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Highly efficient phosphine-catalyzed aza-Michael reactions of α,β-unsaturated compounds with carbamates in the presence of TMSCl

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Abstract—Aza-Michael reactions of enones with carbamates took place efficiently in the presence of a catalytic amount of phosphine and TMSCl to afford the total products in high yields. The new catalytic system was also efficient in the aza-Michael reaction of chalcone, which was difficult to react with carbamates by transition metal salts catalysts.

With the growing realization that some β-amino carbonyl compounds display significant biological activities, the development of novel synthetic methods leading to β-amino ketone, β-amino acids or their derivatives has attracted much attention in organic synthesis.[1] Among the traditional methods for generating β-amino carbonyl compounds, Mannich-type reaction is one of the classical and powerful methods, the reactions of enolates either with imines are established processes for the synthesis of these moieties through carbon–carbon bond formation.[2] However, due to the harsh reaction conditions and the long reaction times, the classic Mannich reaction presents serious disadvantages.[3] Alternatively, owing to simplicity and atom economy, the more widely used method is the conjugated addition of nitrogen nucleophiles to α,β-unsaturated enones (aza-Michael reaction). Aza-Michael addition of a nitrogen-centered nucleophile is a convenient way to introduce amine-based functionality to a β-carbon attached to an electron-withdrawing group.[4] Following this strategy, very recently various nitrogen linked functionalized Michael adducts have been synthesized.[5] The conjugated addition of nucleophiles to α,β-unsaturated compounds usually requires basic conditions or acid catalysis.[6] To avoid typical disadvantages resulting from the presence of such catalyst, a large number of alternative procedures have been developed in the past few years.[7–11] However, most methods for intermolecular conjugated addition to unsaturated ketones reported to date describe the addition of alkyl or aryl amines. Because carbamates are weakly nucleophiles, many catalysts are practically ineffective in catalyzing a similar reaction with carbamates.[4,12] Although recent advances have made this route more attractive, development of cheaper, simpler and more efficient catalyst, especially which can be applied to weakly nucleophilic carbamates, is highly desirable.

Phosphines and their derivatives were used as stoichiometric reagents or catalyst in organic synthesis and organic reaction, including the Wittig reaction,[13] Staudinger reaction,[14] Mitsunobu reaction,[15] Baylis–Hillman[16] and other well-known 'name' reaction.[17] However, to the best of our knowledge, there has not been reported the aza-Michael reaction of α,β-unsaturated compounds catalyzed by phosphine and it's derivatives.

The previous works[5] promoted us to investigate the aza-Michael addition reactions of chalcone. At first, we discovered that the phosphine ligand alone with TMSCl was actually a more active catalyst. In the presence of catalytic amounts of triphenylphosphine and TMSCl, we observed that the direct addition of carbamates to α,β-unsaturated ketones in high yield. Several phosphines were tested using the 2-cyclohexen-1-one as a

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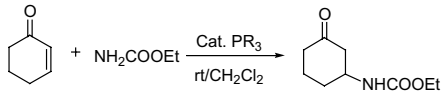
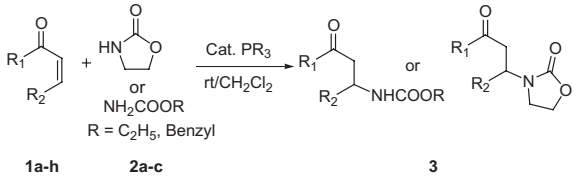
Table 1. Evaluation of phosphine as catalysts in aza-Michael reaction of cyclohexenone with ethyl carbamate



Entry[a]	Phosphines	Additives	Time (h)	Yields (%)[b]
1	PPh_3	—[c]	24	0
2	PPh_3	TMSCl	15	95
3	PPh_3	TMSCl	8	82
4	$P(n\text{-}Bu)_3$	—[c]	24	0
5	$P(n\text{-}Bu)_3$	TMSCl	15	Quant.
6	TPPTS[d]	TMSCl	15	96
7	Et_3N	TMSCl	24	Trace
8	Pyridine	TMSCl	24	Trace

[a] Reactions were conducted with catalyst (10 mol %), enone (1 mmol), ethyl carbamate (1.2 mmol), Me_3SiCl (1.1 mmol) in dichloromethane (4 mL) at room temperature.
[b] Isolated yield.
[c] No addition of Me_3SiCl.
[d] TPPTS is tris(3-sulfophenyl)phosphine.



Scheme 1.

benchmark (Table 1). Tributylphosphine was more reactive than triphenylphosphine under the same conditions, and nitrogen-based catalysts were not effective in this aza-Michael reaction. And there are no product for this reaction in the absence of TMSCl.

Aza-Michael reactions of other various chalcone derivatives with carbamates in dichloromethane at room temperature were also investigated (Scheme 1, Table 2). These enones provided the corresponding β-amino ketone in good isolated yields. In contrast to previous transition metal catalysts, PBu_3/TMSCl catalytic system could also mediate aza-Michael addition of carbamates to chalcone and its derivatives. Simple carbamates such as ethyl carbamate, were suitable nucleophiles and moderate yields were obtained with the synthetically more useful benzyl carbamate. Although carbamates are very weakly nucleophiles, some chalcone derivatives were similarly effective substrates in the aza-Michael reaction, which allows the introduction of the amide group. However, electro-poor Br or NO_2-substituted chalcones worked unfavorably to give corresponding in low yields (entries 7–9). In this conjugate addition reaction, good to excellent yields of β-amino ketones were obtained with several cyclic and acyclic enones (entries 1, 2 and 10). Benzyl carbamate, ethyl carbamate reacted smoothly with 2-cyclohexen-1-one, 3-penten-2-

Table 2. Aza-Michael reactions of various carbamates with enones[19]

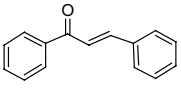
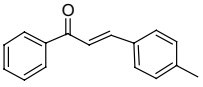
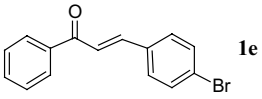
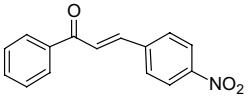
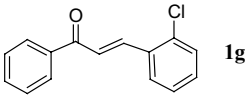
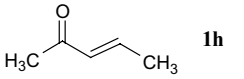
Entry[a]	Enone	Carbamate	Yield (%)[b]
1	 **1a**	NH_2CBZ **2a**	98
2	 **1b**	NH_2CBZ **2a**	92
3	 **1c**	NH_2CBZ **2a**	64
4	**1c**	NH_2COOEt **2c**	68
5	**1c**		45
6	 **1d**	NH_2COOEt **2c**	63
7	 **1e**	NH_2CBZ **2a**	38

Table 2 (*continued*)

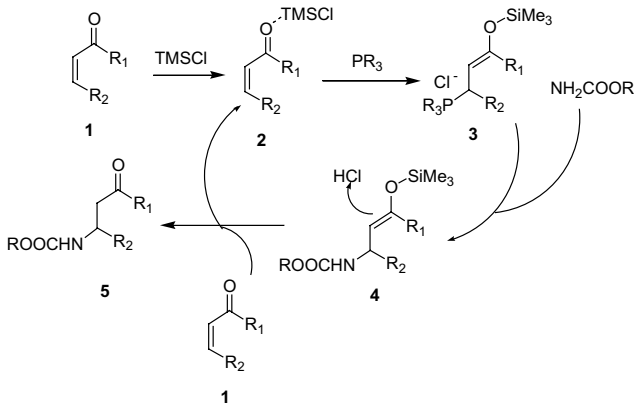
Entry[a]	Enone	Carbamate	Yield (%)[b]
8	 **1f**	NH_2COOEt **2c**	trace
9	 **1g**	NH_2COOEt **2c**	32
10	 **1h**	NH_2CBZ (**2a**)	98

[a] Reactions were conducted with catalyst ($P(n\text{-}Bu)_3$, 10 mol%), enone (1 mmol), 1.2 mmol of ethyl carbamate or benzyl carbamate (NH_2CBZ), Me_3SiCl (1.1 mmol) in dichloromethane (4 mL) at 30 °C for 24 h.
[b] Isolated yield.

one and 2-cyclopetenone to give corresponding aza-Michael adducts in high yields.

Although the role of TMSCl is not completely understood, it may be explained in terms of Lewis acid, which activates the carbonyl group. A plausible mechanism for the aza-Michael reaction was similarly to the previous related mechanism,[18] initial interaction by the TMSCl to the α,β-unsaturated ketone **1** results in activation of enones, and phosphinium enolate **3** was obtained by the conjugate addition of phosphine. Then phosphinium enolate was deprotonate an equivalent of carbamate to form the intermediate **4**, which facilitated the conjugate addition. Proton transfer and elimination of TMS-group from the intermediate gave the corresponding β-amino ketone **5** and resulted in the regeneration of TMSCl and intermediate to complete the cycle (Scheme 2).

In conclusion, we have demonstrated that the conjugate addition of enones especially chalcone with a less nucleophilic carbamates can be accomplished on phosphine/TMSCl catalyst system under very mild conditions. Apart from experimental simplicity, the advantages of this methodology is the use of a very cheap catalyst and the insensitivity of the reaction mixture towards air. The catalyst systems based on the combination of phosphine and TMSCl was found to be a highly active catalyst for aza-Michael reaction of chalcone and cyclic enones with carbamates. Although the mechanism of the reaction is still unclear, asymmetric catalysis based on the catalyst might be possible. We are currently investigating the development of an enantioselective catalytic process. Further study along this line is now in progress.



Scheme 2.

Acknowledgements

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19. General procedure for conjugate addition of carbamate to enone: Phopshine (0.1 mmol), carbamate (1.2 mmol) and the enones (1 mmol) were dissolved in dichloromethane (3 mL). Then TMSCl (1.1 mmol) was added in one portion. The mixture solution was stirred at 30 °C and was monitored by TLC (general for 24 h). After completion of the reaction, the mixture was quenched with 5 mL saturated aqueous sodium hydrogen carbonate, and the aqueous layer was extracted with chloroform. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (eluting solvent EtOAc/petrol ether). All the compounds were identified by GC–MS (Agilent 6890N GC/5973N MS, HP-5MS) and usual spectral methods. Selected spectral data of new compounds, Table 1, entry 2: ^{1}H NMR: δ 4.96 (br s, 1H), 4.05 (m, 2H), 3.89 (m, 1H), 2.63 (m, 2H), 2.34–2.00 (m, 4H), 1.62 (m, 2H), 1.19 (d, $J = 6.4$, 3H); ^{13}C NMR: δ 209.4, 157.8, 61.3, 50.2, 48.1, 41.0, 31.3, 22.1, 14.7; GC–MS, m/z 185. Anal. Calcd for $C_9H_{15}NO_3$: C 58.38, H 8.11, N 7.57. Found: C 58.33, H 8.13, N 7.59. Table 2, entry 3: ^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.88 (d, $J = 7.2$ Hz, 2H), 7.54 (t, $J = 7.2$ Hz, 1H), 7.44–7.22 (m, 12H), 5.89 (br s, 1H), 5.33 (d, $J = 6.0$ Hz, 1H), 5.09 (s, 2H), 3.68 (dd, $J = 16.7$ Hz, $J = 4.2$ Hz, 1H), 3.45 (dd, $J = 16.7$ Hz, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHZ, $CDCl_3$): δ 197.8, 155.7, 141.2, 136.6, 136.3, 133.4, 128.6, 128.5, 128.1, 127.5, 126.3, 66.8, 51.8, 43.9. GC–MS, m/z 359. IR (Solid) $\nu_{max}/cm^{-1} = 3366$, 3029, 2965, 1721, 1681, 1526, 1291, 1241, 1221, 1022, 746, 699. Anal. Calcd for $C_{23}H_{21}NO_3$: C 76.88, H 5.85, N 3.90. Found: C 76.86, H 5.85, N 3.92. Entry 4: ^{1}H NMR: δ 7.88 (d, $J = 7.2$ Hz, 2H), 7.55–7.21 (m, 8H), 5.72 (br s, 1H), 5.28 (dd, $J_1 = 6.4$ Hz, $J_2 = 14.0$ Hz, 1H), 3.67 (m, 2H), 3.40–3.46 (m, 1H), 1.21 (t, $J_1 = 6.4$ Hz, $J_2 = 14.0$ Hz, 3H); ^{13}C NMR: δ 198.2, 159.8, 156.2, 141.6, 136.8, 133.6, 128.9, 128.3, 127.7, 61.2, 51.9, 44.2, 14.8; GC–MS, m/z 297, 224, 208, 178, 134, 105, 77, 51, 29. Anal. Calcd for $C_{18}H_{19}NO_3$: C 72.73, H 6.40, N 4.71. Found: C 72.71, H 6.39, N 4.72. Entry 5: ^{1}H NMR: δ 7.95 (d, $J = 7.2$ Hz, 2H), 7.54 (t, $J = 7.24$ Hz, 1H), 7.45–7.24 (m, 7H), 5.36 (dd, $J_1 = 6.0$ Hz, $J_2 = 8.6$ Hz, 1H), 4.22 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz, 1H), 3.57 (br s, 2H), 3.43 (dd, $J_1 = 8.0$ Hz, $J_2 = 16.0$ Hz, 1H); ^{13}C NMR: δ 197.2, 157.9, 138.7, 136.6, 133.7, 129.1, 129.0, 128.4, 127.5, 62.2, 54.6, 43.4, 40.6; GC–MS: m/z 295; Anal. Calcd for $C_{18}H_{17}NO_3$: C 73.24, H 5.76, N 4.75. Found: 73.21, H 5.75, N 4.79. Entry 6: ^{1}H NMR: δ 7.88 (d, $J = 7.2$ Hz, 2H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.41 (d, $J = 7.6$ Hz, 2H), 7.22 (m, 2H), 7.09 (m, 2H), 5.64 (br s, 1H), 5.23 (dd, $J_1 = 6.4$ Hz, $J_2 = 12.0$ Hz, 1H), 4.08 (dd, $J_1 = 6.8$ Hz, $J_2 = 14.0$ Hz, 2H), 3.65 (m, 1H), 3.40 (dd, $J_1 = 6.0$ Hz, $J_2 = 16.4$ Hz, 1H), 2.27 (s, 3H); 1.20 (t, $J_1 = 6.4$ Hz, $J_2 = 15.2$ Hz, 3H); ^{13}C NMR: δ 197.9, 155.9, 138.4, 137.1, 136.6, 133.3, 129.3, 128.6, 128.1, 126.3, 60.9, 51.4, 44.1, 31.5, 14.2; GC–MS, m/z 311. Anal. Calcd for $C_{19}H_{21}NO_3$: C 73.31, H 6.75, N 4.50. Found: C 73.26, H 6.72, N 4.54. Entry 7: ^{1}H NMR: δ 7.85 (d, $J = 7.2$ Hz, 2H), 7.57–7.20 (m, 12H), 6.00 (br s, 1H), 5.26 (dd, $J_1 = 6.0$ Hz, $J_2 = 13.2$ Hz, 1H), 4.77 (br s, 2H), 3.65 (m, 1H), 3.40 (dd, $J = 5.2$ Hz, $J = 16.8$ Hz, 1H); ^{13}C NMR: δ 197.9, 157.0, 156.0, 140.7, 136.6, 136.5, 133.9, 132.0, 129.0, 128.7, 128.5, 128.3, 127.9, 121.5, 67.1, 51.4, 43.8. Anal. Calcd for $C_{23}H_{20}NO_3Br$: C 63.01, H 45.66, N 3.20. Found: C 62.99, H 45.65, N 3.25. Entry 9: ^{1}H NMR: δ 7.88 (d, $J = 7.2$ Hz, 2H), 7.57 (m, 1H), 7.41 (m, 2H),7.24 (m, 2H), 6.81 (m, 2H), 5.63 (br s, 1H), 5.22 (dd, $J_1 = 6.4$ Hz, $J_2 = 14.0$ Hz, 1H), 4.07 (dd, $J_1 = 6.8$ Hz, $J_2 = 14.0$ Hz, 2H), 3.64–3.74 (m, 2H), 3.37–3.43 (m, 1H), 1.20 (t, $J_1 = 6.4$ Hz, $J_2 = 15.2$ Hz, 3H); ^{13}C NMR: δ 198.2, 159.0, 156.1, 136.9, 133.7, 133.6, 128.9, 128.3, 127.8, 114.2, 61.1, 55.5, 51.5, 44.3, 14.8. Anal. Calcd for $C_{18}H_{18}NO_3Cl$: C 65.16, H 5.43, N 4.22. Found: C 65.12, H 5.41, N 4.25.