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Efficient catalytic aza-Michael additions of carbamates to enones: revisited dual activation of hard nucleophiles and soft electrophiles by $InCl_3$/TMSCl catalyst system

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Abstract—The aza-Michael reaction of a variety of chalcones with weaker nucleophilic carbamates catalyzed by $InCl_3$ in the presence of TMSCl via the entry of dual activation of both hard nucleophiles (carbamates) and soft electrophiles (enones) to provide the corresponding adducts in good yields. The first example of enantioselective aza-Michael reaction of chalcones with carbamates was also investigated in the presence of the present catalyst system.

The addition of nitrogen nucleophilies to α,β-unsaturated carbonyl compounds or activated olefins, the so-called aza-Michael reaction, is of great interest because of the versatility of the corresponding β-amino carbonyl derivates.[1] In the past few years, the development of novel and efficient synthetic methods leading to chiral β-amino ketones, β-amino acids, and their derivatives has attracted much attention in organic synthesis,[2] and much effort has been expended on seeking transition metal catalysts for aza-Michael reactions.[3] However, most methods for intermolecular aza-Michael addition to unsaturated ketones (enones) or other related compounds reported to date described the addition of hydroxylamines, alkyl or aryl amines, aldoximes, hydrazoic acid or azide ion. The aza-Michael reaction of carbamates that it was weaker nucleophiles and recognized as an important N-protected amines, proven to be more difficult, was only recently realized catalytically through the use of Brønsted acids and several expensive transition metal-based Lewis acids.[4] Although recent advances have made this route more attractive, there remains much room to develop an efficient catalytic aza-Michael addition of carbamates to various enones under mild conditions. Herein, we reported a new entry in the catalytic aza-Michael reaction of carbamates and chalcones using indium(III) salts and TMSCl catalyst system. Preliminary mechanistic studies based on experimental results are also discussed. We described the application of this catalyst system to the formation of chiral aromatic N-protected β-amino ketone via aza-Michael reaction of ethyl carbamate and β-phenylenone.

Over the past decade, the dual activation of nucleophiles and electrophiles has been receiving much attention and has opened up a new field in the development of homogeneous and asymmetric catalysis.[5] With suitable activation of the reactants, an enhancement of enantioselectivity or an acceleration of the reaction rate is expected. Various catalysts with dual activation, such as heterobimetallic catalysts, Lewis acid–Lewis base catalysts, and Lewis acid–Lewis acid catalyst, could be achieved with efficient and excellent enantioselective reactions under mild conditions.[6] Application of this bifunctional strategy seems to be one of the most promising solutions for developing a catalytic aza-Michael addition of carbamates and enones. From this point of view, the dual activation of hard nucleophiles (carbamates) and soft electrophiles (enones-activated olefin)

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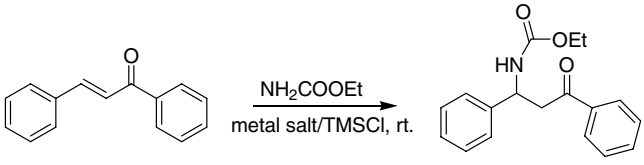
is important and perfect. We postulated that the combination of soft Lewis acid and hard Lewis acid might be suitable for this purpose, which could activate two substrates simultaneously in a hemolytic addition, and it would enhance the reactivity rate with a high chemoselectivity and enantioselectivity. It is well known that chlorotrimethylsilane (TMSCl) is an efficient Lewis acid and has been used as a catalyst for several organic transformation.[7] TMSCl may facilitate the conjugate addition of organocopper and other organometallic reagents to different acceptors efficiently,[8] and has been widely used as a promoter or additive in several transition metal or Lewis acid-catalyzed reaction transformations.[9] These features prompted us to examine the combination of TMSCl and transition metal salts for aza-Michael addition via dual activation.

In our previous work, we have found that aza-Michael reaction of chalcones with weaker nucleophilic carbamates can be accomplished with transition metal salts/TMSCl catalyst system under mild conditions.[10] Inspired by these findings of aza-Michael reactions, we surveyed the catalytic activity of other cheaper and nontoxic transition metal salts in the aza-Michael addition of ethyl carbamate and β-phenylenone (chalcone) under reported conditions (Table 1). Excepted previous transition metal salts, such as $FeCl_3$, $RhCl_3$, $PdCl_2(CH_3CN)_2$, $RuCl_3$, we found $InCl_3$ showed a better catalytic activity in the present reaction. As shown in Table 1, the presence of chlorotrimethylsilane (TMSCl) is essential for the aza-Michael reaction. In the absence of chlorotrimethylsilane, no 1,4-addition takes place, the starting enones being recovered intact. The combined catalyst system of $InCl_3$/TMSCl[4e] was effective in different solvents, such as toluene (entries 13–15), CH_3CN (entry 10), and there was no any transformation in CH_3OH (entry 11) and THF (entry 12) under the same conditions. Toluene is the most suitable solvent in this aza-Michael reaction with the present catalyst system ($InCl_3$/TMSCl).

Table 1. Catalytic activity of metal salts/TMSCl catalyst system in aza-Michael reaction of chalcone



Entry[a]	Metal salts	TMSCl (equiv)	Solvent	Time (h)	Yield[b] (%)
1	—	1.0	CH_2Cl_2	24	Trace
2	$FeCl_3$	—	CH_2Cl_2	24	0
3	$FeCl_3$	1.1	CH_2Cl_2	24	48
4	$PdCl_2(CH_3CN)$	—	CH_2Cl_2	24	0
5	$PdCl_2(CH_3CN)$	1.1	CH_2Cl_2	24	60
6	$RuCl_3$	1.1	CH_2Cl_2	24	52
7	$RhCl_3{\cdot}3H_2O$	1.1	CH_2Cl_2	24	65
8	—	1.0	Toluene	24	27
9	$InCl_3$	—	Toluene	120	0
10	$InCl_3$	1.0	CH_3CN	24	68
11	$InCl_3$	1.0	CH_3OH	24	Trace
12	$InCl_3$	1.0	THF	24	Trace
13	$InCl_3$	1.0	Toluene	48	47
14	$InCl_3$	1.0	Toluene	24	74
15	$InCl_3$	1.0	Toluene	24	70[c]

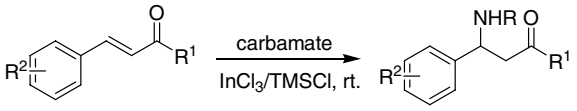
[a] Chalcone/carbamate = 1/1.2, 10 mol % of metal salt and 1.0 equiv of TMSCl, at room temperature.
[b] Isolated yields.
[c] Using 5 mol % of $InCl_3$ as catalyst.

These fascinating results prompted us to further investigate aza-Michael reactions of various carbamates and chalcones to produce versatile N-protected β-amino ketones. As shown in Table 2, the combination of a catalytic amount of $InCl_3$ and TMSCl was used as a catalyst in the aza-Michael reactions of various substrates under optimized conditions, and it showed a moderate to good catalytic activity in most cases. In this reaction, chalcones with electron-donating groups as CH_3 and Cl (entries 3–5) gave better yields, but those with electron-withdrawing groups such as NO_2 afforded lower yields (entry 9). Interesting, *o*-substituted chalcones (entries 4 and 6) worked favorably to give good isolated yields. It is reasonable that *o*-substituted group fascinated the interaction of activated olefin bond with $InCl_3$, which increased the reactivity of enone in aza-Michael reaction of carbamate. Various carbamates with different structures, such as NH_2CBZ, NH_2COOEt, and 2-oxazolidinine, gave similar results in the aza-Michael reactions (see Table 2).

Although it is known that TMSCl could activate the carbonyl group by the initial interaction of TMSCl with enones and fascinated the next step of reaction,[11] the complete reaction mechanism of transition metal salts/TMSCl-catalyzed aza-Michael reaction of carbamate with enones was not clear in the past. The results shown above manifest in Tables 1 and 2 that transition metal salts-based Lewis acid and TMSCl should work synergistically with the dual activation in the hetero-Lewis acidic catalyst system. A possible working model is depicted in Scheme 1. The well-known 'hardness' of silicon suggests the usefulness of silyl groups as the acidic portion of effective reagents, which would be coordinated with hard heteroatom, such as N, and O, involving a six-centered transition state.[12] The activation of carbonyl compounds and comparable enones was also well-understood.[13] The dual activation of both hard nucleophiles and soft electrophiles shown in Scheme 1 was confirmed by UV, IR, and NMR spectroscopic studies and supported by experimental results.[10] From IR and NMR spectra, the strong interaction of $InCl_3$/TMSCl with chalcone or carbamate was existed, which showed that the dual activation of both hard nucleophiles and soft electrophiles was crucial and reasonable to the aza-Michael reaction.

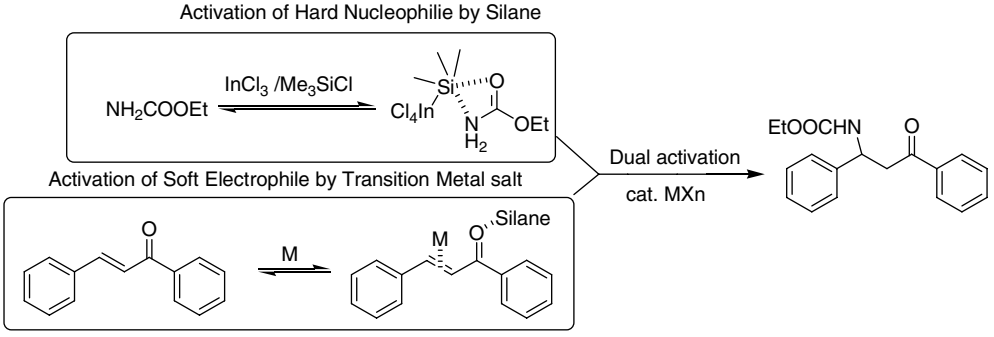
Next, we want to establish a novel entry of enantioselective aza-Michael reactions of chalcones with carbamates. While these recent methods directly afforded usefully aromatic N-protected β-amino carbonyl adducts, the catalytic, enantioselective aza-Michael reactions, which are of potentially great practical importance, have until now remained elusive,[14] in other words, it is still one of the major challenges in synthetic

Table 2. Aza-Michael reactions of various carbamates with chalcones catalyzed by indium salt/TMSCl catalyst system



Entry[a]	Solvent	R^1	R^2	H-NR	Yield[c] (%)
1	Toluene	Ph	H	2-Oxa.[b]	46
2	CH_3CN	Ph	H	NH_2CBZ	49
3	CH_3CN	Ph	*p*-Cl	NH_2COOEt	47
4	Toluene	Ph	*o*-Cl	NH_2COOEt	72
5	Toluene	CH_3	H	NH_2COOEt	86
6	Toluene	Ph	*o*-OCH_3	NH_2COOEt	70
7	CH_3CN	Ph	*p*-OCH_3	NH_2COOEt	34
8	Toluene	*p*-OCH_3–C_6H_4	H	NH_2COOEt	47
9	Toluene/CH_3CN[d]	Ph	*p*-NO_2	NH_2COOEt	21
10	Toluene/CH_3CN[d]	*p*-OCH_3–C_6H_4	*p*-CH_3	NH_2COOEt	34
11	CH_3CN/CH_2Cl_2[e]	Ph	*p*-CH_3	2-Oxa.[b]	59
12	CH_3CN	Ph	*p*-CH_3	NH_2CBZ	52
13	CH_3CN	Ph	*p*-OCH_3	NH_2CBZ	45
14	CH_3CN	Ph	*o*-Cl	NH_2CBZ	56

[a] All reactions were carried out using 10 mol % of $InCl_3$ as the catalyst, 100 mmol % of TMSCl as an additive, chalcone (0.5 mmol), carbamates (0.6 mmol) in 2 mL solvent, 24 h, at rt.
[b] 2-Oxa. is refer to oxazolidinine.
[c] Isolated yield.
[d] Toluene–CH_3CN = 1:1.
[e] CH_3CN–CH_2Cl_2 = 2:1.



Scheme 1. Aza-Michael addition via dual activation of carbamates and chalcones in combination of catalytic transition metal salt and TMSCl.

organic and organometallic chemistry. Now, we wish to report subsequently the additional enantioselective aza-Michael reactions of carbamates and chalcones using the effective transition metal salts/TMSCl catalyst system firstly.

In a preliminary screen of aza-Michael reaction, we evaluated different ligands, such as diamines, amino acids, in this combined catalyst system ($InCl_3$–TMSCl) for the catalysis of ethyl carbamate with β-phenylenone. The best results were obtained with D-camphoric acid (**2**) as the ligand, which afforded the N-protected β-amino carbonyl adduct in 55% ee and 35% yield after 24 h (Fig. 1).[15] Although L-proline (**1**) displayed a moderate stereoselectivity in this model reaction, the conversion is low (below 20%). We also compared a variety of different commercially available chiral amines under standard conditions with the same catalyst system and failed to give significant amounts of the desired product (below 10% yield). As revealed in Figure 1, this enantioselective aza-Michael reaction is readily accomplished in CH_3CN and toluene with a good stereoselectivity. THF is not a suitable solvent in the aza-Michael reaction with the present catalyst system.

During the course of screening studies for aza-Michael reaction catalyst, various transition metal salts were identified as promising catalysts (Table 3). $InCl_3$ gave the best results compared to other transition metal salts. Although most of transition metal salt-based catalyst systems gave a moderate stereoselectivity, the conversion is not good because acid is an unfavorable reagent for destroying of TMSCl in this reaction. The stronger Lewis acid, $ZrOCl_2$, could promote the reaction occurred in a higher yield, unfortunately, the value of ee % is low. A low temperature can increase the stereoselectivity of the product largely, but the conversion is poor and most of start material could be recovered.

In conclusion, we developed a new catalytic aza-Michael reaction of chalcones and carbamates promoted by the combination of indium(III) salts and TMSCl. Dual acti-

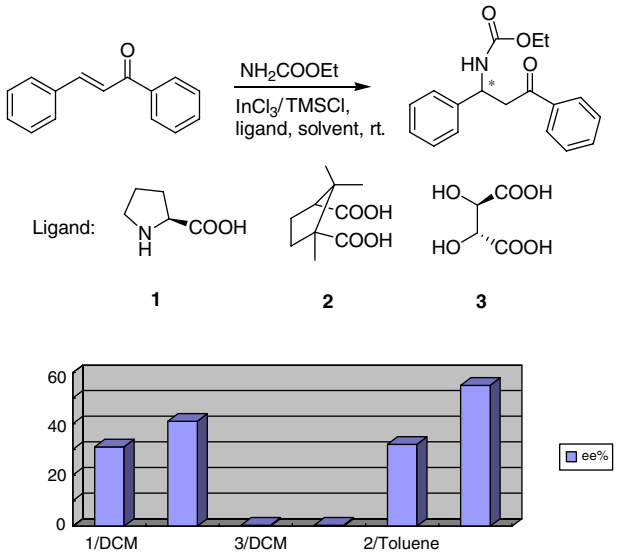


Figure 1. The effects of chiral acids and solvents in the stereoselectivity of aza-Michael addition product: 0.25 mmol of chalcone, 1.2 equiv of ethyl carbamate, 10 mol % of $InCl_3{\cdot}4H_2O$, 1.2 equiv of TMSCl, 20 mol % of chiral organic acid used as ligand, 2 mL of solvent, room temperature, 24 h.

Table 3. Catalytic activity of transition metal salts in enantioselective aza-Michael reaction of ethyl carbamate and chalcone[a]

Entry	Lewis acid catalyst	Yield[b] (%)	ee (%)
1	$InCl_3{\cdot}4H_2O$	31	60
2	$Cu(OTf)_2$	27	38
3	$FeCl_3{\cdot}6H_2O$	20	46
4	$Mg(ClO_4)_2$	27	45
5	$Ni(ClO_4)_2{\cdot}6H_2O$	14	52
6	$Sc(OTf)_3$	19	50
7	$ZrOCl_2{\cdot}8H_2O$	59[c]	14

[a] Reaction conditions: 0.25 mmol of chalcone, 1.2 equiv of carbamate, 10 mol % of Lewis acid, 4 equiv of TMSCl, 2 mL CH_3CN, D-camphoric acid, 20 mol %; at room temperature, for 24 h.
[b] Isolated yields.
[c] GC yield.

vation of both hard nucleophiles and soft electrophiles is the key to this reaction. This work offers good examples for the combination of Lewis acid and TMSCl catalyst systems for the novel aza-Michael reactions of carbamates with chalcones. Application to enantioselective variants also discussed in this article, and a moderate stereoselectivity (up to 60% ee) was obtained when D-camphoric acid used as the ligand. Further studies are currently underway to expand the scope of the reaction to other enones with carbamates and overcome the low reactivity with chalcones.

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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.2006.12.137.

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14. For enantioselective aza-Michael reaction, see review: Xu, L. W.; Xia, G. C. *Eur. J. Org. Chem.* **2005**, 633, and references cited therein.
15. The analysis of enantiomeric excess was performed using a Hewlett–Packard HPLC and a Daicel Chiral OJ column (25% *i*-PrOH–75% *n*-hexane, flow 0.5 mL/L, 243 nm), $t = 18.5$ min (minor), $t = 25.2$ min (major).