Indium Metal and Its Halides in Organic Synthesis

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This review highlights the applications of indium metal and indium(III) halides in organic synthesis with particular reference to regio-, stereo-, and chemoselectivity. Indium-mediated reactions include the regioselective allylation of alkynes, the stereoselective debromination of *vic*-aryl-substituted dibromides, the homocoupling of alkyl/aryl halides, and the reduction of α-halocarbonyl compounds. Indium trichloride has been used as a Lewis acid catalyst in epoxide rearrangements, in the synthesis of α-amino phosphonates, and in the construction of the quinoline system. Indium triiodide has proven to be a very efficient catalyst for transesterification processes.

1. Introduction

Since the successful introduction of magnesium metal in Grignard reactions for carbon−carbon bond formation, the utilization of other metals of the Periodic System for organic synthesis has received widespread interest and one of the latest additions is indium. Although indium was briefly used for synthetic purposes early in the 20th century,[1] studies of the utility of indium reagents for organic transformations have been carried out only very recently.[2] During the last decade, indium has emerged as a metal of high potential in organic synthesis because of certain unique properties that it possesses. Indium metal is unaffected by air or oxygen at ambient temperatures and can be handled safely without any apparent toxicity. Generally speaking, indium exhibits a low heterophilicity in organic reactions and thus oxygen- and nitrogen-containing functional groups are usually tolerated by organoindium reagents. Moreover, indium-assisted reactions display a low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity. However, although indium has been used extensively in carbonyl addition reactions,[3] its potential in other domains, including addition to other electron-deficient systems, has not yet been explored to any great extent.[4] Because indium closely resembles magnesium, zinc, and tin in several respects, including its first ionization potential, indium metal could also represent a suitable reagent for SET (single electron transfer) processes.

The present review deals with work carried out in this laboratory on the applications of indium in these less explored areas. The first part of this article describes the use of indium metal for the regioselective allylation of alkynes, the stereoselective debromination of *vic*-dibromides, the homocoupling of alkyl/aryl halides, and the chemoselective reduction of α-halocarbonyl compounds and benzyl halides. In the second part, the use of indium(III) chloride and iodide as Lewis acids in facilitating several important chemical transformations, such as the rearrangement of epoxides, the synthesis of α-aminophosphonates, the construction of the quinoline system, and transesterification, is demonstrated.

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Brindaban Chandra Ranu was born in 1949 in West Bengal, India. He received his early education at Calcutta University. In graduate studies, he worked with Professor Ernest Wenkert at Rice University, Houston, USA, and with Professor U. R. Ghatak at the Indian Association for the Cultivation of Science, Calcutta. He then took up a postdoctoral position at Virginia Tech, Blacksburg, USA, with Professor T. Hudlicky. After returning to India in 1985, he started independent research at the Department of Organic Chemistry, IACS, Calcutta, as a Lecturer and was promoted to Professor in 1996. He received an N. S. Narasimhan Award in Organic Chemistry in 1993 and was elected Fellow of the Indian Academy of Sciences in 1995. He was a Visiting Professor at the Universidad de Extremadura, Badajoz, Spain, during 1995−96. His research interests include the development of new reactions and novel reagents, metalloorganic chemistry, and green chemistry.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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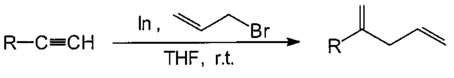
2. Indium Metal Mediated Reactions

2.1 Regioselective Allylation of Alkynes

Allylmetallation of carbon−carbon triple bonds by allylmetal compounds is useful for the synthesis of 1,4-dienes. Although the carbometallation of activated alkynes, such as alkynyl ketones, proceeds readily with various allylmetal compounds,[5] the carbometallation of unactivated alkynes is not so easy and only a few metals have been successfully employed for this purpose.[6] Recently, a procedure has been reported for the allylation of alkynols using indium powder and allylic bromides in DMF at elevated temperature, leading to allylalkenols predominantly by anti Markovnikov addition.[7] However, the presence of a hydroxy functionality adjacent to the triple bond was found to be essential for facilitating this addition and thus the allylation of non-functionalized alkynes could only be accomplished in low yields (12−28%), even at higher temperatures. Moreover, hydroxy-protected alkynes could not be allylated at all.[7] Nevertheless, the author's group has observed a very significant effect on the course of indium-mediated allylation reaction through a change of solvent and slight modification of the experimental conditions.[8] Thus, unactivated (non-functionalized and hydroxy-protected) alkynes have been found to undergo efficient allylation by Markovnikov addition simply by treating them with allyl bromide and indium metal in THF at room temperature (Scheme 1).[8]



Scheme 1. Allylation of alkynes

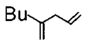
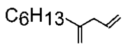
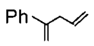
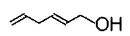
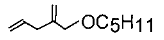
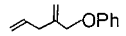
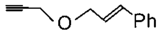
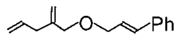
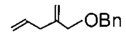
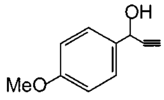
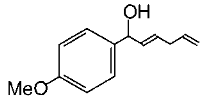
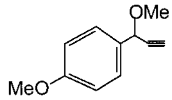
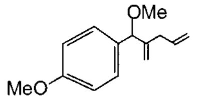
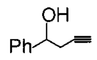
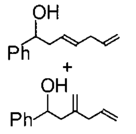
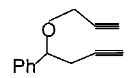
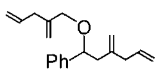
Several structurally diverse terminal alkynes have been allylated according to this procedure to furnish the corresponding 1,4-dienes. The results are summarized in Table 1. Non-functionalized alkynes such as hex-1-yne, oct-1-yne, and phenylacetylene produced Markovnikov addition products as the sole isolable compounds in high yields. Very interestingly, although the alkynols (Entries 4, 9, and 11) furnished almost exclusively or predominantly the anti Markovnikov addition products, the corresponding ethers (Entries 5−8, 10, and 12) underwent exclusive Markovnikov coupling. This reversal of regioselectivity on protection of the hydroxy group is very significant from a synthetic point of view.

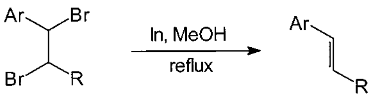
In general, the reactions are very clean, and no side-products have been isolated. However, no reaction occurred with internal alkynes. THF has proved to be the solvent of choice for these reactions; attempts to perform them in water and in aqueous THF were not successful. At lower temperatures (0−5 °C), no efficient coupling was observed.

2.2 Stereoselective Debromination of *vic*-Dibromides

The protection−deprotection of olefins through bromination−debromination is an important process in organic synthesis. Although bromination generally proceeds smoothly and stereospecifically to give high yields of dibromides, debromination at a later stage in the synthesis often proves more difficult. This is primarily because the efficiency of the process is strongly dependent on the stereoselectivity of the debromination step and on the compatibility of the reagent with the carbon−carbon double bond formed and other functionalities present in the substrates. Many reagents,[9] including metals such as Zn, Mg, and Sm, have been reported in the literature to be effective in this reaction, but most of them are associated with limitations regarding selectivity and compatibility. In this laboratory, it has been discovered[10] that aryl-substituted *vic*-dibromides undergo smooth debromination to produce the corresponding (*E*)-alkenes when treated with indium metal in MeOH (Scheme 2).

Table 1. Allylation of alkynes with allyl bromide and In metal in THF

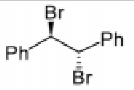
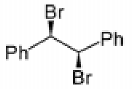
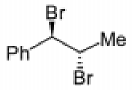
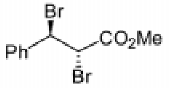
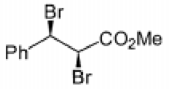
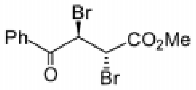
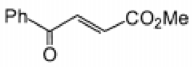
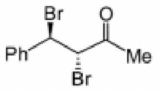
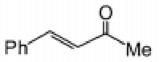
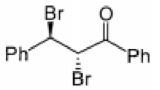
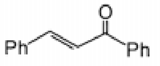
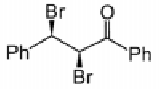
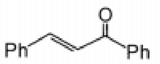
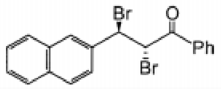
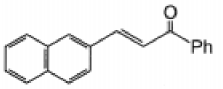
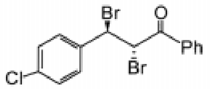
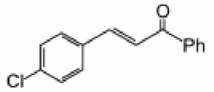
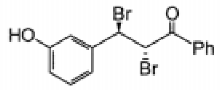
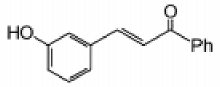
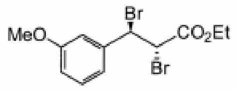
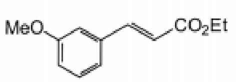
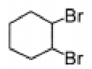
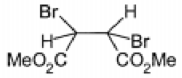
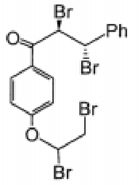
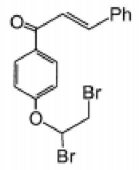
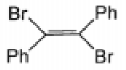
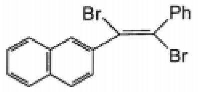
Entry	Alkyne	Product	Time / h	Yield (%)
1	Bu—≡		3	86
2	C_6H_{13}—≡		3	85
3	Ph—≡		3	90
4	≡—CH_2OH		3	80
5	≡—$CH_2OC_5H_{11}$		5	85
6	≡—CH_2OPh		6	86
7			6	85
8	≡—CH_2OBn		24	75
9			8	83
10			8	90
11			6	85 (55:45)
12			7	86



Scheme 2. Indium-mediated debromination

A wide range of aryl-substituted *vic*-dibromides have been debrominated according to this procedure to furnish the corresponding alkenes. The results are presented in Table 2. Very interestingly, only *trans*-olefins are obtained from all the substrates, irrespective of whether they are *meso*/*erythro* or *dl*/*threo*. If debrominations were to occur by the usual *trans* elimination, *meso*/*erythro*- and *dl*/*threo*-*vic*-

Table 2. Debromination of aryl-substituted *vic*-dibromides with In metal in MeOH

Entry	Substrate	Product	Time/h	Yield (%)
1			2	88
2			8	85
3			7	94
4			4	90
5			9	92
6			12	90
7			12	89
8			2	85
9			1	88
10			2	91
11			9	92
12			9	86
13			19	90
14		No reaction	12	–
15		No reaction	12	–
16			3.5	86
17		$Ph-C\equiv C-Ph$	8.5	88
18			7	82

dibromides would give *trans*- and *cis*-alkenes, respectively. It is therefore suggested that the reaction proceeds via a common, relatively stable radical intermediate, collapse of which leads directly to the (*E*)-alkene. This hypothesis is supported by the observation that *cis*-stilbene does not undergo isomerization to the *trans* isomer on refluxing with indium metal or with oxidized indium products derived from a debromination reaction in methanol, even after 8 h. No *cis*-stilbene was detected when the debromination reaction of *vic*-dibromides of stilbene was quenched at an intermediate stage.

In general, the reactions are very clean and high-yielding. Methanol has been found to be the best solvent for this reaction; in pure acetonitrile the debromination does not proceed at all. Several sensitive functional groups, such as ketone carbonyl, carboxylic ester, hydroxy, methoxy, and chloro groups on aromatic rings, remained unaffected under the present reaction conditions. No further reduction of the resulting alkene was observed with any substrate, in contrast to the reported reactions using Sm[9] and Mg.[11] As this reagent is unreactive towards alkyl-substituted dibromides (Entries 14, 15), selective debromination of aryl-substituted *vic*-dibromide moieties may be achieved in the presence of alkyl-substituted dibromide functions (Entry 16). This procedure is also effective for the debromination of *vic*-dibromoalkenes to give the corresponding alkynes (Entries 17, 18).

2.3 Homocoupling of Alkyl and Aryl Halides

The synthesis of bialkyls and biaryls is of considerable interest. The classical methods for the synthesis of bialkyls and biaryls rely on the Wurtz[12] and Ullmann[13] reactions, respectively. The Wurtz reaction for the coupling of alkyl halides mediated by sodium metal has serious limitations in the case of secondary alkyl halides. Moreover, sodium metal has its own inconveniences. On the other hand, one of the major disadvantages of the Ullmann reaction is that high temperatures are required. There are, however, several modifications of this reaction involving palladium[14] and other copper-derived compounds.[15] In this laboratory, it has been found that both alkyl and aryl iodides undergo smooth homocoupling on refluxing in DMF in the presence of indium metal to provide the corresponding dialkyls and diaryls.[16a] No coupling was observed at room temperature.[16b]

Table 3. Indium-promoted reductive homocoupling of alkyl/aryl iodide

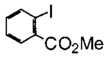
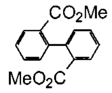
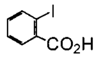
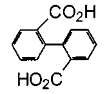
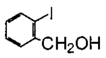
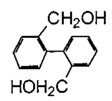
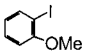
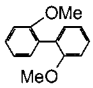
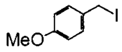
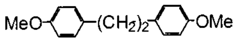
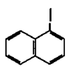
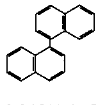
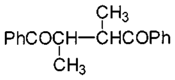
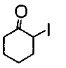
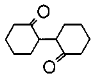
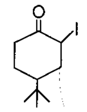
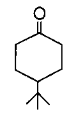
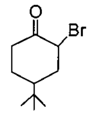
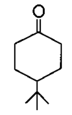
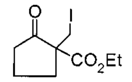
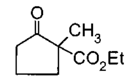
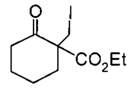
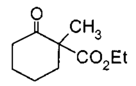
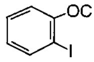
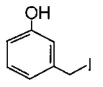
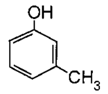
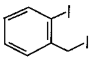
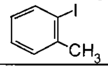
Entry	Substrate, R-I	Product , R-R	Time/h	Yield (%)
1	$PhCH_2$-I	$Ph(CH_2)_2Ph$	8	89
2	$CH_3(CH_2)_{14}CH_2$-I	$CH_3(CH_2)_{30}CH_3$	12	92
3	Ph-CH=CH-CH_2-I	PhCH=CH$(CH_2)_2$CH=CHPh	8.5	80
4	Ph-I	Ph-Ph	14	78
5			12.5	82
6			15	75
7			13	78
8			11	88
9			8	90
10			13	80
11	$PhCOCH_2$-I	$PhCO(CH_2)_2COPh$	7	60
12	$PhCOCH(CH_3)$-I	 $\mathrm{PhCO\overset{CH_3}{C}H{-}\underset{CH_3}{C}HCOPh}$	8.5	57
13			8	53

Table 4. Reduction of α-halocarbonyl compounds and benzyl halides by In/H_2O

Entry	Substrate	Product	Time/h	Yield(%)
1	$PhCOCH_2I$	$PhCOCH_3$	3	90
2	$PhCOCH_2Br$	$PhCOCH_3$	8	86
3	$PhCOCH(CH_3)I$	$PhCOCH_2CH_3$	3	87
4	$PhCOCH(C_2H_5)I$	$PhCOCH_2C_2H_5$	3.5	91
5	$PhCOCH(C_2H_5)Br$	$PhCOCH_2C_2H_5$	7.5	85
6	$BrCH_2CO_2CH_2CH_3$	$CH_3CO_2CH_2CH_3$	6.5	78
7			2.5	89
8			8	83
9			3.5	88
10			4.5	85
11	$ICH(CO_2Et)_2$	$CH_2(CO_2Et)_2$	6	75
12	$CH_3(CH_2)_{13}CH_2I$	No reaction	19	–
13		No reaction	24	–
14	$PhCH_2I$	$PhCH_3$	5	85
15			5	86
16			11	85

Several structurally diverse alkyl and aryl halides have been coupled according to this procedure to furnish the corresponding bialkyls and biaryls. The results are reported in Table 3. Different types of alkyl iodides, such as long-chain saturated, benzylic, and allylic, were coupled without any difficulty. Aryl iodides bearing both electron-withdrawing and electron-donating substituents underwent smooth coupling. This procedure has also proved to be effective for the coupling of α-iodo ketones to produce the corresponding 1,4-diketones, which are of considerable synthetic potential, although in this case the yields of the coupled products are relatively low owing to competing reduction.[16c] The reactions are, in general, reasonably fast and high-yielding. This procedure has been found to be compatible with several sensitive functionalities. Alkyl bromides also undergo coupling, but the process is rather slow.

2.4 Chemoselective Reduction of α-Halocarbonyl Compounds and Benzyl Halides

Reduction with indium metal has only been explored very recently.[17] Because the first ionization potential of indium is similar to those of sodium and zinc, indium may be envisaged as a potential reducing agent. As mentioned above, in investigations of the coupling of alkyl and aryl halides by indium in dry DMF, a competing reduction process was observed in the case of α-iodo ketones. It was subsequently discovered that the reduction of α-halocarbonyl compounds by indium metal proceeds very efficiently in water under sonication.[18]

A wide range of structurally diverse α-iodo and α-bromo ketones and esters have been reduced according to this procedure to provide the corresponding dehalogenated carbonyl compounds. The results are reported in Table 4. The reactions of the bromo compounds were found to be slow compared to those of the iodo compounds. Although alkyl- and aryl-substituted iodides are inert under these conditions, benzyl iodides are reduced. Also, the selective reduction of a side-chain-substituted iodo functionality may be achieved in the presence of iodo substituents on the aromatic ring. One very important aspect of this procedure is the use of water as a reaction medium, which has attracted considerable interest in recent times in the context of green chemistry. It may be assumed that these reductions involve a SET process, like other metal-mediated reactions in aqueous media. The reduction of α-halocarbonyl compounds and benzyl halides by indium is of great significance with regard to the potential of indium metal as a reducing agent.

3. Use of Indium(III) Halides as Lewis Acids

Along with the growth of indium metal chemistry, indium(III) halides have also emerged as useful Lewis acid catalysts for carbon−carbon bond formation.[19] The unique feature of indium(III) chloride is that it is effective in both organic solvents and aqueous media.

3.1 Rearrangement of Epoxides

One of the most frequently used atom-economical reactions of epoxides is their rearrangement to carbonyl compounds; a number of reagents, including a variety of Lewis acids,[20] have been elaborated for this purpose. In principle, two types of rearrangements are possible for substituted epoxides depending on the migration pathways following Lewis acid promoted C−O bond cleavage. Rearrangement involving hydride or alkyl/aryl migration would lead to a ketone or aldehyde, respectively. Unless there is a structural or a stereochemical bias, a mixture of products is usually obtained due to the lack of regioselectivity in the ring-opening step. Thus, an efficient method for the regioselective rearrangement of epoxides to either aldehydes or ketones would be highly desirable. The author's group has discovered that indium(III) chloride is very efficient in effecting the rearrangement of epoxides in THF solution to give the corresponding carbonyl compounds very selectively.[21]

Various epoxides have been subjected to $InCl_3$-mediated rearrangement according to this procedure to provide the corresponding carbonyl compounds in good yields, as summarized in Table 5. 1-Aryl-, 1,1-diaryl-, and 1-alkyl-1-aryl-substituted epoxides were found to undergo rearrangement exclusively through a hydride shift to give the respective aryl-substituted acetaldehydes as the only isolable compounds. The rearrangement of tri- and tetrasubstituted aryl epoxides is greatly influenced by the nature of the substituent at the carbon atom β to the aryl ring. In a competition between hydride and methyl (or substituted methyl), hydride migration occurred selectively leading to the corresponding methyl ketones. However, methyl migration is observed in substrates bearing two CH_3 groups at the β-position. In aromatic ring fused and aryl-substituted cycloalkene oxides, exclusive β-hydride migration occurs, giving the corresponding ketones. On the other hand, phenyl group migration occurs more readily than hydride migration, as observed in the isomerization of stilbene oxides to the corresponding diphenylacetaldehydes. These reactions are often problematic with other Lewis acids due to competing hydride versus phenyl migration.[22] Acetyl and benzoyl groups also migrate in preference to hydride, as seen in the reactions of 1-acetyl- and 1-benzoylstyrene oxides. However, the benzoyl epoxide (Entry 18), after initial benzoyl shift, undergoes retro aldol cleavage with loss of

Table 5. Rearrangement of epoxide with $InCl_3$ in THF

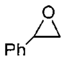
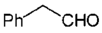
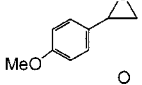
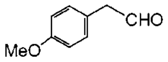
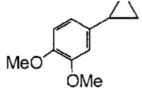
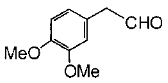
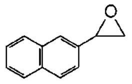
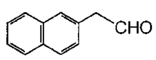
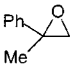
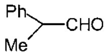
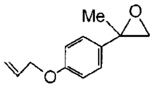
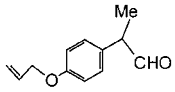
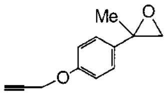
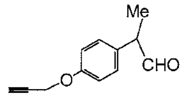
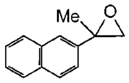
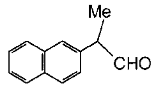
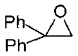
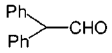
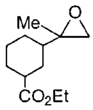
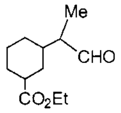
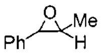
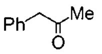
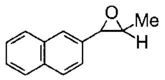
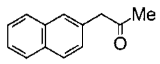
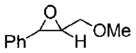
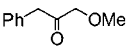
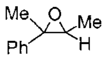
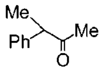
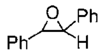
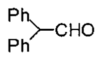
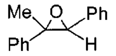
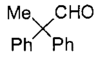
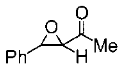
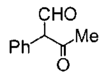
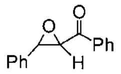
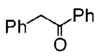
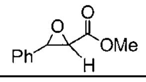
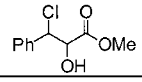
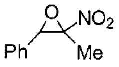
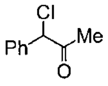
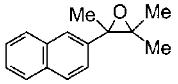
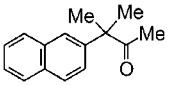
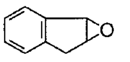
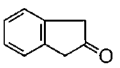
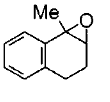
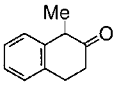
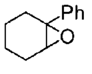
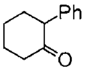
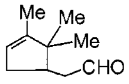
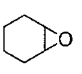
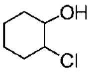
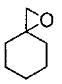
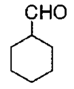
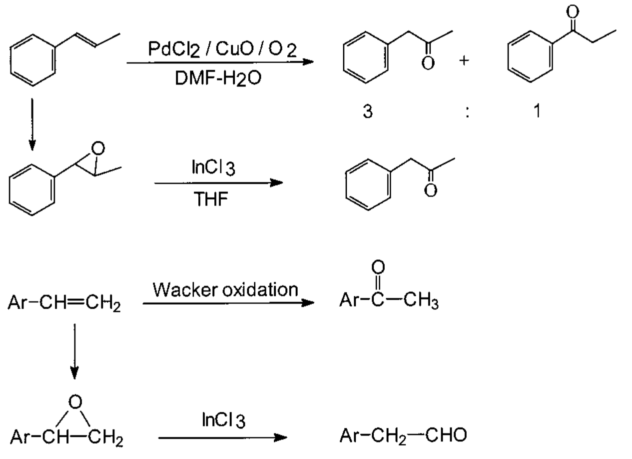
Entry	Epoxide	Product	Time(min)	Yield(%)
1			15	85
2			10	90
3			10	91
4			15	89
5			30	86
6			30	95
7			30	92
8			15	88
9			15	90
10			50	88
11			50	90
12			45	88
13			60	65
14			60	86
15			25	90
16			60	86
17			60	72
18			210	75
19			120	80

Table 5 *(Continued)*

Entry	Epoxide	Product	Time(min)	Yield(%)
20			90	70
21			360	78
22			45	85
23			45	87
24			40	88
25			20	85
26			50	90
27			30	50

the formyl group to give the final ketone. The incorporation of electron-withdrawing groups such as CO_2Me and NO_2 at the β-carbon atom retards the usual isomerization to carbonyl compounds through hydride or alkyl shift, presumably because of the decreased electron density at the β-center, and thus the oxirane ring is cleaved by nucleophilic attack of a Cl^- ion from $InCl_3$ to produce the corresponding chloro compound. The rearrangement of non-aromatic epoxides to carbonyl compounds using the present procedure is not very encouraging. Presumably, the incipient carbocation formed by the initial cleavage of the epoxide is much less stabilized in the case of alkyl-substituted epoxides compared to their aryl-substituted counterparts. Thus, while in the case of α-pinene oxide, where the carbocation is better stabilized on a tertiary center, rearrangement leads to the expected aldehyde, with cyclohexene oxide, where such stabilization is absent, chlorohydrin is formed by the nucleophilic attack of the Cl^- ion. Methylenecyclohexane oxide, being an intermediate case, leads to a mixture of products containing cyclohexanealdehyde, chlorohydrin, and some other unidentified compounds. In general, it was found that non-aromatic epoxides lacking a strong carbonium-stabilizing component afforded a mixture of products, of which chlorohydrin was the main constituent.

The above reactions are usually fast and high-yielding. The requirement for $InCl_3$ in these reactions is catalytic rather than stoichiometric; however, use of an optimum amount is necessary. Most significantly, $InCl_3$ is unique in pushing the reaction in one direction so as to provide one compound exclusively or predominantly, the best comparison being the rearrangement of 2-nitro-1-phenyl-1,2-epoxypropane (Entry 20), where a BF_3-catalyzed reaction furnished a mixture of five compounds.[23] Moreover, its mode of action in epoxide rearrangements is possibly different from that of other Lewis acids; while treatment of 1-phenyl-1,2-epoxycyclohexane with BF_3 or SbF_5 produced the ring-contracted 1-phenylcyclopentane aldehyde with complete selectivity,[20] the $InCl_3$-mediated reaction afforded 2-phenylcyclohexanone as the major product with less than 5% of the ring-contracted aldehyde. In another example, *trans*-stilbene oxide produced mixtures of the corresponding ketone and aldehyde in varying amounts with $MgBr_2$,[20] while with the present procedure the aldehyde was obtained as the sole product. $InCl_3$ is mild enough not to induce any isomerization in allyl or propargyl moieties. Acid-sensitive functionalities such as methoxy and methoxycarbonyl proved to be inert under the reaction conditions. The unique selectivity provided by this $InCl_3$-catalyzed procedure makes this reaction a viable alternative to the Wacker oxidation of vinyl arenes[24] and the homologation of carbonyl compounds to higher members through traditional methods (Scheme 3).



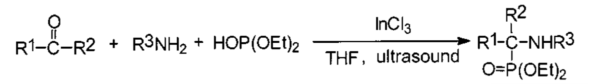
Scheme 3. Alternative to Wackers oxidation

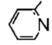
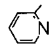
3.2 Synthesis of α-Aminophosphonates

α-Aminophosphonates, due to their structural analogy to α-amino acids, have been the subject of considerable recent interest. The potential of α-aminophosphonates as peptide mimetics, enzyme inhibitors, antibiotics, and pharmacological agents has been established. Thus, an efficient synthesis of these compounds is of considerable importance. A number of synthetic methods for α-aminophosphonates have been developed during the past two decades.[25,26] Of these, the nucleophilic addition of phosphites to imines, as catalyzed by a base or an acid, is the most convenient. Lewis acids such as $SnCl_2$, $SnCl_4$, BF_3Et_2O, $ZnCl_2$, and $MgBr_2$ have been used. However, these reactions cannot be carried out in a one-pot operation starting from a carbonyl compound, an amine, and dialkyl phosphite because the amines and water present during imine formation are likely to decompose or deactivate Lewis acids. This disadvantage has been overcome by a recent procedure[27] that employs a combination of a lanthanide triflate and magnesium sulfate. However, although this approach is satisfactory for reactions involving aromatic aldehydes and amines, aminophosphonates are obtained from aliphatic aldehydes and amines only in low or moderate yields. Thus, an efficient general procedure allowing the synthesis of α-aminophosphonates from both aldehydes and ketones with aliphatic as well as aromatic amines is needed. In view of the special characteristics of $InCl_3$, it was considered to be an ideal reagent for this purpose. Indeed, it was found that sonication of a mixture of a carbonyl compound, an amine, and diethyl phosphite in THF in the presence of a catalytic amount of $InCl_3$ produced α-aminophosphonates in a one-pot operation very efficiently.[28]

In this way, a wide range of structurally diverse carbonyl compounds were converted into the corresponding α-aminophosphonates in high yields. The results are summarized in Table 6. It was found that both aromatic and aliphatic aldehydes could be treated with aromatic as well as aliphatic amines to form the corresponding α-aminophosphonates. Moreover, the procedure proved to be equally effective for the conversion of open-chain, cyclic, or aromatic ketones to the respective α-aminophosphonates. Aldehydes were found to be more reactive than ketones. No difficulties were encountered in the reaction of conjugated aldehydes. However, conversions of conjugated ketones were not always satisfactory. Several sensitive functionalities such as OH, OMe, NO_2, CO_2Et, and the C−C double bond are unaffected under the present reaction conditions. Thus, this procedure offers an improved and more practical alternative to the existing methodologies for the synthesis of α-aminophosphonates.

Table 6. Synthesis of α-aminophosphonates from aldehydes/ketones and amines catalyzed by $InCl_3$

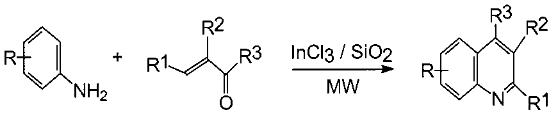


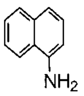
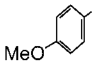
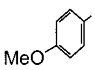
Entry	R1	R2	R3	Time(h)	Yield(%)
1	Ph	H	Ph	5	93
2	Ph	H	$PhCH_2$	5	95
3	Ph	H	$Ph\overset{*}{C}H(Me)$	6	90
4	Ph	H	$MeCH_2CH_2$	5	90
5	Ph	H		7	90
6	*p*-OMe−Ph	H	Ph	6	92
7	*p*-OMe−Ph	H	Me_2CH	7	90
8	*p*-NO_2−Ph	H	Ph	7	82
9	PhCH=CH (*trans*)	H	Ph	6	85
10	*m*-OH−Ph	H	Ph	6	93
11		H	Ph	7	92
12		H	$Ph\overset{*}{C}H(Me)$	7	90
13	*n*Pr−CH=C(Et) (*trans*)	H	$PhCH_2$	7	89
14	Me_2CH	H	$PhCH_2$	6	88
15	*n*Pr	H	Me_2CH	6	87
16	$Me_2C=CH(CH_2)_2C(Me)=CH$ (*trans*)	H	$PhCH_2$	6	89
17	Et	Et	$PhCH_2$	9	82
18	Ph	Me	$PhCH_2$	9	85
19	PhCH(OH)CH(Me)	CH(Me)CH(OH)Ph	$PhCH_2$	9	90
20	cyclohexanone		$PhCH_2$	6	87
21	4-*t*Bu-cyclohexanone		$PhCH_2$	7	80
22	indanone		$PhCH_2$	6	80
23	Ph-CH=CH (*trans*)	Me	$PhCH_2$	7	76
24	Me	CH_2COOEt	$PhCH_2$	7	85

3.3 Synthesis of Quinolines

The synthesis of quinolines and their derivatives has been of considerable interest to organic and medicinal chemists for many years as a large number of natural products and drugs contain this heterocyclic nucleus. The classical method for quinoline synthesis involves Skraup's procedure. However, it requires a large amount of sulfuric acid at temperatures in excess of 150 °C and the reaction is often viol-

Table 7. $InCl_3$-catalyzed synthesis of quinolines from anilines and alkyl vinyl ketones



Entry	Aniline R	Alkyl Vinyl Ketone R1	R2	R3	Time (min)	Yield(%)
1	H	H	H	Me	5	85
2	*o*−Me	H	H	Me	10	81
3	*m*−Me	H	H	Me	10	84
4	*p*−Me	H	H	Me	10	85
5	*o*−OMe	H	H	Me	12	80
6	*p*−OMe	H	H	Me	10	83
7	*m*−OH	H	H	Me	10	81
8	*m*−Cl	H	H	Me	5	87
9	*p*−Cl	H	H	Me	12	80
10	*p*−Br	H	H	Me	7	80
11	*o*−Me, *p*−I	H	H	Me	10	83
12		H	H	Me	7	82
13	H	Me	H		9	81
14	*m*−Cl	Me	H		7	83
15	H	*n*Pr	Et	Me	12	55

ent. Many methods have subsequently been developed for the synthesis of quinolines,[29] but most of them are not fully satisfactory with regard to yield, reaction conditions, generality, and operational simplicity. Thus, a simple, general, and efficient procedure for the synthesis of this important heterocycle is needed. In this laboratory, a microwave-assisted one-pot procedure for the synthesis of 4-alkylquinolines has been developed, in which amines and alkyl vinyl ketones react on the surface of silica gel under the catalysis of $InCl_3$.[30]

Several substituted anilines and alkyl vinyl ketones have been subjected to this procedure, affording the corresponding quinolines in quite high yields. The results are presented in Table 7. In general, the yields of quinolines are not affected by the nature of the substituents on the aniline and vinyl ketone components. Using *m*-substituted anilines, only one regioisomeric quinoline corresponding to *p*-cyclization is formed. Presumably, this process involves a Michael addition of the aniline to the vinyl ketone,[31] with subsequent cyclization and aromatization under the catalysis of $InCl_3/SiO_2$. However, this reaction does not proceed with acrolein (or vinyl aldehydes in general) yielding instead the corresponding imine. The reaction in the presence of $InCl_3$ alone is sluggish, while reaction on the silica gel surface in the absence of $InCl_3$ leads to imine formation. Conventional heating rather than microwave activation induces considerable polymerization of the vinyl ketones, drastically reducing the yield of quinolines.

3.4 Transesterification

Transesterification is an important reaction that has wide applications in academic as well as industrial research. Thus, numerous procedures catalyzed by a variety of protic and Lewis acids, organic and inorganic bases, or enzymes and antibodies have been developed.[32] Surprisingly, although these reports contain many examples of transesterifications of esters to give the corresponding analogues with higher alcohol moieties, examples of the reverse transformations are few and far between. Thus, a need was identified for an efficient transesterification procedure with general applicability involving simple operations and a non-toxic reagent. It has been found that transesterification catalyzed by indium triiodide proceeds very efficiently.[33]

Various types of carboxylic esters, including open-chain, cyclic, and aromatic compounds, have been subjected to transesterification using a variety of alcohols according to this procedure. The results are presented in Table 8. The reaction proceeds smoothly with primary, secondary, as well as tertiary alcohols, although transesterifications with *tert*-butyl alcohol and benzyl alcohol have been carried out under sonication. Conversions of methyl esters to higher homologues and of higher esters to lower homologues have

Table 8. InI_3-catalyzed transesterification

Entry	Carboxylic ester	Alcohol	Product	Time/h	Yield(%)
1	$PhCH_2CO_2\textit{i}Pr$ → $PhCH_2CO_2Me$				

been achieved with uniform efficiency using this procedure. The transformation of a menthyl ester to a methyl ester, which is very difficult to accomplish by other methods, is particularly illustrative of the efficacy of this reagent. Transesterification to a *tert*-butyl ester, which is often problematic in acid-catalyzed reactions, can also be realized using this reagent. This procedure is also suitable for transesterifications of chiral esters without any racemization. Several functional groups, such as the C−C double bond, nitro, methoxy, and hydroxy, are unaffected under the present reaction conditions. The reactions are, in general, very clean and give very high yields; no side-products have been isolated. The transesterification of aliphatic esters usually proceeds more rapidly than that of aromatic esters.

4. Conclusions

The synthetic advantages of indium-mediated reactions have been demonstrated with examples of the work carried out in this laboratory. It is clear from this review that indium is of high potential and has its own unique style of functioning. The study of indium-mediated reactions is still in its infancy and more fascinating chemistry is expected to originate from this area. An aim of the present review is to attract more attention to this branch of chemistry.

Acknowledgments

The results described herein were accomplished through the skill, creativity, and hard work of a number of my co-workers. I am deeply indebted to these young people whose names are cited in the following references. Financial support of this investigation from the CSIR, New Delhi [Grant No. 01(1504)/98] is gratefully acknowledged.

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