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Imine Generation

Acid-Catalyzed In Situ Generation of Less Accessible or Unprecedented *N*-Boc Imines from *N*-Boc Aminals**

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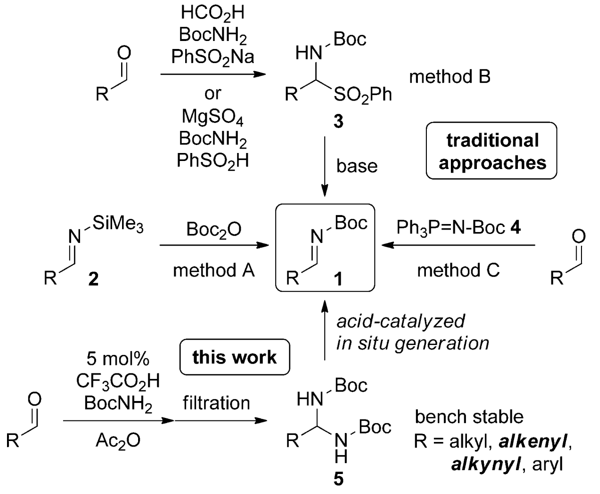
Imines are valuable reagents that are capable of producing a wide variety of nitrogen-containing compounds by addition reactions, reduction, and cycloaddition in synthetic chemistry.[1–9] Among them, imines **1** (Scheme 1) that have an easily handled Boc group are frequently used in organic synthesis owing to the high synthetic utility of the resulting product.[10] However, available Boc-protected imines are limited because of their high reactivity and the difficulty of their synthesis.

While *N*-Boc-protected imines **1** are prepared by the reaction of trimethylsilyl-protected imines **2** with di-*tert*-butyl dicarbonate (Boc_2O; Scheme 1, method A), this preparation proceeds in low yield and requires successive distillation of both imine **1** and **2**.[11,12] Sulfinic acid adducts of imines **3** are obtained from aldehydes, *tert*-butyl carbamate ($BocNH_2$), and sulfinic acid sodium salt (or sulfinic acid). These imine precursors **3** can be converted into imines **1** by treatment with a base, such as K_2CO_3 (method B). This procedure also enables in situ generation of reactive imines **1** and is the most commonly used in synthetic chemistry.[13,14] The aza-Wittig reaction between aldehydes and iminophosphorane **4** is an alternative approach to *N*-Boc imines (method C).[12,15] Unfortunately, however, the precursor of iminophosphorane **4**, *tert*-butoxycarbonyl azide, is recognized as being explosive, and its use is therefore discouraged. While somewhat stabilized *N*-Boc imines having an aromatic substituent on the carbon atom are obtainable by either methods, *N*-Boc imines with alkyl substituent are less accessible owing to the fact that such imines are readily isomerized to the corresponding enecarbamate.[16–21] To the best of our knowledge, only one *N*-Boc imine having an alkenyl substituent has been reported,[22] and furthermore, *N*-Boc imines with an alkynyl group are unprecedented.[23] Accordingly, development of the general method to generate reactive *N*-Boc imines **1** is of great significance in synthetic chemistry.



Scheme 1. Generation of *N*-Boc-protected imines **1**.

We have recently become interested in the gradual in situ generation of reactive *N*-Boc imines **1**, and especially those with an alkynyl group, under the influence of acid catalyst.[14,16–21,24] Slow generation and rapid consumption of reactive imines would avoid their accumulation and decomposition. We then focused on *N*-Boc aminals **5** as an imine precursor, which could be readily prepared by condensation of aldehydes and $BocNH_2$.[19] The desired *N*-Boc imine would be gradually generated in situ with one $BocNH_2$ departing with the aid of acid catalyst. In this reaction system, the neutral byproduct $BocNH_2$ is not expected to affect the reaction of *N*-Boc imines with other reagents. Indeed, *N*-Boc aminal **5** ($R = PhC{\equiv}C$) was obtained as a white solid only by treatment of 3-phenylpropiolaldehyde with $BocNH_2$ in a dehydrating agent, acetic anhydride in the presence of a catalytic amount of trifluoroacetic acid and subsequent filtration (Figure 1). In the presence of copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) as a Lewis acid catalyst, the reaction between **5** and diethyl malonate proceeded to give the Mannich-type product **6** ($R = PhC{\equiv}C$) in good yield (Table 1, entry 1). This result indicated that the hitherto

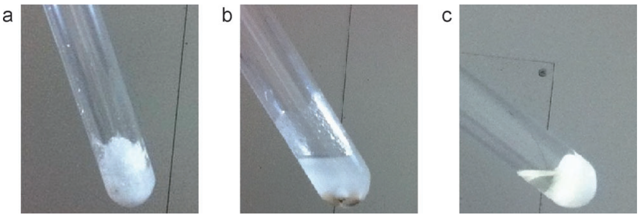


Figure 1. Images of the reaction setup of 3-phenylpropiolaldehyde with $BocNH_2$ in the presence of trifluoroacetic acid (5 mol %) in acetic anhydride. a) Reaction mixture before mixing all compounds. b) Reaction mixture after mixing all compounds (5 min). c) Reaction mixture after completion the reaction (15 min).

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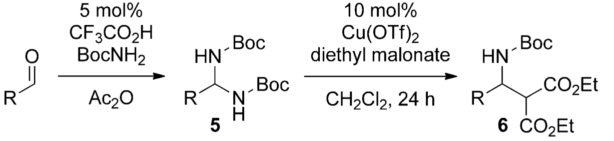
Table 1: Scope of *N*-Boc aminal synthesis and $Cu(OTf)_2$-catalyzed tandem *N*-Boc imine generation/Mannich-type reaction.[a]



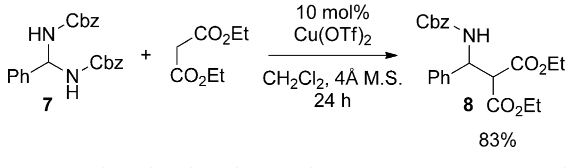
Entry	R	Yield of **5** [%][b]	Yield of **6** [%][b]
1[c,d]	$PhC\equiv C$	92	67
2[c,d]	$4\text{-}MeOC_6H_4C\equiv C$	89	74
3	$4\text{-}BrC_6H_4C\equiv C$	81	60
4[c]	$C_5H_{11}C\equiv C$	73	57
5[c,d]	$c\text{-}C_6H_{11}C\equiv C$	84	55
6	$PhCH{=}CH$	54	84
7	$PhCH_2CH_2$	71	72
8	Et	91	76
9	cyclohexyl	85	89
10[e]	Ph	77	93
11[e]	$4\text{-}MeOC_6H_4$	64	82
12[e]	$4\text{-}BrC_6H_4$	66	97
13[e]	$2\text{-}MeC_6H_4$	62	84
14[e]	1-naphthyl	81	95
15	2-furyl	57	88

[a] See the Supporting Information for details. [b] Yield of isolated product. [c] Use of CuOTf·toluene instead of $Cu(OTf)_2$. [d] Use of 1,2-dichloroethane instead of dichloromethane. [e] Use of 4 Å molecular sieves.

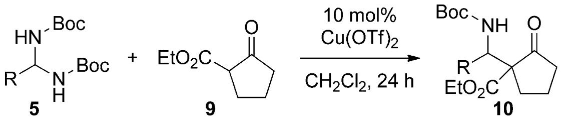
inaccessible N-Boc imine with an alkynyl group could be first generated in situ.

Fortunately, various *N*-Boc aminals **5** were also obtained as an air-, water-, and light-stable white solid from aldehydes having an alkynyl, akenyl, alkyl, or aryl group on the carbonyl carbon by the simple procedure (Table 1).[25] All of these aminals **5** reacted with diethyl malonate to give the corresponding Mannich-type products **6** in the presence of $Cu(OTf)_2$ catalyst (Table 1).[26] These results suggest that a wide variety of less-accessible or unprecedented *N*-Boc imines could be readily generated in situ from *N*-Boc aminals **5** under acid-catalyzed conditions.

Aminal **7** protected by the commonly used benzyloxycarbonyl (Cbz) groups[27] instead of Boc group was also obtained as a stable white solid, and was applicable to the reaction with diethyl malonate (Scheme 2). In the reaction with other common nucleophilic reagents, such as ketoester **9** and silyl enol ether **11**, *N*-Boc aminals played a role of an imine surrogate, giving addition products **10** and **12**, respectively (Scheme 3 and Scheme 4).[28,29] In the present imine generation, some acid catalysts other than $Cu(OTf)_2$ were also applicable (Table 2). For instance, the reaction of *N*-Boc aminals **5** (R = Ph) with acetylacetone (**13**) was promoted not only by $Cu(OTf)_2$ but organic Brønsted acids as exemplified by trifluoroacetic acid (TFA) to give the Mannich-type product **14** (R = Ph) in good yield (entries 1 and 2). The reaction using a chiral Brønsted acid catalyst (*S*)-**15** gave **14** (R = Ph) in high enantioselectivity (entry 3).[30,31] With (*S*)-**16** or (*S*)-**17**, unprecedented Mannich-type products **14** having various alkynyl groups were obtained in high yield and enantioselectivity (entries 5–7).[32]

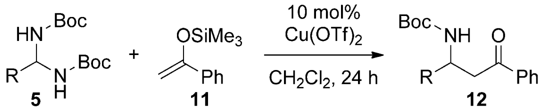


Scheme 2. Acid-catalyzed tandem *N*-Cbz imine generation/Mannich-type reaction of diethyl malonate.



R = $PhC\equiv C$ 97% (d.r. = 1.3/1)
R = $PhCH{=}CH$ 82% (d.r. = 1.5/1)
R = $PhCH_2CH_2$ 75% (d.r. = 1.4/1)
R = Ph 99% (d.r. = 6.0/1)

Scheme 3. Acid-catalyzed tandem *N*-Boc imine generation/Mannich-type reaction of ketoester **9**.

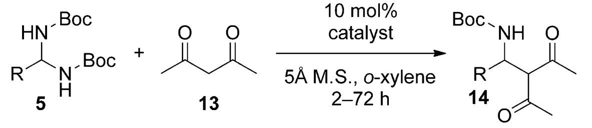


R = $PhC\equiv C$ 73%
R = $PhCH{=}CH$ 87%
R = $PhCH_2CH_2$ 33%
R = Ph 77%

Scheme 4. Acid-catalyzed tandem *N*-Boc imine generation/Mannich-type reaction of silyl enol ether **11**.

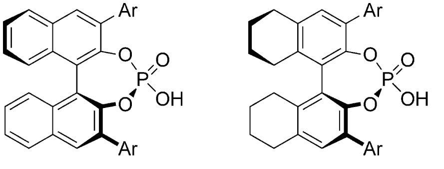
To investigate the nature of *N*-Boc aminal **5** as an imine precursor, the following reaction was conducted. When the mixture of *N*-Boc aminal **5**, *N*-Cbz aminal **7** and a catalytic

Table 2: Acid-catalyzed tandem *N*-Boc-substituted imine generation/Mannich-type reaction of acetylacetone.[a]

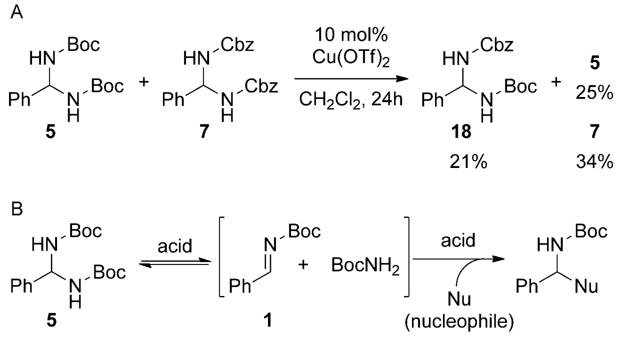


Entry	Catalyst	R	Yield [%][b]	*ee* [%][c]
1[d]	$Cu(OTf)_2$	Ph	77	–
2[d]	TFA	Ph	72	–
3	(*S*)-**15**	Ph	92	92
4	(*S*)-**15**	$4\text{-}BrC_6H_4$	98	90
5[e]	(*S*)-**16**	$C_5H_{11}C\equiv C$	80	88
6[e]	(*S*)-**17**	$tBuC\equiv C$	80	92
7[f]	(*S*)-**16**	$Me_3SiC\equiv C$	73	90

[a] See the Supporting Information for details. [b] Yield of isolated product. [c] Determined by HPLC analysis using chiral-phase column. [d] The reaction was performed using 4 Å molecular sieves in CH_2Cl_2. [e] Use of CH_2Cl_2–AcOEt (1:2) as solvent. [f] Use of CH_2Cl_2 as solvent.



(*S*)-**15** (Ar = $3,5\text{-}Ph_2(C_6H_3)$) (*S*)-**16** (Ar = $3,5\text{-}(3,5\text{-}Me_2C_6H_3)_2(C_6H_3)$)
(*S*)-**17** (Ar = $3,5\text{-}Ph_2(C_6H_3)$)



Scheme 5. Mechanistic study and working model.

amount of $Cu(OTf)_2$ was stirred under the identical conditions to the Mannich-type reaction, aminal **18** having both Boc and Cbz groups was obtained and the imine itself was not observed (Scheme 5 A). This result suggested that elimination of $BocNH_2$ (or $CbzNH_2$) is reversible and also only a trace amount of *N*-Boc imine is generated by an acid catalyst. Based on this experimental result, the Mannich-type reaction of aminals **5** was found to proceed through the reversible and gradual generation of imines **1** (or the corresponding iminium salt) by acid-catalyzed elimination of $BocNH_2$ and the subsequent carbon–carbon bond formation (Scheme 5 B). In these processes, the acid catalyst played double roles of the imine generation and the acceleration of Mannich-type reaction.

In summary, utility of *N*-Boc aminals as a precursor of reactive *N*-Boc imines has been demonstrated and generation of less accessible or unprecedented imines was realized. *N*-Boc aminals are readily accessible from commercially available reagents and isolated as a stable and easily handled solid. This acid-catalyzed in situ generation of reactive *N*-Boc-protected imines will open the way for the application in asymmetric synthesis of nitrogen-containing compounds using chiral acid catalysts. We believe that these results will have broad implications for use in synthesis, enabling the preparation of valuable molecules for biological and pharmaceutical research as well as in materials science.

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