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One-Pot Synthesis of Less Accessible *N*-Boc-Propargylic Amines through BF_3-Catalyzed Alkynylation and Allylation Using Boronic Esters

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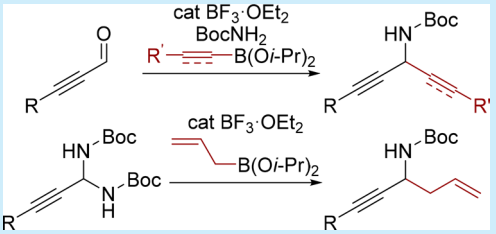
Supporting Information

ABSTRACT: An efficient synthesis of α-alkynyl- or α-allyl-substituted *N*-Boc-propargylic amines is described via an alkynylation or allylation of alkynyl-substituted *N*-Boc-imines. Our strategy relies on the BF_3-mediated in situ generation of alkynyl imines followed by alkynylation or allylation with the corresponding boronic esters. A range of less accessible *N*-Boc-propargylic amines were obtained in moderate to good yields under mild and acidic conditions with higher atom economy compared to the previous methods.



Propargylic amines represent an important class of versatile building blocks for the synthesis of nitrogen-containing organic compounds.[1] The alkynyl moiety can be subject to a variety of reactions, and the easily deprotectable *tert*-butoxycarbonyl (Boc) is one of the most commonly used protecting groups for propargylic amines. Synthetically useful *N*-Boc-protected propargylic amines are readily prepared by the nucleophilic addition of alkynyl metal reagents to *N*-Boc-imines. Since reactive *N*-Boc-imines are prone to be hydrolyzed or isomerized to the corresponding enecarbamates, they are often generated in situ by treatment of its precursors with bases including basic nucleophiles and used without isolation.[2,3] However, this method is limited to *N*-Boc-imines with a *C*-aryl, *C*-alkyl, or a handful of *C*-alkenyl groups, as most *N*-Boc-imine precursors with *C*-alkynyl group still remain unobtainable probably due to their instability. Accordingly, in the synthesis of *N*-Boc-propargylic amines, alkynyl groups should be introduced as nucleophiles and not as part of electrophiles (Scheme 1a), and hence some *N*-Boc-propargylic amines have been inaccessible directly.

Recently we have developed *N*-Boc-aminals **1**,[4a] which generate unprecedented alkynyl-substituted *N*-Boc-imines under basic conditions, and the synthesis of previously inaccessible α-alkynyl- or α-alkenyl-substituted *N*-Boc-propargylic amines **2** has been achieved via the reaction between **1** and Grignard reagents (Scheme 1b).[4b] This reaction requires an excess amount of Grignard reagents as both nucleophile and base. Additionally, formation of the metal salt of $(Boc)_2NH$ as a byproduct makes this method less atom-efficient. Moreover, preparation of **1** requires a time-consuming protocol to introduce the third Boc group.[4a] Use of strong base at low temperature limits providing a practical and general procedure, thus leaving plenty of room for improvement.

We then became interested in employing boronic ester **3**, which can be used as a nucleophile under acidic conditions, instead of organometallic reagents such as Grignard reagents.[5−7] Addition reactions using **3** to imines or enones are known to be promoted by ligand exchange with an equimolar amount of BF_3 or a catalytic amount of BINOL on the boron atom.[6] Herein we describe the efficient synthesis of α-alkynyl or alkenyl-substituted *N*-Boc-propargylic amines **2** under mild conditions through the reaction between the activated **3** and the alkynyl-substituted *N*-Boc-imines, which are generated in situ from aldehydes and $BocNH_2$ with the aid of an acid catalyst (Scheme 1c). Allyl-substituted *N*-Boc-imines as well as alkynyl-substituted ones are inaccessible due to rapid isomerization to α,β-unsaturated imines or enecarbamates. Accordingly α-allyl-substituted *N*-Boc-propargylic amines **6** cannot be synthesized by alkynylation. Synthesis of **6** via allylation of in situ generated alkynyl imines from *N*-Boc-aminals **4** with allylboronic ester **5** is also presented.

We began our investigation with the expectation that alkynylboronic ester **3**[6] could be activated with an equimolar amount of $BF_3{\cdot}OEt_2$ through ligand exchange. When *N*-Boc-aminal **4a**[8,9] was treated with 3 equiv of **3a** and $BF_3{\cdot}OEt_2$, respectively, in CH_2Cl_2 at room temperature, a small amount of the desired *N*-Boc-propargylic amine **2a** was observed (Scheme 2). With 1 equiv of $BF_3{\cdot}OEt_2$, the yield was significantly increase to 57%. Interestingly, use of a catalytic amount of $BF_3{\cdot}OEt_2$ led to a similar yield (63%).

Encouraged by the successful BF_3-mediated alkynylation of **4a**, we then investigated the possibility of using other acid catalysts as shown in Table 1. In the case of Brønsted acids such as diphenyl phosphate and trifluoroacetic acid, **2a** was obtained, albeit in low yields (entries 1 and 2), while use of sulfonic acids completely shut down the reaction (entries 3 and

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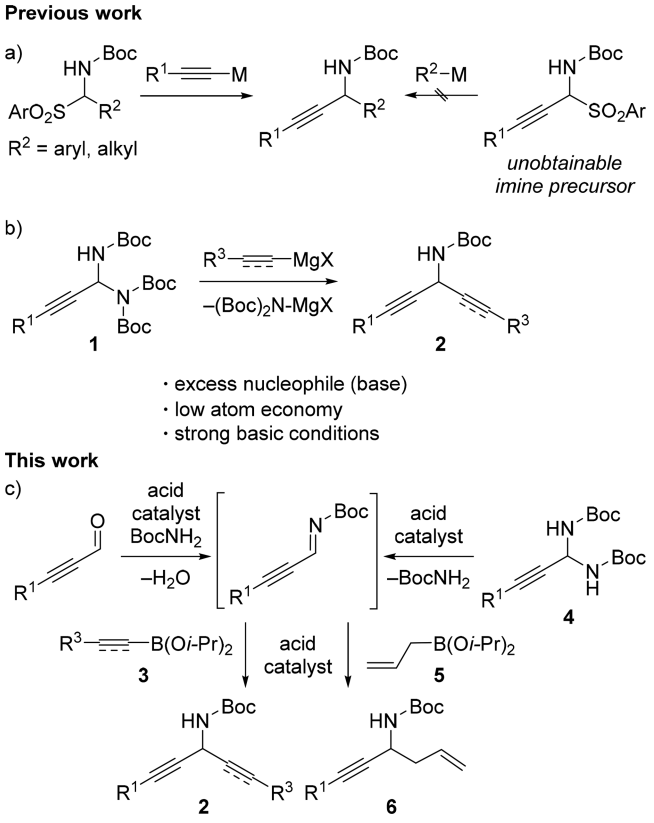
Scheme 1. One-Pot Synthesis of *N*-Boc-Propargylic Amines



Scheme 2. Alkynylation of the in Situ Generated *N*-Boc-Imine from *N*-Boc-Aminal

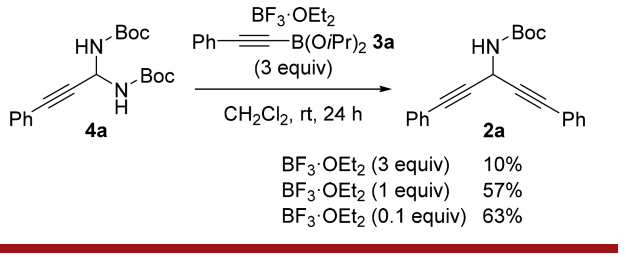
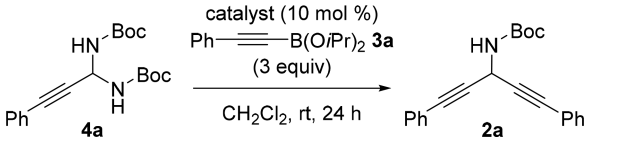


Table 1. Catalyst Screening for the Alkynylation of *N*-Boc-Aminal 4a with Alkynylboronic Ester 3a[a]



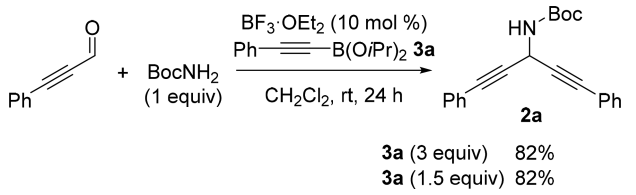
entry	catalyst	yield (%)[b]	entry	catalyst	yield (%)[b]
1	$(PhO)_2PO_2H$	25	8	$In(OTf)_3$	14
2	CF_3CO_2H	24	9	$TiCl_4$	7
3	PTSA	0	10	$ZnCl_2$	0
4	TfOH	0	11	$GaCl_3$	33
5	Me_3SiOTf	0	12	$BF_3{\cdot}OEt_2$	63
6	$Sc(OTf)_3$	41	13[c]	$BF_3{\cdot}OEt_2$	60
7	$Cu(OTf)_2$	0	14[d]	$BF_3{\cdot}OEt_2$	78

[a]Reactions were performed on a 0.1 mmol scale in 1.0 mL of CH_2Cl_2. [b]^1H NMR yield utilizing DMF as internal standard. [c]Performed in 1,2-dichloroethane at 70 °C. [d]Use of 20 mol % of $BF_3{\cdot}OEt_2$.

4). Among Lewis acids tested, $Sc(OTf)_3$, $In(OTf)_3$, $TiCl_4$, and $GaCl_3$ gave **2a** in low to moderate yields (entries 6, 8, 9, and 11); however, they were found to be less effective catalysts compared to $BF_3{\cdot}OEt_2$ (entry 12). Based on these result, $BF_3{\cdot}OEt_2$ was selected as the catalyst of choice for further studies. A higher reaction temperature did not increase the yield (entry 13). An increase in the catalyst loading (20 mol %) resulted in a higher yield (entry 14).

To improve the yield, the in situ generation of the alkynyl imine from phenylpropiolaldehyde and $BocNH_2$ (1 equiv), in which the total amount of Lewis basic $BocNH_2$ is reduced compared to the previous method using *N*-Boc-aminal **4a**, was then examined (Scheme 3).[10] Under identical conditions, the

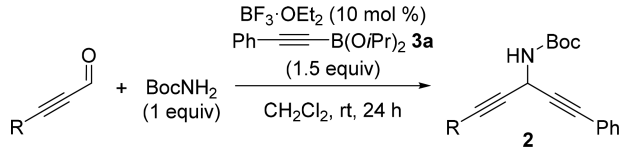
Scheme 3. Alkynylation of the in Situ Generated *N*-Boc-Imine from 3-Phenylpropiolaldehyde and $BocNH_2$



yield was improved to 82%. The amount of boronic ester **3a** could be reduced to 1.5 equiv without deleterious effects. This method was found to be superior in terms of atom economy to the previous one.

With the optimized conditions in hand, the scope of the reaction was studied (Table 2). Both electron-deficient and

Table 2. Alkynylation of the in Situ Generated *N*-Boc-Protected Alkynyl Imines[a]



entry	R		yield (%)[b]
1	Ph	**2a**	83
2	4-MeO-C_6H_4	**2b**	63
3	4-Br-C_6H_4	**2c**	75
4	4-MeO_2C-C_6H_4	**2d**	75
5	Bu	**2e**	81
6	Cy	**2f**	86
7	Me_3Si	**2g**	70

[a]Reactions were performed on a 0.1 mmol scale in 1.0 mL of CH_2Cl_2. [b]Isolated yield.

electron-rich arylpropiolaldehydes gave the corresponding α-alkynyl-substituted *N*-Boc-propargylic amines **2** in moderate to good yields (entries 2−4), and this method was applicable to the synthesis of **2d**, which cannot be synthesized by the previous method using Grignard reagents due to the base-labile ester group.[4b] Alkyl- and trimethylsilyl-substituted propiolaldehydes also provided the respective addition products in good yields (entries 5−7). In addition, the reaction of aldehydes bearing an alkyl, aryl, or alkenyl group with **3a** gave *N*-Boc-propargylic amines **7** in satisfactory yields (Scheme 4).[2,4b]

We next examined the scope of the reaction by varying the alkynylboronic ester used (Table 3). Use of electron-rich alkynylboronic ester led to a moderate yield due to the

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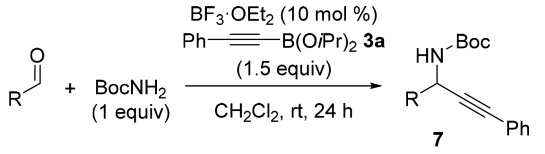
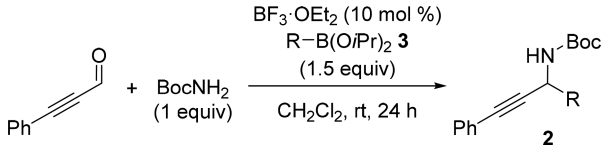
Scheme 4. Alkynylation of the in Situ Generated *N*-Boc-Imines



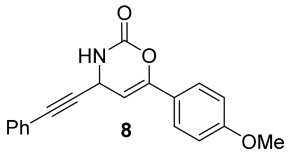
7a (R = Pent) 79%
7b (R = $PhCH_2CH_2$) 85%
7c (R = Ph) 73%
7d (R = (*E*)-Ph-CH=CH) 68%

Table 3. One-Pot Synthesis of *N*-Boc-Propargylic Amines 2[a]



entry	R		yield (%)[b]		
1[c]	4-MeO-C_6H_4-C≡C	**2b**	41	**8**	15
2	4-Br-C_6H_4-C≡C	**2c**	72		
3[d]	Bu-C≡C	**2e**	70		
4[d]	Cy-C≡C	**2f**	65		
5[d]	(*E*)-Ph-CH=CH	**2h**	64		

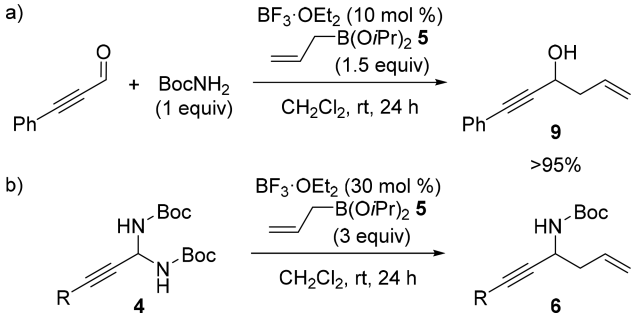
[a]Reactions were performed on a 0.1 mmol scale in 1.0 mL of CH_2Cl_2. [b]Isolated yield. [c]Performed at 0 °C. [d]Use of 20 mol % of BF_3·OEt_2.



concomitant formation of cyclic carbamate **8** (entry 1),[11] while electron-deficient alkynylboronic ester afforded a good yield of product (entry 2). Since alkyl-substituted alkynylboronic esters were less reactive compared to aryl-substituted ones, higher catalyst loadings (20 mol %) were used (entries 3 and 4). When styrylboronic ester was employed, a 64% yield of the desired alkenylation product was obtained (entry 5).

We then examined the allylation of the in situ generated *N*-Boc-imine using allylboronic ester **5** (Scheme 5).[12,13] However, the allylation of phenylpropiolaldehyde proceeded smoothly to give propargyl alcohol **9** in quantitative yield, and the desired *N*-Boc-propargylic amine **6a** was not observed (Scheme 5a).[14] In order to prevent the undesired allylation of aldehyde, *N*-Boc-aminal **4a** (R = Ph) instead of phenylpropiolaldehyde was then employed as the imine precursor under identical conditions, and α-allyl-substituted *N*-Boc-propargylic amines **6a** was obtained in 39% yield without forming propargyl alcohol **9**. With increased amounts of BF_3·OEt_2 (30 mol %) and **5** (3 equiv), the reaction of **4** afforded **6** in good yields (Scheme 5b).[15] These results clearly demonstrated the advantage of using *N*-Boc-aminals, which are more suitable imine precursors, when the imine formation from aldehydes is slower than the addition reaction of nucleophiles to aldehydes.

Scheme 5. Allylation of the in Situ Generated *N*-Boc-Imines



6a (R = Ph) 76%
6b (R = 4-MeO-C_6H_4) 86%
6c (R = 4-Br-C_6H_4) 74%
6d (R = Pent) 84%

A catalytic cycle and plausible transition state models for the present reaction are proposed in Figures 1 and 2. We believe

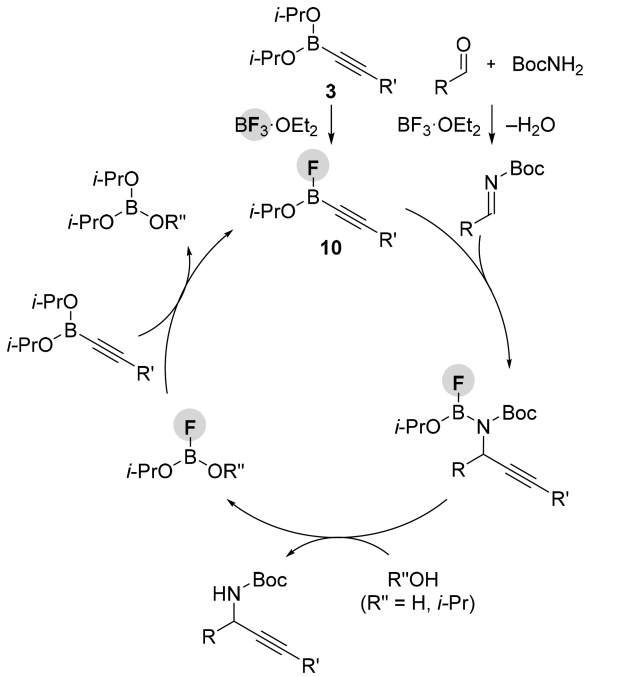


Figure 1. Proposed catalytic cycle.

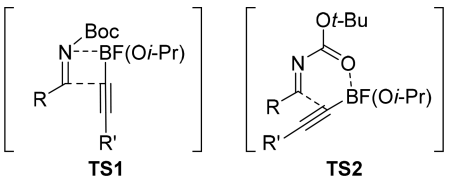


Figure 2. Plausible transition state models.

that BF_3·OEt_2 plays two different roles: one is the Lewis acid catalyst for the in situ imine generation, and the other is the activation of boronic ester. Boronic ester **3** is known to form the more Lewis acidic fluoroborane intermediate **10** by the ligand exchange with BF_3·OEt_2.[6b,16] The alkynyl group adds to the imine, which is activated by coordination to the boron center, through either a four-membered transition state **TS1**[6d] or a six-membered transition state **TS2** (Figure 2).[6b] A catalytic amount of fluoride source is employed in the present reaction, and triisopropyl borate was observed in the ^1H NMR spectrum of the reaction mixture. These facts indicate the recycling of fluoride as shown in Figure 1.

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In summary, we have synthesized *N*-Boc-protected propargylic amines via the BF_3-catalyzed addition reaction of alkynyl and allylboronic esters to the in situ generated *N*-Boc-imines. This method is performed under mild reaction conditions and allows direct synthesis of less accessible α-alkynyl, α-alkenyl, and α-allyl-substituted *N*-Boc-propargylic amines in a more operationally simple and atom economic process compared to the previous reactions using strongly basic organometallic reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00931.

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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■ REFERENCES

(1) For representative reviews on the synthesis of propargylic amines, see: (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (b) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(2) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970.

(3) (a) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731. (b) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, *2007*, 3503. (c) Blay, G.; Brines, A.; Monleón, A.; Pedro, J. R. *Chem. - Eur. J.* **2012**, *18*, 2440.

(4) (a) Kano, T.; Kobayashi, R.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 8471. (b) Kano, T.; Kobayashi, R.; Maruoka, K. *Org. Lett.* **2016**, *18*, 276.

(5) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.

(6) (a) Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. *Tetrahedron Lett.* **1990**, *31*, 247. (b) Fujishima, H.; Takada, E.; Kara, S.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 695. (c) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244. (d) Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337. (e) Lundy, B. J.; Jansone-Popova, S.; May, J. A. *Org. Lett.* **2011**, *13*, 4958. (f) Le, P. Q.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2012**, *14*, 6104.

(7) For alkynylation of imines with boron compounds, see: (a) Gonzalez, A. Z.; Canales, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 3331. (b) Stas, S.; Tehrani, K. A. *Tetrahedron* **2007**, *63*, 8921. (c) Tehrani, K. A.; Stas, S.; Lucas, B.; De Kimpe, N. *Tetrahedron* **2009**, *65*, 1957. (d) Stefani, H. A.; Manarin, F.; Khan, A. N.; Vasconcelos, S. N. S. *Eur. J. Org. Chem.* **2014**, *2014*, 1236. (e) Xie, Z.; Jia, J.; Liu, X.; Liu, L. *Adv. Synth. Catal.* **2016**, *358*, 919.

(8) (a) Kano, T.; Yurino, T.; Asakawa, D.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 5532. (b) Kano, T.; Yurino, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 11509. (c) Kano, T.; Aota, Y.; Asakawa, D.; Maruoka, K. *Chem. Commun.* **2015**, *51*, 16472. (d) Yurino, T.; Aota, Y.; Asakawa, D.; Kano, T.; Maruoka, K. *Tetrahedron* **2016**, *72*, 3687. (e) Bai, J.-F.; Sasagawa, H.; Yurino, T.; Kano, T.; Maruoka, K. *Chem. Commun.* **2017**, *53*, 8203.

(9) Boc-protected imines having an alkynyl group can also be genarated from Boc-protected hemiaminal ethers; see: (a) Wang, Y.; Mo, M.; Zhu, K.; Zheng, C.; Zhang, H.; Wang, W.; Shao, Z. *Nat. Commun.* **2015**, *6*, 8544. (b) Wang, Y.; Jiang, L.; Li, L.; Dai, J.; Xiong, D.; Shao, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 15142.

(10) Kano, T.; Homma, C.; Maruoka, K. *Org. Biomol. Chem.* **2017**, *15*, 4527.

(11) Kano, T.; Yasumoto, K.; Maruoka, K. *Asian J. Org. Chem.* **2018**, *7*, 1575.

(12) For allylation of alkynylimines with allylboronic esters, see: (a) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216. (b) Jiang, Y.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2017**, *56*, 1544.

(13) For allylation of imines with allylboronic esters, see: (a) Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, *1983*, 2000. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814. (c) Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1531. (d) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398. (e) Barker, T. J.; Jarvo, E. R. *Org. Lett.* **2009**, *11*, 1047. (f) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332. (g) Kojima, M.; Mikami, K. *Chem. - Eur. J.* **2011**, *17*, 13950. (h) Cui, Y.; Yamashita, Y.; Kobayashi, S. *Chem. Commun.* **2012**, *48*, 10319. (i) Ghosh, D.; Bera, P. K.; Kumar, M.; Abdi, S. H. R.; Khan, N. H.; Kureshy, R. I.; Bajaj, H. C. *RSC Adv.* **2014**, *4*, 56424. (j) Zhao, Y.-S.; Liu, Q.; Tian, P.; Tao, J.-C.; Lin, G.-Q. *Org. Biomol. Chem.* **2015**, *13*, 4174.

(14) Lachance, H.; Hall, D. G. *Org. React.* **2009**, *73*, 1.

(15) Use of 10 mol % of diphenyl phosphate gave **6a** in 69% yield. A chiral phosphoric acid catalyst derived from BINOL also promoted the reaction, but afforded the racemic product.

(16) Allylation of **4a** with allylboronic acid pinacol ester did not proceed, and this result suggests that boronic esters may be activated through ligand exchange on the boron atom.

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