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Trimethylchlorosilane-promoted aza-Mannich reaction of enecarbamates and aldimines

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ABSTRACT

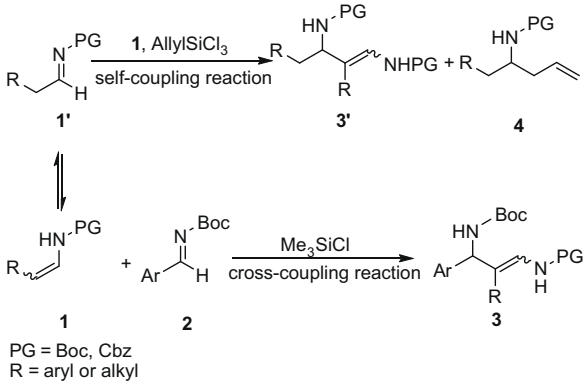
A trimethylchlorosilane-promoted aza-Mannich reaction is reported utilizing enecarbamates as the nucleophile and aromatic *N*-Boc aldimines as the electrophile. A variety of nucleophiles and electrophiles are tolerated by the reaction conditions, delivering the adduct products in excellent yields with high *E*-stereoselectivities.

The Mannich reaction is one of the most fundamentally important carbon–carbon bond forming reactions in organic synthesis, which provides an easy access to the versatile β-functionalized amine products.[1] In situ formed or performed enols are known as classical nucleophilic donors for the Mannich reaction. Enamines are also effective donors, but mainly as in situ formed transient active intermediates in the amine-catalyzed Mannich reaction of ketones or aldehydes.[2] Performed enamines, for example, enamides and enecarbamates, have rarely been utilized as the nucleophilic donor in the Mannich reactions, the so-called aza-Mannich reaction.[3–5] On the one hand, the electron-withdrawing groups on the nitrogen atom endow these enamines with required stability for isolation. On the other hand, the electron-withdrawing property of these groups causes dramatic decreases in the nucleophilicity of the performed enamines and thus renders them virtually inactive under normal Mannich reaction conditions.

Recently, Kobayashi[4] and Terada[5] reported that the enamides and enecarbamates participated Mannich reaction could be realized using either Lewis acidic metal complexes or Brønsted acidic organic phosphoric acids as catalysts. Unlike the typical Mannich reactions that always give β-oxo amine products, isolable β-imino amines, albeit not very stable, are obtained as the products in the aza-Mannich reactions, which could be either hydrolyzed to give β-oxo amines or easily converted to 1,3-diamine products upon reduction. Herein, we report a practical new method for the aza-Mannich reaction of enecarbamates with *N*-Boc aryl imines promoted by trimethylchlorosilane, which affords fairly stable β-amino enecarbamates as the products in high yields and stereoselectivities.

During our recent studies on the allylation of *N*-carbamoyl imine using allyltrichlorosilane promoted by Lewis base,[6] a self-coupling reaction product **3′** was observed as a side product under the allylation conditions when aliphatic *N*-Boc imine **1′** was used (Scheme 1). We speculated that this self-coupling reaction was promoted by the Lewis acidic allyltrichlorosilane following an aza-Mannich reaction pathway. The aliphatic *N*-carbamoyl imine is a known typical Mannich acceptor, which tautomerizes into enecarbamate and thus serves as the Mannich donor. We envisioned that a similar cross-coupling aza-Mannich reaction could be developed as a high-yielding method for the production of β-amino enecarbamates **3** if the more-reactive non-tautomerizable aromatic imines **2** were used as the acceptor (Scheme 1).

Phenylpropionaldehyde-derived enecarbamate **1a** and *N*-Boc benzaldimine **2a** were first utilized as testing substrates and different chlorosilanes $SiCl_4$, $MeSiCl_3$, Me_2SiCl_3, and Me_3SiCl as the Lewis acid promoters. Delightfully, the expected aza-Mannich reaction went smoothly with all the four Lewis acid promoters in a mixture solvent of *N*,*N*-dimethyl formamide (DMF) and dichloromethane



Scheme 1. The aza-Mannich reaction of enamine with imine. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

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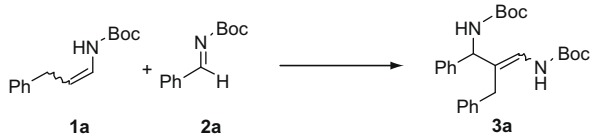
(DCM) (v/v = 1:1) at −20 °C, affording the desired β-amino enecarbamate product **3a** as a mixture of the *E* and *Z* stereoisomers in excellent yield (90–96%) in 24 h (Table 1, entries 1–4).[7]

To further optimize the reaction conditions, we selected Me_3SiCl as the Lewis acid promoter and tested different reaction parameters. When the reaction temperature was increased from −20 to 0 °C, only slightly decreased *E*/*Z* selectivity was observed, whereas the yield was not affected (entries 4 and 5). At room temperature, some decreases in both yield and stereoselectivity were seen (entry 6). A mixture solvent of DMF and DCM was found to be favorable to the reaction. High yield and good *E*/*Z* selectivity were obtained with a DMF/DCM ratio of either 1:1 or 1:4 (entries 5 and 7). Without the use of DMF, both the yield and the selectivity were significantly decreased (entry 8). If only DMF was used as the solvent, lower yield was achieved with a slightly higher *E*/*Z* selectivity (entry 9). Increasing the Me_3SiCl amount from 1.0 to 2.0 equiv had little effect on both the high yield and the *E*/*Z* selectivity (entry 10), whereas lowering the Me_3SiCl amount from 1.0 to 0.5 equiv caused a substantial decrease in the yield, albeit no change with the *E*/*Z* selectivity (entry 11).

The stereoisomers (*E*)-**3a** and (*Z*)-**3a** were easily separated by flash chromatography and the *E* and *Z* configurations were determined by NOESY. For the stereoisomer (*E*)-**3a**, clear correlations were observed between H(1) and H(3) and H(4) and between H(2) and H(5). In contrast, for stereoisomer (*Z*)-**3a**, H(1) has no correlation with either H(3) or H(4), but has a clear correlation with H(2) (Fig. 1).

Table 1
Aza-Mannich reaction of enecarbamate **1a** and aldimine **2a**[a]



1a **2a** **3a**

Entry	Lewis acid	Temp (°C)	Solvent (DMF/DCM)	Yield[b] (%)	*E*/*Z*[c]
1	$SiCl_4$	−20	1:1	90	90:10
2	$MeSiCl_3$	−20	1:1	92	94:6
3	Me_2SiCl_2	−20	1:1	94	94:6
4	Me_3SiCl	−20	1:1	96	94:6
5	Me_3SiCl	0	1:1	92	89:11
6	Me_3SiCl	rt	1:1	71	83:17
7	Me_3SiCl	0	1:4	90	88:12
8	Me_3SiCl	0	0:1	56	69:31
9	Me_3SiCl	0	1:0	80	93:7
10[d]	Me_3SiCl	−20	1:1	95	94:6
11[e]	Me_3SiCl	−20	1:1	57	95:5

[a] Unless stated otherwise, reactions were performed on a 0.2 mmol scale with **1a**/**2a**/silane as 1:1:1 in 1.0 mL of DMF/DCM (v/v 1:1) for 24 h.
[b] Isolated yield of **3a** as *E*/*Z* mixture.
[c] The *E*/*Z* ratio of **3a** was analyzed by ^1H NMR and HPLC.
[d] 2.0 equiv Me_3SiCl was used.
[e] 0.5 equiv Me_3SiCl was used.

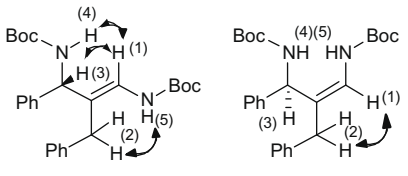
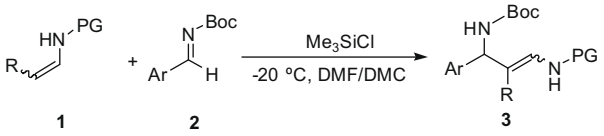


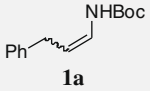
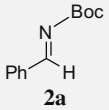
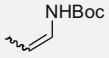
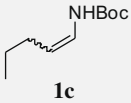
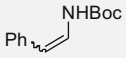
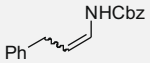
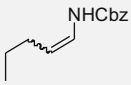
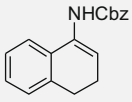
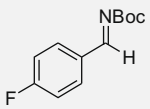
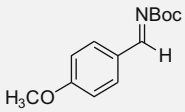
Figure 1. Assignment of the stereochemistry of the *E* and *Z* stereoisomers of **3a** by NOESY.

To probe the generality of the present aza-Mannich reaction, various aldehyde-derived enecarbamates **1a–f** were reacted with *N*-Boc benzaldimine **2a** under optimal conditions.[8] As shown in Table 2, all the reactions proceeded smoothly to give the desired adducts **3** in high yields (94–96%) with high *E* selectivities (83:17–97:3) (entries 1–6). The cyclic enecarbamate **1g** derived from 1-tet-

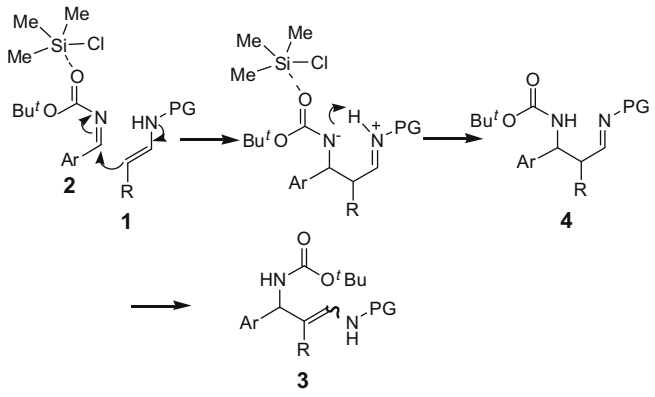
Table 2
Aza-Mannich reaction of various enecarbamates **1** with *N*-Boc aryl aldimins **2**[a]



1 **2** **3**

Entry	Enecarbamate **1**	Aldimine **2**	Yield[b] (%)	*E*/*Z*[c]
1	 **1a**	 **2a**	96	92:8
2	 **1b**	**2a**	94	97:3
3	 **1c**	**2a**	95	96:4
4	 **1d**	**2a**	95	91:9
5	 **1e**	**2a**	91	90:10
6	 **1f**	**2a**	90	83:17
7	 **1g**	**2a**	86	—
8	**1a**	 **2b**	93	92:8
9	**1a**	 **2c**	93	91:9

[a] All reactions were performed on a 0.2 mmol scale with **1**/**2**/Me_3SiCl as 1:1:1 in 1.0 mL of DMF/DCM (1:1) at −20 °C for 24 h.
[b] Isolated yield of **3** as *E*/*Z* mixture.
[c] The *E*/*Z* ratio of **3** was analyzed by ^1H NMR and HPLC.



Scheme 2. Proposed reaction mechanism.

ralone also underwent the aza-Mannich reaction with **2a** to afford product **3g** in 86% yield (entry 7). In this case, the *E*/*Z* selectivity is not an issue since the geometry of the C=C double bond is fixed in the six-membered ring. Other than **2a**, *N*-Boc aryl aldimines **2b** and **2c** bearing electron-donating and electron-withdrawing groups, respectively, were also found to react with **1a** to give excellent results (entries 8 and 9).

According to the aza-ene-type pathway that Kobayashi proposed for the Lewis acidic metal complex-catalyzed addition of enamines with imines,[4] a similar reaction mechanism was proposed for the present aza-Mannich reaction promoted by chlorosilane (Scheme 2). Trimethylchlorosilane coordinates with *N*-Boc benzaldimine **2** to facilitate the electrophilic addition to enecarbamate **1** to form the imino adduct **4**,[9] which subsequently tautomerizes into the thermodynamically more stable *E*-isomer of **3**.

In summary, a trimethylchlorosilane-promoted aza-Mannich reaction of enecarbamates with aldimines has been developed as a highly efficient method for the preparation of β-amino enecarbamates in high yields with high *E*-selectivities. The proposed reaction mechanism follows an aza-ene-type pathway, wherein trimethylchlorosilane plays a Lewis acid role for the activation of the aldimine.

Acknowledgment

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References and notes

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6. Wu, P.; Sun, J. *Synth. Commun.* **2008**, *38*, 1003.
7. (*E*)-**3a**, white solid, mp 123–125 °C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 1.42 (s, 9H), 3.23 and 3.30 (AB system, 2 × d, *J* = 16.5 Hz, 2H), 4.79 (s, 1H), 5.27 (s, 1H), 6.12 (d, *J* = 10.1 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 6.8 Hz, 2H), 7.13–7.36 (m, 8H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.2, 28.3, 33.5, 58.3, 117.4, 122.8, 126.5, 127.1, 127.4, 128.2, 128.6, 128.8, 137.9, 140.6, 152.7, 154.9. HRMS (ESI): *m/z* [M+Na$^+$] calcd for $C_{26}H_{34}N_2O_4$: 461.2411, found 461.2407; (*Z*)-**3a**, oil liquid. ^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.41 (s, 9H), 1.48 (s, 9H), 3.05 and 3.18 (AB system, 2 × d, *J* = 15.0 Hz, 2H), 4.55 (d, *J* = 9.1 Hz, 1H), 5.63 (d, *J* = 10.9 Hz, 1H), 6.57 (d, *J* = 10.9 Hz, 1H), 7.00 (d, *J* = 6.9 Hz, 2H), 7.24 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.9, 31.0, 35.3, 59.2, 120.8, 123.3, 125.2, 126.3, 128.1, 128.4, 128.7, 129.2, 129.8, 129.9, 146.1, 150.7. HRMS (ESI): *m/z* [M+Na$^+$] calcd for $C_{26}H_{34}N_2O_4$: 461.2411, found 461.2411.
8. *Typical experimental procedure for the aza-Mannich reaction*: Enecarbamate **1** (0.2 mmol) and *N*-Boc imine **2** (0.2 mmol) were dissolved in a 1.0 mL v/v 1/1 mixture of DMF and DCM. Me_3SiCl (0.2 mmol) was added dropwise at −20 °C. The reaction mixture was stirred at the same temperature for 24 h and then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic extracts were combined, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give pure product **3**.
9. For activation of imine by Me_3SiCl, see example: Hou, X. L.; Zheng, X. L.; Dai, L. X. *Tetrahedron Lett.* **1998**, *39*, 6949.