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Oxidative Mannich Reaction of *N*-Carbobenzyloxy Amines with 1,3-Dicarbonyl Compounds

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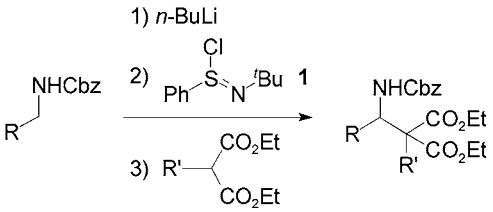
ABSTRACT



Efficient carbon–carbon bond formation at the α-position of nitrogen was established by one-pot oxidative Mannich reaction of *N*-carbobenzyloxy (Cbz) amines with 1,3-dicarbonyl compounds using *N-tert*-butylbenzenesulfinimidoyl chloride as an oxidant.

The Mannich reaction is a fundamental carbon−carbon bond-forming reaction in organic synthesis,[1] and a variety of nitrogen-containing pharmaceuticals and bioactive molecules such as *β*-amino acids and *β*-lactams are synthesized by this reaction. Recently, catalytic enantioselective Mannich reactions have been dramatically developed, and they offer a practically useful method for the preparation of optically active amino compounds.[2,3] However, inherent weak points of the Mannich reaction have not yet been solved: it is well-known that Mannich reaction of aliphatic aldimines that have enolizable α-protons does not give a sufficient yield of Mannich product because the aliphatic imines are prone to isomerize to enamines, causing self-condensation with imines as a side reaction.[4] More problems in the isolation and stability of imines are encountered when an electron-withdrawing protecting group is attached on the nitrogen of aliphatic imines. Therefore, development of a new synthetic methodology for Mannich reactions with broader applicability is strongly needed.

To establish a widely applicable Mannich reaction, the following three points are essential: (1) the mild generation of imines, (2) the addition of carbon nucleophiles to imines under mild conditions, and (3) the easy cleavage of the N-protecting group after the Mannich reaction. We considered that the first point would be possible by utilizing the oxidation of amines with *N-tert*-butylbenzenesulfinimidoyl chloride (**1**),[5] which oxidizes various amines to the corre-

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(1) Reviews: Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 893.

(2) Reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (b) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, *4*, 563−572. (c) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis Supplement I*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Chapter 29.5. (d) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102−112. (e) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089−2100. (f) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348−352.

(3) For recent reports of catalytic asymmetric Mannich reactions, see: (a) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778−2779. (b) Mitsumori, S.; Zhang, H.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040−1041. (c) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622−17623. (d) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700−6704. (e) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408−16409. (f) Ihori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 15528−15535. (g) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564−4567. (h) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256−11257.

(4) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489−508.

10.1021/ol0618095 CCC: $33.50

sponding imines under mild conditions.[6] The second and third points would be possible by generation of more electrophilic imines that have an electron-withdrawing N-protecting group such as the Cbz and Boc[7] groups and by employing carbon nucleophiles that show nucleophilicity under neutral conditions, e.g., active methylene compounds. Thus, we planned the one-pot oxidative Mannich reaction[8] of N-protected amines **2** that consisted of (i) oxidation (dehydrogenation) of **2** to the corresponding imine **3** and (ii) trapping **3** with carbon nucleophiles (Figure 1). We describe here the results obtained in the oxidative Mannich reaction of *N*-carbobenzyloxy (Cbz) amines with 1,3-dicarbonyl compounds such as malonate esters, β-keto esters, and 1,3-diketones using oxidation with **1**.

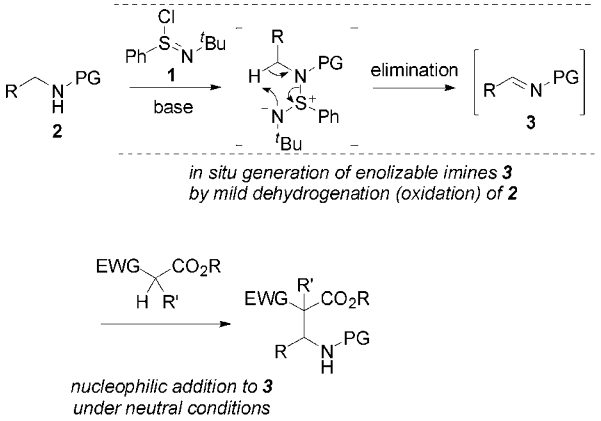
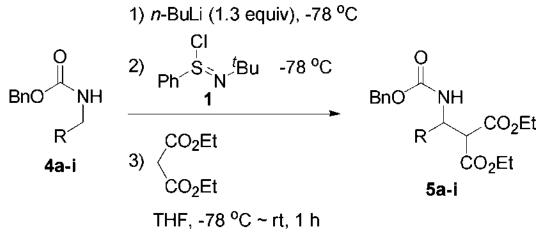


Figure 1. Oxidative generation of N-protected imines **3** from **2** and nucleophilic trapping.

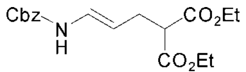
First, *N*-Cbz benzylamine (**4a**) was oxidized by treating lithiated **4a** with **1** at −78 °C, and the resulting *N*-Cbz imine was reacted with diethyl malonate in a one-pot manner. It was found that the **1**-mediated oxidation of **4a** proceeded smoothly at −78 °C, and diethyl malonate reacted with the formed *N*-Cbz imine during warming to room temperature to afford Mannich product **5a** in 92% isolated yield (Table 1, entry 1). Oxidative Mannich reaction of other *N*-Cbz benzylamine derivatives such as **4b** and **4c** also gave Mannich adducts **5b** and **5c** in 92 and 86% yields, respectively (entries 2 and 3). Interestingly, *N*-Cbz alkylamines such as **4d**−**h** gave the Mannich adducts **5d**−**h** in good to high yields (entries 4−7), though sterically hindered **4f** required a longer reaction time (10 h) (entry 6). These results suggest that enolizable aliphatic *N*-Cbz aldimines were readily formed by the oxidation with **1**, and the *N*-Cbz aldimines reacted with diethyl malonate efficiently under mild conditions. Protecting groups such as TBS and benzyl groups were not influenced in the oxidative Mannich reaction (entries 7 and 8). When *N*-Cbz allylamine (**4i**) was subjected to the present oxidative Mannich reaction, 1,4-adduct **5i′** was obtained as a major isomer along with 1,2-adduct **5i** in 89% combined yield (**5i**/**5i′** = 30/70, entry 9).

Table 1. One-Pot Oxidative Mannich Reaction of Various *N*-Cbz Amines **4a**−**i** with Diethyl Malonate



entry	R	product	yield (%)[a]
1	Ph (**4a**)	**5a**	92
2	4-MeC_6H_4 (**4b**)	**5b**	92
3	4-MeOC_6H_4 (**4c**)	**5c**	86
4	Ph$(CH_2)_2$ (**4d**)	**5d**	82
5	$CH_3(CH_2)_2$ (**4e**)	**5e**	88
6[b]	$(CH_3)_2CH$ (**4f**)	**5f**	73
7	*t*-BuMe$_2$SiOCH$_2$CH$_2$ (**4g**)	**5g**	87
8	BnO$(CH_2)_4$ (**4h**)	**5h**	92
9	CH_2=CH (**4i**)	**5i**	89[c]

[a] Isolated yield. [b] The reaction mixture was stirred for 10 h after the addition of diethyl malonate. [c] A mixture of **5i** and **5i′** (**5i**/**5i′** = 30/70).



5i′

1,3-Dicarbonyl compounds other than diethyl malonate were employed in the oxidative Mannich reaction of *N*-Cbz *p*-methoxybenzylamine (**4c**) (Table 2). First, some diethyl alkylmalonates (alkyl = methyl, ethyl, allyl, and benzyl) were used as a carbon nucleophile, and in each case, the Mannich products **6**−**9** bearing a quaternary carbon center were obtained in high yields (entries 1−4). Not only malonate esters but also β-keto esters efficiently reacted with *N*-Cbz imines: ethyl acetoacetate gave the adduct **10** in 89% yield as a mixture of diastereomers (55/45, entry 5). On the other hand, cyclic β-keto esters such as 2-carboethoxycyclopentanone and 2-carboethoxycyclohexanone gave the Mannich adducts **11** and **12** in 95 and 89% yields, respectively, as a single diastereomer (entries 6 and 7). 1,3-Diketone, acetylacetone, also reacted with *N*-Cbz aromatic imine to afford **13** in 92% yield (entry 8).

Oxidative Mannich reaction of *N*-Cbz alkylamine with various 1,3-dicarbonyl compounds was investigated using *N*-Cbz butylamine (**4e**) as a model substrate (Table 3). Similar to the results obtained in Mannich reaction of *N*-Cbz

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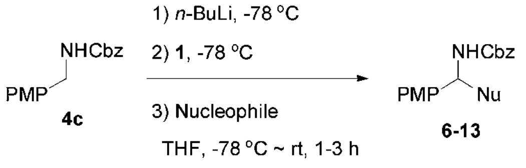
(5) Rewiew: Matsuo, J.-i. *J. Synth. Org. Chem. Jpn*. **2004**, *62*, 574−583.

(6) (a) Mukaiyama, T.; Kawana, A.; Fukuda, Y.; Matsuo, J.-i. *Chem. Lett*. **2001**, 390−391. (b) Matsuo, J.-i.; Kawana, A.; Fukuda, Y.; Mukaiyama, T. *Chem. Lett*. **2001**, 712−713. (c) Matsuo, J.-i.; Tanaki, Y.; Kido A.; Ishibashi, H. *Chem. Commun*. **2006**, 2896−2898.

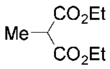
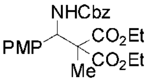
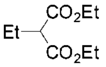
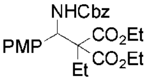
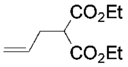
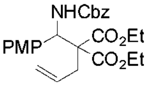
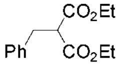
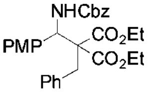
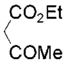
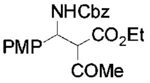
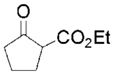
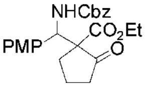
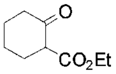
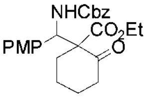
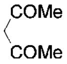
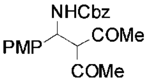
(7) *N*-Boc imines were prepared in two steps: Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem*. **1994**, *59*, 1238−1240.

(8) Catalytic oxidative Mannich reaction of tertiary amines: (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc*. **2003**, *125*, 15312−15313. (b) Li, Z.; Li, C.-J. *Eur. J. Org. Chem*. **2005**, 3173−3176. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc*. **2005**, *127*, 3672−3673. (d) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed*. **2005**, *44*, 6931−6933.

Table 2. One-Pot Oxidative Mannich Reaction of **4c** with Various 1,3-Dicarbonyl Compounds



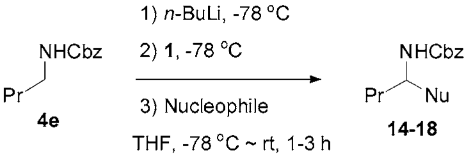
PMP: *p*-methoxyphenyl

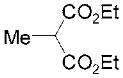
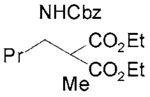
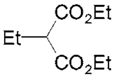
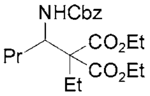
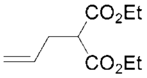
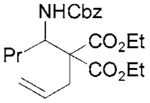
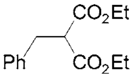
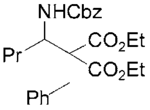
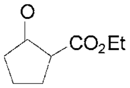
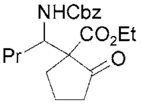
entry	nucleophile	product		yield (%)[a]
1			**6**	97
2			**7**	87
3			**8**	80
4			**9**	67
5			**10**	89[b]
6			**11**	95[c]
7			**12**	89[c]
8			**13**	92

[a] Isolated yield. [b] Diastereoisomeric ratio: 55/45. [c] A single diastereomer was obtained.

benzylic amine **4c** (Table 2), 1,3-dicarbonyl compounds efficiently reacted with *N*-Cbz aliphatic imine at room temperature to afford various Mannich adducts **14**−**18** in high yields. When cyclic *β*-keto ester was employed, a Mannich adduct (**18**) was obtained in 89% yield as a single diastereomer (entry 5).

Table 3. Oxidative Mannich Reaction of *N*-Cbz Butylamine (**4e**) with 1,3-Dicarbonyl Compounds



entry	nucleophile	product		yield (%)[a]
1			**14**	81
2			**15**	85
3			**16**	83
4			**17**	91
5			**18**	89

[a] Isolated yield.

The proposed mechanism of the present oxidative Mannich reaction is shown in Figure 2. Lithiated *N*-Cbz amines smoothly reacted with **1** at −78 °C to afford the intermediate **19**, and *N*-Cbz arylimines were formed immediately at −78 °C by elimination of *N*-*tert*-butylbenzenesulfenamide (**20**) via a five-membered transition state. On the other hand, the elimination of sulfenamide **20** was slow in the case of generating *N*-Cbz alkylimines, and it required elevated reaction temperatures (∼room temperature). In situ prepared *N*-Cbz imines were readily trapped with carbon nucleophiles by attack of the carbanion of the 1,3-dicarbonyl compound to protonated *N*-Cbz imines under neutral conditions.

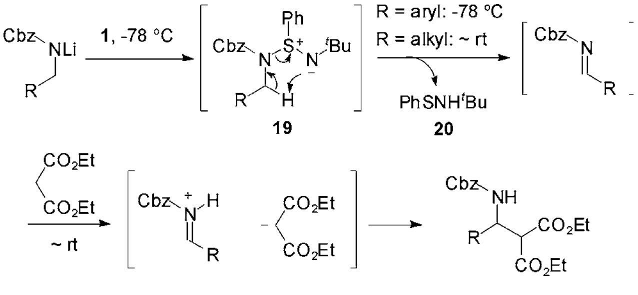


Figure 2. Proposed mechanism.

In summary, a variety of Mannich products have been directly obtained from *N*-Cbz amines by oxidation of *N*-Cbz amines with **1**, followed by addition of 1,3-dicarbonyl compounds. The characteristic point of the present method is that various *N*-Cbz aliphatic amines efficiently reacted with various 1,3-dicarbonyl compounds, which has been considered to be difficult.[9] Though several methods of carbon−carbon bond formation at the α-position of nitrogen have been reported, our method is straightforward and convenient.[10] It is expected that the synthetic utility of the present oxidative Mannich reaction will be broadened by developing a stereoselective reaction using chiral catalysts.[11]

Acknowledgment. The authors are grateful for the financial support from Takeda Science Foundation, and this work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: Experimental procedures and spectral data for Mannich adducts (**5a−i**, **6−18**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) An efficient nitro-Mannich reaction of aliphatic imines was reported: Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem*. **2005**, *70*, 549−555.

(10) (a) Stork, G.; Jaconson, R. M.; Levitz, R. *Tetrahedron Lett.* **1979**, 771−774. (b) Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* **1977**, *110*, 1852−1865. (c) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172−1176.

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