Organic LETTERS

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Synthesis of *N*-Boc-Propargylic and Allylic Amines by Reaction of Organomagnesium Reagents with *N*-Boc-Aminals and Their Oxidation to *N*-Boc-Ketimines

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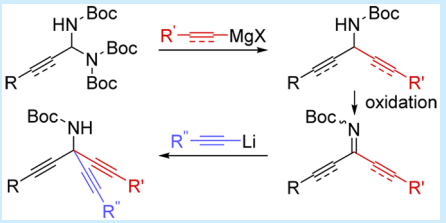
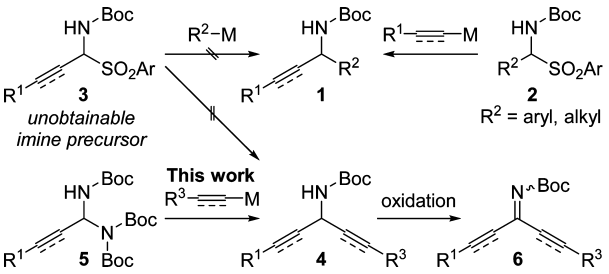
Supporting Information

ABSTRACT: Previously inaccessible *N*-Boc-protected propargylic and allylic amines were synthesized by the reaction between *N*-Boc-aminals and organomagnesium reagents through the in situ generated *N*-Boc-imine intermediates. The obtained *N*-Boc-propargylic amines could be readily converted into unprecedented *N*-Boc-ketimines by oxidation with manganese dioxide.



Propargylic and allylic amines represent an important class of versatile building blocks for the synthesis of nitrogen-containing organic compounds.[1] Among these, synthetically useful *N*-Boc-protected propargylic and allylic amines **1** are readily prepared from the nucleophilic addition of alkynyl and alkenyl metal reagents to *N*-Boc-imines, which can be generated from their precursors **2** upon treatment with bases including basic nucleophiles (Scheme 1).[2,3] However, this

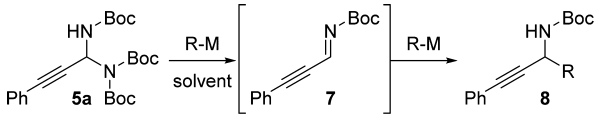
Scheme 1. Synthesis of *N*-Boc-Protected Propargylic and Allylic Amines



method is applicable to *N*-Boc-imines with *C*-aryl or *C*-alkyl groups, as most *N*-Boc-imine precursors **3** with a *C*-alkynyl or *C*-alkenyl group still remain unobtainable.[4] Accordingly, in the synthesis of *N*-Boc-protected propargylic and allylic amines **1**, alkynyl and alkenyl groups should be introduced as nucleophiles and not as part of electrophiles. Therefore, *α*-alkynyl and *α*-alkenyl-substituted *N*-Boc-propargylic and allylic amines **4** have not been synthesized to date.[5] Herein, we report the synthesis of previously inaccessible *N*-Boc-propargylic and allylic amines **4** via the reaction of *N*-Boc-aminals **5** with organomagnesium reagents and the subsequent oxidation to furnish unprecedented *N*-Boc-ketimines **6** that can be used for the generation of tetrasubstituted carbon centers.

We have previously reported that the treatment of *N*-Boc-protected aminals with an inorganic base can generate *N*-Boc-imines with various substituents on the imine carbon atom.[6] Based on these results, we initially examined the synthesis of *N*-Boc-propargylic amines via the in situ generated *N*-Boc-imine **7** from the reaction of *N*-Boc-aminal **5a** with organometallic bases and nucleophiles (Scheme 2). When butyllithium was

Scheme 2. Reactions of *N*-Boc-Aminal 5a with Organometallic Reagents



BuLi, THF-hexane, −78 °C, 15 min **8a** (R = Bu) 25%
MeMgBr, THF, −20 °C, 20 min **8b** (R = Me) 93%
Et_2Zn, CH_2Cl_2-hexane, 0 °C, 1 h **8c** (R = Et) 88%

employed at −78 °C, *N*-Boc-aminal **5a** was consumed immediately. However, the desired addition product **8a** (R = Bu) was obtained in low yield, probably due to the presence of multiple reaction sites in **5a** and **7**. Indeed, cleavage of the Boc group was observed for **5a**. Conversely, treatment of **5a** with methylmagnesium bromide at −20 °C afforded the desired adduct **8b** (R = Me) cleanly.[7] Furthermore, diethylzinc could also be used for the synthesis of propargylic amine **8c** (R = Et). Consequently, we chose the readily available organomagnesium reagents as nucleophiles for further investigations into the scope of this reaction.

Initially, *N*-Boc-aminals **5** with *C*-alkynyl and *C*-alkenyl groups were treated with alkynyl and alkenylmagnesium halides in THF at −20 °C (Table 1). The desired 1,2-addition to the resulting *N*-Boc-imines proceeded exclusively and furnished unprecedented *N*-Boc-propargylic and allylic amines **4** in good yields, while possible 1,4-adducts were not observed. The

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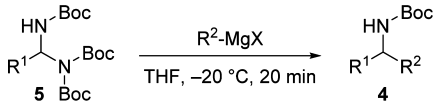
Table 1. Synthesis of α-Alkynyl and α-Alkenyl-Substituted *N*-Boc-Propargylic and Allylic Amines 4[a]



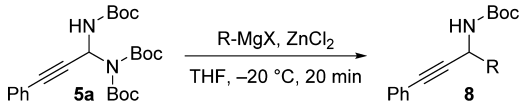
entry	R^1	R^2-MgX	(equiv)		yield (%)[b]
1[c]	Ph—≡—§	Bu—≡—MgCl	3.3	**4a**	78
2		Cy—≡—MgCl	3.3	**4b**	64
3		Ph—≡—MgBr	4.4	**4c**	82
4		$(EtO)_2C$—≡—MgCl	3.3	**4d**	74
5		TMS—≡—MgCl	3.3	**4e**	81
6[d]		MgBr	2.2	**4f**	90
7		MgBr	2.2	**4g**	81
8	Pent—≡—§	TMS—≡—MgCl	4.4	**4h**	75
9		MgBr	2.2	**4i**	99
10[e]	Ph	Ph—≡—MgBr	6.6	**4j**	84
11[f]		TMS—≡—MgCl	6.6	**4k**	85
12[f]		MgBr	2.2	**4l**	82
13[g]	Ph	Ph—≡—MgBr	6.6	**4m**	84
14[g]		TMS—≡—MgCl	6.6	**4n**	71
15[g]		MgBr	2.2	**4o**	90

[a]The reaction between **5** (0.05 mmol) and the corresponding organomagnesium reagent (0.11−0.33 mmol) was carried out in THF (0.5 mL) at −20 °C. [b]Isolated yield. [c]Performed on a 2.2 mmol scale. [d]Performed on a 1.0 mmol scale. [e]*Cis*/*trans* = 15/1. [f]*Cis*/*trans* = >20/1. [g]*Cis*/*trans* = 1/>20.

reactions of *N*-Boc-imine intermediates containing a *C*-alkenyl group afforded the corresponding *cis*/*trans* isomerized product in only trace amounts (entries 10−15).

We then investigated the scope of this method by examining a variety of alkyl and arylmagnesium reagents (Table 2). While the reaction of **5a** with linear alkylmagnesium reagents afforded the desired adducts **8a** (R = Bu) and **8b** (R = Me) in good yields (entries 1 and 2), the use of isopropylmagnesium chloride resulted in the generation of **8d** (R = *i*-Pr) in low yield on account of the undesired reduction of the *N*-Boc-imine intermediate (entry 3). Interestingly, the addition of zinc chloride proved to be effective in suppressing this side reaction, leading to a significantly increased yield (entry 4).[8] Positive effects of zinc chloride were also observed in the reaction of allylmagnesium chloride (entry 6 vs 7). Aromatic and heteroaromatic magnesium reagents also furnished *N*-Boc-propargylic amines **8g** (R = Ph) and **8h** (R = 2-furyl) in good yields (entries 8 and 9).

Table 2. Synthesis of Various *N*-Boc-Propargylic Amines 8[a]

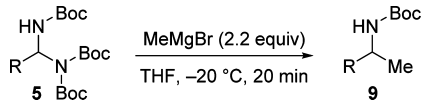


entry	R-MgX	(equiv)	$ZnCl_2$ (equiv)		yield (%)[b]
1	Bu-MgCl	2.2	0	**8a**	70
2	Me-MgBr	2.2	0	**8b**	93
3	*i*-Pr-MgCl	3.3	0	**8d**	19
4	*i*-Pr-MgCl	3.3	1.1	**8d**	93
5	*t*-Bu-MgCl	4.4	1.5	**8e**	69
6	Allyl-MgCl	3.3	0	**8f**	19
7[c]	Allyl-MgCl	3.3	1.1	**8f**	78
8	Ph-MgBr	2.2	0	**8g**	93
9	2-Furyl-MgBr	3.3	0	**8h**	89

[a]The reaction between **5a** (0.05 mmol) and the corresponding organomagnesium reagent (0.11−0.22 mmol) was carried out in the presence of $ZnCl_2$ (0−0.08 mmol) in THF (0.5 mL) at −20 °C. [b]Isolated yield. [c]*t* = 40 min.

The present method was found to be applicable to a wide variety of *N*-Boc-aminals (Table 3). The in situ generated *N*-Boc-imine intermediate from an *N*-Boc-aminal with a 1-heptynyl group contains an acidic proton at the γ-position, and its deprotonation under basic conditions seems to be a possible side reaction. However, even with highly basic methylmagnesium bromide, the desired adduct **9a** (R = 1-heptynyl) was obtained in good yield (entry 1). The addition of methylmagnesium bromide to an *N*-Boc-aminal carrying a 2-phenylethyl group proceeded in preference to the deprotonation of the α-proton of the in situ generated *N*-Boc-imine intermediate (entry 4). The use of a phenyl-substituted *N*-Boc-aminal afforded adduct **9e** (R = Ph) in high yield (entry 5), and the reaction of Cbz-protected aminal **10** with methylmagnesium bromide furnished Cbz-protected propargylic amine **11** in good yield (Scheme 3).

Table 3. Synthesis of *N*-Boc-Amines 9 Having Various α-Substituents[a]



entry	R		yield (%)[b]	entry	R		yield (%)[b]
1	Pent—≡—§	**9a**	83	4	Ph§	**9d**	94
2[c]	Ph	**9b**	92	5	Ph-§	**9e**	99
3[d]	Ph§	**9c**	85				

[a]The reaction between **5** (0.05 mmol) and the corrsponding organomagnesium reagent (0.11 mmol) was carried out in THF (0.5 mL) at −20 °C. [b]Isolated yield. [c]*Cis*/*trans* = >20/1. [d]*Cis*/*trans* = 1/>20.

The obtained α-vinyl-substituted *N*-Boc-propargylic amine **4f** could be converted into *N*-Boc-protected 1,2-aminoalcohol **12** in good yield by an ozonolysis and a subsequent reduction with $NaBH_4$ (Scheme 4). In this transformation, the vinyl group reacted with ozone selectively, despite the presence of the phenylethynyl group.[9]

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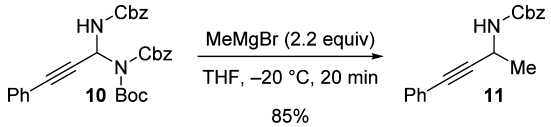
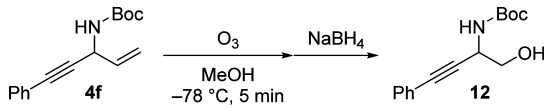
Scheme 3. Reaction of *N*-Cbz-Aminal 10 with Methylmagnesium Bromide

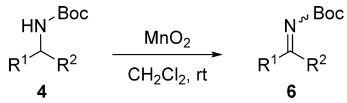


Scheme 4. Synthesis of *N*-Boc-1,2-Aminoalcohol 12



N-Boc-protected ketimines are valuable prochiral electrophiles to produce *N*-Boc-protected chiral α-tertiary amines.[10] To the best of our knowledge, however, available *N*-Boc-ketimines have been limited to those substituted with aryl or electron-withdrawing groups.[11] In the course of the present study on *N*-Boc-protected imines, we became interested in developing an efficient method for the synthesis of novel *N*-Boc-ketimines. We found that the oxidation of α-alkynyl and alkenyl-substituted *N*-Boc-propargylic amines **4** with manganese dioxide afforded unprecedented *N*-Boc-protected dialkynyl ketimines and alkenyl alkynyl ketimines **6** in good yields (Table 4).[12,13] While *N*-Boc-dialkynyl ketimines were obtained as a 1:1 mixture of *E*- and *Z*-isomers (entries 1−3 and 5), *Z*-ketimine **6d** was formed exclusively in the case of an *N*-Boc-alkenyl alkynyl ketimine (entry 4), and a *cis*/*trans* isomerization of the styryl group was not observed (entry 4).[14]

Table 4. Oxidation of *N*-Boc-Propargylic Amines 4 To Furnish *N*-Boc-ketimines 6[a]

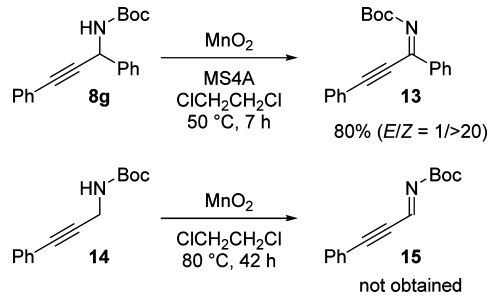


entry	R^1	R^2	time (h)		yield (%)[b]
1[c,d]	Ph—	Bu—	11	**6a**	93
2		Ph—	23	**6b**	99
3		TMS—	14	**6c**	75
4[c,e,f]		Ph	3	**6d**	81
5[g]	Pent—	TMS—	14	**6e**	85

[a]The reaction between **4** (0.05 mmol) and manganese dioxide (1.0 mmol) was carried out in dichloromethane (0.5 mL) at room temperature. [b]Isolated yield. [c]Performed in 1,2-dichloroethane at 50 °C. [d]Performed on a 1.0 mmol scale. [e]*E*/*Z* = 1/>20. [f]*Cis*/*trans* = 1/>20. [g]Performed in 1,2-dichloroethane at 80 °C.

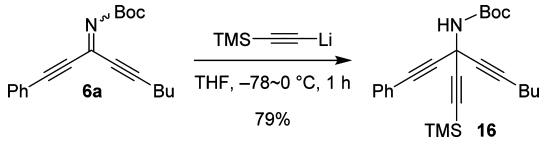
While oxidation of *N*-Boc-protected α-phenylpropargylic amine **8g** with manganese dioxide afforded the corresponding *N*-Boc-ketimine **13** exclusively as the *Z*-isomer in good yield,[11q] the reaction of the non-α-substituted *N*-Boc-propargylic amine **14** did not yield the desired *N*-Boc-aldimine **15**, even at higher temperature (Scheme 5). These results suggested that the presence of an alkynyl, alkenyl, or aryl substituent is necessary at the α-position for the oxidation to proceed.

Scheme 5. Effects of the α-Substituent in *N*-Boc-Propargylic Amines on the Oxidation To Give *N*-Boc-Imines



Treatment of the obtained dialkynyl imine **6a** with lithium trimethylsilylacetylide resulted in the formation of the *N*-Boc-protected tris(alkynyl)methylamine **16** with three different terminal substituents (Scheme 6).[15] The Boc group was cleanly deprotected by treatment with trimethylsilyl iodide in acetonitrile (see Supporting Information).

Scheme 6. Synthesis of *N*-Boc-Tris(alkynyl)methylamine 16



In summary, we have synthesized *N*-Boc-protected propargylic and allylic amines via the reaction between *N*-Boc-aminals and organomagnesium reagents, in which *N*-Boc-imines are generated as reactive intermediates under basic conditions and are subsequently subjected to an addition reaction. This process allows direct synthetic access to unprecedented α-alkynyl and α-alkenyl-substituted *N*-Boc-propargylic and allylic amines in an operationally simple process. The obtained *N*-Boc-propargylic and allylic amines are readily oxidized by manganese dioxide to afford previously unobtainable ketimines. Accordingly, this method represents a rare example for the oxidation of *N*-Boc-amines to *N*-Boc-ketimines. We are currently exploring applications of the newly obtained *N*-Boc-ketimines in other transformations including catalytic asymmetric reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03446.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The oxidation of *N*-Boc-propargylic amine **4j** with manganese dioxide afforded the *N*-Boc-protected phenylethynyl *cis*-styryl imine, which readily underwent *cis*/*trans* isomerization of the styryl group to give *trans*-isomer **6d** as a major stereoisomer at room temperature.

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