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Highly efficient indium-catalyzed chemoselective allylation–etherification and reductive etherification of aromatic aldehydes with functional silanes

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Abstract—Indium(III) chloride is an effective Lewis acid catalyst for one-pot allylation–etherification and reductive etherification of aromatic aldehydes with functional silanes, allyltriethoxysilane, and triethoxysilane, at room temperature to afford corresponding ethers in excellent yields. Additionally, the $InCl_3$-catalyzed reactions in the presence of TMSCl offer significant advantages in its ease of working-up for the preparation of unsymmetrical ethers under mild conditions.

Indium-mediated or catalyzed organic reactions have elicited considerable attention since the discovery of the remarkable reactivity of this metal in organic or aqueous media.[1] Indium(III) salts are water-tolerant and non-toxic or environmental benign reagents, and these properties have resulted in an increase and more widespread application as efficient Lewis acid catalysts for various important organic synthetic transformations in recent years.[2] Although In(III) salts are powerful Lewis acid catalysts recently in Mukaiyama-type reaction,[3] intramolecular cyclization,[4] alkynylation,[5] allylation,[6] Michael addition,[7] and versatile organic reactions,[8] it is not an all-purpose Lewis acid catalyst and still exhibited limits or no catalytic activity in many organic reactions. Furthermore, the combination of chlorotrimethylsilane and indium(III) salt expanded the catalytic application of indium-based catalysts in organic reactions, such as Friedel–Crafts alkylation, hydrosilylation, and allylation.[9] It was pointed out that for these reactions, neither chlorotrimethylsilane nor indium(III) chloride or bromide was effective alone and the reactions proceeded only when chlorotrimethylsilane and indium(III) chloride were combined. In our previous study, we have developed a new catalytic aza-Michael reaction of chalcones and carbamates promoted by the combination of indium(III) salts and TMSCl.[10] Such a remarkable enhancement of Lewis acidity of chlorotrimethylsilane by indium(III) chloride exhibited good catalytic activity in this reaction. This work also offered good examples for the combination of Lewis acid and TMSCl catalyst systems for related transformations.[11] As an extension of previous studies of $InCl_3$ catalyzed organic transformations, herein we reported a mild and convenient procedure for one-pot allylation–etherification and reductive etherification of aldehydes with functional silanes.

The homoallyl ethers are synthetically useful organic molecules or building blocks in organic synthesis,[12] which are usually obtained by the reaction of acetals or ketals with allylsilane. Stoichiometric Lewis acidic activators that have been used for this reaction, include $TiCl_4$, $AlCl_3$, $BF_3{\cdot}Et_2O$, liquid SO_2, and CuBr/microwave.[13] Alternatively, catalytic entries that have been developed for this transformation include Lewis acids such as TMSOTf, TMSI, trityl perchlorate, montmorillonite, diphenylboryl triflate, $TMSN(SO_2F)_2$, $TiCp_2(CF_3SO_3)_2$, $BiBr_3$, TMSNTf, $Sc(OTf)_3$, $Bi(OTf)_3$, $FeCl_3$, $AlBr_3$/CuBr, $NbCl_5/AgClO_4$, and Brønsted acid catalyzed allylation of acetals or ketals.[14] Most of these methods suffer from drawbacks such as the involvement of compounds that are corrosive, difficult to handle,

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expensive, or toxic. Others require strictly anhydrous conditions or less practical reaction temperatures.[14–17] And furthermore, the preparation of homoallyl ethers from aldehyde requires a two-step conversion comprising acetalization of aldehydes and subsequent allylation of acetals. From the synthetic viewpoint, it is very significant to prepare homoallyl ethers starting from aldehydes directly. Therefore the development of one-pot synthesis of homoallyl ethers from aldehydes is highly desired. Although Markó,[15] Oriyama,[16] and Mohan[17] et al. have reported one-pot synthesis of homoallyl ethers from aldehydes and allyltrimethylsilane catalyzed by TMSOTf and $FeCl_3$ respectively, we planned to elaborate another novel one-pot synthetic procedure for the preparation of homoallyl ethers by the use of allyltrialkyloxysilanes.

It is well-understood that the low reactivity of allyltrialkyloxysilanes has limited their synthetic utility.[18] To overcome the low reactivity of allyltrialkyloxysilane, we attempted at first to use the catalyst system of the combination of $InCl_3$ with TMSCl in the allylation of aromatic aldehydes because the good catalytic Lewis acid activity of $InCl_3$ in the presence of TMSCl might be better than that of general Lewis acids.

Initially, we examined the allylation reaction of benzaldehyde with allyltriethoxysilane using 10 mol % of $InCl_3$ in the presence of 1.5 equiv TMSCl. Fortunately, the reaction of benzaldehyde with allyltriethoxysilane promoted by the combination of $InCl_3$ (10 mol %) with TMSCl (1.5 equiv) in CH_2Cl_2 to give the homoallyl ether in excellent yield (98%, Table 1, entry 1). We then found that the obtained product was not homoallylic alcohol but homoallyl ether, and the yield was only 19% in the absence of TMSCl (entry 2), and for this reaction, TMSCl did not show any catalytic or promoted activity in the absence of $InCl_3$ (entry 3).

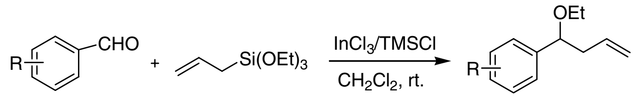
Encouraged by these results, we carried out the reaction with various aromatic aldehydes. As shown in Table 1, the allylation–etherification of aromatic aldehydes proceeded cleanly in most cases with yields up to 99% (entries 3–6). Electron-deficient aromatic aldehydes having halogen or nitro substituents were allylated and etherificated in excellent yields (entries 4–6). However, reaction of electron-rich aromatic aldehyde having methoxy substituent on the benzene ring with allyltriethoxysilane showed lower reactivity and the corresponding product was obtained in only 10% (entry 7). Otherwise, electron-rich aromatic aldehyde with *p*-methyl substituent proceeded efficiently (entry 8, 98% yield).

Considering the above-mentioned successful results, we speculated that one-pot synthesis of ethers from aldehydes could be accomplished by using triethoxysilane ($HSi(OEt)_3$). The reductive etherification of carbonyl compounds is known as an alternative method of the Williamson synthesis of ether, which is one of the most important functional groups.[19] It is well-documented that several groups have reported the reductive etherification of aldehydes by using the combination of aldehydes, triethylsilane ($HSiEt_3$), and alkyl alcohol or alkoxytrialkylsilane in the presence of catalysts or promoters, such as TFA, TMSCl, TMSOTf, $BiCl_3$, $BiBr_3$, $TrClO_4$, $B(C_6F_5)_3$, and $FeCl_3$.[20] Surprisingly, to the best of our knowledge, there are no reports on indium-mediated reductive etherification with low reactive trialkyloxysilane ($HSi(OR)_3$).

Initially triethoxysilane ($HSi(OEt)_3$) was subjected to one-pot reductive etherification with *p*-bromobenzaldehyde in the presence of catalytic indium(III) chloride and 1.5 equiv TMSCl in dichloromethane (CH_2Cl_2) to give 73% yield. And additional experimental results showed other solvents, such as toluene and THF were not suitable media for this reaction. Similarly to the allylation–etherification of aldehydes, only $InCl_3$ or TMSCl did not promote the reductive-etherification successfully.

These results prompted us to expose the $HSi(OEt)_3$ to other aldehdyes. As shown in Table 2, in most cases, excellent and uniformly consistent results were obtained.

Table 1. $InCl_3$-catalyzed allylation–etherification of aromatic aldehyde using allyltriethoxysilane in the presence of TMSCl

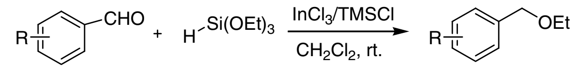


Entry[a]	Aldehyde (R)	$InCl_3$ (mol %)	TMSCl (equiv)	*T* (h)	Yield[b] (%)
1	H	10	1.5	3	95
2	H	10	—	6	19
3	H	—	1.5	6	Trace
4	*p*-Br	10	1.5	3	98
5	*p*-NO_2	10	1.5	3	99
6	*o*-Cl	10	1.5	3	98
7	*p*-OMe	10	1.5	5	10
8	*p*-Me	10	1.5	3	98

[a] Reaction conditions: 10 mol % of $InCl_3$ and 1.5 equiv TMSCl, 1.0 mmol of aldehyde, 1.5 mmol of allylsilane (allyltriethoxysilane), 2 mL of solvent (CH_2Cl_2), at room temperature.[21]

[b] GC yield.

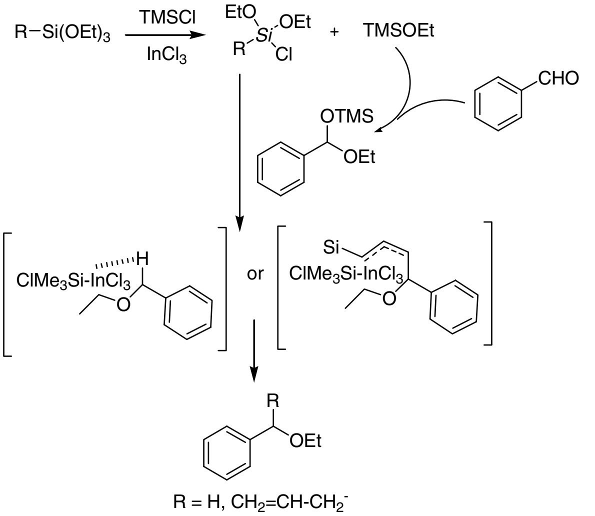
Table 2. $InCl_3$-catalyzed reductive etherification of aromatic aldehyde using triethoxysilane in the presence of TMSCl



Entry[a]	R	Solvent	$InCl_3$ (mol %)	TMSCl (equiv)	Yield[b] (%)
1	*p*-Br	THF	10	1.5	0
2	*p*-Br	Toluene	10	1.5	6
3	*p*-Br	CH_2Cl_2	10	1.5	73
4	*p*-Br	CH_2Cl_2	—	1.5	0
5	*p*-Br	CH_2Cl_2	10	—	Trace
6	H	CH_2Cl_2	10	1.5	93
7	*p*-CH_3	CH_2Cl_2	10	1.5	91
8	*p*-NO_2	CH_2Cl_2	10	1.5	81
9	*o*-Cl	CH_2Cl_2	10	1.5	53

[a] Reaction conditions: 10 mol % of $InCl_3$ and 1.5 equiv TMSCl, 1.0 mmol of aldehyde, 1.5 mmol of silane ($HSi(OEt)_3$), 2 mL of solvent (CH_2Cl_2), at room temperature, for 3 h.

[b] GC yield.



Scheme 1. Possible mechanistic pathway for allylation–etherification and reductive etherification of aldehyde with functional silane.

Although the present limitation that only unsymmetrical ethyl ethers were obtained in this reaction existed, we believe the perspective versatile ethers could be prepared by using different trialkyloxysilanes.

For the above allylation–etherification and reductive etherification of silane, we proposed that they carried out similar mechanism. A likely mechanistic pathway for these transformations is shown in Scheme 1. It is reasonable to assume that in situ formed silyl ether and chlorosilane via the exchange reaction of TMSCl with allyltriethoxysilane or triethoxysilane. And the catalyst system (InCl$_3$ in the presence of TMSCl) activates the aldehyde toward the nucleophilic attack by the silyl ether to give an intermediate, which undergoes a fragmentation to give an oxonium species.[22] The oxonium species undergoes reduction or allylation with the corresponding silane reagent leading to the formation of the product, homoallylether or ether.

In summary, the InCl$_3$ in the presence of TMSCl was efficient catalyst for the synthesis of unsymmetrical ethers by allylation–etherification and reductive etherification of aldehydes with functional silanes, allyltriethoxysilane, and triethoxysilane. The catalyst system offers significant advantages in its ease of preparation and handling, and most importantly, in its ability to catalyze the formation of unsymmetrical ethers from aromatic aldehydes in almost quantitative yields directly. It is also notable that it is a first example by using low reactive triethoxysilane and allyltriethoxysilane in the preparation of versatile ethers via catalytic allylation–etherification and reductive etherification, which would open new entries to the synthesis of ethers and related compounds by using functional silanes.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.062.

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21. Typical procedure of allylation–etherification or reductive etherification: $InCl_3$ (0.1 mmol) and TMSCl (1.5 mol) was added into a solution of aldehyde (1.0 mmol) and allyltriethoxysilane or triethoxysilane (1.5 mmol) in CH_2Cl_2 (3 mL). After stirring at room temperature for 3 h, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with aqueous HCl and then washed with aqueous $NaHCO_3$, organic layers was dried (Na_2SO_4), concentrated in vacuo, and purified by column chromatography on silica gel (EtOAc–petro ether, 1:20) to gain the pure product. All the products were known and were fully characterized and confirmed by GC–MS, and usual spectral methods (NMR and IR).
22. The ^{1}H NMR spectra of substrates in the presence of $InCl_3$ or TMSCl were gave in Supplementary data.