Phase-transfer catalytic aza-Michael addition of *tert*-butyl benzyloxycarbamate to electron-deficient olefins†

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A highly efficient phase-transfer catalytic aza-Michael addition of *tert*-butyl benzyloxycarbamate to a wide range of electron-deficient olefins is presented (90–99%).

Since the β-amino carbonyl functionality has been recognized as not only a key structure of biologically important natural products including β-lactams but also a versatile nitrogen-containing intermediates such as amino alcohols, diamines, and β-amino acid derivatives, numerous methods have been developed for the efficient synthesis of β-amino carbonyl compounds.[1] The synthetic strategies for the β-amino carbonyls reported to date, can be categorized into two basic types as shown in Scheme 1: (A) C–C bond formation by the Mannich-type reaction;[2] the addition of carbon nucleophiles to imines and (B) C–N bond formation by the aza-Michael-type reaction;[3] the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds or activated olefins.

Most of aza-Michael reactions (B) use aliphatic/aromatic amines, alkoxyamines, aldoximes, hydrazoic acid, and azide ion as nitrogen nucleophiles.[4] While sufficiently reactive nitrogen nucleophiles (such as amines) can perform the aza-Michael reactions by themselves, less reactive nucleophiles generally require catalysts (Brønsted or Lewis acid catalysts) or catalytic amounts of a strong base which can activate either the Michael acceptor or the nitrogen nucleophiles, respectively.

Among the less reactive nucleophiles, carbamates also usually need Brønsted acids or several expensive transition metal-based Lewis acids.[5] Furthermore, the scope of the substrate was restricted to α,β-unsaturated ketones (enones) or α,β-unsaturated aldehydes (enals). In this communication, a new convenient aza-Michael reaction system using carbamates as a nucleophile with a wide range of substrate scope is reported.

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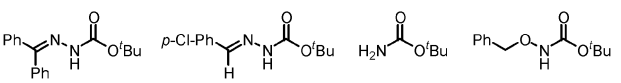
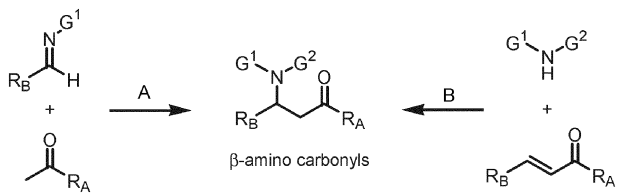


2 3 4 5

To develop a new efficient and versatile aza-Michael reaction, we attempted to use a phase-transfer catalytic reaction system because it provides various advantages in terms of operational simplicity as well as economic- and environmetal-concerns.[6] We first designed carbamate-type aza-Michael donors such as **2** and **3**, nitrogen variant of the O'Donnell substrate **1**. It is well known that **1** is an excellent Schiff base of a glycine ester frequently used for the preparation of various α-amino acid derivatives by the alkylation of its enolate under phase-transfer catalytic conditions.[7] The newly prepared carbamates (**2**, **3**) and commercially available *tert*-butyl carbamate (**4**) were employed to examine if they are suitable nitrogen nucleophiles in the phase-transfer catalytic aza-Michael addtion. Reactions of each carbamate with 2-cyclohexen-1-one (**6a**) as the Michael acceptor and solid KOH in the presence of 10 mol% of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst (PTC) in toluene, however, did not afford the Michael adduct except the self-aldol product of **6a** (10–25%) (entries 1–3, Table 1). The further variation in the amount of each reagent with the combination of other solvents at different reaction temperatures were not effective. In the negative results of the serial attempts, the reactivities of the Boc-hydrazones (**2**, **3**) and the normal carbamate (**4**) were not strong enough under the phase-transfer catalytic reaction conditions. We envisioned that such a low nucleophilicity of the anions of the carbamates in the PTC-mediated aza-Michael reaction could be increased by introducing an oxygen moiety such as a benzyloxy group at the nitrogen of the carbamates, through the α-effect.[8] Among the obtainable *N*-oxycarbamate compounds, *tert*-butyl



Scheme 1 Approaches to β-amino carbonyl compounds.

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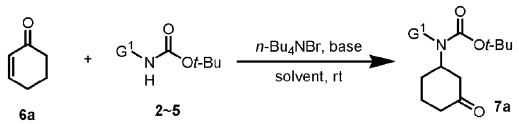
† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for all new compounds, copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/b800130h

Table 1 System screening for the phase-transfer catalytic aza-Michael reaction[a]



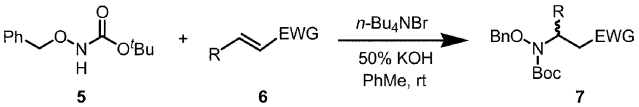
Entry	Carbamate	Base (equiv.)	Solvent	Time	Yield (%)[b]
1	**2**	Solid KOH (2.0)	PhMe	24 h	NR[c]
2	**3**	Solid KOH (2.0)	PhMe	24 h	NR[c]
3	**4**	Solid KOH (2.0)	PhMe	24 h	NR[c]
4	**5**	Solid KOH (2.0)	PhMe	10 h	44
5	**5**	50% KOH (2.0)	PhMe	10 h	76
6	**5**	50% KOH (1.2)	PhMe	10 min	99
7	**5**	50% KOH (1.2)	Et_2O	20 min	90
8	**5**	50% KOH (1.2)	CH_2Cl_2	20 min	75

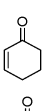
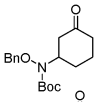
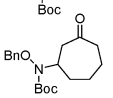
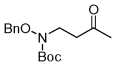
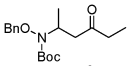
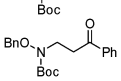
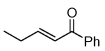
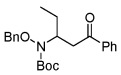
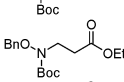
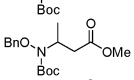
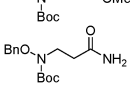
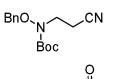
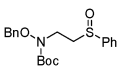
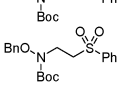
[a] All reactions were carried out with TBAB (0.1 mmol), enone **6a** (1.0 mmol) and carbamate **2–5** (2.0 mmol) under the given conditions at room temperature. [b] Isolated yield of **7a** after purification by flash column chromatography. [c] No desired reaction occurred.

benzyloxycarbamate (**5**) was selected as a reinforced aza-Michael donor because of not only its enhanced nucleophilicity but also its conversion to various functionalities by selective reduction and its commercially availability.[9] Fortunately, as we expected, **5** afforded the aza-Michael adduct **7a** even though the yield (44%) and the reaction time (10 h) needed to be improved (entry 4, Table 1). We presumed that the modest chemical yield and the slightly longer reaction time might be due to the self-aldol condensation of enone and a retro-aza-Michael reaction of the initially formed product under the basic conditions. A dramatic increase in the chemical yield (99%) without the self-aldol condensation and a remarkable decrease in the reaction time (10 min) were finally accomplished both by employing 50% aqueous KOH solution as a base instead of solid KOH, and by reducing the amount of the base from 2.0 equiv. to 1.2 equiv. (entry 6).[10] The subsequent solvent screen proved that toluene was the most effective. It should be noted that it took more than 20 h with low chemical yield (33%) under the same reaction conditions without PTC.

To explore the scope of the reaction, a number of electron-deficient olefins were examined under the optimized conditions (Table 2). As shown in Table 2, newly established phase-transfer catalytic aza-Michael reaction system was highly effective for cyclic and acyclic enones (entries *a–f*) as well as for various carboxylic acid derivatives and their sulfur analogs

Table 2 Scope of the phase-transfer catalytic aza-Michael addition[a]

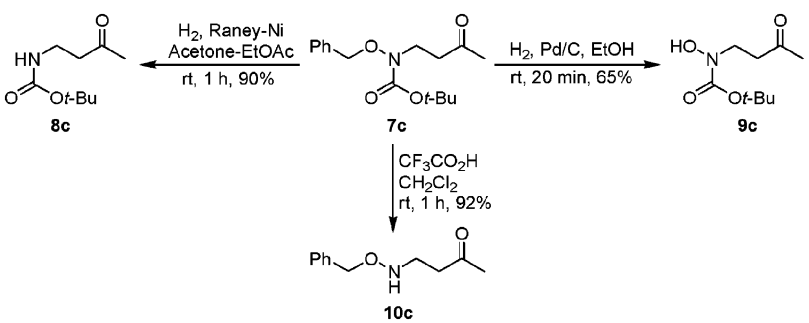


Entry	6	7	Time	Yield (%)[b]
a			5 min	99
b			10 min	99
c			10 min	99
d			20 min	99
e			5 min	90
f			5 min	96
g			5 min	95
h			12 h	94
i			3 h	90
j			5 min	96
k			5 min	99
l			5 min	99

[a] All reactions were carried out with TBAB (0.1 equiv.), electron-deficient olefin **6** (1.0 equiv.), *tert*-butyl benzyloxycarbamate **5** (2.0 equiv.), 50% *aq.* KOH (1.2 equiv.) in toluene at room temperature. [b] Isolated yield of **7** after purification by flash column chromatography.

(entries *g–l*). To the best of our knowledge, this is the first report to employ carbamate as a nitrogen atom Michael donor in a phase-transfer catalytic Michael reaction to afford a wide range of carbonyl compounds and their analogs having β-amino-functionality with very high chemical yields.

Then we investigated the conversion of **7c** to various useful intermediates. From the point of view of further



Scheme 2 Deprotection of the aza-Michael adduct.

transformation of the amino functionality, it would be better to remove the benzyloxy protective group prior to the Boc group. With the deprotection of benzyloxy group, we were interested in removing the benzyl moiety only, leaving the oxygen bound to the nitrogen atom since the hydroxyamino functional group also has a quite useful synthetic utility. From a series of trials on the regeneration of amino- or hydroxyamino-functionality, the hydrogenolysis with Raney nickel catalyst in a mixed solvent of acetone and ethyl acetate, and hydrogenolysis with palladium on activated carbon in ethanol afforded the debenzyloxylated product **8c** (90%) and the debenzylated product **9c** (85%), respectively (Scheme 2). Selective deprotection of Boc group of **7c** (92%) was accomplished by treatment with trifluoroacetic acid as well.

In summary, we developed a highly efficient phase-transfer catalytic aza-Michael reaction with commercially available *tert*-butyl benzyloxycarbamate as a protected nitrogen nucleophile. The notable features of this novel aza-Michael reaction system lie, especially, in the wide scope of substrates and the advantages came from phase-transfer catalysis. We are currently investigating an asymmetric version of this methodology, and it will be reported in the near future.

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9 Compound **5** can be purchased from Aldrich Co.

10 Other bases such as LiOH, NaOH, CsOH, K_2CO_3, BEMP, P2-Et as well as more diluted aqueous KOH solutions than 50% aq. KOH did not provide better result than 50% aq. KOH.

