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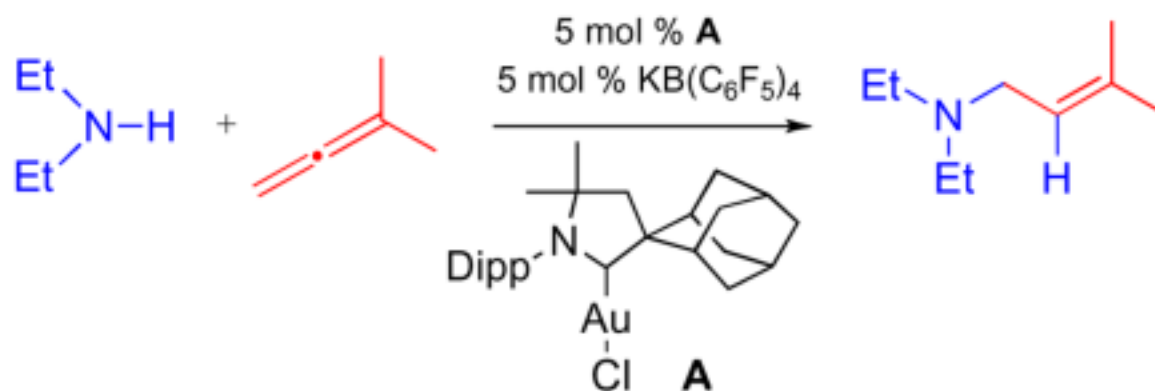
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Gold Catalyzed Intermolecular Markovnikov Hydroamination of Allenes with Secondary Amines

Xiaoming Zeng[‡], Michele Soleilhavoup, and Guy Bertrand^{*}

UCR-CNRS Joint Research Chemistry Laboratory (UMI 2957), Department of Chemistry, University of California, Riverside, CA 92521-0403 (USA)

Abstract



A cationic (CAAC)gold(I) complex promotes the addition of all types of non-tertiary amines to a variety of allenes, affording allylic amines in good to excellent yields; the amino fragment always adds to the less substituted terminus of the CCC skeleton.

The most widely used chemical reaction for the functionalization of alkenes, alkynes and allenes is the addition of an A-B bond across a carbon-carbon π -bond.¹ Since nitrogen-carbon bonds are ubiquitous in molecules and of significant importance in human life, as well as for the chemical industry;² the so-called hydroamination reaction has attracted considerable interest.³ However, a close look at the literature reveals that although the intramolecular hydroamination of allenes⁴ has been widely studied,⁵ the intermolecular version has received limited attention. Depending on the regiochemistry, this reaction can lead to imines, enamines or allylamines. The allylamines, (Markovnikov adducts) are especially interesting since they are among the most versatile intermediates in synthesis, components of many naturally occurring and biologically active molecules, and of industrial importance.⁶ In 1992, Bergman reported that zirconium bis(amides) were efficient catalysts to promote the addition of primary arylamines to 1,2-propadiene giving the corresponding imines,⁷ and more recent papers confirm that early transition metal catalysts lead to the anti-Markovnikov adducts (Scheme 1, top).⁸ The Markovnikov addition has first been achieved in the presence of equimolar amounts of mercury(II), palladium(II) and platinum(II) salts,⁹ and then used a palladium(0) catalyst in

guy.bertrand@ucr.edu.

*Present address: Key Laboratory of Green Chemistry & Technology of Ministry of Education at Sichuan University, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China.

Supporting Information Available: General catalytic procedure, experimental details and characterization of complexes **I** and **II**, as well as ^1H , ^{13}C , and MS spectra for new catalytic products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

the presence of triethylammonium iodide¹⁰ or acetic acid¹¹ as cocatalysts. Gold catalysts¹² have more recently been developed.¹³ Yamamoto et al., have first demonstrated that 10 mol % of AuBr₃ allowed the room temperature addition of primary arylamines to allene to afford allylic amines,^{14a} and then described the addition of morpholine to mono- and disubstituted allenes at 80 °C, using 10 mol % of a 1/1 mixture of (Ar₃P)AuCl and AgOTf (Scheme 1, middle).^{14b} In 2008, Widenhoefer reported the Markovnikov hydroamination with N-unsubstituted carbamates using catalytic amounts of an equimolar mixture of LAuCl and AgOTf (L = NHC, phosphine) (Scheme 1, bottom).¹⁵ Interestingly, an opposite regioselectivity was observed, when compared with Yamamoto's results.^{14b} Recently, we have shown that cationic gold(I) complexes (**Cat**) (Figure 1),¹⁶ featuring a bulky cyclic (alkyl)(amino)carbene (CAAC),¹⁷ as ancillary ligand, efficiently promoted the addition of NH₃ to non-activated alkynes and allenes.¹⁸ These first examples of hydroamination reaction with ammonia prompted us to investigate the scope of application of our catalytic system. Here we show that **Cat1** [a 1/1 mixture of (CAAC)AuCl and KB(C₆F₅)₄] is efficient to promote the intermolecular Markovnikov hydroamination of allenes **A-C** (scheme 2) with a variety of primary and, more importantly, secondary amines.

Since, as mentioned above, several catalytic systems are known to promote the hydroamination of allenes with primary amines, we briefly investigated if **Cat1** was efficient as well (Table 1, Entries 1–3). In the presence of 5 mol % of **Cat1**, we were pleased to observe that after 12 h at 70 °C, aniline reacted with 1,1-dimethyl allene **A** to afford a 60/40 mixture of N-allyl- and N,N'-diallylaniline in 95% yield (Entry 1). Clearly, the N,N'-diallylaniline results from the addition of the primarily formed N-allylaniline on allene **A**, which gives a clear indication that secondary arylamines are suitable substrates for our catalytic system. Mesitylamine, and even the strongly basic and bulky *tert*-butylamine react with **A**, although under more drastic conditions, giving the secondary allylamines in 74 and 54% yield, respectively (Entries 2 and 3).

Then, we turned our attention to secondary (aryl)(alkyl)amines using again 5 mol % of **Cat1** (Table 1, Entries 4–9). In an initial experiment, 1,1-dimethylallene **A** was treated with N-methylaniline, and after 12 h at only 70 °C, the desired hydroamination product was obtained in 98% yield (Entry 4). Para-substitution of the aniline by a chlorine or methoxy group are well tolerated, the corresponding adducts being formed in 97% yields (Entries 5 and 6). 1,2,3,4-Tetrahydroquinoline and indoline have been recognized as important synthetic intermediates,¹⁹ and exhibit extensive biological activities and potential pharmaceutical applications. Using allene **A**, their allylic amine derivatives have been prepared using our catalytic procedure with up to 99% yield (Entries 7 and 8). The hydroamination reaction with secondary (aryl)(alkyl) amines is not limited to 1,1-disubstituted allenes. The parent allene **B** can also be used as shown in Entry 9.

Based on these positive results, we investigated the catalytic activity of **Cat1** for the hydroamination of allenes with more basic secondary amines (Table 2). By analogy with the work of Yamamoto, we first reacted morpholine with allenes **A-C**, and in all cases the Markovnikov adduct was obtained in good to excellent yields (Entries 1–3). Benzylic and benzocyclic amines also smoothly react with allenes **A** and **B** at temperatures between 70 and 90 °C affording the hydroamination products in 93 to 99% yields after only 8 to 12 h (Entries 4–7). Lastly, we used diethylamine as the prototypical secondary alkylamine. Although drastic conditions are required (130–165 °C, 24 to 36 h), the addition occurred to yield the Markovnikov adduct in 61 to 98% yields (Entries 8–10). These results emphasize the robustness of the catalyst.

To gain insight into the mechanism of the gold(I)-catalyzed hydroamination of allenes, the following experiments were performed (Scheme 3). Addition of excess allene **A** to complex

Cat2 did not give the desired allene gold complex at room temperature and even upon heating at 50 °C. This is in marked contrast with the case of alkynes, for which an η^2 -alkyne complex was readily formed and isolated.^{18,20} On the other hand, upon exposure at room temperature of a solution of **Cat2** in deuterated benzene to one equivalent of diethylamine, the amine complex **I** was spontaneously and quantitatively obtained. Then, addition of excess allene **A** to a C₆D₆ solution of **I** gives after 16 h at 70°C, complex **II**, which was isolated in 95% yield. These observations call into questions an outer sphere mechanism involving the attack of the amine to an initially formed gold π -allene complex,¹⁵ and rather suggest an inner sphere mechanism with transient formation of a tricoordinated gold complex, as proposed by Yamamoto¹⁴ and Tanaka²¹ for gold-catalyzed hydroamination of allenes and alkynes, respectively, with arylamines. Moreover, it seems quite likely that the amine complex **I** is the resting state of the catalyst, just as **Cat3** is in the case of the hydroamination with ammonia.¹⁸

Since we have already shown that **Cat1** promotes the addition of ammonia to allenes,¹⁸ it appears that the catalytic system described here has a broad scope of application; many types of non-tertiary amines can be used, as well as a variety allenes. Importantly, the regioselectivity observed (Markovnikov addition) is opposite to that obtained with early transition metal catalysts (anti-Markovnikov addition).^{7,8} The regioselectivity is also different from that reported by Windehoefer,¹⁵ using unsubstituted carbamates and a cationic gold(I) complex bearing an NHC or a phosphine ligand; the Markovnikov adduct was formed but at the more substituted terminus of the allene (Scheme 1). This striking difference has not yet been rationalized, and mechanistic studies are under active investigation. Moreover the hydroamination of 1,3-disubstituted allenes allows for the formation of a chiral center, and we are investigating the possibility of using gold(I) complexes bearing an optically active CAAC ligand for the preparation of enantiomerically enriched allylic amines.²²

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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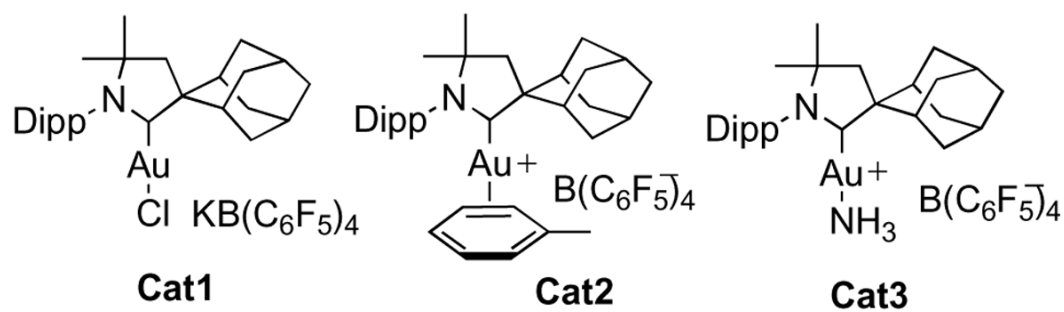
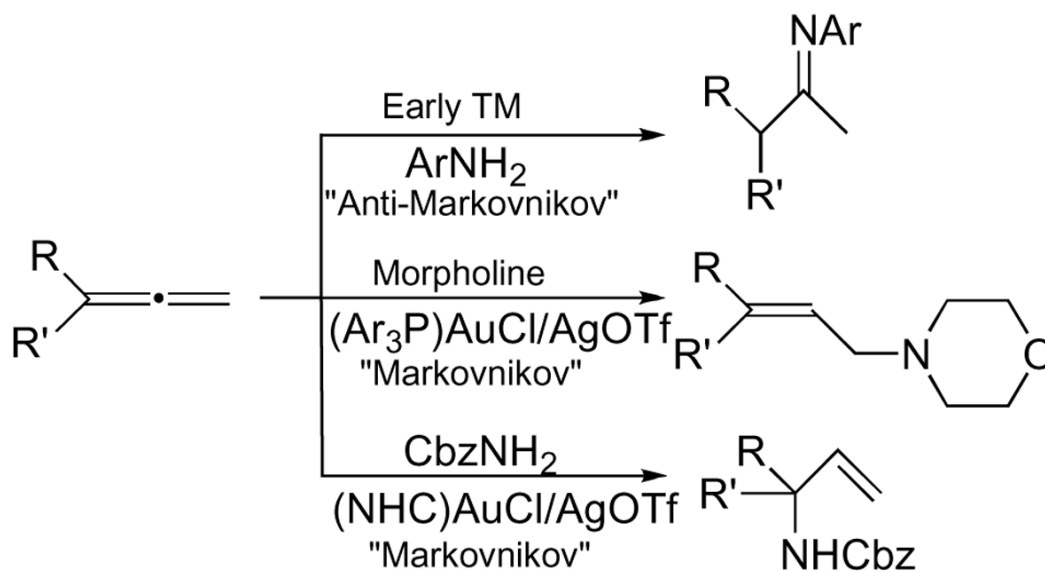
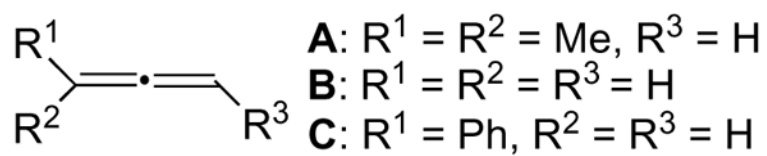


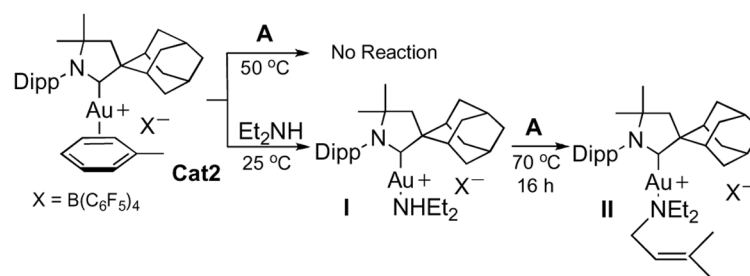
Figure 1.
Cationic gold(I) complexes promoting the addition of NH₃ to non-activated alkynes and allenes.



Scheme 1.
Previous results for the hydroamination of allenes

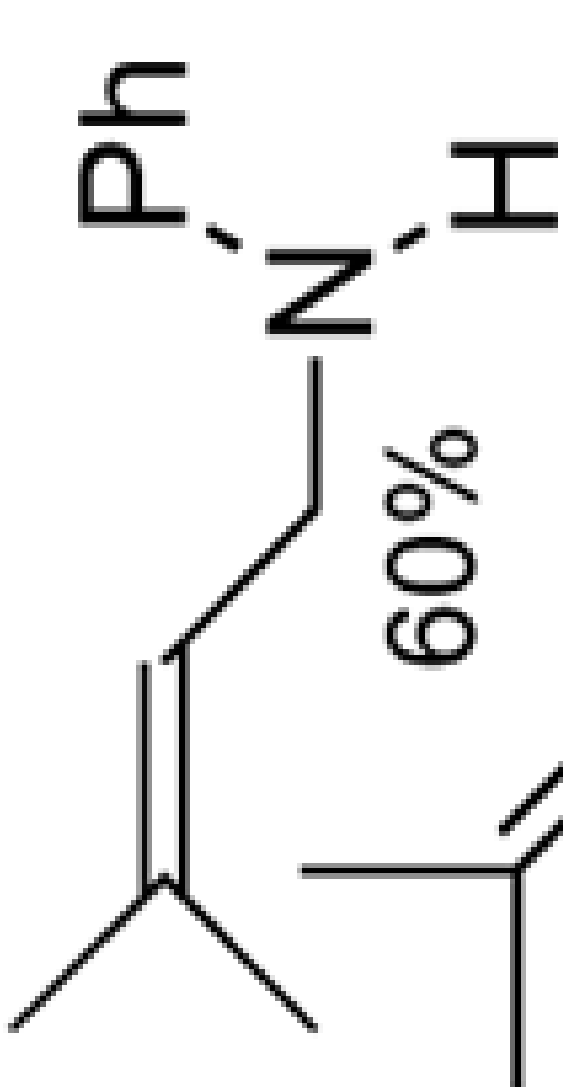



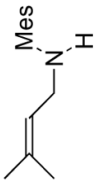
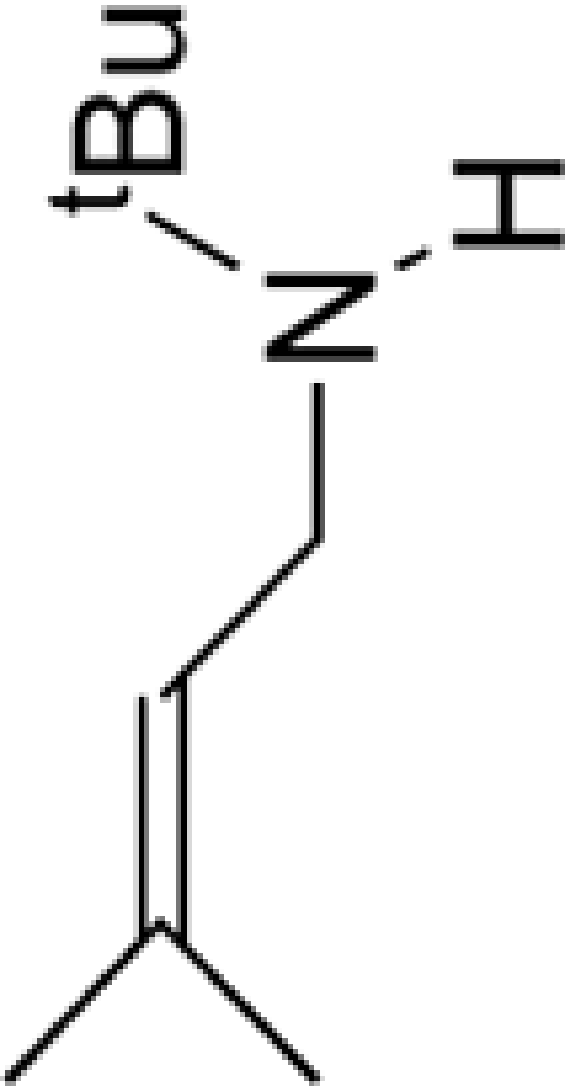
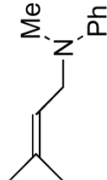
Scheme 2.
Allenes **A-C** used in this study

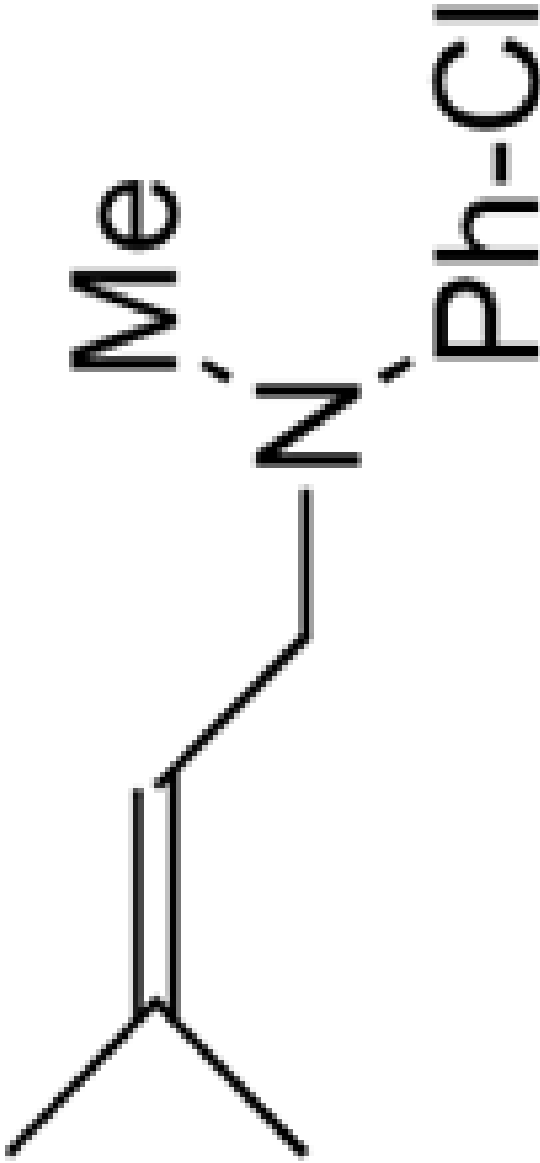
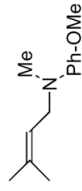
**Scheme 3.**

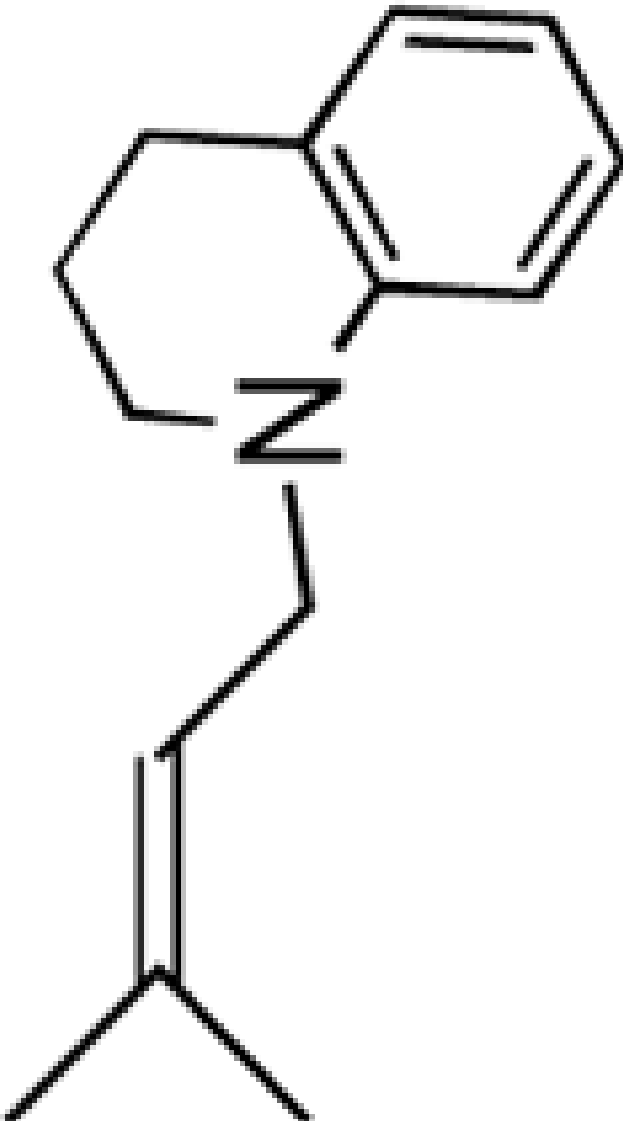
Experiments to approach the reaction mechanism


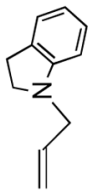
Table 1

allene	t (°C)	time (h)	product	yield ^b
A	70	12		95 ^c
				

allene	t (°C)	time (h)	product	yield ^b
A	100	5		74
A	150	30		54
A	70	12		98

allene	<i>t</i> (°C)	time (h)	product	yield ^b
A	70	12		97
A	70	12		97

allene	t (°C)	time (h)	product	yield ^b
A	70	9		99

allene	<i>t</i> (°C)	time (h)	product	yield ^b
A	70	3		99
B	70	3		87 ^d

^a CatI (5 mol %), amine (0.5 mmol), allene (0.5 mmol), C₆D₆ (0.4 mL).

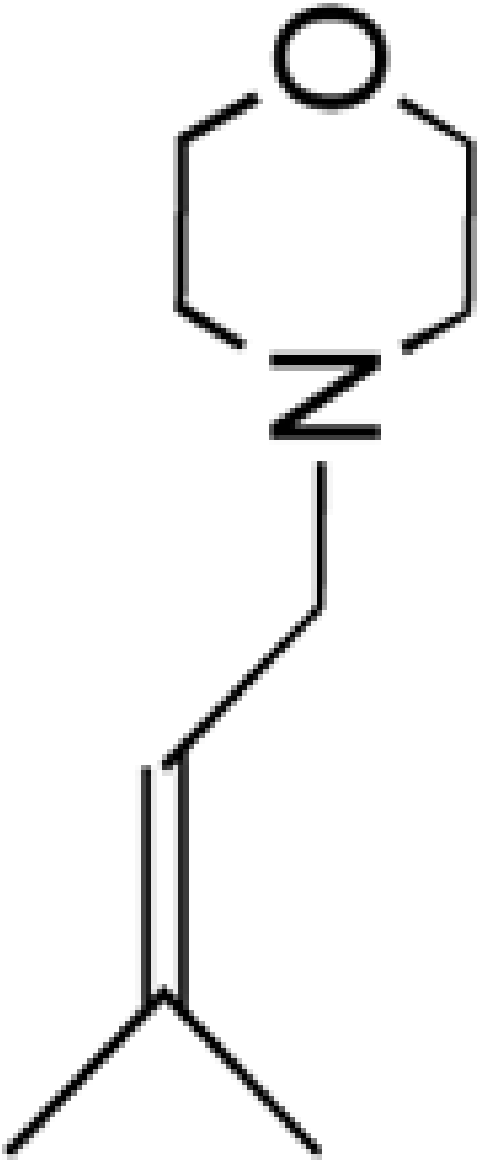
^b Yields are determined by ¹H NMR using benzylmethyl ether as an internal standard.


^c Yield based on allene.


^d Excess allene was used.


Table 2

allene	t (°C)	time (h)	product	yield ^b
A	100	12		92



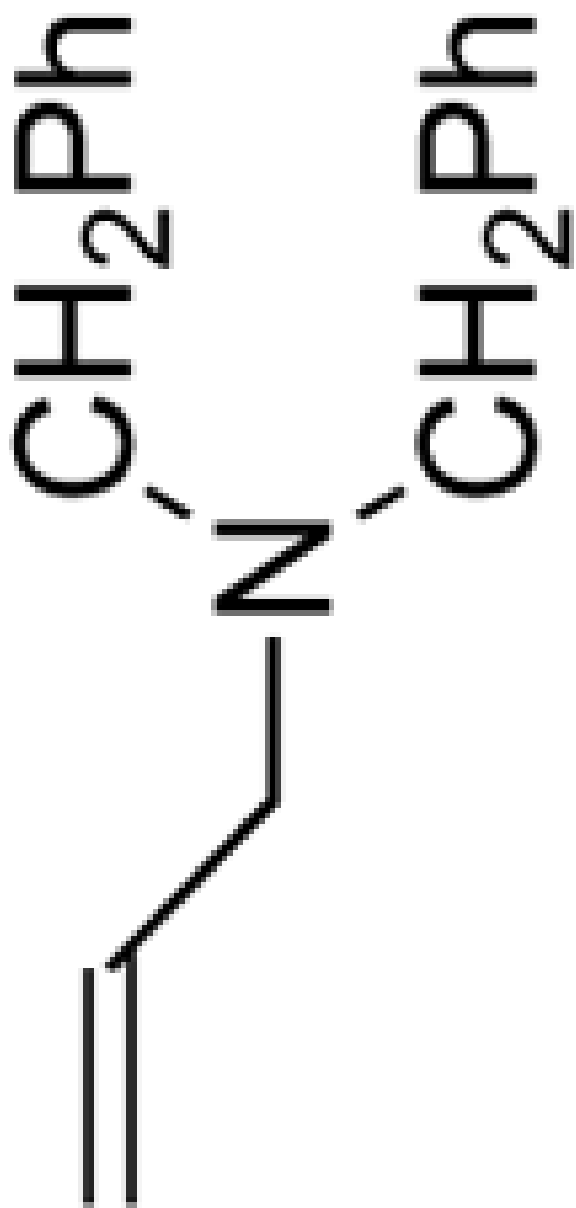
allene	t (°C)	time (h)	product	yield ^b
B	100	12		89 ^c

allene	t (°C)	time (h)	product	yield ^b
C	130	24		66 ^{d,e}

allene	t (°C)	time (h)	product	yield ^b
A	80	12		99

yield^b

94^c



98



12

90

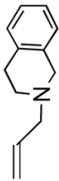
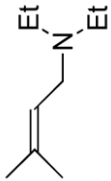
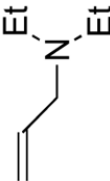
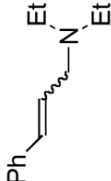
allene

B

product

time (h)

t (°C)

allene	t ($^{\circ}\text{C}$)	time (h)	product	yield ^b
B	90	8		93 ^c
A	130	36		98
B	150	24		82 ^c
C	165	24		61 ^{e,f}

^d_{E/Z} = 2.2.

^e Two equivalents of allene was used, yield based on amine.

^f_{E/Z} = 3.4.