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N-Bromoimide/DBU Combination as a New Strategy for Intermolecular Allylic Amination

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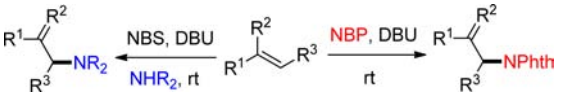
ABSTRACT



Allylic amination reactions of alkenes, with an NBP (*N*-bromophthalimide) or NBS (*N*-bromosuccinimide)/DBU combination, were developed, in which both internal and external nitrogen nucleophiles can be installed directly. Dual activation of NBS or NBP by DBU leads to more electrophilic bromine and more nucleophilic nitrogen atoms simultaneously. This protocol may provide a novel and complementary access to allylic amination under mild conditions.

Allylic amines represent an important structural motif frequently found in natural products, pharmaceuticals, as well as a versatile building block for the synthesis of organic molecules of higher complexity.[1] To date, commonly used approaches for the allylic amination of olefins include (i) metal-based oxidative allylic amination[2−5] and vinylation of imine or aminals,[6] and (ii) metal-free allylic amination,[7] for example, by the introduction of a selenium reagent[7a,b] or a hypervalent iodine(III) reagent[7c] in a recent report (Scheme 1, top). Although the above-mentioned elegant methods appear to be general and efficient, new synthetic methods are still required.

In our research on halogen-mediated organic reactions,[8] we discovered that NBS activated by DBU via a halogen bond interaction brings about simultaneously enhanced

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(1) (a) Brown, E. G. *Ring Nitrogen and Key Biomolecules*; Springer: Boston, MA, 1998. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (c) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643.

(2) Selected examples of palladium-catalyzed allylic amination: (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (c) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (d) Du, H.; Zhao, B.; Yian, S. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (e) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (f) Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224. (g) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (h) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (i) Fu, R.; Zhao, B.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 7577. (j) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (k) McDonald, R. I.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5529. (l) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931. (m) Weinstein, A. B.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11505.

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(4) Iron-catalyzed intra- and intermolecular allylic C—H amination: (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (b) Liu, Y.; Che, C.-M. *Chem.—Eur. J.* **2010**, *16*, 10494. (c) Huang, D.; Wang, H.; Xue, F.; Shi, Y. *J. Org. Chem.* **2011**, *76*, 7269. (d) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036.

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(6) Selected examples: (a) Wipf, P.; Kendal, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (b) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652. (d) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941. For Pd-catalyzed vinylation of aminals, see: (e) Xie, Y.; Hu, J.; Wang, Y.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 20613.

(7) Metal-free allylic amination: (a) Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269. (b) Bruncko, M.; Khuong, T. A. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 454. (c) Souto, J. A.; Zian, D.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 7242. (d) Trillo, P.; Baeza, A.; Nájera, C. *J. Org. Chem.* **2012**, *77*, 7344.

(8) With NBS/DBU combination: (a) Wei, Y.; Lin, S.; Liang, F. *Org. Lett.* **2012**, *14*, 4202. (b) Wei, Y.; Lin, S.; Liang, F.; Zhang, J. *Org. Lett.* **2013**, *15*, 852. With NBS/carboxylic acid combination: (c) Wei, Y.; Lin, S.; Zhang, J.; Niu, Z.; Fu, Q.; Liang, F. *Chem. Commun.* **2011**, *47*, 12394. (d) Wei, Y.; Lin, S.; Xue, H.; Liang, F.; Zhao, B. *Org. Lett.* **2012**, *14*, 712. (e) Xue, H.; Tan, H.; Wei, D.; Wei, Y.; Lin, S.; Liang, F.; Zhao, B. *RSC Adv.* **2013**, *3*, 5382.

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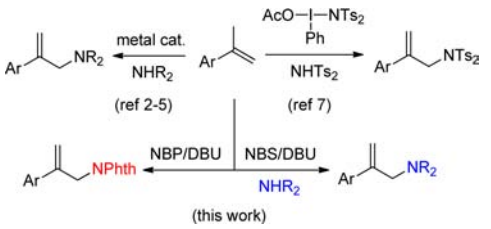
Scheme 1. Allylic Amination Using *N*-Haloimide/DBU Combination



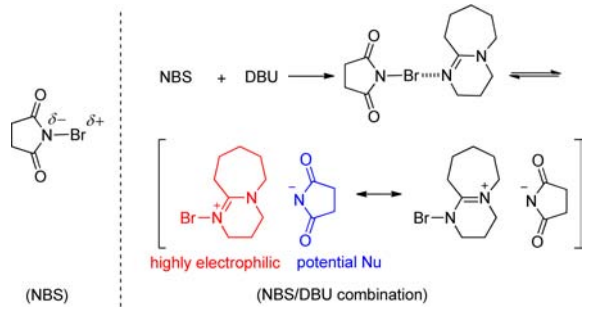


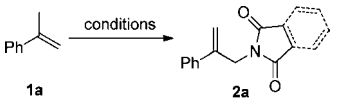
Figure 1. Dual activation mode of NBS by DBU.

electrophilic reactivity for bromine and nucleophilicity for the imido-nitrogen atom (in a contact ion pair form, Figure 1). As such, direct installation of nitrogen functionality in an economic fashion has been achieved in the reactions of alkyl aryl ketones and α,β-unsaturated enones with NBS/DBU combination, respectively.[8a,b] Intrigued by this unique reactivity, we envisioned that it is possible to develop the *N*-haloimide/DBU combination to be one type of atom-efficient and versatile aminating reagent applicable to a variety of useful transformations. With this idea in mind, we start to explore the reaction of various substrates with the *N*-haloimide/DBU combination in the continued work. Herein, we would like to communicate a novel NBS(P)/DBU combination strategy toward allylic amination of alkenes (Scheme 1, bottom), in which the nucleophilic nitrogen sources may either arise from the internal NBP itself (with NBP/DBU combination) or external amines having an acidic NH group (with NBS/DBU combination). This protocol may provide a complementary access to allylic amination.

Table 1 summarizes the optimization of the reaction conditions. Initially, the model reaction of α-methylstyrene **1a** with NBS (1.2 equiv) in the presence of DBU (1.2 equiv) was examined, but no reaction occurred in CH_2Cl_2 at room temperature (entry 1). To our delight, upon simply replacing NBS by NBP, the reaction did take place, furnishing the allylic amination product **2a** in 86% yield (entry 2).[9] A highly polar complex might be formed,

(9) The feeding sequence for alkenes, NBP, and DBU is vital for the reaction to occur!

Table 1. Optimization of the Reaction Conditions[a]



entry	*N*-haloimide	activator	solvent	yield (%)[b]
1	NBS	DBU	CH_2Cl_2	0
2	**NBP**	**DBU**	**CH_2Cl_2**	**86**
3	NBP	DBN	CH_2Cl_2	82
4	NBP	pyridine	CH_2Cl_2	5
5	NBP	DABCO	CH_2Cl_2	0
6	NBP	PPh_3	CH_2Cl_2	0
7[c]	NBP	DBU	CH_2Cl_2	0
8	NBP	DBU	MeCN	79
9	NBP	DBU	DMF	74
10	NBP	DBU	toluene	65

[a] Reactions were carried out with **1a** (1.0 mmol), *N*-haloimide (1.2 equiv), and activator (1.2 equiv) in solvent (2.0 mL) at rt for 24 h. [b] Isolated yield. [c] With 0.2 equiv of DBU.

as observed on the TLC plate, in the mixture of NBP and DBU in CH_2Cl_2. To further verify the hypothesis of the existence of the interaction between DBU and NBP,[10] we surveyed a series of Lewis bases as electrophilic activators. DBN exhibited similar behavior to DBU (entry 3), while pyridine, DABCO and PPh_3 proved to be less effective or even inefficient (entries 4–6). Catalytic amount of DBU (e.g., 0.2 equiv) was not enough to drive the reaction to completion (entry 7). Solvent screening indicates that CH_2Cl_2 was the most efficient. Other solvents such as MeCN, DMF, and toluene gave relatively low yields of **2a** (entries 8–10).

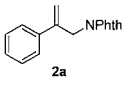
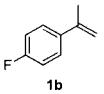
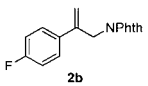
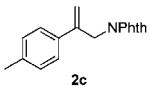
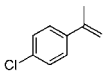
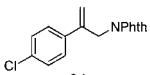
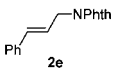
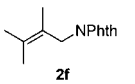
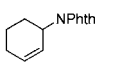
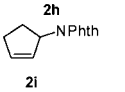
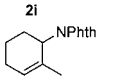
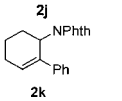
Under the optimized conditions (Table 1, entry 2), a range of reactions was carried out with various alkenes **1** and NBP (1.2 equiv) in the presence of DBU (1.2 equiv) in CH_2Cl_2 (Table 2). The reactions of acyclic alkenes proceeded smoothly to afford the corresponding allylamines **2a**–**f** in good to excellent yields (61–91%). The alkene substrates investigated include substituted α-methylstyrenes (methyl, Cl, and F), allylic benzene, and 2,3-dimethylbutene (entries 1–6). As for tetrasubstituted alkenes, like tetramethylethene, the corresponding bromoamination product was obtained in 57% yield (entry 7). Cyclic alkenes such as cyclohexane and cyclopentene generate a mixture of the bromoamination[11] and allylic amination products (**2h**, 26% yield; **2i**, 13% yield) (entries 8 and 9).[12] To our delight, 1-methylcyclohexene and 1-phenylcyclohexene afforded

(10) Examples for the formation of halogen bond complexes: (a) Castellote, I.; Morön, M.; Burgos, C.; Alvarez-Builla, J.; Martin, A.; Gomez-Sal, P.; Vaquero, J. J. *Chem. Commun.* **2007**, 1281. (b) Crowston, E. H.; Lobo, A. M.; Prabhakar, S.; Rzepa, H. S.; Williams, D. J. *Chem. Commun.* **1984**, 276. (c) Raatikainen, K.; Rissanen, K. *Chem. Sci.* **2012**, *3*, 1235. (d) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928.

(11) Examples with an imido moiety from NBS or NBP itself as the *N*-nucleophile are scarce. For a recent example, see: Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389.

(12) The bromoamination and the allylic amination products are inseperable over silica gel chromatography. The ratio was calculated based on ^{1}H NMR spetra.

Table 2. Allylic Amination Using NBP/DBU Combination[a]

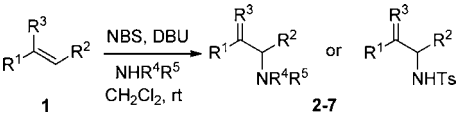
entry	alkene **1**	product **2**	yield (%)[b]
1	 **1a**	 **2a**	86
2	 **1b**	 **2b**	84
3	 **1c**	 **2c**	91
4	 **1d**	 **2d**	83
5	 **1e**	 **2e**	84
6	 **1f**	 **2f**	61
7	 **1g**	—	57[c]
8	 **1h**	 **2h**	26[d]
9	 **1i**	 **2i**	13[e]
10	 **1j**	 **2j**	87
11	 **1k**	 **2k**	88

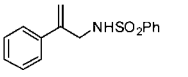
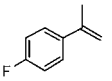
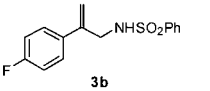
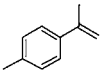
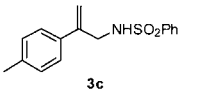
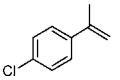
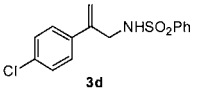
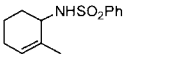
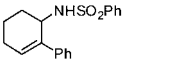
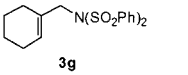
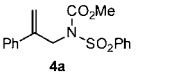
[a] Reactions were carried out with **1** (1.0 mmol), NBP (1.2 equiv), and DBU (1.2 equiv) in CH_2Cl_2 (2.0 mL) for 12–24 h. [b] Isolated yield. [c] Bromoamination product. [d] Bromoamination product in 41% NMR yield. [e] Bromoamination product in 47% NMR yield.

exclusively the desired allylic amination product **2j** and **2k** in 88 and 87% yields, respectively (entries 10 and 11).

Considering that the reaction of NBS/DBU with **1a** gave no allylamine product (Table 1, entry 1), we decided to introduce external nitrogen nucleophiles to the reaction system. First, bistosylimide was selected and subjected to the reaction sequence. As a result, *N*-(2-phenylallyl)-benzenesulfonamide (**3a**) was obtained in 82% yield (Table 3, entry 1). The structure of **3a** was confirmed by the single-crystal X-ray diffraction (Figure 2). Then, a variety of alkenes **1b**–**d** and **1j**–**l** were reacted with bistosylimide, giving the corresponding allylamines **3b**–**g** in 62–88% yields (entries 2–7). Note that, in most cases, one tosyl group was hydrolyzed, directly giving rise to the deprotected allylamines **3a**–**f** (entries 1–6). For *trans*-*β*-methylstyrene, the corresponding bromoamination product was obtained in 81% yield (entry 8).[13] The scope of external amines appears broad, and the reactions of

Table 3. Reactions of Alkenes and NBS/DBU Combination in the Presence of External Nitrogen Sources[a]



entry	alkene **1**	amine	product **2-7**	yield (%)[b]
1	 **1a**	Ns_2NH	 **3a**	82
2	 **1b**		 **3b**	74
3	 **1c**		 **3c**	88
4	 **1d**		 **3d**	71
5	 **1j**		 **3e**	85
6	 **1k**		 **3f**	86
7	 **1l**		 **3g**	62
8	 **1m**		—	88[c]
9	 **1a**	$NsNHCO_2Me$	 **4a**	89
10		$TsNHCO_2R$	**4b**: R = Me	88
11			**4c**: R = Bn	90
12		$PhSO_2NHMe$	**5**	75
13			**2a**: R = H	81
14			**2l**: R = Me	78
15			**2m**: R = NO_2	85
16			**6**	91
17			**7**	71

[a] Reactions were carried out with **1** (1.0 mmol), NBS (1.2 equiv), DBU (1.2 equiv), and amine (1.2 equiv) in CH_2Cl_2 (2.0 mL) for 12–24 h. [b] Isolated yield. [c] Bromoamination product.

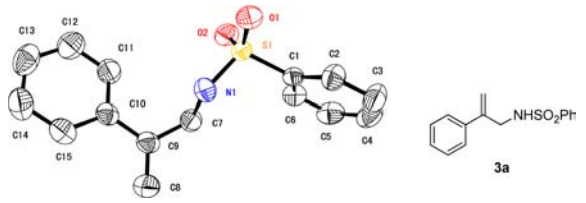


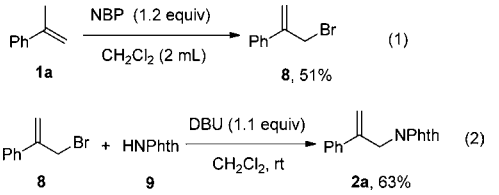
Figure 2. X-ray crystal structure of **3a**.

α-methylstyrene **1a** with *O*-alkyl-*N*-arylsulfonylcarbamates (alkyls = methyl and benzyl; aryls = phenyl and 4-tolyl), *N*-methyltosylamine, phthalimide, and substituted phthalimides (4-methyl and 4-NO_2), saccharin, and 1*H*-benzo[*d*]-[1,2,3]triazole afford the corresponding allylamines **4a**–**c**, **2a**, **2l**, **2m**, and **5**–**7** in high to excellent yields (entries 9–17). From above, one can see that the installation of the external amino group is dependent on the pK_a values of the imides employed. For instance, succimide (pK_a = 14.7) is unable to be introduced, while amines having a more acidic NH group can be used as the nitrogen sources in the allylic amination.[14]

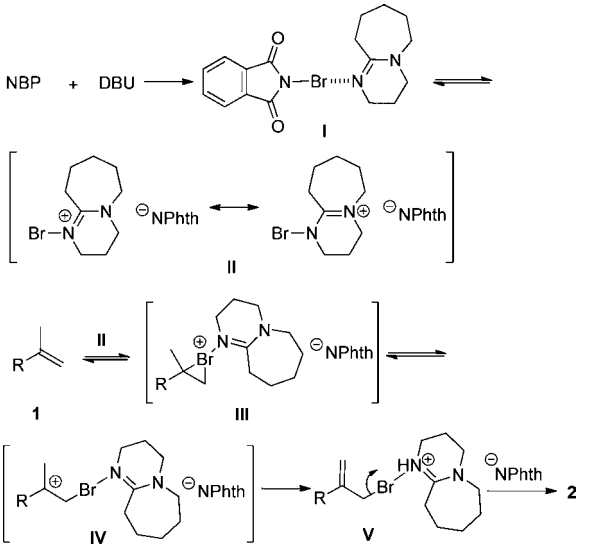
To gain insight into the mechanism, control experiments were performed (Scheme 2). In the absence of DBU, the reaction of **1a** with NBP gave allyl bromide **8** in 51% yield, with a certain amount of **1a** intact (eq 1). However, in the presence of DBU, no **8** could be observed. The reaction of allyl bromide **8**, phthalimide **9** (1.1 equiv), and DBU (1.1 equiv) at room temperature for 20 h gave product **2a** in 63% yield (eq 2). The experimental results indicate that the allyl bromide intermediate might be involved in the mechanism, and DBU in the reaction system listed in Tables 1–3 is supposed to promote allyl bromide formation, as well as further nucleophilic substitution.

On the basis of all the results described above, along with the work by White[2g] and us,[8a,b] a possible mechanism for the allylic amination of alkenes was proposed, as depicted in Scheme 3. First, a highly electrophilic bromine species **II**[15] is generated from the 1:1 NBP/DBU halogen bond adduct **I**.[10] Second, alkene reacts with ion pair **II** to furnish a DBU-stabilized bromonium ion **III**[16] and its open form **IV**.

Scheme 2. Control Experiments



Scheme 3. Proposed Mechanism



Third, allyl bromide **V** is formed via proton elimination. Finally, nucleophilic substitution by the phthalimide anion leads to allylamine **2**.[17] The dual activation of NBP by DBU is exemplified by providing both a more electrophilic bromine and a more nucleophilic nitrogen source.[18]

In conclusion, a novel and atom-efficient one-pot allylic amination of alkenes has been developed by using an NBP/DBU combination, in which NBP is dual activated by DBU to be a highly electrophilic bromine and nucleophilic nitrogen via a preformed halogen bonding interaction. External *N*-nucleophiles can also be introduced efficiently in the cases of the utilization of NBS/DBU combination. The tandem reaction features mild conditions, relatively broad substrate scope, readily available reagents, and high bond forming and atom efficiency.

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Supporting Information Available. Experimental details and characterization for all new compounds and crystal structure data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) See Supporting Information. The formation of the allylic amines and/or bromoamination product mainly depends on the structure of alkene substrates employed.

(14) For the pK_a values of the investigated imides, please refer to: (a) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (c) Cotton, F. A.; Stokely, P. F. *J. Am. Chem. Soc.* **2012**, *92*, 294.

(15) For a recent review of NBS activation by Lewis base, see: (a) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. Selected papers: (b) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (c) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899. (d) Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653.

(16) For Lewis-base-stabilized bromonium intermediates, see: (a) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655. (b) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 16492. (c) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (d) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985.

(17) The possible mechanism for the formation of **3** is given in Supporting Information.

(18) For double duty of alkynyl (cyanogen) halides, see: (a) Trofimov, A.; Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 13538. (b) Li, Z.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2808.