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

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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

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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.

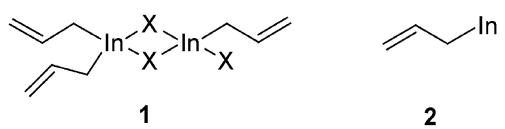
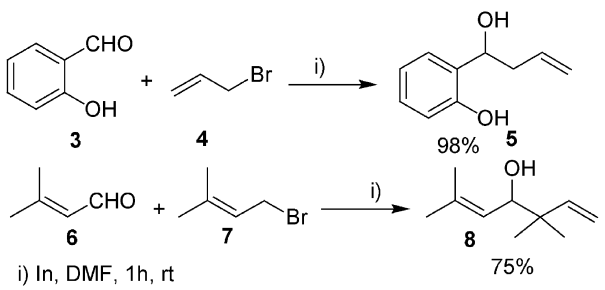


Figure 1.



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

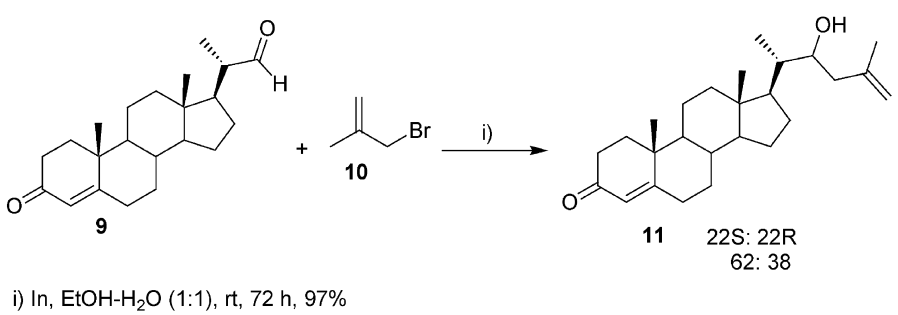
2.1. Allylation reactions

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]

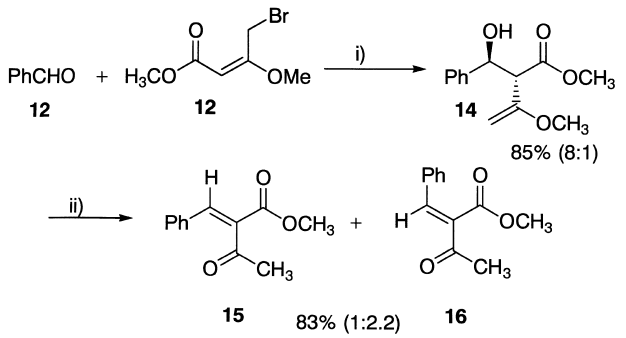
Indium-mediated allylation of the steroidal aldehyde **9** in an aqueous medium provides easy access to a wide variety of



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

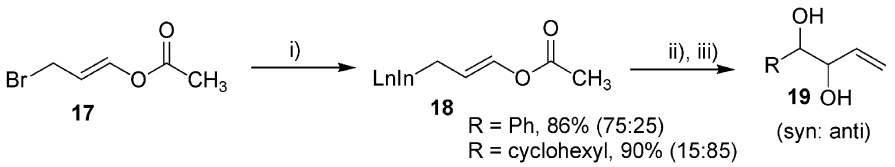
Scheme 3.

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]

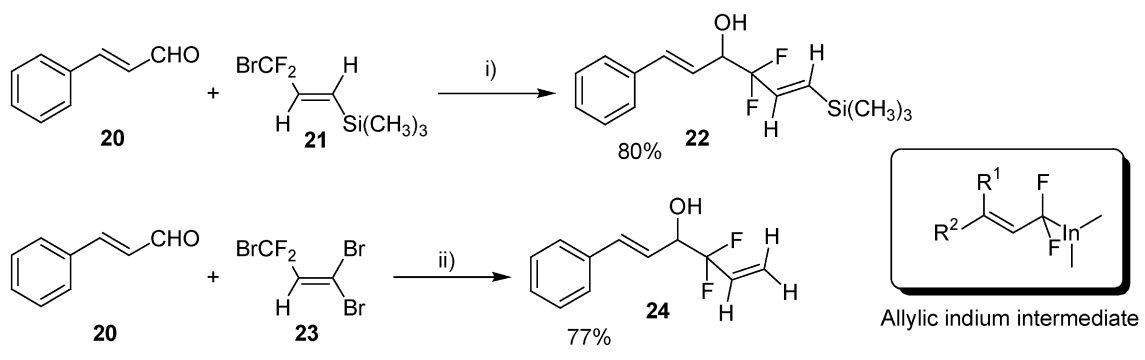
The organoindium reagent derived from 5-bromo-1,3-pentadiene and indium metal reacts with a variety of aldehydes and ketones with excellent regioselectivity to afford the non-conjugated diene products (γ-pentadienylation) in respectable yields. In addition, the trienes derived from the dehydration of 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



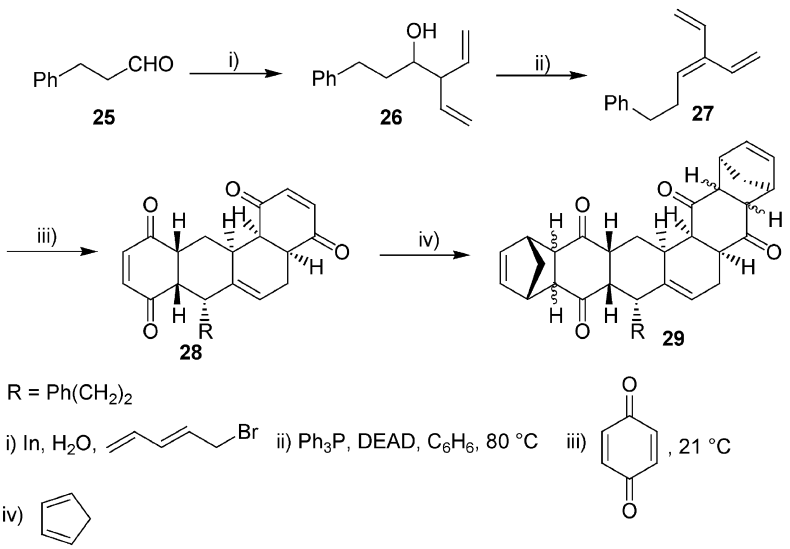
i) In, THF, 0°C-rt, 4h ii) RCHO, 0°C, 4h iii) K_2CO_3, MeOH, Overnight

Scheme 4.

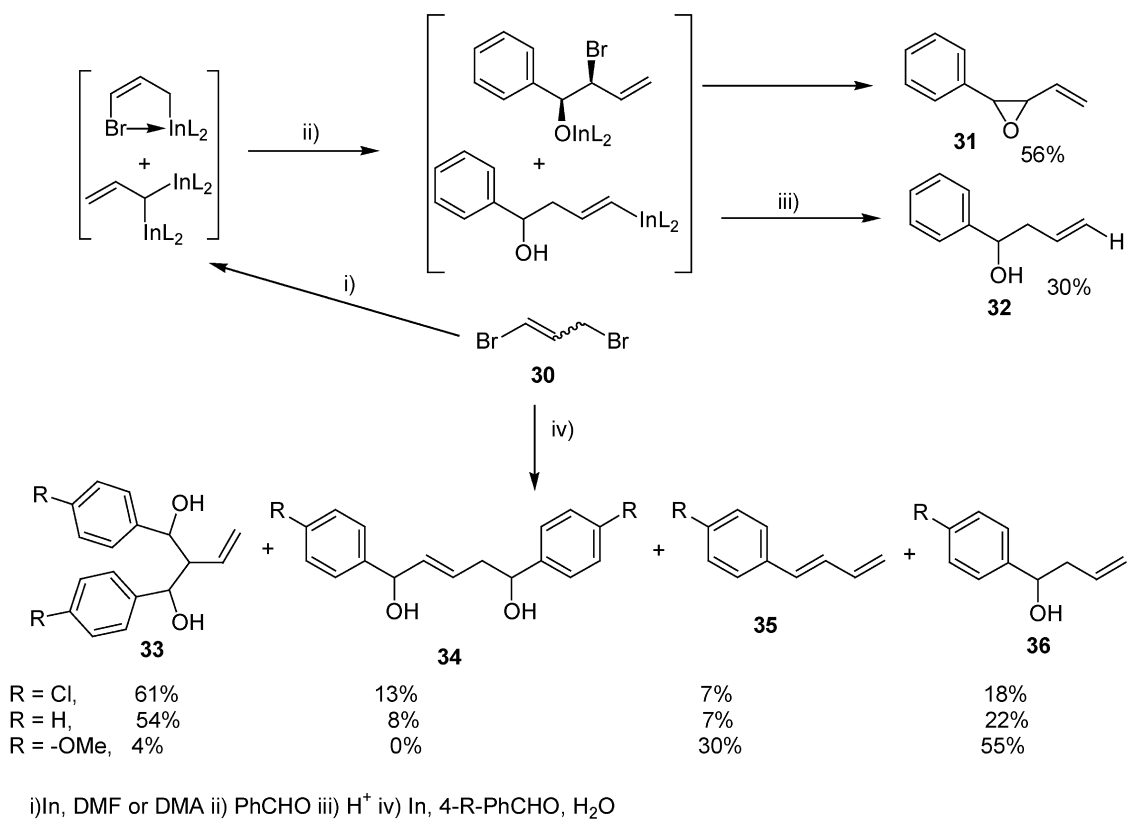


i) In, LiI, DMF, rt ii) In, LiI, DMF, 50 °C

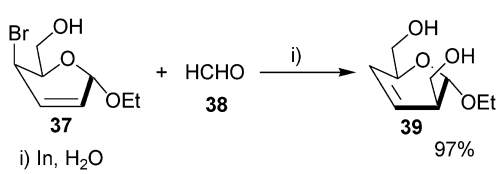
Scheme 5.



Scheme 6.



Scheme 7.

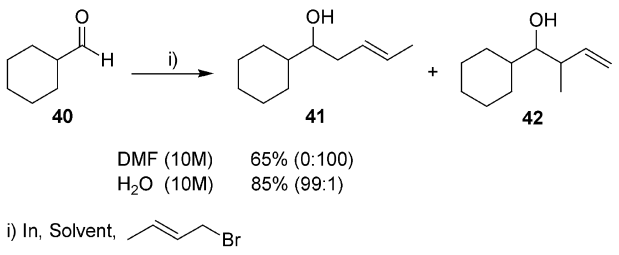


Scheme 8.

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]

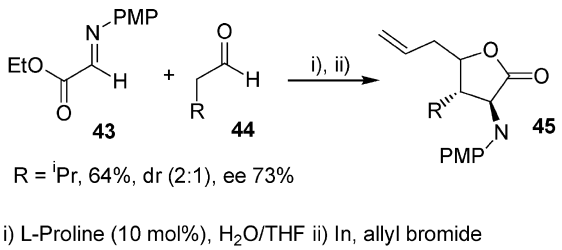
In general, allylation of an aldehyde with a γ-substituted allylic indium reagent occurs regioselectively at the



Scheme 9.

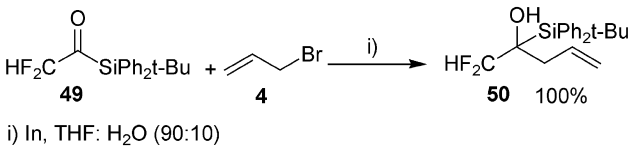
γ-position to afford the γ-homoallylic alcohol in the absence of a sterically-bulky substituent at the carbonyl or allyl bromide. Loh et al., however, have succeeded in synthesising the α-homoallylic alcohol via indium-mediated allylation without the use of a sterically-hindered substituent (Scheme 9).[18] 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]

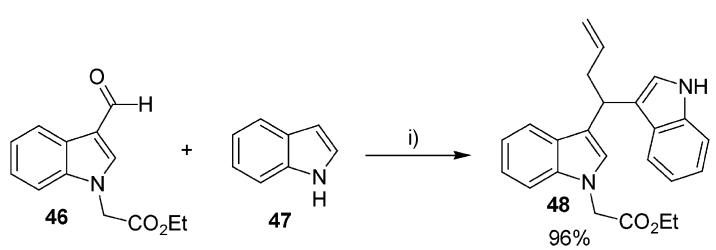
Indium-mediated allylation of α-chloro carbonyl compounds with various allyl bromides in aqueous media gave the corresponding homoallylic chlorohydrins, which could be transformed in to the corresponding epoxides in the presence of a base (Scheme 13).[22] These reactions are strongly dependent on both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

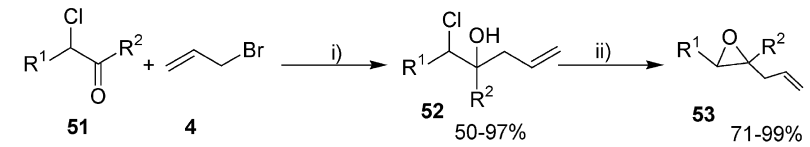
The regioselectivity of the reactions of α,β-enones with allylindium reagents in the presence of TMSCl has also been studied. In the absence of TMSCl, 2-cyclohexen-1-one reacted regioselectively with the allylindium reagent to produce the 1,2-addition product, whereas only the 1,4-addition product was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

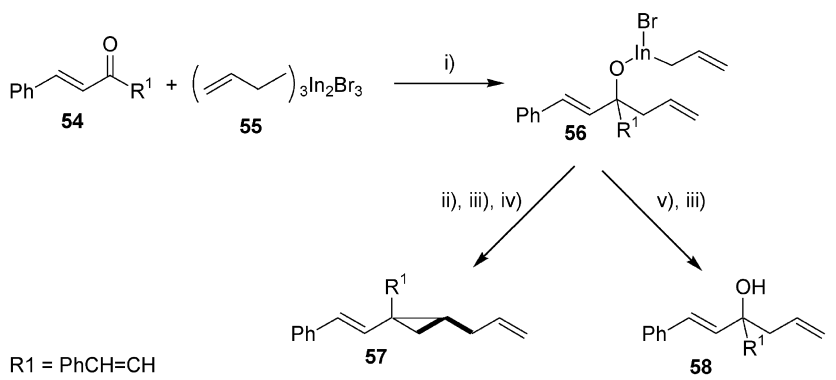


Scheme 11.



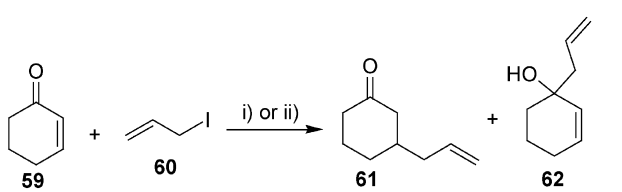
R^1 = H, alkyl, carbonyl compounds
R^2 = aromatic, alkyl, carbonyl compounds
i) In, THF-H_2O
ii) base

Scheme 13.

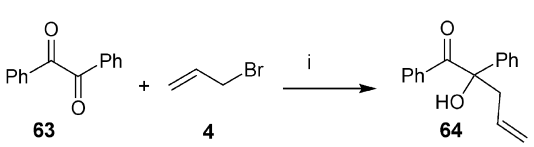


i) THF, 25 °C, ii) LiBr, iii) Et_2O, iv) H_3O^+ (O_2), v) H_3O^+

Scheme 14.



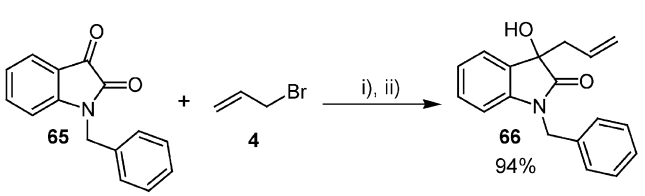
Scheme 15.



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

Scheme 16.

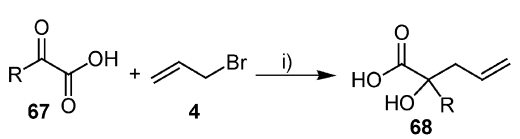
reacts chemoselectively with isatins to afford the oxindole derivatives. In the case of substituted allylic bromides such as cinnamyl and prenyl bromides, exclusive γ-regioselectivity was observed (Scheme 17).[26]



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.

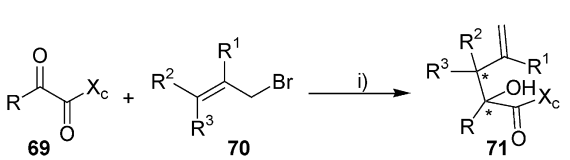


i) In, THF/H_2O, rt

Scheme 18.

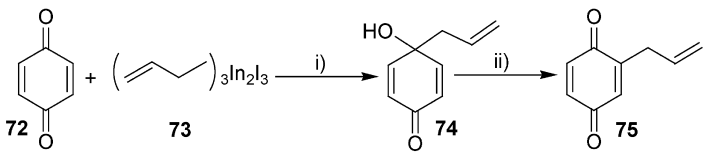
Indium-mediated allylation of α-ketoimides derived from Oppolzer's sultam was accomplished in aqueous THF in good yields and excellent diastereomeric excesses (Scheme 19).[28] This method is very attractive for the preparation of enantiopure α-hydroxyacids.

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

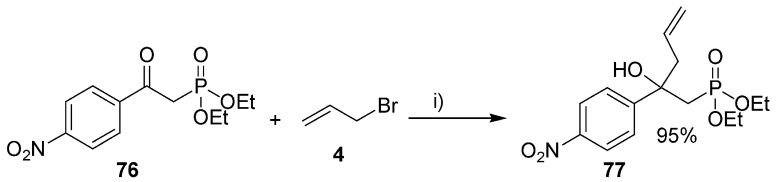


X_c = (+) or (-) Oppolzer's sultam, R = phenyl , thiophenyl , furyl
i) In, aq. THF

Scheme 19.



Scheme 20.

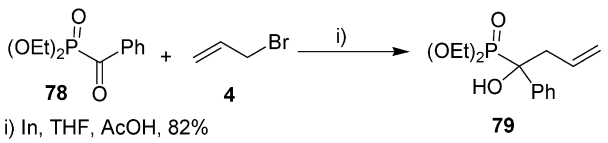


Scheme 21.

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]

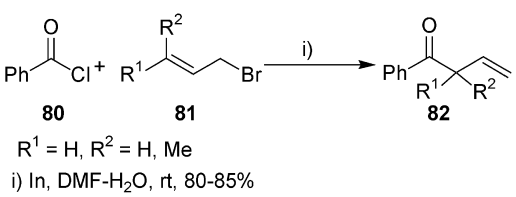
Treatment of aryl phosphonates with allylindium reagents in the presence of acetic acid afforded the corresponding α-hydroxy alkylphosphonates in good yields under mild conditions. This process works well with several different allylic bromides and does not appear to be sensitive to steric hindrance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



Scheme 22.

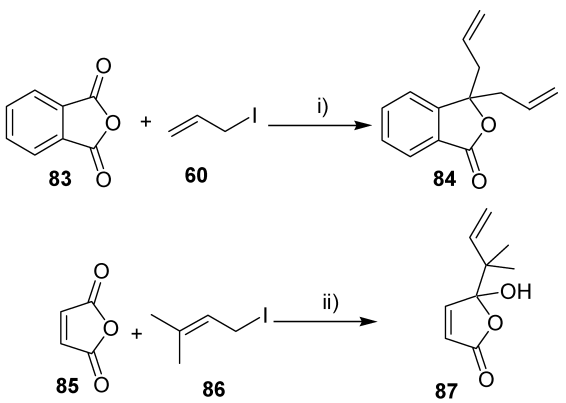
The allylation of acid chlorides with allyl, crotyl or prenyl bromide and indium in DMF at room temperature provides a mild and efficient method for the preparation of β,γ-unsaturated ketones (Scheme 23).[32a] The indium-mediated allylation of acyl cyanides with allyl halides in aqueous media also affords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

Allylation of cyclic acid anhydrides with allyl halides and



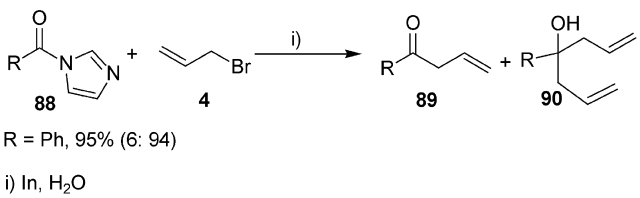
Scheme 23.

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.

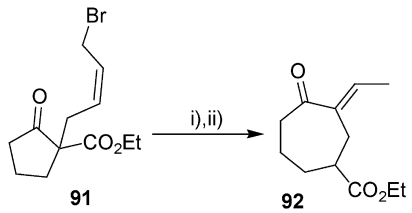
The indium-mediated reaction of allyl bromide with acylimidazoles or pyrazoles in aqueous media gives a mixture of the tertiary alcohol and ketone (Scheme 25).[34] The reaction of simple alkyl and aryl acylimidazoles with



Scheme 25.

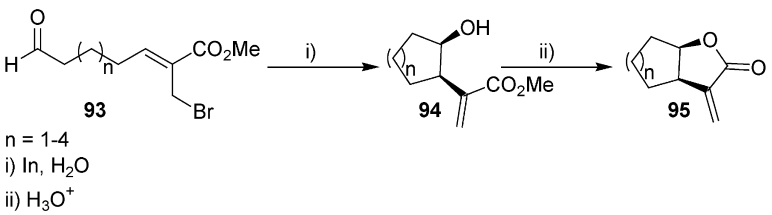
indium and allyl bromide gives predominantly the tertiary alcohol, whereas the reaction of acylpyrazoles under identical conditions results in the predominant formation of the homoallylic ketone.

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]



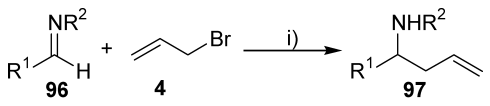
Scheme 26.

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]



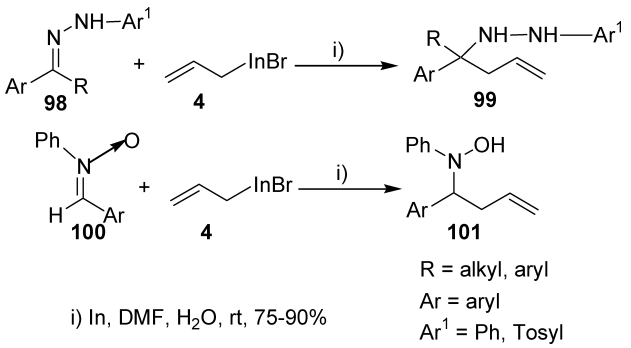
Scheme 27.

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]



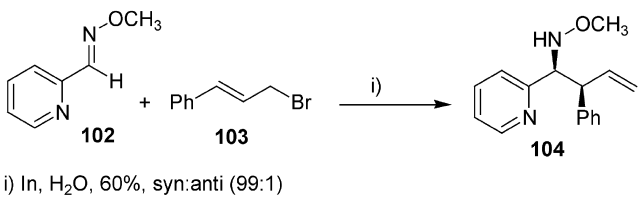
Scheme 28.

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.

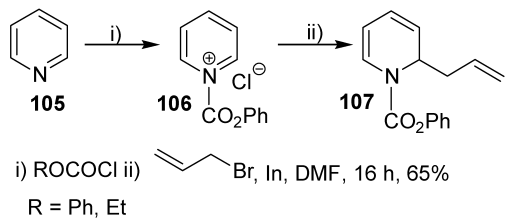
Oxime ethers derived from 2-pyridinecarboxaldehyde and glyoxylic acid can be efficiently allylated in water with allylic bromides promoted by indium (Scheme 30).[39] When the metal is positioned in the proximity of flanking heteroatomic centers, chelation by indium is indeed operative and affects both 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.



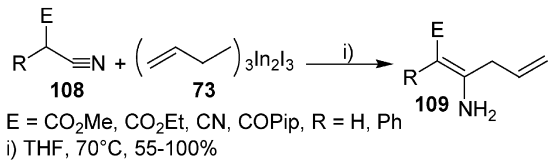
Scheme 30.

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



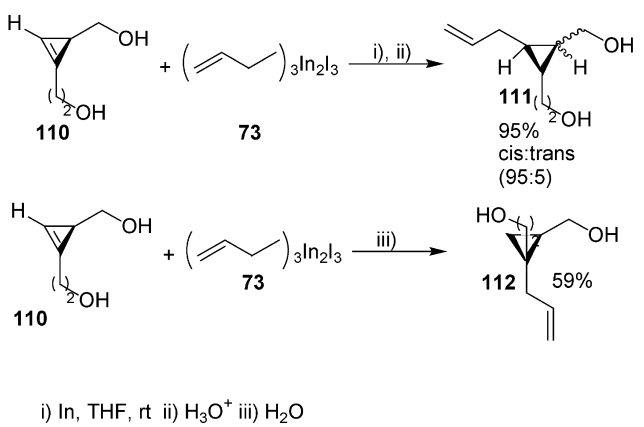
Scheme 31.



Scheme 32.

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

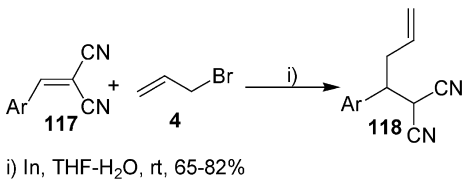
2.1.2. Allylation reactions of compounds with carbon–carbon multiple bonds. The hydroxyl-bearing cyclopropenes undergo clean allylindation with allylindium reagents in both organic and aqueous media, in which chelation of the hydroxyl group to indium plays a central role. The regio- and stereoselectivity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



Scheme 33.

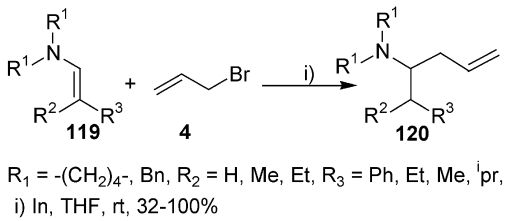
The allylindation of non-activated carbon–carbon double bonds of norbornenols proceeds with high regio- and stereoselectivity to afford the allylated products, together with iodinated and oxygenated products (Scheme 34).[43] The product distribution can be controlled by changing the reaction solvent. 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.



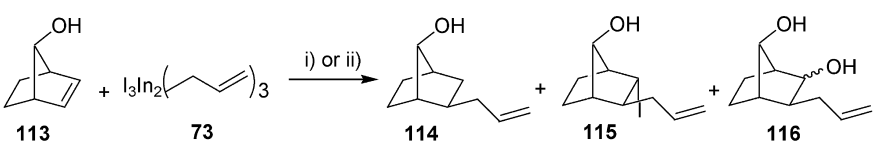
Scheme 35.

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.



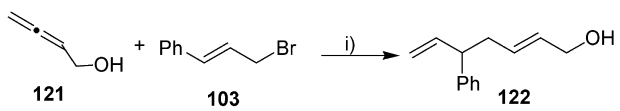
Scheme 36.

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.



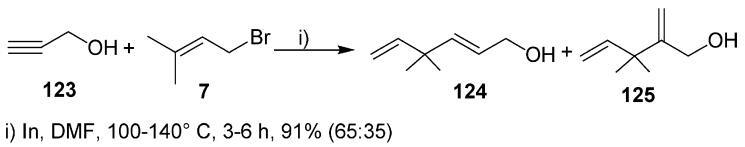
i) THF, reflux	26	16	32
ii) NMP, 180°C	72	0	0

Scheme 34.



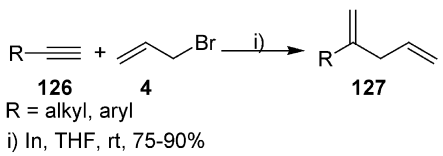
Scheme 37.

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.

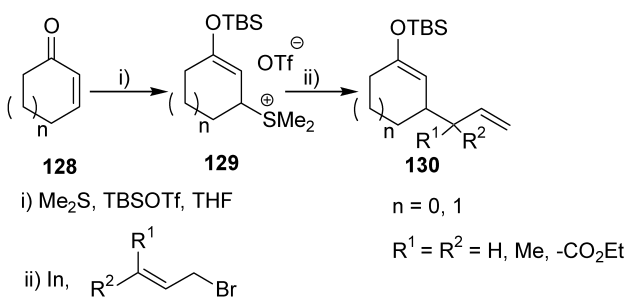
The reaction of unactivated terminal alkynes with allyl bromide and indium in THF at room temperature produces the 1,4-dienes via regioselective addition (Scheme 39).[48] In the case of unprotected alkynols, the regioisomeric outcome is found to depend upon the distance between the hydroxyl group and 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.

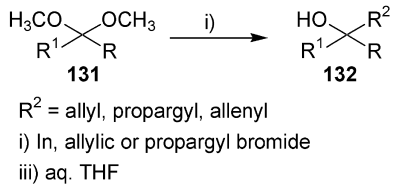
2.1.3. Allylation reactions of compounds with other functional groups. The 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts **129**, derived from the reaction of α,β-enones with dimethyl sulphide in the presence of TBSOTf, undergo a novel nucleophilic substitution with allylindium reagents to 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



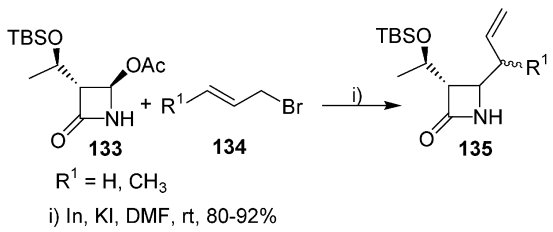
Scheme 40.

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.

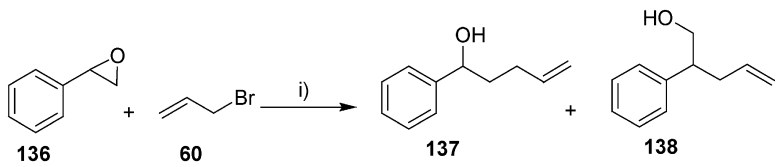
Allylindium, prepared from allyl bromide and indium metal in THF, reacts with terminal epoxides at room temperature to afford the corresponding bishomoallyl alcohols in excellent yields and with good regioselectivity (Scheme 43).[52]

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

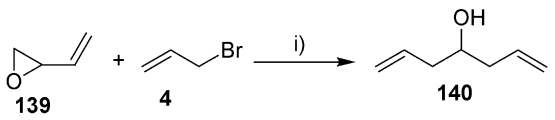
With a variety of organic electrophiles such as aryl and vinyl triflates, vinyl halides, dibromoolefins and alkynyl iodides, allylindiums generated in situ underwent palladium-catalysed allyl cross-coupling reactions (Scheme 45).[54] The presence of various alkyl substituents at the α-and γ-positions 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,



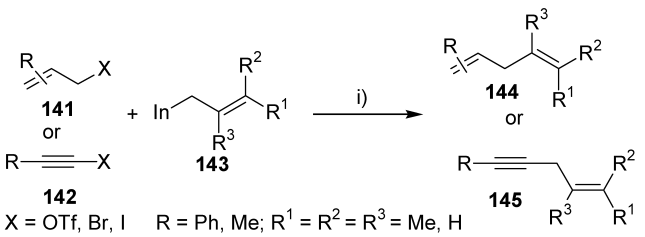
i) In, THF, rt, 90% (90:10)

Scheme 43.



i) In, THF, rt, 87%

Scheme 44.

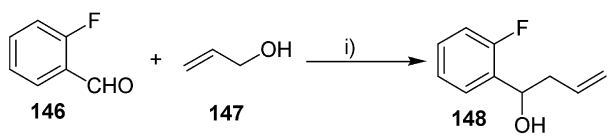


X = OTf, Br, I R = Ph, Me; $R^1 = R^2 = R^3$ = Me, H

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]

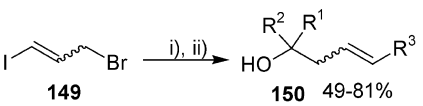


i) In, $InCl_3$, $Pd(PPh_3)_4$, $THF:H_2O$, rt, 100%

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]



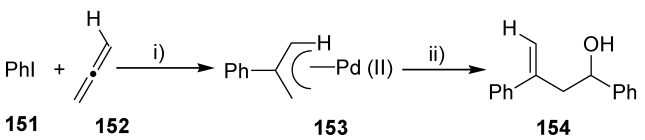
R^1 = alkyl, phenyl, R^2 = H, CH_3,

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.

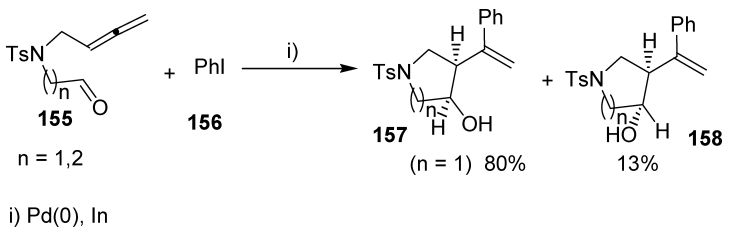
The tandem palladium-catalysed and indium-mediated arylative cyclisation of allenyl aldehydes and ketones to form homoallylic cyclopentanols and cyclohexanols has been reported (Scheme 49).[58a] A similar reaction was observed with allenyl sulfonimines; in contrast to allenyl aldehydes, the *trans* isomer 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]

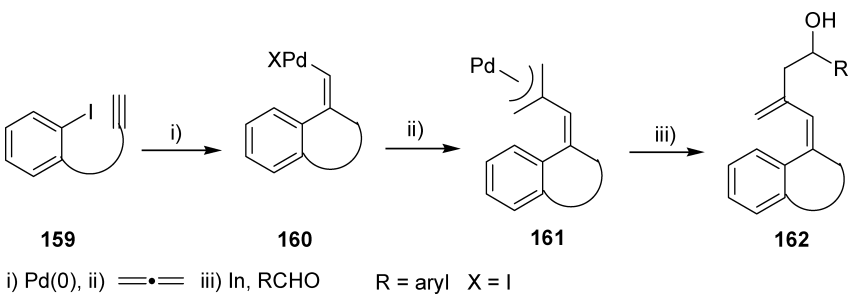
Allenylindium intermediates generated by the reaction of indium with propargyl bromides were employed as effective partners in palladium-catalysed coupling reactions with a variety of electrophiles to produce allenes, polyallenes and unsymmetrical bis(allenes) in excellent yields with complete regio-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

2.3. Propargylation reactions

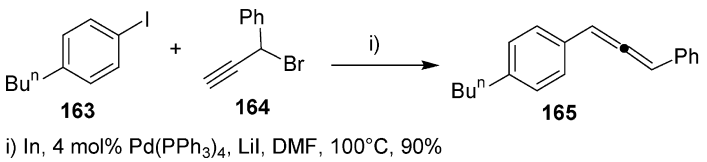
Among the many metals employed for propargylation reactions, indium has attracted special attention, due to its mild reaction conditions, as well as its wide functional group compatibility. Compared to the well-established allylic indium chemistry, however, the synthetic potential



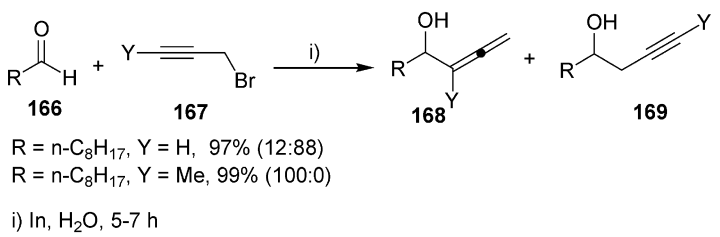
Scheme 49.



Scheme 50.



Scheme 51.



Scheme 52.

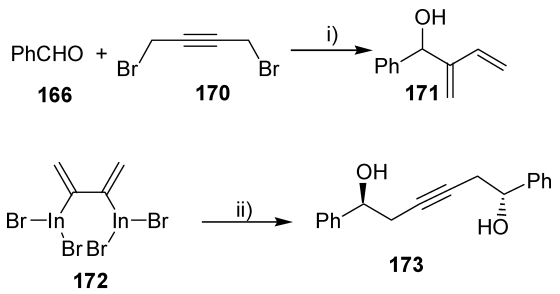
of propargylic indium reagents has not yet been fully exploited.

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]

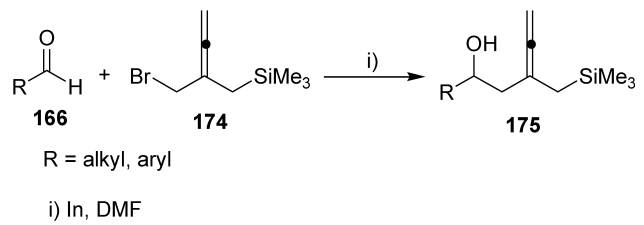
Indium-mediated coupling of 1,4-dibromo-2-butyne with carbonyl compounds in aqueous media proceeded regioselectively to give good yields of the 1,3-butadien-2-ylmethanols. 2,3-Dibutadienyldiindium tetrabromide, formed by the reaction of 1,4-dibromobutyne with indium, adds to different carbonyl compounds 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

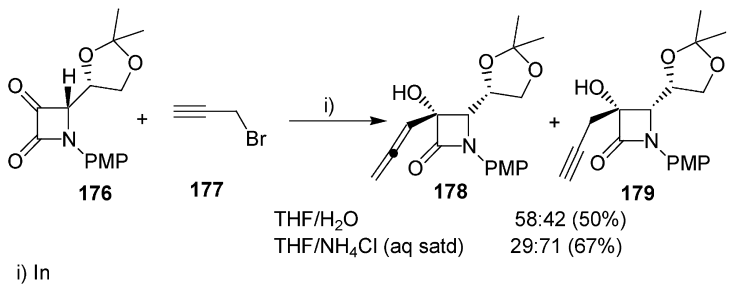


Scheme 53.

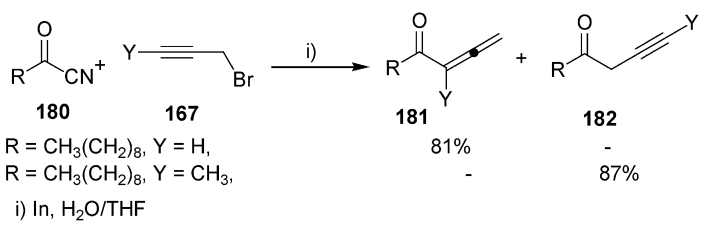


Scheme 54.

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.



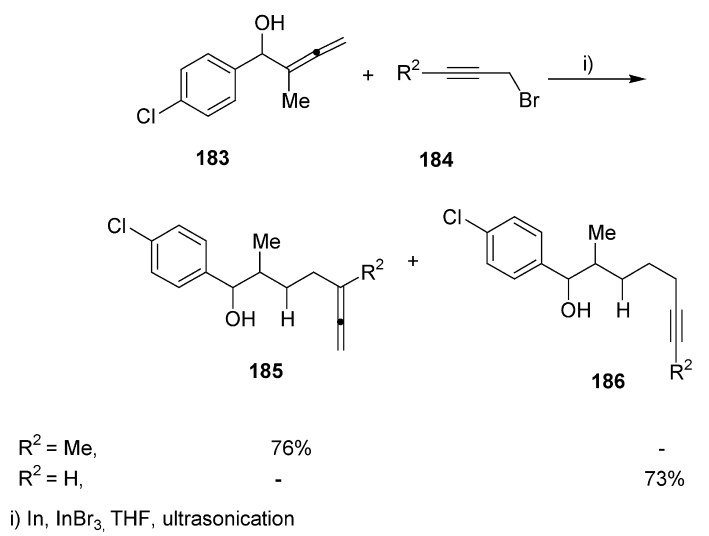
Scheme 56.

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

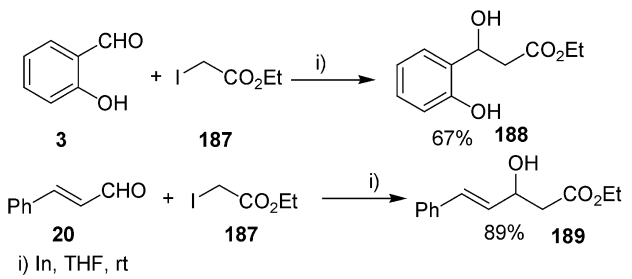
The Reformatsky reaction, because of its selectivity and wide applicability, is a valuable method for the synthesis of



Scheme 57.

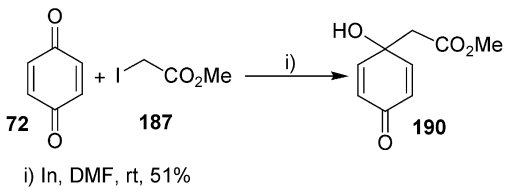
hydroxyesters and their dehydration products. This reaction involves the treatment of an α-bromoester with zinc in the presence of an aldehyde or ketone to afford the β-hydroxyester. Recently, several modified Reformatsky reactions using other metals such as manganese, samarium, etc. have been described.

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]



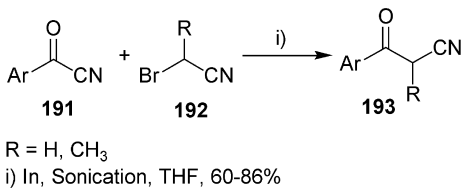
Scheme 58.

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.

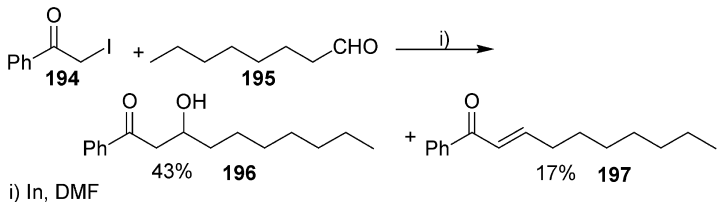
Recently, the In/$InCl_3$-mediated cross-coupling of methyl vinyl ketone with benzaldehydes in aqueous media has been reported (Scheme 63).[72] In this reaction, the end product was the β,γ-unsaturated ketone and not the pinacol.

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.

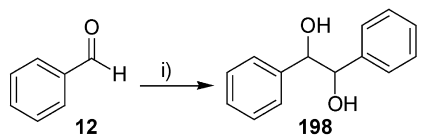
The indium-mediated 1,4-addition of an alkyl radical to β-substituted conjugated alkenes in the presence of the radical hydrogen source 1-ethylpiperidium hypophosphite (EPHP), the surfactant cetyltrimethylammonium bromide (CTAB) and the water-soluble radical initiator 4,4′-azo-bis(4-cyanovaleric) acid (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]

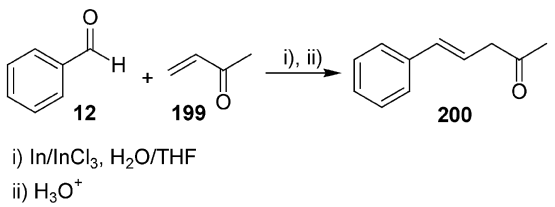
The indium-mediated atom-transfer cyclisations and reductive cyclisations depend upon the ratio of indium and iodine used (Scheme 67).[76] Treatment of an iodoalkyne with indium (0.5 equiv.) and iodine (0.5 equiv.) in methanol promotes the atom-transfer 5-exo cyclisation. In contrast, the reaction with 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.



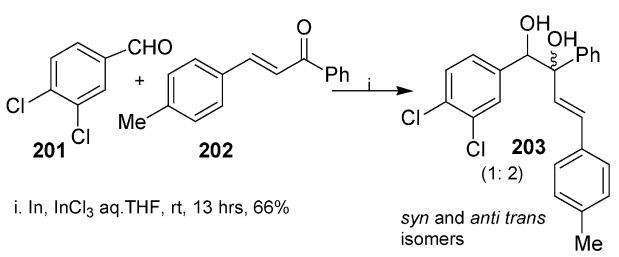
Scheme 61.



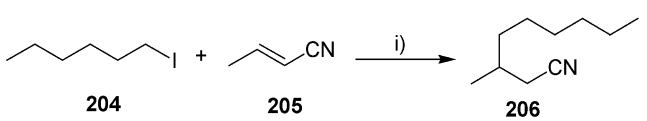
Scheme 62.



Scheme 63.

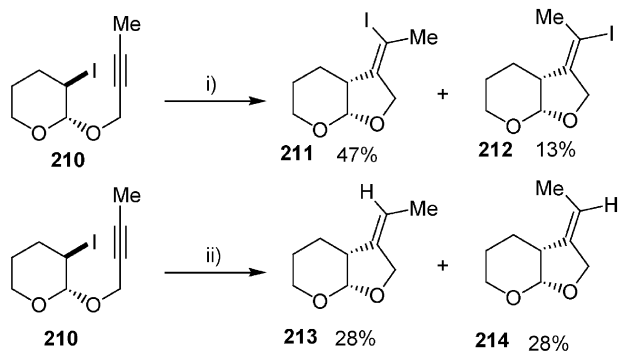


Scheme 64.



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]

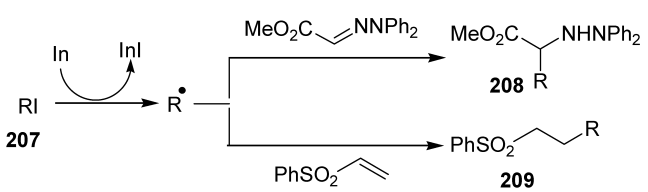


Scheme 67.

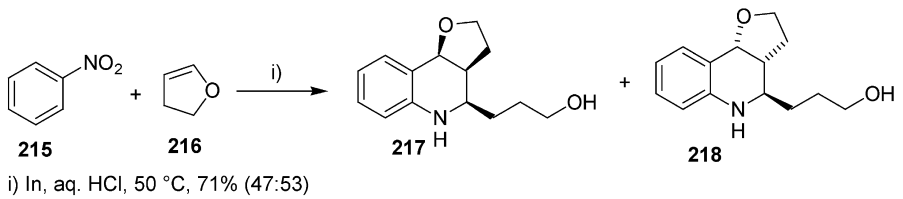
Indium-catalysed aromatic Friedel–Crafts allylation in the presence of $CaCO_3$ and 4 Å molecular sieves results in the formation of the corresponding allylated products in high yields (Scheme 69).[78] The high yields of the reaction in an open vessel, using a catalytic amount of indium which is re-usable 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.

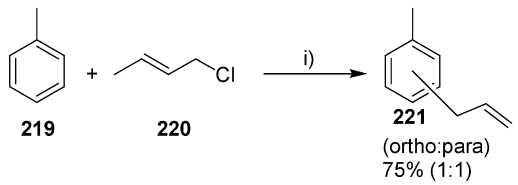
Indium can efficiently mediate the reaction between some β-aminovinyl chlorodifluoromethyl ketones and a series of



Scheme 66.



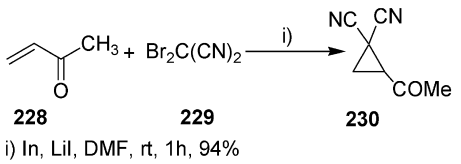
Scheme 68.



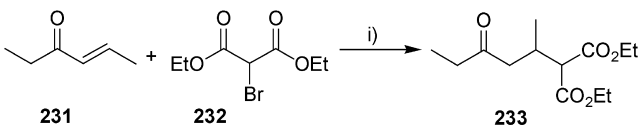
Scheme 69.

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]



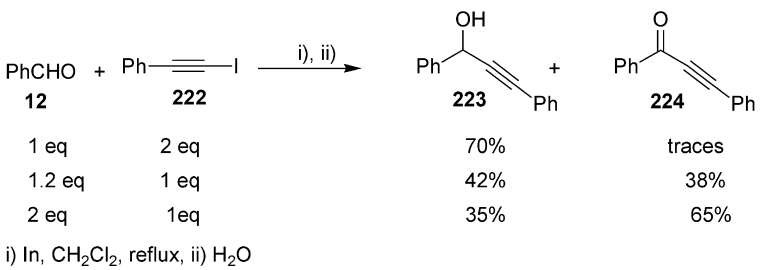
Scheme 72.



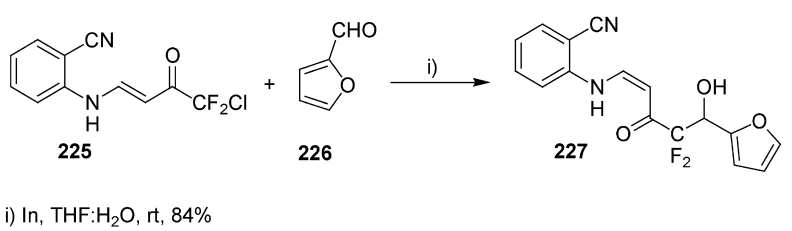
Scheme 73.

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.

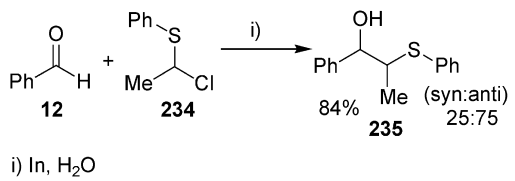
The α-chloro sulfides are used to control the stereoselectivity in indium-promoted C–C couplings at room temperature under aqueous and mixed aqueous/organic



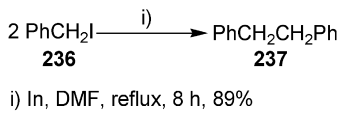
Scheme 70.



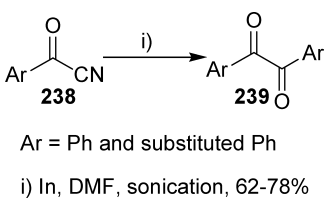
Scheme 71.



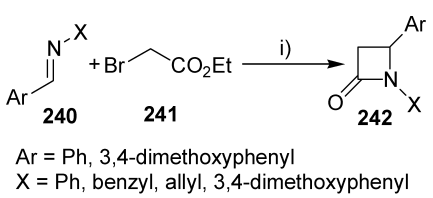
Scheme 74.



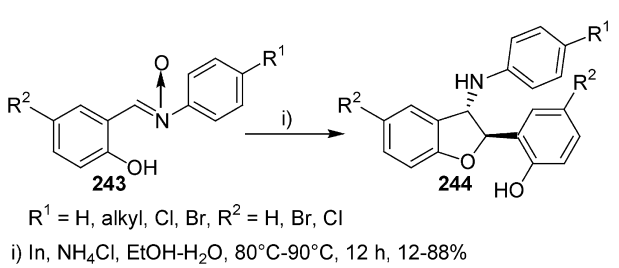
Scheme 75.



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.

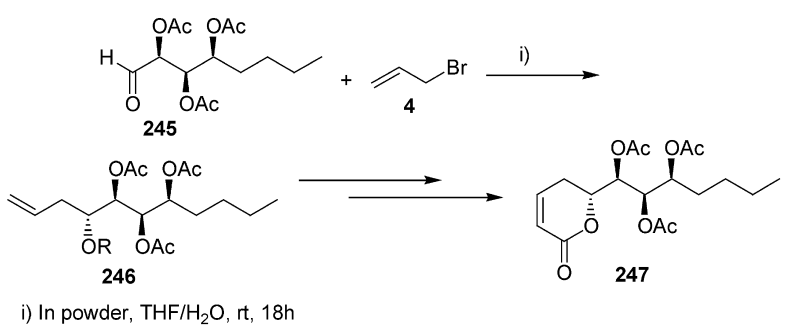
Nitrones undergo deoxygenative reductive coupling and subsequent cyclisation to the 3-arylamino-2,3-dihydrobenzofuran derivatives in the presence of indium under aqueous conditions at ambient temperature (Scheme 78).[87]

3. Application to the synthesis of natural products

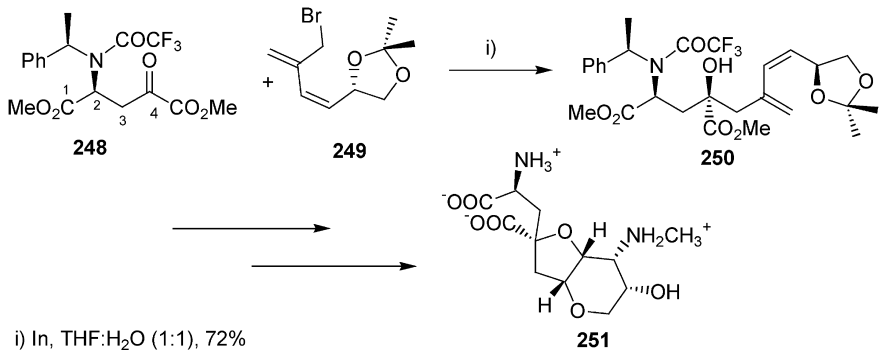
Indium-mediated reactions have found widespread applications in the synthesis of several natural products which are biologically active. This aspect of indium chemistry is briefly described here, with illustrative examples:

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]

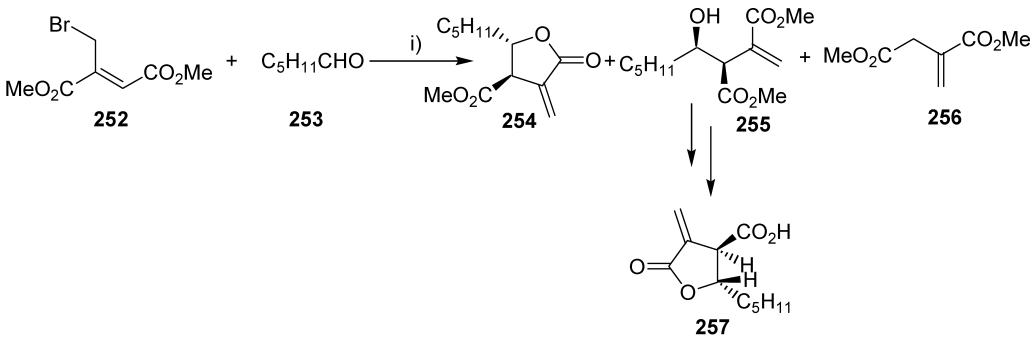
For the total synthesis of dysherbaine **251**, a stereospecific route to the key intermediate based on the indium-mediated allylation reaction in aqueous media has been successfully developed (Scheme 80).[89] A remote phenyl substituent group was used as a control element to achieve a high stereoselectivity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



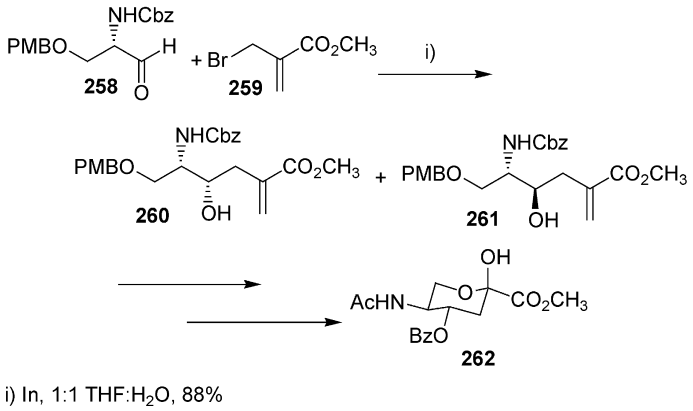
Scheme 79.



Scheme 80.



Scheme 81.



Scheme 82.

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

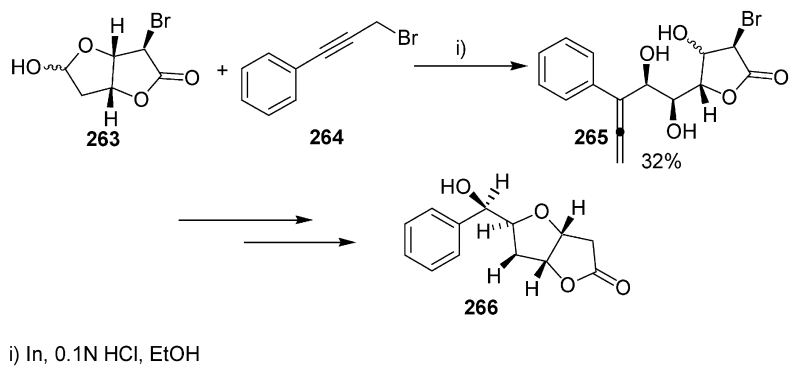
(±)-Methylenolactocin **257**, an antitumour agent, was prepared in five steps in which the indium-mediated allylation reaction forms the key stage (Scheme 81).[90]

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]

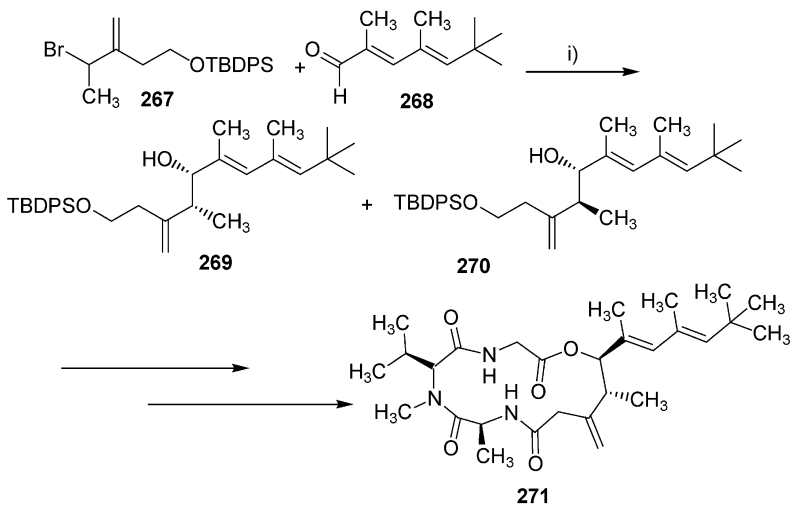
The highly-diastereoselective indium-mediated allenylation of carbonyl compounds bearing an α-hydroxyl group constitutes one of the major steps in the total synthesis of (+)-goniofufurone **266**, a cytotoxic agent (Scheme 83).[92]

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.

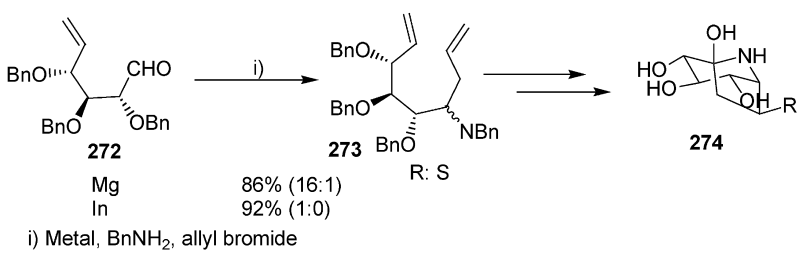
The key step in the total synthesis of calystegine alkaloids employs a zinc-mediated fragmentation of benzyl-protected methyl 6-iodoglycosides, followed by the in situ formation of the benzylimine and Barbier-type allylation with zinc,



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

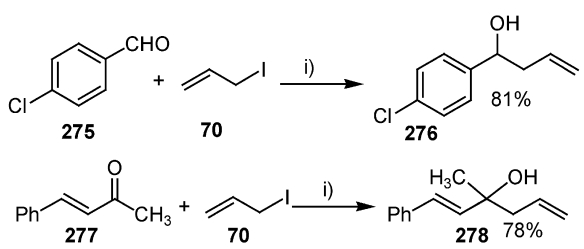
Gallium metal was discovered spectroscopically by the French chemist de Boisbaudran in 1875.[1] The name gallium is coined from the Latin word 'gallio', the former name of France.

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]



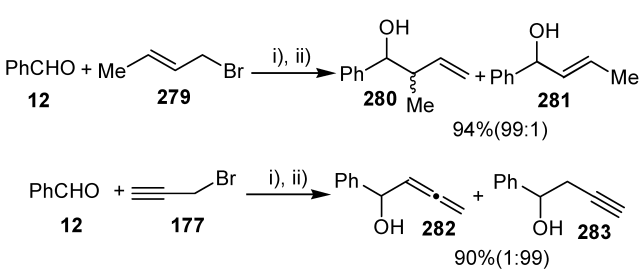
i) Ga, DMF, Ultrasonication, 30 min.

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.

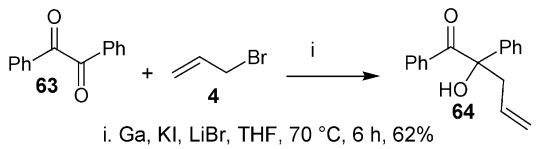
In the presence of potassium iodide, lithium chloride and gallium, aldehydes react with allylic bromides to afford the corresponding α- and γ-adducts (Scheme 87).[96] Interestingly, the reaction shows a very high selectivity towards the γ-adducts. Under the same conditions, the reaction of propargyl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

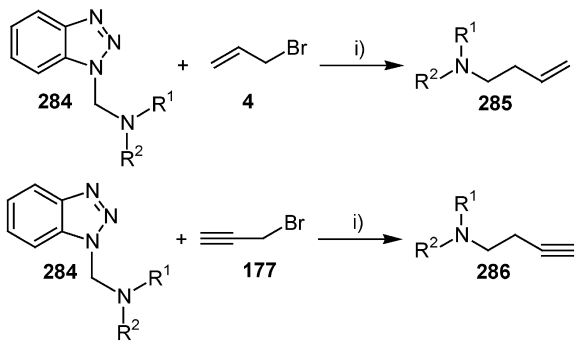
Scheme 87.



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%

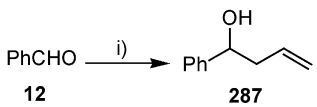
Scheme 89.

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.

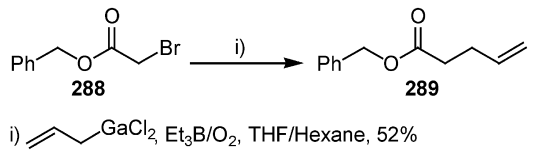
4.1.1. Transmetallation of allylmagnesium bromide using gallium trichloride. The allylic gallium reagents prepared from gallium trichloride and the corresponding allylic Grignard reagent allylated carbonyl compounds in excellent yields in an aqueous medium, as well as in organic solvents (Scheme 90).[99]

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.



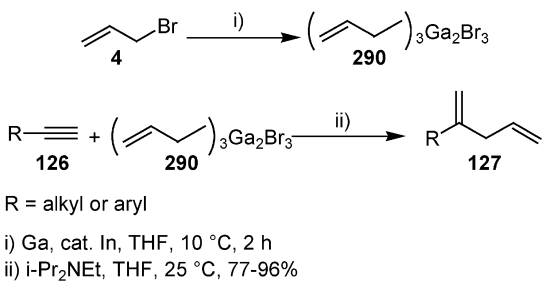
i) $GaCl_2$, THF-Hexane, 0 °C, 30 min., 94%

Scheme 90.



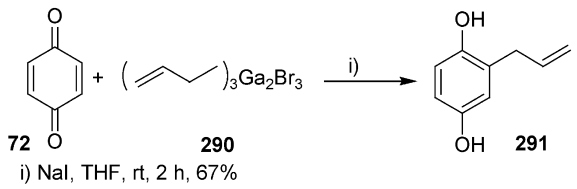
Scheme 91.

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.

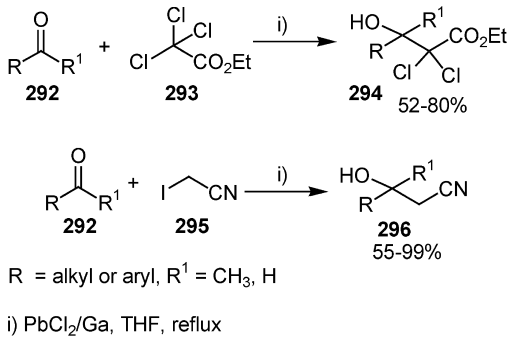
The Grignard-type reaction of 1,4-diones with allylgallium sesquibromide provides a facile and convenient method for the allylation of quinones. Here, the allylgallium sesquihalide is prepared by the reduction of allylic bromides with gallium metal in the presence of a catalytic amount of indium. *p*-Benzoquinone (**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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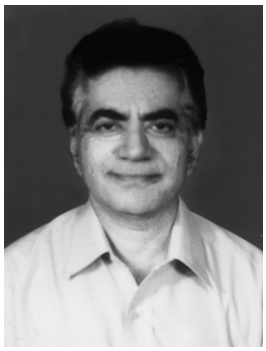
Biographical sketch



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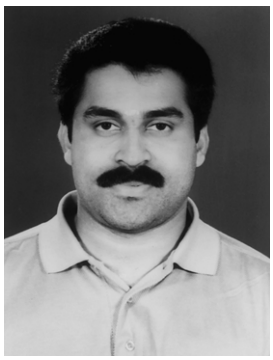

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