Organic LETTERS

Letter

pubs.acs.org/OrgLett

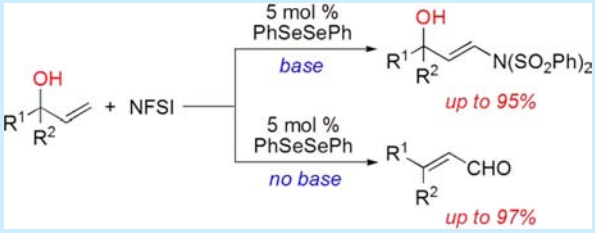
Organoselenium-Catalyzed, Hydroxy-Controlled Regio- and Stereoselective Amination of Terminal Alkenes: Efficient Synthesis of 3-Amino Allylic Alcohols

Zhimin Deng, Jialiang Wei, Lihao Liao, Haiyan Huang, and Xiaodan Zhao*

Institute of Organic Chemistry & MOE Key Laboratory of Bioinorganic and Synthetic Chemistry, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, PR China

Supporting Information

ABSTRACT: An efficient route to prepare 3-amino allylic alcohols in excellent regio- and stereoselectivity in the presence of bases by orangoselenium catalysis has been developed. In the absence of bases α,β-unsaturated aldehydes were formed in up to 97% yield. Control experiments reveal that the hydroxy group is crucial for the direct amination.

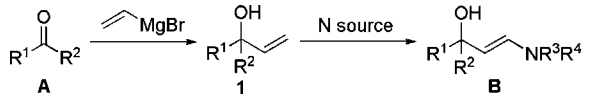


3-Amino allylic alcohols are versatile synthetic intermediates and could be conveniently converted to β-amino acids,[1] hydroxy carboxylic acids,[2] 1,2-amino alcohols,[3] 1,3-amino alcohols and amino cyclopropyl carbinols[4] by known methods. In general, they are prepared in multiple steps with alkynes as starting materials via ynamide intermediates.[1,5] However, multistep manipulations and the utility of alkyne substrates have limited their broad applications in synthesis. Alternatively, allylic alcohol could serve as substrate to afford 3-amino allylic alcohol in several steps involving OH protection, hydroxylation via borylation, and then oxidation followed by amination.[6] Again, this protocol suffers from multistep sequence leading to low efficiency of product generation. Thus, an efficient and direct route to produce 3-amino allylic alcohols from simple compounds is desirable.

Direct amination of carbon−hydrogen bonds is an ideal way to construct nitrogen-containing compounds because of atom economy.[7−9] In recent years, transition metal-catalyzed direct amination of C−H bonds has been well demonstrated with either aryl sp^2 C−H bonds or sp^3 C−H bonds.[8−10] It was rare to use vinyl sp^2 C−H bonds as the substrates since their reactivities dramatically differ from aryl sp^2 C−H bonds.[7b,11] In 2013, Breder and co-workers discovered a novel route to form imide derivatives by PhSeSePh-catalyzed vinyl sp^2 C−H amination.[12] In their work only α,β-disubstituted alkenes with an electron-withdrawing group were utilized as the substrates, otherwise the method is not efficient. To expand this field, an efficient and selective amination of vinyl C−H bonds needs to be further explored. Herein, we report a highly efficient approach to selectively synthesize 3-amino allylic alcohols in one step by organoselenium-catalyzed direct amination of vinyl C−H bond on terminal alkenes.

Organoselenium catalysis has been paid much attention in the past decade.[13,14] Notably, diselenide catalysis has exhibited great achievements in catalytic transformations. We proposed that allylic alcohols **1**, which are either commercially available or easily accessible with the carbonyl compounds **A** and vinyl magnesium bromide, could be transformed to the desired products **B** by diselenide catalysis (Scheme 1). Though normal

Scheme 1. Proposed Synthesis of 3-Amino Allyllic Alcohols by Direct Amination



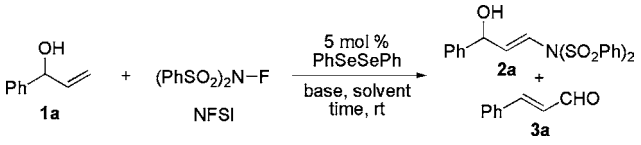
linear alkenes are problematic in orangoselenium catalysis giving the mixture products,[12a] we rationalized that a hydroxy group bearing lone pairs of electrons at the alkene substrate might be able to interact with selenium cation to control selectivity.[15] Consequently, a regio- and stereoselective amination would be conceived to give the desired product.

With this assumption in mind, the allylic alcohol **1a** was employed as the model substrate. We tried different aminating reagents combining various oxidants with PhSeSePh as the catalyst for direct amination. Unfortunately, no desired products were afforded. Excitingly, when the reaction of **1a** with the oxidant NFSI was carried out using 5 mol % PhSeSePh in THF in the presence of $NaHCO_3$, the desired *trans*-aminated product **2a** was formed in 75% yield in excellent selectivity (Table 1, entry 1). No *cis*-aminated and 2-aminated product were observed as well as 3-amino 1-phenyl propanone ketone formed by proton elimination from the hydroxy side. When PhSeSePh was absent or replaced with PhSePh, no desired product was formed (Table 1, entries 2, 3). The yield was a little bit higher than 75% using pyridine as the base (Table 1, entry 4).

Received: January 22, 2015
Published: April 7, 2015

DOI: 10.1021/acs.orglett.5b00213
Org. Lett. 2015, 17, 1834−1837

Table 1. Condition Optimization[a]



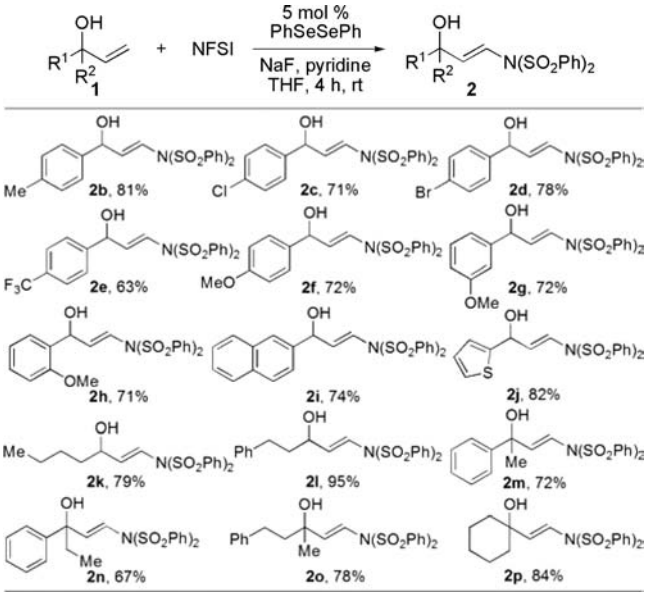
entry	base[b]	solvent	time (h)	yield (%)[c]
1	$NaHCO_3$	THF	4	**2a**, 75
2[d]	$NaHCO_3$	THF	4	**2a**, 0
3[e]	$NaHCO_3$	THF	4	**2a**, 0
4	Py	THF	4	**2a**, 82
5	NaF	THF	4	**2a**, 66
6	NaF + Py	THF	4	**2a**, 86(87)
7	NaF + Py	CH_2Cl_2	4	**2a**, 36
8	NaF + Py	CH_3CN	4	**2a**, 8
9	NaF + Py	EtOAc	4	**2a**, 81
10	–	THF	12	**3a**, 79
11	–	ether	12	**3a**, 84
12	–	dioxane	12	**3a**, 79
13	–	*t*-BuOH	12	**3a**, 64
14	–	EtOAc	12	**3a**, 93(92)
15	–	CH_2Cl_2	12	**3a**, 10
16	–	MeCN	12	**3a**, 36
17	–	toluene	12	**3a**, 33
18	–	hexane	12	**3a**, 27

[a]Reaction conditions: substrate, 0.2 mmol; catalyst, 5 mol %; NFSI, 1 equiv; solvent, 1 mL; room temperature. [b]Inorganic base, 1.2 equiv; pyridine, 1.0 equiv. [c]Refers to ^{1}H NMR yield using quinoline as the internal standard; isolated yield is in parentheses. [d]No PhSeSePh. [e]PhSePh was used instead of PhSeSePh.

Presumably, the presence of pyridine prohibited the formation of ketone by direct oxidation of the hydroxy group.[16] When NaF was utilized as the base, the yield was reduced to 66% (Table 1, entry 5). By combining NaF and pyridine as the bases, the best yield (87% isolated yield) was obtained (Table 1, entry 6). Other inorganic bases, i.e., Na_2CO_3 and K_3PO_4, resulted in lower yields and other organic bases, i.e., Et_3N, shut down the reaction. Other solvents, i.e., CH_2Cl_2, CH_3CN, EtOAc, led to lower yields (Table 1, entries 7–9). Interestingly, when the reaction was run in the absence of base, *trans*-cinnamaldehyde **3a** was produced in 79% yield because the aminated product **2a** decomposed in HF acidic conditions (Table 1, entry 10). Different solvents were screened. It was found that ethyl acetate was best to give the product **3a** in 92% isolated yield (Table 1, entry 14). Nonoxygen-containing compounds as the solvents, i.e., CH_2Cl_2, CH_3CN, toluene and hexane, were less effective (Table 1, entries 15–18). The lower yields of **3a** did not stem from the slow decomposition of the intermediate **2a**, instead, a lot of starting material **1a** remained.

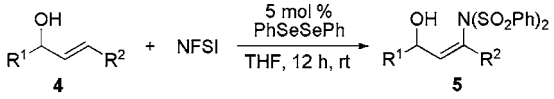
Next, we explored the substrate scope using the optimized conditions (Scheme 2). When 1-aryl allylic alcohols were employed as the substrates, the desired products **2b**–**2j** could be produced in 63–82% yields. The aromatic group could be substituted phenyl and heterocyclic rings. Electron-withdrawing $-CF_3$ and electron-donating $-$OMe substutents affected the amination slightly. When sterically hindered 1-(*ortho*-methoxyl phenyl) allylic alcohol was employed, the desired product **2h** was still afforded in 71% yield. It is worthy to mention that these 3-amino 1-aryl allylic alcohol products are not quite stable in acidic conditions. They were usually stored in basic solvent to prevent decomposition. 1-Alkyl allylic alcohols produced the

Scheme 2. Amination of Substituted Allylic Alcohols[a]



[a]Reaction conditions: substrate, 0.2 mmol; catalyst, 5 mol %; NFSI, 1 equiv; NaF, 1.2 equiv; pyridine, 1.0 equiv; THF, 1 mL; room temperature.

corresponding imides in good to excellent yields (**2k**, 79%; **2l**, 95%). They are more stable than 3-amino-1-aryl allylic alcohol. Satisfyingly, when the tertiary allylic alcohols, i.e., 1,1-aryl, alkyl or 1,1-alkyl, alkyl-substituted allylic alcohols, were utilized as the substrates, the desired products were formed in good yields as well (**2m**–**2p**) despite the bulky quaternary carbon connects to the double bond. In contrast, 3-amino tertiary allylic alcohols could not be accessed by the known methods.[1−6]



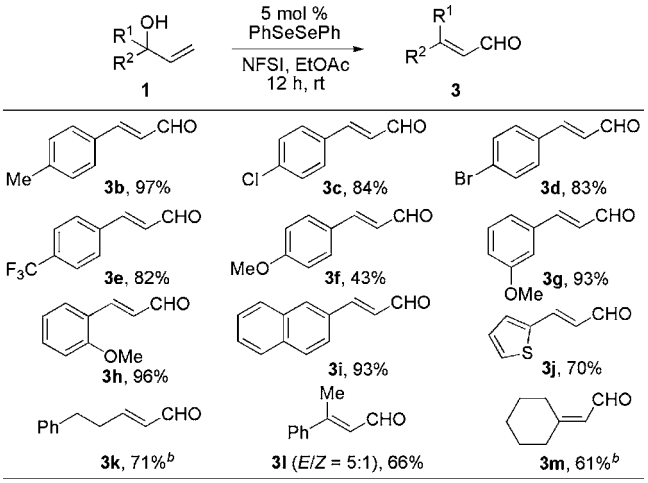
5a (R^1 = Ph, R^2 = Me), 81%; **5b** (R^1 = Ph, R^2 = *n*-Pr), 71%
5c (R^1 = Me, R^2 = *n*-Pr), 76%; **5d** (R^1 = $PhCH_2CH_2CH_2$, R^2 = Me), 92%

This method is general and also fits the oxidative amination of *α,β*-disubstituted alkenes. Under the similar conditions, the *cis*-amino products **5** were produced in 71% to 92% yields in excellent regio- and stereoselectivity. These aminated products are more stable in comparison with **2a** analogues so that the amination reactions could be carried out without any bases just in longer time of 12 h. It is worth mentioning that the mixture would be formed according to the literature if there is no hydroxy group on the substrates **4**.[12a]

We turned our attention to produce *α,β*-unsaturated aldehydes from alcohols **1** in one pot. The products **3** were obtained in 43% to 97% isolated yields (Scheme 3). 1-Aryl allylic alcohols were easily transformed to the corresponding products in good to excellent yields at room temperature except that the product **3f** was generated in 43% yield. The low yield resulted from the corresponding allylic imide formed along with **3f**. The alkyl-substituted *α,β*-unsaturated aldehydes were formed at elevated temperature of 60 °C because the intermediates **2l** and **2p** are more stable than **2a** analogues. When tertiary alcohol was employed as the substrate, the aldehyde **3l** was obtained in 66% yield in *E*/*Z* = 5:1 mol ratio. This method is a new way to synthesize *α,β*-unsaturated aldehydes using easily achievable allylic alcohols.[17]

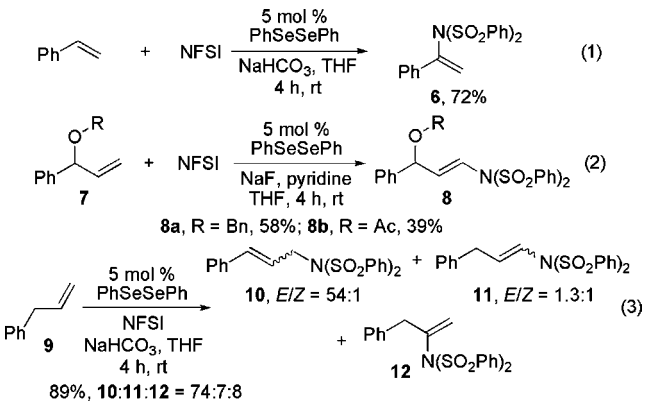
DOI: 10.1021/acs.orglett.5b00213
Org. Lett. 2015, 17, 1834–1837

Scheme 3. Formation of α,β-Unsaturated Aldehydes from Substituted Allylic Alcohols[a]



[a]Reaction conditions: substrate, 0.2 mmol; catalyst, 5 mol %; NFSI, 1 equiv; EtOAc, 1 mL; room temperature under nitrogen atmosphere. [b]The reaction was carried out at 60 °C.

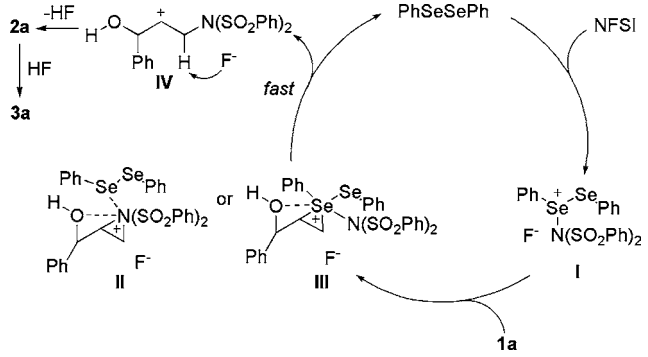
To elucidate the importance of hydroxy group on the substrates, control experiments were conducted under similar conditions. Styrene as the starting material resulted in the formation of α-amino styrene **6** in 72% yield (eq 1). No



β-amino styrene was observed. The reaction site was completely switched from terminal to the other side of double bond in contrast to **1**. The reactivity is similar to the α,β-disubstituted alkenes in the literature.[12a] When hydroxy group was protected by benzyl or acyl group, the desired products **8** were isolated in lower yields (**8a**, 58%; **8b**, 39%) (eq 2). The results reveal that protecting group-free hydroxy group is superior to Bn or Ac protected OH. Presumably the hydroxy group provides better electron-donating effect than the others. In contrast, when hydroxy-free allyl benzene **9** was employed under the similar conditions, a mixture of allyl amines **10** (E/Z = 54:1), 1-amino allylbenzene **11** (E/Z = 1.3:1) and 2-amino allylbenzene **12** were obtained in total yield of 89% (eq 3). The yield ratio of **10**:**11**:**12** is 74:7:8. These results clearly indicate that hydroxy group is significantly important for selective amination. In situ NMR studies were investigated, which reveal that the generation of product **10** is not from the isomerization of **11** (see Supporting Information). When the amination reactions were run for longer than 4 h, or the mixture of products **10**−**12** were treated with acids or bases, the mole ratio of **10**, **11** and **12** did not change. The fact further solidifies that the amination products **10** were formed directly in the catalytic cycle. When 3-phenyl-1-butene (**13**) or 1-hexene (**14**) was treated with NFSI under the similar conditions, a mixture of amination products was generated as well. The difference is the mole ratio for amination products comparable to the reaction of allylbenzene with NFSI (see Supporting Information).

A reasonable mechanism is proposed according to the literature[12a] and our observations (Scheme 4). PhSeSePh reacts

Scheme 4. Proposed Mechanism



with NFSI to produce the intermediate **I**. However, it is hard to exclude the possibility that the reaction of diselenide with NFSI could not generate $PhSeN(SO_2Ph)_2$ and PhSeF. When the allylic alcohol **1a** is present in the reaction, **I** could interact with the hydroxy group on **1a**.[15] Then the adduct aziridinium **II** or selenonium **III** is formed. The hydroxy group provides a lone pair of electrons to stabilize the onium ions. The species **IV** is formed fast by the removal of the catalyst. Possibly, the assitance of hydroxy group and the fast formation of **IV** lead to high selectivity of the amination and even inhibit the formation of 2-aminated product and 3-amino 1-phenyl propanone ketone. In the presence of bases, HF can be eliminated and **2a** is easily formed. Without bases **2a** would be converted to **3a**.

In summary, we have demonstrated an efficient route to synthesize 3-amino allylic alcohols with easily accessible allylic alcohols and NFSI in the presence of bases by organoselenium catalysis. The direct amination proceeded in excellent regio- and stereoselectivity. When bases were absent under similar conditions, α,β-unsaturated aldehydes were formed in 43−97% isolated yields. Control experiments indicate that the hydroxy group is crucial in the reactions. Detailed mechanistic study is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, copies of NMR spectra and X-ray crystallographic data of **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhaoxd3@mail.sysu.edu.cn.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.5b00213
Org. Lett. 2015, 17, 1834−1837

■ ACKNOWLEDGMENTS

This work is financially supported by the start-up funding from Sun Yat-Sen University and a grant from the "One Thousand Youth Talents" Program of China. We thank Prof. Yiqian Wan at SYSU for discussion on the configuration determination of compounds **5**.

■ REFERENCES

(1) (a) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111. (b) Harker, W. R. R.; Carswell, E. L.; Carbery, D. R. *Org. Biomol. Chem.* **2012**, *10*, 1406.

(2) Hirano, S.; Fukudome, Y.; Tanaka, R.; Sato, F.; Urabe, H. *Tetrahedron* **2006**, *62*, 3896.

(3) (a) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245. (b) Barbazanges, M.; Meyer, C.; Cossy, J. *Tetrahedron Lett.* **2008**, *49*, 2902. (c) Barbazanges, M.; Meyer, C.; Cossy, J.; Turner, P. *Chem.—Eur. J.* **2011**, *17*, 4480.

(4) Valenta, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 14179.

(5) (a) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (b) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727. (c) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829.

(6) Castro, J.; Coterón, J. M.; Fraile, M. T.; García-Ochoa, S.; Gómez de las Heras, F.; Martín-Cuesta, A. *Tetrahedron Lett.* **2002**, *43*, 1851.

(7) For selected reviews, see: (a) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931. (b) Obora, Y.; Ishii, Y. *Catalysts* **2013**, *3*, 794. (c) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901.

(8) For selected examples on sp^2 C−H amination, see: (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (b) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (c) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (d) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. (e) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. (f) Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 5904.

(9) For selected examples on sp^3 C−H amination, see: (a) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (b) Neumann, J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (c) Shimizu, Y.; Obora, Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372. (d) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647. (e) Souto, J. A.; Zian, D.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 7242. (f) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141.

(10) (a) Iglesias, Á.; Álvarez, R.; R. de Lera, Á.; Muñiz, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2225. (b) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 1244. (c) Xiong, T.; Li, Y.; Mao, L.; Zhang, Q.; Zhang, Q. *Chem. Commun.* **2012**, *48*, 2246. (d) Boursalian, G. B.; Ngai, M.-Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278. (e) Wang, S.; Ni, Z.; Huang, X.; Wang, J.; Pan, Y. *Org. Lett.* **2014**, *16*, 5648.

(11) (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444. (b) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170. (c) Liwosz, T. W.; Chemler, S. R. *Chem.—Eur. J.* **2013**, *19*, 12771. (d) Kim, J.; Chang, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 2203.

(12) (a) Trenner, J.; Depken, C.; Weber, T.; Breder, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 8952. (b) Breder, A. *Synlett* **2014**, *25*, 899.

(13) For reviews, see: (a) *Organoselenium Chemistry: Synthesis and Reactions*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2011. (b) Sarma, B. K.; Mugesh, G. *Org. Biomol. Chem.* **2008**, *6*, 965. (c) Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649. (d) Freudendahl, D. M.; Santoro, S.; Shahzad, S. A.; Santi, C.; Wirth, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8409.

(14) For selected examples, see: (a) Tunge, J. A.; Mellegaard, S. R. *Org. Lett.* **2004**, *6*, 1205. (b) Crich, D.; Zou, Y. *J. Org. Chem.* **2005**, *70*, 3309. (c) Santoro, S.; Santi, C.; Sabatini, M.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2008**, *350*, 2881. (d) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504. (e) Curran, S. P.; Connon, S. J. *Org. Lett.* **2012**, *14*, 1074. (f) Tay, D. W.; Tsoi, I. T.; Er, J. C.; Leung, G. Y. C.; Yeung, Y.-Y. *Org. Lett.* **2013**, *15*, 1310. (g) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (h) Press, D. J.; McNeil, N. M. R.; Hambrook, M.; Back, T. G. *J. Org. Chem.* **2014**, *79*, 9394. (i) Yu, L.; Li, H.; Zhang, X.; Ye, J.; Liu, J.; Xu, Q.; Lautens, M. *Org. Lett.* **2014**, *16*, 1346. (j) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915.

(15) (a) Fukuzawa, S.-i.; Takahashi, K.; Kato, H.; Yamazaki, H. *J. Org. Chem.* **1997**, *62*, 7711. (b) Zhao, L.; Li, Z.; Wirth, T. *Eur. J. Org. Chem.* **2011**, 7080. (c) Back, T. G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* **2002**, *67*, 499. (d) Uehlin, L.; Fragale, G.; Wirth, T. *Chem.—Eur. J.* **2002**, *8*, 1125. (e) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3131.

(16) Balkrishna, S. J.; Prasad, C. D.; Panini, P.; Detty, M. R.; Chopra, D.; Kumar, S. *J. Org. Chem.* **2012**, *77*, 9541.

(17) For selected examples, see: (a) Alacid, E.; Nájera, C. *Eur. J. Org. Chem.* **2008**, 3102. (b) Chen, H.; Jiang, H.; Cai, C.; Dong, J.; Fu, W. *Org. Lett.* **2011**, *13*, 992. (c) Liu, J.; Ma, S. *Org. Lett.* **2013**, *15*, 5150. (d) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777. (e) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750. (f) Li, J.; Tan, C.; Gong, J.; Yang, Z. *Org. Lett.* **2014**, *16*, 5370.

DOI: 10.1021/acs.orglett.5b00213
Org. Lett. 2015, 17, 1834−1837