Asymmetric Catalysis

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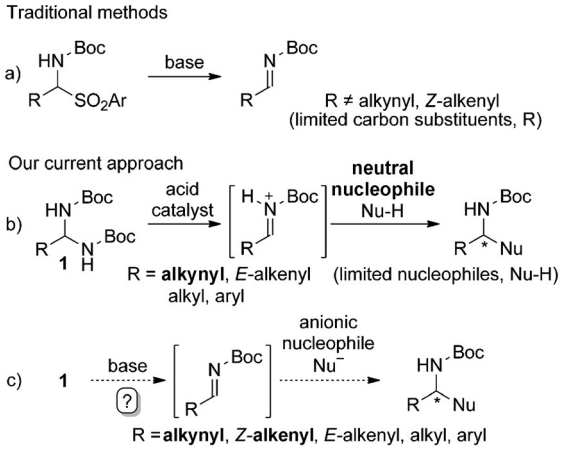
Versatile In Situ Generated *N*-Boc-Imines: Application to Phase-Transfer-Catalyzed Asymmetric Mannich-Type Reactions**

*Taichi Kano, Ryohei Kobayashi, and Keiji Maruoka**

Abstract: *The efficient construction of nitrogen-containing organic compounds is a major challenge in chemical synthesis. Imines are one of the most important classes of electrophiles for this transformation. However, both the available imines and applicable nucleophiles for them are quite limited given the existing preparative methods. Described herein are imine precursors which generate reactive imines with a wide variety of substituents under mild basic conditions. This approach enables the construction of various nitrogen-containing molecules which cannot be accessed by the traditional approach. The utility of the novel imine precursor was demonstrated in the asymmetric Mannich-type reaction under phase-transfer conditions.*

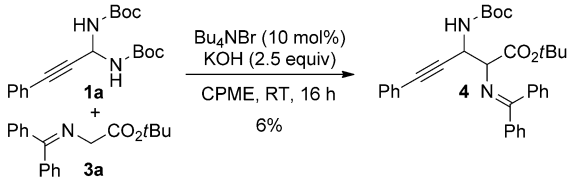
Imines are one of the most important and versatile electrophiles for the synthesis of nitrogen-containing compounds.[1–9] Among them, *tert*-butoxycarbonyl-protected imines (*N*-Boc-imines) are frequently used because of their high reactivity and the broad synthetic utility of the resulting products. Most *N*-Boc-imines are prepared by the treatment of imine precursors with a base (Scheme 1 a).[10] However, the availability of such reactive *N*-Boc-imines are limited, and alkynyl- and some alkenyl-substituted *N*-Boc-imines cannot be prepared by the traditional methods. Recently a novel method for the in situ generation of *N*-Boc-imines under acidic conditions was developed, and various *N*-Boc-imines (or iminiums), including alkynyl-substituted *N*-Boc-imines, can be successfully generated in situ from the corresponding *N*-Boc-aminals **1** with an acid catalyst (Scheme 1 b).[11,12] However, applicable nucleophiles in the subsequent addition to *N*-Boc-imines under acidic conditions are limited to neutral nucleophiles. In this context, the in situ generation of *N*-Boc-imines from **1** under basic conditions, if realized, would significantly expand the scope of the imine chemistry to include a wide variety of anionic nucleophiles (Scheme 1 c). Our interest is to realize such possibility through phase-transfer-catalyzed reactions, including their asymmetric variants.



Scheme 1. Generation of *N*-Boc-imines under either acidic or basic conditions.

Accordingly, the in situ generation of an *N*-Boc-imine from the alkynyl-substituted *N*-Boc-aminal **1a** under basic conditions was first examined by a phase-transfer-catalyzed Mannich-type reaction with the glycine Schiff base **3a**[13–15] to give the α,β-diamino-acid derivative **4** (see Scheme 2), which is the key structural motif in many biologically active compounds.[16] The expectation was that we could extend it to catalytic asymmetric synthesis. Unfortunately, however, the attempted reaction with a catalytic amount of tetrabutylammonium bromide (TBAB) in cyclopentyl methyl ether (CPME) gave only a trace amount of the desired Mannich-type adduct **4**, even with a strong base such as KOH (Scheme 2). Since **3a** is known to be deprotonated and activated as a nucleophile under mild phase-transfer conditions,[17] the observed low yield might be attributed to the decomposition of **1a** by KOH and insufficient generation of alkynyl-substituted *N*-Boc imines through elimination of *tert*-butyl carbamate.

To improve the leaving ability of *tert*-butyl carbamate in the unreactive *N*-Boc-aminals **1**, an additional Boc group was introduced by treatment of **1** with di-*tert*-butyl dicarbonate



Scheme 2. Unsuccessful in situ generation of *N*-Boc-imines from the alkynyl-substituted *N*-Boc-aminal **1a**. THF = tetrahydrofuran.

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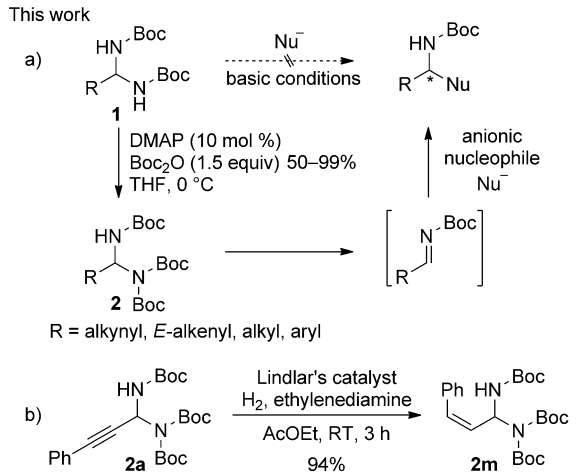
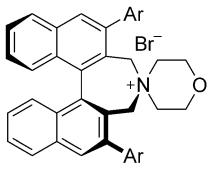
(Boc_2O) in the presence of 10 mol% of 4-dimethylaminopyridine (DMAP), and the corresponding *N*-Boc-aminals **2** were obtained in moderate to good yields without forming undesired aminals having four Boc groups (Scheme 3a; see



Scheme 3. Preparation of the *N*-Boc-aminals **2**.

the Supporting Information). The synthetic utility of the new alkynyl-substituted *N*-Boc-aminals **2** was demonstrated by transforming them into the corresponding *Z*-alkenyl-substituted *N*-Boc-aminals, by partial catalytic hydrogenation, for further elaboration into asymmetric Mannich-type reactions under basic conditions (Scheme 3b). For example, the *N*-Boc-aminal **2m**, having a *Z*-styryl group, was readily prepared by Lindlar reduction of the *N*-Boc-aminal **2a** having a phenylethynyl group.

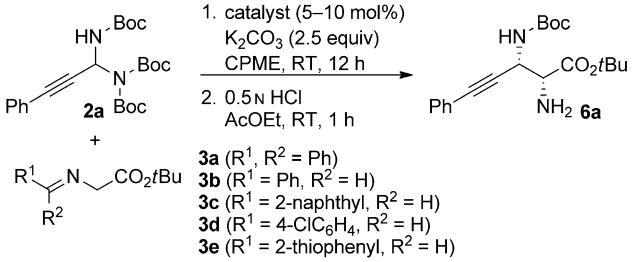
As expected, the reaction of **2a** and the glycine Schiff base **3a** in the presence of K_2CO_3 and 10 mol% of TBAB proceeded smoothly to give the desired Mannich-type adduct **6a** in good yield with high diastereoselectivity (Table 1, entry 1). Since no reaction was observed in the absence of the catalyst (entry 2), we then attempted to render this reaction asymmetric with 5 mol% of binaphthyl-based chiral phase-transfer catalysts.[18–20] In all cases examined, low to moderate enantioselectivities were observed (see the Supporting Information), whereas the morpholine-derived catalyst (*S*)-**5**, having bulky substituents at the 3,3′-positions



(*S*)-**5**, Ar = 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$

of binaphthyl, was found to be most effective (entry 3). To improve the enantioselectivity, several glycine Schiff bases (**3b–e**) were prepared and reacted with **2a** in the presence of (*S*)-**5** (entries 4–7). A change from the ketimine Schiff base **3a** to the aldimine Schiff base **3e** led to a drastic increase in

Table 1: Optimization of the Mannich-type reaction.[a]



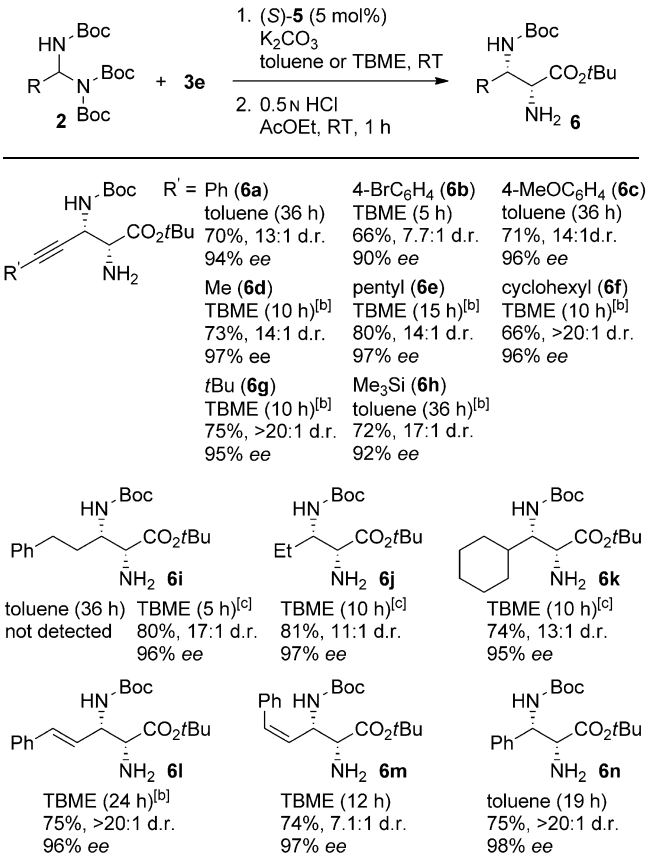
Entry	Catalyst	3	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1[e]	TBAB	**3a**	79	90:10	–
2	–	**3a**	n.d.	–	–
3	(*S*)-**5**	**3a**	84	95:5	43
4	(*S*)-**5**	**3b**	53	77:23	63
5	(*S*)-**5**	**3c**	73	88:12	68
6	(*S*)-**5**	**3d**	72	86:14	81
7[e]	(*S*)-**5**	**3e**	71	90:10	92
8[f]	(*S*)-**5**	**3e**	78	89:11	92
9[g]	(*S*)-**5**	**3e**	70	93:7	94

[a] Performed with **2a** (0.05 mmol), **3** (0.05 mmol), K_2CO_3 (0.125 mmol), and (*S*)-**5** (0.0025 mmol) in CPME (0.5 mL). [b] Yield of the isolated **6a** as a mixture of diastereoisomers. [c] Diastereomeric ratio determined by ^{1}H NMR analysis. [d] Enantiomeric ratio of the major diastereomer determined by HPLC analysis using a chiral stationary phase. [e] Performed for 24 h. [f] Performed for 24 h in TBME. [g] Performed with **3e** (0.06 mmol) for 36 h in toluene.

enantioselectivity, whereas a longer reaction time was required (entry 7).[21] When the reaction was performed in toluene, both diastereo- and enantioselectivities were slightly improved (entry 9). The absolute configuration of **6a** was determined by comparison of the optical rotation of **6a** with the literature value after hydrogenation of the alkynyl substituent (see the Supporting Information).

With the optimized reaction conditions in hand, the substrate scope was examined, and the generality of the present method for the in situ imine generation as well as the Mannich-type reaction was demonstrated (Table 2). In the presence of 5 mol% of (*S*)-**5**, the reactions of the *N*-Boc-aminals **2a–h**, having various alkynyl groups, with **3e** gave the corresponding Mannich-type adducts **6a–h** in good diastereo- and enantioselectivities. In some cases, the solvent was switched to *tert*-butyl methyl ether (TBME), which tends to give better yields of the Mannich-type adducts (**6d–g**). We then tested the scope of the reaction by varying the substituents on the aminal carbon atom of **2**. When the reaction of the alkyl-substituted *N*-Boc-aminal **2i** (R = 2-phenylethyl) was performed in toluene, the desired product **6i** was not obtained. Fortunately, the reaction with a stronger base, K_3PO_4, in TBME proceeded smoothly to give **6i** in good yield with high diastereo- and enantioselectivity. Similar results were obtained when applying this protocol to other alkyl-substituted *N*-Boc-aminals **2j** (R = ethyl) and **2k** (R = cyclohexyl), which led to the formation of the Mannich-type adducts **6j** and **6k**, respectively. The reactions using the alkenyl-substituted *N*-Boc-aminals **2l** (R = *E*-styryl) and **2m** (R = *Z*-styryl) also gave the Mannich-type adducts **6l** and **6m**, respectively, in high diastereo- and enantioselectivities. To the

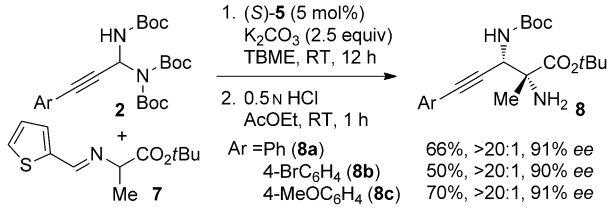
Table 2: Substrate scope.[a]



[a] Performed with **2** (0.05 mmol), **3e** (0.06 mmol), K_2CO_3 (0.125 mmol), and (*S*)-**5** (0.0025 mmol) in a solvent (0.5 mL). Yield is that of the isolated product as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR analysis, and the enantiomeric ratio of the major diastereomer was determined by HPLC analysis using a chiral stationary phase. [b] Performed with K_2CO_3 (0.25 mmol). [c] Performed with K_3PO_4 (0.125 mmol) instead of K_2CO_3.

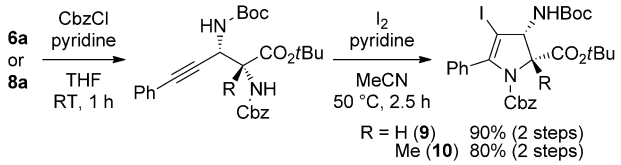
best of our knowledge, this is the first example of the generation of *Z*-alkenyl-substituted *N*-Boc-imine under basic conditions. It is noteworthy that no *E*/*Z* isomerization of the styryl groups of **6l** and **6m** was observed, and that the reaction of **2m**, catalyzed by TBAB, gave a complex mixture which included both **6l** and **6m**. The present Mannich-type reaction using *N*-Boc-aminals was also found to be applicable to the aryl-substituted *N*-Boc-aminal **2n** (R = phenyl), thereby indicating the broad substrate scope.

The Mannich-type reactions of several *N*-Boc-aminals (**2**) with the alanine Schiff base **7** were also examined using the



Scheme 4. Asymmetric Mannich-type reaction of **2** with the alanine Schiff base **7**.

chiral phase-transfer catalyst (*S*)-**5** (Scheme 4).[22] In all cases, *syn* diastereomers of the corresponding Mannich-type adducts **8a–c**, having a tetrasubstituted carbon atom, were obtained exclusively in high enantioselectivities. The absolute configuration of **8a** was unambiguously determined by X-ray crystallographic analysis after derivatization (see the Supporting Information). The obtained Mannich-type adducts **6a** and **8a** were readily converted into multifunctional 2,3-dihydropyrroles **9** and **10**, respectively, by treatment with iodine and pyridine after protection of the amino group with benzyloxycarbonyl (Cbz) group (Scheme 5).[23,24]



Scheme 5. Syntheses of the 2,3-dihydropyrroles **9** and **10**.

In summary, we have developed a novel method for in situ generation of various *N*-Boc-imines, including the less-accessible alkynyl-substituted imines and the unprecedented *Z*-alkenyl-substituted imines under basic conditions, thus providing a practical entry to the synthesis of various nitrogen-containing compounds. The present method has proven particularly useful, as demonstrated in the highly stereoselective synthesis of α,β-diamino acid derivatives through phase-transfer-catalyzed Mannich-type reactions of in situ generated *N*-Boc-imines with either glycine or alanine Schiff bases. The methodology described herein may also stimulate related research on stereoselective reactions with other anionic nucleophiles, including a wide variety of organometallic compounds.

Keywords: amino acids · asymmetric catalysis · imines · organocatalysis · phase-transfer catalysis

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