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1,4-Diazabicyclo[2.2.2]octane-Promoted Aminotrifluoromethylthiolation of α,β-Unsaturated Carbonyl Compounds: *N*-Trifluoromethylthio-4-nitrophthalimide Acts as Both the Nitrogen and SCF_3 Sources

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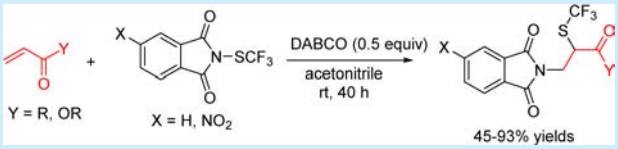
Supporting Information

ABSTRACT: A novel difunctionalization reaction is described. It uses *N*-trifluoromethylthio-4-nitrophthalimide as the reagent, which serves as both the nitrogen and SCF_3 sources. In the presence of DABCO (1,4-diazabicyclo[2.2.2]octane), the nitrogen and SCF_3 groups can be incorporated into α,β-unsaturated carbonyl compounds easily and give versatile β-amino ketones and esters in good yields. This difunctionalization reaction features mild reaction conditions, high atom-economy, and efficient access to α-SCF_3 amino acids.



There has been a resurgence of interest in organofluorine chemistry over the past several years.[1] Among various established fluoroalkyl groups, much attention is devoted to the trifluoromethanesulfenyl group (−SCF_3) due to its unique features: remarkable electron-withdrawing character[2] and excellent lipophilicity (cf. Hansch hydrophobic parameter, π = 1.44).[3] Indeed, this −SCF_3 group is exceptionally useful in isostere-based drug design. Thus, methods for assembling this fluorinated moiety into organic molecules are always needed for drug discovery in pharmaceutical and agrochemical industries.

The development of a useful SCF_3-containing reagent and a straightforward protocol for the incorporation of the −SCF_3 group to organic molecules have recently emerged.[4] In particular, methods for integrating the −SCF_3 group to the α-position of carbonyl compounds are very valuable to a wide range of bioactive and natural compounds. Expedient examples of electrophilic trifluoromethylthiolation reagents have been reported for these transformations (Figure 1), for instance, Billard's SCF_3 reagent **1a**,[5] Shen and Lu's SCF_3 reagent **2**,[6] SCF_3-ether **3** reported by Buchwald, Shen, and Lu,[7] Shibata's SCF_3-iodonium ylide **4**,[8] Munavalli's SCF_3-phthalimide **5a** (recently reintroduced by Rueping, Shen, and Lu),[9] and SCF_3-saccharine **6** developed by Shen.[10] Substrates of keto-esters and β-diketones, as well as some related asymmetric reactions, were investigated. α-Bromoketones,[11] oxindoles,[7b,9c,12] and α-diazoesters[13] are also applicable substrates for the formation of the corresponding α-SCF_3 carbonyl compounds. Nevertheless, under the reported reaction conditions, these reagents serve only as the −SCF_3 source, while the other counterpart is regarded as the side product. In fact, it would be attractive if both components of this reagent could be used in atom-economical synthetic chemistry.

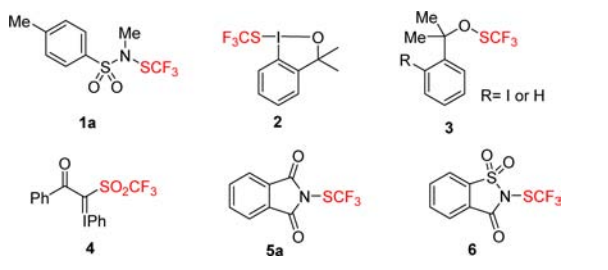


Figure 1. Examples of electrophilic trifluomethylthiolation reagents of carbonyl compounds.

Difunctionalization reactions of alkenes are particularly important, as they can be used to produce highly complex molecular architectures. There has been no example reported concerning the difunctionalization of a carbon−carbon double bond only with a SCF_3-phthalimide reagent. β-Amino ketones and esters are important structural motifs in a number of biologically active compounds, and many synthetic approaches to this class of compounds have been developed in recent years.[14] Herein we report our efforts in developing an effective reagent and protocol for facile access to the α-SCF_3-β-amino carbonyl skeleton from α,β-unsaturated carbonyl compounds by a difunctionalization reaction. This method provides a highly atom-economical preparation of α-SCF_3-β-amino acids and their corresponding peptides.

We embarked upon this investigation using phenyl vinyl ketone **7a** as the benchmark substrate and SCF_3-phthalimide **5a** as the trifluoromethylthiolation reagent (Table 1). Commonly used DBU (1,8-diazabicyclo[5.4.1]undec-7-ene), an activator of *N*-haloimides in difunctionalization of carbon−carbon multiple bonds,[15] only gave a trace amount of expected product (entry 1). To our delight, DABCO (1,4-diazabicyclo[2.2.2]octane) was

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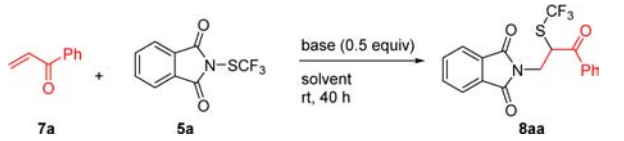
Table 1. Optimization of Aminotrifluoromethylthiolation of Vinyl Phenyl Ketone 7a with SCF_3-phthalimide 5a[a]



7a 5a 8aa

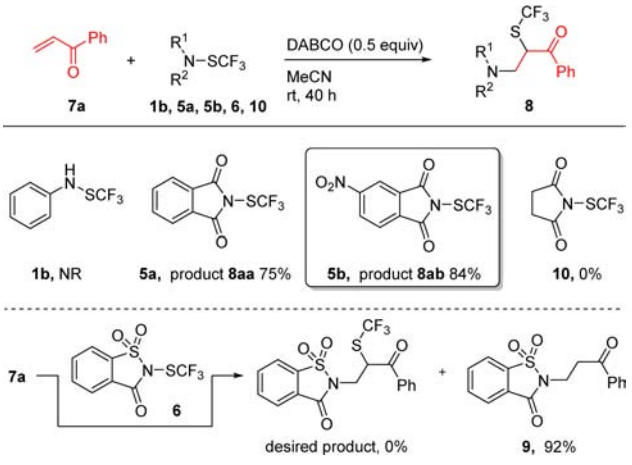
entry	base	solvent	yield (%)[b]
1	DBU	MeCN	trace
2	DABCO	MeCN	75
3	DMAP	MeCN	59
4	*i*-Pr_2NEt	MeCN	NR
5	4-methylmorpholine	MeCN	52
6	(*S*)-sparteine	MeCN	39[c]
7	K_2CO_3	MeCN	trace
8	DABCO	THF	52
9	DABCO	CH_2Cl_2	47
10	DABCO	dioxane	32
11	DABCO	DCE	41
12	DABCO	toluene	37
13[d]	DABCO	MeCN	61

[a]Reaction conditions: **7a** (0.1 mmol), **5a** (0.15 mmol), and base (0.05 mmol) in solvent (0.3 mL) were stirred at room temperature for 40 h under air. [b]Yield of isolated products. [c]There was essentially no ee value observed. [d]With 0.2 equiv of base. NR = no reaction.

found to be an efficient promotor to give the product **8aa** in 75% yield (entry 2). In addition to DABCO, DMAP (4-dimethylaminopyridine), 4-methylmorpholine, and sparteine were surveyed, albeit in lower product yield (entries 3, 5, and 6). Solvents such as THF, DCM, DCE, dioxane, and toluene resulted in poor yields (entries 8–12). When the reaction was carried out in 0.2 equiv DABCO, the yield was decreased from 75 to 61% (entry 2 vs 13).

Besides SCF_3-phthalimide **5a**, the efficacy of other known stable electrophilic *N*-SCF_3 sources was tested (Scheme 1). A

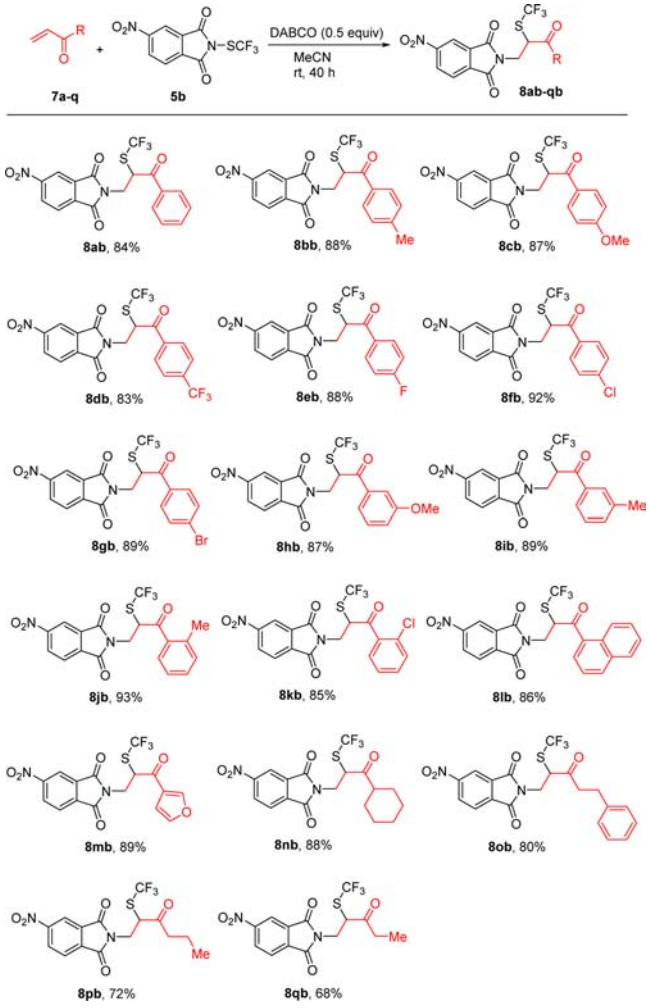
Scheme 1. SCF_3 Reagent Screening for DABCO-Promoted Aminotrifluoromethylthiolation of Phenyl Vinyl Ketone 7a



significant electronic effect of R^1 and R^2 groups on amine part was observed. *N*-SCF_3-aniline **1b** presumably is not electrophilic enough to react with phenyl vinyl ketone **7a**. To our surprise, SCF_3-saccharine **6**, which always has superior reactivity, did not give the expected product. Yet, only byproduct **9** was obtained in 92% yield (Scheme 1). SCF_3-succinimide **10** gave complex reaction mixtures, and no desired product was identified as judged by GC-MS analysis. With the initial result of SCF_3-phthalimide **5a** in hand, we intended to prepare a more reactive reagent. We employed a strategy of using a strong electron-withdrawing group attached to the arene to make the SCF_3-phthalimide reagent more easily activated. With the newly developed reagent **5b**, the product yield of **8ab** was increased to 84%. It should be noted that this electrophilic reagent features high moisture and air stability.

Under the optimized reaction conditions, a range of various α,β-unsaturated ketones **7a–q** were examined with SCF_3-4-nitrophthalimide **5b** (1.5 equiv) in acetonitrile at room temperature (Scheme 2). The reactions proceeded well to afford

Scheme 2. Aminotrifluoromethylthiolation of α,β-Unsaturated Ketone 7 with SCF_3-4-nitrophthalimide 5b[a,b]



[a]Reaction conditions: **7a–q** (0.15 mmol), **5b** (0.225 mmol), and DABCO (0.075 mmol) in MeCN (0.5 mL) were stirred at room temperature for 40 h under air. [b]Yield of isolated products.

the corresponding α-SCF_3-β-phthalimide ketones **8ab–8qb** in good to high yields. No significant electronic effect was observed on ketone substrates toward the efficiency of the reaction. Naphthyl ketone **7l** and furyl ketone **7m** were also suitable substrates. A slight decrease in product yields was observed when aliphatic ketone substrates were employed (i.e., **8nb–8qb**). No desired products were obtained for α- or β-substituted enones.

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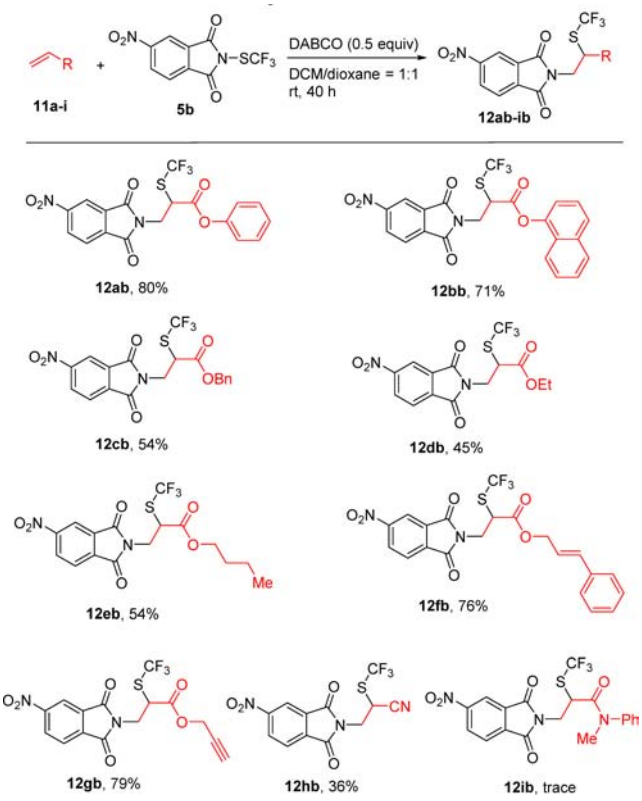
To extend the substrate scope, acrylates, acrylonitrile, and acrylamide were tested (Scheme 3). Further optimization

Scheme 3. Aminotrifluoromethylthiolation of α,β-Unsaturated Carbonyl Compounds 11a−g with SCF_3-phthalimide 5a,b[a,b]

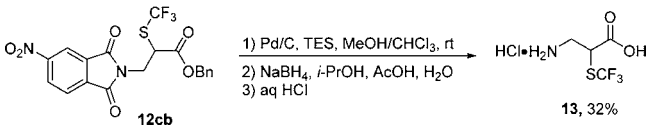


[a]Reaction conditions: **11a−i** (0.15 mmol), **5b** (0.225 mmol), and DABCO (0.075 mmol) in 0.45 mL of DCM/dioxane (1:1) were stirred at room temperature for 40 h under air. [b]Yield of isolated product.

disclosed that the addition of SCF_3-4-nitrophthalimide **5b** to α,β-unsaturated esters performed better in the mixed solvent (DCM/dioxane = 1:1). Aryl acrylate esters **11a,b** performed similarly well despite their activity which was weaker than that of ketones, affording the corresponding α-SCF_3-β-amino esters in 71−80% yields. When aliphatic acrylate esters **11c−g** were used as substrates, decreased yields (45−79%) were obtained. Acrylonitrile resulted in a relatively sluggish reaction and provided the expected product **12hb** in 36% yield. Attempted investigation of α,β-unsaturated amide gave no desired product essentially.

We attempted to use α-SCF_3-β-*N*-phthaloylamino acid ester to transform to the β-amino acid (Scheme 4). The acid group was deprotected by hydrogenation with triethylsilane, then removal of the phthaloyl group on **12cb** by treatment with sodium borohydride gave α-SCF_3-β-alanine hydrochloride (**13**·HCl) in

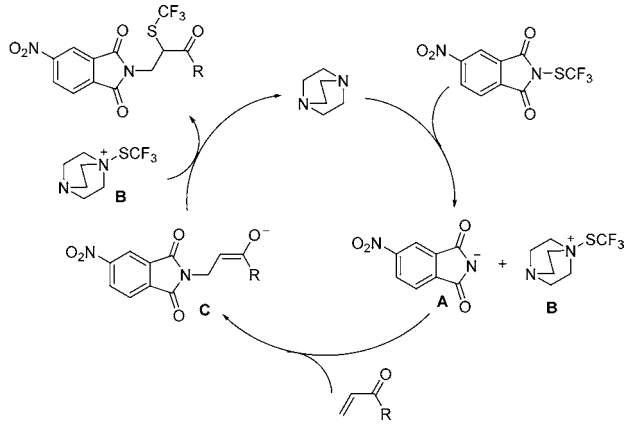
Scheme 4. Synthesis of α-SCF_3-β-alanine



32% yield.[16] Indeed, this method provided a new and practical approach for the synthesis of novel SCF_3-substituted β-amino acids.

A proposed mechanism is shown in Scheme 5.[17] The nucleophilic promoter DABCO activates the SCF_3-4-nitrophthalimide to generate a more nucleophilic nitrogen source **A** and a more electrophilic SCF_3 species **B**. The first step proceeds through the 1,4-addition of phthalimide anion **A** to the α,β-unsaturated ketone to generate the enolate **C**. In the second step, the enolate adds to electrophilic SCF_3 species **B**. Consequently, SCF_3-4-nitrophthalimide functions as both the electrophilic SCF_3 and nitrogen sources. Although we were not able to separate and confirm the active SCF_3 intermediate **B** at this time, the ^{19}F NMR study showed the existence of new SCF_3 species under the current system (see the Supporting Information).

Scheme 5. Plausible Mechanism of the Reaction



In conclusion, we have developed a novel DABCO-promoted aminotrifluoromethylthiolation of α,β-unsaturated carbonyl compounds with *N*-trifluoromethylthio-4-nitrophthalimide as both the nitrogen and SCF_3 sources. This protocol features mild conditions, a relatively broad scope, and high atom-economy in generating an array of α-SCF_3-β-amino ketones and esters with high efficiency. Remarkably, it provides a versatile approach for the synthesis of new SCF_3-containing β-amino acids and their corresponding peptides. Further investigations are underway to probe the mechanism and to extend the scope of the aminotrifluoromethylthiolation reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03116.

Experimental procedures and characterization/HPLC data of products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*; Wiley-VCH: Weinheim, 2013. (c) Becker, A. *Inventory of Industrial Fluoro-biochemicals*; Eyrolles: Paris, 1996. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, 2006. (f) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (g) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (h) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (i) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2014**, *20*, 16830. (j) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, *14*, 941. (k) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135. (l) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (m) Cresswell, A. J.; Davies, S. G.; Roberts, P. M.; Thomson, J. E. *Chem. Rev.* **2015**, *115*, 566. (n) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (o) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612. (p) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (q) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683−730. (r) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (s) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* **2015**, *115*, 931. (t) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V. *Chem. Rev.* **2015**, *115*, 973.

(2) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(3) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

(4) For selected reviews, see: (a) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, *2014*, 2415. (b) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880. (c) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476. (d) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (e) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513. (f) Lin, J.-H.; Ji, Y.-L.; Xiao, J.-C. *Curr. Org. Chem.* **2015**, *19*, 1541. (g) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (h) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227.

(5) (a) Ferry, A. L.; Billard, T.; Langlois, B. R.; Bacque, E. *J. Org. Chem.* **2008**, *73*, 9362. (b) Alazet, S.; Zimmer, L.; Billard, T. *Chem. - Eur. J.* **2014**, *20*, 8589. (c) Alazet, S.; Zimmer, L.; Billard, T. *J. Fluorine Chem.* **2015**, *171*, 78. (d) Alazet, S.; Billard, T. *Synlett* **2015**, *26*, 76.

(6) (a) Shao, X.; Wang, W.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457. (b) Wang, X.; Yang, T.; Cheng, X.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 12860. (c) Deng, Q.-H.; Rettenmeier, C.; Wadepohl, H.; Gade, L. H. *Chem. - Eur. J.* **2014**, *20*, 93.

(7) (a) Vinogradova, E. V.; Müller, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3125. (b) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *J. Org. Chem.* **2015**, *80*, 3012. (c) Shao, X.; Liu, T.; Lu, L.; Shen, Q. *Org. Lett.* **2014**, *16*, 4738. (d) Hu, F.; Shao, X.; Zhu, D.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 6105.

(8) (a) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782. (b) Arimori, S.; Takada, M.; Shibata, N. *Org. Lett.* **2015**, *17*, 1063.

(9) (a) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30*, 2847. (b) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856. (c) Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun.* **2014**, *50*, 2508. (d) Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1650. (e) Kang, K.; Xu, C.-F.; Shen, Q. *Org. Chem. Front.* **2014**, *1*, 294.

(10) (a) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316. (b) Maeno, M.; Shibata, N.; Cahard, D. *Org. Lett.* **2015**, *17*, 1990. (c) Wang, Q.; Qi, Z.; Xie, F.; Li, X. *Adv. Synth. Catal.* **2015**, *357*, 355. (d) Xu, C.; Shen, Q. *Org. Lett.* **2015**, *17*, 4561.

(11) (a) Huang, Y.; He, X.; Li, H.; Weng, Z. *Eur. J. Org. Chem.* **2014**, *2014*, 7324. Huang, Y.; He, X.; Lin, X.; Rong, M.; Weng, Z. *Org. Lett.* **2014**, *16*, 3284.

(12) (a) Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192. (b) Yang, T.; Shen, Q.; Lu, L. *Chin. J. Chem.* **2014**, *32*, 678.

(13) (a) Lefebvre, Q.; Fava, E.; Nikolaienko, P.; Rueping, M. *Chem. Commun.* **2014**, *50*, 6617. (b) Wang, X.; Zhou, Y.; Ji, G.; Wu, J.; Li, M.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, *2014*, 3093. (c) Hu, M.; Rong, J.; Miao, W.; Ni, C.; Han, Y.; Hu, J. *Org. Lett.* **2014**, *16*, 2030.

(14) For selected reviews and examples, see: (a) Juaristi, E.; Soloshonok, V. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.: Wiley: Hoboken, NJ, 2005. (b) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366. (c) Weiner, B.; Szymański, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656. (d) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794. (e) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V.; Sorochinsky, A. *Synthesis* **2011**, *19*, 3045. (f) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (g) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (h) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (i) Wang, J.; Shao, Z.; Ding, K.; Yu, W.-Y.; Chan, A. S. C. *Adv. Synth. Catal.* **2009**, *351*, 1250. (j) Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464. (k) Inamoto, Y.; Kaga, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2013**, *15*, 3452. (l) Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708. (m) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56. (n) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (o) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064. (p) Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708. (q) Sibi, M. P.; Chen, J. *Org. Lett.* **2002**, *4*, 2933. (r) Sibi, M. P.; Patil, K. *Tetrahedron: Asymmetry* **2006**, *17*, 516.

(15) (a) Li, M.; Yuan, H.; Zhao, B.; Liang, F.; Zhang, J. *Chem. Commun.* **2014**, *50*, 2360. (b) Wei, Y.; Lin, S.; Liang, F. *Org. Lett.* **2012**, *14*, 4202. (c) Wei, Y.; Lin, S.; Liang, F.; Zhang, J. *Org. Lett.* **2013**, *15*, 852. (d) Wei, Y.; Liang, F.; Zhang, X. *Org. Lett.* **2013**, *15*, 5186.

(16) (a) Mandal, P. S.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599−6601. (b) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093−2096.

(17) Lone, A. M.; Bhat, B. A. *Org. Biomol. Chem.* **2014**, *12*, 242.

DOI: 10.1021/acs.orglett.5b03116
Org. Lett. 2015, 17, 6090−6093