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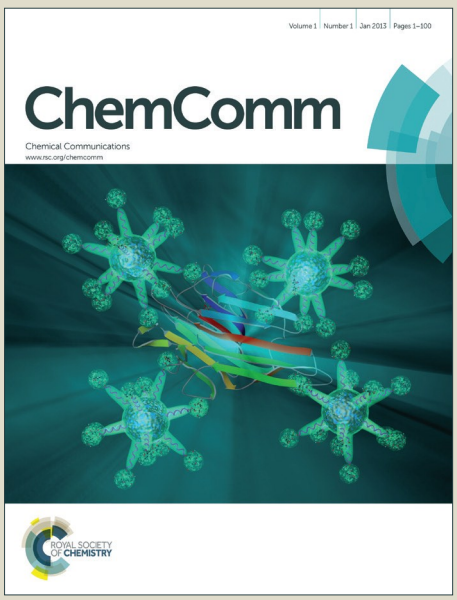

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Brønsted acid-catalyzed Mannich reaction through dual activation of aldehydes and *N*-Boc-imines

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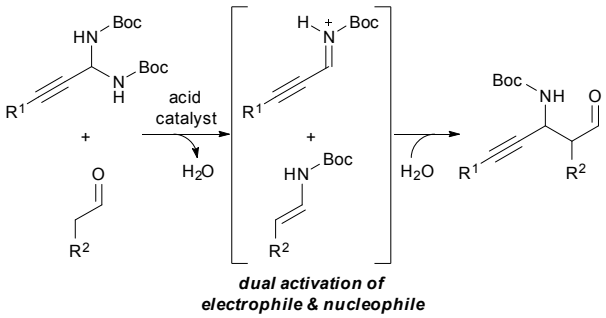
In the presence of a Brønsted acid catalyst, both aldehydes and *N*-Boc-aminals were converted to enecarbamates and *N*-Boc-iminium salts as activated nucleophiles and electrophiles, respectively, giving unprecedented Mannich adducts. The asymmetric variant of the present Mannich reaction has also been demonstrated with a chiral phosphoric acid catalyst.

Enolizable aldehydes have been used as nucleophiles in synthetic organic chemistry. In general, such aldehydes are required to be activated by converting to the corresponding enolates, enamines, enamides or enecarbamates,[1] due to minuscule amounts of nucleophilic enol form in the keto-enol equilibrium. Enamine catalysis, in which aldehydes and ketones form reactive enamine intermediates with amine catalysts in-situ, has been an active area of research for over a decade.[2] For instance, a number of amine-catalyzed Mannich reactions of in-situ generated enamines with imines have been developed to date, while applicable imines are somewhat limited.[2–4]

Recently we have developed a method for the in-situ generation of unprecedented *N*-Boc-imines having *C*-alkynyl groups from *N*-Boc-aminals under acidic conditions;[5] however, attempts to apply our method to the amine-catalyzed Mannich reaction were not successful probably due to the deactivation of the acid catalyst to generate imines by the amine catalyst. In this context, we became interested in the in-situ generation of enecarbamates instead of enamines to prevent the use of the amine catalyst under acidic conditions. In the presence of an acid catalyst, *N*-Boc-aminal is converted to *N*-Boc-imine (or *N*-Boc-iminium salt) as an activated electrophile along with the generation of *tert*-butyl carbamate, which might react with an aldehyde to give the corresponding enecarbamate as an activated nucleophile (Scheme 1). Herein, we report a Brønsted acid-catalyzed Mannich reaction of aldehydes with *N*-Boc-imines generated from *N*-Boc-aminals through dual activation of nucleophiles and electrophiles.



Scheme 1 Brønsted acid-catalyzed Mannich reaction through dual activation of *N*-Boc-aminals and aldehydes.

We first examined the in-situ generation of an enecarbamate from an aldehyde and an alkyl carbamate by a Brønsted acid catalyst. In the presence of a catalytic amount of binaphthol-derived phosphoric acid, the mixture of 3-phenylpropanal and *tert*-butyl carbamate in CH_2Cl_2 was found to give the desired enecarbamate and its derivatives (See the Supporting Information for details). Based on this result, the Mannich reaction between the in-situ generated *N*-Boc-imine and enecarbamate was then examined in the presence of a Brønsted acid catalyst.[6] The reaction of *N*-Boc-aminal **1a**, which is known to give the corresponding *N*-Boc-imine and *tert*-butyl carbamate under acidic conditions, with 3-phenylpropanal in CH_2Cl_2 did not proceed in the presence of benzoic acid and its derivatives (Table 1, entries 1–3). With more acidic catalysts, on the other hand, the desired Mannich adduct **2a** was obtained in low to moderate yields (entries 4–7), and diphenyl phosphate was found to afford the best result in terms of yield (entry 4). In the presence of a catalytic amount of diphenyl phosphate, the reactions of several *N*-Boc-aminals **1** with aldehydes afforded the corresponding *anti*-Mannich adducts **2** as major diastereomers (Table 2).

To evaluate the possibility of an asymmetric variant of the present reaction, binaphthol-derived chiral phosphoric acid (*S*)-

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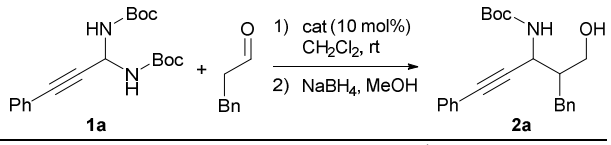
Table 1 Mannich reaction between *N*-Boc-aminal **1a** and 3-phenylpropanal[a]

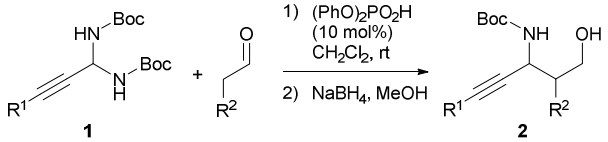


1a **2a**

Entry	Cat	Time (h)	Yield[b] (%)	*anti*/*syn*[c]
1	$PhCO_2H$	24	n.d.	-
2	$2\text{-}NO_2\text{-}C_6H_4CO_2H$	24	n.d.	-
3	$2,6\text{-}(HO)_2\text{-}C_6H_3CO_2H$	24	n.d.	-
4	$(PhO)_2PO_2H$	7	67	4.0/1
5	CF_3CO_2H	12	37	4.3/1
6	TsOH	4	41	4.8/1
7	TfOH	1.5	26	5.6/1

[a] The reaction of **1a** (0.10 mmol) with 3-phenylpropanal (0.30 mmol) was carried out in the presence of an acid catalyst (0.010 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. [b] Isolated as an inseparable diastereomixture. [c] Determined by ^1H NMR.

Table 2 Diastereoselective Mannich reaction between *N*-Boc-aminals **1** and aldehydes[a]



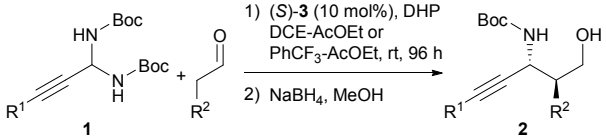
1 **2**

Entry	R^1	R^2	Time (h)	Yield[b] (%)	*anti*/*syn*[c]
1	Ph	Bn	7	67	4.0/1
2	Ph	*i*-Pr	12	62	2.7/1
3	Ph	Ph	10	66	3.0/1
4	$4\text{-MeO-}C_6H_4$	Bn	12	55	3.4/1
5	$4\text{-Br-}C_6H_4$	Bn	11	49	1.9/1
6	pentyl	Bn	8	44	18/1
7	Me_3Si	Bn	10	50	4.7/1

[a] The reaction of **1** (0.10 mmol) with an aldehyde (0.30 mmol) was carried out in the presence of diphenyl phosphate (0.010 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. [b] Isolated as an inseparable diastereomixture. [c] Determined by ^1H NMR.

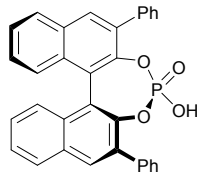
3 was then employed as catalyst.[7] In all cases examined, the enantiomerically enriched Mannich adducts were obtained in moderate yields (Scheme 2).[8] In the absence of 3,4-dihydro-2H-pyran (DHP), which can capture the generated *tert*-butyl carbamate, the yield was slightly decreased probably due to hydrolysis of *N*-Boc-aminal coupled with enecarbamate generation. The absolute configurations of the Mannich adduct were determined to be (3*R*,4*S*) by conversion to the known compound and comparison of HPLC retention times with the literature value.[9]

Mechanistically, we propose that the combination of *N*-Boc-aminal **1** and aldehyde in the presence of an acid catalyst led to the formation of the iminium intermediate **4** and the enecarbamate **5** (Scheme 3), which gave the coupling product **6** and then hydrolyzed Mannich adduct **7** (Path A). Alternatively, the reaction of the iminium intermediate **4** with enol as nucleophile could occur to give the Mannich adduct **7** (Path B). We then compared 3-phenylpropanal and its enecarbamate **5a** in the reaction with the isolable and available *N*-Boc-imine **8**[10] to determine which pathway is operative, and found that the reaction involving the enecarbamate was much faster (Scheme 4). Since the reaction using the enecarbamate does not



1 **2**

R^1 = Ph, R^2 = Bn: 54%, dr = 3.1 (80% ee) : 1 (8% ee)
R^1 = 4-MeO-C_6H_4, R^2 = Bn: 55%, dr = 3.3 (85% ee) : 1 (7% ee)
R^1 = 4-MeO-C_6H_4, R^2 = *i*-Pr: 43%, dr = 8.1 (88% ee) : 1 (26% ee)

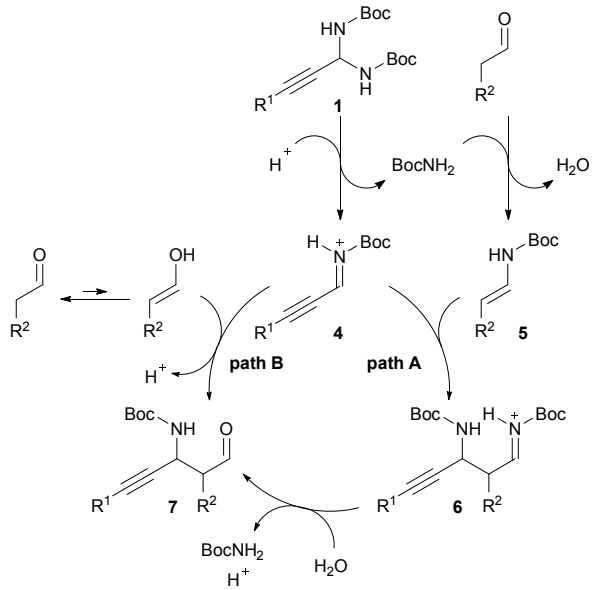


(*S*)-**3**

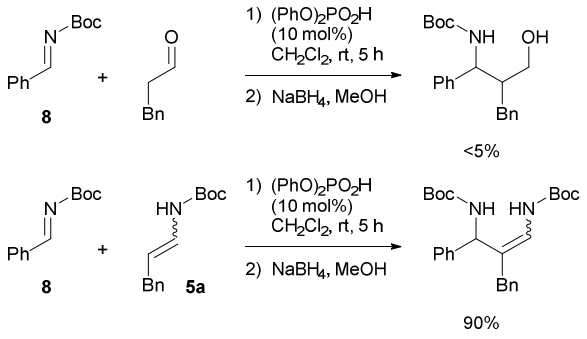
Scheme 2 Asymmetric Mannich reaction between *N*-Boc-aminals **1** and aldehydes.

generate water, the reaction product was obtained as the enecarbamate but not the hydrolyzed product. The enecarbamate **9**, which generates iminium intermediate **6a** under acidic conditions, was hydrolyzed to the Mannich adduct **7a** under the reaction condition (Scheme 5).[11] This result suggests that the stereochemical information of the Mannich adduct **7a** might be lost via interconversion of iminium salt **6**a and enecarbamate **9**. However, since the enantiomeric excesses showed large differences between two diastereomers obtained in the catalytic asymmetric reactions as shown in Scheme 2, most of iminium intermediate **6a** seems to be hydrolyzed before converting to enecarbamate **9** and the stereochemistry formed in the carbon-carbon bond formation is largely retained.

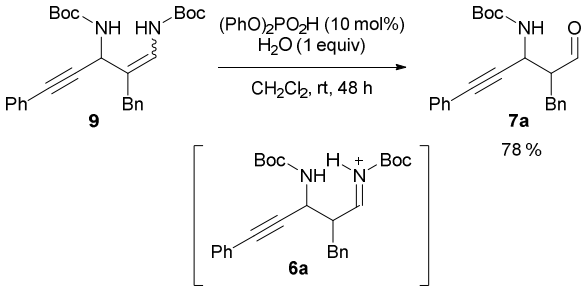
In the phosphoric acid-catalyzed reaction, both nucleophile and electrophile are believed to be activated by the catalyst



Scheme 3 Plausible reaction mechanism.



Scheme 4 Comparison of the reactivity of aldehyde and enecarbamate toward *N*-Boc-imine **8**.



Scheme 5 Hydrolysis of enecarbamate **9** through iminium salt **6a**.

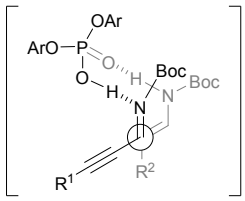


Fig. 1 Proposed transition state model.

through two hydrogen bonds.[7c] Additionally, since *anti*-Mannich adducts were obtained as major diastereomers, *N*-Boc-imines might react with (*E*)-enecarbamates more favorably than (*Z*)-isomers as shown in the plausible transition state model (Fig. 1). In the asymmetric reaction catalyzed by (*S*)-**3**, enecarbamate is seemed to approach the *Re*-face of imine based on the observed stereochemistry.

In summary, we have developed the Mannich-type reactions of aldehydes with *N*-Boc-aminals catalyzed by phosphoric acids, in which both substrates are activated as enecarbamates and *N*-Boc-imines (or *N*-Boc-iminium salts). In the present reaction, hitherto less accessible Mannich adducts having various alkynyl substituents could be obtained and the possibility of an asymmetric reaction was also demonstrated by using a chiral phosphoric acid. We believe that the propargylamine motif in the product can serve as a useful synthetic handle for further elaboration into valuable compounds.

Notes and references

1 For reviews on enamides and enecarbamates as nucleophiles, see: (*a*) R. Matsubara and S. Kobayashi, *Acc. Chem. Res.*, 2008, **41**, 292; (*b*) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599; (*c*) G. Bernadat and G. Masson, *Synlett*, 2014, **25**, 2842.
2 For reviews, see: (a) M. Marigo and K. A. Jorgensen, *Chem. Commun.*, 2006, 2001; (b) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (c) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138.
3 For reviews on asymmetric Mannich reaction, see: (*a*) A. Ting and S. E. Schaus, *Eur. J. Org. Chem.*, 2007, 5797; (*b*) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29.
4 Among imines having *C*-alkynyl groups, only *N*-aryl protected imines have been employed in amine-catalyzed Mannich reactions, see: E. Gómez-Bengoa, J. Jiménez, I. Lapuerta, A. Mielgo, M. Oiarbide, I. Otazo, I. Velilla, S. Vera and C. Palomo, *Chem. Sci.*, 2012, **3**, 2949.
5 (*a*) T. Kano, T. Yurino, D. Asakawa and K. Maruoka, *Angew. Chem. Int. Ed.*, 2013, **52**, 5532; (*b*) T. Kano, T. Yurino and K. Maruoka, *Angew. Chem. Int. Ed.*, 2013, **52**, 11509.
6 Representative Mannich reactions between imines and enecarbamates, see: (*a*) R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem. Int. Ed.*, 2004, **43**, 1679; (*b*) M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem. Int. Ed.*, 2006, **45**, 2254; (*c*) M. Terada, K. Machioka and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 10336; (*d*) M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem., Int. Ed.*, 2009, **48**, 2553 (*e*) G. Dagousset, J. Zhu and G. Masson, *J. Am. Chem. Soc.,* 2011, **133**, 14804.
7 Pioneering reports and a representative review on chiral phosphoric acid catalysts, see: (*a*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem. Int. Ed.*, 2004, **43**, 1566; (*b*) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356; (*c*) M. Terada, *Synthesis*, 2010, 1929.
8 Lower enantioselectivities were observed in the reactions using several other binaphthol-derived chiral phosphoric acids having modified phenyl groups, such as 4-*t*-butylphenyl, 3,5-diphenylphenyl and 2,4,6-trimethylphenyl, at 3,3'-positions of binaphthyl.
9 T. Urushima, H. Ishikawa and Y. Hayashi, *Chem. Eur. J.*, 2011, **17**, 8273.
10 *N*-Boc-imines having a *C*-alkynyl group have not been isolated to date probably due to their lower stability compared to **8**.
11 Mannich adduct **7a** was isolated after reduction to **2a** by $NaBH_4$.