Recent Advances in Indium-Promoted Organic Reactions

Jacques Augé,* Nadège Lubin-Germain, Jacques Uziel
Département de Chimie, UMR CNRS-ESCOM-Université de Cergy-Pontoise, Neuville-sur-Oise, 95031 Cergy-Pontoise, France
Fax +33(1)34257071; E-mail: jacques.auge@u-cergy.fr
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Abstract: This review deals with organic reactions which are promoted by indium metal or indium salts, with a focus on recent advances in stoichiometric and catalytic pathways. Applications to transmetalations, cross-coupling reactions and carboindation, in which an organoindium species may be postulated, are highlighted, as well as the reactions in which a radical is the key intermediate. Special attention is placed on the role of indium metal as a reducer, and on the Lewis acidity of indium salts in catalytic processes.

1 Introduction
Indium-mediated organometallic reactions have elicited considerable attention since the discovery of the remarkable reactivity of this metal in organic1 or aqueous media.2 Several authors have highlighted the special interest in using indium metal in aqueous media as it is not affected by water or by air.3–7 Other aspects of indium(0) or indium(III) chemistry were recently reviewed.8–11 Organometallic species may be postulated when either indium(0) or indium(I) is inserted into a carbon–halogen bond,12 but in many cases, indium(0), acting as a reducing agent, may induce a radical intermediate.13 Indium(III) in the presence of various hydrides may give rise to a powerful reducing agent, thereby allowing for new reactivities.14,15 Indium(III) salts are water-tolerant additives and this property has resulted in an increase in the interest of using such Lewis acids in catalytic processes.16 This review focuses on the recent advances of indium-promoted organic reactions, whatever the oxidation state of indium.

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When indium(I) iodide is used as the promoter in tetrahydrofuran, allylindium(III) diiodide, arising from oxidative addition, is presumably the reactive species, as evidenced by the $^1$H NMR signal at 2.14 ppm. Such an oxidative addition of an indium(I) salt in tetrahydrofuran solution was evidenced by a single-crystal analysis of In(C$_6$F$_5$)Br$_2$·2THF obtained from bromopentafluorobenzene and indium(I) bromide. Chan and Yang have carefully investigated the reaction of indium(0) with allyl bromide. The $^1$H NMR signal at 1.7 ppm observed in water was attributed to an allylindium(I) species, since the same signal was observed after transmetalation of diallylmercury with either indium or indium(I) iodide. Moreover, the authors suggested that the two signals observed at 1.7 and 2.15 ppm, when they performed the reaction of allyl bromide with indium in $N,N$-dimethylformamide, might result from the formation of a mixture of allylindium(I) and allylindium(III) dibromide. According to this hypothesis, two successive reactions might occur in $N,N$-dimethylformamide. The fact that only the first reaction is observed in water is probably a consequence of the rapid disproportionation of indium(I) halide in water.

$$\text{RX} + 2 \text{In} \rightarrow \text{RIn} + \text{InX}_2$$
$$\text{RX} + \text{InX} \rightarrow \text{RInX}_2$$

By summation, $2 \text{RX} + 2 \text{In} \rightarrow \text{RIn} + \text{RInX}_2$

Substrates other than alkyl halides may insert indium(I) halides under non-aqueous conditions. Thus, oxidative addition of InX may occur with disulfides or diselenides, which produce sulfides or selenides as nucleophiles in various reactions.

**Biographical Sketches**

**Jacques Augé** graduated from the École Nationale Supérieure de Chimie de Paris, and received his PhD from the Université de Paris-Sud (Orsay) in 1978, under the supervision of Professor Serge David. After post-doctoral work with Professor George Whitesides at Massachusetts Institute of Technology in Cambridge, Massachusetts, he returned back to Orsay to develop aqueous organic chemistry with Professor André Lubineau. His current interests focus on carbohydrate chemistry, reaction medium effects and indium chemistry.

**Nadège Lubin-Germain** studied organic chemistry at the Université de Paris-Sud (Orsay). In 1992, she obtained her PhD under the supervision of Professor André Lubineau where she developed projects on chemistry in aqueous media and 2-keto-3-deoxyoctulosonic acid (KDO) synthesis. After a postdoctoral fellowship with Professor C. Wandrey and Dr. Claudine Augé at the Forschungszentrum, Jülich, she moved to Université de Cergy-Pontoise in 1994 and joined the group of Professor J. Augé. Her research interests currently deal with organometallic chemistry applied to carbohydrates.

**Jacques Uziel** was born in Athens, Greece, in 1964. He obtained his PhD in organic chemistry at the Université Pierre et Marie Curie (Paris VI) under the supervision of Professor Jean-Pierre Genêt. Since 1992, he has been Maître de Conférences at the Université de Cergy-Pontoise, initially in the group of Professor Sylvain Jugé, where he worked on stereogenic phosphorus chemistry and functionalized amino acid synthesis. In 2000, he spent a year at the University of Florence working on solid-phase peptide synthesis in the group of Professor Anna Maria Papini. His current research activity deals with $C$-glycoside synthesis by organometallic catalysis.
Both indium(I) iodide and indium(III) iodide are commercially available, though in some cases it has proven better to prepare them. To accomplish this, indium(III) iodide, which is very hygroscopic, is prepared as a fine yellow powder, from indium and iodine in xylene at reflux. Indium(I) iodide is obtained by addition of indium(III) iodide into a suspension of indium powder in xylene; the stable complex In(IInI₄) thus obtained is broken up by addition of diethyl ether to form a mixture of insoluble indium(I) iodide and soluble indium(III) iodide.²⁴

3 Barbier-Type Additions

3.1 Carbonyl Allylation

The use of indium metal as a reducing agent in Barbier-type carbonyl additions was first introduced by Araki and Butsugan for the allylation of carbonyl compounds in N,N-dimethylformamide.¹ Considerable progress was made by Li and Chan, who reported the first carbonyl alkylation mediated by indium in water without any additives or special activation.² The aqueous indium-mediated allylation of unprotected sugars or hemiacetals, as masked aldehydes, have been shown to undergo indium-mediated allylation; this was recently exploited in the aqueous allylation of unprotected sugars or dihydrofurans after their indium(III)-catalyzed hydrolysis into lactols.²⁹ Compared to other metals, indium was particularly efficient in the promotion of the allylation of fluorinated alcohols into lactols, leading to α-trifluoromethylated homoallylic alcohols in water or N,N-dimethylformamide.³⁰

With α,β-unsaturated carbonyl compounds, the indium-mediated allylation generally leads to the [1,2]-addition product, but in some cases the homoallylic indium alkoxide intermediates undergo deoxygenative carbon–carbon bond formation to provide cyclopropyl or α,α-dialyl derivatives.³¹ If an external nucleophile, such as a heterocyclic enamine, is present, then it is prone to attack the electrophilic intermediate to bring about the formation of a new carbon–carbon bond. Thus, indole-3-carboxaldehyde (3) was able to provide symmetrical bisindanyl alkane and was also allowed to react with other heterocyclic enamines, such as pyrrole, pyrazole, imidazole and 2-aminouracil. The mechanism of the reaction (Scheme 3) was recently investigated, with the results indicating that alkylation of 3 was followed by dehydration and nucleophilic addition of the heterocycle, or of another allylindium reagent.³²

It has been shown that in polar organic solvents, the stoichiometric ratio (indium:allyl bromide:ketone) of the reaction was 2:3:2.¹ In water, the stoichiometric ratio is 1:1:1, owing to the likely existence of allylindium as a transient, but discrete, intermediate.¹² However, a parallel process involving the metal surface could not be completely ruled out. Decreases of the amount of metallic indium down to 0.1 and even 0.01 equivalent was made possible in tetrahydrofuran by the addition of manganese and trimethylsilyl chloride as reducing and oxophile agents.²⁶ Albeit providing lower yields, the reaction was also effective when manganese was replaced by tetraakis(dimethylamino)ethylene, which evidences the regeneration of indium(0) by this powerful reducer.²⁷

Whereas the allylation of the fluorinated acylsilanes 1 with Grignard reagents was followed by Brook rearrangement and consequent defluorination, such side-reactions were avoided in the aqueous indium-mediated synthesis of the fluorinated alcohols 2 (Scheme 2).²⁸

Hemiacetals, as masked aldehydes, have been shown to undergo indium-mediated allylation; this was recently exploited in the aqueous allylation of unprotected sugars or electrophilic intermediate to bring about the formation of a new carbon–carbon bond. Thus, indole-3-carboxaldehyde (3) was able to provide symmetrical bisindanyl alkane and was also allowed to react with other heterocyclic enamines, such as pyrrole, pyrazole, imidazole and 2-aminouracil. The mechanism of the reaction (Scheme 3) was recently investigated, with the results indicating that alkylation of 3 was followed by dehydration and nucleophilic addition of the heterocycle, or of another allylindium reagent.³²

The allylation reaction with γ-substituted allyl bromides is γ-selective except when the γ-substituent is too bulky. Even with cyclic allylic bromides, such as 4-bromo-2-enopyranosides, a total γ-regioselectivity was observed in the aqueous indium-promoted allylation of aldehydes leading to C-branched sugars and C-disaccharides.³³

The reaction generally gave moderate anti diastereoselectivity. High diastereoselectivities were observed, however, in the indium-mediated allylation of aldehydes with the chloroallylic sulfones 4 (Scheme 4). The γ-substitu-
ents played a pivotal role in the diastereoselection. With a methyl substituent, the six-membered chair-like transition state led to the homoallylic alcohol anti-5, whereas a phenyl substituent induced a twist-boat transition state and led to syn-5.34

\[
\text{Scheme 4} \quad \text{Diastereoselective allylation with chloroallylic sulfoxides}
\]

Loh et al. have shown that the γ-adduct was produced under kinetic control, whereas the α-adduct could be obtained after equilibration.35 They have developed a highly α-regioselective preparation of E-configured homoallylic alcohols from γ-substituted allylic bromides in the presence of indium in a small amount of water. Table 2 shows the vital role of the solvent on the regioselectivity of the reaction. Whereas γ-regioselectivity was observed in classical aqueous or non-aqueous conditions, a total α-regioselectivity appeared when 6 equivalents of water were used as the solvent; when the reaction was carried out with 12 equivalents of water, no α-adduct was detected, even after the reaction was stirred for up to 72 hours. To illustrate the importance of the activity of water, Loh and co-workers proposed that an in situ hemiacetalization between the aldehyde and the γ-adduct 6 was immediately followed by a 2-oxonia[3,3]-sigmatropic rearrangement with the removal of a molecule of water, which might be an indication that the activity of water should not be too high; in contrast, a molecule of water is required in the second stage of the mechanism to bring about the α-adduct 7 (Scheme 5).36

\[
\text{Table 2} \quad \text{Regioselectivity of the Indium-Mediated Allylation of Cyclohexanecarboxaldehyde with Crotyl Bromide}
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Amount (equiv)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio γ/α</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>6</td>
<td>72</td>
<td>65</td>
<td>100:0</td>
</tr>
<tr>
<td>EtOH</td>
<td>6</td>
<td>72</td>
<td>97</td>
<td>100:0</td>
</tr>
<tr>
<td>H₂O</td>
<td>12</td>
<td>72</td>
<td>90</td>
<td>100:0</td>
</tr>
<tr>
<td>H₂O</td>
<td>6</td>
<td>24</td>
<td>85</td>
<td>1:99</td>
</tr>
<tr>
<td>DMF–H₂O</td>
<td>6:6</td>
<td>72</td>
<td>80</td>
<td>100:0</td>
</tr>
<tr>
<td>THF–H₂O</td>
<td>6:6</td>
<td>72</td>
<td>95</td>
<td>100:0</td>
</tr>
<tr>
<td>CH₂Cl₂–H₂O</td>
<td>6:6</td>
<td>24</td>
<td>68</td>
<td>1:99</td>
</tr>
</tbody>
</table>

The allylation reaction of aldehydes with 3-bromo-1-acetoxypropene in the presence of indium in tetrahydrofuran is γ-regioselective, affording monoprotected 1-ene-3,4-diols in good yields through Grignard or Barbier-type protocols; saturated aldehydes afford anti adducts, whereas the conjugated aldehydes preferentially lead to the syn adducts.37 The indium-mediated coupling of 3-bromo-1-acetoxypropene (8) with aldehydes was advantageously applied in a straightforward stereoselective synthesis of 1,4-dideoxy-1,4-L-iminoribitol (Scheme 6).38 With 3-bromopropenyl methylcarbonate, the γ-regioselectivity is also observed, and the indium alkoxide is prone to cyclize, thereby affording cis and trans 4,5-disubstituted 5-vinyl-1,3-dioxolan-2-ones in high yields; the cis/trans ratio is controlled by the nature of the carbonyl compound.39

\[
\text{Scheme 5} \quad \text{Rearrangement of γ-adducts into α-adducts}
\]

A salient feature in the indium-mediated allylation deals with the facial selectivity towards the aldehyde. The reactions with α-hydroxy aldehydes and β-hydroxy aldehydes are respectively syn and anti stereoselective as a consequence of chelation control even in water.40 Such a chelation was also observed with α-aminoaldehydes, as recently described in the synthesis of castanospermine41 and anti-SARS agents.42 In the latter case, the high diastereoselectivity was interpreted by a second chelation between indium and the nitrogen atom of the isoxazole group of 9 (Scheme 7).42

Can one exploit the efficiency of indium to coordinate, even in aqueous conditions, oxygen and nitrogen in order to induce enantioselection? Indeed, such an enantioselective allylation was achieved in the presence of (−)-cinchonidine in the synthesis of a key precursor of antilatitoxin.43 More recently, a chiral ligand bearing vicinal hydroxyl and amino groups (10) was found to be efficient in the indium-mediated allylation of both aromatic and aliphatic aldehydes (Scheme 8).44
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Scheme 7 Diastereoselective allylation of \( \alpha \)-amino aldehydes

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{Br} & \quad + \quad \text{In} \\
\text{CO}_2\text{Me} & \quad \text{InOH} \\
\text{syn/anti} & = 98:2
\end{align*}
\]

Scheme 8 Enantioselective allylation of aldehydes

With the \( \alpha,\beta \)-unsaturated aldehydes 11, indium-mediated allylation could be followed by an intramolecular cyclopropanation; when the reaction was conducted in the presence of (S)-methyl mandelate, enantioenriched products were obtained.\(^{35}\) This methodology was applied to the synthesis of enantioenriched 1-styrylnorcarene via compound 12 (Scheme 9).

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{Br} & \quad + \quad \text{In} \\
\text{CO}_2\text{Me} & \quad \text{InOH} \\
\text{ee} & = 88\%
\end{align*}
\]

Scheme 9 Enantioselective homoallyl-cyclopropanation of dibenzylideneacetone

3.2 Carbonyl Propargylation and Allenylation

The transient organoindium intermediates formed in the reaction of propargyl bromide (13) with indium in water and in tetrahydrofuran were investigated by \( ^1\)H NMR and \( ^{13}\)C NMR spectroscopy,\(^{46}\) and a strong analogy was found to the results obtained previously with allyl bromide.\(^{12}\) In water, allenylindium(I) (14) was proposed to be the reactive species, whereas a mixture of allenylindium(I) and allenylindium(III) dibromide (15) was formed in tetrahydrofuran, with the first species being the more reactive towards an aldehyde. With methyl-substituted propargyl bromide, the allenylindium/propargyllindium equilibrium was shifted towards the propargyl species; in tetrahydrofuran, 16 reacted with indium to give propargyllindium(I) (17) and propargyllindium(III) dibromide (18), whereas in aqueous media, propargyllindium(I) is the first detected species (Scheme 10).

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{Br} & \quad + \quad \text{In} \\
\text{D}_2\text{O} & \quad \text{In} \\
\text{InOH} & \quad \text{1 equiv}, \text{pyridine} (1 \text{ equiv}) \\
\text{HO} & \quad \text{(1 equiv)} \\
\text{NH}_2 & \quad \text{1 equiv} \\
\text{–78 °C, 1.5 h, THF–hexane} \\
\text{yield} & \quad 90–99\% \\
\text{ee} & \quad \text{up to 93%}
\end{align*}
\]

Scheme 10 Influence of solvent and methyl substitution on the propargyl–allenylindium system

These observations could explain why the homopropargylic alcohols are the major products formed from unsubstituted propargylic bromide, whereas substituted propargylic bromides preferentially give allenyl alcohols. In tetrahydrofuran propargylation of aldehydes with unsubstituted propargyl bromide is totally regioselective; enantioselectivities up to 85% were obtained in the presence of a stoichiometric amount of (–)-cinchonidine.\(^{47}\) Whereas the reaction was slightly regioselective in favor of the allenic compound with trimethylsilyl propargyl bromide (19) in water, excellent regioselectivities in favor of the thermodynamically more stable homopropargylic alcohols 20 were obtained when the reactions were carried out at reflux in tetrahydrofuran in the presence of 2 equivalents of indium and 0.1 equivalent of indium(III) bromide or indium(III) fluoride.\(^{48}\) As a hypothesis, a possible chelation of the silicon with the halide of indium can shift the reaction towards the formation of the homopropargylic alcohol 20. Such a chelation was rendered more difficult with bulky silanes in aqueous media, so that reverse regioselectivity in favor of the allenyl alcohol 21 was then obtained with the bulky trialkysilyl propargyl bromide 22 (Scheme 11).

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{R} & \quad \text{R} \\
\text{H} & \quad \text{H} \\
\text{ee} & \quad \text{88%}
\end{align*}
\]

Scheme 11 Synthesis of homopropargylic and allenic alcohols

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Indium-mediated propargylation of aldehydes with 1,4-dibromobut-2-yn-1-ene (23) in aqueous media gave good yields of the 1,3-butadien-2-ylmethanols 24 (Scheme 12). A novel diindium intermediate (25) was evidenced in tetrahydrofuran by \(^1\)H NMR spectroscopy and electrospray ionization mass spectrometry; this remarkable, stable compound could be stored in tetrahydrofuran by \(^1\)H NMR spectroscopy and gave pure \(\text{anti}\) acetylenic 1,6-diols 26 with various aldehydes in the presence of zinc fluoride; the stereoselection was rationalized by a chelation of the allenylindium with the oxygen of the transient indium alcoholate.50

**Scheme 12** Propargylation and allenylation with dibromobutyne

In the indium-mediated \(\text{gem}\)-difluoropropargylation of aldehydes, an innovation was recently introduced with the combined use of zinc (0.9 equiv) and indium (0.1 equiv) in the presence of iodine (0.1 equiv). Although the resulting \(\text{gem}\)-difluorohomopropargyl alcohols were obtained in moderate yields, the reaction was highly regioselective, as the corresponding fluoroallenyl alcohols were not obtained.52

### 3.3 Aldol-Type Reactions

Reformatsky reactions may be considered as aldol-type reactions in which the metal enolate is formed by the insertion of a metal into the carbon–halogen bond of \(\alpha\)-haloesters or \(\alpha\)-halonitriles. In the presence of indium metal, these derivatives were allowed to react in organic solvents with various carbonyl compounds.10,11

Indium(I) bromide has also been shown to promote a Reformatsky-type reaction; thus \(\alpha,\alpha\)-dichloroketones gave the corresponding 2-chloro-3-hydroxypropan-1-one derivatives upon addition to carbonyl compounds.53

The diastereoselectivity of the indium Reformatsky-type reaction of ketones with the \(\alpha\)-bromo substituted esters 27 was carefully investigated (Scheme 13). The reaction led to the \(\text{anti}\) isomers 28 arising from a cyclic chair-like transition state, either with indium metal or indium(I) bromide, the former being advantageous in terms of reactivity.54 The diastereoselectivity with respect to ketones was studied with the \(\alpha\)-alkoxy ketone 29 and the \(\beta\)-keto ester 30, which were exposed to the \(\alpha\)-iodo ester 31. Excellent \(\text{syn}\) selectivities arising from a chelated transition state were obtained when indium(I) chloride was used in dry toluene under ultrasonication (Scheme 13). It was suggested from NMR measurements that a low-valent indium species was formed in toluene.

![Scheme 13](image-url) Diastereoselective Reformatsky reactions mediated by indium and indium(I)

### 3.4 Additions to Carbon–Nitrogen Multiple Bonds

Owing to the ease of hydrolysis of imines under aqueous conditions, the indium-mediated allylation of imines was first tested under anhydrous conditions.10 It was found, however, that pyridine-2-imines and quinoline-2-imines, as water-stable activated imines, could undergo indium-mediated Barbier allylation in aqueous media to provide homoallylic amines in very good yields.56 For hydrolyzable imines, it was possible to use anhydrous alcohols as solvent; thus, chiral aldime derived from \(\text{(R)}\)-phenylglycinol were diastereoselectively allylated in anhydrous methanol.57 With glyceraldehyde 32 prepared from the chiral pool substance \(\text{(R)}\)-2,3-\(\text{O}\)-isopropylidendeglyceraldehyde, allylation in \(\text{N},\text{N}\)-dimethylformamide gave rise to high diastereoselectivity,58 which was believed to arise through an indium-chelated six-membered transition state (Scheme 14).

The indium-mediated allylation of imines in ionic liquids was also investigated.59 Selective formation of monoallylic amines was achieved by adjusting the amount of water-stable activated imines, could undergo indium-mediated Barbier allylation in aqueous media to provide homoallylic amines in very good yields.56 For hydrolyzable imines, it was possible to use anhydrous alcohols as solvent; thus, chiral aldime derived from \(\text{(R)}\)-phenylglycinol were diastereoselectively allylated in anhydrous methanol.57 With glyceraldehyde 32 prepared from the chiral pool substance \(\text{(R)}\)-2,3-\(\text{O}\)-isopropylidendeglyceraldehyde, allylation in \(\text{N},\text{N}\)-dimethylformamide gave rise to high diastereoselectivity,58 which was believed to arise through an indium-chelated six-membered transition state (Scheme 14).

![Scheme 14](image-url) Diastereoselective allylation of glyceraldehyde

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dibromide, the first species being more reactive than the second. The dynamic equilibrium between these two species could be shifted by addition of bromide anion; when bromide was present in greater than 8.5%, it retarded conversion of allylindium(I) into allylindium(III) dibromide, which accounts for the formation of bis-allylated amines as by-products.

Enol ethers could be used as an aldehyde equivalent for the generation of imines in the indium-mediated one-pot three-component reaction of aromatic amines 33, enol ethers 34 and allylic bromides 35, affording N-aryl-substituted homoallylamines 36 (Scheme 15).65

Scheme 15 Indium-mediated three-component reaction

Azirines,41 oxime ethers62,63 and hydrazones64 have also been allylated under Barbier-type conditions. Oxime ethers derived from 2-pyridinecarboxaldehyde and glyoxylic acid gave syn γ-allylation products with respect to the chelation by indium.62 With chiral hydrazones derived from oxazolidinones,64 essentially complete diastereoselectivity was obtained as well. Enantioselectivity in the allylation of hydrazones could be realized with the use of a catalytic amount of BINOL ligands.65

The sulfinyl group, which can be removed under acidic conditions, was recently evidenced as a chiral auxiliary in a diastereoselective addition of allyl bromides to N-tert-butylsulfinyl aldimines.66

A salient reaction is the indium(I) iodide promoted 1,2-addition of allyl and benzyl bromides to α,β-unsaturated nitriles that gives the corresponding conjugated imines; high 1,2-selectivity was observed, and surprisingly only 20 mol% of indium(I) iodide was required in the reaction.67

4 Carbonyl Alkynylation

4.1 Indium(0)-Mediated Alkynylation

Barbier-type alkynylation – that is, the addition of acetylenic halide upon carbonyl compounds in the presence of a metal – is unusual. The first example of the use of a metal(0) in such a reaction involved indium.68 For the reaction, alkynyl iodides 37 were first prepared from alkyne and iodine in the presence of morpholine. With an excess of these reagents and indium metal in refluxing dichloromethane, aldehydes and ketones afforded the corresponding propargylic alcohols 38. When the aldehyde was in excess, the propargylic ketones 39 were formed, arising from an Oppenauer-type oxidation of the indium(III) alkoxyde intermediate; the formation of 39 from the aromatic or non-enolizable aldehydes proceeded smoothly in refluxing dichloroethane (Scheme 16). The propargylic ketones 39 were also obtained by indium-mediated alkynylation of acyl chlorides.69 This methodology was applied in C-glycoside synthesis.70

RCHO + R' =\[\text{In} + \text{RCHO} \rightarrow \text{R'}] 37

Scheme 16 Indium-mediated alkynylation of carbonyl compounds

4.2 Indium(III)-Catalyzed Alkynylation

The indium(0)-mediated alkynylation requires the prior formation of alkynyl iodides, but the advantage of this reaction lies in the fact that the alkynylation proceeds in neutral conditions. A new angle appeared with the direct use of a terminal alkyne which could be metalated by indium(III) salts under basic conditions, in order to be added to carbonyl compounds. In this strategy, indium acetylide is formed when stoichiometric amounts of indium(III) bromide and triethylamine are mixed with an alkyne in diethyl ether, thereby giving access to propargylic alcohols from aromatic aldehydes and aliphatic non-enolizable aldehydes.71 Interestingly, propargylic amines were prepared from N,O-acetals under the same conditions.

The catalytic version of the indium(III)/tertiary amine reaction of alkynes with aldehydes was recently revisited.72 Under the following conditions (10 mol% InBr3, 20 mol% DIPEA, 2 equiv of the terminal alkyne), aromatic aldehydes were smoothly converted into the corresponding propargylic alcohols. Except for cyclohexanecarboxaldehyde, which reacted with an excellent yield, other aliphatic aldehydes gave unsatisfactory results due to either their self-condensation (for aldehydes with a primary alkyl group) or their low reactivity (for aldehydes with a tertiary alkyl group). Optimized catalytic conditions for the alkynylation were determined to be 20 mol% indium(III) triflate and 50 mol% N,N-disopropylethylamine in 1,2-dimethoxyethane. Spectroscopic studies showed that dual activation of both the terminal alkyne and the carbonyl group by indium(III) salts occurred (Scheme 17).

A slight modification of the catalytic system made the alkynylation of aldehydes enantioselective: the addition of a chiral ligand resulted in the reaction proceeding via an indium(III)–BINOL complex. Excellent enantioselectivities for propargylic alcohols were obtained with various aldehydes and alkenes. The reaction was performed in
dichloromethane at 40 °C using dicyclohexylmethylamine (50 mol%) as a base, and indium(III) bromide (10 mol%) as a catalyst. For the easily enolizable aldehydes, slow addition of the aldehyde prevented self-condensation. (R)-BINOL (10 mol%) induced the nucleophilic attack of the indium acetylide on the Re face of the aldehyde; strong positive nonlinear effects were observed, suggesting a bimetallic mechanism in the catalytic cycle.73

5 Carbonyl Additions via Transmetalation

5.1 Indium(III) and Indium(I)-Mediated Allylation

Allyldichloroindium has been prepared from allylstannanes and indium(III) chloride in various donor solvents. In order to use this reactive species in carbonyl additions, a premixing of the aldehyde and indium(III) chloride before the addition of the stannane was found to be crucial. With crotyl tri-n-butylstannane, the reaction led to homoallylic alcohols with total γ-regioselectivity and excellent anti stereoselectivity in acetone or acetonitrile, even at room temperature. With α-alloxy crotylstannane 40 of >95% ee, the addition of aldehyde at –78 °C in the presence of a stoichiometric amount of indium(III) chloride led to the anti homoallylic alcohols 41 with total α-regioselectivity and excellent anti stereoselectivity and enantioselectivity (Scheme 18).74

Recently, a catalytic amount (20 mol%) of a chiral complex prepared from (S)-BINOL and indium(III) chloride75 [or indium(III) bromide]76 was used in an efficient enantioselective allylation of aldehydes with allyltributylstannane (42) (Scheme 19). The reaction was first tested under anhydrous conditions, but it turned out that some moisture could be tolerated.77 With 20 mol% of indium(III) triflate and chiral PYBOX, however, the allylation of aldehydes and ketones with allyltributyltin required the presence of chlorotrimethylsilane to afford the corresponding homoallylic alcohols in moderate to high enantioselectivities.78–80 The preceding methodologies were tested in ionic liquids; according to the chiral ligand used, the enanto- 

![Scheme 17] Dual activation in alkynylation reaction

![Scheme 18] Synthesis of anti-homoallylic alcohols

![Scheme 19] Enantioselective allylation of aldehydes

The indium(III)-catalyzed addition of allylstannanes was successfully achieved with imines; with ortho-alkynylarylaldimines a subsequent activation of the triple bond by indium(III) triflate brought about in situ cyclization affording 1,2-dihydroisoquinolines.84

A related reaction using allyltrimethylsilane instead of allyltributylstannane gave β,γ-unsaturated ketones from acyl chlorides.85 There was no evidence of a transmetalation step, and the activation of the carbonyl moiety by indium(III) bromide as a Lewis acid was not excluded in that reaction.

The indium(III)-mediated allylation of carbonyl compounds always requires the preparation of allylic organo-metallic species, such as silanes or stannanes, from the allylic halides. The Barbier allylation reactions also require the use of halides. A new strategy, the reductive transmetalation of a π-allylpalladium(II) complex with indium(I) salts, has enabled the use of more accessible allylic compounds, including allylic alcohols and their derivatives 43 (Scheme 20).86 The reaction is rapid at room temperature for all substrates except allylic alcohols; the use of nickel(II) acetylacetonate instead of tetraakis(triphenylphosphine)palladium(0) made the reaction easier to perform. In this process, indium(I) iodide was used to reduce nickel(II) acetylacetonate into nickel(0) which was itself involved in the formation of a π-allylnickel complex; transmetalation with indium(I) iodide then led to a (Z)-allylindium(III) species and thereby induced a syn selectivity after addition of the aldehyde.87 Noteworthy is the combined use of indium and indium(III) instead of indium(I) salt in the palladium-catalyzed allylation in aqueous media of various allylic substrates, including alcohol, chloride, acetate and carbonate.88

![Scheme 20] Transmetalation of π-allylpalladium complexes by indium(I) iodide

In another notable reaction, the allylation of glyoxylic oxime ether 44 with alcohol derivatives 45 in the presence of a stoichiometric amount of indium(I) iodide and a catalytic amount of palladium(0) complex gave either the kinetic α-adducts 46 in aqueous tetrahydrofuran or the thermodynamic α-adducts 47 in anhydrous tetrahydrofuran (Scheme 21).89

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5.2 Indium(III)- and Indium(I)-Mediated Propargylation

By S$_2$2$'$ displacement of secondary chiral propargylic mesylates with tributyltin–copper complex, it was possible to form allenylstannanes which underwent transmetalation with indium(III) chloride to produce anti homopropargylic alcohols from aldehydes. More interesting was the straightforward preparation of such enantiomeric alcohols directly from enantiomeric mesylates. A catalytic amount of [1,1$'$-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [Pd(dpff)Cl$_2$] and a stoichiometric amount of indium(I) iodide gave rise to an allenylindium which added to aldehydes with good diastereo- and enantioselectivity. Curiously, the reaction worked in the absence of catalyst but with a lower yield (66%) and no enantioselectivity; diastereoselectivity was, however, preserved.

Both enantiomers of 4-tri(isopropyl)silylbut-3-yn-2-ol are obtained directly from enantiomeric mesylates in >95% enantiomeric purity by reduction of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor. After conversion of the mesylate derivative 48 into a transient allenylindium reagent in the presence of a catalyst derived from palladium(II) acetate/triphenylphosphine and indium(I) iodide, the addition of the ynone precursor.

5.3 Indium(III)-Mediated Alkynylation

In analogy to the transmetalation of allylstannanes with indium(III) salts, it is also possible to transmetalate alkynylstannanes with indium(III) chloride to form alkynylidichlorindium, which smoothly adds to aldehydes in acetonitrile. In this reaction, a catalytic amount of indium(III) chloride (10 mol%) is sufficient, owing to the presence of chlorotrimethylsilane as an oxphile that regenerates the indium salt. In the silane reactant series, chlorotrimethylsilane can be omitted, so that the alkynylsilanes undergo coupling with acid chlorides in the presence of 5 mol% of indium(III) bromide at 0 °C to afford the corresponding α,β-acetylenic ketones (Scheme 23).

6 Carbometalation of Alkynes

In tetrahydrofuran, even inactivated terminal alkynes underwent indium-mediated allylation with allyl iodide or bromide to afford the Markovnikov adducts. As expected, alkynols afforded the anti-Markovnikov adducts. As a possible mechanism of the allylindation of terminal alkynes, Schmid suggested that an indium acetylide was first formed, and then the addition of one equivalent of indium to the allenylindium would give rise to a vinylic a,a-bis(indium) intermediate and subsequently to the branched 1,4-dienes; alternatively, the intermediate could be quenched with N-bromo(or iodo)succinimide to form the gem-dihalo-1,4-dienes. This mechanism could be applied even to alkynols in which the hydroxyl group is remote from the alkyne function. In contrast, propargylic alcohol gave the linear 1,4-diene, suggesting the involvement of a bicyclic chelation-controlled transition state; quenching of the intermediate with an N-halosuccinimide yielded the monohalogenated dienes (Scheme 24).

Carbometalation of allenyl alcohols is also possible with propargylicallenyl indium compounds under sonication, but indium(III) bromide is required as an additive. Thus, the reaction between prop-2-ynyl bromide and 1,2-disubstituted allene in the presence of a stoichiometric amount of indium, carried out in tetrahydrofuran, gave (E)-1,2-disubstituted hepta-2-en-6-yn-1-ol. With but-2-ynyl bromide, the reaction led to (E)-1,2-disubstituted 5-methylhepta-2,5,6-trien-1-ol. This product could also be obtained directly from two equivalents of but-2-ynyl bromide and the corresponding aldehyde.

Allylation was also found to proceed via intramolecular addition: the cyclization of 1-bromo-2,7-enynes and 1-bromo-2,8-enynes mediated by indium in the presence of 5 mol% of indium(III) bromide at 0 °C to afford the corresponding a,β-acetylenic ketones.
be performed in aqueous tetrahydrofuran or in anhydrous tetrahydrofuran in the presence of an organic acid; it was also mediated by stoichiometric indium(I) or substoichiometric indium(III) with zinc as a co-reductant.98

As an alternative, the Barbier-type pathway was replaced by a transmetalation method. Starting from 8-tributylstannyl-oct-6-en-1-yne 59, the addition of 1 equivalent of indium(III) chloride gave an allylindium reagent which underwent cyclization to afford a vinylindium species which was prone to hydrolysis into 2-allyl-1-methylene-cyclopentane 60. With only 0.2 equivalent of indium(III) chloride, the cyclization led to vinylstannane 61, which was isolated and hydrolyzed to give 60 in 87% overall yield (Scheme 25).99 With silanes instead of stannanes, the reaction proceeds via electrophilic activation of the triple bond by indium salt.100

Scheme 25  Indium(III)-promoted addition of allylstannanes to alkynes

Noteworthy is the beneficial influence of indium(III) chloride as a cocatalyst in the cross-coupling of alkenylaluminum and alkenylzirconium, prepared by hydrometalation of alkynes, with vinyl halides.106

7.2  Coupling of Organoindium Reagents Prepared from Indium Metal

As shown in Scheme 24, vinylindium compounds could be prepared from indium metal by allylation of alkynes; these species were reported to couple to iodobenzene in the presence of palladium(0) catalyst.95 Vinylindium reagents could also be obtained in the allylation of carbon–oxygen and carbon–nitrogen double bonds with 3-bromo-1-iodopropene (64) and immediately coupled with aryl, alkenyl or allyl halides in a tandem reaction to give 65 or 66 (Scheme 27).107

Scheme 27  Cascade coupling reactions
7.3 Sonogashira-Type Reaction

The indium acetylides formed in situ from terminal alkynes and a catalytic amount (0.05 equiv) of indium(III) bromide in the presence of piperidine were shown to react with aryl iodides in the presence of bis(triphenylphosphine)palladium(II) dichloride (0.05 equiv) to give the corresponding cross-coupling product (Scheme 28).108

\[
\text{Ph}_{3}\text{In} + \text{CuCl}_2(0.5 \text{ equiv}) \text{ MeCN–THF, r.t. up to } 98\%
\]

Scheme 28 Indium(III)-catalyzed Sonogashira-type reaction

7.4 Tsuji–Trost-Type Reaction

Triorganoindium and tetraorganoindates with aryl, alkenyl and methyl groups reacted with cinnamyl and geranyl chlorides, bromides and acetates in the presence of 5 mol% tris(dibenzylideneacetone)dipalladium(0) [Pd2(dba)3] to afford exclusively the SN2 products.109 For optimal results, a stoichiometric amount of indium was required. The reaction proceeded with inversion of configuration, which is consistent with the mechanistic pathway of oxidative addition, transmetalation and reductive elimination; β-hydride elimination was observed with tributylindium compounds.

In an optimized procedure, 0.5 equivalent of triarylindium reagent was used in the nucleophilic substitution of allylic acetates in carbocyclic derivatives.110 The reaction proceeded with inversion of configuration in the presence of 1–3 mol% tris(dibenzylideneacetone)dipalladium(0) and 4 mol% triphenylphosphine. Cyclization was observed when allylic acetates were present in the alkyne molecule (Scheme 29).111

\[
\text{PhIn} + \text{CO}_2\text{Me} \rightarrow \text{PhCH}_2\text{CHO}_2\text{Me} + \text{R} \rightarrow \text{PhCH}_2\text{CHO}_2\text{Me} \rightarrow \text{PhCH}_2\text{CHO}_2\text{Me}
\]

Scheme 29 Palladium-catalyzed reactions of acetoxyenynes with triphenylindium

In order to prepare allenes, allylic substrates were replaced by propargyl starting materials. Thus, stoichiometric amounts of aryl, alkenyl, alkynyl and methyl triorganoindium reagents reacted with propargylic acetates, benzoates and carbonates under palladium catalysis via an SN2 rearrangement to give allenes in good yields and with high regioselectivity.112 The reaction of triphenylindium with the enantiopure propargylic esters 67 gave the enantiopure allenes 68, consistent with an anti stereoselectivity (Scheme 30).

7.5 Other Coupling Reactions

A three-component coupling of triorganoindium reagents with imines and acid chlorides was recently reported to take place under catalysis by copper(I) chloride (Scheme 31). No coupling reaction was observed when the triorganoindium reagent was used without any catalyst, nor did a palladium catalyst lead to a reaction. All three organic groups attached to the indium, whether alkyl, alkenyl or aryl, were transferred to the transient N-acyl iminium salt, thereby affording α-substituted amides.113

\[
\text{Reagent} + \text{Im} + \text{R}_2\text{Cl} \rightarrow \text{R}_2\text{CON} = \text{C} = \text{N} \rightarrow \text{R}_2\text{CON} = \text{C} = \text{N} \rightarrow \text{R}_2\text{CON} = \text{C} = \text{N}
\]

Scheme 31 Three-component coupling of organoindium reagents

8 Nucleophilic Substitutions

8.1 Allylation of Epoxides

With a Grignard-type protocol, the indium-mediated allylation of vinyl epoxide gave bis(homoallyl) alcohol with total regioselectivity.114 This result, which is in contradiction with the general ring opening of epoxides giving rise to 1,2- or 1,4-nucleophilic substitutions, was explained by a transient carbocation which undergoes a [1,2]-sigmatropic rearrangement. Similar results were observed in the allylation of other epoxides with allylindium prepared from allyl iodide and indium.115 According to the authors, the allylindium species had enough Lewis acidity to induce the rearrangement of epoxide 69 into aldehyde 70 prior to the direct allylation, affording the corresponding homoallylic alcohols 71 irrespective of the nature of the epoxide substituent. In contrast, the allylindate species reacted with epoxides to give the classical ring-opening products 72 or 73, depending on the epoxide substituent (Scheme 32).

\[
\text{Ph}_{3}\text{In} + \text{CO}_2\text{Me} \rightarrow \text{PhCH}_2\text{CHO}_2\text{Me} + \text{R} \rightarrow \text{PhCH}_2\text{CHO}_2\text{Me} \rightarrow \text{PhCH}_2\text{CHO}_2\text{Me}
\]

Scheme 32 Allylation of epoxides
8.2 Allylation and Propargylation of Sulfonium

Novel nucleophilic substitutions such as allylation, propargylation and allenylation were carried out with 3-(tert-butylidimethylsilyloxy)alk-2-enylsulfonium triflate (74). These smooth reactions, carried out at –78 °C over 30 minutes, can be described as dimethylsulfide/indium-promoted conjugate additions (Scheme 33).116

![Scheme 33 Indium-mediated conjugate addition to enones](image)

8.3 $S_2^2$' Reactions

Trialkylindium and triarylindium reagents are soft nucleophiles towards cinnamyl and geranyl halides and phosphates. At –30 °C, in the presence of copper(II) triflate as a catalyst and triethylphosphite as a copper ligand, the reaction led to $S_2^2$' products with good yields and regioselectivity.117 Under these conditions, organometallics were able to transfer only one of the groups attached to indium.

A particular case was reported concerning the stoichiometric reaction between allenols 75 and indium(III) halide, leading to the 2-halo-1,3-dienes 76: indium(III) halide coordinates to allenol to form a six-membered transition state which delivers the halide anion at the electrophilic carbon according to an $S_2^2$' pathway (Scheme 34).118

![Scheme 34 Indium(III) halide mediated $S_2^2$' reaction of allenols](image)

8.4 C-Glycosylation

Glycal derivatives are readily converted into 2,3-unsaturated glycosyl compounds with oxygen, carbon, nitrogen or sulfur substituents at the anomeric position.119 This specific $S_2^2$' reaction, named the Ferrier rearrangement, is useful in the preparation of C-glycosides. An indium-mediated Ferrier rearrangement was recently described to take place under non-acidic conditions in the preparation of C-aryl, C-vinyl and C-propargyl glycosides from the corresponding triorganoindium reagents obtained through transmetallation.120 The reactions were performed in diethyl ether at room temperature and $\alpha$-selectivity was predominantly observed. Under Barbier conditions in refluxing dichloromethane, tri-O-acetyl glucal (77) afforded alkynyl derivatives 78 with $\alpha$-selectivity (Scheme 35).121

The same conditions were applied to the direct C-glycosidation of simple acetylated carbohydrates. To avoid the participation of the O-acetyl protecting group at C-2, only 2-deoxy sugars were used in the pyranose series. C-Alkynylglycosides were obtained in good yields with $\alpha$-selectivity.121

![Scheme 35 Indium-promoted Ferrier rearrangement](image)

9 Radical Reactions

Because of the low first ionization potential of indium, indium is capable of promoting single-electron processes. The formation of a reactive species by reduction of indium(III) chloride with various hydrides is discussed in the following section, hydroindation.

9.1 Radical Substitutions Initiated by Triethylborane

The formation of ethyl radical by triethylborane in the presence of dioxygen was exploited in the radical indium-mediated substitution of $\alpha$-halo carbonyl compounds.122 Thus, allylindium reagents prepared by transmetallation of Grignard reagents with indium(III) chloride transferred their allyl moiety to $\alpha$-iodo (or $\alpha$-bromo) amides or esters such as 79 in aqueous tetrahydrofuran solution. With alkynylindium reagents, the reaction was carried out in diethyl ether. Starting from an ester such as 80, the stereochemistry of alkynylindiums was essentially retained, so that the $E/Z$ configurational ratio of the product was approximately that of the starting alkenyl bromide. In the same way, phenylethynylindium dichloride and phenylindium dichloride were added to $\alpha$-iodo esters such as 81. In all these reactions, dichloroindium(II) radical was used as an efficient radical mediator (Scheme 36).

9.2 Radical Cyclizations

Indium reacts with iodine in aromatic solvents under reflux to produce indium(I), indium(II) and indium(III) salts.24 As observed recently, low-valent indium species can initiate radical processes. Thus, treatment of iododelkynes such as 82 with a catalytic amount of indium
(0.1 equiv) and iodine (0.05 equiv) promoted an atom-transfer 5-exo cyclization to give the five-membered alkanyl iodide products such as 83. With an excess of indium, cyclization was followed by reduction of the alkynyl iodide to give 84 (Scheme 37). When the starting alkene contained a leaving group at the propargylic position, allenic products were produced selectively.

With iodoalkenes instead of iodoalkynes, the reaction was performed with two equivalents of indium and one equivalent of iodine; 5-exo cyclization also occurred in methanol, giving the corresponding alkylindium intermediate, which was isolated for analytical purposes. This compound was not further hydrolyzed but gave either the alkyl iodide or the alcohol, after the addition of hydrogen peroxide. With alkynes bearing leaving groups at the allylic position, the 5-exo cyclization was accompanied by the elimination of these groups.

In some cases, the indium–molecular bromine couple turned out to be more efficient than the indium–molecular iodine couple for inducing the radical cyclization. Furthermore, it was revealed that pyridinium tribromide (Py·HBr₃) could be used instead of molecular bromine. Such conditions were used in the 5-exo radical cyclization of iodo-ynamide 85 leading to the vinylnilindium intermediate, which could be quenched by a proton to give 86 or which could, after addition of aryl iodide, undergo a palladium-catalyzed cross-coupling reaction to afford 87 (Scheme 38).

Intramolecular cyclization of allylindium compounds was found to be promoted by photolysis; thus allylindium compounds formed from 8-bromo- or 8-iodoocat-1,6-dienes gave the 5-exo-trig products, after photolysis-induced homolytic cleavage of the carbon–indium.

9.3 Indium(Ι) as a Radical Initiator

In the aqueous zinc–copper(I) iodide mediated alkylation of aromatic aldehydes with unactivated alkyl halides, optimized conditions were obtained in aqueous sodium oxide with indium(I) chloride as a catalyst (0.1 equiv), which was presumed to transfer one electron to the carbon–iodine oxygen.

In the intramolecular cyclization of δ-bromoalkynes 88, indium(I) iodide was used in a stoichiometric amount under sonication, and gave rise to a vinylindium intermediate according to a mechanism similar to that observed with the stoichiometric indium–iodine or indium–bromine protocol. After hydrolysis, the corresponding substituted 4-methylpentetrahydrofurans 89 were obtained in yields ranging from 62% to 80% (Scheme 39).

9.4 Indium(0) as a Radical Initiator

Indium was used as a radical initiator in aqueous media to promote intermolecular alkyl addition to oxime and hydrazone carbon–nitrogen double bonds and to electron-deficient carbon–carbon double bonds. The reaction gave good yields with five equivalents of secondary alkyl iodides in the presence of seven equivalents of indium in aqueous methanol or dichloromethane–water mixtures.

Another example of single-electron processes initiated by indium was the one-carbon ring expansion of the α-io- domethyl cyclic β-keto esters 90 in aqueous tert-amyl alcohol at reflux; the primary radical formed by reduction of the iodide underwent a 3-exo-trig cyclization and a subsequent β-cleavage to afford 91 (Scheme 40).
Hydroindation

Transmetalation between indium(III) chloride and a metallic hydride can generate dichloroindium hydride. The transient formation of ·InCl₂ as a radical intermediate is the driving force of the subsequent hydroindation of various functionalities.

10.1 Hydroindation from Tributyltin Hydride and Indium(III) Chloride

Dichloroindium hydride was generated for the first time by transmetalation of indium(III) chloride with tributyltin hydride at –78 °C; the solution was found to be stable in tetrahydrofuran at room temperature and could be used in the reduction of carbonyl compounds or alkyl bromides. The hydroindation of 1,3-dienes gave allylic indiums which further reacted with carbonyl or imine moieties in a one-pot process (Scheme 41).

In these reactions, the alkyl halides RX presumably gave the radical species R, which were prone to evolve. In a similar way, the reduction of the bromo moiety of 2,3-epoxybromides was followed by selective carbon–oxygen bond cleavage to afford the corresponding allylic alcohols.

The combination of a catalytic amount of indium(III) chloride and sodium borohydride in acetonitrile was found to reduce, with transposition, the hydroxyl group of Baylis–Hillman adducts 93 (Scheme 42). This remarkably chemoselective reduction which afforded exclusively the E-isomers 94 was applied to the synthesis of two alarm pheromones.

10.2 Hydroindation from Sodium Borohydride and Indium(III) Chloride

The non-toxic couple sodium borohydride/indium(III) chloride in acetonitrile turned out to be an interesting alternative for the preparation of dichloroindium hydride. Only a catalytic amount of indium(III) chloride was required in the radical reduction of alkyl halides and in 3-exo-trig radical cyclizations. With vicinal dibromides, the reaction gave the (E)-alkenes with transposition.

In the presence of diaryliodonium salts, aryl terminal alkynes underwent cross-coupling via the vinylindiums generated by hydroindation, but under the same conditions, the aliphatic terminal alkynes did not react very well. It was mentioned, however, that the hydroindation of various terminal alkynes with this system could lead to enynes by dimerization.

The carbon–selenium bond in gem-difluorinated organoselenium compounds was also reduced by the sodium borohydride and stoichiometric indium(III) chloride in acetonitrile system. Thus, these compounds could undergo reduction or reductive radical cyclization and could be added to styrene.
10.3 Hydroindation from Diisobutylaluminum Hydride and Indium(III) Chloride

Treatment of indium(III) chloride in tetrahydrofuran with diisobutylaluminum hydride at 0 °C yields dichloroindium hydride, which can further react with terminal alkynes in the presence of a catalytic amount of triethylborane to give (Z)-alkenylindium dichlorides. In addition to dichloroindium hydride, the reaction between silanes and indium(III) chloride afforded chlorosilanes, which were used in organometallic catalysis to afford chlorosilanes, the Lewis acidities of which were enhanced by bonding with indium(III) chloride. To overcome this problem, acid-sensitive substrates, indium(III) chloride was replaced by InCl2OMe in the transmetalation with diphenylsilane. In the presence of triethylborane, this system promoted intramolecular radical coupling of the enyne to give a-halo esters to give the corresponding α-alkenyl esters.

Dichloroindium hydride prepared from indium(III) chloride and diisobutylaluminum hydride in the presence of triethylborane reduced alkyl bromides and induced radical cyclizations. A catalytic process (20 mol% InCl3) was applied to the 5-exo-trig-cyclization of iodide (Scheme 45). In addition to dichloroindium hydride, the reaction between silanes and indium(III) chloride afforded chlorosilanes, the Lewis acidities of which were enhanced by combination with indium(III) chloride. To overcome this problem, acid-sensitive substrates, indium(III) chloride was replaced by InCl2OMe in the transmetalation with diphenylsilane. In the presence of triethylborane, this system promoted intramolecular radical coupling of the enyne to give a-halo esters to give the corresponding α-alkenyl esters.

11 Reduction of Functional Groups

11.1 Reduction of Nitrogen-Containing Groups

The reduction of nitrogen-containing groups includes the reduction of imines, the reduction of quinolines or other benzo-fused nitrogen heterocycles, the reduction of activated oximes, of nitro compounds, of azides into amines, and the deprotection of 4-nitrobenzyl ethers or esters. Such a domino reduction–acetylation reaction was also described in the preparation of N-arylamides from nitroarones in methanol.

Dibromoindium hydride, generated from triethylsilane and indium(III) bromide, added to enones in a 1,4 manner in propionitrile to give the transient indium enolate which was then quenched with an aldehyde to afford the aldol product with an excellent syn selectivity.

The 1,4-reduction of enones with phenylsilane in the presence of a catalytic amount of indium(III) acetate was facilitated by the use of ethanol as solvent, and the formation of the dimerization product was avoided. The intermediary indium enolates were used for inter- and intramolecular aldol reactions and intramolecular Michael additions. The phenylsilane/indium(III) acetate reduction system was particularly efficient in the reduction of organic halides in ethanol containing a small amount of 2,4-lutidine.

In addition to dichloroindium hydride, the reaction between silanes and indium(III) chloride afforded chlorosilanes, the Lewis acidities of which were enhanced by bonding with indium(III) chloride. To overcome this problem, acid-sensitive substrates, indium(III) chloride was replaced by InCl2OMe in the transmetalation with diphenylsilane. In the presence of triethylborane, this system promoted intramolecular radical coupling of the enyne to give a-halo esters to give the corresponding α-alkenyl esters.

Dichloroindium hydride prepared from indium(III) chloride and diisobutylaluminum hydride in the presence of triethylborane reduced alkyl bromides and induced radical cyclizations. A catalytic process (20 mol% InCl3) was applied to the 5-exo-trig-cyclization of iodide (Scheme 45). In addition to dichloroindium hydride, the reaction between silanes and indium(III) chloride afforded chlorosilanes, the Lewis acidities of which were enhanced by combination with indium(III) chloride. To overcome this problem, acid-sensitive substrates, indium(III) chloride was replaced by InCl2OMe in the transmetalation with diphenylsilane. In the presence of triethylborane, this system promoted intramolecular radical coupling of the enyne to give a-halo esters to give the corresponding α-alkenyl esters.

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For nitroarenes with an appropriate functional group at the ortho position, reductive heterocyclization gave interesting results (Scheme 47). The reaction was performed in methanol at 50 °C; under these conditions, the combined use of indium (3 equiv) and iodine (0.8 equiv) transformed 2-nitroacylbenzenes such as 102 into 2,1-benzisoxazoles such as 103, independent of the electronic effect of the aromatic substituents. Under similar conditions, 2-nitroiminobenzene 104 gave a mixture of 2,1-benzisoxazole 105 and 3-anilino-2-phenyl-2H-indazole (106).156

Scheme 47  Reductive heterocyclization

11.2 Reduction of Oxygen-Containing Groups

Deoxygenation of epoxides bearing a radical-stabilizing group was performed with indium in ethanol in the presence of two equivalents of ammonium chloride. Use of indium(I) chloride (2 equiv) instead of ammonium chloride considerably decreased not only the total time of the reaction, but also the number of equivalents of indium metal required (from 7 equiv to 2.5 equiv). The presence of a small quantity of water in the solvent was necessary for the deoxygenation; for sensitive aryl epoxides that are susceptible to nucleophilic attack by alcohols, aqueous tert-butyl alcohol is the better solvent system (Scheme 48).157

Reduction of benzophenones, benzaldehydes and acetophenones by a stoichiometric indium(III) chloride–aluminum couple in aqueous ethanol at 80 °C gave the corresponding pinacol coupling products.158

Scheme 48  Indium-promoted deoxygenation of epoxides

11.3 Reduction of Disulfides

A stoichiometric amount of indium(I) iodide was found to reduce dialkyl or diaryl disulfides to give bis(thioalkyl/thioaryl)iodindium(III) as a source of thiolate anions (2 equiv), which, in refluxing tetrahydrofuran, could undergo Michael additions to α,β-unsaturated ketones, aldehydes, esters and nitriles,159 or anti-Markovnikov additions to styrenes in the presence of a catalytic amount of zinc chloride (15 mol%).160 The strategy has been used for the regioselective nucleophilic ring opening of epoxides in the presence of indium(III) chloride, thereby producing the corresponding β-hydroxyphenyl sulfides.161

Arylthiolates generated in this way gave, at room temperature, thioethers and thioesters from alkyl and acyl halides.162 Aromatic vinyl bromides underwent the reaction when tetrakis(triphenylphosphine) palladium(0) was added as the organometallic catalyst.163 The conversion of (E)-vinyl bromides 108 was remarkably stereoselective in giving the (E)-vinyl phenylsulfides 109 (Scheme 49).

Scheme 49  Reduction of disulfides with indium(I) iodide and subsequent palladium(0)-catalyzed coupling with vinylcyclobromides

11.4 Reduction of Disele nides

11.4.1 Reduction with Indium(I)

In the same way as for disulfides, indium(I) iodide reduces diphenyl diselenides to give bis(phenylseleno)iodindium(III) as a source of PhSe⁺, which reacts with alkyl and aryl halides to give the parent selenoethers and esters.162,164 As before, the conversion of (E)-vinyl bromides produces (E)-vinyl phenylselenides in the presence of a catalytic amount of palladium(0).163

In deoxygenated aqueous ethanol, a stoichiometric mixture of indium(I) bromide and diphenyl diselenide gave BrIn(SePh)₂, which promoted, alternatively, the Markovnikov hydroxyselenation or hydration of terminal alkynes, depending on the experimental conditions. Thus, under reflux conditions, the terminal aliphatic alkynes 110 gave the methyl ketones 111 (Scheme 50).165

The nucleophilic substitution of glycosyl bromides with indium(III) phenyl and butyl selenolates was found to constitute a convenient preparation of selenoglycosides.166

Scheme 50  Markovnikov hydration of alkynes mediated by indium(I) bromide

11.4.2 Reduction with Indium(0)

In the indium-promoted synthesis of alkyl phenyl selenides from alkyl halides, indium metal is presumed to

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first reduce the alkyl halide. As a matter of fact, alkyl iodides are more reactive than alkyl bromides, and tertiary alkyl halides are more reactive than secondary or primary alkyl halides. The reaction requires only 0.5 equivalent each of diphenyl diselenide and indium.167

With chlorotrimethylsilane, diphenyl diselenide gave PhSeSiMe3, which provided the selenoacetals 112 from aliphatic aldehydes (Scheme 51). With aromatic aldehydes, the selenoacetals were partially reduced into the corresponding alkyl phenyl selenides.168 Alternatively, the same intermediate, PhSeSiMe3, underwent Michael addition with α,β-unsaturated carbonyl compounds to yield β-phenylselenocarbonyl compounds.169

\[
\text{RCHO} + \text{HSiMe}_2\text{Cl} \xrightarrow{\text{InCl}_3} \text{RCH(SePh)}_2 \text{Cl}
\]

Scheme 51  Indium-mediated formation of selenoacetals

### 11.5 Reduction of Carbon–Halogen Bonds

The reduction of the carbon–halogen bond by indium metal in organic solvents leads to a mixture of organoindium species.20 Various reactions in which the carbon–halogen bond is reduced by indium metal, including reduction of vicinal dibromides, aryl-substituted geminal dibromides and α-halo carbonyl compounds, reductive coupling of aryl and alkyl halides, or deprotection of trichloroacetyl- and trichloroethoxycarbonyl-protected alcohols and amines, have been reviewed recently.10 More recently, reductive elimination of halohydrins, such as chlorohydrin and bromohydrin, by indium metal was carefully investigated (Scheme 52). It was determined that the reaction required the addition of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (0.02 equiv) and indium(III) chloride as a special catalyst was mentioned in the reaction of O-trimethylsilyl monothioacetals with triethylsilane and silylated carbon nucleophiles. It was pointed out that, for these reactions, neither chlorotrimethylsilane nor indium(III) chloride was effective alone and the reactions proceeded only when chlorotrimethylsilane and indium(III) chloride were combined.171 Such a remarkable enhancement of Lewis acidity of chlorosilane by indium(III) chloride was later emphasized in various reactions such as aza-Michael additions of carbamates to enones,172 Friedel–Crafts alkylation, hydrosilylation and reductive allylation (Scheme 53).173

With indium(III) hydroxide instead of indium(III) chloride, the addition of chlorodimethylsilane to ketones gave the corresponding chloroalkanes.174 Chloroalkanes were also prepared from alcohols with stoichiometric chlorodimethylsilane/stoichiometric benzil/catalytic indium(III) chloride system.175 The driving force in this reaction is the fast complexation of benzil, followed by the release of dihydrogen and the complexation by indium(III) chloride of the chlorosilyl ether that facilitates the transfer of chloride and liberation of siloxane (Scheme 54). In the presence of indium(III) chloride, there was also release of dihydrogen and formation of siloxane when mixing chlorodimethylsilane with carboxylic acids. The transient acid chloride could then undergo the Friedel–Crafts reaction with aromatic ethers.176

\[
\text{PhSeSePh + In, TMSCl} \xrightarrow{\text{MeCN, reflux}} \text{RCH(SePh)}_2 \text{up to 80%}
\]

Scheme 52  Indium-mediated reductive elimination

\[
\text{RCH(SePh)}_2 \xrightarrow{\text{In, InCl}_3, \text{Pd(0)}} \text{RCH(SePh)}_2 \text{up to 98%}
\]

Scheme 53  Activation of Lewis acidity of silicium by indium(III) chloride

\[
\text{InCl}_3 \xrightarrow{\text{PhSeSePh}} \text{PhSeSiMe}_3, \text{PhSeSePh}
\]

With indium(III) hydroxide instead of indium(III) chloride, the addition of chlorodimethylsilane to ketones gave the corresponding chloroalkanes.174 Chloroalkanes were also prepared from alcohols with stoichiometric chlorodimethylsilane/stoichiometric benzil/catalytic indium(III) chloride system.175 The driving force in this reaction is the fast complexation of benzil, followed by the release of dihydrogen and the complexation by indium(III) chloride of the chlorosilyl ether that facilitates the transfer of chloride and liberation of siloxane (Scheme 54). In the presence of indium(III) chloride, there was also release of dihydrogen and formation of siloxane when mixing chlorodimethylsilane with carboxylic acids. The transient acid chloride could then undergo the Friedel–Crafts reaction with aromatic ethers.176

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\]
um(III) chloride acted as a Lewis acid to accelerate the deoxygenation of the resulting intermediate that accompanied the hydride transfer and the consecutive formation of the siloxane. This system showed high chemoselectivity in multifunctional compounds.177

In analogy to this reaction driven by the removal of hydrochloric acid in chlorinated solvents, allylchlorodimethylsilane was added to alcohols in the presence of a catalytic amount of indium(III) chloride. Hydroxyl groups in secondary and tertiary alcohols were then substituted by allyl groups.178 The direct substitution of the hydroxy group in alcohols could even be performed with non-chlorinated silanes, such as allyl-, propargyl- and alkynyltrimethylsilanes.

The bromotrimethylsilane–indium(III) chloride couple as a strong Lewis acid was able to catalyze, even in hexane, the nucleophilic substitution of alcohols with silyl nucleophiles such as methallyl-, cinnamyl-, propargyl-, allyl-, allenyl- and allenylmethylsilanes.179 The reaction is limited to alcohols that are susceptible to forming a stabilized carbocation. Highly chemoselective allylations towards a hydroxyl moiety over both ketone and acetoxy groups were observed.180

13 Indium(III)-Catalyzed Reactions

We have seen that indium(III) chloride and indium(III) bromide have been added in catalytic amounts to organo-metallics in order to induce reactive organoindium reagents by transmetalation. In addition, a section was devoted to the activation of silicon by indium(III) salts to metallics in order to induce reactive organoindium reagents by transmetalation. This final section deals with all the other indium(III)-catalyzed reactions. Indium(III) salts have often been used as water-tolerant Lewis acids, especially in allylations, aldol-type reactions, conjugate additions or cycloadditions.16 Protons could, however, be the active catalysts as evidenced in the indium(III) triflate catalyzedaza-Michael addition reactions.181

Indium(III) salts were also effective in ionic liquids, thus allowing the recycling of a BINOL–In(III) complex in an enantioselective Diels–Alder reaction.182

In a few cases, indium(III) salts have been used as Bronsted bases; thus, a catalytic amount of indium(III) isopropoxide was effective as a base in the Mannich-type reaction of N-(2-hydroxyacetyl)pyrrole with o-tosyl- imines; in the presence of a BINOL ligand, excellent diastereo- and enantioselectivities were obtained.183

13.1 Aldol-Type and Related Reactions

In aldol-type and related reactions, indium(III) salts are used as Lewis acids which coordinate the oxygen or the nitrogen atom of the carbonyl or imine compounds. Thus, the use of indium(III) triflate showed significant advantages in the condensation of 3-substituted 1-methyl-2-thiohydantoins with aromatic aldehydes, giving the 5-arylidenecounterparts.184

The indium(III) chloride catalyzed Mukaiyama aldol reaction was recently revisited in different solvents. The solvent of choice turned out to be propan-2-ol in water (95:5), which gave rise to an excellent syn diastereoselectivity with (Z)-enolsilanes, but only in moderate yield.185 The Mukaiyama aldol reaction was found to be more efficient with indium(III) triflate than with indium(III) chloride. Thus the reaction could be carried out at –40 °C in dichloromethane in the presence of a chiral PYBOX ligand to achieve enantioselectivities up to 92%.186

In the indium(III)-catalyzed Mannich-type reaction, the imine is preferred before the addition of silyl enol ethers. High yields and high selectivities were obtained when chiral amines were used with indium(III) chloride (20 mol%) in methanol187 or ionic liquids.188

Another reaction is the domino indium(III)-catalyzed formation of enamines followed by its addition to imines.189

As a multicomponent reaction, the Biginelli reaction has received much attention for its direct preparation of dihydropyrimidinones from 1,3-dicarbonyl compounds, aldehydes and urea. A large variety of aldehydes and 1,3-dicarbonyl compounds were mixed with urea or thiourea in the presence of indium(III) chloride (10 mol%) in refluxing tetrahydrofuran, thereby affording the corresponding dihydropyrimidinones in good yields.191

Trichloromethylated tetrahydropyrimidinones 117 were recently prepared according to this method, with indium(III) bromide instead of indium(III) chloride (Scheme 55).192

Scheme 55 Biginelli reaction catalyzed by indium(III) bromide

13.2 α-Amination and α-Alkylation of Carboxyl Compounds

By adding silica gel to a solution of indium(III) chloride and then evaporating the solvent, it is possible to obtain a solid-supported indium catalyst. This catalyst was successfully used in the α-amination of 1,3-dicarbonyl compounds.193

A fascinating reaction with total atom-economy was recently described; it concerned the indium(III)-catalyzed addition of active methylene to terminal alkenes (Scheme 56). It is supposed that indium enolates, generated from the β-carbonyl compounds 118 and indium(III)
triflate, add across the triple bond of terminal alkynes to give 119. This carboindation process (see section 6) was evidenced by the higher reactivity of electron-rich alkynes, suggesting a coordination of the indium atom to the alkynie. With acetylene gas, which is sensitive to acidity, this procedure did not operate, but was successful after addition of molecular sieves, and thereby allowed for an easy access to α-vinyl keto esters.

Another reaction that involves active methylene compounds was discovered recently when ethers were used to give dialkyl-4-halo-tetrahydropyrans.199 Substituted tetrahydropyrans or thiacyclohexanes were further prepared directly from homoallylic primary alcohols or thiols with aldehydes in the presence of a stoichiometric amount of indium(III) chloride, according to a mechanism involving an oxonium ion.200 Excellent diastereoselectivity was observed with the trans homoallylic alcohols which provided (up-down-up) 2,3,4-trisubstituted tetrahydropyran derivatives.

In contrast with the method of formation of 4-chloro-2,4-dialkytetrahydropyrans that required a stoichiometric amount of indium(III) chloride, the method using allylchlorosilane as allylating agent with aldehydes required only a catalytic amount of indium(III) triflate.201 Similarly, the use of chloro- or bromotrimethylsilane as additive was found to be efficient in the synthesis of cross 2,6-disubstituted 4-chloro- or 4-bromotetrahydrofuran products from secondary homoallylic alcohols and aldehydes in the presence of a catalytic amount of indium(III) triflate.202 Especially noteworthy was the excellent stereoselectivity observed where only the all-cis configuration products were obtained, except in specific cases.203 In order to apply the methodology to an enantioselective synthesis, optically active alcohols were engaged in the process; indium(III) bromide as a weaker Lewis acid turned out to be more efficient than indium(III) triflate to reduce the rate of epimerization of the homoallylic alcohol 120, which led to an 84% enantiomeric excess of a precursor (121) of (–)-centrolobine (Scheme 58). With stoichiometric indium(III) chloride, but in the absence of chlorotrimethylsilane, the enantiomeric excess was increased to 90%.204

**13.3 Prins-Type and Related Reactions**

The discovery of the indium(III)-catalyzed Prins-type reaction arose from the identification of side-products observed during the investigation of the indium(0)-mediated allylation of aldehydes. Indeed, the transient homoallylic alcohol reacted with the starting aldehyde to give cis-2,4-dialkyl-4-halo-tetrahydropyrans.199 Substituted tetrahydropyrans or thiacyclohexanes were further prepared directly from homoallylic primary alcohols or thiols with aldehydes in the presence of a stoichiometric amount of indium(III) chloride, according to a mechanism involving an oxonium ion.200 Excellent diastereoselectivity was observed with the trans homoallylic alcohols which provided (up-down-up) 2,3,4-trisubstituted tetrahydropyran derivatives.

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According to the groups of Li and Loh, the mechanism of the indium(III)-mediated Prins-type reaction goes through an oxonium intermediate that is formed by attack of the nucleophilic alcohol upon the aldehyde activated by indium(III) salts. The subsequent cyclization, which is formerly an intramolecular Prins reaction, is diastereoselectively controlled by a chair-like transition state. The silyl version of the Prins reaction with 4-methylsilylbut-3-en-1-ols and aldehydes relies on the stabilization of the carbocation by the silicon atom at the β-position. The methodology was extended to thioles and to amines in the preparation of unsaturated nitrogen and sulfur heterocycles.

An intermolecular version of the indium(III) Prins reaction was recently carried out in ionic liquids. Thus, alkenes underwent condensation with paraformaldehyde in the presence of 10 mol% indium(III) bromide in 1-butyl-3-methylimidazolium hexafluorophosphate or tetrafluoroborate to afford the corresponding 1,3-dioxane derivatives.

When operating with chiral substrates, the main problem that may occur is the epimerization of the homoallylic alcohol under the reaction conditions. Such an epimerization, particularly important with indium(III) triflate, comes from a retro-cleavage of the homoallylic alcohol into an aldehyde, followed by the formation of an oxonium intermediate between the homoallylic alcohol and the liberated aldehyde and then by a 2-oxonia[3,3]-sigmatropic rearrangement (see Scheme 5). However, since the 2-oxonia[3,3]-sigmatropic rearrangement is mediated by indium(III) triflate, it is possible to transfer an allyl group from a ramified homoallylic alcohol to an aldehyde; at low temperature the self-transfer could be avoided in enantioselective α-regioselective allylation of aldehydes. An enantioselective allyl transfer from a linear homoallylic alcohol to an aldehyde is even possible via a double 2-oxonia[3,3]-sigmatropic rearrangement, provided that the substrates are chosen with accord to thermodynamic considerations.

A propargylic transfer, assisted by silicon, was also observed when an allenic alcohol was treated with an aldehyde in the presence of 1 mol% of indium(III) triflate; the transfer of chirality was also achieved through a 2-oxonia[3,3]-sigmatropic rearrangement.

The reaction of homoallylic alcohols, in which the double bond is dimethylated at the terminal position (α-prenyl alcohols), with aldehydes in the presence of a catalytic amount of indium(III) triflate led to an oxonium intermediate, which underwent a (3,5) oxonium-ene-type cyclization at 0 °C to afford polysubstituted tetrahydrofurans; tetrahydropyrans were similarly obtained from the homologated bishomoallylic alcohols. Based on this chemical reaction, a kinetic resolution of bishomoallylic alcohols was developed with the aid of the steroidal aldehyde as the chiral inducer (Scheme 59). Both enantiomers of the bishomoallylic alcohol can form an oxonium intermediate with the chiral aldehyde, but only the enantiomer that forms a matched pair in the transition state of the ene cyclization is reactive; the other is recovered with an enantioselectivity ranging from 92% to more than 99%.

An intermolecular carbonyl-ene reaction can also be catalyzed by indium(III) triflate, as recently observed in the reaction between methylene cyclohexane and aldehydes; the resulting homoallylic alcohol was not isolated because of the subsequent (2,5) oxonium-ene cyclization, which gives new opportunities to prepare tetrahydropyran rings.

In contrast with α-prenyl alcohols, the γ-prenyl alcohols, when exposed to aldehydes in the presence of a catalytic amount of indium(III) triflate, gave an oxonium intermediate which could not undergo carbonyl-ene reaction; the unique possibility lay with a 2-oxonia[3,3]-sigmatropic rearrangement, which was then followed by a facile oxonium-ene cyclization and led to tetrahydrofuran derivatives. In order to suppress this ene reaction, the oxonium intermediate was trapped with a hydroxyl group, installed in a judicious position, to form the cyclic ketal which, after hydrolysis, gives the desired α-prenyl alcohol (Scheme 60). With chiral 1,5-diols, transfer of chirality during the [3,3]-rearrangement was possible, providing a highly enantioselective prenylation of aldehydes.
13.4 Protection of Carbonyl Compounds, Alcohols and Amines

Indium(III) chloride catalyzes the protection of aldehydes and ketones as their corresponding 1,3-dioxolanes or dialkyl acetals in refluxing cyclohexane. The reverse reaction, namely the deprotection, is carried out in refluxing aqueous methanol under catalysis by indium(III) chloride.217 The acetalization of carbonyl compounds was also found to be particularly efficient with trialkyl orthoformal and with diols in the presence of indium(III) triflate.218

Thioacetalization of aldehydes and ketones was performed under catalysis by indium(III) bromide in dichloromethane at room temperature; in contrast to the behavior of diacetics, dithioacetals are stable under aqueous conditions in the presence of indium(III) salts, so that dithioacetalization was even possible in aqueous medium.219 Thioacetalization of carbonyl compounds or thiodioacetalization of diacetics into dithioacetals were also performed in the presence of indium(III) triflate.220

The protection of aldehydes into acylals (geminal diacetals) was achieved under catalysis by indium(III) bromide under solvent-free conditions at room temperature;221 the deprotection occurred in refluxing water with indium(III) bromide as catalyst.222 Acetylation of alcohols with acetic anhydride was catalyzed by indium(III) chloride under microwave conditions,223 or directly by indium(III) triflate.224

A convenient protection of alcohols as their trimethylsilyl ethers was performed in dichloromethane with hexamethyldisilazane in the presence of indium(III) bromide (5 mol%).225 The catalyst formed a complex with hexamethyldisilazane, making the silylating agent more electrophilic. Both of the trimethylsilyl groups were transferred to the alcohol, thereby liberating a mole of ammonia (Scheme 61). On the other hand, indium(III) bromide and indium(III) chloride catalyze the N-tert-butoxycarbonylation of amines with Boc anhydride at room temperature under solvent-free conditions.226

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Scheme 61 Silylation of alcohols catalyzed by indium(III) bromide

13.5 Friedel–Crafts Reactions

Acylation of activated benzenes was carried out with catalytic amounts of indium in solvent (refluxing dioxane) or under solvent-free conditions.227 Water was used as the solvent in the indium(III) triflate catalyzed Friedel–Crafts reaction of aniline and anisole derivatives with methyl trifluopyruvate.228

In the presence of a catalytic amount of indium(III) salts, indoles reacted at the 3-position with a variety of electrophiles, such as cyclic allylic acetates,229 acetic anhydride,230 aryl sulfonyl chlorides231 or secondary benzyl alcohols.196 In the latter reaction, water was eliminated; such an elimination occurs in the preparation of diarylmethanes from trioxane as the electrophile, in the presence of indium(III) chloride as the catalyst.232

Indium(III) triflate was used to activate the carbon–carbon triple bond of a terminal alkyne in the Friedel–Crafts alkenylation of arenes; double addition occurred with heterocyclic arenes to afford 2:1 adducts, where two heterocyclic arenes regioselectively attacked the same alkyne carbon atom.233 With propargyl ethers, 2-arylindoles gave annulated carbazoles with the use of a Lewis acid stronger than indium(III) triflate, such as indium(III) nonaflate (Scheme 62).234

Scheme 62 Annulation of heterocyclic arenes catalyzed by indium(III) nonaflate

13.6 Activation of Carbon–Carbon Multiple Bonds

Indium(III) chloride and indium(III) triflate were found to be efficient catalysts for the regiospecific Markovnikov-type addition of thioacetic acid to alkenes. The reactions were, for the most part, carried out in refluxing dichloroethane with 5 mol% of catalyst.235 When indium(III) triflate was used as catalyst in refluxing nitromethane, thiols added to alkenes in a regiospecific manner, by either an inter- or an intramolecular pathway.236

In the chemoselective dimerization of vinylarenes at 0 °C, the first step is the activation of the carbon–carbon double bond by indium(III) bromide as catalyst.237

We have already seen that the triple bond of a terminal alkyne could be activated by indium(III) species in Friedel–Crafts reactions or in the α-alkylation of carbonyl compounds. When propargylamines or alcohols add to ethenicetrifluoroacetates according to a Michael process, the indium enolate intermediate undergoes a cyclization via the activation of the triple bond by indium(III) bromide, providing methylenepryrorolide or methylenetrotryrohydrop-
furan derivatives. An indium(III) bromide catalyzed cyclization also occurred with the 2-alkynylaniline 131, leading to the indole 132. When the reaction was carried out using a substrate with a trimethylsilyl group or with no substituent group on the terminal carbon, such as 133, dimerization occurred and led to the quinoline derivative 134 (Scheme 63).

In the presence of indium(III) chloride as catalyst, 1,6-enynes with a terminal triple bond gave 1-vinylcycloalkenes after activation of the triple bond by indium(III); with an alkyl group on the extremity of the triple bond, a skeletal reorganization occurs.

![Scheme 63](image)

**Scheme 63** Cyclization of 2-alkynylanilines promoted by indium(III) bromide

### 13.7 Activation of an Oxygen or a Halogen Atom in a Single Bond

The rearrangement and ring opening of epoxides have been correlated to the heterophilicity of indium(III) salts, allowing, for example, a convenient conversion of epoxides into thiranes to take place with thiocyanates.

Allylic and benzylic acetates were found to be reactive towards allyltrimethylsilane in the presence of a catalytic amount of indium(III) bromide (5 mol%); this deoxygenative allylation was possible even directly from benzylic alcohols, owing to the possible activation by silicon (see below).

In the Beckmann rearrangement, the hydroxyl group of an oxime is first activated by an acid; in a recent application of this rearrangement catalyzed by indium(III) chloride, oxazoloquinolines were prepared directly from the corresponding 3-acyl-4-quinolinone ketoximes.

Cyclization between allylic halide and alkyne moieties in 1,6-enynes 135 occurred with halogen transfer in dichloromethane; indium(III) chloride as catalyst was purported to activate the allylic halogen, whereas the alkyne function acted as the nucleophilic partner. Depending on the alkyne substitution pattern, a bromine atom was transferred from the substrate, or a chlorine atom was transferred from the solvent, to give either 136 or 137 (Scheme 64).

![Scheme 64](image)

**Scheme 64** Atom-transfer cyclization catalyzed by indium(III) bromide

### 13.8 Ferrier Rearrangement and Glycosylation

In the first report of the indium(III) chloride catalyzed Ferrier rearrangement, it was mentioned that treatment of tri-O-acetyl glucal with various alcohols and phenols at room temperature in dichloromethane gave the alkyl and aryl 2,3-unsaturated glycosides rapidly, with a preferred α-selectivity (62–92%). The reaction was since extended to other glycals in acetonitrile under microwave conditions. With 2-C-acetoxyethyl glycidyl derivatives in the presence of a catalytic amount of indium(III) chloride, alcohols gave the corresponding 2-C-methylene glycosides with exclusive α-selectivity, except in one case.

The Ferrier rearrangement applied to silyl nucleophiles, such as allyltrimethylsilane, trimethylsilyl cyanide, trimethylsilyl azide and alkynyltrimethylsilanes, gave the corresponding 2,3-unsaturated allylic glycosides, glycosyl cyanides, glycosyl azides and alkynyl glycosides with high α-selectivity when the reaction was performed in the presence of indium(III) bromide (5 mol%) in dichloromethane at room temperature. Under microwave conditions, the reaction was achieved in less than one minute. Another method for the preparation of α-alkynyl glycosides from alkynyltrimethylsilanes was recently reported; this method used δ-hydroxy-α,β-unsaturated aldehydes via indium(III) bromide mediated hemiacetalization followed by C-glycosylation.

In the synthesis of C-aryl glycosides with a free amino functionality, aryl amines were put together with tri-O-acetyl glucal 77 in the presence of indium(III) bromide (10 mol%); the Ferrier rearrangement was followed by an intramolecular nucleophilic substitution by the amine function and afforded the benzo-fused heterocycle 138 (Scheme 65). In addition to glycals, glycosyl halides can be useful as electrophilic partners for carbon nucleophiles in the synthesis of C-glycosides. Thus, C-glycosyl indoles and pyrroles were prepared within a few minutes through the
coupling of acetylated glycosyl bromides with indoles and pyrroles in the presence of indium(III) chloride (10 mol%).

Similarly, O-glycosylation was performed through the coupling of acetylated glycosyl bromides with alcohols in the presence of indium(III) chloride (40 mol%), thereby providing the corresponding O-glycosides with pronounced β-selectivity owing to the presence of a participating group at the C2 position. With thiols instead of alcohols, peracetylated sugars were reactive enough to afford the corresponding β-thioglycosides, but the presence of titanium(IV) chloride (20 mol%) along with indium(III) chloride (20 mol%) was required.

14 Conclusion

This review shows the large diversity of reactions that are promoted by indium. The low first ionization potential of indium(0) is responsible for its facility to reduce various chemical functions even in aqueous media. Thus, indium metal is a suitable agent for mediating carbon–carbon bond reactions, as it can tolerate oxygen and nitrogen functionalities. Furthermore, indium does not form the corresponding oxides when exposed to air. Indium is an interesting alternative to toxic tin hydride in radical cyclizations. The higher chemo-, regio-, stereo- and enantio-selectivities displayed by allyl-, propargyl-, allenyl- or alkynylindium reagents, compared to Grignard reagents, make them useful tools in organic synthesis. For a better understanding of the reactions, the organoindium species, which differentiate according to the solvent, were identified by NMR measurements.

The chemical applications of indium(I) in synthesis is still in its infancy, probably because of its propensity to disproportionate. In the presence of an oxidizing agent, indium(I) yields the metastable indium(II) species which is rapidly oxidized to the stable indium(III) species.

In contrast, the reduction of indium(III) chloride with hydrides generates dichloroindium hydride and thereby paves the way to new reactions, known as hydrideation reactions. In addition, new reactivities have been demonstrated since the discovery of a synergistic effect of silicium and indium atoms, both linked to oxygen or chlorine atoms. Lewis acidity is then enforced. Of the indium(III) salts used as Lewis acids, indium(III) bromide is the weakest, but the striking difference observed between indium(III) chloride or indium(III) bromide and indium(III) triflate comes from the lack of nucleophilicity of the triflate anion compared to the halide anion. Although these salts tolerate water in many reactions, they are more easily hydrolyzable than lanthanide salts, as evidenced by their pKₐ (Kₐ = hydrolysis constant) values (4 for In⁺ compared to 7.7 for Yb⁺).

A new challenge in indium chemistry might come from the faculty of indium(III) chloride to form binary ionic liquids, such as butylmethylimidazolium tetrachloroindate, with a low viscosity and a high density, facilitating both the stirring and the product separation process.

References

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