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Secondary Amine Formation from Reductive Amination of Carbonyl Compounds Promoted by Lewis Acid Using the $InCl_3/Et_3SiH$ System

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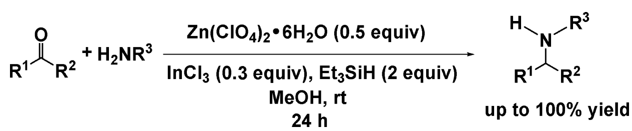
ABSTRACT



A robust and reliable method has been developed for reductive amination of primary amines with various aldehydes and ketones using $Zn(ClO_4)_2{\cdot}6H_2O$ as a catalyst. [In−H] generated in situ via a combination of $InCl_3$ and Et_3SiH is employed as an effective reducing system. A variety of secondary amines can be synthesized in a one-pot procedure in excellent yields.

Secondary amines constitute an important class of chemical compounds that has a prodigious potential for industrial,[1] pharmaceutical,[2] and agrochemical[3] applications. For the synthesis of secondary amines,[4] methods involving reductive amination of carbonyl compounds remain the simplest approach. However, overalkylation of amines (in particular, with aldehydes), a commonly encountered problem with this approach, has been widely reported in the literature.[5] In practice, conditions including catalytic hydrogenation[6] and reduction of imine intermediates by $NaBH_3CN$[7] are frequently employed. Unfortunately, the utility of these has been limited by a number of unfavorable factors: specifically, hydrogenation is not compatible with olefinic functional groups, while the use of the highly toxic $NaBH_3CN$ generates many safety and environmental issues. Recently, alternative reagents including $NaBH(OAc)_3$ have been developed for this purpose.[5,8]

However, the utility of those reagents in reductive amination has not yet been fully covered. Although some indirect methods for synthesis from alkynes[9] have also been reported, these entail extra experimental procedures, which are not preferred in synthetic chemistry.[10,11] To extend the scope

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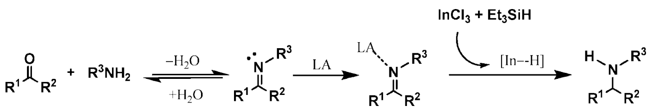
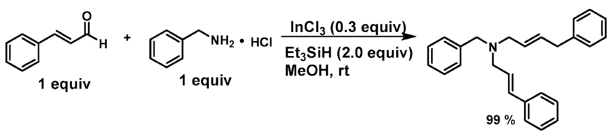
and improve the selectivity of reductive amination reactions, several other reagents have been developed.[12]

We reported the $InCl_3/Et_3SiH/MeOH$ system[13] as a highly chemoselective, mild reducing agent that can be used in reductive amination reactions to afford tertiary amines. Extending our scope to secondary amine formation, we observed the formation of overalkylation products as major product between *trans*-cinnamaldehydes and benzylamine HCl salts (eq 1). On the other hand, replacing benzylamine HCl salts with benzylamines failed to produce the desired product (eq 2). To address the problem, we employed Lewis acid, as catalysts in reductive amination.[14] In Scheme 1, an imine intermediate is predominantly formed between the carbonyl compound and primary amine, and its reactivity toward reduction could be enhanced by binding to a Lewis acid.

Scheme 1. Concept of Lewis Acid-Promoted Reductive Amination Reaction





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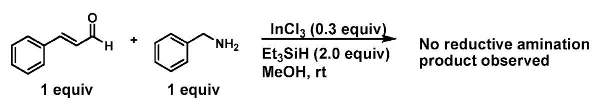
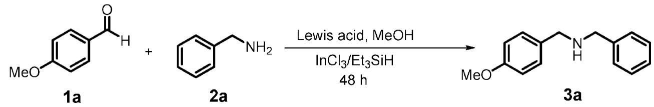


(2)

We started off by screening various Lewis acids for reductive amination between 4-methoxybenzaldehyde (**1a**) and benzylamine (**2a**). The reaction was carried out with a 1:1 ratio of aldehyde and amine in the presence of 0.5 equiv of Lewis acid,[15] 0.3 equiv of $InCl_3$, and 2.0 equiv of Et_3SiH in MeOH at room temperature. Organosilanes[12f,g,16,17] were used in the reactions for their mild reducing ability, low toxicity, and low environmental impact. We focused on screening Lewis acids derived from the transition metal series[18] and found that Fe(II) and Zn(II) complexes gave the best results (Table 1). Among these, quantitative yield was achieved with $Zn(ClO_4)_2{\cdot}6H_2O$ (entry 2). Other hydrated Lewis acids such as $FeSO_4{\cdot}7H_2O$ and $Fe(ClO_4)_2{\cdot}xH_2O$ could also catalyze the reactions effectively (78% and 73% yields, respectively; entries 3 and 4). This finding provided corroborative evidence

Table 1. Effects of Lewis Acids on Reductive Amination Reactions[a]



entry	Lewis acid	yield (%)[b]
1	$Zn(OTf)_2$	85
2	$Zn(ClO_4)_2{\cdot}6H_2O$	100
3	$FeSO_4{\cdot}7H_2O$	78
4	$Fe(ClO_4)_2{\cdot}xH_2O$	73
5	–	nr[d]
6[c]	$Zn(ClO_4)_2{\cdot}6H_2O$	nr[d]

[a] Unless otherwise indicated, all reactions were carried out in MeOH at room temperature using 0.5 mmol of **1a**, 0.5 mmol of **2a**, 0.3 equiv of $InCl_3$, 0.5 equiv of Lewis acid, and 2 equiv of Et_3SiH. [b] Yields were determined by ^1H NMR using DMF as an internal standard. [c] No $InCl_3$ was added. [d] No reaction.

that the system has its advantage upon water allowance as reported by our group.[13] Notably, no reaction was found in the absence of Lewis acid (entry 5), suggesting the necessity of Lewis acid activation. Most importantly, no conversion of substrate was found in the absence of $InCl_3$ (entry 6), which confirms that In(III) was responsible for the reduction via in situ generated [In−H] species and that it did not act as a Lewis acid in catalyzing reductive amination.

We then explored reductive amination reactions of aldehydes with primary amines, as illustrated in Table 2. A wide scope of small to bulky primary amines including benzylic, allylic, aliphatic, cyclic, and aryl amines were successfully tested. Reductive amination reaction with 4-methoxybenzaldehyde to produce secondary amines was observed in excellent to quantitative yields (entries 1−5). Reactions of less electron-rich benzaldehyde and *p*-tolualdehyde with benzylamine could also proceed smoothly (entries 6 and 7). Heteroaromatic aldehydes (for example, 2-furaldehyde) resulted in efficient reaction (entry 8). Apart from aromatic aldehydes, a number of unsaturated aldehydes were also

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(15) When the Lewis acid loading was reduced to 0.3 equiv or lower, poor conversion and product yield were observed.

Table 2. Reductive Amination of Aldehydes with Primary Amines[a]

entry	aldehyde	amine	product	yield (%)[b]
1	**1a**	**2a**	**3a**	100 (88)[c]
2	**1a**	**2b**	**3b**	89
3	**1a**	**2c**	**3c**	89
4	**1a**	**2d**	**3d**	100
5	**1a**	**2e**	**3e**	100
6	**1b**	**2a**	**3f**	87 (61)[c]
7	**1c**	**2a**	**3g**	100 (79)[c]
8	**1d**	**2a**	**3h**	100
9	**1e**	**2a**	**3i**	80 (1:6.7)[d]
10	**1e**	**2b**	**3j**	93 (66)[c] (1:8.3)[d]
11	**1e**	**2c**	**3k**	90 (1:7.7)[d]
12	**1f**	**2a**	**3l**	90 (79)[c]
13	**1f**	**2c**	**3m**	90
14	**1g**	**2a**	**3n**	75

[a] Unless otherwise indicated, all reactions were carried out in MeOH (1 mL) at room temperature using 0.5 mmol of aldehyde, 0.5 mmol of primany amine, 0.3 equiv of $InCl_3$, 0.5 equiv of $Zn(ClO_4)_2$•$6H_2O$, and 2 equiv of Et_3SiH for 24 h. [b] Yields were determined by ^1H NMR using DMF as an internal standard. [c] Isolated yield in parentheses. [d] The *Z*:*E* ratio is in parentheses.

Table 3. Lewis Acid-Promoted Reductive Amination of Ketones with Primary Amines[a]

entry	ketone	amine	product	yield (%)[b]
1	**1h**	**2a**	**3o**	100 (71)[c]
2	**1i**	**2a**	**3p**	100
3	**1j**	**2a**	**3q**	100
4	**1k**	**2a**	**3r**	69 (51)[c]
5	**1m**	**2a**	**3s**	70[d] (57)[c]
6	**1n**	**2a**	**3t**	59 (50)[c]
7	**1h**	**2b**	**3u** (•HCl)	100[e] (90)[c]
8	**1h**	**2c**	**3v** (•HCl)	100[e] (88)[c]
9	**1i**	**2d**	**3w** (•HCl)	100[e] (92)[c]
10	**1i**	**2e**	**3x**	95
11	**1n**	**2d**	**3y** (•HCl)	100[e] (92)[c]
12	**1n**	**2e**	**3z**	70 (55)[c]

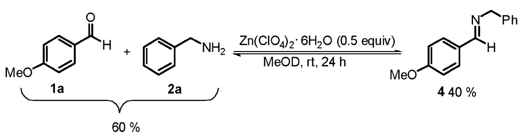
[a] Unless otherwise indicated, all reactions were carried out in MeOH (1 mL) at room temperature using 0.5 mmol of ketone. 0.5 mmol of primany amine, 0.3 equiv of $InCl_3$, 0.5 equiv of $Zn(ClO_4)_2$•$6H_2O$, and 2 equiv of Et_3SiH for 24 h. [b] Yields were determined by ^1H NMR using DMF as an internal standard. [c] Isolated yield in parentheses. [d] Yield based on 84% conversion. [e] The HCl salts were prepared.

examined, including α,*β*-unsaturated aldehydes (entries 9−13). The observation of minor *Z*-product in entries 9−11 revealed partial double bond isomerization may occur during the reduction process.[19] Saturated aldehyde **1g** reacted smoothly with benzylamine to afford product in 75% yield (entry 14). Most importantly, none of the entries gave overalkylation products, suggesting that the system is highly effective with various sizes of amines.

We next explored the reactions involving different ketones (**1h**−**n**), and the results are summarized in Table 3. The reactivity of the system depends on the ability of different ketones to form the imine intermediate. Reactions of benzylamine with various aliphatic cyclic ketones were highly efficient, affording products in high to quantitative yields (entries 1−4). In contrast, aromatic ketones displayed lower reactivity, and the reaction between 1-indanone and benzylamine thus proceeded slowly with only 84% conversion (entry 5). Apart from benzylamine, other types of amines also exhibited excellent reactivity toward ketones (entries 7−10). In addition, the simple aliphatic ketone **1n** also delivered promising results (entries 6, 11, and 12). Again, no overalkylation products were detected, indicating good chemoselectivity of the reaction system.

We believe that the Lewis acids play an important part in activating the imine intermediate toward reduction. To gain insights into the role of Lewis acids, we conducted control experiments for illustration.

First, we investigated if there is any effect of Lewis acid $Zn(ClO_4)_2$•$6H_2O$ on the equilibrium among aldehyde, amine, and imine. The studies on imine formation between 4-methoxybenzaldehyde and benzylamine were compared. Surprisingly, the addition of $Zn(ClO_4)_2$•$6H_2O$ resulted in an equilibrium with 40% of imine formation (eq 3). On the other hand, 99% of imine was formed in the absence of $Zn(ClO_4)_2$•$6H_2O$ (eq 4). The equilibrium was further supported by the reverse experiment described in eqs 5 and 6. Upon addition of $Zn(ClO_4)_2$•$6H_2O$ to imine **4**, a shift in the equilibrium occurred in the backward reaction, giving 65% 4-methoxybenzaldehyde and 35% imine, a ratio similar to that between aldehyde and amine as starting materials. These results implied that $Zn(ClO_4)_2$•$6H_2O$ altered the equilibrium position in the imine formation process; however, it did not directly relate to the enhanced reactivity observed in reactions.



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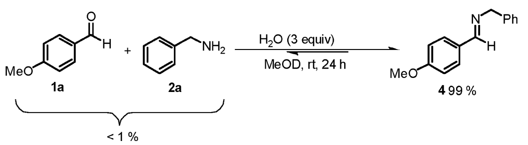

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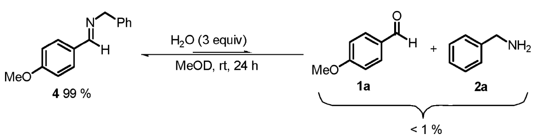
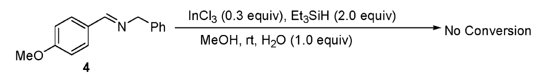


(6)

Additionally, we investigated the effect of Lewis acid on the reactivity of the reduction system. The imine intermediate **4** was isolated and subjected to reduction by $InCl_3$/Et_3SiH in MeOH. It can be inferred that Lewis acid is necessary for promoting successful reductions. Thus, no conversion of imine **4** occurred in the absence of $Zn(ClO_4)_2$•$6H_2O$ (eq 7), whereas 56% yield of **3a** was obtained with the addition of the Lewis acid (eq 8). The results also strongly suggest that $Zn(ClO_4)_2$•$6H_2O$ can serve as a Lewis acid to activate imine, which enhanced the electrophilicity of the C=N group for hydride delivery.



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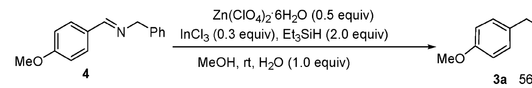

(8)

In conclusion, we have developed a new method of wide scope for Lewis acid-promoted reductive amination to give secondary amines using an $InCl_3$/Et_3SiH/MeOH system. With this robust system, both aldehydes and ketones can be applied. In addition, the system has a number of advantages in terms of convenience, low toxicity, and nonwater sensitivity. We have further demonstrated that the role of Lewis acids in the direct reductive amination reaction is to activate the in situ generated imine toward reduction. Asymmetric reductive amination of ketones and amines constitutes another promising area for future investigation.

Acknowledgment. This work was supported by The University of Hong Kong and the Hong Kong Research Grants Council.

Supporting Information Available: Experimental procedures and spectral data for **3a**−**z** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) No desired product was observed with Lewis acids CuBr, $CuBr_2$, $Cu(OTf)_2$, $Fe(NO_3)_3$•$9H_2O$, $Fe(acac)_3$, $Zn(OAc)_2$, $ZnCl_2$, ZnI_2, $Ni(acac)_2$, and $Ni(ClO_4)_2$•$6H_2O$.

(19) No partial double bond isomerization was observed when **1e** and the Lewis acid were stirred with or without amine, suggesting that the partial double bond isomerization is unlikely to be caused by the Lewis acid itself.