InCl\textsubscript{3} in organic syntheses

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A review on the use of InCl\textsubscript{3} in organic syntheses is described.

Introduction

Lewis acid catalysed carbon-carbon bond forming reactions have found widespread applications in organic synthesis\textsuperscript{1,2}. The attractive features of these reactions are their mild reaction conditions, improved stereo- and chemo-selectivities and the prospect of catalytic asymmetric induction via use of chirally modified Lewis acid catalysts. Although several Lewis acids, based on main group and transition metal salts, have already been used for these purposes, newer Lewis acids are being regularly scanned in search of improved efficiencies. In recent years, InCl\textsubscript{3} has evolved as a versatile Lewis acid catalyst for a variety of organic transformations, e.g., aldol condensations, Diels-Alder reactions, Michael additions, glycosylation reactions, etc. Compared to the conventional Lewis acids, a number of advantages have already been noted for InCl\textsubscript{3} viz., low catalyst loading, moisture compatibility and catalyst recycling, which promises broader ramifications in years to come. The purpose of this review is to highlight these and other interesting features of InCl\textsubscript{3} as applied to organic synthesis\textsuperscript{2}.

Nucleophilic addition to carbonyl compounds

(i) Mukaiyama-aldol reactions: Since the discovery of Mukaiyama-aldol reaction\textsuperscript{3a,b} a wide variety of Lewis acids have been explored\textsuperscript{3b-g} for this reaction. In fact, Mukaiyama and coworkers\textsuperscript{4} were the first to successfully utilise InCl\textsubscript{3} as a catalyst for aldol reactions in organic solvents (Scheme I). They showed that while aldehydes and acetals reacted with trimethyl or triethylsilyl enol ethers, only the former underwent reaction with the sterically more hindered silyl enol ethers.

Subsequently, Loh and coworkers\textsuperscript{5} described a highly improved InCl\textsubscript{3}-catalysed Mukaiyama-aldol reaction in aqueous solutions. The procedure which owes its success to the unique hydrolytic stability of InCl\textsubscript{3}, however, is highly dependent on the order of addition of the reagents. Best results were obtained when the silyl enol ether was added to a mixture of the aldehyde and InCl\textsubscript{3} followed by water\textsuperscript{6} (Scheme II). High yields in InCl\textsubscript{3} catalysed aldol reactions have also been reported in solvent free conditions or under micellar systems\textsuperscript{7}. The catalytic ability of the reagent was compared\textsuperscript{8} with that of other metal salts in aqueous medium using the model Mukaiyama-aldol reaction of benzaldehyde with (Z)-1-phenyl-1-(trimethylsiloxy) propane. An InCl\textsubscript{3} induced highly stereoselective Mukaiyama-aldol reaction has been applied for chain elongation of a glucose derived silyl enol ether\textsuperscript{9}.

(ii) Prins type reactions: Lewis acid catalysed Prins reactions\textsuperscript{10a-c} between aliphatic aldehydes and alkoxyallylsilanes usually produce the respective tetrahydropyran derivatives in good yields; aromatic aldehydes are usually unreactive\textsuperscript{10a-c}. In contrast, Li et al.\textsuperscript{11a-c} have shown that InCl\textsubscript{3} mediated Prins reaction of both aliphatic and aromatic aldehydes with
homoallylalcohols led to the corresponding tetrahydrofuran derivatives in excellent yields with high diastereoselectivity.

Recently, we have successfully carried out the Prins reactions of benzaldehydes, m-chloro- and m-bromo benzaldehyde with allyltrichlorosilane leading to the respective pyran derivatives in moderate to good yields.

(iii) Carbon-carbon bond formation via transmetallation of organometallic compounds with InCl₃: In situ generation of organoindium reagents via transmetallation between conventional organometallics and InCl₃ has found considerable use in organic synthesis. An allylindium species generated via transmetallation of allylmagnesium bromide with InCl₃ was used by Whitesides et al., for diastereoselective addition to free aldehydes leading to higher sugars. Similar in situ generated γ-alkoxyallylindium reagents and their addition reactions to aldehydes has also been reported by Hirasita et al. Triorganoindium reagents derived from organolithium compounds and InCl₃ have been used for 1,4-addition reactions to enones in the presence of nickel catalysts (Scheme III).

InCl₃ mediated transmetallation of α-alkoxyallyl stannanes for carbon-carbon bond formation in reaction with different aldehydes including sugar based aldehydes, leading to the corresponding coupling products in high yields and anti selectivity, was first demonstrated by Marshall et al. (Scheme IV). The observed stereospecific and diastereoselective $S_{E2}$ addition to aldehydes generating the major anti adducts, have been rationalised by involving a transient organoindium intermediate ($A/A'$). Ethyl acetate has been found to be the solvent of choice for this exchange and coupling reaction leading to higher yield and diastereoselectivity of the products with the exclusion of the γ-adduct.

A number of InCl₃ catalysed addition reactions of allyltin compounds to aldehydes, trifluoroacetaldehyde hydrate and hemiacetal, and ketones have been reported. Nishigaichi and coworkers studied the reactions of α-oxygenated aldehydes (1a-c) and tributylpentadienyltin 2 in the presence of various Lewis acids (Scheme V) and found that InCl₃ catalysed reactions with benzyl protected aldehydes produced practically one isomer- the syn γ-adduct 4. Among the solvents examined, acetonitrile was found to give the best result with respect to yield, regio- and stereoselectivity and the rate of the reaction. The reacting species was supposed to be an in situ generated dichloropentadienylindium 2a which reacted via chelation controlled six membered transition state (B) (Scheme VI).

Yasuda and coworkers have investigated the alkynylation of aldehydes with alkynylindium species generated via transmetallation from alkynyltin and InCl₃ in the presence of chlorotrimethylsilane (Scheme VII). Formation of the product C from the

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*Notes and References*

1. Our unpublished results

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*Equations and Diagrams*
addition of alkynyltributyltin A to aldehyde B in the presence of chlorotrimethylsilane has been assumed to follow a catalytic cycle as illustrated in Scheme VIII.

InCl₃ catalysed transmetallation of the organotin compound 5 followed by an intramolecular cyclisation reaction has been reported to produce the cis-cis cyclic compound (7) with high stereoselectivity. ³⁵

(iv) Miscellaneous reactions: InCl₃ catalysed addition of allyl-, aryl-, vinyl-, ethynyl- and propargyl silanes to chloral and chloroacetone and of allyltributyltin to acyl chlorides has been reported. InCl₃-AgClO₄ mixture has been shown to be an effective catalyst system for addition reactions of various silyl nucleophiles to acyl chlorides and to acrylates, crotonates, acrylonitriles etc. can be carried out in water in moderate to good yields with InCl₃ as the catalyst.³⁶

Michael reactions

Lewis acid catalysed Michael reactions are of considerable current interest in view of their non-basic and mild reaction conditions. InCl₃ catalysed Michael reaction of silyl enol ethers to α,β-unsaturated carbonyl compounds has recently been reported. (Scheme X).

Again, due to the exceptional hydrolytic stability of InCl₃, Michael addition of primary and secondary amines to acrylates, crotonates, acrylonitriles etc. can be carried out in water in moderate to good yields with InCl₃ as the catalyst.³⁷ (Scheme XI).

Diels-Alder reactions

Diels-Alder reaction is amongst the most widely used carbon-carbon bond forming methods in organic synthesis. A variety of Lewis acid catalysts, in both organic and aqueous media and under different conditions of temperature and pressure have been investigated for Diels-Alder reactions. InCl₃ catalysed aqueous Diels-Alder reaction has been shown to proceed in good to excellent yields with high endo/exo selectivity. The catalysts in these reactions could be recovered and recycled without loss in activity. (Scheme XII) Ab initio calculations have established a three-centre orbital interaction for the model Diels-Alder reaction of butadiene and acrolein catalysed by InCl₃ as well as for few other metal chlorides.
InImo Diels-Alder reactions of Schiff's bases with cyclopentadiene and cyclohept-2-ene have been carried out with 20% anhydrous InCl₃ as the catalyst to produce cyclopentaquinoline and azabicyclononane derivatives in good yields (Scheme XIII). InCl₃ catalyzed one-pot imine formation-imino Diels-Alder reaction has also been carried out with cyclopentadienes and 3,4-dihydro-2H-pyrans affording new quinoline derivatives in good yields. The method has also been used for the synthesis of pyranoquinolines, indenoquinolines and phenanthridine derivatives. A similar sequence has been reported for the Diels-Alder reaction of in situ generated heteroaromatic imines with cyclopentadiene. A stereo- and regioselective synthesis of cis-pyroloquinolines has been carried out by InCl₃ induced imino Diels-Alder reaction of aniline derived imines and cyclic enamides.

Friedel-Crafts reactions

(i) Acylation: While in Friedel-Crafts acylation reactions a stoichiometric amount of Lewis acid is generally required, in case of activated molecules the reaction may proceed with catalytic amounts of Lewis acids. InCl₃-AgClO₄ combination has been reported to be an effective mediator for Friedel-Crafts acylation of anisole in good yields. Art et al. successfully effected the acylation of 2-methoxynaphthalene with acid chlorides using catalytic amounts of various Lewis acids and have shown that 2-acyl-6-methoxynaphthalene could be produced predominantly over 1-acyl-7-methoxynaphthalene by using InCl₃ as the catalyst.

(ii) Reductive Friedel-Crafts reaction: Alkylation of aromatic systems with carbonyl compounds via Reductive Friedel-Crafts reaction, is a potentially useful synthetic methodology. GaCl₄, Sc(OTf)₃ and trifluoromethanesulfonic acid have been used as the catalysts for these reactions. Recently, Miyai and coworkers have reported the Reductive Friedel-Crafts alkylation of aromatic compounds with aldehydes and ketones in the presence of catalytic amounts of InCl₃ and chlorodimethylsilane as the hydride source (Scheme XIV). A plausible mechanism for this reaction has been proposed involving (i) hydrosilylation of the carbonyl component, (ii) generation of a carbocation by desiloxylation and (iii) alkylation of the aromatic substrate, as depicted in Scheme XV. Both hydrosilylation and alkylation steps were shown to proceed only in the presence of InCl₃.
Glycosylation reactions

Due to the manyfold biological utilities of oligosaccharides, glycoconjugates\textsuperscript{55a–e} and C-glycosyl compounds\textsuperscript{52a–d}, glycosylation reactions (O\textsuperscript{51a–e} and C\textsuperscript{53a–c}) are of much current interests.

Recently, we have used InCl\textsubscript{3} as a mediator for C-glycosylation reaction of peracetylglycals with allyltrimethylsilane\textsuperscript{54}. This C-glycosylation reaction proceeded in good yields and with high anti diastereoselectivity (1, 5-anti diastereoselectivity with peracetylated hexopyranoglycals and 1,4-anti-diastereoselectivity with peracetylpentopyranoglycals) (Scheme XVI).

The InCl\textsubscript{3}-AgClO\textsubscript{4} system has been shown to be quite useful for O-glycosylation of benzyl protected glycosyl acetates\textsuperscript{55}. Babu and Balasubramanian\textsuperscript{56} have reported an efficient synthesis of 2,3-unsaturated glycopyranosides via InCl\textsubscript{3} catalysed Ferrier reactions of tri-O-acetyl-D-glucal with a number of alcohols and phenols.

Miscellaneous reactions

In addition to the aforementioned examples, there are number of additional applications of InCl\textsubscript{3} in organic synthesis. Recently, Sengupta \textit{et al.}\textsuperscript{59} has successfully used InCl\textsubscript{3} as a catalyst for some reactions with diazacarbonyl compounds \textit{viz.}, S-H insertion reactions, nitrile cyclisations and addition reactions to aldehydes and ketones (Scheme XVII). InCl\textsubscript{3} catalysed reactions of diazoacetates with imines have also been reported by the same authors to produce \textit{cis}-aziridine carboxylates with high diastereoselectivity\textsuperscript{57}.

InCl\textsubscript{3} catalysed rearrangement of aryl substituted epoxides leads to substituted benzylic aldehydes and ketones\textsuperscript{58} (Scheme XVIII). Alkyl substituted epoxides also undergo similar rearrangement but with lower selectivity. The reaction tolerates several functionalities such as -OMe, -CO\textsubscript{2}Me, -C=C-, -C≡C- etc.

Dichloroindium hydride generated \textit{in situ} via transmetallation of tributyltinhydride with InCl\textsubscript{3} has been used for reductions of aldehydes, ketones and bromo compounds\textsuperscript{59}. With \(\alpha,\beta\)-unsaturated systems this reagent led to regioselective 1,4-reduction of the double bonds. Indium hydride generated from Bu\textsubscript{3}SnH and InCl\textsubscript{3} in the presence of added phosphines has been reported to reduce acid chlorides to the respective aldehydes\textsuperscript{60}. Hydrodechlorination of 1,1,2-trifluoroethane over Bi-Pd, supported on metal oxides in the presence of InCl\textsubscript{3}, proceeded in high yield to produce trifluoromethane\textsuperscript{61}. Reductive deoxygenation of arylketones and secondary benzylic alcohols have been reported using the InCl\textsubscript{3}–Me\textsubscript{3}SiCl combination, where functionalities as halogen, ester and ethers were tolerated during the reduction\textsuperscript{62}. InCl\textsubscript{3} has also been used in the splitting of ether by chlorotrimethylsilane and in the reaction of trialkylhydroxylsilane with ketones\textsuperscript{63}.

InCl\textsubscript{3} has been reportedly used for chlorination of chlorophenylsilane\textsuperscript{64} and pyridine\textsuperscript{65} and for bromination of quinoline\textsuperscript{66}. A bimetallic system (Al-InCl\textsubscript{3}) has been found to be effective for alkylation of imines derived from vinylmellitate\textsuperscript{67} and that of enamines\textsuperscript{58}. InCl\textsubscript{3} has been used as a versatile catalyst for

\begin{align*}
\text{Me}_2\text{SiClH} + \text{InCl}_3 & \rightarrow \text{Me}_2\text{SiCl} + \text{InCl}_2 \\
\text{R}_1\text{CHO} + \text{InCl}_3 & \rightarrow \text{R}_1\text{COCl} + \text{InCl}_2
\end{align*}
polymerisation reactions. It has also been used as an efficient mediator for various other reactions as mentioned in patent abstract.

The utility of InCl₃ in combination with other catalysts for the following reactions are also worth mentioning. InCl₃-TMSCl combination has been shown by Mukaiyama and coworkers to catalyse the reaction of O-trimethylsilylmonothioacetalcs, trimethylsilane and silylated carbon nucleophiles leading to sulphide derivatives. The authors have modified the method for one pot synthesis of sulphides in high yield from aldehydes, trimethylsilylalkyl or arylsulphide and trialkylsilane using this catalyst system. Synthesis of carboxylic ester or S-phenylethanolactones were achieved via anhydride based esterification using InCl₃-AgClO₄ catalyst system. Reports have also been made on hydrolysis of phosphate ester using InCl₃ as a cooperative catalyst with La(III).

Although it is not possible to include the references of the increasing use of other indium halides, it may be mentioned that InF₃, In₃Cl₁, In₂, In₃, as well as In(OTf)₃ etc. have also found important applications in organic synthesis.

Conclusions

InCl₃ has emerged as an excellent reagent for various organic transformations. The advantages of this catalyst are its low toxicity and hydrolytic stability. Due to the latter, many reactions with InCl₃ can be performed effectively in water under environmentally benign conditions. Moreover, InCl₃ can be recovered and recycled without appreciable loss in its reactivity. InCl₃ has thus acquired a special importance in contemporary organic synthesis and has considerable potential for further exploration particularly in developing large scale synthetic products in aqueous media.

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Addendum


References

3. Although several recent reviews have described the use of indium metal in organic synthesis, none so far have comprehensively dealt with the use of InCl₃ as a Lewis acid besides the mention of a few of its uses in aqueous medium in the recent account: Li C-J & Chan T-H. Tetrahedron, 35, 1999, 1149.