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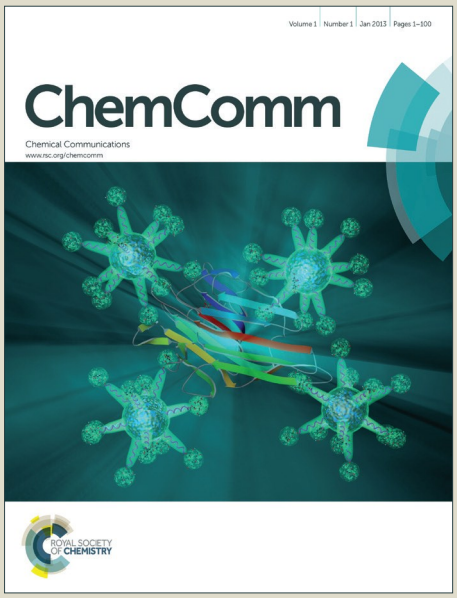

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Diaza [1,4] Wittig-type rearrangement of *N*-allylic-*N*-Boc-hydrazines into γ-amino-*N*-Boc-enamines

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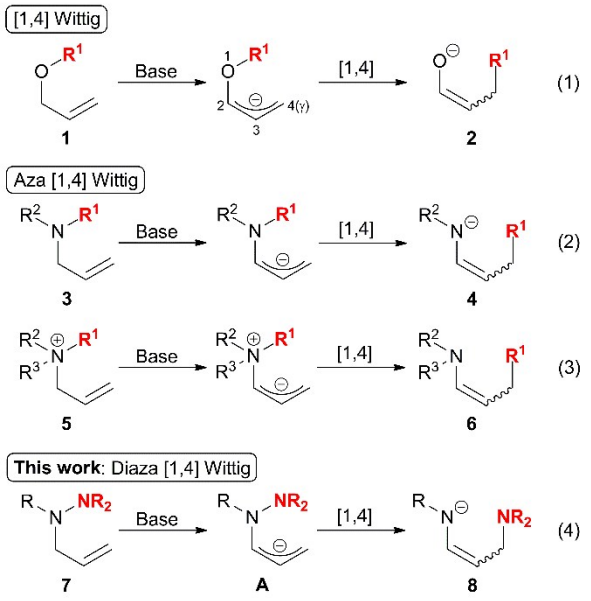
Diaza [1,4] Wittig-type rearrangement of *N*-allylic-*N*-Boc-hydrazines into γ-amino-*N*-Boc-enamines was demonstrated. The scope and limitation, experimental mechanistic studies, and a proposed reaction mechanism were also described.

The [1,4] Wittig rearrangement of allylic carbanion generated from alkyl allylic ethers **1** in the presence of a base is one of the most unique transformations in organic synthesis. The reaction provides enolates **2** via a C–O bond cleavage followed by a 1,4-shift of a migrating group to form a new C–C bond at the γ-position of the allylic moiety (Scheme 1, eqn (1)).[1-3] The resulting enolates **2** can be trapped as the enol ethers, or they can be converted into the corresponding carbonyl compounds by protonation. The aza version[4,5] of this [1,4] rearrangement of allylic amines **3** is also of interest because the reaction would provide enamines that are valuable building blocks for the synthesis of nitrogen-containing compounds (eqn (2)). Unfortunately, previous examples of this aza-[1,4] Wittig rearrangement are severely limited. No successful example of the [1,4] rearrangement of allylic amines **3** has been reported because of the chemical instability of the product enamine anion **4** or its protonated secondary enamine. To the best of our knowledge, only a few examples of the [1,4] rearrangement of *N*-allylic ammonium salts **5** into enamines **6** have been reported (eqn (3)).[6] Our group hypothesized that when *N*-allylic hydrazines **7** are subjected to the base-promoted [1,4] Wittig rearrangement, an N–N bond cleavage[7] from the allylic carbanion **A** might proceed smoothly followed by a 1,4-shift of an amino migrating group into the 4-position, providing the γ-amino enamine anion **8**[8] (eqn (4)). Thus, we began investigating this transformation.



Scheme 1 [1,4] Wittig (and analogous) rearrangements.

Because efficient preparation methods of various types of *N*-Boc-hydrazine derivatives have already been reported by Maeorg's group,[9] we selected 1-allylic-1-Boc-2-methyl-2-phenylhydrazine **9** as a substrate (Table 1). Additionally, the Boc substituent is able to stabilize the product enamine anion **8** depicted in Scheme 1 and the protonated secondary *N*-Boc-enamine **10**. First, we examined a reaction of *N*-allyl derivative **9a** with 2.4 equivalents of ^{n}BuLi in THF at –78 °C for 3 h. The reaction provided γ-amino-*N*-Boc-enamine **10a** in 72% yield as essentially a single *E*-isomer (entry 1, *E*/*Z* = 97/3). The stereochemistry of *E*- and *Z*-**10a** were determined by the ^{1}H NMR coupling constant of the double bond protons (*E*-**10a**: *J* = 14 Hz, *Z*-**10a**: *J* = 9 Hz). The reaction in diethyl ether resulted in lower yield (entry 2) but the use of LDA in THF improved the yield of **10a** to 81% (entry 3). When the reactions were carried out with 1.2 equivalents of ^{n}BuLi or LDA, the yields of **10a** were

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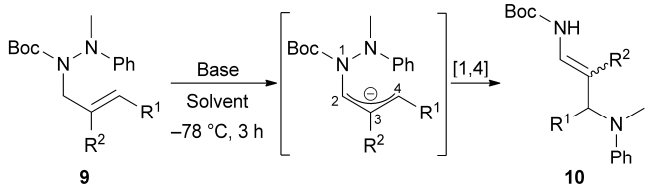
slightly decreased (entries 4 and 5). The use of analogous bases, such as LiTMP, did not improve the yield of **10a** (entry 6), and the less basic LiHMDS and KHMDS would not generate the allylic carbanion leading to **10a** but instead led to quantitative recovery of **9a** (entries 7 and 8). To define the scope and limitation of *N*-allylic substituents, we prepared *trans*-crotyl (**9b**), cinnamyl (**9c**), and methallyl (**9d**) derivatives and examined their reactions. The reactions of **9b** and **9c** were unsuccessful (entries 9 and 10) and provided *N*-methylaniline (**12a**) as the N–N bond cleaved product. The migrating group derived from **9b** and **9c** did not form a C–N bond at the γ-position of the γ-substituted allylic moieties. In contrast, a reaction of **9d**, which has a β-substituted allylic moiety, proceeded similarly to that of **9a**, and the desired **10d** was obtained in 75% yield with *E*-selectivity (entry 11, *E*/*Z* = 95/5).[10]

Table 1 Base-promoted 1,4-Shift of 1-allylic-1-Boc-2-methyl-2-phenylhydrazines **9**

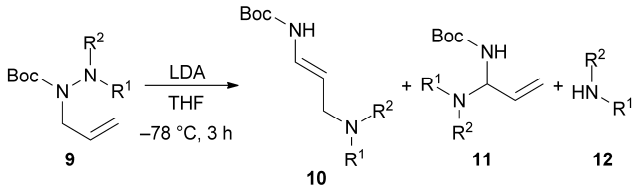


Entry	Base (eq)	R^1	R^2		Solvent	Yield (%)[a]	*E*/*Z*[b]
1	*n*BuLi (2.4)	H	H	**a**	THF	72	97/3
2	*n*BuLi (2.4)	H	H	**a**	Et_2O	46	96/4
3	LDA (2.4)	H	H	**a**	THF	81	98/2[c]
4	*n*BuLi (1.2)	H	H	**a**	THF	67	94/6
5	LDA (1.2)	H	H	**a**	THF	76	97/3
6	LiTMP (1.2)	H	H	**a**	THF	60[d]	97/3
7	LiHMDS (1.2)	H	H	**a**	THF	0[e]	–
8	KHMDS (1.2)	H	H	**a**	THF	0[e]	–
9	LDA (2.4)	Me	H	**b**	THF	0[f]	–
10	LDA (2.4)	Ph	H	**c**	THF	0[g]	–
11	LDA (2.4)	H	Me	**d**	THF	75	95/5

[a] Isolated yield. [b] Determined by the isolated yields of *E*- and *Z*-**10** unless otherwise noted. [c] Determined by the ^{1}H NMR assay of a mixture of *E*- and *Z*-**10a**. [d] Recovered **9a** in 21% yield. [e] Recovered **9a** in quantitative yield. [f] *N*-Methyaniline (**12a**) was obtained in 79% yield. [g] *N*-Methyaniline (**12a**) was obtained in 64% yield.

Next, we prepared a series of substrates **9e**–**p** to further explore the scope and limitations of migrating groups. The reactions were carried out with 2.4 equivalents of LDA (Table 2). Reactions of *para*-methoxy-, *para*-methyl-, and *para*-chloro-substituted **9e**–**g** afforded the corresponding enamides **10e**–**g** in moderate yields (entries 1–3); however, *para*-ethoxycarbonyl derivative **9h** gave complicated products formed by undesirable side reactions (entry 4). Thus, this unsuccessful reaction was reexamined with 1.2 equivalents of LDA to minimize the side reactions (entry 5). The desired product **10h** was obtained in 37% yield, along with the formation of a small amount of **12h** as the N–N bond cleaved product. A stronger electron-withdrawing group (EWG) on the aromatic ring most likely caused undesirable side reactions and decreased the yield of **10**. Reactions of *meta*-methyl- and *meta*-chloro-substituted **9i** and **9j** proceeded similarly to that of *para*-derivatives, and the corresponding **10i** and **10j** were obtained in modest yields (entries 6 and 7). In contrast, a reaction of *ortho*-methyl derivative **9k** was relatively unsuccessful. The desired **10k** was obtained in only 14% yield, while the N–N bond cleaved **12k** was isolated in 66% yield (entry 8). The steric repulsion of the *ortho*-methyl substituent may inhibit the formation of a C–N bond at the γ-position of the *N*-allyl substituent. Thus, we prepared cyclized *ortho*-substituted **9l** and **9m** to reduce the steric repulsion and examined their reactions. As expected, the 1,4-shift proceeded to afford **10l** and **10m** in better yields than **10k** (entries 9 and 10). To clarify the substituent effects around the nitrogen atom of the migrating groups, we investigated the reactions of *N*-allyl (**9n**) and *N*,*N*-diphenyl (**9o**) derivatives. Although the desired *N*-allyl product **10n** was obtained in 65% yield (entry 11), the yield of *N*,*N*-diphenyl product **10o** was lowered to 48% with the isolation of the N–N bond cleaved **12o** in 52% yield (entry 12). It is believed that two aromatic *N*-substituents may reduce the reactivity of the migrating group by steric effect or electron delocalization. Furthermore, a reaction of *N*-Boc-*N*-phenylamino derivative **9p** did not produce 1,4-shifted **10p** (entry 13). Instead, the formation of aminal **11p** derived by a 1,2-shift and *N*-Boc-aniline (**12p**) was observed. In this case, the Boc substituent, the migrating group of **9p**, reduced the electron density on the nitrogen atom, and the mobility of the migrating group was significantly reduced.

Table 2 Base-Promoted 1,4-Shift of 1-allyl-1-Boc-2-methyl-2-arylhydrazines **9**[a]

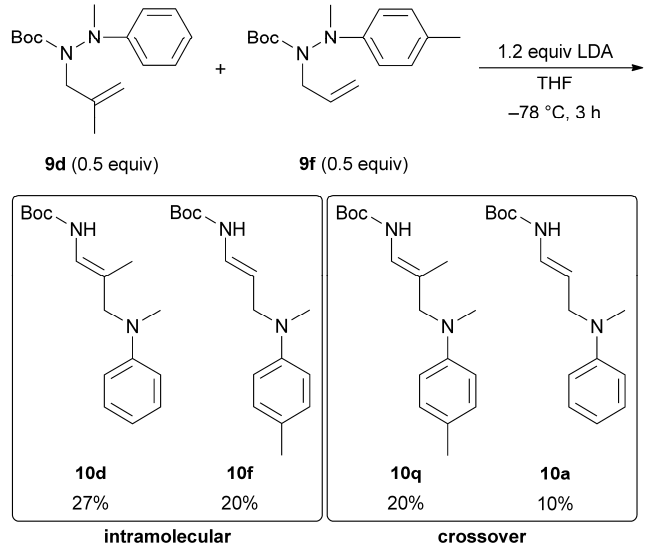


Entry	R^1	R^2		**10** (%)[b]	**11** (%)[b]	**12** (%)[b]
1	*p*-MeO-C_6H_4	Me	**e**	68	–	–
2	*p*-Me-C_6H_4	Me	**f**	70	–	–
3	*p*-Cl-C_6H_4	Me	**g**	78	–	–
4	*p*-EtOCO-C_6H_4	Me	**h**		messy	
5[c]	*p*-EtOCO-C_6H_4	Me	**h**	37	–	10
6	*m*-Me-C_6H_4	Me	**i**	62	–	9
7	*m*-Cl-C_6H_4	Me	**j**	79	–	–
8	*o*-Me-C_6H_4	Me	**k**	14	–	66
9	1,2,3,4-tetrahydroquinolin-1-yl		**l**	57	–	–
10	indolin-1-yl		**m**	46	–	–
11	Ph	$CH_2CH{=}CH_2$	**n**	65	–	–
12	Ph	Ph	**o**	48	–	52
13[d]	Ph	Boc	**p**	0	8	60

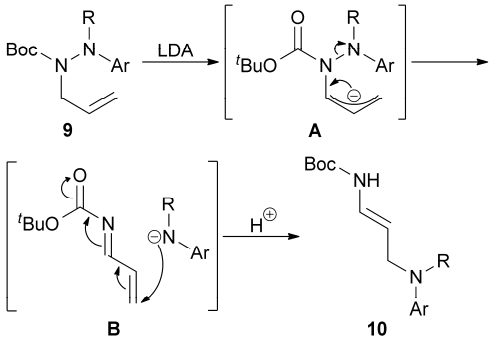
[a] Unless otherwise noted, the reactions were carried out with 2.4 equiv. of LDA and the products **10** were obtained as nearly a single *E*-stereoisomer. [b] Isolated yield. [c] LDA: 1.2 equiv. [d] Recovered **9p** in 28% yield.

To clarify the mechanistic origin of this 1,4-shift, we examined a crossover experiment (Scheme 2). When an equimolar mixture of **9d** and **9f** was treated with LDA, the intramolecular products (**10d**, **10f**) and the crossover products (**10q**, **10a**) were produced without selectivity. Using this observation and the results shown in Tables 1 and 2, the reaction mechanism of this

1,4-shift was proposed (Scheme 3). We believe the reaction proceeds as follows: (i) formation of allylic carbanion (**9** to **A**), (ii) heterolytic cleavage of an N–N bond to form an anilide anion and an *N*-Boc-conjugated imine (**A** to **B**), and (iii) conjugate addition of the anilide anion to the more thermodynamically stable *s-trans*-*N*-Boc-conjugated imine (**B**). The γ-substituted allylic moieties, as well as electron-deficient and/or sterically hindered migrating groups, inhibit the conjugate addition to form **10**. We termed this reaction a "diaza [1,4] Wittig-type rearrangement".[11]



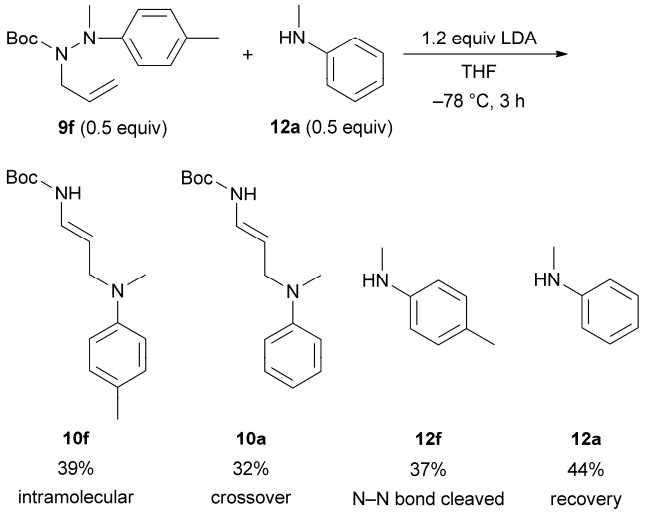
Scheme 2 Crossover experiment.



Scheme 3 Proposed reaction mechanism.

To eliminate the possibility of a radical cleavage–recombination process, a reaction of an equimolar mixture of **9f** and *N*-methylaniline **12a** was investigated (Scheme 4). The conditions generate the allylic carbanion derived from **9f** and the anilide anion derived from **12a** in the initial step. The enamide **10f** derived by the intramolecular reaction of **9f** and the enamide **10a** derived by the crossover reaction between **9f** and **12a** were generated without selectivity. The corresponding eliminated **12f** and unreacted **12a** were also obtained. Therefore, the proposed conjugate addition of anilide anion (**B**) depicted in Scheme 3 was confirmed.

In conclusion, we have reported the base-promoted diaza [1,4] Wittig-type rearrangement of *N*-allylic-*N*-Boc-hydrazine derivatives involving an N–N bond cleavage. The 1,4-shift of an amino migrating group to the γ-position of the allylic moiety provided synthetically valuable γ-amino enamides with high *E*-selectivities. Mechanistic studies employing crossover experiments clarified that the reaction mechanism proceeded via the formation of the anilide anion and *N*-Boc-conjugated imine as intermediates, followed by conjugate addition. Although the diaza [1,4] Wittig-type rearrangement has substrate limitations,[12] our method provides unique access to substituted *N*-Boc-enamines.



Scheme 4 Diaza [1,4] Wittig-type rearrangement in the presence of *N*-methylaniline.

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‡Electronic supplementary information (ESI) available: Experimental details (including selected NMR spectra).

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