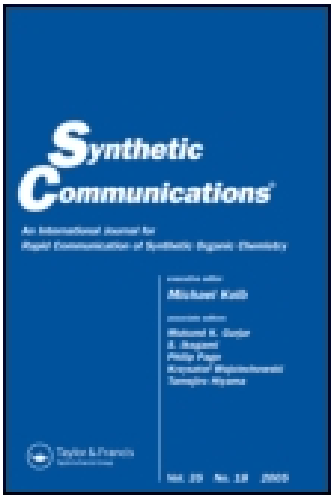

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Facile Allylation of N-Boc and N-Cbz Imines with Allyltrichlorosilane promoted by DMF

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Facile Allylation of *N*-Boc and *N*-Cbz Imines with Allyltrichlorosilane promoted by DMF

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Abstract: Facile allylation of various *N*-Boc and *N*-Cbz imines with allyltrichlorosilane has been effected using *N*,*N*-dimethylformamide (DMF) as the activator. The *N*-Boc and *N*-Cbz homoallylic amines were obtained in good to high yields under mild conditions.

Keywords: Allylation, allyltrichlorosilane, *N*-Boc imines, *N*-Cbz imines, DMF

INTRODUCTION

Homoallylic amines are important precursors to versatile nitrogen-containing compounds of biological importance, and hence continuous efforts have been devoted to the development of methods for the preparation of these compounds.[1–4] The allylation of imines has been widely recognized as a direct and efficient method for the synthesis of homoallylic amines.[2] Among various allylic reagents used for the allylation of imines, allyltrichlorosilane is a preferable choice because of its easy availability and low toxicity, and it has been extensively used in the allylation of aldehydes.[3] Kobayashi first reported that when *N*,*N*-dimethylformamide (DMF) or hexamethylphosphoramide (HMPA) was used as activator, imine equivalents *N*-acylhydrazones were

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smoothly allylated with allyltrichlorosilane to afford homoallylic amines in high yield under mild reaction conditions.[4] However, simple imines failed to undergo the same reaction, on the basis of which imines were once believed to be resistant to allyltrichorosilane.[4] Later, the same research group found that smooth allylation could occur with *N*-(*o*-hydroxylphenyl)imines using DMF, HMPA, or pyridine *N*-oxide as activator.[5] The adjacent hydroxy group of these imines proved to be indispensable for the high reactivity. Thus, the apparent limitation of the current imine allylation method using allyltrichlorosilane was the special requirements of the *N*-substituent of imines, which undoubtedly thwart the usefulness of this because removal of these substituents is not trivial. Herein, we report the first facile allylation of *N*-Boc and *N*-Cbz imines[6] with allyltrichorosilane as the allylating agent and DMF as the activator.

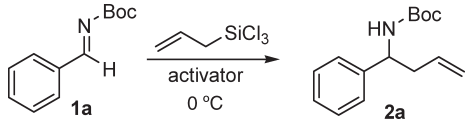
RESULTS AND DISCUSSION

The tert-butoxycarbonyl group (Boc) is a favorite protection group for amines. It is easy to install and remove and is quite stable under nonacidic conditions. Aldimines derived from *N*-Boc amines and aldehydes (*N*-Boc aldimines) are preferable substrates for nucleophilic additions from the viewpoint of practical application. Thus, in this study, *N*-Boc imines were first examined as substrates for the allylation with allyltrichlorosilane. Initially, **1a** was subjected to the allylation with DMF as solvent at 0 °C using 1.5 equiv. of allyltrichlorosilane. To our delight, the reaction proceeded to give the desired product *N*-Boc allylamine **2a** in 53% yield in 8 h (entry 1, Table 1). Interestingly, a mixed solvent system of DMF–CH_2Cl_2 was found to be favorable to the reaction (entries 2–4), and the yield varied with different ratios of DMF–CH_2Cl_2. The highest yield of 80% was obtained at a DMF–CH_2Cl_2 ratio of 1:4 (entry 3). In the absence of DMF, the reaction failed to proceed (entries 5 and 6).

We also examined the effects of several other potential organic activators on the allylation of *N*-Boc aldimines (entries 7–10). Surprisingly, although DMSO, HMPA, and triphenylphosphine were all shown to be effective activators for the allylation of *N*-acylhydrazones,[4] none of them exhibited detectable activity in the allylation of **1a** (entries 7–9); neither did triethylamine (entry 10). DMF thus seems to be unique as an effective organic activator for the allylations of *N*-Boc aldimines. Some other solvents were also surveyed for the allylation of **1a** in the presence of DMF (entries 11–14, Table 1). Although dichloroethane, toluene, and THF all afforded much lower yields than CH_2Cl_2, acetonitrile (CH_3CN) gave a slightly better yield than CH_2Cl_2 (entry 11 vs. 3) and is hence a suitable solvent.

We next carried out the allylation of various *N*-Boc aldimines with allytrichlorosilane at 0 °C using a mixed solvent of DMF–CH_3CN (1:4). As shown in Table 2, the selected electron-rich and electron-deficient aromatic imines **1a**–**l** all reacted well to give the desired products **2a**–**l** in good to excellent yields (entries 1–12).

Table 1. Allylation of *N*-Boc aldimine with allyltrichlorosilane[a]



Entry	Activator/solvent	Yield (%)[b]
1	DMF/DMF	53
2	DMF/CH_2Cl_2 (v/v = 1/1)	62
3	DMF/CH_2Cl_2 (v/v = 1/4)	80
4	DMF/CH_2Cl_2 (v/v = 1/9)	31
5	-/CH_2Cl_2	0
6	-/CH_3CN	0
7	DMSO/CH_2Cl_2 (v/v = 1/4)	<5
8	HMPA/CH_2Cl_2 (v/v = 1/4)	0
9	$Ph_3P=O$/CH_2Cl_2 (2.6 M)	0
10	TEA/CH_2Cl_2 (v/v = 1/4)	0
11	DMF/CH_3CN (v/v = 1/4)	84
12	DMF/Toluene (v/v = 1/4)	30
13	DMF/$ClCH_2CH_2Cl$ (v/v = 1/4)	47
14	DMF/THF (v/v = 1/4)	<5

[a]Reaction condition: C = 0.2 M: reaction time: 8 h.
[b]Isolated yield based on imine.

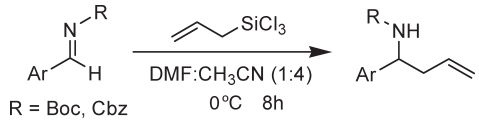
Becasue the *N*-Cbz group, another well-known useful protection group, is structurally and electronically similar to the *N*-Boc group, we also examined the allylation of *N*-Cbz aldimines under optimal conditions. As expected, imines **3a**–**d** also underwent smooth allylation to afford products **4a**–**d** in good yields (Table 2, entries 13–16).

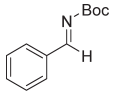
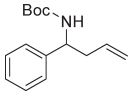
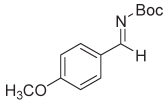
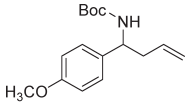
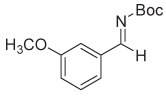
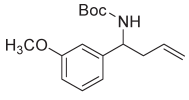
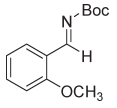
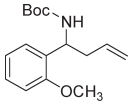
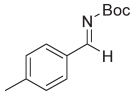
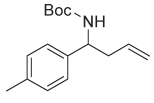
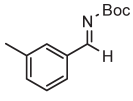
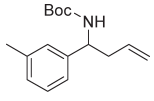
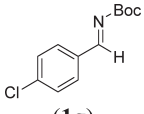
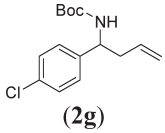
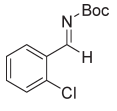
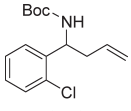
Notably, when either the aliphatic *N*-Boc or *N*-Cbz imine **5** was subjected to the same reaction conditions, the major product obtained was not the desired allylation product **6** but a self-condensation product **7** (Scheme 1).[7]

The crotylation of **1a** with (*E*)-crotyltrichlorosilanes was also tested under similar conditions. As illustrated in Scheme 2, the desired product **8** was obtained as a *syn*/*anti* mixture in good yield at −20 °C. The s*yn*/*anti* ratio was determined by ^1H NMR analysis. Becasue of severe side reactions, a much lower yield was achieved at 0°C. The poor diastereoselectivity, in contrast to the high diastereoselectivities observed in the crotylation of *N*-acylhydrazones and *N*-(*o*-hydroxylphenyl)imines,[3,4] seems to imply that this reaction proceeds through an open acyclic transition state.

We propose that *N*-Boc and *N*-Cbz imines be allylated with allyltrichlorosilane through a similar pathway as *N*-acylhydrazones (Scheme 3).[3] DMF behaves as a Lewis basic activator. As for the transition state, while the one

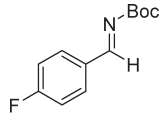
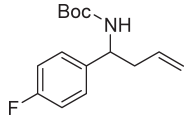
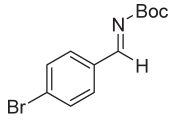
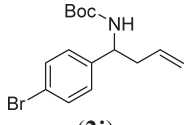
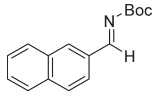
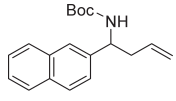
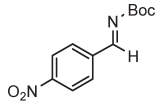
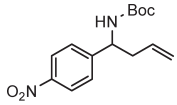
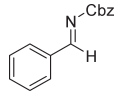
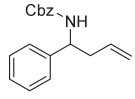
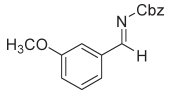
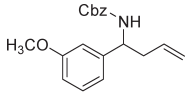
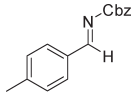
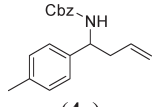
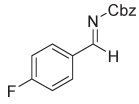
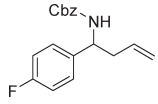
Table 2. Allylation of various *N*-Boc and *N*-Cbz aldimines with allyltrichlorsilane[a]



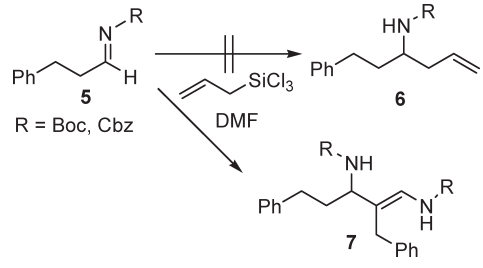
Entry	Imine	Product	Yield (%)[b]
1	 **(1a)**	 **(2a)**	84
2	 **(1b)**	 **(2b)**	93
3	 **(1c)**	 **(2c)**	86
4	 **(1d)**	 **(2d)**	96
5	 **(1e)**	 **(2e)**	87
6	 **(1f)**	 **(2f)**	74
7	 **(1g)**	 **(2g)**	66
8	 **(1h)**	 **(2h)**	75

(*continued*)

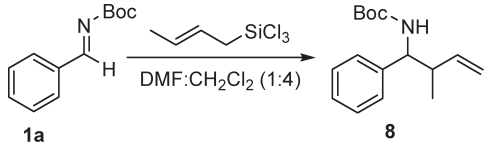
Table 2. Continued

Entry	Imine	Product	Yield (%)[b]
9	 **(1i)**	 **(2i)**	78
10	 **(1j)**	 **(2j)**	62
11	 **(1k)**	 **(2k)**	64
12	 **(1l)**	 **(2l)**	68
13	 **(3a)**	 **(4a)**	80
14	 **(3b)**	 **(4b)**	65
15	 **(3c)**	 **(4c)**	56
16	 **(3d)**	 **(4d)**	78

[a]Reaction condition: C = 0.2 M.
[b]Isolated yield based on imine.



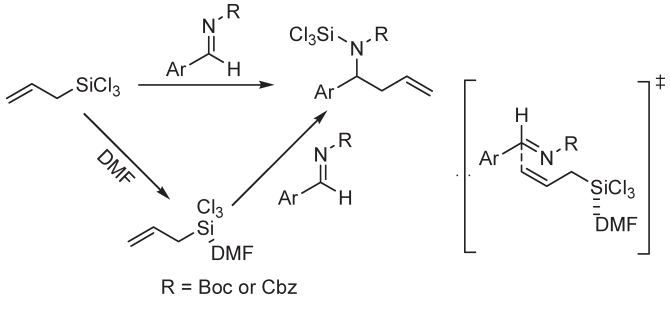
Scheme 1.



Scheme 2. 0 °C: yield 37%, *syn:anti* (5:6); −20 °C: yield 78%, *syn:anti* (4:6).

proposed for the allylation of *N*-acylhydrazones is a closed six-membered cycle,[1c,3] the allylation of *N*-Boc and *N*-Cbz imines most likely adopts an open acyclic transition state given the observed poor stereoselectivity and the slim possibility of coordination of the nitrogen atom of such imine with the silicon atom becasue of the strong electron-withdrawing effects of the Boc and Cbz groups.

In summary, facile allylation of various *N*-Boc and *N*-Cbz imines with allyltrichlorosilane has been effected using DMF as the activator. The *N*-Boc and *N*-Cbz homoallylic amines were obtained in good to high yields under mild conditions. The asymmetric version of this reaction using chiral DMF analogs as catalyst[8] is currently under investigation in this laboratory.



Scheme 3.

EXPERIMENTAL

Typical Experimental Procedure for the Allylation of *N*-Boc and *N*-Cbz Aldimines

Aldimine (0.2 mmol) was dissolved in 0.2 mL of DMF and 0.8 mL of CH_3CN. Allyltrichlorosilane (0.3 mmol) was added dropwise at 0 °C. The reaction was stirred at 0°C overnight and was then quenched with a saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with ether. The oganic phase was combined, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash-column chromatography on silica to give the pure product.

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