DOI: 10.1002/ejoc.200900895

Recent Developments in Indium Metal and Its Salts in Organic Synthesis

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Keywords: Indium / Organoindium reagents / Chiral indium complexes / Chirality / Reaction mechanisms / Synthetic methods

Indium and its salts have emerged as promising catalysts for effecting various functional group transformations in last two decades. There are a great number of reported reactions involving indium reagents; the versatility and the applicability of these reactions makes it a hot field to explore, and it attracts much interest from organic chemists. The development of indium reagents in C–C bond-formation reactions, coupling reactions, asymmetric synthesis in the presence of chiral-metal ligand complexes, etc. has made this field more attractive. Indium salts have pronounced Lewis acid character and are also attractive because of their moderate stability to water. Here we highlight developments in indium chemistry reported in the last eight years.

Introduction

The element indium, named for the luminous indigo line in its spectrum, was discovered in 1863 by German chemist Ferdinand Reich, together with his assistant Theodor Richter.[1] Although indium was discovered very early, and even though the discovery of the Grignard reaction in 1900 prompted scientific investigation into the use of metals in synthetic organic chemistry, organic chemists took little interest in indium or its salts until the early 1990s.

Recently, however, roles of indium in organic synthesis have widened to include a variety of applications. As a result of these efforts, indium and its salts have found use in various functional group transformations and other organic reactions such as ring-openings of epoxides and aziridines,[2] Mukaiyama-type reactions,[3] intramolecular Prins-type cyclizations,[4] Diels–Alder cycloadditions,[5] reductive Friedel–Crafts alkylations and acylations,[6] thioacetalizations of aldehydes and ketones,[7] etc. As well as indium halides, organoindium reagents and chiral indium complexes have also been explored, highlighting the synthetic potential of indium and its derivatives in the field of organic chemistry.

The wide application of indium metal is attributable to its diverse physical properties. Unlike most of the other metals, indium is stable to air and moisture, which offers the potential for recovery and recycling of the catalyst,[8] whereas the fact that it is non-toxic enables its reactions to be handled very easily. The low first ionization potential of this metal makes it an ideal reagent to participate in SET reactions[9] and its lower heterophilicity makes it an effective catalyst or reagent for C–C bond-formation reactions, due to the fact that it can readily tolerate other functional groups containing N, O, S, etc.

Because of its particular importance in topical fields of research, a number of reviews of the role of indium in current organic synthesis have appeared previously. Cintas reviewed the chemistry of organoindium reagents in 1995,[10] and in 1999 Li and Chan summarized reactions mediated by indium metal and indium compounds in aqueous media.[11] Within the last eight years, Ranu reviewed its significance in 2001,[12] Podlech and Maier later comprehensively covered developments in indium up to 2001,[13] and Vijay Nair evaluated indium's roles in the forms of the metal, its salts, organoindium reagents, and chiral indium complexes.[14] A 2007 review by Auge et al.[15] focused mainly on the utility of indium in Barbier-type reactions.

In this review we focus particular interest on those topics not yet covered, along with other newer developments relating to indium chemistry. The topics can be broadly classified into:

1. Ring-Opening of Cyclic Compounds
2. Allylation Reactions
3. Coupling Reactions
4. Addition and Condensation Reactions
5. Annulation Reactions
6. Halogenation Reactions
7. Synthesis of Glycosides
8. Synthesis of Heterocycles
9. Miscellaneous Reactions

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1. Ring-Opening Reactions of Cyclic Compounds

1.1. Reactions of Aziridines

Aziridines have special importance in organic synthesis because this system is one of the major building blocks for most nitrogen-containing natural products.[16] As a result, many methodologies for nucleophilic ring-opening reactions of aziridines have been developed.[17] Arenes have recently been found to open the aziridine ring regioselectively.[18] In this method, indium triflate has been utilized for *C*-arylation of *N*-tosylaziridines, to yield β-arylamines regioselectively as the major products. This method works both with activated and with unactivated arenes. In cases of aryl-substituted aziridines, arenes (nucleophiles) attack selectively at benzylic positions, as demonstrated in Table 1.

Similar reactions between *N*-tosylaziridines and heteroaromatic compounds in the presence of $InCl_3$ have also been reported.[19] Here selectivity of the nucleophilic attack between the benzylic carbon and the other carbon in the aziridine ring (termed terminal carbon) can also be achieved. The preferential attack of pyrrole at the benzylic position gives mixtures of 2- and 3-alkylated pyrroles (Scheme 1), whereas furan and thiophene furnish mixtures of both benzylic and terminal-attack products.

1.2. Reactions of Epoxides

Catalytic asymmetric ring-opening of *meso*-epoxides has proven to be a valuable tool for the straightforward synthesis of enantiomerically pure 1,2-difunctionalized fine chemicals. A number of methodologies for these conversions have been reported.[20]

1. 2.1. Asymmetric Thiolysis of meso-Epoxides

A chiral complex of indium bromide and a bipyridine ligand (shown in Figure 1) has been reported to catalyze the highly enantioselective thiolysis of *meso*-epoxides.[21] The use of this new catalyst to effect the enantioselective thiolysis of epoxides eliminated some of the disadvantages associated with the already available gallium-lithium-BINOL complex catalyst,[22] which unavoidably requires the use of *tert*-butyl thiol, limiting its application to a rather small number of substrates. Taking all these facts into consideration, the establishment of the new catalyst is of particular interest because it provides a very good substrate scope. In reactions between *meso*-epoxides and either anilines or aliphatic alcohols it has been well established to furnish 1,2-amino alcohols or 1,2-diol monoethers,[23] respectively.

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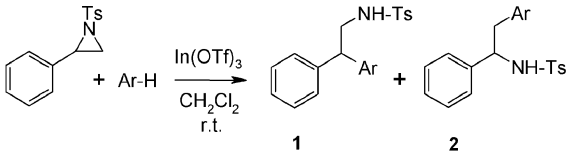
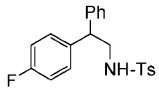
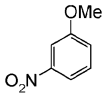
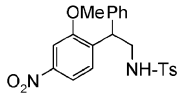
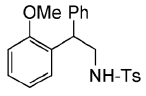
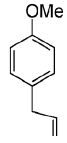
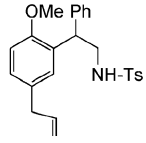
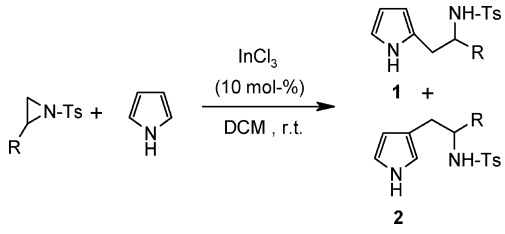
B. V. Subba Reddy was born in Andhra Pradesh and obtained his Ph.D. from the IICT under the supervision of Dr. J. S. Yadav in 2003. After completion of two years of post-doc study with Prof. E. J. Corey at Harvard University, he returned to India and took up a scientist position at IICT in June 2006. Presently, he is focusing on the development of green protocols using environmentally friendly reagents/solvents for the synthesis of biologically active compounds. Apart from green chemistry, he is also working on asymmetric catalysis for new chemical entities.

Table 1. Indium-triflate-catalyzed ring-opening of aryl aziridines with arenes.



Aziridine	Arene	Product	Ratio (1 : 2)
			100 : 0
"			95 : 5
"			95 : 5
"			94 : 6



Scheme 1. Ring-opening of aziridines with pyrrole.

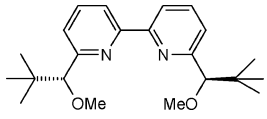
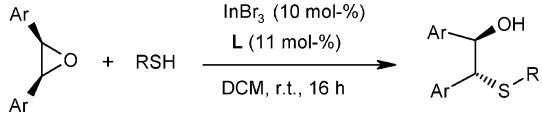


Figure 1. Chiral bipyridine ligand.

This ligand has been applied together with indium metal to the enantioselective synthesis of 1,2-mercapto alcohols from *meso*-epoxides and aliphatic or aromatic thiols. Only aromatic *meso*-epoxides undergo thiolysis under these conditions; aliphatic *meso*-epoxides fail to give the desired products. The scope of this method, with regard both to *meso*-epoxides and to thiols, is demonstrated in Table 2.

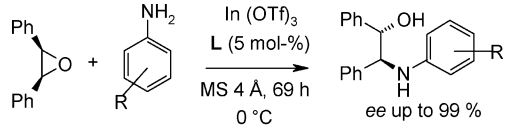
Table 2. Indium-bipyridine-catalyzed thiolysis of *meso*-epoxides.



Ar	R	Yield (%)	*Ee* (%)
C_6H_5	$C_6H_5CH_2$	80	92
C_6H_5	4-Me-C_6H_4	79	96
C_6H_5	*n*Bu	90	95
2-naphthyl	$C_6H_5CH_2$	82	96
3-Me-C_6H_4	C_6H_5	67	91
4-Me-C_6H_4	$C_6H_5CH_2$	68	92
4-Cl-C_6H_4	C_6H_5	84	92

1.2.2. Enantioselective Ring-Opening of meso-Epoxides with Anilines

Enantioselective ring opening has been reported with various aniline derivatives[24] (Scheme 2). Chirality has been achieved with a new proline-based *N,N′*-dioxide-indium tris(triflate) complex (shown in Figure 2).



L: $In(OTf)_3$ ratio is (1.1:1)

Scheme 2. Indium-triflate-catalyzed ring-opening of *meso*-epoxides.

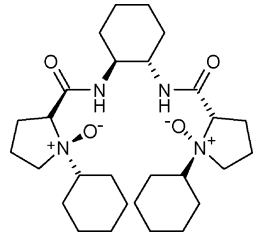


Figure 2. Proline-based *N,N′*-dioxide ligand.

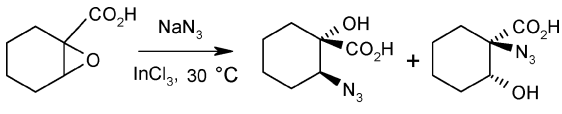
Anilines bearing either electron-withdrawing or electron-donating groups either at their *ortho* or their *para* positions give chiral β-amino alcohols. Optical purities of up to 99% can be achieved under these reaction conditions.

1.2.3. Azidolysis of Epoxides

$InCl_3$ catalyzes the azidolysis of α,β-epoxycarboxylic acids with sodium azide in a highly regio- and diastereoselective manner either in aqueous media or in acetonitrile.[25] Although the azidolysis of methyl and ethyl α,β-epoxycarboxylates has been extensively investigated,[26] α,β-epoxycarboxylic acids remain relatively unexplored.[27] This method also has the distinction of being more environmentally benign, because the reaction medium is water. The selective formation of β-azidocarboxylic acids in which the azido group is *syn* to the carboxylic group has been achieved by this protocol. The acidity of the aqueous medium has a pronounced effect on the efficiency of the cata-

lyst and it is highest at a pH of 4. The effects of solvent, pH, and the concentration of the catalyst on the reaction are shown in Table 3.

Table 3. Indium-chloride-catalyzed azidolysis of epoxides.

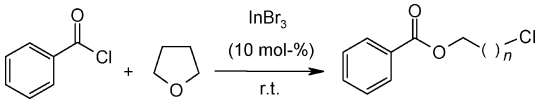


1 2

Medium	pH	$InCl_3$ [mol-%]	Yield (%)	Ratio (1:2)
MeCN		0	7	99:1
MeCN		1	>99	99:1
MeCN		30	>99	99:1
H_2O	7	0	50	80:20
H_2O	7	1	89	99:1
H_2O	7	30	>99	98:2
H_2O	4	0	10	99:1
H_2O	4	0	38	99:1
H_2O	4	0	>99	99:1
H_2O	4	1	>99	99:1
H_2O	4	10	>99	99:1

1.3. Reactions of Cyclic Ethers

Cleavage of cyclic ethers with acid chlorides in the presence of $InBr_3$ has also been reported[28] (Scheme 3). This reaction is of particular interest because benzylic and allylic ethers are frequently used as protecting groups for hydroxy functions, and their subsequent cleavage is a very interesting route to polyfunctional molecules.[29]



Scheme 3. $InCl_3$-catalyzed cleavage of cyclic ethers with acid chloride.

By this protocol, the corresponding halo esters have been synthesized with enhanced selectivities under mild reaction conditions.

2. Allylation and Vinylation Reactions

The synthesis of enantiomerically enriched homoallylic alcohols is always an attractive target in organic synthesis because they can be converted into a variety of synthetically useful compounds. Many methods directed towards this goal have therefore been developed,[30] but chiral indium complexes are as yet relatively unexplored. Use of these complexes in asymmetric synthesis has recently begun to be exploited. Chiral indium complexes have been reported to catalyze enantioselective allylation reactions of carbonyl compounds and keto phosphonate esters.

2.1. Allylation of Aldehydes

A chiral indium-PYBOX complex (ligand is shown in Figure 3) has been shown to be an effective catalyst for the enantioselective allylation of a variety of aldehydes, including aromatic, aliphatic, and α,β-unsaturated aldehydes, both in organic solvents and in ionic liquids[31] (Scheme 4). Allyltributylstannane is used as the allylating agent to afford the corresponding homoallylic alcohols. This protocol allows the recovery of the ligand without any racemization, which makes the cost of the chiral catalyst irrelevant. Furthermore, this reaction is highly chemoselective, taking place only with aldehyde functionalities even in the presence of keto groups.

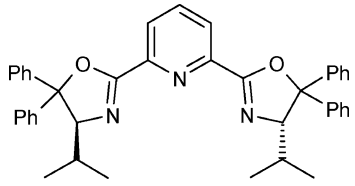
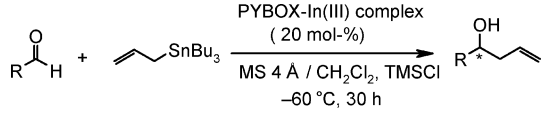


Figure 3. Chiral PYBOX ligand.



Scheme 4. Indium-PYBOX-catalyzed allylation of aldehydes.

2.2. Allylation of Ketones

Aromatic ketones have also been reported to undergo enantioselective allylation in the presence of chiral indium complexes.[32] Many methods for the enantioselective allylation of ketones in the presence of BINOL-indium or PYBOX-indium complexes have already been developed.[33] Despite all the progress achieved, the development of new approaches for this reaction is still in demand because of the reduced reactivities and lower binding affinities of ketones.[34] A ligand derived from (*S*)-picolinic acid *N*,*N*′-dioxide (Figure 4) in complexation with indium metal is used as the chiral catalyst together with tetraallyltin as the allylating agent. Aromatic ketones with electron-poor substituents afford homoallylic alcohols with high levels of enantiomeric excess, whereas the use of aliphatic alcohols gives only moderate results. The details are given in Table 4.

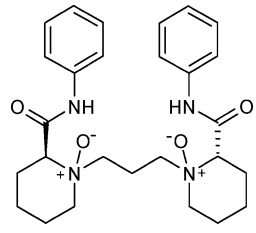


Figure 4. *N*,*N*′-Dioxide ligand.

Table 4. The enantioselective allylation of ketones.

Ketone	Product	*ee* (%)
acetophenone (**1a**)	**3a**	80
2-methoxyacetophenone (**1b**)	**3b**	83
4-methylacetophenone (**1c**)	**3c**	81
4-fluoroacetophenone (**1d**)	**3d**	81
3-chloroacetophenone (**1e**)	**3e**	70
2-acetonaphthone (**1f**)	**3f**	73
2,2,2-trifluoroacetophenone (**1g**)	**3g**	73

A non-asymmetric version of this reaction with a diallyldibutyltin reagent has also been reported.[32]

2.3. Allylation of Keto Phosphonates

Phosphonates are a very attractive class of compounds with a great range of applications in organic chemistry as intermediates, antibiotics, enzyme inhibiters, etc.[35] Because of their wide applications, the synthesis of structurally and functionally different phosphonates is of great importance.

2.3.1. Allylation of α-Keto Phosphonates

A ramipril-derived *N*,*N*′-dioxide ligand (Figure 5) in complexation with indium metal has been reported to be an effective catalyst for the enantioselective allylation of α-keto phosphonates to afford α-hydroxyallylic phosphonates[36] (Scheme 5). The presence of electron-withdrawing or -donating groups at either the *para* or the *meta* positions of the aromatic rings in the α-keto phosphonates furnishes excellent results, whereas *ortho*-substituted variants gives lower enantiopurities. A variety of ketones have been allylated by this protocol, as is demonstrated in Table 5. This reaction is of particular importance because many of the compound analogues have biological activity and pharmaceutical applications.[37]

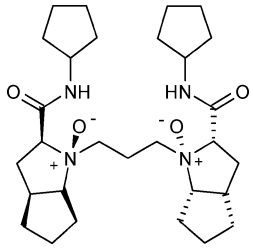
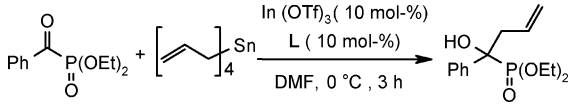
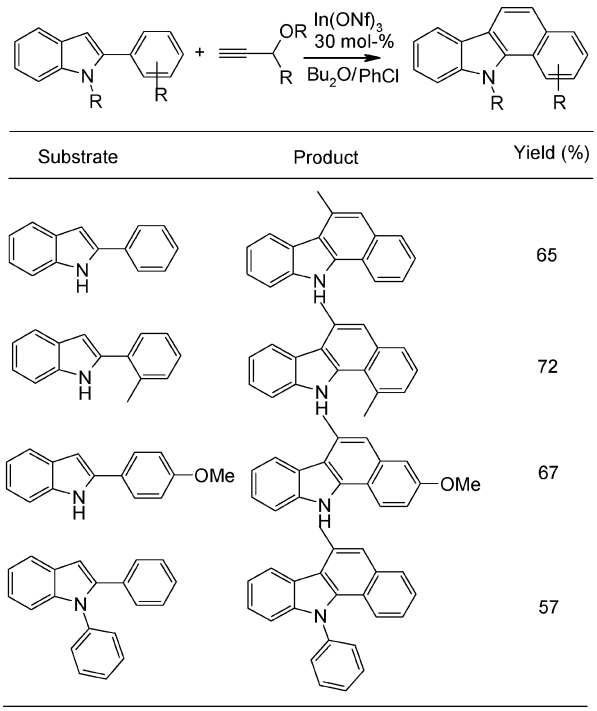


Figure 5. Ramipril-derived *N*,*N*′-dioxide ligand (**L**).



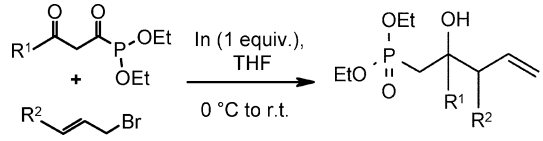
Scheme 5. Indium/*N*,*N*′-dioxide-catalyzed allylation of keto phosphonates.

Table 5. Annulations of 2-(2-heteroaryl)indoles.



2.3.2. Allylation of β-Keto Phosphonates

Allylation of β-keto phosphonates, which remains unsuccessful with Grignard reagents, has been reported to be successful in the presence of allylindium reagents[38] (Scheme 6). Here, allylindium generated in situ reacts with the β-keto phosphonate without any catalyst.

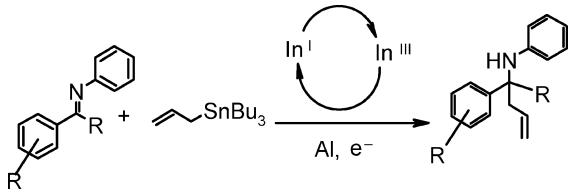


Scheme 6. Indium-mediated allylation of β-keto phosphonates.

β-Keto phosphonates with alkyl groups or cycloalkyl or aromatic rings at their β-positions and cyclic β-keto phosphonates also react smoothly under these conditions.

2.4. Allylation of Aldemines

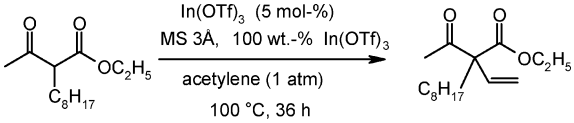
A lower-valent indium(I) reagent has been reported to catalyze the allylation of aldimines[39] (Scheme 7). Here the catalyst is regenerated under electrochemical conditions. This protocol furnishes homoallylic amines from aniline-derived aldimines. This method suffers from the disadvantage that competing side reactions predominate to give reduction products in cases involving ketimines and electron-poor aldimines.



Scheme 7. Allylation of aldemines.

2.6. Vinylation of β-Keto Esters

$In(OTf)_3$ has been shown to catalyze the vinylation of β-keto esters with acetylene gas to afford the corresponding α-vinylated keto esters[40] (Scheme 8).



Scheme 8. $In(OTf)_3$-catalyzed vinylation of β-keto esters.

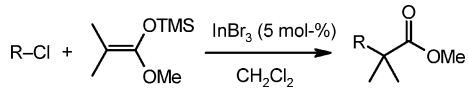
In comparison with existing methods that utilize acetylene gas, which suffer from many problems such as the acid- and base-sensitivity of acetylene, this method provides a highly practical protocol for the vinylation of keto esters, allowing the use even of welding-grade acetylene, which contains both acetone and water. Another feature of this method is the high atom efficiency. This method tolerates acid-sensitive groups and it is also applicable to substituted acetylenes.

3. Coupling Reactions

Coupling reactions to make new C–C bonds have always been a fascinating area of research in the field of organic synthesis. Indium or its salts have now emerged as valuable tools to fulfill these requirements. Indium and its compounds have thus functioned both as reagents and as catalysts in some carbon–carbon bond-forming reactions, such as allylation of carbonyl compounds,[41] Reformatsky reactions,[42] Aldol reactions,[43] Diels–Alder reactions,[44] Michael reactions,[45] Friedel–Crafts reactions,[46] and reductive coupling reactions.[47] More developments in such coupling reactions have taken place recently, with indium salts having provided very reliable and practically useful alternatives to already available methods.

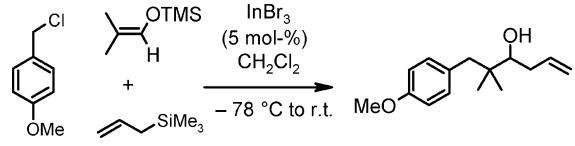
3.1. Reactions of Alkyl Halides

Coupling reactions between alkyl chlorides and silyl enolates of various aldehydes to give α-alkylated carbonyl compounds are some of the interesting examples that have been reported in the recent past[48] (Scheme 9).



Scheme 9. $InBr_3$-catalyzed couplings of alkyl halides with silyl enolates.

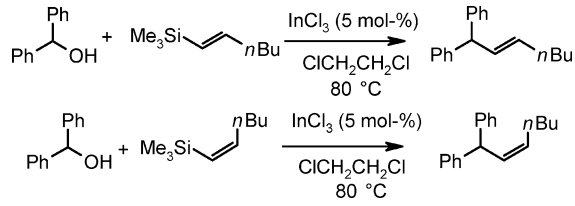
This method has the distinction of providing a good variety of substrates, and has attracted much interest in relation to the available methods catalyzed by zinc halides,[49] because these alkyl halides are much more weakly activated. Additionally, not much work has done with aldehyde-derived enolates because of their lesser nucleophilicity.[50] Another advantage of this method is that whereas most of the other previously reported methods use a halogenated solvent, it can give satisfactory yields in hexane as solvent, which is interesting as far as green chemistry is concerned. These indium halides can also catalyze three-component reactions of aldehyde enolates, alkyl chlorides, and allyl- or alkynylsilanes to afford homoallyl alcohols (Scheme 10).



Scheme 10. $InBr_3$-catalyzed three-component reactions of aldehyde enolates, alkyl chlorides, and allylsilanes.

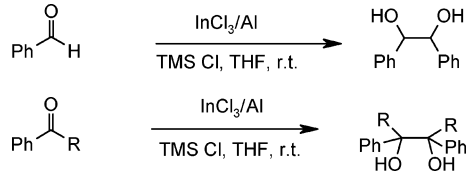
3.2. Reactions of Alcohols

Indium(III) halides have also been reported to catalyze direct coupling reactions of alcohols (alkyl, benzylic or allylic) with alkenylsilanes (Scheme 11).[51] These reactions are important because of the fact that they successfully overcome the poor leaving ability of the hydroxy group. This report represented the first direct coupling of alcohols other than allylic alcohols with metallic nucleophiles, previous reports having been limited only to allylic alcohols.[52] Here, *cis*-alkenylsilanes give *cis* products and *trans*-alkenylsilanes give *trans* products.



Scheme 11. $InCl_3$-catalyzed coupling of alcohols with alkenylsilanes.

These indium(III) halides can also catalyze homocoupling reactions of various aromatic aldehydes, ketones, and imines[53] (Scheme 12).

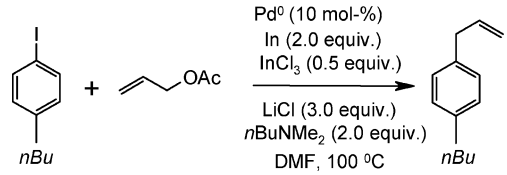


Scheme 12. $InCl_3$-catalyzed homocoupling of aldehydes and ketones.

3.3 Cross-Coupling Reactions of Aryl Halides

3.3.1. Allyl Cross-Coupling Reactions with Aryl Halides or Triflates

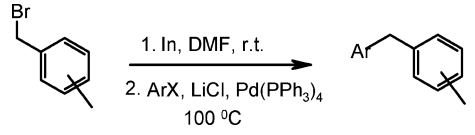
Organoindium reagents have recently been successfully employed in Pd-catalyzed allyl cross-coupling reactions of aryl halides or triflates.[54] Many similar metal-catalyzed reactions have been reported with organoindium reagents,[55] because of their reactivity and selectivity, ease of preparation and handling, operational simplicity, and low toxicity. The use of allylindium reagents provides a useful alternative to the frequently used allylstannane reagents.[56] Because the preparation of these is limited only to allyl halides, allylindium reagents provide a practically useful alternative because they can be prepared from more readily accessible starting materials such as acetates. By this protocol, both intermolecular and intramolecular cross-coupling reactions have been achieved. An intermolecular cross-coupling reaction is shown in Scheme 13.



Scheme 13. Pd^0-catalyzed cross-coupling.

3.3.2. Cross-Coupling Reactions of Benzylindium Reagents and Aryl Iodides

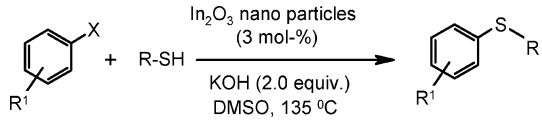
Palladium-catalyzed cross-coupling reactions between benzylindium reagents and aryl iodides have also been reported recently[57] (Scheme 14). Here, benzylindium, generated in situ, is coupled with aryl iodides. This method provides a simpler method for the synthesis of diarylmethanes.



Scheme 14. Palladium-catalyzed cross-coupling with indium reagents.

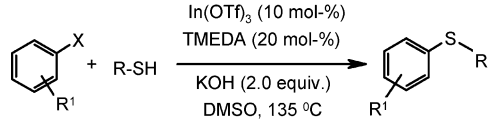
3. 3. c. Cross-Coupling Reactions of Aryl Halides and Thiols

Nano-In_2O_3 has recently been reported to be an efficient catalyst for cross-coupling of aryl halides and thiols[58] (Scheme 15). Aliphatic and aromatic thiols reacts smoothly under these reaction conditions.



Scheme 15. Nano-In_2O_3-catalyzed cross-coupling of thiols and aryl halides.

Indium-triflate-catalyzed cross-coupling of aryl halides and thiols has also been reported recently[59] (Scheme 16). Here TMEDA was used as an additive.



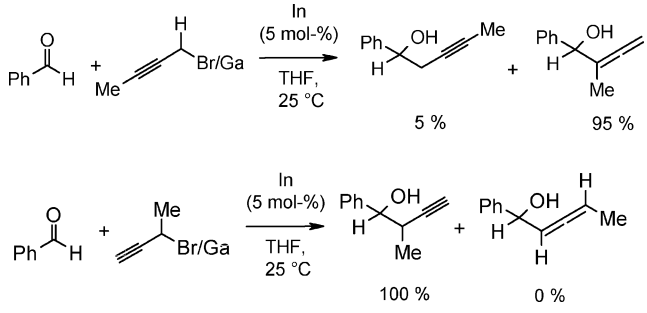
Scheme 16. $In(OTf)_3$-catalyzed cross-coupling of thiols and aryl halides.

4. Addition and Condensation Reactions

4.1. Addition of Carbonyl Compounds

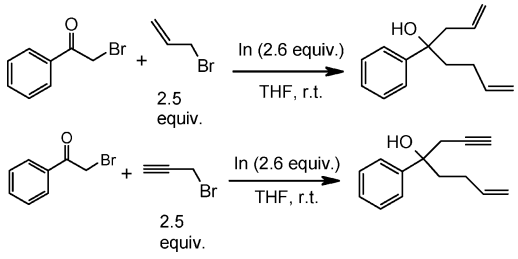
Regioselective additions of propargylgallium reagents to carbonyl compounds are a relatively unexplored area in relation to the use of propargylindium.[60] These reactions, which result in the formation of homopropargyl alcohols, has their own importance in the field of organic synthesis.[61] Although many methods have already been developed,[62] selective nucleophilic allenylations or propargylations of carbonyl compounds are still very desirable reactions to achieve. Recently, selective preparations either of homoallenyl alcohols or of homopropargyl alcohols through cat-In/InX_3-mediated (X = F or Br) reactions between 3-bromo-1-(trialkylsilyl)prop-1-ynes and various aldehydes have been reported.[63] This selectivity can also be achieved with propargylgallium in the presence of indium metal.[64] Depending on the substitution on the propargylgallium, selectivity between homopropargyl alcohols and homoallenyl alcohols can be achieved. A substituent at the γ-carbon atom of the propargylgallium reagent favors the formation of a homoallenyl alcohol, except in the case of a γ-trimethylsilyl substituent. Formation of homopropargylic alcohols is favored when a substituent is present at the α-carbon atom of the propargylgallium (Scheme 17).

This method tolerates aromatic or aliphatic carbonyl compounds and the order of their reactivity is found to be in the order: aromatic aldehyde > aliphatic ketone > aro-



Scheme 17. Additions of organoindium species, generated in situ, to aldehydes.

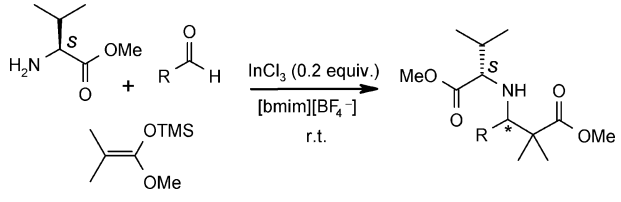
matic ketone. *vic*-Dipropargylated or *vic*-diallylated compounds have recently been prepared from phenacyl bromide through the use of propargylindium or allylindium reagents[65] (Scheme 18).



Scheme 18. Indium-mediated diallylations.

4.2. Mannich-Type Condensations of Aldimines

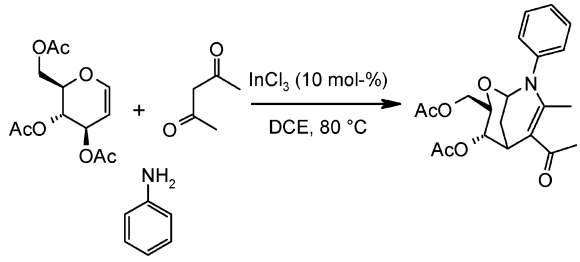
Indium(III) chloride has been reported to be an efficient catalyst for Mannich-type condensations of aldimines with silylenol ethers or silylketene acetals. With $InCl_3$, Mannich-type reactions in pure water, to afford various β-amino ketones, have been reported for the first time.[66] A symmetric version of the reaction with aromatic aldimines has also been reported.[67] L-Valine methyl ester has been used as a chiral auxiliary with enolate equivalents such as silylenol ethers or silylketene acetals. Rather than using a chiral catalyst, this method uses the chiral amine to generate a chiral imine, thereby producing a diastereomeric pair of products (Scheme 19).



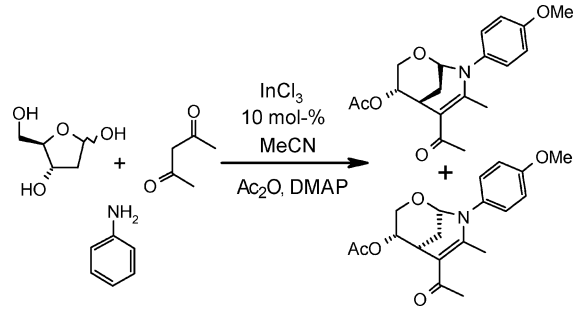
Scheme 19. $InCl_3$-catalyzed Mannich-type reactions for the synthesis of β-amino esters.

4.3. Condensation Reactions of Sugars

The ready availability of a wide range of carbohydrates in nature and their multi-chiral architectures, coupled with their well-defined stereochemistry, make them attractive starting materials in organic synthesis.[68] In particular, glycals (1,5-anhydrohex-1-enitols)[69] and 2-deoxy-D-ribose[70] are valuable synthetic intermediates for various organic transformations. $InCl_3$ has proven to be an effective catalyst for three-component coupling of glycals, 1,3-dicarbonyl compounds, and arylamines (Scheme 20).[71] The β-enaminoketones or β-enaminoesters, generated in situ from the 1,3-dicarbonyl compounds and arylamines, reacted with a variety of glycals to give oxa-azabicyclononene scaffolds. 2-Deoxyribose also underwent the same reaction under similar conditions[72] (Scheme 21).



Scheme 20. Three-component $InCl_3$-based coupling of glucal, a 1,3-diketone, and aniline.



Scheme 21. Three-component $InCl_3$-based coupling of a deoxysugar, a 1,3-diketone, and aniline.

5. Annulation Reactions

Annulation is an important reaction in organic chemistry. There are several examples of reported annulation reactions, including Robinson annulation,[73] Hauser annulation,[74] and Wichterle reaction.[75]

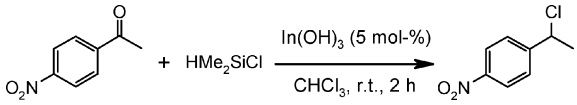
Heteroaryl annulated carbazoles are always an attractive target in synthetic chemistry in view of their biological and pharmaceutical applications. Indolo[2,3-*a*]carbazoles attract much attention because carbazole alkaloids such as tjipanazoles and staurosorine contain this system in their core structures. Many methodologies for the synthesis of indolo[2,3-*a*]carbazoles have been reported.[76] One of the major methods involves annulation of various 2-arylindoles with propargyl ethers in the presence of $In(ONf)_3$. Other indium-based Lewis acids such as $In(OTf)_3$ add $InCl_3$ also promote this reaction.[77]

$In(ONf)_3$-catalyzed annulations of 2-(2-heteroaryl)indoles with propargyl ethers are shown in Table 5.

Halogen compounds have widespread applications in the field of organic chemistry and organometallic reagents. Grignard reactions, Wittig reagents, Reformatsky reactions, and Suzuki coupling demonstrate the continuous applications of organohalogens. There are several available methods for the synthesis of organohalogens with the aid of PCl_3, $SOCl_2$, Vilsmeier–Haack reagent, Viehe salt,[78] etc. Indium(III)-catalyzed halogenation has been reported recently.

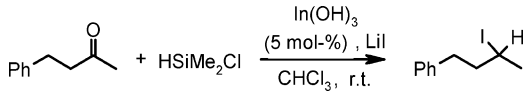
6.1. Halogenation of Carbonyl Compounds

There are different methods available for the synthesis of organohalogen compounds, but deoxygenative halogenation of carbonyl compounds remains a field still to be developed. Only a few methodologies for the syntheses of alkyl halides from aldehydes and ketones are available, but these too involve multistep reactions with reduction of carbonyl and then halogenation.[79] Direct conversion of carbonyl compounds into alkyl halides through the use of indium as catalyst and chlorodimethylsilane has been reported recently[80] (Scheme 22).



Scheme 22. $In(OH)_3$-catalyzed halogenation of ketones.

The peculiarity of the method is that the hydrogen and the chlorine atoms originate from the same reagent – dimethylchlorosilane. An attractive feature is its selectivity: the reaction functions exclusively for ketones and aldehydes and tolerates functional groups such as carboxyl, cyano, ester, etc. in the presence of the carbonyl compounds. Deoxygenative iodination has also been carried out successfully (Scheme 23).

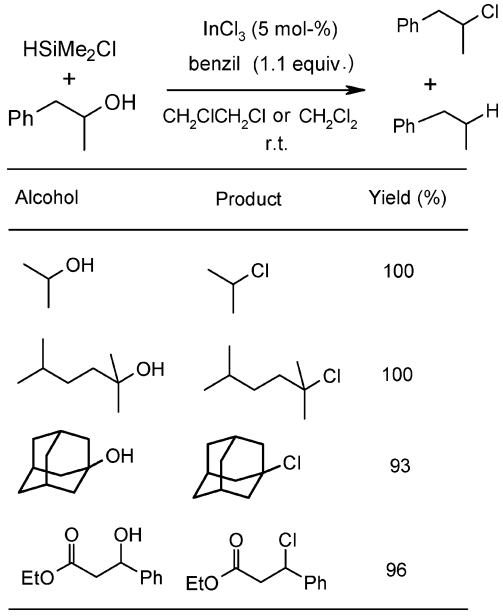


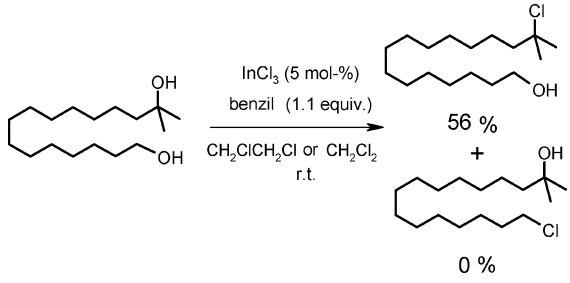
Scheme 23. $In(OH)_3$-catalyzed iodination of ketones.

6.2. Chlorination of Alcohols

Chlorination of alcohols is facilitated by Lewis acid catalysts such as $Sc(OTf)_3$ and $AlCl_3$,[81] but the recently reported $InCl_3$-catalyzed chlorination provides a much simpler method.[82] The versatility of the method is shown in Table 6. Most of the reported routes describe the synthesis of alkyl halides from primary hydroxy groups, but the major advantage of this methodology is that if the substrate contains both primary and tertiary hydroxy groups, it undergoes reaction to provide tertiary alkyl halides exclusively (Scheme 24).

Table 6. $InCl_3$-catalyzed chlorination of various alcohols.





Scheme 24. Selective halogenation of a tertiary alcohol.

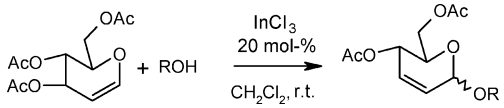
7. Synthesis of Glycosides

Glycosides have wide application in the fields of biologically active natural products and organic synthesis. Most of the reported methodologies for the synthesis of glycosides are based on acid-catalyzed Ferrier rearrangement of tri-*O*-acetylglucal.[83] Other than this, Lewis-acid-catalyzed syntheses of glycosides have been attracting more interest in recent years.[84] All of the reported Lewis-acid-catalyzed methods had disadvantages such as lack of selectivity, no reusability of the catalyst, etc. Methodologies involving indium(III) halide catalysis offer a good alternative and assure high diastereoselectivity.

7.1. Diasterioselective Synthesis of 2, 3-Unsaturated Glycopyranosides

Syntheses of alkyl and aryl 2,3-unsaturated glycopyranosides through Ferrier rearrangements of alcohols and phenols with tri-*O*-acetyl-D-glucal in the presence of $InCl_3$ as a catalyst have been reported[85] (Scheme 25). The attractive

aspect of these reactions is the selectivity achieved; reported anomeric excesses were highly in favor of the α-isomers (α/β = 9:1).

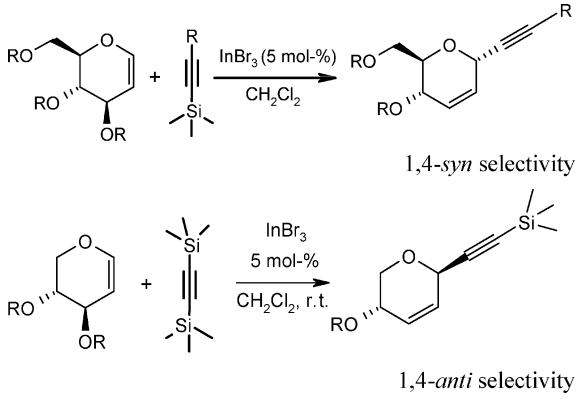


Scheme 25. $InCl_3$-catalyzed synthesis of 2,3-unsaturated glycopyranosides.

The low yields of 2,3-unsaturated aryl glucopyranosides obtained in the case of phenols are due to further $InCl_3$-catalyzed "O" to "C" rearrangements. With longer reaction times, *O*-arylglycosides are consumed with simultaneous formation of 2,3-unsaturated *C*-arylglycosides. $InCl_3$ is very selective in this rearrangement, which makes it possible to achieve both 2,3-unsaturated *C*-aryl and *O*-aryl glycosides. The synthesis of thioglycosides with $InCl_3$ has also been reported.[86]

7.2. Stereoselective Synthesis of Alkynylsugars

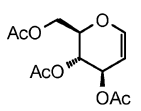
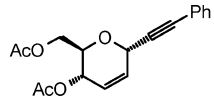
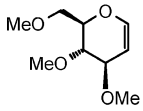
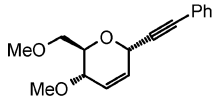
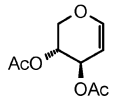
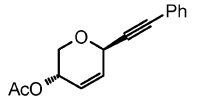
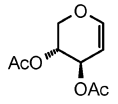
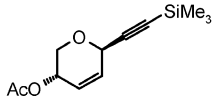
C-Glycosidation is of great application in the synthesis of many biologically active natural products such as palytoxin, spongistatin, halichondrin,[87] etc. $InBr_3$ has been reported to be one of the best catalysts for synthesis of alkynyl sugars, with fair selectivity.[88] Alkynylation of glycals with alkynylsilane in the presence of $InBr_3$ affords products with high α selectivity (Scheme 26). Synthesis of *C*-(alkynyl)-pseudo glycals from δ-hydroxy-α,β-unsaturated aldehydes has also been reported. [89]



Scheme 26. $InBr_3$-catalyzed synthesis of alkynylsugars.

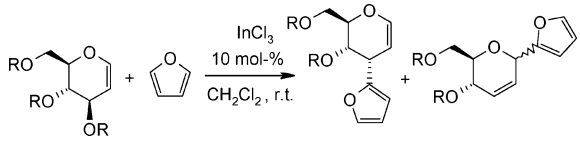
The reactivities of different alkynylsilanes towards different glycals are shown in Table 7. It has been found that all hexose sugars give 1,4-*syn* selectivity and that all pentose sugars give 1,4-*anti* selectivity (Scheme 25). The scope and applicability of this methodology to different glycals and pentose sugars is shown in Table 7.

Table 7. Reactivities of different glycals and pentose sugars.

Substrate	Product	Yield (%)
		93
		80
		85
		75

7.3. Synthesis of *C*-Glycosyl Heteroaromatics

C-Glycosidation is an important method for the introduction of carbon chains into sugars.[90] Glycosides bearing cross-linked heterocycles are of high value due to their antiviral and antitumor activities.[91] Glycosylfurans are precursors for the synthesis of many *C*-glycosyl antibiotics.[92] There are several reported methods for the synthesis of *C*-glycosyl heteroaromatics, but methods for the synthesis of furan and pyrrole derivatives are limited due to polymerization under acidic conditions. *C*-Glycosidation of glycals with furan, pyrrole, indole, and thiophene in the presence of $InCl_3$ has recently been reported.[93] Treatment of 3,4,6-tri-*O*-acetyl- or benzoyl-D-glucal with furan resulted in the formation of the C-glycosylfurans (Scheme 27). Of the two product types formed – *C*-1 glycosyl and *C*-3 glycosyl – the latter is the major.



Scheme 27. $InCl_3$-catalyzed synthesis of *C*-glycosyl heteroaromatics.

In all cases, the *C*-3-substituted glycals were obtained with inversion of configuration at the *C*-3-position in the glucal. Thiophene and pyrrole also reacted well to form the corresponding glycosides.

8. Synthesis of Heterocycles

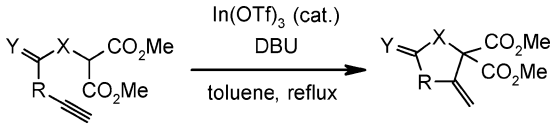
The synthesis of heterocyclic compounds has always been a fascinating field of research because these systems form the core structures of most of the available natural products of biological importance. Even DNA also con-

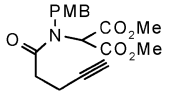
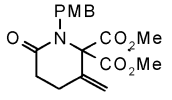
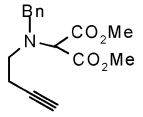
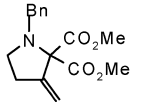
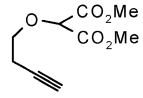
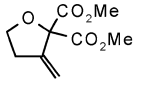
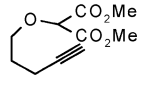
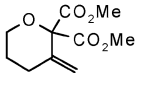
tains heterocycles in its core structure. Among heterocyclic compounds, nitrogen heterocycles are of very great importance with respect to the synthesis of drug molecules.

8.1. Synthesis of Pyrrolidinones through Indium-Catalyzed Conica-Ene Reactions

There are several natural products that contain differently functionalized pyrroldinone cores, including salinoporamide A, lactacytin,[94] and oxazolomycin.[95] The Conica-ene reaction is one well-established method for the synthesis of pyrrolidinones from amidomalonates. Different methods for the synthesis of pyrrolidinones with different metal-based catalysts have been reported, but these methods suffer from many drawbacks such as low yields and are limited only to 3-methylpyrrolidinones. An efficient and versatile indium-catalyzed methodology for the synthesis of pyrrolidinones and its application to the synthesis of salinoporamide A has recently been reported.[96] The cyclization proceeded with *E* selectivity, without any racemization at high temperature and also with high atom efficiency. The reactivities of different substrates in indium catalyzed Conica-ene reactions are shown in Table 8.

Table 8. $In(OTf)_3$-catalyzed Conica-ene reactions.[a]



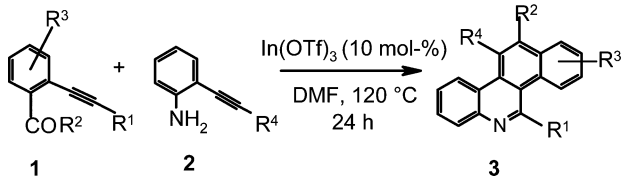
Substrate	Product	Yield %
		84
		93
		74
		75

[a] *Note:* here the $In(OTf)_3$/DBU ratio is 1:1.

8.2. Synthesis of Phenanthridines

Because of their importance in pharmaceutical applications, the synthesis of phenanthridines is always of interest, but still only a small number of methodologies for their synthesis has been reported.[97] Electrophilic cyclization of phenylacetylenes with aldehyde or imino groups at their *ortho* positions is very familiar method for the synthesis of different phenanthridines. It has been reported recently that $In(OTf)_3$ can act as a efficient catalyst for the synthesis of phenanthridines through cyclizations of phenylacetylene-carbaldehydes with *ortho* alkynylanilines.[98] Phenylacetylene-carbaldehydes bearing electron-withdrawing groups on their aromatic rings are better substrates than those with electron-donating groups. The application of this methodology to various substrates is shown in Table 9.

Table 9. Reactions between phenylacetylene-carbaldehydes and *ortho*-alkynylanilines.



1 **2** **3**

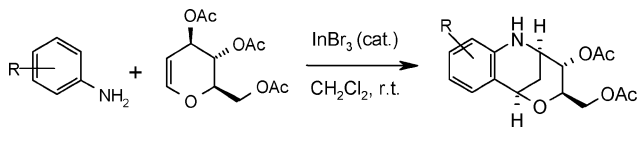
1a R^1 = Ph, R^2 = H, R^3 = H
1b R^1 = Bu, R^2 = H, R^3 = H
1c R^1 = Ph, R^2 = H, R^3 = 4-Me
1d R^1 = Ph, R^2 = H, R^3 = 5-F
1e R^1 = Ph, R^2 = H, R^3 = 6-F

2a R^4 = H
2b R^4 = Bu

1	2	Product	Yield (%)
1a	2a	3aa	71
1b	2a	3ba	51
1c	2a	3ca	73
1d	2a	3da	62
1e	2a	3ea	75

8.3. Synthesis of Benzo-Fused Heterobicycles from D-Glucal

Many methods for the synthesis of different glycosides through Ferrier rearrangements of glucal with different nucleophiles have been reported. Different indium-catalyzed methods for glycosidation with different nucleophiles such as alcohols, phenols, thiols, etc. have also been reported. Extension of the same procedure to anilines as nucleophiles gave benzobicyclo compounds with high stereoselectivity[99] (Scheme 28). It has been found that the 2,6-disubstituted anilines do not give the result. One of the important aspects of this method is that the reaction is also performable in water.

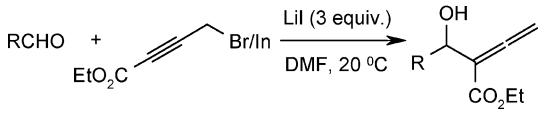


Scheme 28. $InBr_3$-catalyzed reaction of anilines with glucal.

9. Miscellaneous Reactions

9.1. Synthesis of (α-Hydroxyalkyl)allenic Esters

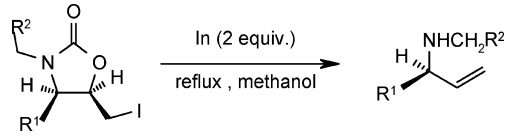
Functionalized (α-hydroxyalkyl)allenic esters are useful structural intermediates for many important natural products and pharmaceuticals.[100] There are several reported methodologies with Lewis acids but all are unsatisfactory, due either to toxic reagents or to poor yields. Very recently, one indium-mediated methodology for the synthesis of such compounds from aldehydes and ethyl 4-bromobutynoate has been reported[101] (Scheme 29).



Scheme 29. Synthesis of (α-hydroxyalkyl)allenic esters.

9.2. Synthesis of Chiral Allylic Amines

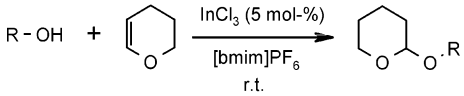
Chiral allylic amines are reliable as peptide mimetics, β-turn promoters,[102] and intermediates for aza-Claisen rearrangements.[103] There are several reported methods for their synthesis, such as asymmetric allylic amination,[104] asymmetric addition to alkynes,[105] etc. Indium-mediated conversion of 5-iodomethyl-2-oxazolidones into chiral allenic amines has also been reported[106] (Scheme 30). The advantage over the other existing methods is that under these reaction conditions there is no decomposition or racemization of the product.



Scheme 30. Indium-mediated synthesis of chiral allylic amines.

9.3. Tertrahydropyranation and Furanation of Alcohols

Protection of alcohols is an essential matter because hydroxy compounds are very important throughout synthetic chemistry. Tetrahydropyranyl ethers are protecting groups[107] stable towards basic reagents, oxidation reagents, reduction with metal hydrides, Grignard reagents, alkylating agents, etc. As far as environmentally favorable methodologies are concerned, ionic liquids are good choices as reaction media. Tetrahydropyranylation and furanation of alcohols catalyzed by indium chloride immobilized on ionic liquid has been reported recently[108] (Scheme 31).

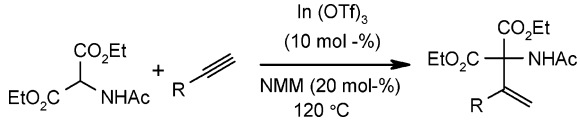


Scheme 31. Tetrahydropyranation of alcohols.

Treatment of alcohols with 3,4-dihydro-2*H*-pyran in the presence of $InCl_3$ in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) gives tetrahydropyranyl derivatives. Furanation with 2,3-dihydrofuran in place of 3,4-dihydro-2*H*-pyran has also been achieved under the same conditions.

9.4. Synthesis of β-Branched α-Amino Acids

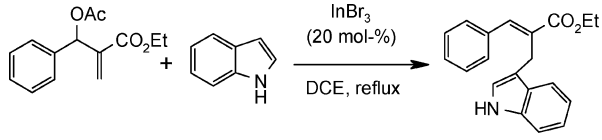
Even though a lot of methods for the synthesis of optically pure α-amino acids are available,[109] enantioselective synthesis of β-branched α-amino acids still remains a challenge.[110] It has been reported recently that In(OTf)$_3$-catalyzed additions of diethylacetamido malonates to terminal alkynes in the presence of *N*-methylmorpholine give an addition product which can easily be converted into β-branched α-amino acids in two steps with high enantiomeric purity[111] (Scheme 32).



Scheme 32. Synthesis of β-branched α-amino acids.

9.5. *C*-Alkylation of Indoles

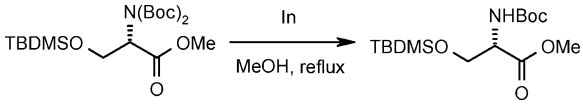
Functionalized indoles are very important synthetic intermediates. *C*-Alkylation of indoles with Baylis–Hilman acetates[112] is one method for introducing different functionalities and can be catalyzed by $InBr_3$[113] (Scheme 33). Various substituted indoles also reacted smoothly to form the corresponding 3-substituted indoles.



Scheme 33. $InCl_3$-catalyzed *C*-alkylation of indoles.

9.6. Cleavage of *tert*-Butoxycarbonyl Groups

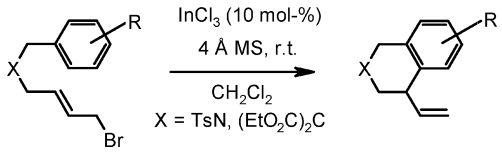
Protection and deprotection of amino groups is important in multistep synthesis, but selective removal of only one Boc group from a di-Boc-protected amine is very rare. Indium-mediated selective removal of only one Boc group from such a system has been reported[114] (Scheme 34). One advantage of this method is that *N*-Boc-protected amines remain unaffected and it works only with *N*-(Boc)$_2$-protected amines to give mono-Boc-protected amines with complete retention of configuration.



Scheme 34. Indium-mediated cleavage of *tert*-butoxycarbonyl groups.

9.7. Intramolecular Friedel–Crafts Cyclization

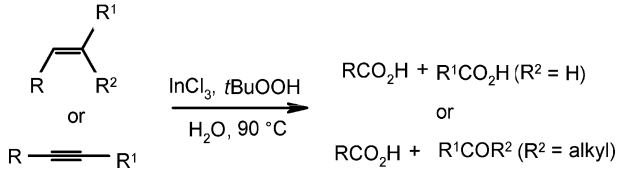
The Friedel–Crafts reaction is a very popular method for electrophilic aromatic substitution. Conventional Friedel–Crafts reactions have the disadvantage of requiring stoichiometric equivalents of Lewis acids such as $AlCl_3$, $FeCl_3$, etc. and also need strictly anhydrous reaction conditions. Alternatively, indium chloride, a Lewis acid relatively stable towards air and moisture, has been reported to be an efficient catalyst for intermolecular Friedel–Crafts reactions[115] (Scheme 35). Electron-rich arenes react well in this protocol in the presence of only 10 mol-% of $InCl_3$.



Scheme 35. $InCl_3$-catalyzed Friedel–Crafts cyclization.

9.8. Oxidative Cleavage of C–C Multiple Bonds by *tert*-Butyl Hydroperoxide

Oxidative cleavage of alkenes or alkynes to afford acids, aldehydes, and ketones is a very important reaction in organic chemistry. Even though several methods such as ozonolysis, treatment with OsO_4, etc. are available, these suffer from the toxicities of the reagents. A relatively inexpensive and safe method for the oxidative cleavage of C–C multiple bonds is very much in demand in organic synthesis. Oxidative cleavage of C–C multiple bonds in alkynes and alkenes with hydroperoxide to afford the corresponding acids or ketones has been achieved in the presence of catalytic amounts of $InCl_3$[116] (Scheme 36).



Scheme 36. $InCl_3$-catalyzed oxidative cleavage of C–C multiple bonds.

Conclusions

This review covers more recent developments relating to indium chemistry and its application in organic synthesis. Even though a lot of progress has reported in the last decade, the scope of indium chemistry still remains a field deserving further exploration. From this review it is clear that indium provides useful alternatives to existing methodologies for functional group transformations through its high reactivity and the unique selectivity that it has shown in its reactions. We hope more astonishing applications of this metal will be revealed in the near future, and that this review may light a candle for the same.

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Received: August 6, 2009
Published Online: November 6, 2009

