CH_2Cl_2–MeOH (5:1), −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 75%; (d) K_2CO_3, MeOH, room temperature. 4 h, 83%; (e) PCC, NaOAc, CH_2Cl_2, room temperature, 2 h, 88%.

silver nitrate impregnated silica gel column chromatography (see Section 2). After creating the requisite new chiral quaternary carbon atom, the original chiral centre was disposed off via degradation of the isopropenyl group employing a Criegee rearrangement.[9] Thus, ozonolysis of the compound **13** in methylene chloride-methanol followed by treatment of the resulting methoxy-hydroperoxide with acetic anyhydride, triethylamine and 4-dimethylaminopyridine (DMAP) in refluxing benzene generated the acetate **15** in 75% yield. Hydrolysis of the acetate group followed by oxidation of the resultant alcohol with pyridinium



Scheme 3. Reagents, conditions and yields: (f) Li, liq. NH_3, THF, 0.5 h 83%; (g) K_2CO_3, MeI, $Me_2C{=}O$, room temperature, 4 h, 92%; (h) PCC, silica gel, CH_2Cl_2, 85%; (i) NaI, MeI, DME, room temperature, 12 h, 72%; (j) $NH_2NH_2.H_2O$, digol, 125 °C, 3 h; KOH, 190 °C, 12 h, 72%; (k) BBr_3, CH_2Cl_2, 0 °C–room temperature, 2 h, 76%.

chlorochromate (PCC) in the presence of sodium acetate transformed the acetate **15** into the ketone (−)-**16** $[\alpha]_D^{25}=-290$ (*c* 1.28, $CHCl_3$). Quite expectedly, the same sequence transformed the minor isomer **14** into the enantiomeric ketone (+)-**16**, $[\alpha]_D^{24}=+320$ (*c* 1.25, $CHCl_3$).

Next attention was turned to the conversion of the ketone (−)-**16** into α-herbertenol **1b**. It was contemplated that reductive methylation of the keto ether **16**, employing alkali metal in liquid ammonia and methyl iodide, followed by Wolff–Kishner reduction of the resulting phenolic ketone **17** would directly furnish **1b**. However, all our attempts (which include different experimental procedures of lithium or sodium in liquid ammonia with and without proton source; samarium iodide; zinc and acetic acid; etc.) to convert the tricyclic compound **16** directly into the ketone **17** were unsuccessful, and reductive cleavage of the central ring using lithium in liquid ammonia conditions furnished only the diol **18**, in 83% yield.[10] Treatment of the diol **18** with potassium carbonate and methyl iodide followed by oxidation of the resultant monomethyl ether **19** furnished the cyclopentanone **20**. The stereochemistry of the secondary methyl group in **20** was assigned as *trans* to aryl group on the basis of the chemical shift of the secondary methyl group (δ 1.02 ppm) in the ^{1}H NMR spectrum. Alkylation of the ketone **20** with sodium hydride and methyl iodide in dimethoxyethane (DME) generated the ketone **21**, which on Wolff–Kishner reduction furnished the methyl ether **22** of α-herbertenol. Finally, boron tribromide mediated cleavage of the methyl ether **22** furnished (+)-α-herbertenol **1b**, $[\alpha]_D^{26}=+52.9$ (*c* 0.7, $CHCl_3$) {lit.[1b] for (−)-**1b**, $[\alpha]_D=-55$}. The methyl ether **22** and α-herbertenol exhibited spectroscopic data (IR, ^{1}H and ^{13}C NMR) identical to those reported in the literature.

In conclusion, we have developed a convenient methodology for the stereoselective synthesis of α-herbertenol **1b** starting from the readily available monoterpene (*R*)-limonene. Since the natural α-herbertenol has already been transformed[5f] into natural herbertenediol **1d** and mastigophorenes **3a** and **3b**, the present sequence provides a convenient route for the synthesis of the optical antipodes of these natural products. Currently, we are investigating the extension of the methodology for the enantiospecific synthesis of other herbertane and cuparene sesquiterpenoids.

2. Experimental

2.1. Data for compounds

2.1.1. (+)-((5*S*)-5-Isopropenyl-2-methylcyclopent-1-enyl)methyl 4-methylphenyl ether (10). To a magnetically stirred solution of triphenylphosphine (4.12 g, 15.8 mmol) in dry THF (4 ml) was added DIAD (2.84 ml, 14.46 mmol) and stirred for 15 min at room temperature. A solution of the allyl alcohol[7] **12** (2.0 g, 13.15 mmol) and *p*-cresol (1.42 g, 13.15 mmol) in dry THF (2 ml) was added to the reaction mixture and stirred for 10 h at room temperature. It was then diluted with CH_2Cl_2 (15 ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the allyl aryl ether **10** (2.7 g, 85%) as colourless oil. $[\alpha]_D^{25}=100$ (*c* 1.03, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3070, 1644, 1510, 1235, 1009. ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 7.00 (2H, d, *J*=7.2 Hz), 6.76 (2H, d, *J*=7.2 Hz), 4.67 (2H, s), 4.48 and 4.23 (2H, 2×d, *J*=10.5 Hz), 3.51 (1H, m), 2.50–2.15 (2H, m), 2.26 (3H, s), 2.15–1.95 (1H, m), 1.78 (3H, s), 1.75–1.55 (1H, m), 1.62 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 157.2 (C), 147.5 (C), 139.9 (C), 132.5 (C), 129.7 (2 C, CH), 129.5 (C), 114.6 (2 C, CH), 110.9 (CH_2), 63.1 (CH_2), 54.8 (CH), 38.0 (CH_2), 28.0 (CH_2), 20.5 (CH_3), 19.3 (CH_3), 14.3 (CH_3). Mass: *m*/*z* 242 (M^+, 2%), 241 (3), 199 (10), 149 (11), 135 (15), 134 (15), 121 (26), 119 (23), 108 (100), 107 (47), 93 (35), 91 (41). HRMS: *m*/*z* Calcd for $C_{17}H_{23}O$ (M+1): 243.1749. Found: 243.1752.

2.1.2. (3*S*,3a*S*,8b*S*)-*cis*-3-Isopropenyl-3a,7,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta-(*b*)benzofuran (13). A solution of the allyl aryl ether **10** (2.2 g, 9.09 mmol) and *N*,*N*-dimethylaniline (1.2 ml) was placed in a sealed tube under N_2 atmosphere and heated to 180 °C for 3 days in an oil bath. The reaction mixture was then cooled and diluted with hexane. It was stirred with 6 N HCl for 1 h and then extracted with hexane (3×5 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using benzene–hexane (1:20) as eluent furnished a 5:3 mixture of cyclised products **13** and **14** (1.4 g, 65%) as oil. Further separation on a silver nitrate impregnated silica gel column furnished **13** (885 mg, 41%) as oil, and **14** (520 mg, 24%) as a colourless solid, which was recrystallised from hexanes.

Major isomer **13**: $[\alpha]_D^{26}=-83.9$ (*c* 1.18, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1644, 1609, 1245, 887, 808. ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.85 (2H, brs), 6.58 (1H, d, *J*=8.4 Hz), 4.88 (1H, s), 4.70 (1H, s), 2.64 (1H, dd, *J*=9.0 and 9.0 Hz), 2.28 (3H, s), 2.15–1.85 (2H, m), 1.86 (3H, s), 1.70–1.55 (2H, m), 1.21 (3H, s), 1.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 154.7 (C), 144.9 (C), 138.3 (C), 129.5 (C), 128.4 (CH), 123.8 (CH), 111.3 (CH_2), 109.6 (CH), 98.4 (C), 56.2 (CH), 53.7 (C), 39.1 (CH_2), 26.5 (CH_2), 24.6 (CH_3), 23.5 (CH_3), 21.0 (CH_3), 16.7 (CH_3). Mass: *m*/*z* 242 (M^+, 42%), 227 (19), 174 (15), 173 (10), 161 (39), 160 (100), 159 (65), 145 (23). HRMS: *m*/*z* Calcd for $C_{17}H_{22}ONa$ (M+Na): 265.1568. Found: 265.1577.

Minor isomer **14**: mp 122–123 °C (crystallised from hexane). $[\alpha]_D^{25}=116.4$ (*c* 1.40, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3071, 1640, 1611, 1262, 1137, 1062, 912, 889, 807. ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.81 (1H, d, *J*=7.5 Hz), 6.79 (1H, s), 6.51 (1H, d, *J*=7.5 Hz), 4.93 (1H, s), 4.80 (1H, s), 2.50–2.25 (2H, m), 2.26 (3H, s), 2.00–1.90 (1H, m), 1.81 (3H, s), 1.65–1.50 (2H, m), 1.33 (3H, s), 1.32 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 156.7 (C), 144.4 (C), 135.6 (C), 129.1 (C), 128.5 (CH), 123.4 (CH), 113.7 (CH_2), 108.3 (CH), 98.9 (C), 58.7 (CH), 54.3 (C), 42.4 (CH_2), 27.7 (CH_2), 23.7 (CH_3), 22.1 (CH_3), 21.0 (CH_3), 20.6 (CH_3). Mass: *m*/*z* 242 (M^+, 37%), 227 (18), 174 (18), 161 (47), 160 (100), 159 (72), 145 (25), 135 (16). HRMS: *m*/*z* Calcd for $C_{17}H_{23}O$ (M+1): 243.1749. Found: 243.1758.

2.1.3. (−)-(3*R*,3a*R*,8b*S*)-*cis*-3a,7,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta(*b*)benzofuran-3-yl acetate (15). Pre-cooled dry ozone in oxygen gas was passed through a cold (−70 °C) suspension of the ether **13** (400 mg, 1.65 mmol) and $NaHCO_3$ (5 mg) in 4:1 CH_2Cl_2–MeOH (5 ml) until reaction mixture turns blue and then the excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo and the residue was taken in dry benzene (3 ml). Acetic anhydride (2.33 ml, 24.75 mmol), triethylamine (2.3 ml, 16.5 mmol) and a catalytic amount of DMAP (5 mg) were added to the reaction mixture and refluxed for 4 h. It was then cooled, diluted with water and extracted with ether (3×4 ml). The ether extract was washed with 3 N aqueous HCl and brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the acetate **15** (320 mg, 75%) as oil. $[\alpha]_D^{23}=-58.6$ (*c* 2.54, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1742, 1610, 1237, 1072, 810. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.83 (1H, d, *J*=7.8 Hz), 6.80 (1H, s), 6.53 (1H, d, *J*=8.1 Hz), 5.26–5.18 (1H, m), 2.26 (3H, s), 2.07 (3H, s), 2.00–1.55 (4H, m), 1.36 (3H, s), 1.30 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 169.3 (C), 155.5 (C), 135.4 (C), 129.7 (C), 128.8 (CH), 123.5 (CH), 109.0 (CH), 98.7 (C), 81.8 (CH), 53.5 (C), 41.3 (CH_2), 29.0 (CH_2), 22.9 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 17.0 (CH_3). Mass: *m*/*z* 260 (M^+, 30%), 218 (25), 203 (100), 173 (14), 161 (18), 160 (29), 159 (48), 145 (29). HRMS: *m*/*z* Calcd for $C_{16}H_{20}O_3Na$ (M+Na): 283.1310. Found: 283.1314.

2.1.4. (−)-(3*R*,8b*S*)-*cis*-3a,7,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-3-one (16). To a magnetically stirred solution of the acetate **15** (300 mg, 1.15 mmol) in methanol (4 ml) was added K_2CO_3 (317 mg, 2.30 mmol) and stirred at room temperature for 2 h. Water (10 ml) was then added to the reaction mixture and extracted with CH_2Cl_2 (3×4 ml). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the alcohol (208 mg, 83%) as oil, {$[\alpha]_D^{25}=-34.3$ (*c* 4.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3351, 1607, 1264, 1241, 1024, 809. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.82 (1H, d, *J*=7.5 Hz), 6.81 (1H, s), 6.51 (1H, d, *J*=7.5 Hz), 4.16 (1H, brs), 2.26 (3H, s), 2.06 (1H, ddd, *J*=12.0, 12.0, 6.9 Hz), 1.86 (1H, ddd, *J*=12.0, 6.9, 2.3 Hz), 1.80–1.50 (3H, m), 1.37 (3H, s), 1.35 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 155.5 (C), 136.1 (C), 129.6 (C), 128.5 (CH), 123.6 (CH), 108.7 (CH), 99.6 (C), 80.2 (CH), 53.0 (C), 41.0 (CH_2), 31.1 (CH_2), 23.3 (CH_3), 21.0 (CH_3), 16.8 (CH_3)}, which was taken in 2 ml of CH_2Cl_2 and added to a magnetically stirred suspension of PCC (490 mg, 2.30 mmol) and sodium acetate (490 mg) in CH_2Cl_2 (2 ml). The reaction mixture was stirred at room temperature for 2 h, filtered through a silica gel column, and the column was eluted with more CH_2Cl_2. The solvent was evaporated to furnish the ketone **16** (217 mg, 88%) which was recrystallised from ether. Mp 96–98 °C. $[\alpha]_D^{25}=290.6$ (*c* 1.28, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1744, 1608, 1233, 1056, 819. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.90 (2H, brs), 6.23 (1H, d, *J*=8.4 Hz), 2.40–2.20 (2H, m), 2.28 (3H, s), 2.03 (1H, ddd, *J*=18.0, 12.3, 9.0 Hz), 1.85 (1H, ddd, *J*=12.3, 12.3, 7.2 Hz), 1.35 (3H, s), 1.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 215.6 (C), 155.9 (C), 133.2 (C), 130.8 (C), 129.4 (CH), 123.3 (CH), 109.6 (CH), 91.4 (C), 51.3 (C), 35.6 (CH_2), 32.4 (CH_2), 23.5 (CH_3), 21.0 (CH_3), 14.6 (CH_3). Mass: *m*/*z* 216 (M^+, 20%), 202 (13), 187 (19), 173 (17), 160 (100), 159 (59), 145 (34), 115 (13). HRMS: *m*/*z* Calcd for $C_{14}H_{16}O_2Na$ (M+Na): 239.1048. Found: 239.1045.

2.1.5. (−)-2-[(1*R*,2*S*,3*R*)-3-Hydroxy-1,2-dimethylcyclopentyl]-4-methylphenol (18). To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (100 ml) in a two necked flask, equipped with Dewar condenser, was added freshly cut lithium (25 mg, 3.68 mmol) followed by a solution of the ketone **16** (200 mg, 0.92 mmol) in anhydrous THF (3 ml). The resulting blue coloured solution was stirred for 15 min. at −33 °C and then the reaction was quenched with solid NH_4Cl. After evaporation of ammonia, the residue was taken in water (5 ml) and extracted with ether (3×5 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:5) as eluent, furnished the diol **18** (168 mg, 83%) which was recrystallised from ether. Mp 72–74 °C. $[\alpha]_D^{25}=-23.6$ (*c* 0.93, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3349, 1608, 1251, 1213, 1124, 1047, 1000, 813. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.95 (1H, s), 6.83 (1H, d, *J*=8.1 Hz), 6.58 (1H, d, *J*=8.1 Hz), 3.97 (1H, q, *J*=6.5 Hz), 2.55–2.40 (2H, m), 2.26 (3H, s), 2.15–1.90 (1H, m), 1.80–1.55 (3H, m), 1.23 (3H, s), 0.99 (3H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.0 (C), 134.8 (C), 128.9 (C), 127.8 (CH), 127.5 (CH), 117.0 (CH), 81.0 (CH), 49.2 (CH), 45.5 (C), 36.9 (CH_2), 33.1 (CH_2), 22.5 (CH_3), 21.0 (CH_3), 13.5 (CH_3). Mass: *m*/*z* 220 (M^+, 20%), 202 (60), 187 (100), 173 (40), 159 (80), 147 (40), 133 (20), 118 (40), 105 (20). HRMS: *m*/*z* Calcd for (M-OH) $C_{14}H_{19}O$: 203.1436. Found: 203.1436.

2.1.6. (−)-(1*R*,2*S*,3*R*)-2,3-Dimethyl-3-(2-methoxy-5-methylphenyl)cyclopentanol (19). To a magnetically stirred solution of the diol **18** (150 mg, 0.68 mmol) in acetone (4 ml) was added K_2CO_3 (188 mg, 1.36 mmol) and MeI (0.43 ml, 1.36 mmol) and stirred at room temperature for 4 h. Water (5 ml) was then added to the reaction mixture and extracted with CH_2Cl_2 (3×4 ml). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the methyl ether **19** (145 mg, 92%) as oil. $[\alpha]_D^{24}=-36.1$ (*c* 0.36, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3368, 1288, 1239, 1052, 1032, 807. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.95 (1H, s), 6.92 (1H, d, *J*=8.1 Hz), 6.72 (1H, d, *J*=8.1 Hz), 3.88 (1H, q, *J*=7.2 Hz), 3.80 (3H, s), 2.40–2.00 (3H, m), 2.28 (3H, s), 1.82 (1H, ddd, *J*=12.5, 8.0, 8.0 Hz), 1.75–1.50 (2H, m), 1.18 (3H, s), 1.03 (3H, d, *J*=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 156.0 (C), 137.5 (C), 129.1 (C), 127.5 (CH), 127.2 (CH), 111.6 (CH), 80.0 (CH), 55.1 (CH_3), 49.2 (CH), 45.7 (C), 37.0 (CH_2), 33.0 (CH_2), 22.7 (CH_3), 21.0 (CH_3), 13.2 (CH_3). Mass: *m*/*z* 234 (M^+, 17%), 165 (100), 149 (15), 147 (23), 145 (15), 135 (15), 119 (18), 105 (11). HRMS: *m*/*z* Calcd for $C_{15}H_{22}O_2Na$ (M+Na): 257.1517. Found: 257.1512.

2.1.7. (+)-(2*S*,3*R*)-2,3-Dimethyl-3-(2-methoxy-5-methylphenyl)cyclopentanone (20). To a magnetically stirred suspension of PCC (258 mg, 1.20 mmol) and silica gel (258 mg) in 2 ml dry CH_2Cl_2 was added a solution of the alcohol **19** (140 mg, 0.60 mmol) in 2 ml dry CH_2Cl_2 and stirred vigorously for 2 h at room temperature. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent furnished the ketone **20** (118 mg, 85%) as oil. $[\alpha]_D^{22}$=31.2 (*c* 1.25, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3030, 1738, 1610, 1234, 1071, 808. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.98 (1H, d, *J*=8.1 Hz), 6.96 (1H, s), 6.77 (1H, d, *J*=8.1 Hz), 3.82 (3H, s), 3.02 (1H, q, *J*=6.9 Hz), 2.50–2.10 (4H, m), 2.30 (3H, s), 1.22 (3H, s), 1.02 (3H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 219.9 (C), 156.2 (C), 134.6 (C), 129.4 (C), 127.9 (2 C, CH), 111.7 (CH), 55.1 (CH_3), 51.8 (CH), 45.9 (C), 35.0 (CH_2), 32.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 9.5 (CH_3). Mass: *m*/*z* 232 (M^+, 79%), 217 (51), 199 (22), 175 (100), 161 (40), 149 (43), 147 (50), 145 (35), 115 (31), 105 (39), 91 (40). HRMS: *m*/*z* Calcd for $C_{15}H_{21}O_2$ (M+1): 233.1541. Found: 233.1547.

2.1.8. (+)-(3*S*)-2,2,3-Trimethyl-3-(2-methoxy-5-methylphenyl)cyclopentanone (21). To a magnetically stirred suspension of NaH (2.8 mg, 60% dispersion in oil, 0.07 mmol, washed with dry hexane) in DME (1 ml) was added a solution of the ketone **20** (20 mg, 0.086 mmol) in DME (1 ml), and stirred for 0.5 h at room temperature. Methyl iodide (0.05 ml) was then added to the reaction mixture and stirred for 12 h. It was then quenched with water (2 ml) and extracted with ether (3×3 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the ketone **21** (10 mg, 72%, based on the starting material consumed) as oil.[5i] $[\alpha]_D^{26}$=58.9 (*c* 0.9, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1738, 1501, 1244, 1029, 807. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.08 (1H, d, *J*=1.8 Hz), 6.98 (1H, d, *J*=8.1 Hz), 6.72 (1H, d, *J*=8.1 Hz), 3.73 (3H, s), 2.60–2.35 (3H, m), 2.30 (3H, s), 2.15–1.85 (1H, m), 1.38 (3H, s), 1.21 (3H, s), 0.64 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 222.1 (C), 156.0 (C), 134.5 (C), 129.1 (C), 128.6 (CH), 127.7 (CH), 111.0 (CH), 54.2 (CH_3), 52.3 (C), 48.7 (C), 34.5 (CH_2), 32.8 (CH_2), 23.5 (CH_3), 22.0 (CH_3), 21.9 (CH_3), 21.0 (CH_3). Mass: *m*/*z* 246 (M^+, 74%), 231 (16), 213 (14), 197 (14), 175 (100), 161 (32), 147 (45), 115 (33), 105 (36), 91 (46). HRMS: *m*/*z* Calcd for $C_{16}H_{22}O_2Na$ (M+Na): 269.1517; Found: 269.1536.

2.1.9. (+)-(*R*)-1-(2-Methoxy-5-methylphenyl)-1,2,2-trimethylcyclopentane (22). A solution of the ketone **21** (5 mg, 0.02 mmol), potassium hydroxide (11 mg, 0.2 mmol) and hydrazine hydrate (0.2 ml, 0.4 mmol) in diethylene glycol (2 ml) was taken in a sealed tube and heated to 125 °C for 3 h and then to 190 °C for 12 h. The reaction mixture was then cooled, acidified with 3 N aqueous HCl (5 ml) and extracted with CH_2Cl_2 (3×3 ml). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the deoxygenated product **22** (3.5 mg, 72%) as oil.[6b] $[\alpha]_D^{26}$=41.0 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1607, 1241, 1179, 1034, 806. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.04 (1H, s), 6.88 (1H, dd, *J*=8.1, 1.8 Hz), 6.68 (1H, d, *J*=7.8 Hz), 3.74 (3H, s), 2.60–2.45 (1H, m), 2.26 (3H, s), 1.80–1.40 (5H, m), 1.33 (3H, s), 1.13 (3H, s), 0.66 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.7 (C), 135.8 (C), 129.6 (CH), 128.7 (C), 127.1 (CH), 111.5 (CH), 54.8 (CH_3), 51.3 (C), 44.3 (C), 42.3 (CH_2), 40.0 (CH_2), 27.9 (CH_3), 26.2 (CH_3), 23.2 (CH_3), 21.1 (CH_3), 20.7 (CH_2). Mass: *m*/*z* 233 (M+1, 12%), 232 (74), 175 (30), 162 (63), 161 (29), 150 (30), 149 (100), 147 (70), 145 (31), 135 (34), 119 (29), 105 (22), 91 (28).

2.1.10. (+)-4-Methyl-2-(*R*-1,2,2-trimethylcyclopentyl)-phenol (α-herbertenol 1b). A solution of BBr_3 (1 M in CH_2Cl_2, 0.04 ml, 0.04 mmol) was added drop wise to a solution of the ether **22** (5 mg, 0.02 mmol) in CH_2Cl_2 (1.5 ml) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×3 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished *ent*-α-herbertenol **1b** (3.5 mg, 76%) as oil. $[\alpha]_D^{26}$=52.8 (*c* 0.7, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3531, 1506, 1251, 1165, 808. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.03 (1H, s), 6.80 (1H, d, *J*=8.1 Hz), 6.50 (1H, d, *J*=8.1 Hz), 4.51 (1H, s), 2.65–2.45 (1H, m), 2.25 (3H, s), 1.90–1.30 (5H, m), 1.40 (3H, s), 1.17 (3H, s), 0.75 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.3 (C), 132.9 (C), 130.1 (CH), 128.8 (C), 127.3 (CH), 116.7 (CH), 51.1 (C), 44.8 (C), 41.5 (CH_2), 39.6 (CH_2), 27.3 (CH_3), 25.8 (CH_3), 23.1 (CH_3), 21.1 (CH_3), 20.5 (CH_2). Mass: *m*/*z* 218 (M^+, 32%), 161 (23), 148 (81), 147 (38), 135 (83), 121 (36), 105 (22).

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Recyclable 2nd generation ionic liquids as green solvents for the oxidation of alcohols with hypervalent iodine reagents

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Abstract—Alcohols undergo smooth oxidation with iodoxybenzoic acid (IBX) or with Dess–Martin-Periodinane (DMP) in hydrophilic [bmim]BF_4 and hydrophobic [bmim]PF_6 ionic liquids at room temperature under mild conditions to afford the corresponding carbonyl compounds in excellent yields with high selectivity. IBX and DMP promoted oxidations are faster in ionic liquids when compared to conventional solvents such as DMSO, DMF, EtOAc and H_2O. The recovery of the byproduct iodosobenzoic acid (IBA) is especially simple in ionic liquids. The recovered ionic liquids can be recycled in subsequent reactions with consistent activity.

1. Introduction

Hypervalent iodine reagents have attracted increasing interest as oxidants in organic synthesis due to their mild, selective and environmentally benign oxidizing properties.[1] Among various hypervalent iodine reagents, IBX is a versatile oxidizing agent because of its high efficiency, easy availability, mild reaction conditions, and its stability against moisture and air.[2] The wide functional group tolerance and high-yielding reactions without over oxidation have made IBX very familiar for the oxidation of primary alcohols.[3] IBX also oxidizes *vic*-diols to α-diketones without cleaving the glycol C–C bond[4] and allows the selective oxidation of 1,4-diols to γ-lactols.[5] Recently, IBX has been employed as an efficient oxidizing agent in DMSO for the clean oxidation of alcohols to carbonyl compounds even in the presence of thioethers and amino compounds.[6] Subsequently, polymer-supported IBX reagents have also been developed to promote oxidation reactions.[7] In recent reports, the use of IBX as a mild oxidant has been extended to many other elegant oxidative transformations.[8] More recently, practical IBX oxidations have been reported in organic solvents such as acetone, ethyl acetate, chloroform, benzene and acetonitrile.[9] However, IBX oxidations in organic solvents typically require longer reaction times at high temperature to accomplish the reaction. The high temperature reaction conditions are not only detrimental to certain functional groups, but also to the control of chemoselectivity. Owing to the volatile nature of organic solvents, no attempt has been made to recycle them, thereby making the process more convenient, economic and eco-friendly. Recent demand for eco-friendly chemical processes has led to the development of several clean and practical oxidations and still awaits further improvements towards high-yielding, clean, safe and efficient methods for the oxidation of alcohols.

In recent times, ionic liquids have gained recognition as possible environmentally benign alternatives to the more volatile organic solvents.[10] Ionic liquids possess many attractive properties, such as wide liquid range, negligible vapor pressure, high thermal stability and good solvating ability for a wide range of substrates and catalysts, which alleviate some of the environmental issues. Their non-volatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction solvents. Furthermore, ionic liquids are found to be an efficient reaction media for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[11] The hallmark of such ionic liquids is the ability to alter their properties as desired by manipulating their structure with respect to the choice of organic cation or anion and side chain attached to the organic cation (Fig. 1).

These structural variations offer flexibility to the chemist to

n = 1 = [bmim]PF_6 n = 5 = [octmim]PF_6

n = 3 = [hmim]PF_6

Figure 1.

Keywords: Dess–Martin-Periodinane; Iodoxybenzoic acid; Iodosobenzoic acid.

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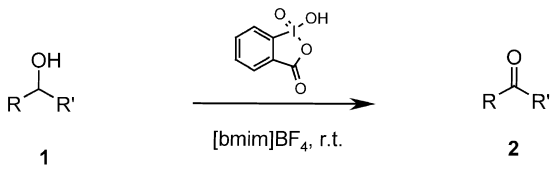
devise the most idealized solvent, catering for the needs of any particular process. Their unprecedented ability to solvate a broad spectrum of substrates of organic and inorganic nature has widened the horizon of their applicability.[12]

2. Results and discussions

With an ever increasing quest for the exploration of newer reactions in ionic liquids, herein we wish to report, for the first time, the use of ionic liquids as novel and recyclable polar reaction media for hypervalent iodine reagent promoted oxidation reactions of alcohols (Scheme 1).

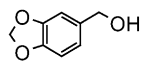
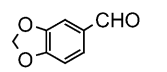
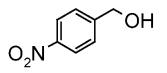
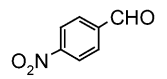
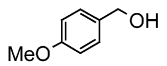
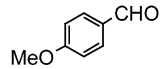
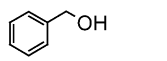
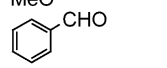
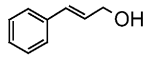
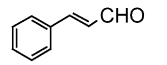
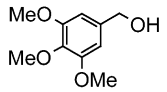
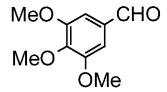
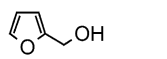
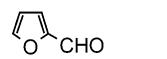
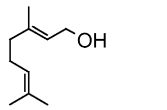
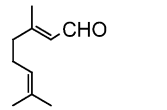
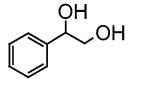
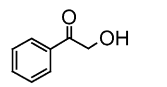
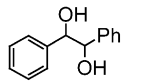
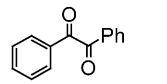
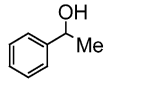
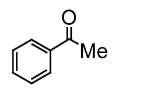
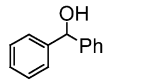
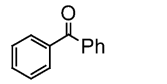
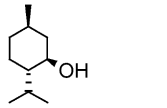
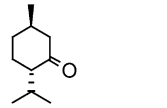
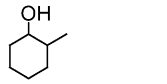
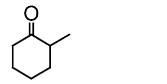
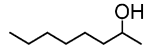
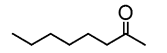
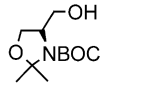
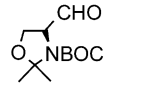


Scheme 1.

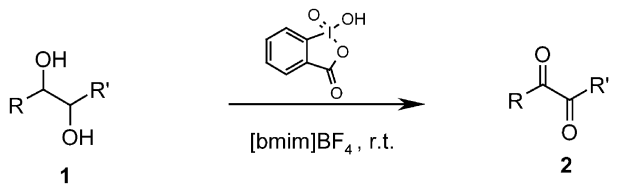
For instance treatment of benzyl alcohol with IBX in hydrophilic [bmim]BF_4 ionic liquid afforded benzaldehyde in 91% yield. The oxidation is very clean and complete within 4.0 h at room temperature. In a similar manner, various primary and secondary alcohols underwent smooth oxidation with IBX to give the corresponding aldehydes and ketones in high yields. In all cases, the reactions proceeded readily at room temperature with high efficiency. The oxidation of chiral primary alcohols proceeds without epimerization (entry p Table 1). α,β-Unsaturated alcohols also oxidized to the corresponding carbonyls in high yields (entries e, h, Table 1). Tertiary alcohols did not undergo oxidation under these conditions. No over oxidation of aldehydes to acids was observed in the case of the oxidation of primary alcohols. The results obtained with alcohols prompted us to extend this process to the oxidation of *vic*-diols. 1,2-Diols such as styrene diol and 1,2-diphenyl ethane-1,2-diol (pinacol) underwent smooth oxidation with IBX to the corresponding 1,2-diketones without the cleavage of the glycol C–C bond (Scheme 2).

Arylcarbinols gave comparatively better yields than aliphatic alcohols. This method is highly selective to oxidize secondary alcohols in the presence of primary alcohols especially in case of styrene diol (entry i, Table 1). The method is very mild and compatible with a wide range of functional groups such as methoxy, methylenedioxy, phenoxy ethers, carbamates and acetonides present in the substrate. IBX shows enhanced reactivity and selectivity in ionic liquids compared to organic solvents. For instance, treatment of 1-phenyl ethanol with IBX in [bmim]BF_4 at room temperature for 4.5 h afforded acetophenone in 93% yield whereas the same reaction in refluxing chloroform or in refluxing ethyl acetate after 8.0 h gave the desired ketone in 75 and 79% yields, respectively. In these organic solvents, high temperature reaction conditions and longer reaction times are typical to achieve comparable yields to those obtained in ionic liquids at room temperature. Lowering the reaction temperature was detrimental to the efficiency of this procedure. Although, IBX promoted oxidations proceed smoothly at room temperature in DMSO, the reactions typically require long reaction times (12–15 h) to obtain the products in good yields. Since the products are fairly soluble in hydrophilic [bmim]BF_4 ionic liquid, they can be easily separated by simple extraction

Table 1. IBX- and DMP-promoted oxidation of alcohols in ionic liquids

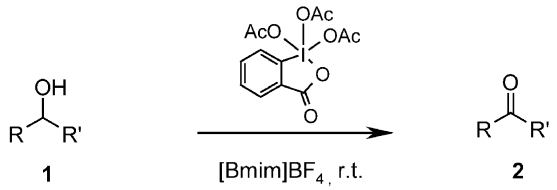
Entry	Alcohol	Aldehyde[a]	IBX		DMP	
	1	**2**	Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
a			3.5	97	2.5	95
b			6.5	90	4.0	93
c			3.0	95	2.0	97
d			4.0	91	3.0	82[c]
e			3.5	93	2.5	91
f			5.0	92	3.0	96
g			3.5	95	2.5	89
h			4.5	94	3.0	90
i			5.5	92	3.5	87
j			6.0	95	4.0	85
k			4.5	93	3.5	96
l			4.0	91	3.5	95
m			6.0	86	4.5	89
n			6.5	87	5.0	91
o			7.5	89	5.0	93
p			5.5	87	4.0	90

[a] All products were charaterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] Fifteen percent of benzoic acid was isolated.



Scheme 2.

with diethyl ether. Then the rest of the ionic liquid was diluted with water and filtered to recover the byproduct iodosobenzoic acid (IBA). The recovered IBA was reoxidized to IBX and could be reused in subsequent reactions. The regenerated IBX is indistinguishable from the freshly prepared one from *o*-iodobenzoic acid. The aqueous phase was lyophilized to recover the ionic liquid. The recovered ionic liquid was recycled in subsequent reactions with consistent activity. The products were obtained of the same purity as in the first run, and no decrease in yield was obtained in runs carried out using recycled ionic liquid. For instance, treatment of cinnamyl alcohol with IBX in hydrophilic [bmim]BF_4 ionic liquid gave 93, 92 and 93% yields over three cycles. Although, similar results were also obtained in hydrophobic [bmim]PF_6, the recovery of IBA is especially simple in [bmim]BF_4 due to its hydrophilic nature. The scope and generality of this process is illustrated with respect to various alcohols and IBX and the results are presented in the Table 1. Furthermore, Dess–Martin-Periodinane (DMP) was also immobilized in ionic liquids to perform oxidation reactions under mild conditions (Scheme 3).



Scheme 3.

In contrast to IBX, the oxidation reactions are faster with DMP in ionic liquids and results are summarized in Table 1. Ionic liquids used in this study were obtained from Fluka. The purity of [bmim]PF_6 is ≥97.0 (NMR).

3. Conclusion

In this paper, we have demonstrated that hydrophilic [bmim]BF_4 ionic liquid is an efficient and polar alternative to conventional solvents for the IBX and DMP promoted oxidations. This method avoids the use of polar organic solvents such as DMSO or DMF and high temperature reaction conditions for IBX oxidations. Enhanced reaction rates, high conversions and greater selectivities are the notable features observed in ionic liquids. The use of an easily accessible and recyclable ionic liquid makes this procedure quite simple, more convenient and environmentally benign.

4. Experimental

4.1. General methods

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H and ^{13}C NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. IBX and DMP were prepared according to the reported procedure in the literature.[13]

4.2. General procedure for the oxidation of alcohols

To a stirred solution of alcohol (1 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4, Fluka, 2 mL) ionic liquid was added IBX (1.2 mmol) or DMP (1.0 mmol) at room temperature and stirring was continued for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the product was extracted with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate–*n*-hexane (2:8) to afford the pure carbonyl compound. The rest of the ionic liquid was diluted with water and filtered to remove the IBA. The aqueous phase was lyophilized to recover the ionic liquid. The products were characterized by comparison of their NMR, IR, Mass, TLC, mixed TLC analysis and physical data with authentic samples. The spectral data of all the products were identical with those of authentic samples.[14] Spectroscopic data for selected products is as follows.

4.2.1. 2a: 3,4-(Methylenedioxy)-benzaldehyde. Low melting solid, mp 35–37 °C, (lit.[14e] 36–37 °C), IR (KBr): ν 3074, 2849, 1704, 1600, 1548, 1436, 1229, 1116, 1083, 912, 860, 781 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.01 (s, 2H), 6.82–7.50 (m, 3H), 9.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, proton decoupled): δ 102.3, 105.2, 108.0, 128.2, 131.7, 148.5, 153.6, 190.2. EIMS: *m*/*z* (%): 150 (M^+, 11), 136 (32), 107 (100), 79 (43), 51 (61).

4.2.2. 2b: 4-Nitro-benzaldehyde. Light yellow solid, mp 104–105 °C (lit.[15a] 106–107 °C), IR (KBr): ν 3093, 2978, 2864, 1713, 1605, 1540, 1343, 1294, 1197, 853, 820, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, J=8.5 Hz, 2H), 8.36 (d, J=8.5 Hz, 2H), 10.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 123.6, 129.9, 139.4, 150.4, 189.8. EIMS: *m*/*z* (%): 151 (M^+, 45), 150 (100), 77 (16), 51 (24).

4.2.3. 2c: 4-Methoxy-benzaldehyde. Colourless liquid (lit.[15a]), IR (neat): ν 1701, 1607, 1386, 1308, 1207, 1169, 847, 808 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.95 (s, 3H), 7.33 (d, J=7.9 Hz, 2H), 7.78 (d, J=7.9 Hz, 2H), 9.97 (s, 1H). EIMS: *m*/*z* (%): 136 (M^+, 60), 135 (100), 107 (26), 92 (18), 77 (45), 63 (21).

4.2.4. 2d: Benzaldehyde. Colourless liquid (lit.[15d]), IR (neat): ν 3064, 3031, 2852, 2820, 2732, 1702, 1654, 1597, 1584, 1455, 1391, 1311, 1204, 1167, 1023, 828, 746, 688,

650 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.67 (m, 3H), 7.87–7.90 (m, 2H), 9.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 129.0, 129.6, 134.4, 136.4, 192.3. EIMS: *m/z* (%): 106 (M^+, 34), 105 (74), 77 (100), 51 (22).

4.2.5. 2e: *trans*-Cinnamaldehyde. Pale yellow liquid (lit.[15a]), IR (neat): ν 3078, 2986, 2834, 1706, 1605, 1534, 1455, 1263, 1075, 876, 687 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.65 (d, J=16.7 Hz, 1H), 6.69 (dd, J=6.5, 16.7 Hz, 1H), 7.43–7.37 (m, 3H), 7.54–7.50 (m, 2H), 9.65 (d, J=6.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.5, 128.6, 129.2, 131.4, 134.1, 152.8, 193.7. EIMS: *m/z* (%): 132 (M^+, 31), 90 (59), 77 (100), 51 (39).

4.2.6. 2f: 3,4,5-Trimethoxy benzaldehyde. Light yellow solid, mp 73–74 °C (lit.[15b] 73–75 °C), IR (KBr): ν 3069, 2987, 2842, 1705, 1600, 1567, 1459, 1384, 1226, 892, 764 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.80 (s, 3H), 3.90 (s, 6H), 7.10 (s, 2H), 9.86 (s, 1H). EIMS: *m/z* (%): 196 (M^+, 40), 165 (68), 103 (100), 74 (27), 49 (32).

4.2.7. 2g: 2-Furfuraldehyde. Pale yellow liquid (lit.[14c]), IR (neat): ν 2985, 1698, 1605, 1519, 1168, 1032, 826, 785 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.60 (d, J=5.0 Hz, 1H), 7.25 (d, J=5.0 Hz, 1H), 7.70 (s, 1H), 9.70 (s, 1H). EIMS: *m/z* (%): 96 (M^+, 17), 67 (11), 84 (38), 43 (30), 41 (100), 26 (26).

4.2.8. 2h: 3,7-Dimethyl-2,6-octadienal (citral). Colorless liquid (lit.[15e]), IR (neat): ν 2850, 1720, 1609, 1533, 1470, 1414, 1370, 1060, 895, 723 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60 (s, 3H), 1.90 (s, 3H), 2.20 (s, 3H), 2.60 (m, 4H), 5.10 (s, 1H), 5.85 (d, 1H, J=7.0 Hz), 9.80 (d, 1H, J=7.0 Hz). EIMS: *m/z* (%): 152 (M^+, 21), 123 (9), 110 (72), 68 (100), 41 (38).

4.2.9. 2i: α-Hydroxy-acetophenone. Pale yellow solid, mp 85–87 °C (lit.[15c] 89–90 °C), IR (KBr): ν 3421, 1689, 1600, 1456, 1409, 1301, 1231, 1106, 970, 761, 683 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.50 (brs, 1H, OH), 4.89 (s, 2H), 7.49–7.67 (m, 3H), 7.92–7.95 (m, 2H). EIMS: *m/z*(%): 136 (M+1), 105 (77), 77 (100), 51 (17).

4.2.10. 2j: Benzil. Yellowish solid, mp. 94–95 °C (lit.[15a] 93–95 °C), IR (neat): ν 2930, 2863, 1721, 1695, 1450, 1428, 1375, 1314, 1156, 1053, 995, 866, 734, 650 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53 (t, 4H, J=8.2 Hz), 7.62 (t, 2H, J=8.2 Hz), 8.0 (d, 4H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.8, 130.2, 132.8, 134.9, 194.5. EIMS: *m/z* (%): 210 (M^+, 11), 133 (27), 105 (100), 77 (60), 51 (40).

4.2.11. 2k: Acetophenone. Colourless liquid (lit.[15c]), IR (neat): ν 3060, 3005, 2924, 1686, 1599, 1582 1359, 1266, 1182, 1078, 1024, 955, 760, 690 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.55 (s, 3H), 7.38–7.46 (m, 2H), 7.48–7.55 (m, 1H), 7.90–7.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 28.2, 128.0, 128.7, 133.0, 137.0, 198.0. EIMS: *m/z* (%): 120 (M^+, 16), 105 (100), 77 (24), 51 (18).

4.2.12. 2l: Benzophenone. White solid, mp. 49–50 °C (lit.[15a] 49–51 °C), IR (neat): ν 3060, 1658, 1598, 1577, 1447, 1317, 1276, 1176, 1150, 1074, 1028, 999, 941. 919, 810, 763, 697, 638 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44 (m, 4H), 7.51–7.57 (m, 2H), 7.87 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 127.7, 129.9, 132.8, 136.5, 196.5. EIMS: *m/z* (%): 182 (M^+, 19), 105 (68), 77 (100), 51 (27).

4.2.13. 2m: Menthone. Colorless liquid (lit.[15e]), IR (neat): ν 2956, 2928, 2871, 1711, 1457, 1711, 1367, 1286, 1246, 1155, 1117, 1093, 1044, 994, 866, 747, 608 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.86 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.2 Hz, 3H), 1.34–1.40 (m, 2H), 1.80–2.20 (m, 6H), 2.18–2.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.7, 21.2, 22.3, 25.9, 27.9, 33.9, 35.5, 50.8, 55.8, 212.0. EIMS: *m/z* (%): 154 (M^+, 18), 111 (35), 83 (100), 55 (43).

4.2.14. 2n: 2-Methyl cyclohexanone. Colourless liquid (lit.[7a]), IR (neat): ν 2930, 2863, 1721, 1450, 1428, 1375, 1314, 1156, 1053, 995, 866, 734, 650 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (d, 3H, J=6.5 Hz), 1.34–1.37 (m, 1H), 1.64–1.82 (m, 3H), 2.10–2.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 25.3, 28.1, 36.1, 41.7, 45.4, 213.7. EIMS: *m/z* (%): 112 (M^+, 11), 97 (21), 84 (38), 69 (43) 56 (100).

4.2.15. 2o: 2-Octanone. Colourless liquid (lit.[15d]), IR (neat): ν 2959, 2932, 2856, 1716, 1593, 1467, 1413, 1363, 1278, 1227., 1167, 1115, 1034, 945, 720 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 0.90 (t, 3H, J=7.0 Hz), 1.30 (m, 6H), 1.56 (m, 2H), 2.16 (s, 3H), 2.44 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.3, 22.5, 24.0, 29.1, 29.9, 31.8, 43.8, 209.2. EIMS: *m/z* (%): 128 (M^+, 39), 85 (100), 57 (72), 29 (21).

4.2.16. 2p: *N*-Boc-D-serinal acetonide (Garner aldehyde). Colourless oil (lit.[14d]), IR (neat): ν 2948, 2835, 1712, 1604, 1546, 1438, 1222, 1064, 932, 878, 764 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.37 (s, 3H), 1.41 (s, 3H), 1.43 (s, 9H), 3.52 (dd, J=8.3, 8.7 Hz, 1H), 3.73 (dd, J=2.9, 8.7 Hz, 1H), 3.90 (m, 1H), 9.34 (brs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.8, 24.7, 25.8, 26.7, 28.3, 63.5, 64.7, 81.1, 81.4, 94.4, 95.1, 151.3, 152.6, 199.5. EIMS: *m/z* (%): 229 (M^+, 16), 156 (21), 128 (47), 86 (100), 72 (41), 54 (29).

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Mechanism of the heterocyclization of *vic*-alkynylanthra- and *vic*-alkynylnaphthoquinone diazonium salts

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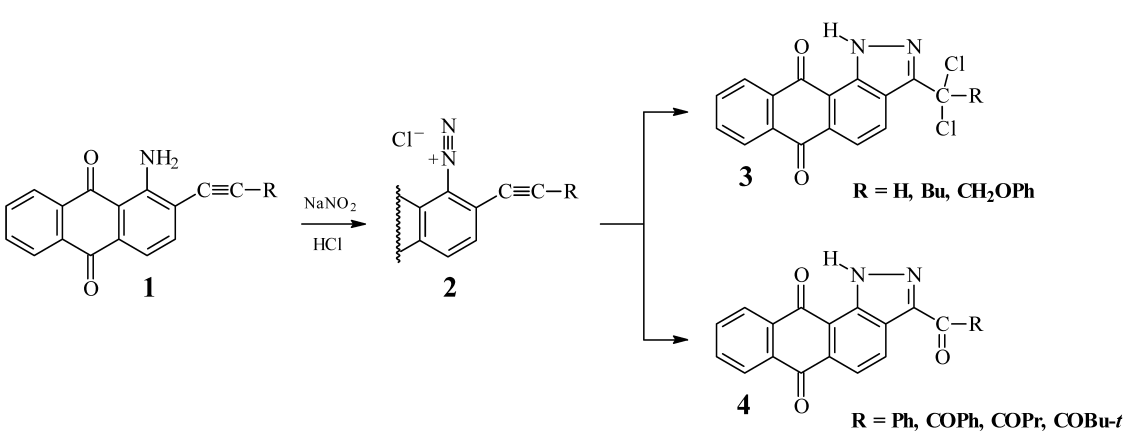
Abstract—On the basis of experimental data and of quantum-chemical calculations, a principal scheme for the mechanism of cyclization of *vic*-alkynylanthra- and *vic*-alkynylnaphthoquinone diazonium salts resulting in the formation of 5- and 6-membered heterocycles is proposed. Within the framework of the new notions of the reaction mechanism, a possibility of controlling the formation of condensed pyrazole or pyridazine rings is demonstrated.

1. Introduction

Cyclization of *ortho*-alkynylbenzene diazonium salts, discovered by Richter more than a century ago,[1] has been used in organic synthesis as a method for preparation of cinnolines.[2,3] At the same time, recently, when studying diazotization and cyclization of 2-alkynyl-1-amino-9,10-anthraquinones **1**, it was demonstrated that cyclization of diazonium salts **2** (Scheme 1) went with closure not of the 6-membered pyridazine ring, but of a 5-membered pyrazole ring.[4–6] Depending on the structure of the acetylenic substituent, formation of derivatives of either 3-(1,1-dichloroalkyl)-1*H*-naphtho[2,3-*g*]indazole-6,11-dione **3**,[5] or of 3-acyl-1*H*-naphtho[2,3-*g*]indazole-6,11-dione **4**[6] is observed (Scheme 1).

The results obtained did not fit into the framework of the generally assumed one-stage mechanism of cyclization of *ortho*-alkynylbenzene diazonium salts proposed by Schofield and Simpson (Scheme 2).[7–9]

This has served as a serious motive for studying the causes of the 'abnormal' behaviour of *vic*-aminoalkynylanthraquinones **1** in the cyclization reaction that goes via a diazonium salt. For this purpose, we studied the behaviour of 5-amino-3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone **5** in diazotization and cyclization reactions (preliminary communication[10]). The choice of compound **5** was not random. Here, the presence of the electron-donating diethylamino group in the quinone ring considerably quenches the acceptor influence of the carbonyl groups. We supposed



Scheme 1.

Keywords: *vic*-Alkynylanthraquinone and *vic*-alkynylnaphthoquinone diazonium salts; Heterocyclization; Mechanisms; Benzoindazolediones; Benzocinnolinetriones.
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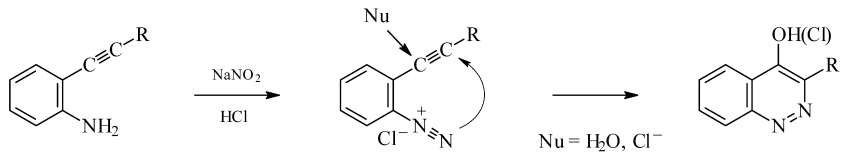


Scheme 2.

that if the change in the cyclization direction of **2** was determined by electronic factors, then, in the cyclization of naphthoquinone **5**, one could expect formation of reaction products with both 5- and 6-membered heterocycles.

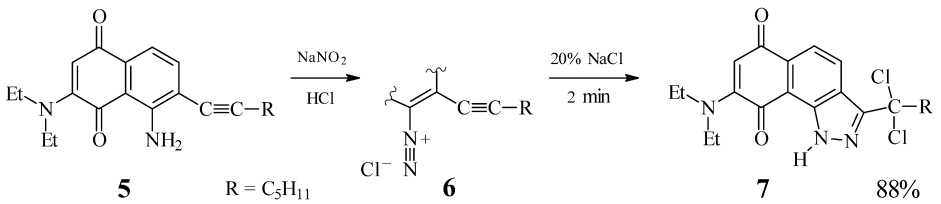
The method of running cyclization of *vic*-aminoalkynylarenes developed many decades ago (via diazotization) was extremely simple. Diazotization and cyclization reactions were run in one flask with heating at the second stage. The combination of a high acidity required at the stage of diazotization, and of a heightened temperature at the cyclization stage was a considerable limitation for introducing into this reaction aminoalkynylarenes, which were sensitive to these rather harsh reaction conditions. So, all the attempts to accomplish cyclization of **5** by this method failed due to the many side reactions, which gave a mixture of reaction products. These circumstances made us develop a new method for this reaction, which would make it possible to remove these limitations. The novelty of the experimental technique consisted in separating the diazotization and cyclization stages. We succeeded in this by creating conditions under which the diazotization rate considerably exceeded that of cyclization. For this, diazotization of **5** was run at room temperature in a water–acetone HCl solution using an excess of $NaNO_2$ (up to 3-fold). Under such conditions, diazotization was complete within about 1 min. The moment of completion was controlled visually by the change of the characteristic color from dark-violet (the solution of the hydrochloride of amine **5**) to light-brown (the solution of the 3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone-5-diazonium chloride **6**). After this, the reaction mixture was rapidly diluted with a 10–30-fold amount of either water or NaCl solution etc. In this way, the cyclization of **6** was carried out under rather mild conditions different from those of diazotization. The possibility of independent variation of the very cyclization conditions made the study of its mechanisms comfortable. The transformations of **6** were observed visually by the change of the solution color and with the help of thin-layer chromatography (TLC). In all the experiments using HCl, the two reactions (diazotization and cyclization) were run at room temperature.

2. Results and discussion

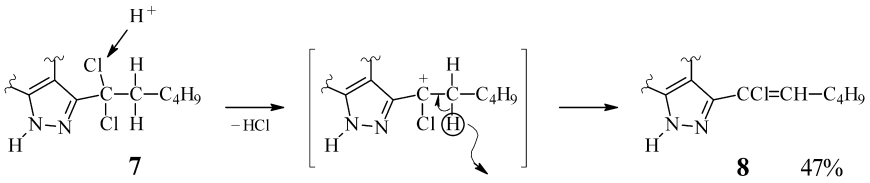
In the course of our studies, it was established that at a 10-fold dilution of the diazonium salt **6** solution with a 20% solution of NaCl, its transformation was completed rapidly, within less than 2 min. The process went with formation of only one reaction product **7** (Scheme 3).

The structure of compound **7** was identified with the help of analytical, spectral and chemical methods. Its IR spectrum dos not contain vibrations of NH_2 and C≡C groups, but has vibrations of the N–H link of the heterocycle. In the ^1H NMR spectrum there are signals of all the aliphatic protons (21H, 0.8–3.8 ppm), of protons of the quinoid (1H, 5.88 ppm) and benzoid (2H, 7.8–8.7 ppm) rings, and a characteristic signal (1H, 11.47 ppm) of the NH link of the heterocycle. The cyclization product **7** is a rather unstable compound with an increased tendency to elimination of HCl. In this connection, in the results of element analysis there was a great dispersion in estimation of chlorine atoms in the molecule >1, but <2. The same peculiarity of **7** was manifested also in its mass spectrum. The extreme right-hand doublet of peaks with *m/z* 385 and 387 corresponds, with respect to the intensity ratio of 3:1, unequivocally to the molecular formula $C_{21}H_{24}ClN_3O_2$ (M^+). The maximal intensity in the spectrum belongs to the peak with *m/z* 356 $(M-C_2H_5)^+$ accompanied, also in accordance with the natural isotope composition (Cl^{35} and Cl^{37}) by a peak with *m/z* 358. The presence of characteristic peak with *m/z* 268 $(M-ClC{=}CHC_4H_9)^+$ without the concomitant peak of 270 indicates that the remaining chlorine atom is in the lateral chain of the pyrazole ring. Therein, elimination of HCl from **7** takes place during heating of the sample in the letting-in chamber.

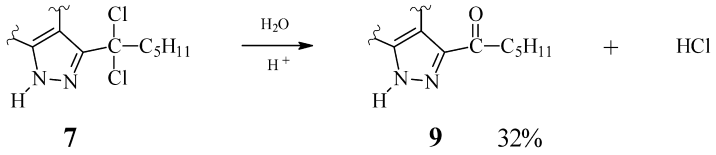
The high lability of **7** was also apparent during chromatography on silica gel in $CHCl_3$. Here, it is completely transformed mainly into two products **8** and **9** in a ratio 3:2. According to the spectral data, one may unequivocally attribute to the compound **8** which has the molecular formula $C_{21}H_{24}ClN_3O_2$, the structure of 3-(1-chlorohexen-1-yl)-8-diethylamino-1*H*-benzo[*g*]indazole-6,9-dione. Indeed, in its ^1H NMR spectrum there are very characteristic chemical shifts of the vinyl proton in the form of a triplet



Scheme 3.



Scheme 4.

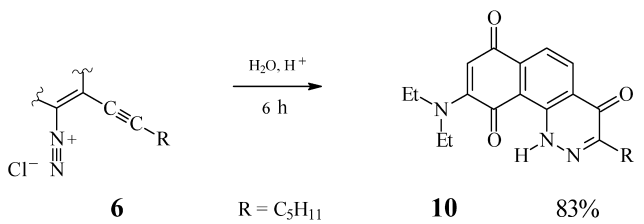


Scheme 5.

(6.55 ppm) and of two protons in the α-carbon atom of the lateral chain in the form of a quartet (2.50 ppm). Most probably, the transformation of the dichloride **7** into **8** goes according to Scheme 4.

Compound **9** with the molecular formula $C_{21}H_{25}N_3O_3$, according to IR and ^{1}H NMR spectra, represents a ketone. It was logical to hypothesize that this ketone was a product of usual hydrolysis of **7**, and the heterocycle in it had the same 5-membered structure (Scheme 5). This hypothesis is confirmed by the proximity of the positions of the vibrations of the N–H bond (IR spectra) and of the NH proton signals (^{1}H NMR spectra) in the spectra of compounds **7**, **8** and **9** (see Section 4).

It turned out that if the obtained solution of the diazonium salt **6** were diluted with a multiple volume of water, the cyclization would go much more slowly. Therein, irrespective of the degree of dilution (10, 15, 20 or 30-fold), the time of transformation of the diazonium salt was equal and amounted to about 6 h. The absence of dependence on the concentration of chloride anions in diluted solutions makes one think that the role of nucleophile here is played by the water molecule. In all cases, the same reaction product **10** is formed (Scheme 6). According to analytical data, this compound has the same molecular formula as **9**, but its melting point is 149–151 °C, which is 4 °C lower than that of the ketone **9** (153–155 °C). The spectral characteristics of these compounds are also different. The greatest difference is in the positions of extinction bands of vibrations of the N–H bond and of the signal of this proton in the ^{1}H NMR spectrum. The shift of this absorption band to the low-frequency field, and that of the proton NH signal to the low field in spectra of **10** as compared to those of **7**, **8**, and **9** suggests a stronger intramolecular hydrogen bond. This fact may be regarded as a corroboration of the 6-membered structure of the heterocycle in **10**. Here, the spatial position of groups (N–H and C=O) is favorable for the formation of a stronger intramolecular hydrogen bond.



Scheme 6.

The final determination of structures of **9** and **10** was made with the help of the mass spectra of these compounds. So, in the mass spectrum of **9** there are peaks corresponding to cations C_5H_{11} (71), COC_5H_{11} (99), (M-COC_5H_{11}) (268) and (M-C_5H_{11}) (296), which unequivocally indicates the presence of a carbonyl group in the side chain. At the same time, the absence of these characteristic peaks in the mass spectrum of **10** suggests that the carbonyl group of this ketone is included in the heterocycle. One has to add that the same ketone **10** is formed in insignificant amounts as a result of transformation of the dichloride **7** during chromatography in $CHCl_3$ on silica gel.

In this way, the experimental data obtained indicate that cyclization of the diazonium salt **6** goes with formation of both a 5-membered ring in the benzo[*g*]indazoledione **7** and a 6-membered one in the benzo[*h*]cinnolinetrione **10**. Naturally, the question arose whether the formation of reaction products with the 5- or 6-membered heterocycle went by two independent mechanisms, or they had common initial stages. Thus, quantum-chemical studies of possible pathways of cyclization of the diazonium salt **6** were carried out. Calculations of standard enthalpies of formation of compounds from simple substances at 298 K (H_f) were carried out by a semi-empiric method AM1.[11] In Figure 1,

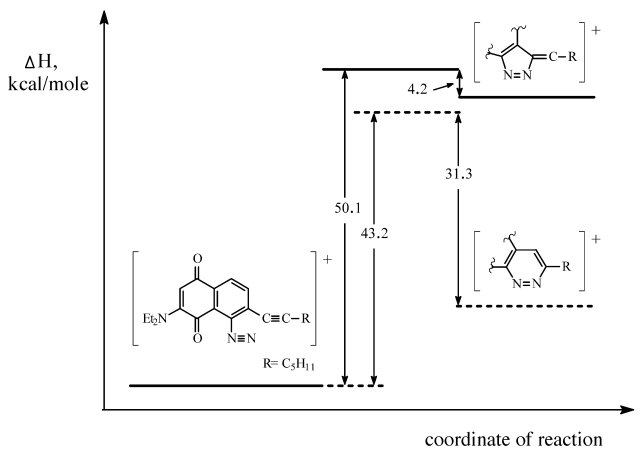


Figure 1. Thermodynamic characteristics for cyclization of the diazonium cation of salt **6**.

changes of cyclization enthalpy are presented depending on the coordinate of cyclization reaction of cation of the diazonium salt **6** with formation of cations with 5- and 6-membered rings are presented. One can see that these are energetically extremely unfavorable processes with activation energies of >43 kcal/mol. The calculation results, in our opinion, are not unexpected. Indeed, all the atoms included in the functional groups (–C≡CR and $-^{+}N{\equiv}N$) have the sp-hybridization, which determines their linear structure. Such geometry is not favorable for intramolecular interaction of functional groups despite their high reaction capacity. The facility of realization of cyclization even at room temperature suggests that the reaction goes in a different way. It is logical to hypothesize that the cyclization process takes place after the interaction of the diazonium salt with the nucleophile. The most likely for such an interaction is the triple bond whose electrophilicity is considerably higher due to the powerful influence of the diazonium group possessing negative inductive and mesomeric effects. As a result, the β-carbon atom of the triple bond acquires a certain positive charge (+0.05), and the α-carbon atom, a negative one (−0.29). Such a distribution of charges ensures quite a definite direction of the nucleophile attack on the β-carbon atom. In model calculations, we used chloride as the nucleophile. A comparison of the calculated heat of the reaction of addition of the anion to the α- and β-carbon atoms of the triple bond shows a greater energy advantage of addition to the latter by 11 kcal/mol. In Figure 2, the dependence of enthalpy of cyclization of a hypothetical neutral molecule ***X*** (chlorine atom at the β-carbon atom of the multiple bond) on the reaction coordinate is presented. One can see that the process of intramolecular cyclization of the neutral molecule already becomes exothermal with an energy gain of 15.6 kcal/mol and activation energy of 24.1 kcal/mol. It is reasonable to hypothesize that in reality the nucleophile addition and cyclization go in a coordinated manner. So, as the C^{β}–Cl bond is formed, the pair of bonding-electrons of the triple bond go to the atom C^{α}. This results in a change of hybridization of carbon atoms, and therefore, to a linear geometry of the multiple bonds, which does not contribute to the convergence of the reaction centers and to their interaction with closure of the ring at the C^{α} atom. As a result, at the first stage of ring formation, according to calculations, a 5-membered 3*H*-pyrazole heterocycle with an *exo*-cyclic double bond in position 3 (structure ***I*** in Fig. 2) must be formed. It is quite obvious that a compound of such structure must be very labile and easily transformed into more stable cyclic products. Thus, transformation of ***I*** into the dichloride **7** can be easily imagined as a result of secondary nucleophilic attack on the same carbon atom by Cl^{-}.

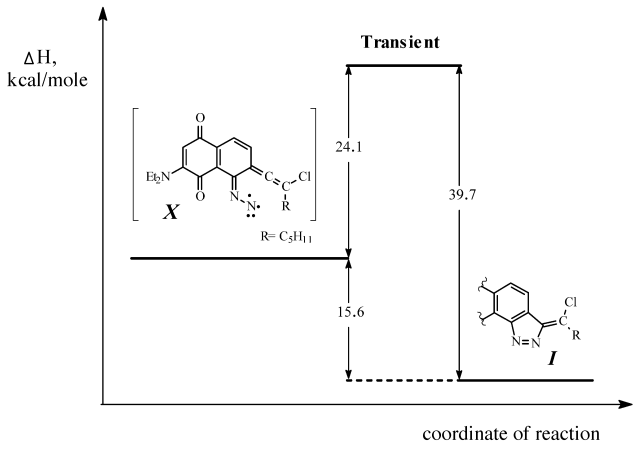
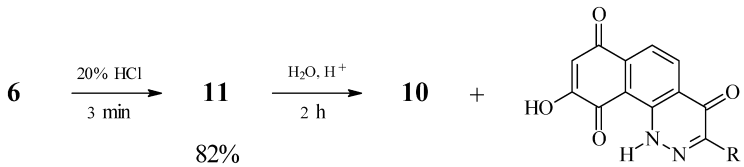


Figure 2. The dependence of enthalpy for cyclization of a hypothetical neutral molecule ***X*** on the reaction coordinate.

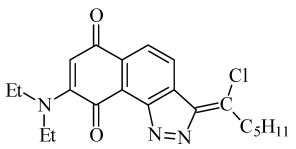
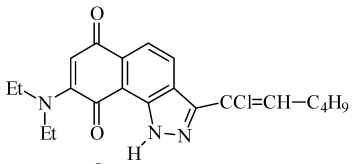
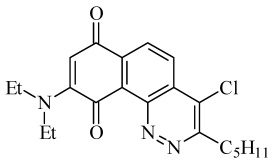
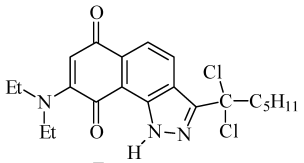
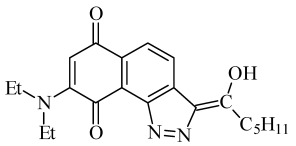
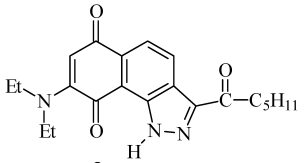
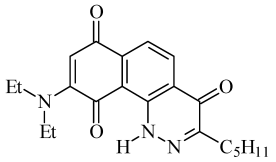
Trying to detect the intermediate in the course of the reaction, we diminished the nucleophilic properties of the medium in order to decrease the probability of attack on the *exo*-cyclic double bond by the nucleophile. For this purpose, the diazonium salt **6** was diluted by 18% HCl, neglecting possible complications caused by side processes. Indeed, under these conditions we observed a change of color of the reaction solution twice: a quick change of the brown color to a red-violet one, and then its gradual conversion to a red-brown one (within about 2 h). With the help of TLC, we also noted the appearance of an unknown reaction product **11** and its subsequent transformation into **10** accompanied by a partial hydrolysis of the diethylamino group (Scheme 7).

Interruption of the reaction after 3 min made it possible to isolate and characterize compound **11**. It was established that it had the same molecular formula as the chlorovinyl derivative **8** ($C_{21}H_{24}ClN_3O_2$), but quite different spectral characteristics. The absence of vibrations of C≡C and N–H bonds in the IR spectrum of **11** indicated that this was a cyclization product. In its ^{1}H NMR spectrum there are signals of all the aliphatic protons, including $N(C_2H_5)_2$, and of three protons of the benzoid and quinoid rings. A distinctive feature of this spectrum is the absence of the N–H signal. It was possible to ascribe to the compound **11**, according to analytical and spectral data, equally the structure of the intermediate ***I***, and the structure of the 4-chloro-9-diethylamino-3-pentylbenzo[*h*]cinnoline-7,10-dione ***Z*** (Table 1). In this connection, it was especially important to study the chemical behaviour of the isolated compound **11**. In the first place, it was necessary to clear up whether it was capable of being transformed into those cyclization products which had been isolated and characterized by us earlier when we carried it out in a slightly acid medium. So, firstly, it was established that an intense stirring of the chloroform solution of **11** with an equal volume of a 20% NaCl solution resulted rapidly and with a



Scheme 7.

Table 1. Enthalpies of formation of intermediates and final products of cyclization of the diazonium salts **6**

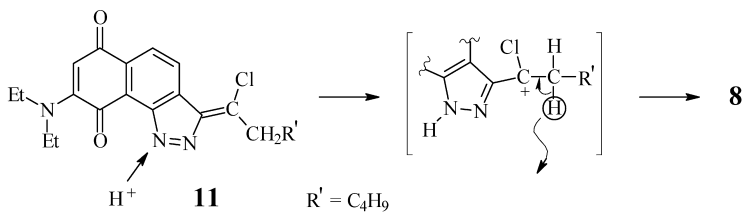
Compound	H_f (kcal/mol)
 **11*(I)***	27.53
 **8**	20.91
 ***Z***	−1.32
 **7**	−3.02
 **11a**	−10.29
 **9**	−22.59
 **10**	−38.40

high yield in the formation of dichloride **7**. Secondly, if in this case one takes, instead of NaCl solution, a 18% HCl, then cyclization goes, although rapidly, but with formation of a mixture of reaction products: **7** (60%), **8** (15%) and **10** (25%) (the total yield of 90%). Further on, during the chromatography on silica gel in $CHCl_3$, **11** is also transformed into a mixture of the compounds **8**, **9**, and **10** in an approximate ratio of 2:2:1 (the total yield of 80%). One can see that the experimental data obtained are in a rather good accordance with the structure ***I*** for the intermediate compound **11**. It was a quantum-chemical calculation of energies of formation of possible intermediate and final reaction products that permitted us making a final choice between structures ***I*** and ***Z*** (Table 1). Demonstrative in this aspect is the comparison of the values H_f for isomer compounds **11**, **8** and ***Z***. Whereas, the transformation of ***Z*** into **8** is an endothermic process, (reaction enthalpy is +22.2 kcal/mol), the transformation of **11** into **8**, on the contrary, is an exothermic process with an energy gain of 6.6 kcal/mol. The facility of transformation of **11** into **8** at room temperature is serious evidence in favor of structure ***I***. Most probably, this transformation can be imagined as a prototropic isomerization catalyzed by hydrogen ions (Scheme 8).

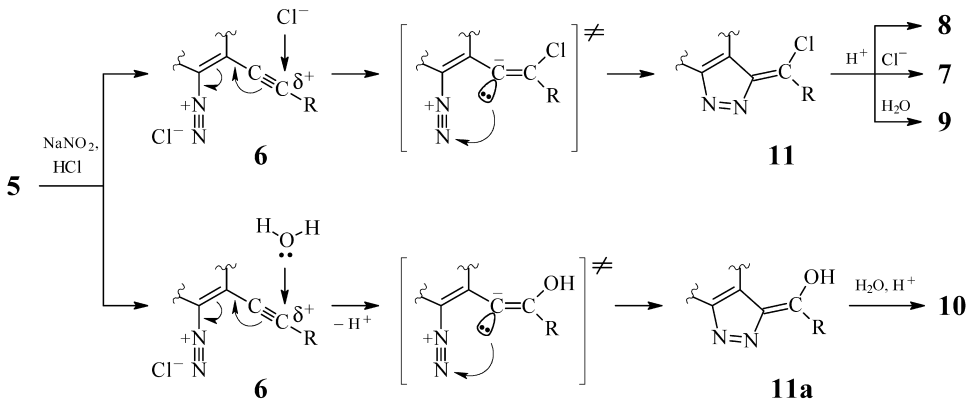
As a result, on the basis of a thorough analysis of experimental and calculated data, we have proposed a principal scheme of the mechanism of cyclization of the *vic*-alkynylquinone diazonium salt **6** (Scheme 9) which is radically different from the commonly accepted mechanism of cyclization of *ortho*-alkynylbenzene diazonium salts.

This is a multistage process which is initiated by the nucleophile (Cl^-, H_2O) attack on the β-carbon atom of the triple bond carrying a positive charge. Formation of the bond with the nucleophile is accompanied by a change of hybridization of carbon atoms of the multiple bonds (sp on sp^2) and, as a consequence thereof, by a change of its linear geometry. All this contributes to an intramolecular convergence of reaction groups, their interaction with formation of the 5-membered 3*H*-pyrazole ring with an *exo*-cyclic double bond. The formed cyclization product **11** (intermediate), possessing the maximum energy among the possible cyclic products (Table 1), strives to become stabilized with a lowering of energy. Depending on the reaction conditions, its transformations take place either with conservation of the size of the heterocycle and its transformation into a 1*H*-pyrazole ring, or with its extension to a 6-membered pyridazine ring. The question of how such extension of a heterocycle occurs remains open and makes the subject of separate study.

A heightened reaction capacity is characteristic, first of all, of the *exo*-cyclic double bond of the intermediate. Under the general electron acceptor influence of the N=N-fragment of the heterocycle and of the quinoid nucleus, although weakened by the donor diethylamino group, this bond is polarized. According to calculations, the carbon atom incorporated into the ring has a charge of −0.14, and the external carbon atom bound to the chlorine atom has a charge of +0.04. Such a distribution of charges under the conditions of increased nucleophilicity of the medium (dilution of **6** with a 20% NaCl solution) contributes to a repeated attack of chloride anion with formation of dichloride **7**. In this way, the formation of a less stable reaction product **7** takes place under the conditions of kinetic control. As for the formation of the most stable reaction product **10**, it is observed under thermodynamic control when the reaction goes slowly during 6 h (Scheme 6) and 2 h (Scheme 7). The driving force of transformation of **11** and **11a** into **10** going with extension of the heterocycle is its exothermicity. A condensed heterocyclic system with a 6-membered pyridazine ring is more stable than that with a 5-membered pyrazole one (Table 1). It is just by this that one can explain the partial transformation of dichloride **7**



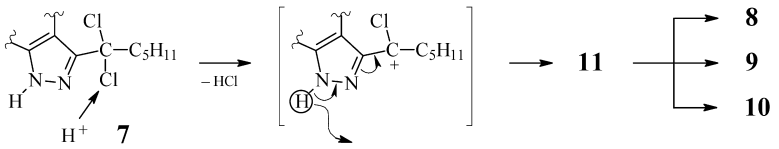
Scheme 8.



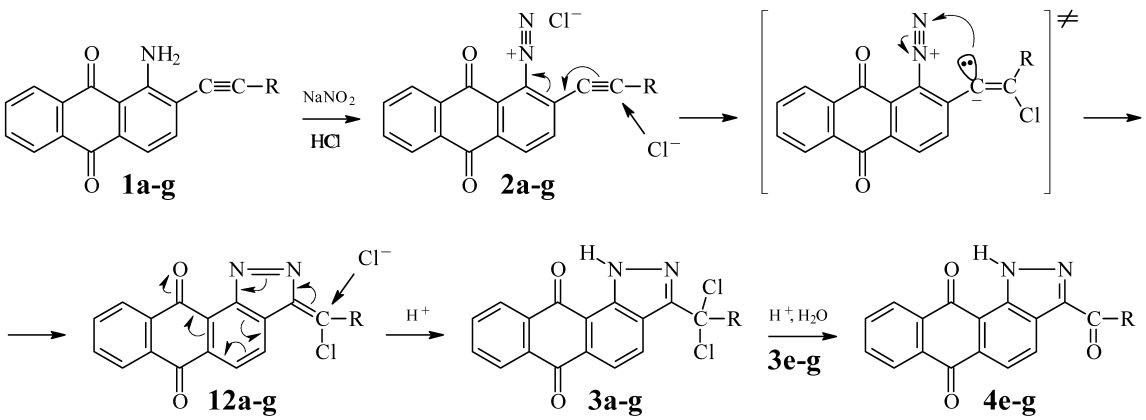
Scheme 9.

into ketone **10** during the chromatography in $CHCl_3$ on silica gel. Proceeding from general reasoning, we believe that its formation goes via the same intermediate **11**. It seems that the initial stage of formation of carbonium ion is the same as that in Scheme 4. However, thereafter the proton goes not from the carbon atom, but from the nitrogen atom (Scheme 10). The probability of the latter event seems to be lower, because the thermodynamic characteristics of **11** are higher than those of vinylchloride **8** (Table 1). Further on, the intermediate, as already noted above, is transformed under these conditions into three products: **8**, **9** and **10**.

The high reaction capacity of the intermediate determines its low stationary concentration. The unique opportunity of observing, in the course of reaction, the formation of intermediate cyclization product (Scheme 7) was a result of a lucky choice of the substrate and of its cyclization conditions. The presence of a strong donor substituent of +C character in the quinoid nucleus lowered the activity of

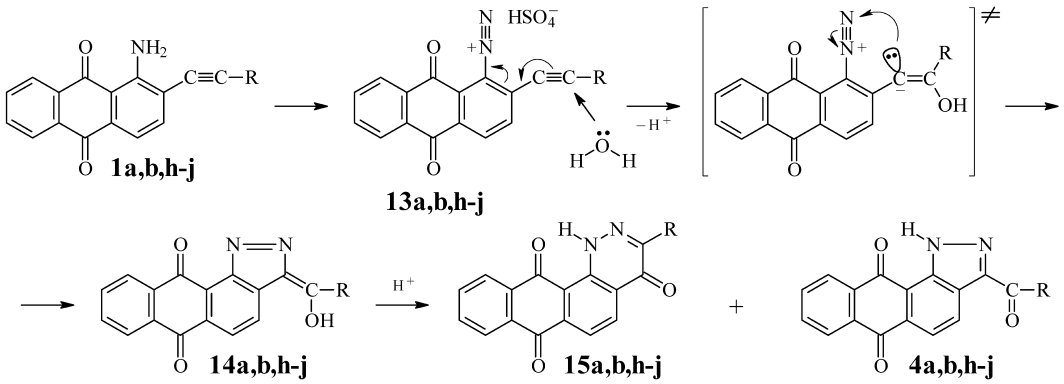


Scheme 10.



a: R = H; **b:** R = Bu; **c:** R = CH_2OPh; **d:** R = 1-HO-*cyclo*-C_6H_{10}; **e:** R = COPh; **f:** R = COBu-*t*; **g:** R = COPr.

Scheme 11.



a: R = H; **b:** R = Bu; **h:** R = C(OH)Me$_2$; **i:** R = CH(OH)Pr; **j:** R = CH(OH)Pr-*i*.

Scheme 12.

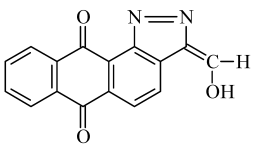
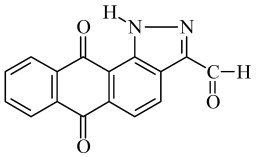
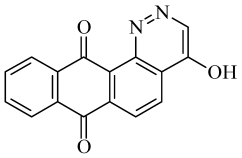
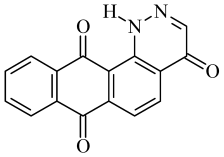
the *exo*-cyclic double bond so much that under certain conditions it became possible to obtain its measurable concentration.

Essential is the fact that under similar conditions, when studying the cyclization of the 2-alkynyl-9,10-anthraquinone-1-diazonium chlorides **2**, we failed to detect the intermediate directly. However, this fact does not disprove but only substantiates the generality of the new notions of the mechanism of cyclization of *vic*-alkynylarene diazonium salts in a series of quinones. In this case, the intermediate (Scheme 11) must have the structure **12**. One can see that here the *exo*-cyclic double bond has to be polarized to a higher degree than in **11** which has a strong donor substituent. This contributes to the fact that even under the conditions of a lowered nucleophilicity of the medium, a rapid interaction with the nucleophile and formation of respective dichlorides **3** takes place. Previously,[12] we showed that the formation of the ketones **4** also goes through dichloride **3** which, due to peculiarities of their structure are prone to a rapid hydrolysis (Scheme 11).

The complete removal of the strong nucleophile (Cl^-) from the reaction mass has permitted us to change the course of reaction.[12] This variant has been used by us when running the diazotization and cyclization reaction in diluted H_2SO_4 (Scheme 12). Under these conditions, the role of the nucleophile is played by the molecule of H_2O. As one could expect from the point of view of the new notions of the cyclization mechanism, the reaction rate slowed down, but apart from the acyl derivatives of naphthoindazole **4**, we also observed the formation of derivatives of naphthocinnolinetriones **15** (Scheme 12). In this case, too, we failed to detect the intermediate **14**, which is also quite natural. In Table 2, calculated data on the energy of formation of the intermediate and of possible final products of cyclization of **13a** are presented. One can see that the maximal value of energy corresponds to the intermediate **14a** which under the reaction conditions tends to become stabilized with a loss of energy. One of the pathways is that of transition to a stable tautomeric form of the ketone **4**. As it is known, it does not require large energy expenditures. Another pathway is isomerization with an extension of the ring and formation of the most stable naphthocinnolines **15** (the enthalpy of this process for **14a** amounts to 25.7 kcal/mol). The mechanism of such ring transformation is very interesting and will be the subject of a further investigation.

We established[12] that the direction of the reaction with an extension of the heterocycle was promoted by an increase of acidity of the medium. An increase of the sulfuric acid concentration at the cyclization stage to 38% purposely permits formation of naphthocinnolinetriones **15** with a high yield. It is of paramount importance that the change of

Table 2. Enthalpies of formation of intermediate and final products of cyclization of the diazonium salts **13a**

Compound	H_f (kcal/mol)
 **14a**	32.31
 **4a**	22.29
 **15a**(tautomer)	8.67
 **15a**	6.61

medium acidity influences only the proportion of reaction products, but not the reaction rate. This fact shows once again that the rate-determining stage is the intermediate formation. All its subsequent transformations are exothermic and go at a high rate. Such a typical situation is the cause of the low stationary concentrations of intermediates, which makes their detection very problematic.

3. Conclusion

In conclusion, the study of cyclization of 3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone-5-diazonium chloride has demonstrated that this is a multistage process. It has been established that the intermediate cyclization product has a 5-membered structure of the 3*H*-pyrazole ring with an *exo*-cyclic double bond. A principal scheme of the mechanism of cyclization of *vic*-alkynylanthra- and *vic*-alkynylnaphthoquinone diazonium salts, which is radically different from that commonly accepted for cyclization of *ortho*-alkynylbenzene diazonium salts is proposed. It has been demonstrated that the direction of further transformations of the intermediate with conservation of the size of the heterocycle or with its extension can be predicted and changed by means of varying the reaction conditions. This has made it possible to obtain from the same *vic*-alkynylamino-9,10-anthraquinones, with a good yield, derivatives of either naphthoindazolediones or naphthocinnolinetriones. The two classes of these compounds are interesting as potential biologically active substances.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker AM-250 spectrometer in $CDCl_3$, internal standard $SiMe_4$, IR spectra were so on a UR-20 spectrophotometer in $CHCl_3$. Mass spectra were obtained on a Finnigan MAT instrument. The control of the course of reaction and of the individual identity of substances was performed with the help of TLC on Silufol UV-254 plates ($CHCl_3$ or benzene–ether).

4.1.1. 5-Amino-3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone (5). 5-Amino-3-diethylamino-6-iodo-1,4-naphthoquinone (1.57 g, 4.2 mmol) was condensed with heptyne-1 (1 mL, 0.74 g, 7.7 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (0.12 g) and CuI (0.12 g) in Et_3N (106 mL) in an inert atmosphere at 50 °C for 7 h, 120 mL of toluene was added, and the obtained solution was decanted. The residue formed after the removal of toluene and Et_3N in vacuum was dissolved in $CHCl_3$ (150 mL), washed with water (600 mL) and $CHCl_3$ was distilled off. The non-purified product was dried in vacuum and chromatographed on silica gel; the admixtures were eluted with toluene, and **5** was so with a mixture of toluene and ether (1:1). Having distilled off the solvent, the substance was recrystallized from hexane (60 mL): 1.28 g (90%) of **5** was obtained as red-orange crystals, mp 72–73 °C (hexane); [Found: C, 74.92; H, 7.73; N, 8.32. $C_{21}H_{26}N_2O_2$ requires C, 74.52; H, 7.74; N, 8.28%]; $\nu_{max}(CHCl_3)$ 3490, 3360 (NH_2), 2230 (C≡C), 1655, 1620 cm^{-1} (C═O); δ_H (250 MHz, $CDCl_3$) 7.45 (1H, d, *J*=7.7 Hz, H-8(7)), 7.29 (1H, d, *J*=7.7 Hz, H-7(8)), 5.77 (1H, s, H-2), 3.47 (4H, q, *J*=7.4 Hz, CH_2N), 2.47 (2H, t, *J*=7.0 Hz, ≡C–CH_2), 1.70–1.55 (2H, m, ≡C–CH_2–CH_2), 1.55–1.15 (4H, m, C(CH_2)$_2CH_3$), 1.25 (6H, t, *J*=7.4 Hz, CH_3CH_2N), 0.90 (3H, t, *J*=6.9 Hz, CH_3).

4.1.2. 3-(1,1-Dichlorohexyl)-8-diethylamino-1*H*-benzo[*g*]indazole-6,9-dione (7). To solution of quinone **5** (0.10 g, 0.3 mmol) in acetone (5 mL) at 20 °C with a strong stirring were successively added: 18% HCl (5 mL), $NaNO_2$ (0.07 g, 1.0 mmol) in water (1 mL), and mixed for 1 min. The solution of the obtained 3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone-5-diazonium chloride (**6**) was immediately poured out into 20% aqueous solution of NaCl (100 mL), stirred for 2 min and extracted with $CHCl_3$. After drying the extract, distilling off the solvent in vacuum and recrystallization from a mixture of toluene and hexane, 0.11 g (88%) of cyclization product **7** was obtained as light-brown crystals; δ_H (250 MHz, $CDCl_3$) 11.47 (1H, br s, NH), 8.50 (1H, d, H-5(4)), 7.92 (1H, d, H-4(5)), 5.88 (1H, s, H-7), 3.60 (4H, q, CH_2N), 2.90 (2H, t, $CClCH_2$), 2.00–1.20 (12H, m, C(CH_2)$_3CH_3$, CH_3CH_2N), 0.95 (3H, t, CH_3); *m*/*z* (EI) 387 (M^+, 24), 385 (M^+, 71), 372 (12), 370 (39), 358 (38), 356 (100), 268 (17%).

4.1.3. 9-Diethylamino-3-pentyl-1*H*-benzo[*h*]cinnoline-4,7,10-trione (10). To solution of **5** (0.10 g, 0.3 mmol) in acetone (5 mL) at 20 °C, with energetic stirring, 18% HCl (5 mL) and $NaNO_2$ (0.07 g, 1.0 mmol) in water (1 mL) were successively added and stirred for 1 min. The solution of the diazonium salt **6** formed was immediately poured out into water (250 mL) and kept at 20 °C for 5 h. The product was extracted with $CHCl_3$, the extract was run through a thin layer of silica gel, and the solvent was distilled off in vacuum; 0.086 g (83%) of chromatographically pure product **10** was obtained as brown crystals, mp 149–151 °C ($CHCl_3$–hexane); [Found: C, 68.44; H, 6.61; N, 11.08. $C_{21}H_{25}N_3O_3$ requires C, 68.64; H, 6.86; N, 11.44%]; $\nu_{max}(CHCl_3)$ 3355 (NH), 1655, 1620 cm^{-1} (C═O); δ_H (250 MHz, $CDCl_3$) 12.95 (1H, br s, NH), 8.60 (1H, d, *J*=7.8 Hz, H-6(5)), 7.97 (1H, d, *J*=7.8 Hz, H-5(6)), 5.90 (1H, s, H-8), 3.55 (4H, q, *J*=7.0 Hz, CH_2N), 2.85 (2H, t, *J*=8.2 Hz, ═CCH_2), 1.85–1.00 (12H, m, C(CH_2)$_3CH_3$, CH_3CH_2N), 0.88 (3H, t, CH_3); *m*/*z* (EI) 367 (M^+, 34), 338 (46), 242 (100%).

4.1.4. Transformations of 3-(1,1-dichlorohexyl)-8-diethylamino-1*H*-benzo[*g*]indazole-6,9-dione 7 on silica gel in $CHCl_3$. 0.150 g of **7** in $CHCl_3$ was placed onto a plate with silica gel and eluted thrice with $CHCl_3$. After separation of stained silica gel bands, and washing-off the substances from them, obtained were:

1. 0.065 g (47%) of 3-(1-chlorohexen-1-yl)-8-diethylamino-1*H*-benzo[*g*]indazole-6,9-dione (**8**) as light-brown crystals, mp 114–115 °C ($CHCl_3$–hexane); [Found: C, 65.37; H, 6.23; Cl, 9.49. $C_{21}H_{24}ClN_3O_2$ requires C, 65.36; H, 6.27; Cl, 9.19%]; $\nu_{max}(CHCl_3)$ 3465 (NH), 1670, 1625 cm^{-1} (C═O); δ_H (250 MHz, $CDCl_3$) 11.55 (1H, br s, NH), 8.30 (1H, d, *J*=8.7 Hz, H-5(4)), 7.85 (1H, d, *J*=8.7 Hz, H-4(5)), 6.55 (1H, t, *J*=6.9 Hz, ═CH), 5.85 (1H, s, H-7), 3.60 (4H, q, *J*=7.0 Hz, CH_2N), 2.50 (2H, q, *J*=6.9 Hz, ═CCH_2),

1.70–1.20 (10H, m, $C(CH_2)_2CH_3$, CH_3CH_2N), 0.95 (3H, t, CH_3).

2. 0.038 g (32%) of 8-diethylamino-3-hexanoyl-1*H*-benzo[*g*]indazole-6,9-dione (**9**) as dark-violet crystals, mp 153–155 °C (toluene); [Found: C, 68.66; H, 6.80; N, 11.65. $C_{21}H_{25}N_3O_3$ requires C, 68.64; H, 6.86; N, 11.44%; $\nu_{max}(CHCl_3)$ 3450 (NH), 1690, 1670, 1625 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 11.75 (1H, br s, NH), 8.58 (1H, d, J=8.2 Hz, H-5(4)), 8.00 (1H, d, J=8.2 Hz, H-4(5)), 5.88 (1H, s, H-7), 3.60 (4H, q, J=7.0 Hz, CH_2N), 3.20 (2H, t, J=7.2 Hz, $COCH_2$), 1.80 (2H, m, $COCH_2CH_2$), 1.60–1.00 (10H, m, $C(CH_2)_2CH_3$, CH_3CH_2N), 0.90 (3H, t, CH_3); *m*/*z* (EI) 367 (M^+, 99), 352 (54), 338 (100), 296 (8), 268 (45), 99 (6), 71 (24%).
3. 0.015 g (13%) of 9-diethylamino-3-pentyl-1*H*-benzo[*h*]-cinnoline-4,7,10-trione **10**.

4.1.5. 3-(1-Chlorohexylidene)-8-diethylamino-3*H*-benzo[*g*]indazole-6,9-dione (11). To solution of **5** (0.14 g, 0.4 mmol) in acetone (7.9 mL) were added successively 18% HCl (7.9 mL) and $NaNO_2$ (0.10 g, 1.5 mmol) in water (2.3 mL) under continuous stirring. The stirring was continued thereupon for another 1 min. The obtained solution of diazo salt **6** was immediately poured into 18% HCl (131 mL) and immediately extracted with stirring with toluene (160 mL). The organic layer was separated, washed with low concentrated aqueous $NaHCO_3$ (~1%) solution and water to neutral reaction. After removal of the solvent in vacuum, the residue was chromatographed on silica gel in a mixture of $CHCl_3$ and ether (10:1). The yield of **11** was 0.13 g (82%): dark-violet crystals, mp 124–125 °C ($CHCl_3$–hexane); [Found: C, 65.55; H, 5.99; Cl, 9.02. $C_{21}H_{24}ClN_3O_2$ requires C, 65.36; H, 6.27; Cl, 9.19%]; $\nu_{max}(CHCl_3)$ 1695, 1625 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 8.45 (2H, s, H-4,5), 5.85 (1H, s, H-7), 3.56 (4H, q, J=7.0 Hz, CH_2N), 3.38 (2H, t, J=7.7 Hz, $=CCH_2$), 1.94 (2H, m, $=CCH_2CH_2$), 1.35 (6H, t, J=7.0 Hz, CH_3CH_2N), 1.25 (4H, s, $C(CH_2)_2CH_3$), 0.90 (3H, t, CH_3).

Acknowledgements

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Synthesis of the marine alkaloid caulersin

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Abstract—A three-step synthesis of caulersin (**3**) from indole-2-acetic acid methyl ester and indole-2-carbonyl chloride is described. As the spectral data of the synthetic sample differed from those reported for the natural product, the structure was determined by X-ray crystallography.

1. Introduction

In connection with previous synthetic studies of indolocarbazoles,[1] the highly potent aryl hydrocarbon receptor ligand indolo[3,2-*b*]carbazole-6,12-dione (**1**) and the corresponding 2,3-*b* isomer (**2**) have been synthesized via new ring closing strategies (Fig. 1).[2] Utilizing a similar ring closing strategy, the related bisindole marine natural product caulersin (**3**), was now considered as a synthetic target. Caulersin was isolated in 1997 from the algae *Caulerpa serrulata*,[3] and represents the only natural product isolated so far containing a bisindole structure bridged by a central troponoid framework. A lengthy synthesis of caulersin (seven steps, 14% reported overall yield) was published in 1999.[4] A structure related to caulersin, the bisindole caulerpin (**4**), isolated from several different green and red algae,[5–8] has showed moderate antitumor activity.[9] Furthermore, **4** acts as a plant growth regulator[10] and has also been shown to inhibit the multixenobiotic resistance (MXR) pump in algae, thus enhancing toxicity of xenobiotics.[11] The synthesis of **4** was reported by Maiti and Thomson who treated indole-2-acetic acid methyl ester with a Vilsmeier salt to produce a low yield of **4**.[12,13] In an oxidative transformation of **4**, several oxygenated adducts were isolated.[14] During the analysis of these structures, caulersin (**3**) was suggested as one of the stabile intermediates formed in the mass spectrometer. As no natural ring-transformed adduct from **4** has been isolated, the possibility of a product–precursor relationship between **3** and **4** does exist. With the objective of subjecting **3** to further biological studies, large quantities of **3** were needed. This encouraged the development of a shorter and higher yielding synthesis of **3**, something that now has been accomplished.

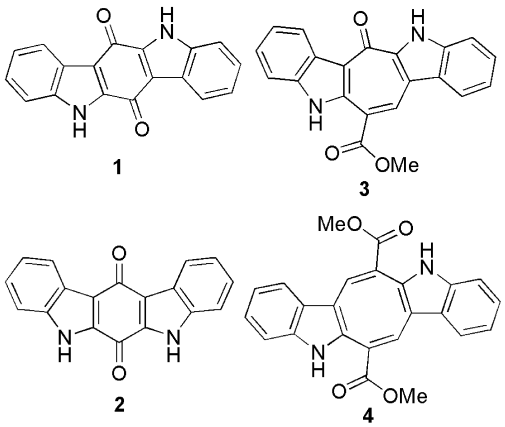

Figure 1. Indolo[3,2-*b*]carbazole-6,12-dione (**1**), indolo[2,3-*b*]carbazole-6,13-dione (**2**), caulersin (**3**) and caulerpin (**4**).

2. Results and discussion

Retrosynthetic analysis of **3** leads to the 2,3-diindolyl ketone **5** by excision of a carbon atom, probably as formaldehyde, from the seven-membered ring. Further scission of **5** gives indole-2-acetic acid methyl ester (**6a**)[15] and indole-2-carboxylic acid (**7**) (Scheme 1).

In practice, treatment of indole-2-acetic acid methyl ester (**6a**) with dimethylaluminium chloride,[16,17] followed by addition of indole-2-carbonyl chloride produced the 3-acylated bisindole **5** in 35% yield together with two other

Keywords: Caulersin; Marine alkaloid; Vilsmeier salt; Indole.
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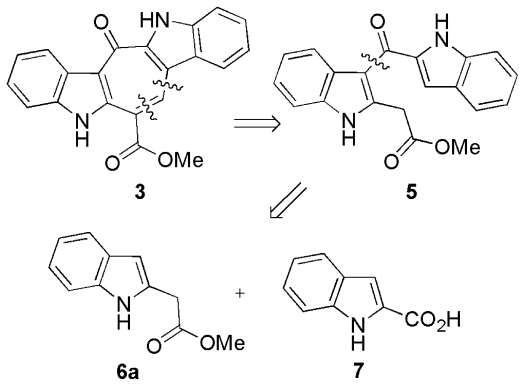
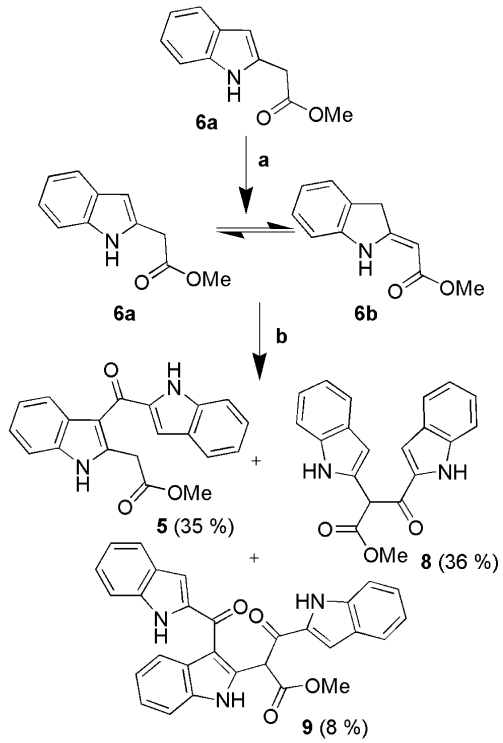
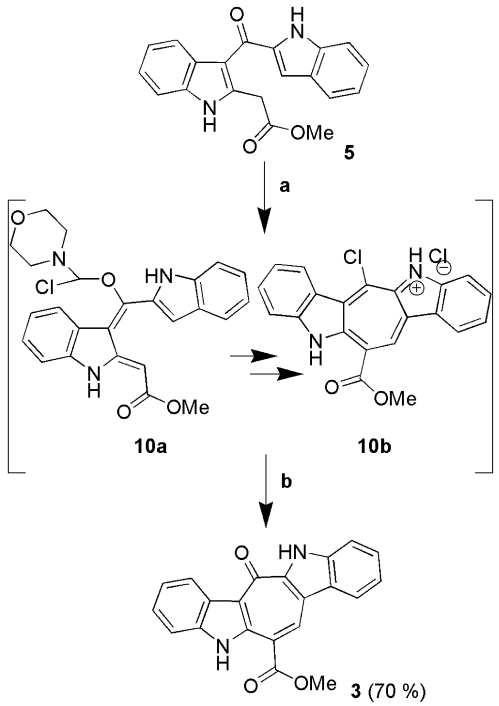


Scheme 1. Retrosynthetic analysis of caulersin (**3**).



Scheme 2. (a) Me_2AlCl, CH_2Cl_2; (b) indole-2-carbonyl chloride.

products arising from the tautomer **6b** (Scheme 2). The acid sensitive indole **6a** undergoes partial isomerization to the enamine **6b** which in turn reacts with indole-2-carbonyl chloride, producing **8** (36%) together with the doubly acylated product **9** (8%), obviously a secondary product of **8**. Initial reaction between **5** and 1 equiv. of chloromethylenemorpholinium chloride,[18] in dichloroethane at 60 °C failed to give **3**. Increasing the number of the Vilsmeier salt equivalents to 3 produced, upon cooling, a red solid. The chemical shift of one of the aromatic doublets and the aromatic singlet were shifted downfield in the ^{1}H NMR spectrum of this intermediate, and the aliphatic triplet had disappeared. This sparingly soluble intermediate was rapidly transformed into **3** in the NMR-tube, no ^{13}C NMR data could therefore be obtained. However, when the ethyl ester analogue of **5** was treated with chloromethylenemorpholinium chloride a red solid formed that proved to be slightly more stable, something that enabled the isolation of the ethyl ester derivative of **10b** as the corresponding free base. Mass spectrometry of the free base showed the



Scheme 3. (a) Chloromethylenemorpholinium chloride 3 equiv., 21–60 °C; (b) DMSO, H_2O, 50 °C.

presence of a chlorine atom incorporated in the structure. This information, suggests that **10a** is the initial product formed (Scheme 3). Secondly, another Vilsmeier salt equivalent reacts with **10a** and is thus further transformed into **10b**. Hydrolysis of **10b** in DMSO/water at 50 °C for 14 h then produced **3** as an orange solid in 70% yield. The total yield of caulersin in this facile three-step procedure was 25%.

When the spectral data of **3** were compared with those recorded for the natural product the proton spectra proved to be essentially identical. However, the reported melting points and the IR spectra differed. During the melting point measurement we noted that the consistency of the powder of **3** changed only marginally at the reported melting point (269–274 °C),[3,4] to a more golden color. The sample finally melted between 352–355 °C, 70 °C higher than previously reported. As other rigid and planar bisindoles exemplified by **1** and **2** have high melting points (>400 °C),[2] the higher melting point recorded in our hands seems reasonable.

When the crystals were analyzed with IR-spectroscopy a similar pattern of peaks, but not identical, could be seen as compared to the material before sublimation. This was attributed to the different packing of the crystals before and after sublimation. In comparison with the previously synthesized material and the isolated natural product, there were small differences for the two NH functionalities of the unsublimed sample. ^{1}H and ^{13}C NMR spectroscopy showed that in solution, the sublimed crystals were identical with the unsublimed material. In the ^{13}C spectrum several differences with the reported data were observed. This is best exemplified by the absence of the chemical shift reported for the position of carbon 20 (C-20) at 146.8 ppm. Instead, a signal at 114.6 ppm was assigned for C-20 (Fig. 2). The ^{13}C spectrum of the isolated **3** obtained from

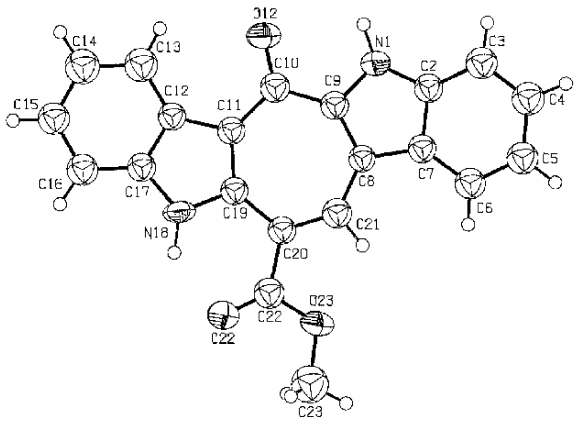
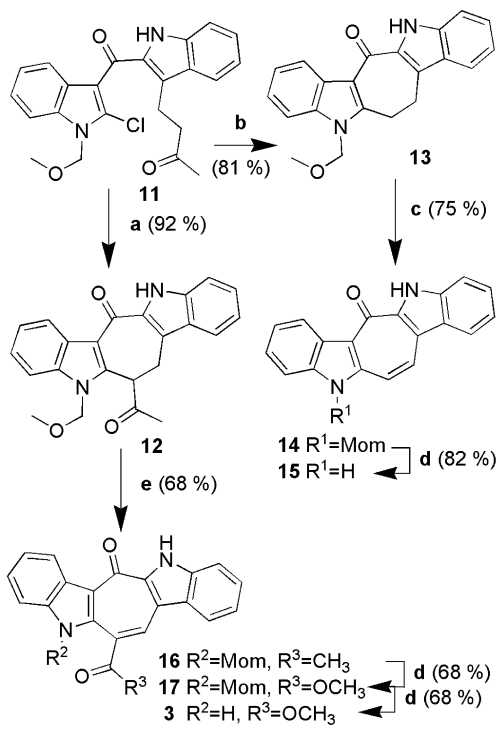


Figure 2. Crystal structure of caulersin (**3**) with atom numbering. CCDC reference number 210210.

Su,[19] had a considerably lower signal to noise ratio compared with the spectrum from our synthetic product. Furthermore, the signal with the lowest intensity, a singlet at 119.3 ppm was not accounted for. We now undertook a detailed 2D NMR study of compound **3**, which enabled us to assign all carbon and hydrogen atoms in the molecule. To further establish the structure, small fine yellow crystals of **3** were obtained by sublimation at 285 °C and 0.35 mbar. The X-ray diffraction study clearly showed that the structure was correct (Fig. 2). Worth to mention here is the extremely high packing coefficient[20] (72.6%), a figure which indicates that the molecules are exceptionally well packed in the crystal.

To verify the structure of the previously reported **3** and the isolated natural product,[3] the synthesis of Fresneda and co-workers was repeated.[4] *o*-Azidobenzaldehyde[21,22] and *N*-methoxymethyl-3-acetyl-2-chloroindole[23] was condensed to produce the expected chalcone which when heated in xylenes, formed the corresponding bisindole ketone. This ketone was treated with methyl vinyl ketone and boron trifluoride diethyl etherate in nitromethane to give the Michael adduct **11**[4] and a small amount of 5-nitro-2-pentanone.[24] During this last reaction several portions of the boron reagent and the methyl vinyl ketone were added to complete the reaction, in contrast to the single addition reported. In the subsequent ring closing reaction with potassium *tert*-butoxide/*tert*-butanol (*t*-BuOK/*t*-BuOH, 2.5 equiv.) the cyclized seven-ring bridged bisindole **12** could be obtained via a modification of the workup procedure (Scheme 4). When several equivalents of *t*-BuOK were used, the unexpected deacylation of **12** readily took place, to produce the deacylated heptacycle **13**. The retention values of **11** and **13** in several different eluent systems are similar, thus precluding the use of TLC to monitor the progress of the reaction. In the selective formation of **13** in 81% yield, multiple equivalents of *t*-BuOK were used. Bisindole **13** was dehydrogenated with DDQ in benzene to give the aromatized molecule **14** in 76% yield. Subsequent deprotection of **14** was carried out with 6 M HCl in refluxing ethanol to produce the parent bisindolotropolone **15** in 82% yield. Dehydrogenation of **12** with DDQ produced the aromatized molecule **16** that was subsequently subjected to treatment with fresh potassium hypochlorite (KOCl) solution.[4,25] The bisindole ester **17** was isolated in 68% using the procedure of Fresneda.[25] The ester **17** was then heated in MeOH with 6 M HCl, to give **3** in 68%, with similar spectroscopic data with material obtained via Scheme 3.



Scheme 4. (a) 2.5 equiv. *t*-BuOK/*t*-BuOH/PhH, reflux; (b) 8.5 equiv. *t*-BuOK/*t*-BuOH/PhH, reflux; (c) DDQ, PhH, reflux; (d) EtOH, 6 M HCl, reflux; (e) DDQ, PhH, reflux; (f) 3 equiv. KOCl, THF/MeOH, 0–21 °C, 5 h;[25] (g) MeOH, 6 M HCl, reflux, 6 h.[25]

3. Conclusions

A simple three-step synthesis in 25% total yield of the marine natural product caulersin (**3**) has been developed by cyclisation of the simple ketoester **5** with the Vilsmeier reagent chloromethylenemorpholinium chloride to yield the central seven-membered ring ketone after in situ treatment with water in DMSO. Unambiguous determination of its structure via an X-ray diffraction study confirmed the structure of **3** and thus verified the new data obtained in this work. The samples of **3** prepared via Schemes 3 and 4 are identical. The main difference between the reported natural product,[3] the previous synthesis of **3**,[4] and this work, is the melting point and ^{13}C NMR data presented here.

4. Experimental

4.1. General aspects

NMR spectra were obtained on a Bruker Avance 300 DPX spectrometer (Bruker, Newark, DE) operating at 300 MHz and a Jeol Eclipse+500 FT NMR spectrometer (Jeol Ltd, Tokyo, Japan) operating at 500 MHz. Spectra were recorded in acetone-d_6, DMSO-d_6 or $CDCl_3$, using the solvent as internal standard at 300 or 500 MHz for ^1H and 75 or 125 MHz for ^{13}C at 298 K if not stated otherwise; δ values are given in ppm and coupling constants are reported in Hz.

IR spectra were recorded on a Perkin–Elmer FT-IR 1600 or on a ThermoNicolet Avatar 330 FT-IR spectrophotometer. Melting points were determined using the capillary method on a Büchi B-545, an Electrothermal IA9200 and on a Heizbank koffler hotbench and are uncorrected. Mass spectra were recorded using an LC/MS system operating in the electron spray ionization (ESI) mode at 70 eV. The elemental analyses were performed by H. Kolbe Microanalytisches Laboratorium, Mühlheim an der Ruhr, Germany. Sublimation was carried out on a Thermal Gradient Sublimer, Esoteric Chemicals AB, Sweden. All reagents were of standard quality and used as received from Lancaster, Aldrich, or Merck. Solvents were purified by distillation or were of HPLC grade. Dichloromethane, dichloroethane and *tert*-butanol were distilled from CaH_2 and stored over activated molecular sieves prior to use. Benzene and *n*-heptane were stored over sodium. Chromatographic separations were performed on silica gel 60 (230–400 mesh). Reactions were monitored by thin-layer chromatography, on silica gel coated plates with a fluorescent indicator.

4.2. Synthesis of compounds 5, 7 and 8

1.0 M Me_2AlCl in hexanes (15.80 mmol, 15.8 mL) was added dropwise to a cold (−40 °C) solution of indole-2-acetic acid methyl ester[15] (**6a**) (2.30 g, 12.16 mmol) in dry CH_2Cl_2 (40 mL) under nitrogen. The temperature was then allowed to rise to −10 °C over 45 min before being lowered to −20 °C whereupon a solution of indole-2-carbonyl chloride (2.84 g, 15.80 mmol) in CH_2Cl_2 (20 mL) was added dropwise at such a rate as to keep the temperature below −10 °C. The temperature was then gradually increased to 21 °C over 16 h. The reaction mixture was poured out on iced water (100 mL) in a 500 mL beaker. After the initial frothing, the yellow suspension was diluted with water (200 mL) and stirred for 1 h. The suspension was extracted with EtOAc (3×100 mL) and filtered through celite and washed with a little EtOAc. The combined organic phases were washed with water (100 mL) and brine (100 mL) before drying over Na_2SO_4. All water phases (approximately 500 mL) were extracted with $CHCl_3$ (2×300 mL), the combined $CHCl_3$ phases were washed with water (200 mL), brine (200 mL) and then dried over Na_2SO_4. The dried organic phases were combined and evaporated to dryness to form an orange solid. This solid was subjected to column chromatography on silica with a gradient eluent system of EtOAc/hexane (20–50%) to give **8** in 0.56 g, **9** in 0.08 g and **5** in 1.07 g. Fractions with more than one substance were combined and evaporated and subjected to a second column chromatography with the gradient eluent Et_2O/hexane (70–90%) gave **8** in 0.91 g, **9** in 0.40 g, and finally **5** in 0.35 g. Compound **8** was isolated in a total yield of 1.47 g (36%), and the trimeric product **9** in 0.48 g (8%) and finally the bisindole **5** in 1.42 g (35%).

4.2.1. 2,3-Bis-(1*H*-indol-2-yl)-3-oxo-propionic acid methyl ester (8). White solid. Mp 179.5–182.5 °C (Et_2O/hexane); IR (KBr) 3346, 3052, 2954, 1721, 1660, 1636, 1518, 1428, 1343, 1276, 1138, 751 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) δ 11.96 (1H, s), 11.17 (1H, s), 7.71 (1H, d, J=8.0 Hz), 7.61 (1H, d, J=1.0 Hz), 7.48–7.44 (2H, m), 7.40 (1H, d, J=8.1 Hz), 7.31 (1H, dd, J=7.7, 7.2 Hz), 7.11–7.03 (2H, m), 6.95 (1H, dd, J=7.3, 7.2 Hz), 6.45 (1H, d, J=0.7 Hz), 6.21 (1H, s), 3.73 (3H, s); ^{13}C NMR (75 MHz; DMSO-d_6) δ 184.5 (s), 168.3 (s), 138.4 (s), 136.5 (s), 133.8 (s), 130.9 (s), 127.5 (s), 126.7 (s), 126.3 (d), 122.9 (d), 121.2 (d), 120.6 (d), 119.8 (d), 119.0 (d), 112.8 (d), 111.5 (d), 111.4 (d), 102.0 (d), 53.5 (d), 52.7 (q). MS ESI m/z $[M+1]^+$ 333, $[M-1]^-$ 331. Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.3; H, 4.85; N, 8.4. Found C, 72.2; H, 4.9; N, 8.4.

4.2.2. 2-[3-(1*H*-Indole-2-carbonyl)-1*H*-indol-2-yl]-3-(1*H*-indol-2-yl)-3-oxo-propionic acid methyl ester (9). Yellow solid. Recrystallized from CH_2Cl_2/*c*-hexane. Mp 130 °C dec.; IR (KBr) 3382, 3061, 2951, 1738, 1646, 1619, 1591, 1521, 1438, 1342, 1174, 1138, 745 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) δ 12.23 (1H, s), 12.00 (1H, s), 11.98 (1H, s), 7.70–7.58 (4H, m), 7.53–7.44 (3H, m), 7.33–7.27 (2H, m), 7.21 (1H, dd, J=7.7, 7.2 Hz), 7.12–7.04 (4H, m), 6.69 (1H, s), 3.75 (3H, s); ^{13}C NMR (75 MHz; DMSO-d_6) δ 183.9 (s), 182.3 (s), 167.7 (s), 138.5 (s), 137.6 (s), 136.8 (s), 136.0 (s), 136.0 (s), 133.8 (s), 126,8 (s), 126.7 (s), 126.4 (d), 125.4 (s), 125.1 (d), 122.9 (d), 122.6 (d), 123.0 (d), 120.6 (2×d), 120.3 (d), 120.1 (d), 114.4 (s), 112.8 (d), 112.6 (d), 112.5 (d), 111.3 (d), 109.9 (d), 52.9 (q), 52.3 (d); MS ESI m/z $[M+1]^+$ 476; FABHRMS Calcd for $C_{29}H_{22}N_3O_4$ 476.1610 $[M+H]^+$ found 476.1608.

4.2.3. [3-(1*H*-Indole-2-carbonyl)-1*H*-indol-2-yl]acetic acid methyl ester (5). Yellow solid. Mp 171 °C dec. (EtOAc/heptane); IR (KBr) 3313, 3175, 1720, 1597, 1435, 1342, 749 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) δ 12.05 (1H, s), 11.84 (1H, s), 7.72 (1H, d, J=7.9 Hz), 7.50–7.47 (2H, m), 7.27 (1H, dd, J=8.0, 7.2 Hz), 7.20 (1H, dd, J=8.0, 7.1 Hz), 7.13–7.04 (2H, m), 7.02 (1H, d, J=1.2 Hz), 4.08 (2H, s), 3.62 (3H, s); ^{13}C NMR (75 MHz; DMSO-d_6) δ 182.1 (s), 169.7 (s), 138.1 (s), 137.4 (s), 136.9 (s), 135.1 (s), 126.8 (s), 126.1 (s), 124.7 (d), 122.4 (d), 122.2 (d), 120.8 (d), 120.1 (d), 120.0 (d), 114.0 (s), 112.5 (d), 111.7 (d), 109.4 (d), 51.9 (q), 33.1 (t); MS ESI m/z $[M-1]^-$ 331. Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.3; H, 4.85; N, 8.4. Found C, 72.1; H, 5.0; N, 8.2.

4.2.4. 6,11-Dihydro-6-oxo-5*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindole-12-carboxylic acid methyl ester. (Caulersin) (3). Solid chloromethylenemorpholinium chloride (427 mg, 2.51 mmol) was added to a suspension of [3-(1*H*-indole-2-carbonyl)-1*H*-indol-2-yl]acetic acid methyl ester (**5**) (278 mg, 0.84 mmol) in dry dichloroethane (20 mL) at 21 °C under nitrogen. The resulting suspension was stirred for 30 min at 30–35 °C, then heated at 50 °C for 4 h and finally at 60 °C for 90 min. The solvent was removed under reduced pressure at 50 °C and the resulting dark red solid suspended in a mixture of DMSO (12 mL) and water (2 mL). The suspension was stirred at 50 °C for 14 h and then poured out on water/brine (1:1, 150 mL). The resulting brown precipitate was collected and washed with water, and then EtOAc until an almost clear filtrate was obtained. The solid was dried at 55 °C/0.35 mbar to give caulersin (**3**) (202 mg, 70%) as an orange powder. This sample changes color to golden crystals at 275–280 °C and melts at 352–355 °C. (lit.[3] mp 269–270 °C, lit.[4] mp 273–274 °C); IR (KBr) 3320, 3169, 1689, 1534, 1496, 1422, 1267, 1241 cm^{-1}; after sublimation; IR (KBr) 3348, 3241, 1667, 1540, 1492, 1418, 1270, 1240 cm^{-1}; for atom numbering

see Fig. 2. ^{1}H NMR (500 MHz; DMSO-d_6) δ 13.10 (1H, s, N*H*, N-1), 12.36 (1H, s, N*H*, N-18), 9.14 (1H, s, C*H*, C-21), 9.06 (1H, d, C*H*, C-13, J=8.2 Hz), 8.36 (1H, d, C*H*, C-6, J=7.8 Hz), 7.95 (1H, d, C*H*, C-16, J=7.8 Hz), 7.77 (1H, d, C*H*, C-3, J=7.8 Hz), 7.57 (1H, dd, C*H*, C-4, J=7.8, 7.4 Hz), 7.51 (1H, dd, C*H*, C-15, J=7.8, 6.9 Hz), 7.43 (1H, dd, C*H*, C-5, J=7.8, 7.3 Hz), 7.40 (1H, dd, C*H*, C-14, J=7.8, 7.4 Hz), 4.09 (3H, –OCH_3, C-23, s); ^{13}C NMR (125 MHz; DMSO-d_6) δ 172.4 (s, C-10), 168.0 (s, C-22), 140.9 (s, C-9), 138.6 (s, C-19), 136.9 (s, C-2), 136.4 (s, C-17), 129.7 (d, C-21), 126.9 (s, C-7), 126.7 (d, C-4), 126.1 (s, C-12), 125.8 (d, C-15), 123.5 (d, C-13), 122.0 (d, C-5), 121.7 (d, C-14), 120.3 (d, C-6), 119.3 (s, C-11), 114.6 (s, C-20), 114.4 (s, C-8), 113.2 (d, C-3), 112.4 (d, C-16), 53.0 (q, C-23); MS ESI m/z [M+1]$^+$ 343. Calcd for $C_{21}H_{14}N_2O_3$, C, 73.7; H, 4.1; N, 8.2. Found C, 73.8; H, 4.0; N, 8.1.

The NMR data of **3** after being heated up to its melting point was identical with the data given above.

4.2.5. Data of Caulersin (3) obtained via Scheme 4. Yellow solid prepared with the method of Fresneda.[25] Mp 349.0–352.5 °C; IR (neat) 3347, 3231, 1667, 1540, 1490, 1417, 1269, 1240 cm^{-1}; ^{1}H NMR (500 MHz; DMSO-d_6) δ 13.10 (1H, s), 12.36 (1H, s), 9.15 (1H, s), 9.06 (1H, d, J=8.2 Hz), 8.36 (1H, d, J=8.2 Hz), 7.95 (1H, d, J=7.8 Hz), 7.77 (1H, d, J=7.8 Hz), 7.58 (1H, dd, J=7.8, 7.4 Hz), 7.51 (1H, dd, J=7.8, 7.4 Hz), 7.44 (1H, dd, J=7.8, 7.4 Hz), 7.40 (1H, dd, J=7.8, 7.4 Hz), 4.09 (3H, s); ^{13}C NMR (125 MHz; DMSO-d_6) δ 172.4 (s), 168.0 (s), 140.9 (s), 138.6 (s), 136.8 (s), 136.4 (s), 129.7 (d), 126.9 (s), 126.7 (d), 126.1 (s), 125.8 (d), 123.5 (d), 122.0 (d), 121.7 (d), 120.3 (d), 119.3 (s), 114.6 (s), 114.3 (s), 113.2 (d), 112.3 (d), 53.0 (q);

4.2.6. Compound 10b. An aliquot from the reaction between **5** and chloromethylenemorpholinium chloride was withdrawn from reaction mixture (before removal of solvent) and quickly filtered under nitrogen, washed with small amounts of dry dichloroethane. The NMR-sample was prepared immediately before the spectrum was recorded. ^{1}H NMR (300 MHz; DMSO-d_6) δ 14.41 (1H, bs), 14.03 (1H, bs), 10.12 (1H, s), 9.40 (1H, d, J=8.3 Hz), 8.88 (1H, d, J=8.0 Hz), 8.35 (1H, d, J=8.1 Hz), 8.14–7.96 (3H, m), 7.82–7.73 (2H, m), 4.45 (3H, s).

4.2.7. 5,11,12,13-Tetrahydro-11-(methoxymethyl)-6*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindol-6-one (13). *t*-BuOK (1.95 g, 16.53 mmol) in *t*-BuOH (50 mL) was added to a solution of **11** (1.69 g, 4.13 mmol) in anhydrous benzene (80 mL) under a flow of nitrogen. The solution was heated at reflux for 1.5 h, when additional *t*-BuOK (2.2 g, 18.65 mmol) was added and the reflux was continued for another hour. After cooling the reaction mixture was washed with saturated NH_4Cl (50 mL) and then extracted with EtOAc (3×50 mL). The combined organic phases were washed with water (50 mL) then brine (75 mL) before drying over $MgSO_4$. The solvents were evaporated to give a yellow solid, which was recrystallized from dichloroethane/heptane to give **13** as golden crystals (1.69 g, 81%). Mp 214–216 °C; IR (KBr) 3283, 3059, 2928, 2823, 1564, 1460, 1419, 1228, 1102, 1047, 747 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 9.31 (1H, s), 8.67–8.64 (1H, m), 7.71 (1H, d, J=8.1 Hz), 7.51–7.45 (2H, m), 7.38–7.32 (3H, m), 7.18 (1H, t, J=7.5 Hz), 5.63 (2H, s), 3.47–3.43 (2H, m), 3.37–3.33 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 179.7 (s), 148.0 (s), 137.2 (s), 136.3 (s), 134.2 (s), 127.6 (s), 127.5 (s), 125.9 (d), 123.8 (d), 123.3 (d), 123.0 (d), 120.8 (d), 120.2 (d), 119.9 (s), 116.1 (s), 112.3 (d), 109.5 (d), 74.2 (t), 56.4 (q), 25.3 (t), 22.0 (t); MS ESI m/z [M+1]$^+$ 331. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.3; H, 5.5; N, 8.5. Found C, 76.2; H, 5.4; N, 8.6.

4.2.8. 6,11-Dihydro-11-(methoxymethyl)-6-oxo-5*H*-Cyclohepta[1,2-*b*:4,5-*b*′]diindole (14). DDQ (0.666 g, 2.94 mmol) was added portionwise to a suspension of **13** (0.485 g, 1.47 mmol) in benzene (30 mL) at 21 °C. The resulting suspension was heated at reflux for 80 min, then cooled to 21 °C and treated with 0.4 M KOH (250 mL), and extracted with EtOAc (3×100 mL). The combined organic phases were washed with water (2×100 mL), then brine (2×100 mL), and dried over $MgSO_4$. Concentration of the solvents to dryness followed by crystallization from dichloroethane afforded **14** (362 mg, 75%) in two crops as a light yellow-greenish solid. Mp 251.5–254.0 °C dec.; IR (KBr) 3287, 3053, 2996, 2900, 1616, 1599, 1577, 1527, 1505, 1415, 1323, 1234, 1113, 1055, 910, 887, 760, 738, 711 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 12.65 (1H, s), 9.11 (1H, d, J=7.8 Hz), 8.41–8.35 (2H, m), 7.95 (1H, d, J=8.2 Hz), 7.82 (1H, d, J=11.4 Hz), 7.73 (1H, d, J=8.2 Hz), 7.60–7.50 (2H, m), 7.44 (1H, dd, J=7.5, 7.4 Hz), 7.36 (1H, dd, J=7.7, 7.3 Hz), 6.05 (2H, s), 3.30 (3H, s); ^{13}C NMR (75 MHz; DMSO-d_6) δ 172.8 (s), 142.2 (s), 139.6 (s), 138.2 (s), 136.8 (s), 126.5 (d), 126.2 (s), 126.0 (s), 126.0 (d), 125.0 (d), 123.8 (d), 122.1 (d), 120.9 (d), 120.8 (d), 119.2 (s), 117.3 (s), 112.8 (d), 112.6 (d), 110.0 (d), 73.6 (t), 55.6 (q); MS ESI m/z [M+1]$^+$ 329 [M−1]$^-$ 327. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.8; H, 4.9; N, 8.5. Found C, 76.7; H, 4.85; N, 8.4.

4.2.9. 6,11-Dihydro-6-oxo-5*H*-cyclohepta[1,2-*b*:4,5-*b*′]-diindole (15). The bisindole **14** (164 mg, 0.50 mmol) was suspended in EtOH (15 mL) and 6 M HCl (10 mL) and heated at reflux for 8.5 h. Upon cooling to 21 °C a yellow solid precipitated. The reaction mixture was diluted with water (175 mL) and then filtered. The precipitate filtered off and washed with an excess of water. The solid was recrystallized from EtOAc to give the bisindolotropolone **15** (117 mg, 82%) in two crops as a yellow powder. Mp 398.5 °C (dec.) IR (KBr) 3252, 1756, 1598, 1558, 1514, 1408, 1216, 740, 707 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 12.54 (1H, s), 12.45 (1H, s), 8.99 (1H, s, J=7.9 Hz), 8.32–8.26 (2H, m), 7.72 (1H, d, J=8.2 Hz), 7.62 (1H, d, J=8.6 Hz), 7.59 (1H, d, J=11.1 Hz), 7.52–7.47 (2H, m), 7.40–7.31 (2H, m); ^{13}C NMR (75 MHz; DMSO-d_6) δ 172.9 (s), 142.6 (s), 139.2 (s), 136.6 (s), 136.5 (s), 126.8 (s), 126.3 (s), 126.1 (d), 125.4 (d), 124.4 (d), 123.5 (d), 121.2 (d), 120.7 (d), 120.6 (d), 117.9 (s), 116.8 (s), 115.0 (d), 112.7 (d), 111.0 (d); MS ESI m/z [M+1]$^+$ 285, [M−1]$^-$ 283. Anal. Calcd for $C_{19}H_{12}N_2O$: C, 80.3; H, 4.25; N, 9.85. Found C, 80.35; H, 4.3; N, 9.7.

4.2.10. 4-[2-[[2-Chloro-1-(methoxymethyl)-1*H*-indol-3-yl]carbonyl]-1*H*-indol-3-yl]-2-butanone (11). Methyl vinylketone (1.32 g, 18.8 mmol) in $MeNO_2$ (15 mL) was added at 21 °C to a suspension of [2-chloro-1-(methoxymethyl)-1*H*-indole-3-yl]-1*H*-indol-2-yl methanone[4] (2.12 g,

6.26 mmol) in $MeNO_2$ (40 mL) under nitrogen. The suspension was cooled to −20 °C and $BF_3{\cdot}OEt_2$ (87 mg, 0.61 mmol) in EtOH (1.0 mL) was added dropwise. The reaction temperature was then allowed to rise to 0 °C and kept at this temperature for 3 h, before further 92 mg of $BF_3{\cdot}OEt_2$ in EtOH (0.5 mL) was added. After 15 h at 0 °C more methyl vinylketone (960 mg) in $MeNO_2$ (1 mL) was added followed by $BF_3{\cdot}OEt_2$ (140 mg) in EtOH (0.3 mL). After 2 h, a saturated solution of $NaHCO_3$ (100 mL) was added, followed by extraction with CH_2Cl_2 (4×50 mL). The combined organic phases were washed with water (100 mL), then brine (100 mL), and dried over $MgSO_4$. Evaporation produced a reddish residue that was subjected to column chromatography (eluent Et_2O/hexane, 8:2) to give 5-nitro-2-pentanone (200 mg) and the bisindole **11** (1.69 g, 66%) identical with the product previously reported.[4]

4.2.11. 5-Nitro-2-pentanone.[24] ^{1}H NMR (300 MHz; $CDCl_3$) δ 4.41 (2H, t, J=6.6 Hz), 2.58 (2H, d, J=6.8 Hz), 2.21 (2H, m), 2.14 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 206.6 (s), 74.7 (t), 39.4 (t), 30.1 (q), 21.2 (t)

4.2.12. 12-Acetyl-5,11,12,13-tetrahydro-11-(methoxymethyl)-6*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindol-6-one (12). *t*-BuOK (412 mg, 3.67 mmol) in *t*-BuOH (35 mL) was added to a solution of **11** (600 mg, 1.47 mmol) in benzene (50 mL) at 21 °C. The mixture was then heated at reflux for 70 min and then cooled (10 °C) and poured into saturated aqueous NH_4Cl (25 mL) and water (50 mL). The phases were extracted with EtOAc (3×50 mL) and the combined organic phases were dried over $MgSO_4$, and then evaporated to give a yellow solid. Titruation with Et_2O produced **12** (511 mg) as yellow crystals, with benzene inclined in the crystals in a ratio 1.00:0.39 as determined by ^{1} H NMR spectroscopy. Conventional drying of the solid failed to remove the benzene. The etheral phases were concentrated to 10 mL and stirred for 1 h at 21 °C to give another crop of **12** (30 mg), free of benzene. In total 502 mg (92%) (without benzene) was obtained of the diindolyl ketone **12**. Crystallization from CH_2Cl_2/hexane produced crystals with identical spectroscopic characteristics as with those reported previously.[4]

4.2.13. 12-Acetyl-5,11-dihydro-11-(methoxymethyl)-6*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindol-6-one (16). DDQ (366 mg, 1.61 mmol) was added in one portion to a suspension of **12** (300 mg, 0.81 mmol) in benzene (125 mL) at 21 °C. The mixture was refluxed for 90 min and then additional DDQ (180 mg) was added. The reflux was continued for 4.5 h and then allowed to cool to 21 °C. 1 M NaOH (200 mL) and EtOAc (100 mL) was added to the solution. The organic solvents were separated and the aqueous phase extracted with EtOAc (2×50 mL). Drying of the organic solvents over $MgSO_4$ and removal of the solvents with evaporation produced a yellow solid. This solid was boiled in Et_2O (60 mL), filtered and then dried to give the yellow bisindole **16** (186 mg). The filtrate was then evaporated and the remaining solid crystallized from EtOAc/heptane to produce more of **16** (16 mg). The total yield of **16** was 202 mg (68%). Mp 225–230 °C; IR (KBr) 3426, 3249, 2926, 1663, 1577, 1550, 1416, 1245, 1089, 746 cm^{-1}; ^{1}H NMR (300 MHz; acetone-d_6) δ 11.91 (1H, s), 9.19 (1H, d, J=8.0 Hz), 8.69 (1H, s), 8.42 (1H, d, J=8.0 Hz), 7.86 (1H, d, J=8.2 Hz), 7.80 (1H, d, J=8.3 Hz), 7.60–7.54 (2H, m), 7.46–7.40 (2H, m), 5.75 (2H, s), 2.96 (3H, s), 2.90 (3H, s); ^{13}C NMR (75 MHz; acetone-d_6) δ 200.4 (s), 174.5 (s), 141.6 (s), 139.6 (s), 139.3 (s), 138.1 (s), 130.6 (s), 128.3 (s), 127.8 (d), 127.6 (s), 127.1 (d), 126.7 (d), 125.1 (d), 123.8 (s), 123.4 (d), 122.7 (d), 121.7 (d), 116.1 (s), 113.9 (d), 111.5 (d), 78.5 (t), 55.9 (q), 29.0 (q); MS ESI m/z $[M+1]^+$ 371, $[M-1]^-$ 369.

4.2.14. 11-(Methoxymethyl)-6-oxo-5*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindole-12-carboxylic acid methyl ester (17). Yellow solid prepared with the method of Fresneda.[25] Mp 246.5–250.5 °C, (lit.[4,25] mp 255–256 °C); IR (neat) 1705, 1579, 1245 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 12.14 (1H, s), 9.40 (1H, d, J=7.8 Hz), 8.08 (1H, s), 8.23 (1H, d, J=7.9 Hz), 7.81 (1H, d, J=8.1 Hz), 7.96–7.59 (2H, m), 7.55–7.49 (2H, m), 7.42 (1H, dd, J=7.6, 7.3 Hz), 5.78 (2H, s), 4.07 (3H, s), 2.96 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 174.2 (s), 169.4 (s), 141.4 (s), 139.9 (s), 138.6 (s), 137.3 (s), 129.6 (d), 127.4 (d), 127.4 (s), 127.0 (s), 126.3 (d), 125.0 (d), 123. 4 (d), 122.3 (d), 120.7 (d), 119.2 (s), 116.4 (s), 113.3 (d), 110.9 (d), 78.5 (t), 56.2 (q), 53.3 (q); MS ESI m/z $[M+1]^+$ 387, $[M-1]^-$ 385.

4.3. X-ray crystallography study

CCDC reference number 210210. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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N-Phosphano nitrogen-containing five-membered aromatic chiral α-sulfoxides as new chiral ligands in asymmetric palladium-catalyzed allylic alkylation: stereoelectronic effects of the substituents on the aromatic rings

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Abstract—New chiral ligands, *N*-diphenylphosphano nitrogen-containing five-membered aromatic compounds bearing chiral sulfinyl groups as the sole chiral source has been developed. The structure of a palladium intermediate derived from the new chiral sulfoxide ligand was determined as a palladium complex with a five-membered chelate ring formed by coordination of the phosphano group and the sulfinyl sulfur atom involved. The stereoelectronic effects of substituents on the aromatic rings are discussed.

1. Introduction

Catalytic asymmetric synthesis has attracted much attention in recent years for the efficient preparation of optically active compounds,[1] particularly for a facile entry to chiral biologically active compounds and chiral pharmaceuticals. A number of asymmetric synthetic methodologies for carbon–carbon bond formation have been developed,[2] and various types of chiral ligands for the catalytic asymmetric synthesis have been devised so far, by utilizing chiral amines, amides, alcohols, phophines, biaryls with axial chirality, and so on.[3] However, hitherto few precedents of chiral sulfoxide ligands have appeared.[4]

Quite recently, we have developed novel several chiral sulfoxide ligands which are useful for transition metal-catalyzed asymmetric carbon–carbon bond formation.[5]

For further development of new chiral ligands possessing chiral sulfinyl groups as sole chiral sources, we have utilized phosphanoamino groups as other coordination sites besides chiral sulfinyl groups. In these cases, the formation of several chelates **1a**–**d** will be possible by coordination of nitrogen or phosphano groups in the phosphanoamines and sulfur or oxygen atoms in the chiral sulfoxides to metal catalysts. In the protocol of our plan, we employed pyrrole or indole skeletons as main frameworks of ligands for the conformational fixation, in which chiral sulfinyl groups were incorporated at the 2 or 7 positions, resultantly providing five- or six-membered chelates **2** and **3** by coordination of phosphano groups. We will discuss sterically and, or electronically the effects of substituents introduced on the skeletons (Scheme 1).

On these lines, we have developed novel chiral sulfoxide ligands consisting of *N*-phosphano nitrogen-containing five-membered aromatics, and demonstrate the usefulness of the ligands in terms of reactivity of the catalysts with the ligands and the resultant enantioselectivity.

2. Results and discussion

2.1. Synthesis of chiral pyrrolyl and indolyl sulfoxide ligands

Novel chiral *N*-phosphanopyrrolyl and -indolyl aryl sulfoxides were prepared as follows. α-Sulfinylation of *N*-*t*-butoxycarbonylpyrroles **4a**,**b**[6] and indoles **8a**–**d** with (−)-menthyl (*S*)-*p*-toluene-, 1-naphthalene-,[7] or 2-methoxy-1-naphthalenesulfinates[8] (**5a**–**c**) was carried out at −78 °C in THF for 24 h using lithium diisopropylamide to give the corresponding α-sulfinylated pyrroles (*S*)-**6a**–**d**

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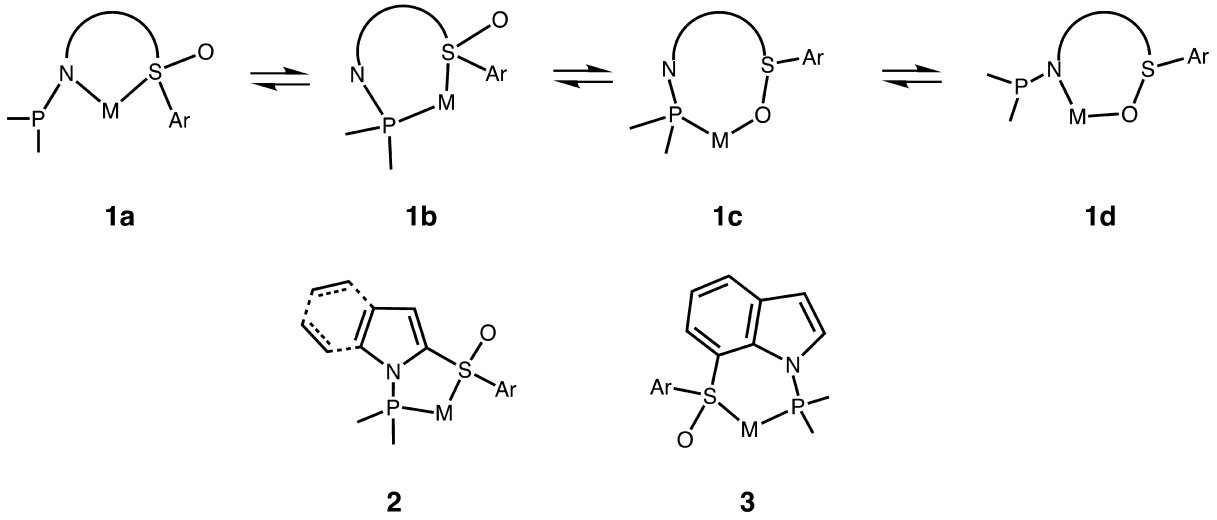


Scheme 1.

and indoles (*S*)-**9a**–**e**. Upon treatment with *n*-butyllithium followed by the reaction with chlorodiphenylphosphane, (*S*)-**6a**–**d** and (*S*)-**9a**–**e** were converted into (*S*)-**7a**–**d** and (*S*)-**10a**–**e**, respectively.

Sulfinylation of 7-bromoindole (**11**)[9] (derived from 2-bromonitrobenzene upon treatment with vinylmagnesium bromide) with (*Ss*)-**5c** using *n*-butyllithium followed by *N*-phosphanation of (*R*)-**12** with chlorodiphenylphosphane gave (*R*)-**13** (Scheme 2).

2.2. Palladium-catalyzed asymmetric reactions with chiral sulfoxide ligands

The effects of the new chiral sulfoxide ligands thus obtained were studied in the palladium-catalyzed asymmetric alkylation of (±)-**14** with dimethyl malonate. The reactions of (±)-**14** with sodium dimethyl malonate (generated by treating with sodium hydride) were carried out in THF at −78 °C in the presence of [PdCl(π-allyl)]$_2$ (0.03 equiv.) and a chiral ligand (*S*)-**7a**–**c** (0.06 equiv.) to give (*S*)-**15** with moderate e.e. Incorporation of a methoxy group at the C_2 position of the naphthalene ring in the sulfoxide provided high enantioselectivity of (*S*)-**15**, presumably due to steric effects of the methoxy substituent. The highest e.e. (74 and 83%) of (*S*)-**15** was obtained with (*S*)-**7c** at −45 and −78 °C, respectively, although in a little lower chemical yield (Scheme 3).

The replacement of the pyrrole skeleton in (*S*)-**7** with an indolyl function ((*S*)-**10**) in the chiral sulfoxide ligands provided a similar stereochemical result. The reaction of (±)-**14** with sodium malonate in THF at 0, −20, or −45 °C using (*S*)-**10a** gave (*S*)-**15** with 56, 60, or 73% e.e., respectively, in high yield (81–92%); similarly the reaction in DME at the same temperature afforded (*S*)-**15** with 59, 65, or 73% e.e., respectively, in high yield (83–94%).

Unambiguous effects of electron-donating groups on the pyrrole and indole rings of the chiral ligands were observed, resulting in remarkable improvement of the reactivity of the catalysts with the ligands and the resultant enantioselectivity. Introduction of two methyl groups at the 3- and 5-positions of the pyrrole ring in (*S*)-**7c** improved dramatically the chemical yield and the e.e. of the products; the palladium-catalyzed reaction of (±)-**14** with sodium malonate using (*S*)-**7d** as a ligand in THF at −20, −45, or −78 °C for 2, 7, or 20 h gave (*S*)-**15** with 65, 80, or 83% e.e. in excellent yields (97 and 96%), respectively, although in a little lower chemical yield (32%) at −78 °C.

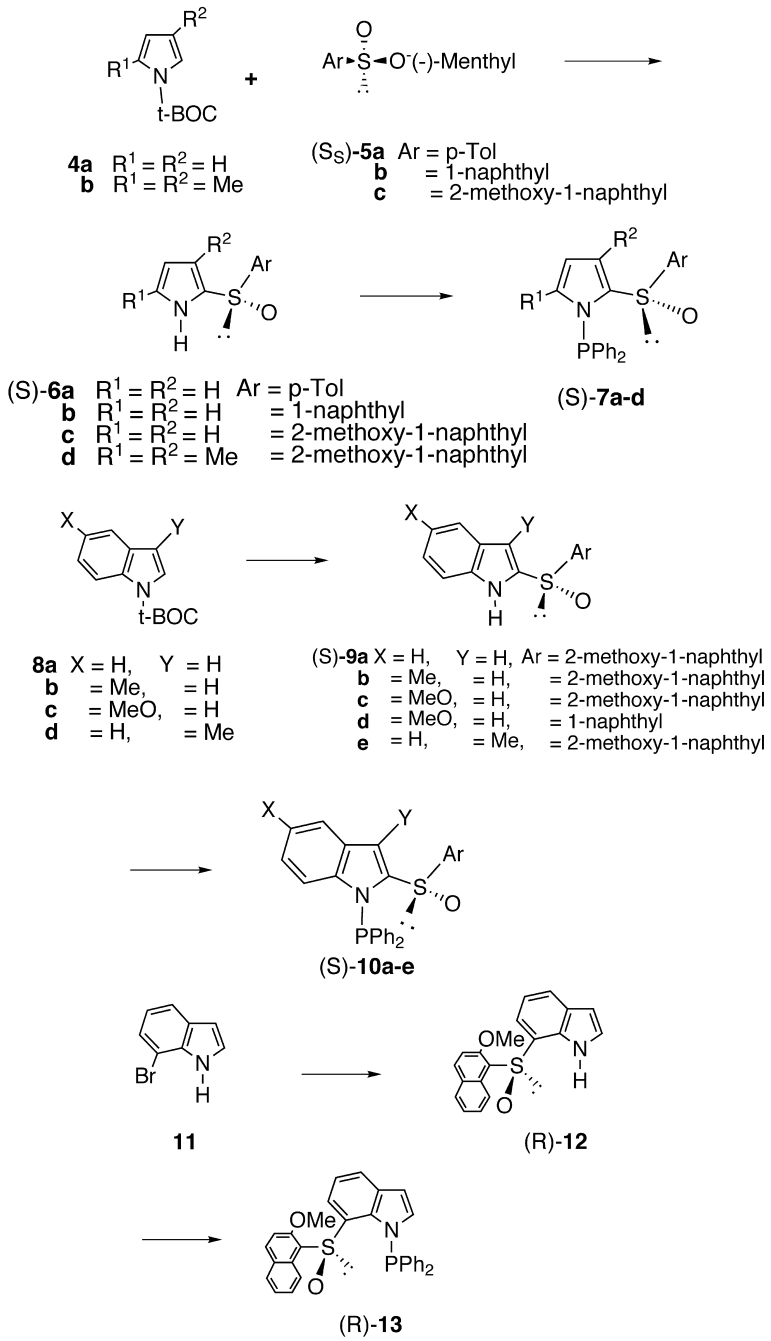
In the case of indole systems the substituents at the 5-positions of the indole rings in **10a**,**b** were marginally effective for the reactivity. Introduction of electron-donating groups (methoxy group) at the 5-positions of the indoles improved electronically the reactivity to provide slightly higher chemical yield (87–90%) with a little lower enantioselectivity, as shown in Table 1, in comparison with those by (*S*)-**10a**. Introduction of a methyl group at the C_5 position, however, was not so effective in achieving high efficiency in terms of the chemical yield and the enantioselectivity, providing a slightly lower chemical yield of (*S*)-**15** with slightly lower e.e.

Introduction of a methyl group at the 3-position of the indole ring ((*S*)-**10e**) provided the highest enantioselectivity (93%) of (*S*)-**15**, presumably owing to the steric control in the conformational equilibrium of the vicinal chiral sulfinyl group.

Interestingly, the existence of a methoxy group on the naphthalene ring in the sulfinyl groups of (*S*)-**10c** was also highly effective in achieving high enantioselectivity and chemical yield, in contrast with those by (*S*)-**10d**.

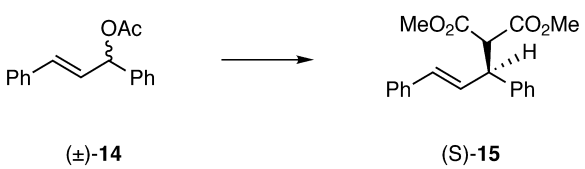
Use of another indolyl sulfoxide (*R*)-**13** as a ligand provided (*S*)-**15** in 76% yield with a slightly lower enantioselectivity, as listed in Table 1.

The molecular structure of the chiral sulfoxide ligand ((*S*)-**10a**)-palladium [$PdCl_2{\cdot}(CH_3CN)_2$] complex was determined as a five-membered chelate **16** formed by

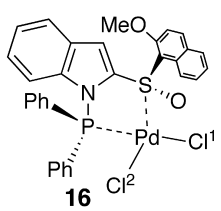


Scheme 2.

coordination of the sulfinyl sulfur atom and the phosphano group to the palladium catalyst, as shown in Figure 1, by the X-ray crystallographic analysis. In comparison with a palladium complex of (*S*)-2-(diphenylphosphano)phenyl 2-methoxy-1-naphthyl sulfoxide reported by us previously,[5f] the molecular structure indicates that the bond lengths



Scheme 3.



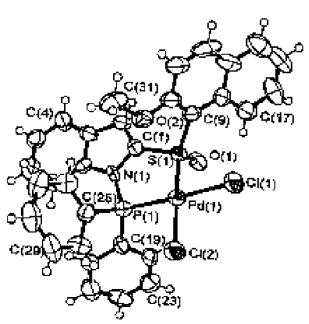


Figure 1. Crystallographic data (ORTEP drawing) for (S)-16. Selected bond distance (Å) and angles (deg): Pd(1)–S(1) 2.229(4), Pd(1)–P(1) 2.222(4), Pd(1)–Cl(1) 2.338(4) Pd(1)–Cl(2) 2.299(4), N(1)–P(1) 1.716(12), S(1)–C(1) 1.716(12) S(1)–Pd(1)–P(1) 88.85(14), S(1)–Pd(1)–Cl(1) 89.42(14).

Table 1. Palladium-catalyzed asymmetric alkylations of **14** using chiral ligands (*S*)-**7**, (*S*)-**10**, and (*R*)-**13**[a]

Ligand	Solvent	Reaction temp. (°C)	Reaction time (*h*)	Yield (%) of (*S*)-**15**	e.e. (%) of (*S*)-**15**[b]
(*S*)-**7a**	THF	0	3	76	17
	THF	−20	24	72	24
(*S*)-**7b**	THF	−20	8	89	29
(*S*)-**7c**	THF	0	1	70	45
	THF	−20	4	78	53
	THF	−40	8	40	74
	THF	−78	23	7	83
	DME	0	2	68	40
	DME	−20	7	53	55
(*S*)-**7d**	THF	−20	2	97	65
	THF	−45	7	96	80
	THF	−78	20	32	83
(*S*)-**10a**	THF	0	80	92	56
	THF	−20	4	92	60
	THF	−45	21	81	73
	DME	0	80	94	59
	DME	−20	4	91	65
	DME	−45	21	83	73
(*S*)-**10b**	THF	0	13	91	52
	THF	−20	13	81	55
	THF	−45	21	43	65
	DME	0	13	79	56
	DME	−20	13	72	61
	DME	−45	21	61	65
(*S*)-**10c**	THF	−20	2	90	57
	THF	−45	8	87	61
(*S*)-**10d**	THF	0	3	88	31
	THF	−20	14	57	32
	THF	−45	14	29	36
	DME	0	3	82	37
	DME	−20	14	45	36
	DME	−45	18	32	48
(*S*)-**10e**	THF	−20	10	93	74
	THF	−45	16	83	82
	THF	−78	24	68	93
(*R*)-**13**	THF	−20	2	93	32
	THF	−45	16	76	41

[a] The reactions of **14** with carbanion of dimethyl malonate (generated by treating with NaH (2.0 equiv.) were carried out in THF or DME in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and a chiral ligand (*S*)-**7**, (*S*)-**10**, or (*R*)-**13** (0.06 equiv.).
[b] The enantiomeric excess (e.e.) of (*S*)-**15** was determined by the HPLC analysis with Chiralpak AD.

between the nitrogen-phosphane and the sulfur-aromatic carbon atoms are slightly shorter, and the Pd–Cl[1] bond length is a little longer, compared with the Pd–Cl[2] bond, owing to the electronic (π-accepting) effects of the phosphorus atom; however, the bond angles between the Pd–P–N and the Pd–S–C are very similar to those in the 2-(diphenylphosphano)phenyl sulfoxide–palladium complex.

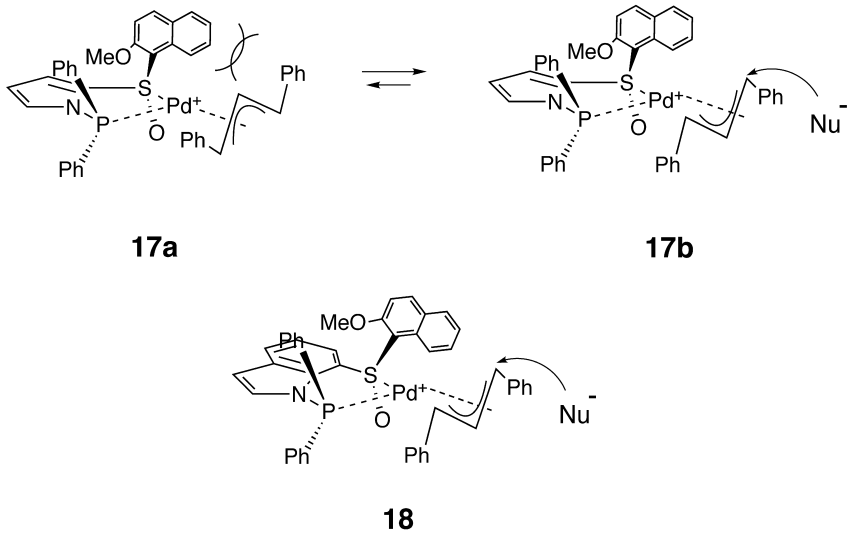
2.3. The mechanism for the asymmetric induction with chiral *N*-phosphano pyrrolyl and indolyl sulfoxides as chiral ligands

The mechanism of the asymmetric induction in these asymmetric alkylations with new chiral ligands is rationalized on the basis of the stereochemical results and the molecular structure of the intermediary palladium complex as follows. In the conformational equilibrium of π-allylpalladium complexes derived from the intermediary palladium-chiral ligand complexes, an M-typed π-allyl intermediate **17b** is sterically preferred to W-typed **17a** because of the existence of steric interference between the aryl substituent on the sulfinyl group and the phenyl of the γ-allyl system in **17a**. The nucleophile (the carbanion of dimethyl malonate) attacks the γ-carbon in the allyl terminus of **17b** *trans* to the better π-accepting atom, which is the phosphano group in the present case, giving (*S*)-**15**. The remarkable increase in enantioselectivity by the 2-methoxy-1-naphthyl sulfoxide (*S*)-**7c** and (*S*)-**10c** over that by (*S*)-**7b** and (*S*)-**10d** is rationalized presumably by the planar fixation of the conformation of the aromatic carbon–sulfur bond in the intermediate ascribed to the dipole–dipole repulsion between the sulfinyl S–O bond and the methoxy group.

A six-membered palladium complex **18** formed by coordination of the sulfinyl sulfur atom and the phosphano group in (*R*)-**13** provided slightly lower enantioselectivity in the allylic alkylations, presumably due to the less effective steric environment involved in the complex (Scheme 4).

3. Conclusion

Thus, evidently it should be concluded that these novel chiral sulfoxide ligands developed by us are very useful as chiral ligands in palladium-catalyzed asymmetric



Scheme 4.

alkylation, and the introduction of the electron-donating substituents on the aromatic rings enables us to improve remarkably the reactivity of the intermediary complexes and the enantioselectivity by the stereoelectronic effects. Our present work is one of the most useful asymmetric synthetic methods with high efficiency using chiral sulfoxides as the sole chiral sources in the ligands, involving studies on the stereoelectronic effects of the substituents on the pyrrole and indole skeletons and the structural determination of an intermediary palladium complex with a chiral β-phosphano sulfoxide.

4. Experimental

4.1. General

Infrared (IR) spectra were obtained in the indicated state with a JASCO DR-81 Fourier-Transform IR spectrometer. NMR spectra were determined in the indicated solvent with a JOEL EX-270 (^{1}H NMR; 270 MHz) high-resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s, singlet; d, doublet; dd, doublet of doublets; m, multiplet. Mass spectra were taken on a JOEL JMS-DX 303/JMA-DA 5000 system. High performance liquid chromatography (HPLC) was performed with a Tosoh UV-8010 CCPM (column: Dicel Chiralpak AD (hexane/*i*-PrOH 20:1), 0.5 ml/min, 254 nm). Optical rotations were measured at 24 °C with a JASCO DIP-370 polarimeter. X-ray diffraction analysis was carried out on a Rigaku RAXIS-IV diffractometer. Flash column chromatography was performed with Merck Silica gel 60 (230–400 mesh). Thin layer or thick layer plates (preparative TLC) were made of Merck Silica gel 60PF-254 activated by drying at 140 °C for 3.5 h.

4.1.1. (*S*)-2-Pyrrolyl *p*-tolyl sulfoxide (6a). A 100 ml two-necked flask equipped with a septum inlet and magnetic stirring bar was flushed with argon, and maintained under a positive pressure of argon. A solution of diisopropylamine (607 mg, 6.0 mmol) in THF (10 ml) was added to the flask. A 1.56 M butyllithium solution in hexane (4.0 ml, 6.0 mmol) was added to the above solution at −78 °C and the mixture was stirred at the same temperature for 30 min. A solution of *tert*-butyl 1-pyrrolecarboxylate (**4a**) (1.0 g, 6.0 mmol) in THF (5 ml) was added to the above solution. After the mixture had been stirred at −78 °C for 1.5 h, a solution of (−)-menthyl (*S*)-*p*-toluenesulfinate (**5a**) (883 mg, 3.0 mmol) in THF (10 ml) was added and the reaction mixture was further stirred at −78 °C for 24 h.

The reaction solution was diluted with ether, quenched with a saturated aqueous NH_4Cl, and washed with a saturated aqueous NaCl. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual oil was subjected to flash column chromatography (ethyl acetate–hexane 1:1) to give (*S*)-**6a** (369 mg, 60% yield).[6]

The sulfinylations of *tert*-butyl 2,4-dimethyl-1-pyrrolecarboxylate (**4b**), *tert*-butyl 1-indolecarboxylate (**8a**), *tert*-butyl 5-methyl-1-indolecarboxylate (**8b**), *tert*-butyl 5-methoxy-1-indolecarboxylate (**8c**), *tert*-butyl 3-methyl-1-indolecarboxylate (**8d**) with (*Ss*)-**5a**, (−)-menthyl (*S*)-1-naphthalenesulfinate (**5b**) or (−)-menthyl (*S*)-2-methoxy-1-naphthalenesulfinate (**5c**) were carried out in the same way as described above to give (*S*)-2-pyrrolyl 1-naphthyl sulfoxide (**6b**), (*S*)-2-pyrrolyl 2-methoxy-1-naphthyl sulfoxide (**6c**), (*S*)-3,5-dimethyl-2-pyrrolyl 2-methoxy-1-naphthyl sulfoxide (**6d**), (*S*)-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**9a**), (*S*)-5-methyl-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**9b**), (*S*)-5-methoxy-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**9c**), (*S*)-5-methoxy-2-indolyl 1-naphthyl sulfoxide (**9d**), and (*S*)-3-methyl-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**9e**), respectively.

4.1.2. Compound (*S*)-6b. Yield 47%. $[\alpha]_D$ +472.4° (c=0.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3227, 3020, 1418, (pyrrole), 1016 (sulfoxide). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.16–6.19 (1H, m, Ar-H), 6.65–6.68 (1H, m, Ar-H), 6.82–6.86 (1H, m, Ar-H), 7.45–8.01 (6H, m, Ar-H), 8.35 (1H, dd, J=1.2,

6.1 Hz, Ar-H), 8.92 (1H, s, NH). MS *m/z* 241 (M^+). Exact mass determination: 241.0558 (calcd for $C_{14}H_{11}NOS$: 241.0561).

4.1.3. Compound (*S*)-6c. Yield 37%. $[\alpha]_D$ +86.5° (*c*=2.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3447, 3018, 1431, (pyrrole), 1026 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 4.07 (3H, s, $-OCH_3$), 6.15–6.18 (1H, m, Ar-H), 6.39–6.42 (1H, m, Ar-H), 6.94–6.97 (1H, m, Ar-H), 7.25–7.57 (3H, m, Ar-H), 7.79–7.98 (2H, m, Ar-H), 8.80 (1H, dd, *J*=0.9, 7.7 Hz, Ar-H), 9.95 (1H, s, NH). MS *m/z* 271 (M^+). Exact mass determination: 271.0693 (calcd for $C_{15}H_{13}NO_2S$: 271.1669).

4.1.4. Compound (*S*)-6d. Yield 29%. $[\alpha]_D$ +46.1° (*c*=1.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3443, 3018, 1431, (pyrrole), 1022 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.18 (3H, s, CH_3), 2.25 (3H, s, CH_3), 4.14 (3H, s, $-OCH_3$), 5.72 (1H, d, *J*=2.8 Hz, Ar-H), 7.31–7.95 (5H, m, Ar-H), 8.77 (1H, dd, *J*=0.8, 7.7 Hz, Ar-H), 8.9 (1H, s, NH). MS *m/z* 299 (M^+). Exact mass determination: 299.0961 (calcd for $C_{20}H_{17}NO_2S$: 299.0980).

4.1.5. Compound (*S*)-9a. Yield 41%. $[\alpha]_D$ +245.2° (*c*=1.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3441, 3016, 1508, 1467 (indole), 1024 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 4.04 (3H, s, $-OCH_3$), 6.58 (1H, dd, *J*=0.9, 1.1 Hz, Ar-H), 7.04–7.63 (7H, m, Ar-H), 7.81–8.02 (2H, m, Ar-H), 8.78–8.81 (1H, m, Ar-H), 9.43 (1H, s, NH). MS *m/z* 321 (M^+). Exact mass determination: 321.0780 (calcd for $C_{19}H_{15}NO_2S$: 321.0824).

4.1.6. Compound (*S*)-9b. Yield 50%. $[\alpha]_D$ +40.3° (*c*=2.53, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3211, 3011, 2943, 1431 (indole), 1022 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.38 (3H, s, CH_3), 4.04 (3H, s, $-OCH_3$), 6.49–6.50 (1H, dd, *J*=0.8, 0.8 Hz, Ar-H), 7.06 (1H, d, *J*=1.2 Hz, Ar-H), 7.26–8.02 (7H, m, Ar-H), 8.80 (1H, d, *J*=1.2 Hz, Ar-H), 9.32 (1H, s, NH). MS *m/z* 335 (M^+). Exact mass determination: 335.0978 (calcd for $C_{20}H_{17}NO_2S$: 355.0980).

4.1.7. Compound (*S*)-9c. Yield 35%. $[\alpha]_D$ +149.5° (*c*=0.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3443, 3018, 1508, 1467 (indole), 1026 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.77 (3H, s, $-OCH_3$), 4.02 (3H, s, $-OCH_3$), 6.49 (1H, dd, *J*=0.8, 1.3 Hz, Ar-H), 6.85–6.94 (1H, m, Ar-H), 7.23–8.05 (7H, m, Ar-H), 8.78–8.81 (1H, m, Ar-H), 9.45 (1H, s, NH). MS *m/z*: 331 (M^+). Exact mass determination: 351.0957 (calcd for $C_{20}H_{17}NO_3S$: 351.0929).

4.1.8. Compound (*S*)-9d. Yield 65%. $[\alpha]_D$ +22.9° (*c*=2.09, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3011, 2856, 1508, 1448 (indole), 1020 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.78 (3H, s, $-OCH_3$), 6.84–6.89 (2H, m, Ar-H), 6.89–6.96 (1H, d, *J*=17.5 Hz, Ar-H), 7.15–7.19 (1H, d, *J*=8.9 Hz, Ar-H), 7.50–8.08 (6H, m, Ar-H), 8.35–8.38 (1H, dd, *J*=1.2, 1.2 Hz, Ar-H), 8.61 (1H, s, NH). MS *m/z*: 321 (M^+). Exact mass determination: 321.0820 (calcd for $C_{19}H_{15}NO_2S$: 321.0823).

4.1.9. Compound (*S*)-9e. Yield 4.6%. $[\alpha]_D$ +51.6° (*c*=0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1504, 1448 (indole), 1020 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.32 (3H, s, $-CH_3$), 4.05 (3H, s, $-OCH_3$), 7.05–7.62 (7H, m, Ar-H), 7.80 (1H, d, *J*=8.2 Hz, Ar-H), 7.98 (1H, d, *J*=9.0 Hz, Ar-H), 8.86 (1H, d, *J*=8.0 Hz, Ar-H), 9.11 (1H, s, NH). MS *m/z* 335 (M^+). Exact mass determination: 335.0961 (calcd for $C_{20}H_{17}NO_2S$: 335.0980).

4.1.10. (*S*)-*N*-(Diphenylphosphano)-2-pyrrolyl *p*-tolyl sulfoxide (7a). A 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar was flushed with argon, and maintained under a positive pressure of argon.

A solution of **6a** (369 mg, 1.80 mmol) in THF (10 ml) was added to the flask. A 1.56 M butyllithium solution in hexane (1.3 ml, 1.98 mmol) was added at −78 °C to the above solution and the mixture was stirred at the same temperature for 45 min. A solution of chlorodiphenylphosphane ($ClPPh_2$) (477 mg, 2.16 mmol) in THF (5 ml) was added to the above solution. After the mixture was stirred at the same temperature for 2 h, the reaction solution was diluted with ether and filtered through celite. The filtrate was concentrated in vacuo. The crude product was subjected to flash column chromatography (ethyl acetate–hexane 2:3) to give (*S*)-**7a** (48 mg, 64% yield).

The phosphanations of (*S*)-**6b**–**d**, (*S*)-**9a**–**d**, or (*R*)-**12** were carried out in the same way as described above to give (*S*)-*N*-(diphenylphosphano)-2-pyrrolyl 1-naphthyl sulfoxide (**7b**), (*S*)-*N*-(diphenylphosphano)-2-pyrrolyl 2-methoxy-1-naphthyl sulfoxide (**7c**), (*S*)-3,5-dimethyl-*N*-(diphenylphosphano)-2-pyrrolyl 2-methoxy-1-naphthyl sulfoxide (**7d**), (*S*)-*N*-(diphenylphosphano)-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**10a**), (*S*)-*N*-(diphenylphosphano)-5-methyl-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**10b**), (*S*)-*N*-(diphenylphosphano)-5-methoxy-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**10c**), (*S*)-*N*-(diphenylphosphano)-5-methoxy-2-indolyl 1-naphthyl sulfoxide (**10d**), (*S*)-*N*-(diphenylphosphano)-3-methyl-2-indolyl 2-methoxy-1-naphthyl sulfoxide (**10e**), and (*R*)-*N*-(diphenylphosphano)-7-indolyl 2-methoxy-1-naphthyl sulfoxide (**13**), respectively.

4.1.11. Compound (*S*)-7a. $[\alpha]_D$ +41.4° (*c*=1.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3460, 3053, 1435, (pyrrole), 1045 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.32 (3H, s, CH_3), 6.25–6.28 (1H, m, Ar-H), 6.53–6.56 (1H, m, Ar-H), 6.61–6.64 (1H, m, Ar-H), 7.09–7.51 (14H, m, Ar-H). MS *m/z* 389 (M^+). Exact mass determination: 389.1024 (calcd for $C_{23}H_{20}NOPS$: 389.1003).

4.1.12. Compound (*S*)-7b. Yield 61%. $[\alpha]_D$ +272.4° (*c*=0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3437, 3057, 1435, (pyrrole), 1043 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 6.11–6.16 (2H, m, Ar-H), 6.61–6.63 (1H, m, Ar-H), 7.16–7.70 (14H, m, Ar-H), 7.83 (1H, d, *J*=8.1 Hz, Ar-H), 7.92 (1H, d, *J*=8.1 Hz, Ar-H), 8.40 (1H, d, *J*=7.3 Hz, Ar-H). MS *m/z* 425 (M^+). Exact mass determination: 425.0986 (calcd for $C_{26}H_{20}NOPS$: 425.1003).

4.1.13. Compound (*S*)-7c. Yield 60%. $[\alpha]_D$ +79.7° (*c*=1.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3422, 3059, 1435, (pyrrole), 1026 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.74 (3H, s, $-OCH_3$), 6.23–6.26 (1H, m, Ar-H), 6.54–6.57 (1H, m, Ar-H), 6.61–6.64 (1H, m, Ar-H), 6.86–7.81 (15H, m, Ar-H), 9.08 (1H, d, *J*=8.7 Hz, Ar-H). MS *m/z* 455 (M^+).

Exact mass determination: 455.1138 (calcd for $C_{27}H_{22}NO_2PS$: 455.1109).

4.1.14. Compound (*S*)-7d. Yield 46%. $[\alpha]_D$ +118.9° (c=1.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3620, 3020, 1425, (pyrrole), 1032 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.18 (3H, s, CH_3), 2.23 (3H, s, CH_3), 3.71 (3H, s, $-OCH_3$), 5.90 (1H, s, Ar-H), 6.78–7.66 (15H, m, Ar-H), 9.28–9.31 (1H, m, Ar-H). MS m/z 483 (M^+). Exact mass determination: 483.1425 (calcd for $C_{29}H_{26}NO_2PS$: 483.1422).

4.1.15. Compound (*S*)-10a. Yield 59%. $[\alpha]_D$ +209.6° (c=0.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3439, 3009, 1508, 1467 (indole), 1026 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 4.01 (3H, s, $-OCH_3$), 6.57–8.02 (20H, m, Ar-H), 8.80 (1H, d, J=9.5 Hz, Ar-H). MS m/z 505 (M^+). Exact mass determination: 505.1302 (calcd for $C_{31}H_{24}NO_2PS$: 505.1266).

4.1.16. Compound (*S*)-10b. Yield 55%. $[\alpha]_D$ −55.6° (c=2.05, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3400, 3053, 2928, 1508, 1467 (indole), 1026 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.33 (3H, s, CH_3), 3.77 (3H, s, –OMe), 6.44–6.47 (1H, d, J=8.7 Hz, Ar-H), 6.62–7.70 (18H, m, Ar-H), 8.90 (1H, d, J=8.7 Hz, Ar-H). MS m/z 519 (M^+). Exact mass determination: 519.1411 (calcd for $C_{32}H_{26}NO_2PS$: 519.1422).

4.1.17. Compound (*S*)-10c. Yield 52%. $[\alpha]_D$ +244.6° (c=0.8, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3450, 3018, 1510, 1431 (indole), 1035 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.76 (3H, s, $-OCH_3$), 3.78 (3H, s, –OMe), 6.46 (2H, d, J=1.5 Hz, Ar-H), 6.64–7.70 (17H, m, Ar-H), 8.91–8.94 (1H, d, J=8.7 Hz, Ar-H). MS m/z 535 (M^+). Exact mass determination: 535.1380 (calcd for $C_{32}H_{26}NO_2PS$: 535.1371).

4.1.18. Compound (*S*)-10d. Yield 58%. $[\alpha]_D$ +104.65° (c=2.06, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3055, 3001, 2831, 1431 (indole), 1033 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.72 (3H, s, $-OCH_3$), 6.55–6.56 (1H, d, J=2.5 Hz, Ar-H), 6.62 (1H, d, J=0.5 Hz, Ar-H), 6.76 (1H, d, J=1.8 Hz, Ar-H), 6.94 (1H, d, J=2.1 Hz, Ar-H), 7.02–7.90 (16H, m, Ar-H), 8.12–8.15 (1H, d, J=8.4 Hz, Ar-H). MS m/z 505 (M^+). Exact mass determination: 505.1198 (calcd for $C_{31}H_{24}NO_2PS$: 505.1265).

4.1.19. Compound (*S*)-10e. Yield 17%. $[\alpha]_D$ +66.6° (c=1.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3177, 2959, 1506, 1450 (indole), 1020 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 2.29 (3H, s, CH_3), 3.94 (3H, s, CH_3), 7.08–7.63 (13H, m, Ar-H), 7.79–7.98 (6H, m, Ar-H), 8.85 (1H, d, J=8.9 Hz, Ar-H). MS m/z 519 (M^+). Exact mass determination: 519.1420 (calcd for $C_{32}H_{26}NO_2PS$: 519.1422).

4.1.20. Compound 13. Yield 58%. $[\alpha]_D$ +9.0° (c=1.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3412, 2988, 1506, 1433 (indole), 1024 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.26 (3H, s, $-OCH_3$), 6.18–6.25 (2H, m, Ar-H), 6.63–7.72 (17H, m, Ar-H), 8.31 (1H, dd, J=1.0, 6.8 Hz, Ar-H), 8.90–8.94 (1H, m, Ar-H). MS m/z 505 (M^+). Exact mass determination: 505.1412 (calcd for $C_{31}H_{24}NO_2PS$: 505.1266).

4.1.21. (*R*)-7-Indolyl 2-methoxy-1-naphthyl sulfoxide (12). A 50 ml two-necked flask equipped with a septum inlet and magnetic stirring bar was flushed with argon, and maintained under positive pressure of argon. A solution of 7-bromoindole (11)[9] (294 mg, 1.5 mmol) in THF (10 ml) was added at −78 °C to the flask. A 1.56 M *n*-butyllithium solution in hexane (2.0 ml, 3.0 mmol) was added to the above solution and the mixture was warmed to 0 °C during 3 h. A solution of (−)-menthyl sulfinate, (*Ss*)-**2c**, (360 mg, 1.0 mmol), in THF (5 ml) was added. After the mixture was stirred at 0 °C for 24 h, the reaction was quenched with a saturated aqueous NH_4Cl, and the mixture was diluted with ether. The solution was washed with a saturated aqueous NH_4Cl and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was subjected to flash column chromatography (ethyl acetate–hexane 1:1) to give **12** (308 mg, 64% yield).

4.1.22. Compound 12. $[\alpha]_D$ +486.4° (c=0.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3427, 3018, 1508, 1431 (indole), 1022 (sulfoxide). ^1H NMR (270 MHz, $CDCl_3$) δ: 3.85 (3H, s, $-OCH_3$), 6.56–6.58 (1H, m, Ar-H), 6.86–7.99 (9H, m, Ar-H), 8.77 (1H, d, J=8.7 Hz, Ar-H), 10.19 (1H, s, NH). MS m/z 321 (M^+). Exact mass determination: 321.0862 (calcd for $C_{20}H_{17}NO_2S$: 321.0824).

4.2. Palladium-catalyzed asymmetric nucleophilic substitution reactions of 1,3-diphenyl-2-propenyl acetate (14) with chiral *N*-(diphenylphosphino) sulfoxide ligands. General procedure

A 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing sodium hydride (60% oil dispersion, 37 mg, 0.912 mmol), was flushed with argon, and maintained under a positive pressure of argon. A solution of dimethyl malonate (120 mg, 0.912 mmol) in THF (2.5 ml) was added at 0 °C to the above flask and stirred for 15 min. Another 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing di-μ-chlorobis (π-allyl) dipalladium $[PdCl(CH_2{=}CHCH_2)]_2$ (5 mg, 0.014 mmol) and chiral *N*-(diphenylphosphano) sulfoxide ligands (0.028 mmol) was flushed with argon, and maintained under a positive pressure of argon. A solution of (±)-1,3-diphenyl-2-propenyl acetate (**14**) (115 mg, 0.456 mmol) in THF (1 ml) was added at room temperature to the above solution, and the mixture was stirred at room temperature for 30 min. The solution was added to the above solution including sodium dimethyl malonate, and the reaction mixture was stirred under the conditions listed in Table 1. The reaction solution was diluted with ether, and the solution was washed with a saturated aqueous NH_4Cl and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was subjected to preparative TLC (ether–hexane 1:4) to give optically active diethyl (1,3-diphenyl-2-propenyl) propanedioate (**15**).[10] The e.e. of product was determined by HPLC analysis with Chiralpak AD (*i*-PrOH–hexane 1:20, flow rate 0.5 ml/min, retention time; 28 min (*R*), 38 min (*S*)). The results are summarized in Table 1.

4.3. Structure determination of Pd-(*S*)-10a complex (16) by X-ray diffraction

A reaction mixture of (*S*)-**10a** (30 mg, 0.06 mmol) and

$PdCl_2{\cdot}(CH_3CN)_2$ (18 mg, 0.06 mmol) in EtOH (3 ml) was stirred at room temperature for 15 min. The yellowish precipitates (16 mg, 40% yield) were collected and recrystallized from CH_2Cl_2–hexane.

A palladium complex (**16**) with (*S*)-**9a** was obtained as yellow prisms.

Diffraction intensities were collected from a crystal of dimensions 0.30×0.15×0.10 mm on a Rigaku AFC-7 FOS four-circle diffractometer. Of the total 2852 unique reflections (complete for $2\theta<136.1°$, 1895 satisfied the criterion $F>3\sigma$ (F) and only these were used in the solution and refinement of the structure. Crystal data $C_{13}H_{24}NO_2SCl_2PPd$, M=682.88, orthorhombic, space group $P2_12_12_1$, a=13.263 (7), b=17.366 (8), c=12.090 (6) Å, V=2784.7 (2) Å^3, Z=4, Dc=1.629 g cm^{-3}, $F(000)$=1376, Cu Kα X-radiation (graphite monochromator), λ=1.54178 Å.

Lists of atomic parameters, bond length, and bond angles have been deposited to the Cambridge Crystallographic Data Centre.

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Mizoroki–Heck reaction, catalysis by nitrogen ligand Pd complexes and activation of aryl bromides☆

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Abstract—Nitrogen ligands are an excellent alternative for the traditional P-ligands in the Pd catalyzed Mizoroki–Heck reaction. Pd complexes of dimethyl glyoxime, 8-hydroxyquinoline, salen, picolinic acid, DAB ligands gave high yields of the *E*-cinnamates and *E*-stilbenes. Acetophenone oxime *N*,*N*-dimethybenzyl amine and ferrocenyl oxime palladacycle were better catalysts and comparable yields, TON (95,000) and TOF's (2500 h^{-1}) to P-ligand catalysts, were obtained. Aryl iodides, aryl bromides and in a few cases, aryl chlorides could be also be activated by these complexes by the use of Lewis acid and $(C_4H_9)_4NI$ as additive. DAB ligands gave good yields with electron rich aryl bromides and the use of ionic liquid improved the yield. These metal complexes can be readily synthesized and the N-ligands possess the advantage of easy functional group modifications and convenient synthetic methods compared to P-ligands. The degradation reactions associated with P-ligands is not observed in the N-ligands, with comparable high thermal, moisture and air stability and insensitivity.

1. Introduction

Nitrogen compounds are commonly used ligand in transition metal chemistry and equal in number and reactions to P-ligands.[1] Palladium complexes with various phosphines as ligands have been most commonly used as catalysts for the Mizoroki–Heck reaction.

Cyclopalladated tris-*o*-tolylphosphine, *N*-heterocyclic carbene, tridentate aryl bisphosphine Pd (II) (PCP), triaryl phosphites, are excellent catalysts giving high yields, TON and TOF for the Mizoroki–Heck reaction.[2] A major drawback of the use of phosphine ligands in such catalytic reactions is the oxidation of the phosphine to a phosphine oxide as well as cleavage of the P–C bond, causing degradation of the ligand, reduction of the metal and termination of the catalytic cycle.[3] Cyclopalladated aromatic rings are the choice systems for such catalysts due to the high thermal, moisture and oxidative stability. A variety of novel C–N, C–S palladacycles incorporating NHC,[4] imine,[5] thioether [6] and oxime[7] have been reported with high turnover numbers upto 10^5–10^6. These palladacycles are thermally stable and insensitive to moisture and air. Several novel Ni, Cu, Co, Ir, Rh, Pt catalysts have also been reported for the Mizoroki–Heck reaction.[8]

Nitrogen based ligands like DMG, 8-hydroxyquinoline, salen, picolinic acid, tmeda and their metal complexes and palladacycles from substituted *N*,*N*-dimethylbenzylamine, benzaldoxime and benzophenone oxime can be easily synthesized from readily available precursors by a variety of convenient synthetic methods.[9] Such ligands are not as readily oxidizable as phosphines and the metal complexes with a covalently bonded Pd to the aromatic ring, could be more stable and efficient catalysts (Scheme 1) and activate unreactive bromides and chlorides.[10] The various ligands also offer scope for electronic tuning by easy functionalization to influence the reaction in the desired direction including asymmetric induction.[11]

2. Results and discussion

Reaction of DMG, DAB, 8-hydroxyquinoline, salen and picolinic acid with $PdCl_2$ by well established procedures gives the corresponding Pd (II) complexes in high yield (Scheme 1).[6,12] In all these complexes, the metal is in the +2 oxidation state. The DAB ligands are readily prepared by the condensation of various amines with glyoxal and 2,3-butanedione (compared with the tedious synthesis of phosphines). The strong σ-donor and π-acceptor properties of the DAB makes them excellent ligand for the activation of the less reactive aryl bromides and chlorides. Salen and

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Keywords: Nitrogen ligands; Oxime palladacycles; Amine palladacycles; Dimethyl glyoxime; Ferrocenyl oxime palladacycle; Picolinic acid; Lewis acid; 8-Hydroxyquinoline.

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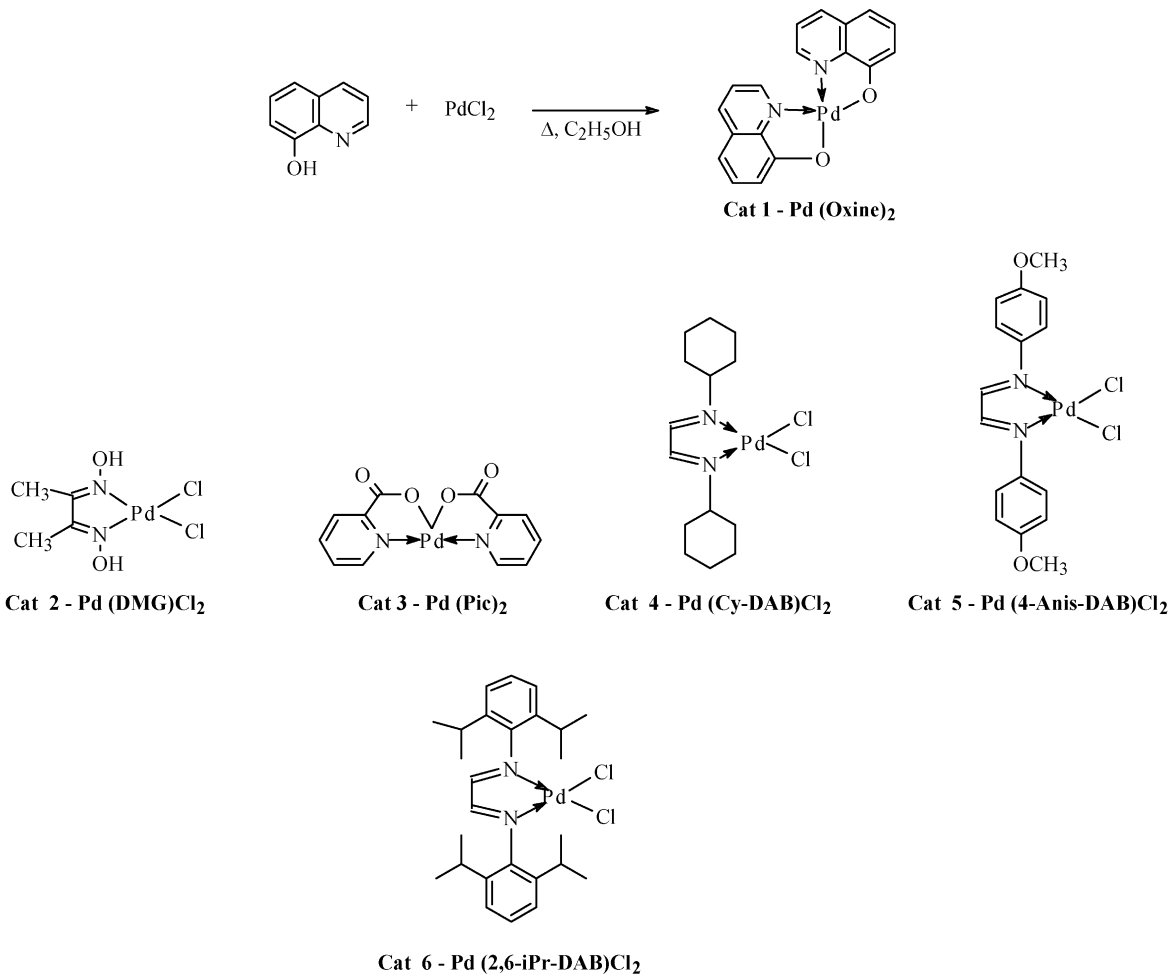
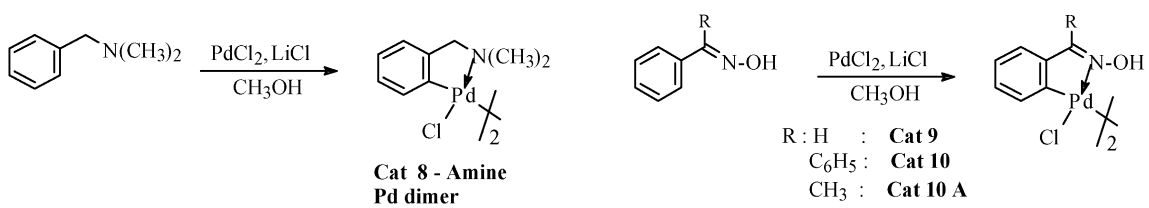


Scheme 1. Preparation of dimethylglyoxime, 8-hydroxyquinoline, diimine palladium complexes.

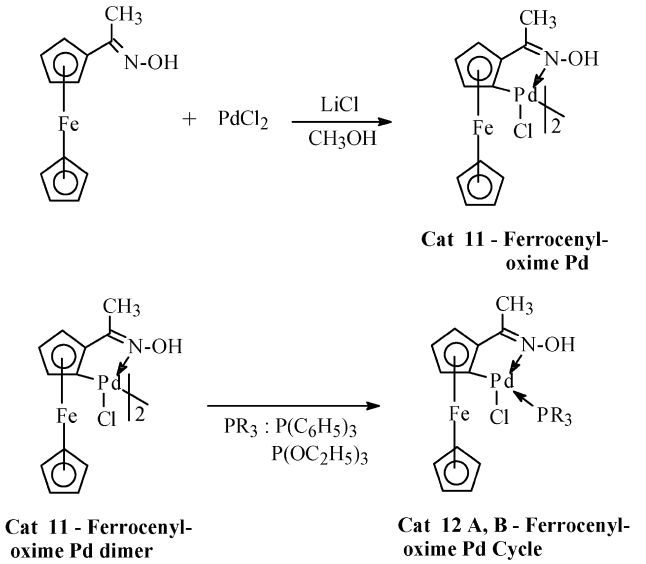
picolinic acid with the −COOH and −OH bonding to Pd, offer different electronic properties to these catalysts.

Cyclopalladation of benzaldehyde oxime, acetophenone oxime, benzophenone oxime, *N*,*N*-dimethyl benzyl amine and acetylferrocenyl oxime is facile and carried out according to the reported literature procedure to give the dimeric palladacycles (Scheme 2).[9] Ferrocene is an electron rich aromatic metal complex and has interesting properties due to its sandwich nature. The electron rich ferrocene is also expected to increase the electron density on the Pd enabling activation of less reactive aryl halides. Monomeric complexes of the dimeric palladacycles were prepared for studying the ligand effect by complexation to $P(C_6H_5)_3$, $P(OC_2H_5)_3$ and saturated *N*-heterocyclic carbenes (Scheme 3).[13] *N*-heterocyclic carbene orthopalladated oxime and amine catalysts were prepared by the refluxing of the corresponding dimeric palladacycles with the saturated *N*-heterocyclic carbene dimers in *m*-xylene in moderate yield. The ferrocene ring and the *N*-heterocyclic carbenes impart greater air, moisture and thermal stability to the palladacycles as well as its activity (Scheme 4).[14]

The Mizoroki–Heck reaction of 4-iodo anisole and 4-chloro iodo benzene with ethyl acrylate and styrene was catalyzed by these Pd complexes (**Cat 1**–**7**) to form the *E*-ethyl cinnamates (**18**, **19**) and *E*-stilbenes (**25**, **36**) in high yields (85–95%, Table 1).[16a,b,j,18] Bromo benzene and 4-bromo phenol could also be activated by these complexes under the reaction conditions studied to give moderate yields of the substituted products (8–48%).[17b,c] As a comparison, other catalysts like MnO_2, Ni, Mn and Cu salen (**Cat**-**17A**,**B**,**C**) complexes were the least active (21–60% yield), requiring high temperatures for the reaction.[17] The heterogeneous Ni/Al_2O_3 gave a 95% yield of *E*-4-methoxy ethyl cinnamate (**18**) in 2 h. $PdCl_2\{P(C_6H_5)_3\}_2$ in conjunction with $ZnCl_2$ or



Scheme 2. Preparation of amine and oxime palladacycles.

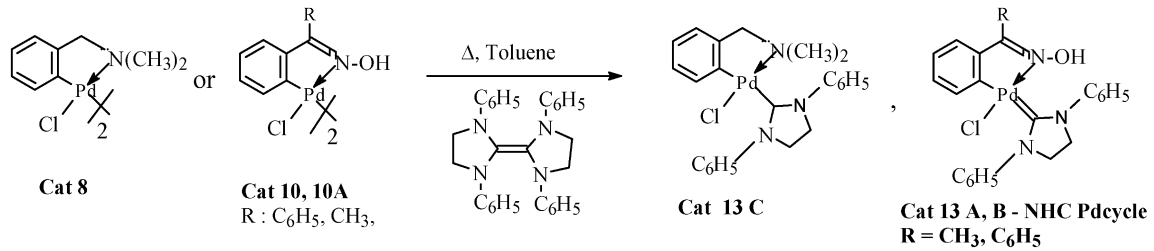


Scheme 3. Preparation of ferrocenyl oxime palladacycle.

PVP (polymeric base) gave yields of 40–90%. Tetrabutyl ammonium bromide and iodide as additives activated 2-chloro pyridine to give the 2-pyridyl ethyl acrylate (**24**)[16f,18] catalyzed by $Pd(OCOCH_3)_2$ (40% yield) and benzophenone oxime palladacycle dimer (60% yield). No reaction with aryl bromides was observed in presence of the salen catalysts.

The reaction of bromobenzene with ethyl acrylate was catalyzed by $PdCl_2$ (cyclohexyl-DAB) (**Cat-4**) to give the *E*-ethyl cinnamate in 63% yield. K_2CO_3 was the base of choice and *N*-methylpyrrolidinone was used as solvent. With the same catalyst, reaction of bromobenzene with styrene gave the *E*-stilbene in 64% yield. 4-Bromophenol and 4-*N*,*N*-dimethyl amino bromobenzene gave only 45 and 46% yield of the substituted ethyl cinnamate (**28**, **29**),[16j,k,18] while 1-bromonaphthalene gave 43% yield (**26**).[16h,18] With styrene, 1-bromonaphthalene and 4-bromophenol gave 89% (**27**)[16i] and 64% (**28**)[16j] yield of the substituted products while 4-*N*,*N*-dimethylamino bromobenzene gave only 10% yield (**30**).[16l,18] Rate acceleration was observed in the reaction of 1-bromonaphthalene with styrene and reaction was complete in 45 min, compared to the long reaction times for other substrates and catalysts. No reaction was observed with 4-chlorotoluene and 4-chloronitrobenzene.

Use of other DAB ligands (**Cat-5**, *p*-anisidine DAB, **Cat-6**, 2,6-diisopropylaniline DAB and **Cat-7**, *p*-anisidine-dimethyl DAB) gave only moderate yields of the substituted products with different aryl bromides. In all these reactions



Scheme 4. Preparation of saturated *N*-heterocyclic carbene palladacycles.

Table 1. DMG, 8-hydroxyquinoline, salen, picolinic acid Pd complexes catalyzed reaction of aryl halides

S. No.	Aryl halide	Cocatalyst/base	Olefin	Catalyst	Time (h)	Yield (%)
1	4-CH_3O·C_6H_4·I	—	$C_5H_8O_2$[a]	**1**–Pd $(C_9H_6NO)_2$	30	90
				2–Pd $(DMG)Cl_2$	6	80
				3–Pd $(2\text{-}COOH.C_5H_4N)_2$	8	89
2	4-Cl·C_6H_4·I	—	$C_5H_8O_2$	**1**–Pd $(C_9H_6NO)_2$	24	69
				2–Pd $(DMG)Cl_2$	8	68
				3–Pd $(2\text{-}COOH.C_5H_4N)_2$	24	84
3	C_6H_5·Br	—	$C_5H_8O_2$	**1**–Pd $(C_9H_6NO)_2$	24	48
				2–Pd $(DMG)Cl_2$	24	48
				3–Pd $(2\text{-}COOH.C_5H_4N)_2$	24	57
4	4-HO·C_6H_4·Br	—	C_8H_8[b]	**1**–Pd $(C_9H_6NO)_2$	24	NR
				2–Pd $(DMG)Cl_2$	24	16
				3–Pd $(2\text{-}COOH.C_5H_4N)_2$	24	8
5	4-CH_3O·C_6H_4·I	—	C_8H_8	**17A**-Ni $(C_{16}H_{14}N_2O_2)$	24	42
6	4-CH_3O·C_6H_4·I	—	C_8H_8	**17B**-Mn $(C_{16}H_{14}N_2O_2)$	24	21
7	4-CH_3O·C_6H_4·I	—	$C_5H_8O_2$	**17C**-Cu $(C_{16}H_{14}N_2O_2)$	24	60
8	4-CH_3O·C_6H_4·I	—	$C_5H_8O_2$	MnO_2	24	80
10	4-CH_3O·C_6H_4·I	PVP[c]	$C_5H_8O_2$	$PdCl_2\{P(C_6H_5)_3\}_2$	12	90
11	4-NO_2·C_6H_4·I	$ZnCl_2$	$C_5H_8O_2$	$PdCl_2\{P(C_6H_5)_3\}_2$	18	40
12	2-Cl·C_5H_4N	$(C_4H_9)_4NI$	$C_5H_8O_2$	**9**$\{PdC_{13}H_{10}ClNO\}_2$[d]	24	60
13	2-Cl·C_5H_4N	$(C_4H_9)_4NBr$	$C_5H_8O_2$	$Pd(OCOCH_3)_2$	4	50
14	4-CH_3O·C_6H_4·I	—	$C_5H_8O_2$	Ni/Al_2O_3	2	95

[a] $C_5H_8O_2$, ethyl acrylate.
[b] C_8H_8, styrene; NR, no reaction.
[c] PVP, polyvinylpyridine.
[d] $\{PdC_{13}H_{10}ClNO\}_2$, di-μ-chlorobis (benzophenoneoxime-6-C,N) dipalladium.

Table 2. $PdCl_2$(DAB) catalyzed reaction of aryl bromides

S. No.	Aryl bromide	Olefin	Catalyst	Time (h)	Yield (%)[a]	TON (TOF)
1	C_6H_5Br (2 mmol)	$C_5H_8O_2$[b]	**4**	24	63	63
			5	45	16	16
			6	20	32	32
			7	24	40	40
2	C_6H_5Br (10 mmol)	$C_7H_{12}O_2$	**4**	24	20	2666 (111)[c]
3	C_6H_5Br (10 mmol)	$C_7H_{12}O_2$	**4A**	24	26.5	132[d] (5)
4	C_6H_5Br (50 mmol)	C_8H_8[e] (50 mmol)	**4**	24	64	64
			4A	48	15	37,600 (783)[f]
			5	24	21	21
			6	29	31	31
			7	24	19	19
5	1-$C_{10}H_7Br$	$C_5H_8O_2$	**4**	24	45	45
			5	24	30	30
			6	24	44	44
			7	—	—	—
6	1-$C_{10}H_7Br$	C_8H_8	**4**	45 mins	89	89
			5	31	44	44
			6	24	78	78
			7	24	22	22
7	11-$C_{10}H_7Br$ (10 mmol)	C_8H_8	**4**	3	86	17,200 (5733)[g]
8	11-$C_{10}H_7Br$ (10 mmol)	C_8H_8	4A	6	76	380 (63)[h]
9	4-HO·C_6H_4·Br	$C_5H_8O_2$	**4**	24	45	45
			5	42	nr	—
			6	24	nr	—
			7	24	8	8
10	4-HO·C_6H_4·Br	C_8H_8	**4**	24	64	64
			5	24	nr	—
			6	24	38	38
			7	24	nr	—
11	4-$(CH_3)_2$N·C_6H_4·Br	$C_5H_8O_2$	**4**	24	46	46
			5	48	nr	—
			6	24	25	25
			7	24	nr	—
12	4-$(CH_3)_2$N·C_6H_4·Br	C_8H_8	**4**	24	10	10
			5	24	nr	—
			6	24	nr	—
			7	24	nr	

[a] Reaction conditions: halide: olefin: base: **Cat-2**: 4: 4: 0.02—temp.: 150 °C.
[b] ($C_5H_8O_2$, Ethyl acrylate.
[c] Reaction conditions: halide: olefin: base: TBAB: **Cat-4**: 10: 10: 15: 1: 0.00075—temp.: 140 °C.
[d] Reaction conditions: halide: olefin: base: **Cat-4A**: Cy-DAB—10: 10: 15: 0.02: 0.04—temp.: 140 °C.
[e] C_8H_8, Styrene (i) nr, no reaction.
[f] Reaction conditions: halide: olefin: base: **Cat-4A**: **Cy-DAB**: 50: 50: 55: 0.0002: 0.0004—temp.: 140 °C.
[g] Reaction conditions: halide: olefin: base: TBAB: **Cat-4**: 10: 10: 15: 1: 0.0005—temp.: 120 °C.
[h] Reaction conditions: halide: olefin: base: **Cat-4A**: Cy-DAB—10: 10: 15: 0.02: 0.04—temp.: 120 °C; solvent-NMP (6–12 ml); **Catalyst-4**,**5**,**6**,**7**—see Scheme 1.

Table 3. $PdCl_2$ (DAB) catalyzed reaction of aryl halides in ionic liquid

S. No.	Aryl bromide	Olefin	Catalyst	Time (h)	Yield (%)
1	C_6H_5Br	$C_7H_{12}O_2$[a]	**4**	24	70
		$C_7H_{12}O_2$	**5**	24	68
		$C_5H_8O_2$	**6**	20	67
		$C_7H_{12}O_2$	**7**	24	45
2	C_6H_5Br	C_8H_8[b]	**5**	24	57
	C_6H_5Br	C_8H_8	**7**	24	35
3	4-HO·C_6H_4·Br	$C_5H_8O_2$	**4**	24	46
4	1-$C_{10}H_7Br$	$C_5H_8O_2$	**4**	24	67
			5	24	50
			6	24	85
5	1-$C_{10}H_7Br$	C_8H_8	**5**	31	87
			7	24	55
6	4-$(CH_3)_2$N·C_6H_4·Br	C_8H_8	**5**	48	52
			6	24	57

Reaction conditions: A: ArBr (3 mmol), butylacrylate (3 mmol), Na_2CO_3 (6 mmol), $HCOONH_4$ (0.1 mmol), $(C_4H_9)_4NBr$ (6 mmol); temperature: 130 °C; B: ArBr (2 mmol), styrene (5 mmol), HCOONa (0.147 mmol), CH_3COONa (2.4 mmol), $(C_4H_9)_4NBr$ (6 mmol), temperature: 130 °C.
[a] $C_5H_8O_2$, ethyl acrylate.
[b] C_8H_8, styrene.

Pd is in the +2 oxidation state. For comparison, Pd $(dba)_2$ (**4A**–Pd-0) as catalyst with Cy-DAB as ligand gave comparable yields to $PdCl_2$(DAB) with bromobenzene and butyl acrylate (**34**, 26.5%, TON- 132, TOF- 5 h^{-1})[16o] and bromonaphthalene and styrene (76%, TON- 380, TOF, 63 h^{-1}). Reaction of bromobenzene (50 mmol) with styrene gave 1.354 g stilbene (15%, TON- 37, 600; TOF- 783 h^{-1}).

These results are comparable to or better than the results obtained with $PdCl_2\{P(C_6H_5)_3\}_2$ as catalyst (20–30% yield) under similar conditions for the same aryl bromides. These results are comparable to the yields obtained with the DMG, picolinic acid and 8-hydroxy quinoline ligands for bromobenzene.

The diimine from the condensation of benzaldehyde and ethylenediamine was also used to prepare a Pd complex. However, the use of this catalyst also gave only moderate yields (24–55%) in the reactions of bromo benzene and bromo naphthalene with ethyl acrylate. The use of

$(C_4H_9)_4NBr$ as ionic liquid-solvent with Pd benzothiazole carbene complex as catalyst has been shown to improve the reactivity and yield in the Mizoroki–Heck reaction.[14,15]The reaction of bromobenzene and bromonaphthalene with ethyl acrylate in $(C_4H_9)_4NBr$ as ionic liquid solvent, catalyzed by $PdCl_2$(Cy-DAB) **Cat-4** gave higher yields (70 and 66%) of the substituted product while the other catalysts **5**, **6** and **7** gave moderate to high yields of the substituted product (52–87%) (Table 3) compared to the reactions in NMP (Table 2).

Orthometallated aryl oxime, amine palladacycles (**Cat 8–10**,**10A**) catalyze the reaction (Table 4) of aryl iodides, bromides and electron deficient chlorides with ethyl acrylate and styrene to give high yields of the substituted products (*E*-cinnamate and *E*-stilbene) with high turn over numbers (72,000–145,454) and TOF's (1625–20,780). The bromides and chlorides take longer reaction times for complete conversion.

Electron withdrawing groups activate aryl chlorides. The use of a Lewis acid ($ZnCl_2$), as a co-catalyst which would help labilize the halide, increased the reaction rate and the yield of the reaction. The reaction of bromobenzene with ethyl acrylate and styrene was catalyzed by the palladacycle **10** giving 90 and 96% yields of *E*-ethyl cinnamate and *E*-stilbene (TON- 450) in 1 h (shorter reaction time compared to the other catalysts). The TON for bromobenzene with the catalyst **8** (87,000-90,000) was higher than with the catalyst **9** (72,000-78,000). When aluminium chloride was used as a co-catalyst, the reaction of 4-chlorotoluene, with styrene, gave the substituted product (**35**, as *E*-isomer) in 18% yield.[16p,18]

$(C_4H_9)_4NI$ was also used as co-catalyst for the reaction of 4-chlorotoluene and 2-chloropyridine with ethyl acrylate and styrene in the presence of palladacycle **10**. The normal substitution products were obtained in moderate yields. Oxime and *N*,*N*-dimethyl benzyl amine palladacycles show high yields, TON's and TOF's in the reaction of aryl iodides and bromides.[1–5] The reaction of 4-iodoanisole and ethyl acrylate or styrene proceeded readily in *N*-methylpyrrolidinone as solvent and catalyzed by ferrocenyl palladacycle **11**, to give (*E*)-4-methoxy ethyl cinnamate and (*E*)-4-methoxystilbene in 74 and 69% yields, respectively.

The monomeric catalysts **12A** and **12B** gave a 93% yield of (*E*)-4-methoxy ethyl cinnamate and 73 and 67% yields of (*E*)-4-methoxystilbene. The reaction of of 4-iodoanisole (25 mmol) with ethyl acrylate (50 mmol) in the presence of 2.6×10^{-4} mmol of catalyst **11**, gave the (*E*)-4-methoxy ethyl cinnamate in 65% yield with a turnover number of 62,500. Increasing the catalyst concentration to 1.3×10^{-3} led to shorter reaction time, but did not improve the yield (76–84%). The catalysts **12A** and **12B** gave 84 and 92% yields of (*E*)-4-methoxy ethyl cinnamate (catalyst concentration 1.5×10^{-3} mmol).

Monomeric complexes **11**, **12A** and **12B** showed appreciable catalytic activity for the reaction of relatively inactive bromobenzene with ethyl acrylate and stilbene to afford 77–85% yields of (*E*)-ethyl cinnamate and (*E*)-stilbene (TON's 5266–15,192). The reaction of 1-bromonaphthalene with both ethyl acrylate and styrene gave ethyl (*E*)-3-(1-naphthyl) propenoate and (*E*)-2-phenyl-1-(1-naphthyl) ethene in 83–97% yield (TON's 25,000–36,153). Sodium acetate was a better base than K_2CO_3. 4-Bromophenol reacted with ethyl acrylate to give the 4-(*E*)-hydroxy ethyl cinnamate in only 20–45% yields.

Activated aryl chlorides, such as 4-chloro nitrobenzene, 4-chloro acetophenone and 4-chloro benzonitrile also reacted with styrene to give the corresponding *E*-stilbenes in moderate yields (22–53%, **31**, **32**, **33**).[16m,n,18] The phosphite complex **12B** gave the highest yields of the substituted products. The acetylferrocenyloxime palladacycles show high activity, though not as active as the acetophenone and benzophenone oxime palladacycles.

Complexes **13A** and **13B** showed high activity for the reaction of aryl bromides with ethyl acrylate and styrene to give 40–88% yield of the substitution products (TON's 2777–91,950). A TON of 91,950 was obtained for the coupling of 1-bromonaphthalene with styrene in the presence of acetophenone oxime carbene complex **13A**. Monomeric phosphine and phosphite analogues **15**, **16** were also prepared for comparison, by the reaction of the dimeric oxime complex **9** with $P(C_6H_5)_3$ (**Cat 15**) and $P(OC_2H_5)_3$ (**Cat 16**).

For the reaction of 1-bromonaphthalene with ethyl acrylate, catalyst **13B** gave the highest yield of 93.2% with a TON of 65,019 and TOF of 9288 h^{-1} compared to the catalyst **15** (yield 65.7%, TON- 49, 773 and TOF- 2074 h^{-1}) and catalyst **16** (yield 76.4%, TON- 48, 000 and TOF- 2274 h^{-1}). For the reaction with styrene, catalyst **13C** gave the highest yield of 86.8%, TON- of 59, 500 and TOF- of 8500 h^{-1} compared to catalyst **15** (yield 89.3%, TON- 67, 575 and TOF- 2941 h^{-1}) and catalyst **16** (yield 82.5%, TON- 51, 725 and TOF- 2343 h^{-1}). The carbene complexes gave higher yields, TON's and TOF's compared to the phosphine and phosphite complexes. The results of the Mizoroki–Heck reactions with these catalysts is shown in Table 4. 4-Chlorobenzonitrile and 4-chloroacetophenone reacted with styrene and ethyl acrylate to give 75.7 and 70% yield of the corresponding *E*-stilbenes and *E*-cinnamates (**37**, **38**, 50%)[16q,18] under similar conditions. The TON's obtained for the aryl chlorides were lower (2500–4100) compared to the bromides.

The orthometallated oxime and amine dimeric palladacycle complexes were expected to show better catalytic activity with these NHC's as ligands co-ordinated to the palladacycle. Increased catalytic activity was already observed with the phosphine and phosphite co-ordinated ferrocenyl oxime palladacycles (**Cat 12A**,**B**). Co-ordination of saturated *N*-heterocyclic carbene ligands to the aryl oxime and amine palladacycles increases the thermal, air and moisture stability. The activity of these complexes are similar to previously reported oxime and amine palladacycle complexes and the stability and reactivity is increased by the *N*-heterocyclic carbenes compared to the phosphine ligands.

A comparison of the results with various catalysts and ligands show the high catalyst activity of the palladacycles compared to the bidentate ligands. These catalysts also

Table 4. Palladacycles catalyzed reaction of aryl halides

S. No.	Aryl halide (mmol)	Olefin (mmol)	Catalyst (mmol)	Time (h)	Yield TON	TOF (h^{-1})
1	4-CH_3O·C_6H_4·I	$C_5H_8O_2$[a]				
	(50 mmol)	(100 mmol)	**8** (0.0005)	8	88 (89,540)	11,190
	(25 mmol)	(50 mmol)	**11** (0.00026)	12	65 (62,500)	5208
	(25 mmol)	(50 mmol)	**12A** (0.00155)	12	84 (14,000)	1166
	(25 mmol)	(50 mmol)	**12B** (0.00026)	12	92 (88,461)	7371
2	4-CH_3O·C_6H_4·I	C_8H_8[b]				
	(50 mmol)	(60 mmol)	**8** (0.0005)	48	76 (76,000)	1740
			9 (0.0005)	48	92 (138,666)	2888
3	C_6H_5·I	$C_5H_8O_2$				
	(50 mmol)	(100 mmol)	**9** (0.0005)	7	96 (145,454)	20,778
4	C_6H_5·Br	$C_5H_8O_2$				
	(50 mmol)	(100 mmol)	**8** (0.0005)	34	90 (90,000)	2647
	(50 mmol)	(100 mmol)	**9** (0.0005)	48	52 (72,000)	240
	(25 mmol)	(55 mmol)	**11** (0.0013)	24	79.3 (15,296)	276
	(25 mmol)	(55 mmol)	**12A** (0.0015)	16	78 (12,954)	808
	(25 mmol)	(55 mmol)	**12B** (0.0013)	24	76.6 (10,945)	456
	(25 mmol)	(30 mmol)	**13A** (0.0004)	24	70 (43,750)	1823
	(25 mmol)	(50 mmol)	**13B** (0.00036)	24	54.7 (38,055)	1590
	(25 mmol)	(50 mmol)	**13C** (0.0004)	24	43.5 (27,514)	1146
5	C_6H_5·Br	C_8H_8				
	(50 mmol)	(60 mmol)	**8** (0.0005)	29	86.6 (86,666)	2988
	(50 mmol)	(60 mmol)	**9** (0.0005)	48	52 (78,000)	240
	(50 mmol)	(60 mmol)	**10** (0.0005)	1	96 (483)	483
	(25 mmol)	(55 mmol)	**11** (0.0013)	16	84 (7000)	808
	(10 mmol)	(10 mmol)	**12A** (0.0015)	24	79.4 (5480)	228
	(10 mmol)	(10 mmol)	**12B** (0.0012)	24	83 (7083)	295
	(25 mmol)	(40 mmol)	**13A** (0.0004)	24	71.6 (41500)	1729
	(50 mmol)	(60 mmol)	**13B** (0.0004)	24	71.2 (44,500)	1854
	(25 mmol)	(40 mmol)	**13C** (0.0004)	24	80.1 (50,000)	2083
6	1-$C_{10}H_7$·Br	$C_5H_8O_2$				
	(10 mmol)	(20 mmol)	**11** (0.0004)	24	83 (31,923)	1330
	(10 mmol)	(20 mmol)	**12A** (0.0003)	27	86.3 (28733)	9577
	(10 mmol)	(23 mmol)	**12B** (0.00026)	8	83 (31,994)	4159
	(25 mmol)	(50 mmol)	**13A** (0.0004)	21	88.4 (55,420)	2638
	(25 mmol)	(50 mmol)	**13B** (0.00036)	7	93.2 (65,019)	9288
	(25 mmol)	(50 mmol)	**13C** (0.0004)	9	86.3 (53,925)	5991
	(25 mmol)	(50 mmol)	**15** (0.00033)	24	65.7 (49,773)	2074
	(25 mmol)	(50 mmol)	**16** (0.0004)	21	76.4 (48,000)	2286
7	1-$C_{10}H_7$·Br	C_8H_8				
	(10 mmol)	(10 mmol)	**11** (0.00026)	2	94 (36,538)	11,529
		(20 mmol)	**12A** (0.0003)	12	91 (30,333)	2608
		(10 mmol)	**12B** (0.00036)	3	97 (27,197)	9065
	(25 mmol)	(30 mmol)	**13A** (0.0002)	36	73.2 (91,950)	2554
	(25 mmol)	(30 mmol)	**13A** (0.0004)	36	92.6 (61,950)	1720
	(25 mmol)	(40 mmol)	**13B** (0.00036)	36	77.9 (54,166)	1504
	(27 mmol)	(35 mmol)	**13C** (0.0004)	7	86.8 (59,500)	8500
	(25 mmol)	(32 mmol)	**15** (0.00033)	23	89.3 (67,575)	2938
	(25 mmol)	(32 mmol)	**16** (0.0004)	22	82.5 (51,725)	2351
8	4-CH_3O·C_6H_4·Br	C_8H_8	**13A** (0.0016)	10	86.5 (5461)	546
	(10 mmol)	(20 mmol)	**13B** (0.0014)	7	67.8 (4923)	703
			13C (0.0018)	24	50 (2777)	116
9	4-NO_2·C_6H_4·Cl	C_8H_8	**8** (0.0005)	31	51 (287)	9
	(5 mmol)	(10 mmol)	**9** (0.0005)	30	60 (300)	10
10	4-NO_2·C_6H_4·Cl	C_8H_8	**8** (0.0005)	42	71 (70,000)	9
	(50 mmol)	(60 mmol)	**9** (0.0005)	40	69 (350)	8
11	4-$COCH_3$·C_6H_4·Cl	C_8H_8				
	(10 mmol)	(16 mmol)	**11** (0.015)	24	30 (38)	1
			12B (0.013)	24	53 (81)	3
			13A (0.0018)	24	54.9 (3103)	129
			13B (0.0023)	24	75.7 (3347)	139
			13C (0.001)	24	61.4 (3070)	128
12	4-CN·C_6H_4·Cl	C_8H_8				
	(5 mmol)	(6 mmol)	**8** (0.0005)	20	78.5 (350)	14
			11 (0.009)	20	22 (28)	1
			12B (0.0016)	24	37 (58)	6
	(10 mmol)	(16 mmol)	**13A** (0.0018)	24	73.4 (4111)	171
			13B (0.0017)	24	70 (3902)	162
			13C (0.002)	24	34 (1705)	71
13	2-Br·C_5H_4·N	$C_5H_8O_2$				
	(5 mmol)	(10 mmol)	**9** (0.0005)	48	68 (4090)	85

[a] Styrene.
[b] Ethyl acrylate.

show high TON and TOF. Use of co-catalysts $(C_4H_9)_4NBr$, $(C_4H_9)_4NI$, Lewis acids $ZnCl_2$ and $AlCl_3$ activate aryl chlorides to give moderate yields. The absence of back bonding (available in the P-ligands) and the σ-donor ability of the N-ligands, causes activation of aryl and vinyl halides in the oxidation addition reactions by assisting in the labilization of the bromides and chlorides. The electron rich ferrocenyl oxime ligands, *N*-palladacycles, NHC's, phosphites, DAB, could be activating ligands, which increase the electron density at the metal. This effect was most successful with the palladacycles and the DAB Pd complexes while the ferrocenyl palladacycle though active did not show the expected high TON and TOF.

3. Experimental

3.1. General

The aryl halides, styrene, ethyl acrylate, glyoxal, ligands and the metal complexes were purchased or prepared according to known procedures.[12] The reactions were monitored by TLC using GF-254 grade silica gel on glass plates. Silica gel (100–200 mesh) was used for column chromatography. The products, intermediates and metal complexes were characterized by spectroscopic methods (IR, NMR, MS) and C, H analysis. ^1H, ^{13}C NMR spectra were recorded in $CDCl_3$ on 200 and 300 MHz NMR instruments. All reactions were carried out under Ar atmosphere.

3.1.1. Preparation of acetophenone oxime, (2-*C*,*N*) chloro(1,3-diphenylimidazolidin-2-ylidene)palladacycle (II).[13,18] 0.2 g (0.4 mmol) of acetophenone oxime palladacycle and 0.16 g of dimeric carbene were refluxed in 5 ml dry *m*-xylene at 120–130 °C for 2 h. A yellow precipitate was formed, filtered and dried. The separated solid was recrystallized from dichloromethane and hexane mixture to get a yellow crystalline powder. Yield: 0.131 g (33%), ^1H NMR (δ, $CDCl_3$, 200 MHz) 9.96 (s, 1H, O*H*), 8.04–8.00 (m, 4H, *Ar*), 7.5–6.6 (m, 15H, *Ar*), 4.5–4.2 (m, 4 H, CH_2), 2.26 (s, 3H, CH_3); IR (cm^{-1}, Nujol): 3163 (ν_{O-H}), 1284 (ν_{C-N}); CHN—analysis calculated (found) for $C_{23}H_{22}N_3OClPd$: C, 55.4 (55.3), H, 4.5 (4.53), N, 8.4 (8.38).

3.1.2. Preparation of chloro(*N*,*N*-dimethylbenzylamine, 2-*C*,*N*) (1,3-diphenylimidazolidin-2-ylidene)palladium (II).[13,18] 0.08 g (0.147 mmol) of *N*,*N*-dimethylbenzylamine palladacycle and 0.066 g of dimeric carbene were refluxed in 5 ml dry *m*-xylene at 120–130 °C for 2 h. The solution was filtered, concentrated and recrystallized from dichloromethane and petroleum ether mixture to get white microcrystalline complex. Yield: 0.03 g (21%), mp: >200 °C, IR (cm^{-1}, Nujol): 1280 (ν_{C-N}); ^1H NMR (δ, $CDCl_3$, 200 MHz) 8.14–6.61 (m, 14H, *Ar*), 4.34–4.32 (m, 4H, CH_2), 3.61 (s, 2H, CH_2), 2.60 (s, 6H, N(CH_3)$_2$); CHN—analysis calculated (found) for $C_{24}H_{26}N_3ClPd$: C, 57.8 (57.92), H, 5.26 (5.27), N, 8.43 (8.24).

3.1.3. Reaction of aryl halide with olefins (Cat-1–10).[18] 4-Iodoanisole (0.234 g, 1 mmol), ethyl acrylate (0.28 g, 3 mmol), catalyst-**1** {Pd(DMG)Cl_2, 0.025 g, 0.09 mmol} and K_2CO_3 (0.276 g, 2 mmol) were taken in a flask with NMP as solvent (6 ml) and the reaction mixture heated to 140 °C for 6 h. After completion of the reaction, monitored by TLC for complete consumption of the aryl halide, the reaction mixture was poured into dilute HCl (25 ml, 10% solution) and extracted with ethyl acetate (3×25 ml). The combined organic fraction was washed with saturated brine, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. Purification by column chromatography over silica gel (100–200 mesh) gave the 2-propenoic acid, 3-(4-methoxyphenyl)-, ethyl ester (**18**, 0.165 g, 80% yield, mp: 47–48.8 °C).[16a] ^1H NMR (200 MHz, $CDCl_3$, δ): 7.68–7.61 (d, 1H, *J*=14 Hz, Ar·C*H*═), 7.50–7.46 (d, 2H, *J*=8 Hz, Ar-H_3, H_5), 6.92–6.88 (d, 2H, *J*=8 Hz, Ar-H_2, H_6), 6.35–6.27 (d, 1H, *J*=16 Hz, ═C*H*·COOC_2H_5), 4.31–4.20 (q, 2H, *J*=8 Hz, –COOCH_2·), 3.84 (s, 3H), 1.37–1.30 (t, 3H, *J*=8 Hz, $COOCH_2$·CH_3); IR (cm^{-1}, Nujol): 2977, 2939, 2839, 1712, 1635, 1512, 1365, 1303, 1250, 1170, 1033, 979, 833, 555, 524; MS (*m*/*e*): 206, 191, 178, 161, 147, 134, 126, 118, 103, 89, 81, 77.

3.1.4. Reaction of 4-iodo anisole with ethyl acrylate catalyzed by palladacycle 8.[18] 4-Iodoanisole (11.7 g, 50 mmol), ethyl acrylate (10 g, 100 mmol), K_2CO_3 (8.28 g, 60 mmol) and 50 ml *N*-methylpyrrolidinone were taken in a round bottomed flask and the Pd complex **8** (0.00027 g, 0.0005 mmol) was added as catalyst. The reaction mixture was heated in a oil bath maintained at 150 °C for 8 h. The usual extractive workup with dilute HCl followed by purification over silica gel (100–200 mesh) to give 2-propenoic acid, 3-(4-methoxyphenyl)-, ethyl ester (**18**, 9.223 g, 88.3%, TON- 89, 540, TOF- 11, 192 h^{-1}).

3.1.5. Reaction of 1-bromonaphthalene with styrene catalyzed by Pd(Cy-DAB)Cl_2 (Cat-4) (27).[18] 5.175 g (25 mmol) of 1-bromonaphthalene was taken in a flask and styrene (3.03 g, 30 mmol), 25 ml *N*-methylpyrrolidinone added to it followed by 2.49 g (30 mmol) of CH_3COONa and 0.00022 g (0.0004 mmol) of the (**Cat-4**) catalyst. The reaction mixture was heated to 140–150 °C in an oil bath till the bromo naphthalene was completely consumed (36 h). Dilute HCl was added to the reaction mixture and extracted with ethyl acetate (3×100 ml). Washing with brine, drying over anhydrous Na_2SO_4, concentration on a rotary evaporator and purification by column chromatography (silica gel: 100–200 mesh) gave 5.32 g (**27**, 92.6%, TON, 61,956, mp: 69.9–70.9 °C)[16i] of naphthalene, 1-[(1*E*)-2-phenylethenyl]- (**27**). ^1H NMR (200 MHz, $CDCl_3$, δ): 8.28–7.14 (m, 14H); IR (cm^{-1}, Nujol): 1595, 1377, 1350, 1141, 1074, 1012, 968, 956, 792, 773, 754, 690; MS (*m*/*e*): 230, 215, 202, 189, 176, 152, 141, 128, 115, 107, 101, 91, 77.

3.1.6. Reaction of bromobenzene with styrene catalyzed by Pd(dba)$_2$/(Cy-DAB) (Cat-4A) (25).[18] Bromobenzene (7.85 g, 50 mmol) was taken in a flask and styrene (5.2 g, 50 mmol), 15 ml *N*-methylpyrrolidinone added to it followed by 7.59 g (55 mmol) of K_2CO_3, 0.00011 g (0.0002 mmol) of the **Cat-4A**, and 0.00008 g (0.0004 mmol) of cyclohexyl DAB. The reaction mixture was heated to 140 °C in an oil bath for 48 h. Dilute HCl was added to the reaction mixture and extracted with ethyl acetate (3×100 ml). Washing with brine, drying over anhydrous Na_2SO_4, concentration on a rotary evaporator

and purification by column chromatography (silica gel: 100–200 mesh) gave 1.354 g (**25**, 15%, TON- 37, 600)[16g] of Benzene, 1,1′-(1,2-ethenediyl)bis- (**25**), mp: 120 °C, ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.5–7.1 (m, 12H, *Ar*, C*H*═); IR (cm^{-1}, Nujol): 1596, 1377, 1330, 1296, 1220, 1155, 1072, 1027, 963, 962, 908, 765, 692; MS (*m*/*e*): 180, 165, 152, 139, 126, 115, 102, 89, 76.

3.1.7. Reaction of 1-bromonaphthalene with styrene catalyzed by benzophenone oxime, (2-*C*,*N*) chloro(1,3-diphenylimidazolidin-2-ylidene)palladacycle (II) (Cat-13B) (27).[18] 5.175 g (25 mmol) of 1-bromonaphthalene was taken in a flask and styrene (3.03 g, 30 mmol), 25 ml *N*-methylpyrrolidinone added to it followed by 2.49 g (30 mmol) of CH_3COONa and 0.00022 g (0.0004 mmol) of the (**Cat-13B**) benzophenone oxime palladacycle carbene catalyst. The reaction mixture was heated to 140–150 °C in an oil bath till the bromo naphthalene was completely consumed (36 h). Dilute HCl was added to the reaction mixture and extracted with ethyl acetate (3×100 ml). Washing with brine, drying over anhydrous Na_2SO_4, concentration on a rotary evaporator and purification by column chromatography (silica gel: 100–200 mesh) gave 5.32 g (92.6%, TON- 61, 956) of Naphthalene, 1-[(1*E*)-2-phenylethenyl]- (**27**).

3.1.8. Di-μ-chlorobis(benzophenoneoxime)dipalladium/$AlCl_3$ catalyzed vinylation of 4-chlorotoluene with styrene (35).[18] Styrene (0.416 g, 4 mmol) and 4-chlorotoluene (0.252 g, 2 mmol)) were taken in a flask and the catalyst **10** (0.01 g, 0.01 mmol), tributyl amine (0.741 g, 4 mmol) and tetrachloroethane (10 ml) as solvent was added. The solution was cooled in an ice bath and $AlCl_3$ (0.266 g, 2 mmol) was added to the reaction mixture. Refluxing for 72 h and the usual work up gave the benzene, 1-methyl-4-[(1*E*)-2-phenylethenyl]- (**35**, 0.150 g, 39%, mp: 120 °C).[17p]

3.1.9. Di-μ-chlorobis(benzophenoneoxime)dipalladium/$(C_4H_9)_4NI$ catalyzed vinylation of 4-chlorotoluene with styrene (35).[18] Styrene (0.416 g, 4 mmol), 4-chlorotoluene (0.254 g, 2 mmol), $(C_4H_9)_4NI$ (0.738 g, 2 mmol), K_2CO_3 (0.552 g, 4 mmol) were taken in a flask and the catalyst **10** (0.015 g, 0.01 mmol) added to it. 1-Methylpyrrolidinone (5 ml) was added as solvent and the reaction mixture heated to 130 °C for 24 h. Usual work up gave the benzene, 1-methyl-4-[(1*E*)-2-phenylethenyl]- (**35**) (0.095 g, 28%).

3.1.10. Reaction of 4-chlorobenzonitrile with styrene catalyzed by carbene palladacycle (13A) (33).[18] 4-Chlorobenzonitrile (1.393 g, 10.17 mmol), styrene (1.709 g, 16.4 mmol) were taken in a flask and 10 ml of *N*-methylpyrrolidinone added to it. NaOAc (1.098 g, 12.5 mmol), $(C_4H_9)_4NBr$ (0.322 g, 1 mmol) and acetophenone oxime palladacycle carbene (**13 A**, 0.0009 g, 0.0018 mmol) was added to it as catalyst and the reaction mixture heated to 140 °C for 24 h until all the starting material was completely consumed. Added water, extracted with ethyl acetate, the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. Purification by column chromatography gave 1.526 g (**33**, 73.4%, TON- 4111)[16m] of benzonitrile, 4-[(1*E*)-2-phenylethenyl]- (**33**), mp: 117.4–117.7 °C, ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.8–6.8 (m, 11H, *Ar*, C*H*═); IR (cm^{-1}, Nujol): 2852, 2225, 1602, 1504, 1377, 1166, 966, 873, 823, 757, 690; MS (*m*/*e*): 205, 190, 176, 165, 151, 139, 127, 113, 102, 89, 76, 63.

3.1.11. Reaction of 4-chloroacetophenone with styrene catalyzed by carbene palladacycle (13B) (32).[18] 4-Chloroacetophenone (1.57 g, 10.2 mmol), styrene (1.680 g, 16.1 mmol) were taken in a flask and 10 ml of *N*-methylpyrrolidinone added to it. NaOAc (1.06 g, 13 mmol), $(C_4H_9)_4NBr$ (0.322 g, 1 mmol) and benzophenone oxime palladacycle carbene (**13B**, 0.0023 g, 0.0023 mmol) was added to it as catalyst and the reaction mixture heated to 140 °C for 24 h until all the starting material was completely consumed. Added water, extracted with ethyl acetate, the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. Purification by column chromatography gave 1.71 g (75.7%, TON- 3347, mp: 148–150 °C)[16n] of ethanone, 1-[4-(2-phenylethenyl)phenyl]- (**32**). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.97–7.93 (d, 2H, *J*=8 Hz, Ar-$H_{2,6}$), 7.61–7.25 (m, 7H, *Ar*·C*H*═), 7.20–7.16 (d, 2H, *J*=8 Hz, Ar-$H_{3,5}$), 2.61 (s, 3H); IR (cm^{-1}, Nujol): 2854, 1677, 1600, 1409, 1357, 1265, 1178, 1074, 966, 867, 821, 756, 725, 692, 592; MS (*m*/*e*): 222, 207, 178, 165, 152, 139, 126, 115, 102, 96, 89, 76, 63, 57.

3.1.12. Reaction of 4-bromo-*N*,*N*-dimethyl aniline with styrene in *N*-methyl pyrrolidinone (13B).[18] 4-Bromo-*N*,*N*-dimethyl aniline (0.395 g, 2 mmol), styrene (0.249 g, 2.4 mmol), K_2CO_3 (0.552 g, 4 mmol) were taken in a flask and 6 ml of *N*-methylpyrrolidinone added to it followed by (0.01 g, 0.017 mmol) of the catalyst (**Cat-6**) and the reaction mixture heated to 140–150 °C for 24 h until all the starting material was completely consumed. Added water, extracted with ethyl acetate, the combined organic extracts washed with brine, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. Purification by column chromatography (Silica gel: 100–200 mesh) gave 0.28 g (**30**, 63%, TON- 73, mp: 147.6–148.7 °C)[16l] of benzenamine, *N*,*N*-dimethyl-4-(2-phenylethenyl)-, (*E*) (**30**) ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.5–7.15 (m, 9H, *Ar*), 7.02–6.94 (d, *J*=16 Hz, 1H, *Ar*·C*H*═), 6.74–6.69 (d, *J*=10 Hz, 1H, C_6H_5–C*H*), 2.98 (s, 6H, $N(CH_3)_2$); IR (cm^{-1}, Nujol): 2923, 2852, 1604, 1519, 1461, 1352, 1222, 966, 810, 748, 690; MS (*m*/*e*): 223, 207, 193, 178, 165, 152, 128, 111, 89, 77.

3.1.13. Reaction of bromobenzene with butyl acrylate in ionic liquid-$(C_4H_9)_4NBr$ (34).[18] $(C_4H_9)_4NBr$ (1.932 g, 6 mmol) was taken in a flask and bromobenzene (0.571 g, 3 mmol), butyl acrylate (0.384 g, 3 mmol), $HCOONH_4$ (0.012 g, 0.2 mmol), Na_2CO_3 (0.636 g, 6 mmol) and **Catalyst-4** (0.012 g, 0.03 mmol) added to it. The reaction mixture was heated to 130 °C for 24 h. Usual extractive workup followed by purification by column chromatography gave 0.430 g, 70% yield of the (*E*)-2-propenoic acid, 3-phenyl-, butyl ester (**34**) (TON- 70).[16o] ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.73–7.65 (d, 1H, *J*=16 Hz, Ar·C*H*═), 7.56–7.31 (m, 5H), 6.49–6.41 (d, 1H, *J*=16 Hz, ═C*H*·$COOC_4H_9$), 4.25–4.18 (t, 2H, *J*=6 Hz, –$COOCH_2$·C_3H_7), 2.05 (s, 3H), 1.80–1.35 (m, 4H, –$COOCH_2$·CH_2·CH_2·CH_3), 1.01–0.93 (t, 3H, *J*=8 Hz,

$-COOCH_2CH_2CH_2{\cdot}CH_3$); IR ($cm^{-1}$, Nujol): 3060, 3028, 2958, 2933, 2873, 1712, 1639, 1311, 1280, 1170, 1066, 979, 864, 767, 709, 684.

3.1.14. Reaction of 4-bromo-*N*,*N*-dimethyl aniline with ethyl acrylate in ionic liquid-$(C_4H_9)_4NBr$ (29).[18] $(C_4H_9)_4NBr$ (2 g, 6.2 mmol) was taken in a flask and 4-bromo-*N*,*N*-dimethyl aniline (0.395 g, 2 mmol), ethyl acrylate (0.4 g, 4 mmol), HCOONa (0.010 g, 0.147 mmol), $NaOCOCH_3$ (0.196 g, 2.4 mmol) and **Catalyst-6** (0.010 g, 0.022 mmol) added to it. The reaction mixture was heated to 130 °C for 15 h. Usual extractive workup followed by purification by column chromatography gave 0.25 g, 57.3% yield (**29**, TON- 50, mp: 76.3–77.8 °C)[16k] of the 2-propenoic acid, 3-[4-(dimethylamino)phenyl]-, ethyl ester (**29**) ^1H NMR (200 MHz, $CDCl_3$, δ): IR (cm^{-1}, Nujol): 7.68–7.60 (d, 1H, J=16 Hz, Ar·C*H*=), 7.46–7.41 (d, J=8 Hz, 2H, *Ar*), 6.70–6.66 (d, J=8 Hz, 2H, *Ar*), 6.28–6.20 (d, J=16 Hz, 1H, Ar·C*H*=), 4.27–4.20 (q, 2H, J=6 Hz, $-COOCH_2{\cdot}CH_3$), 3.03 (s, 6H, $N(CH_3)_2$), 1.37–1.31 (t, J=6 Hz, 3H, $-COOCH_2{\cdot}CH_3$); IR (cm^{-1}, Nujol): 2923, 2854, 1704, 1600, 1525, 1456, 1367, 1305, 1220, 985, 813; MS (*m*/*e*): 219, 190, 174, 146, 130, 118, 102, 98, 87, 72.

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18. Registry numbers of the products: 1. 2-Propenoic acid, 3-(4-methoxyphenyl)-, ethyl ester (**18**) (1929-30-2) 2. 2-Propenoic acid, 3-(4-chlorophenyl)-, ethyl ester, (*E*) (**19**) (24393-52-0) 3. 2-Propenoic acid, 3-phenyl-, ethyl ester, (2*E*) (**20**) (4192-77-2) 4. Phenol, 4-(2-phenylethenyl (**21**) (3839-46-1) 5. Benzene, 1-methoxy-4-[(1*E*)-2-phenylethenyl]- (**22**) (1694-19-5) 6. 2-Propenoic acid, 3-(4-nitrophenyl)-, ethyl ester (**23**) (953-26-4) 7. 2-Propenoic acid, 3-(2-pyridinyl)-, ethyl ester, (2*E*)- (**24**) (70526-11-3) 8. Benzene, 1,1(-(1,2-ethenediyl)bis- (**25**) (103-30-0) 9. 2-Propenoic acid, 3-(1-naphthalenyl)-, ethyl ester, (*E*)- (**26**) (98978-43-9) 10. Naphthalene, 1-[(1*E*)-2-phenylethenyl]- (**27**) (2840-87-1) 11. 2-Propenoic acid, 3-(4-hydroxyphenyl)-, ethyl ester (**28**) (2979-06-8) 12. 2-Propenoic acid, 3-[4-(dimethylamino)phenyl]-, ethyl ester (**29**) (1552-97-2) 13. Benzenamine, *N*,*N*-dimethyl-4-(2-phenylethenyl)-, (*E*) (**30**) (838-95-9) 14. Benzene, 1-nitro-4-[(1*E*)-2-phenylethenyl (**31**) (1694-20-8) 15. Ethanone, 1-[4-(2-phenylethenyl)phenyl]- (**32**) (3112-03-6) 16. Benzonitrile, 4-[(1*E*)-2-phenylethenyl]- (**33**) (13041-79-7) 17. 2-Propenoic acid, 3-phenyl-, butyl ester (**34**) (538-65-8) 18. Benzene, 1-methyl-4-[(1*E*)-2-phenylethenyl]- (**35**) (1860-17-9) 19. Benzene, 1-chloro-4-[(1*E*)-2-phenylethenyl] (**36**) (1657-50-7) 20. 2-Propenoic acid, 3-(4-cyanophenyl)-, ethyl ester, (*E*)- (**37**) (62174-99-6) 21. 2-Propenoic acid, 3-(4-acetylphenyl)-, ethyl ester,(*E*) (**38**) (82989-26-2); 22. **Cat-13B**–palladium,chloro(1,3-diphenyl-2-imidazolidinylidene)[2-[(hydroxyimino)phenylmethyl]-phenyl-*C*,*N*]-, (SP-4-4)-$C_{28}H_{24}ClN_3OPd$-(68248-78-2); 23. **Cat-10**–palladium, di-μ-chlorobis[2-[1-(hydroxyimino)-ethyl]phenyl-*C*,*N*]di-, stereoisomer–$C_{16}H_{16}Cl_2N_2O_2Pd$-(32679-19-9); 24. **Cat-8**–palladium, di-μ-chlorobis[2-[(dimethylamino-*N*)methyl]phenyl-*C*]di- $C_{18}H_{24}Cl_2N_2Pd_2$-(18987-59-2); 25. **Cat-13A**–palladium, chloro(1,3-diphenyl-2-imidazolidinylidene)[2-[1-(hydroxyimino)ethyl]phenyl-*C*,*N*]-, (SP-4-4)-$C_{23}H_{22}ClN_3OPd$-(68248-77-1); 26. **Cat-13B**–palladium,chloro(1,3-diphenyl-2-imidazolidinyl-idene)[2-[(hydroxyimino)phenylmethyl]phenyl-*C*,*N*]-, (SP-4-4)-$C_{28}H_{24}ClN_3OPd$-(68248-78-2); 27. **Cat-13C**–palladium, chloro[2-[(dimethylamino)methyl]phenyl-*C*,*N*](1,3-diphenyl-2-imidazolidinylidene)-, (SP-4-4)- $C_{24}H_{26}ClN_3Pd$ -(68248-79-3).