Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Chiral α-Trifluoromethylamines with 2,2,2-Trifluoroethylamine as a "Building Block"

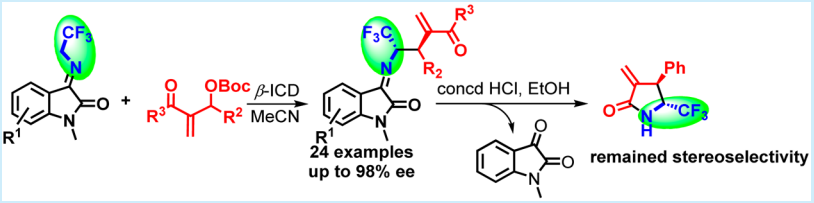
Xiaoyuan Li,[†] Jinhuan Su,[†] Zhourujun Liu,[†] Yuanyuan Zhu,[†] Zhenghao Dong,[†] Shuai Qiu,[†] Jiayi Wang,[†] Li Lin,[†] Zhiqiang Shen,[‡] Wenjin Yan,*[,†] Kairong Wang,*[,†] and Rui Wang*[,†,‡,§]

[†]Institute of Pharmacology, Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic, Medical Sciences, Lanzhou University, Lanzhou 730000, China

[‡]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, Peoples Republic of China

[§]Collaborative Innovation Centre of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

Supporting Information



ABSTRACT: The β-isocupreidine, a *cinchonine* derived alkaloid, catalyzed asymmetric $S_N2'-S_N2'$ reaction between *N*-2,2,2-trifluoroethylisatin ketimines and MBH type carbonates was realized in a simple and efficient way. A series of chiral α-trifluoromethylamines were prepared with excellent yields and stereoselectivities. A subsequent and easy process of deprotection gave γ-trifluoromethyl-α-methylenelactam in a stereoselective manner.

It is well-known that organofluorine compounds play a central role in the fields of pharmaceutical and agrochemistry.[1] Among fluorinated compounds, the trifluoromethyl group occupies a special position especially when incorporated at the α-position to nitrogen, with such compounds often having enhanced lipophilicity and metabolic stability when present in small molecules.[2] Notable drugs containing α-trifluoromethylamines include Cathepsin cysteine protease inhibitors, Odanacatib, 3′-Trifluoromethyl Taxoid, Quazepam, and so on (Figure 1).[3] Moreover, such functional scaffolds are also key motifs of peptidomimetics and peptides with various interesting biological activities.[4] As a consequence, practical synthetic approaches to α-trifluoromethylamines are attracting considerable attention.

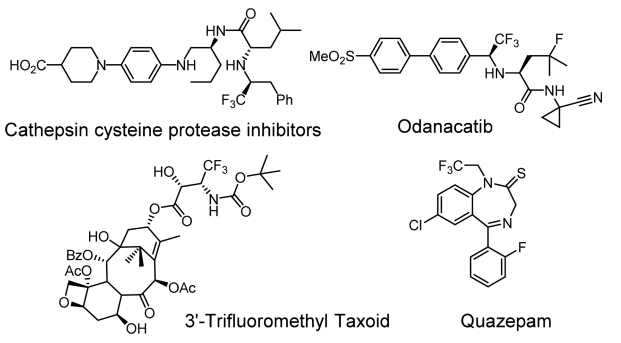


Figure 1. Selected drugs bearing α-trifluoromethylamines.

Much ongoing effort has been devoted to the synthesis of α-trifluoromethylamine scaffolds, their preparation frequently hinging on the reductive amination of ketones, the trifluoromethylation of imines or ketimines, the biomimetic transamination, and so forth.[5] However, most of these approaches are hampered by the multiple-step preparation of the reactants as well as the narrow range of products obtained.

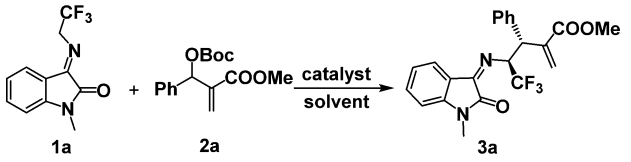
$CF_3-CH_2-NH_2$, a simple α-trifluoromethyl amine unit, has emerged as a CF_3-containing synthon through its direct conversion into the trifluoromethyl diazomethane.[6] This strategy converts this readily available starting material into many versatile building blocks that can be used to provide a highly flexible and efficient synthetic route for the asymmetric synthesis of complex α-trifluoromethylamines.[7] As part of our continuing interest in this area,[8] we now report a convenient method for the construction of chiral α-trifluoromethylamines.

In this regard, *N*-2,2,2-trifluoroethylisatin ketimines[8] were used as nucleophiles and reacted with MBH carbonates and their derivatives[9] to test our ideas. An initial experiment was carried out between nonsubstituted *N*-2,2,2-trifluoroethylisatin ketimine **1a** and MBH carbonate **2a** in DCM with DABCO as catalyst (Table 1, entry 1). Although no enantioselectivity was observed, a nucleophilic substitution product was obtained in 91% yield and 12:1 dr. In order to confer optical activity on the product, the *quinine* alkaloid (**C2** (Figure 2), 10 mol %) and

Received: January 4, 2016

DOI: 10.1021/acs.orglett.5b03566
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening of Reaction Conditions[a]



entry	catalyst	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1**	DCM	1	91	12:1	0
2	**C2**	DCM	36	50	19:1	50
3	**C3**	DCM	48	46	2:1	9
4	**C4**	DCM	72	nd[e]	nd	nd
5	**C5**	DCM	6	90	11:1	85
6	**C5**	DCM	6	64	12:1	65[f]
7	**C5**	1,4-dioxane	4	80	16:1	77
8	**C5**	THF	5	84	18:1	80
9	**C5**	TOL	4	81	13:1	67
10	**C5**	DCE	4	88	13:1	65
11	**C5**	MTBE	18	93	16:1	68
12	**C5**	EA	2	92	13:1	85
13	**C5**	MeCN	2	88	>20:1	86
14	**C5**	MeCN	6	90	>20:1	89[f]
15	**C5**	MeCN	16	91	>20:1	91[g]

[a]Reaction conditions: **1a** (0.20 mmol) and **2a** (0.22 mmol) in MeCN (2 mL) with catalyst (0.02 mmol) reacted at room temperature. [b]Isolated yield. [c]Determined by chiral phase HPLC analysis or ^{1}H NMR. [d]Determined by chiral phase HPLC analysis. [e]No product was found. [f]Reacted at 0 °C. [g]Reacted at −10 °C.

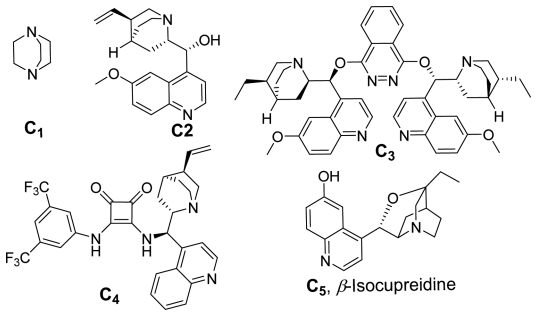
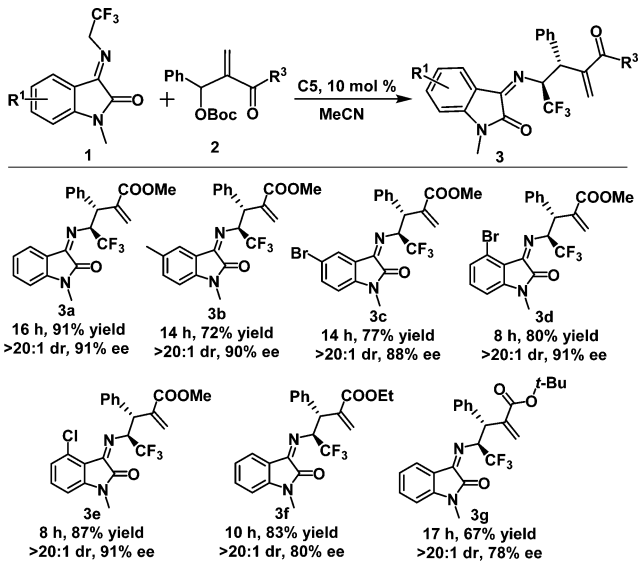


Figure 2. Catalyst for screening.

$(DHQD)_2$ Phal (**C3**, 10 mol %) were tested respectively as DABCO replacements; the former gave product **3a** in 50% yield and 50% ee, and the latter gave a poor result (Table 1, entries 2−3). The *cinchonidine*-squaramide (**C4**, 10 mol %) was also applied as a catalyst and led to an undesired product (Table 1, entry 4). The best result was obtained when *β*-isocupreidine[10] (**C5**, 10 mol %) was applied, the reaction giving **3a** in 90% yield and up to 85% ee after 6 h at room temperature (Table 1, entry 5). Encouraged by this result, solvents and temperature were further optimized (Table 1, entries 6−15). The results revealed that, at −10 °C in combination with **C5** (10 mol %) as a catalyst, the reaction between substrates **1a** (0.20 mmol) and **2a** (0.22 mmol) in MeCN (2 mL) gave the chiral product in excellent yield and stereoselectivity after 16 h (>20:1 dr, 91% ee) (Table 1, entry 15).

Under the optimized conditions, the scope of the *N*-2,2,2-trifluoroethylisatin ketimines **1** was examined, with the use of MBH carbonates, acetates, and *tert*-butyl ester also being demonstrated. As shown in Scheme 1, the enantioselectivity of product **3b**, with a methyl on the 5-position of isatin, was increased compared to product **3c** with a bromine at the same

Scheme 1. Scale of *N*-2,2,2-Trifluoroethylisatin Ketimines and MBH Adducts[a]



[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee values and dr values were determined by HPLC analysis.

position. When the substituent was on the 4-position of isatins, the enantioselectivities of products were better than when the substituent group was on the 5-position (Scheme 1, **3c** and **3d**). The enantioselectivities of **3d** and **3e** were almost the same although 4-Cl substituted **3e** showed a slightly better yield. An ethyl group or a *tert*-butyl in the position of R_3 gave product **3f** and **3g** in lower enantioselectivities.

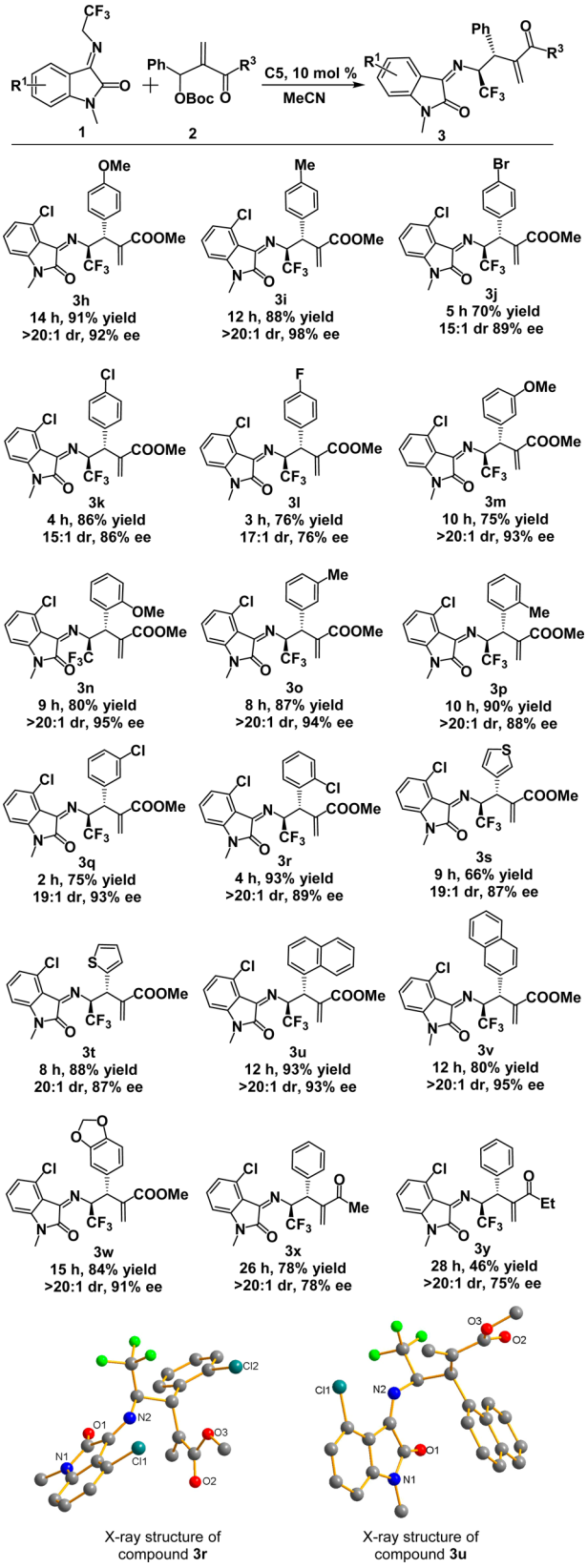
We next focused on the scope of the MBH adducts. As shown in Scheme 2, increasing the electronegativity of the aryl 4-position of MBH carbonates **2** eroded the enantioselectivities and diastereoselectivities of the products, showing a decreasing trend (Scheme 2, **3h**, **3i**, **3j**, **3k**, and **3l**). However, no obvious electronic effect was observed at the 3- and 2-position of MBH carbonates (Scheme 2, **3m**, **3n**, **3n**, **3p**, **3q**, and **3r**). Moreover, when heterocycle compounds such as thienyl were used as alternatives to the aryl group of **2**, enantio- and diastereoselectivities were maintained (Scheme 2, **3s** and **3t**). Although longer reaction times were needed, the reactions showed excellent results when the MBH carbonates derived from 1-naphthaldehdye, 2-naphthaldehdye, and heliotropin (Scheme 2, **3u**, **3v**, and **3w**). Replacement of the methoxycarbonyl of the MBH carbonates by a ketone carbonyl lowered the reactivity and enantioselectivity (Scheme 2, **3x** and **3y**). In the purification process via achiral chromatography, no SDE (self-disproportionation of enantiomers) was observed.[11]

As shown in Figure 3, the *N*-methyl isatin grouping could be easily removed in the concentrated hydrochloric acid/EtOH. The remaining product proceeded to undergo a self-cyclization and was converted into a pharmacophore of *α*-methylenelactams **4a** which are often found in many anticancer drugs due to its cytotoxic properties.[12]

According to the absolute configuration of products **3r** and **3u**, a possible mechanism of this reaction is proposed. As shown in Figure 4, *β*-ICD attacks the MBH carbonate via an S_N2' process. It behaves as a Lewis base chiral catalyst. This is followed by another S_N2'-type process, with the isatinketimine **1a** acting as an active nucleophile.

DOI: 10.1021/acs.orglett.5b03566
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of MBH Adducts[a]



[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee values and dr values were determined by HPLC analysis.

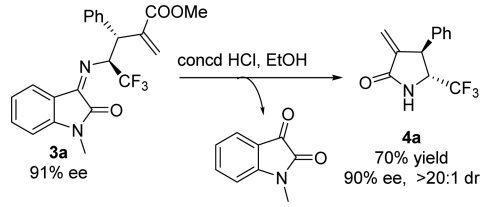


Figure 3. Deprotection of product **3e**.

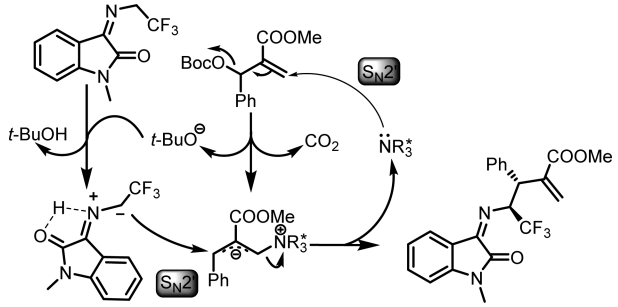


Figure 4. Possible mechanism of this reaction.

In conclusion, a highly flexible and efficient approach to the synthesis of chiral α-trifluoromethylamines via β-ICD catalyzed $S_N2'-S_N2'$ reactions between *N*-2,2,2-trifluoroethylisatin ketimines and MBH carbonates has been achieved. A series of structurally diverse α-trifluoromethylamine compounds were obtained in excellent yields and stereoselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03566.

Experimental procedures and characterization of the products (PDF)
Crystallographic data for compound **3r** (CIF)
Crystallographic data for compound **3u** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yanwj@lzu.edu.cn.
*E-mail: wangkr@lzu.edu.cn.
*E-mail: wangrui@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the grants from the National Natural Science Foundation of China (Nos. 21432003, 21272107, 21272108, 31200584, 91213302, 81573265).

■ REFERENCES

(1) Hiyama, H. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000.
(2) For reviews, see: (a) Waser, M.; Novacek, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14228. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C. D.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (d) Ma, J.-A.; Cahard, D.

DOI: 10.1021/acs.orglett.5b03566
Org. Lett. XXXX, XXX, XXX−XXX

Chem. Rev. **2008**, *108*, PR1. (e) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727.

(3) (a) Yang, X.; Chen, Z.; Cai, Y.; Huang, Y.-Y.; Shibata, N. *Green Chem.* **2014**, *16*, 4530. (b) O'Shea, P. D.; Chen, C.-Y.; Gauvreau, D.; Gosselin, F.; Hughes, G.; Nadeau, C.; Volante, R. P. *J. Org. Chem.* **2009**, *74*, 1605. (c) Gauthier, J. Y.; Chauret, N.; Cromlish, W.; Desmarais, S.; Duong, L. T.; Falgueyret, J.-P.; Kimmel, D. B.; Lamontagne, S.; Léger, S.; LeRiche, T.; Li, C. S.; Massé, F.; McKay, D. J.; Nicoll-Griffith, D. A.; Oballa, R. M.; Palmer, J. T.; Percival, M. D.; Riendeau, D.; Robichaud, J.; Rodan, G. A.; Rodan, S. B.; Seto, C.; Thérien, M.; Truong, V.-L.; Venuti, M. C.; Wesolowski, G.; Young, R. N.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 923. (d) Ojima, I.; Slater, J. C. *Chirality* **1997**, *9*, 487.

(4) (a) Dal Pozzo, A.; Ni, M.; Muzi, L.; de Castiglione, R. D.; Mondelli, R.; Mazzini, S.; Penco, S.; Pisano, C.; Castorina, M.; Giannini, G. *J. Med. Chem.* **2006**, *49*, 1808. (b) Koksch, B.; Sewald, N.; Hofmann, H.-J.; Burger, K.; Jakubke, H.-D. *J. Pept. Sci.* **1997**, *3*, 157.

(5) For selected examples, see: (a) Brusoe, A. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 8460. (b) Luo, H.; Wu, G.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14503. (c) Jiang, J.; Lu, W.; Lv, H.; Zhang, X. *Org. Lett.* **2015**, *17*, 1154. (d) Xie, C.; Mei, H.; Wu, L.; Han, J.; Soloshonok, V. A.; Pan, Y. *J. Fluorine Chem.* **2014**, *165*, 67. (e) Liu, Y.; Liu, J.; Huang, Y.; Qing, F.-L. *Chem. Commun.* **2013**, *49*, 7492. (f) Genoni, A.; Benaglia, M.; Massolo, E.; Rossi, S. *Chem. Commun.* **2013**, *49*, 8365. (g) Grellepois, F.; Jamaa, A. B.; Gassama, A. *Eur. J. Org. Chem.* **2013**, *2013*, 6694. (h) Liu, M.; Li, J.; Xiao, X.; Xie, Y.; Shi, Y. *Chem. Commun.* **2013**, *49*, 1404. (i) Husmann, R.; Sugiono, E.; Mersmann, S.; Raabe, G.; Rueping, M.; Bolm, C. *Org. Lett.* **2011**, *13*, 1044. (j) Mimura, H.; Kawada, K.; Yamashita, T.; Sakamoto, T.; Kikugawa, Y. *J. Fluorine Chem.* **2010**, *131*, 477. (k) Chen, M.-W.; Duan, Y.; Chen, Q.-A.; Wang, D.-S.; Yu, C.-B.; Zhou, Y.-G. *Org. Lett.* **2010**, *12*, 5075. (l) Liu, Z.-J.; Liu, J.-T. *Chem. Commun.* **2008**, 5233.

(6) (a) Morandi, B.; Carreira, E. M. *Angew. Chem.* **2010**, *122*, 950–953; *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (b) Morandi, B.; Carreira, E. M. *Angew. Chem.* **2010**, *122*, 4390; *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (c) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem.* **2011**, *123*, 1133; *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (d) Morandi, B.; Carreira, E. M. *Angew. Chem.* **2011**, *123*, 9251; *Angew. Chem., Int. Ed.* **2011**, *50*, 9085. (e) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (f) Chai, Z.; Bouillon, J.-P.; Cahard, D. *Chem. Commun.* **2012**, *48*, 9471. (g) Liu, C.-B.; Meng, W.; Li, F.; Wang, S.; Nie, J.; Ma, J.-A. *Angew. Chem.* **2012**, *124*, 6331; *Angew. Chem., Int. Ed.* **2012**, *51*, 6227. (h) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. *Angew. Chem.* **2013**, *125*, 6375; *Angew. Chem., Int. Ed.* **2013**, *52*, 6255. (i) Sun, L.; Nie, J.; Zheng, Y.; Ma, J. A. *J. Fluorine Chem.* **2015**, *174*, 88.

(7) (a) Ma, M.; Zhu, Y.; Sun, Q.; Li, X.; Su, J.; Zhao, L.; Zhao, Y.; Qiu, S.; Yan, W.; Wang, K.; Wang, R. *Chem. Commun.* **2015**, *51*, 8789. (b) Sun, Q.; Li, X.; Su, J.; Zhao, L.; Ma, M.; Zhu, Y.; Zhao, Y.; Zhu, R.; Yan, W.; Wang, K.; Wang, R. *Adv. Synth. Catal.* **2015**, *357*, 3187.

(8) For our research with isatin ketimines as a nucleophile: (a) Yan, W.; Wang, D.; Feng, J.; Li, P.; Wang, R. *J. Org. Chem.* **2012**, *77*, 3311. (b) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512. (c) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003. (d) Wang, D.; Liang, J.; Feng, J.; Wang, K.; Sun, Q.; Zhao, L.; Li, D.; Yan, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 548.

(9) For reviews, see: (a) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. For selected examples, see: (d) Zhao, S.; Zhao, Y.-Y.; Lin, J.-B.; Xie, T.; Liang, Y.-M.; Xu, P.-F. *Org. Lett.* **2015**, *17*, 3206. (e) Roy, S. J. S.; Mukherjee, S. *Chem. Commun.* **2014**, *50*, 121. (f) Tong, G.; Zhu, B.; Lee, R.; Yang, W.; Tan, D.; Yang, C.; Han, Z.; Yan, L.; Huang, K.-W.; Jiang, Z. *J. Org. Chem.* **2013**, *78*, 5067. (g) Yang, W.; Tan, D.; Li, L.; Han, Z.; Yan, L.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2012**, *77*, 6600. (h) Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. *Org. Lett.* **2011**, *13*, 3972. (i) Tan, B.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, *133*, 4672. (j) Peng, J.; Huang, X.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 4260. (k) Hong, L.; Sun, W.; Liu, C.; Zhao, D.; Wang, R. *Chem. Commun.* **2010**, *46*, 2856. (l) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 3914. (m) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (n) Furukawa, T.; Kawazoe, J.; Zhang, W.; Nishimine, T.; Tokunaga, E.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 9684. (o) Nishimine, T.; Fukushi, K.; Shibata, N.; Taira, H.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 517.

(10) (a) Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495. (b) von Riesen, C.; Hoffmann, H. M. R. *Chem. - Eur. J.* **1996**, *2*, 680. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

(11) For reviews, see: (a) Soloshonok, V. A.; Roussel, C.; Kitagawa, Q.; Sorochinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180. For selected examples, see: (b) Shibatomi, K.; Kawasaki, Y.; Iwasa, S. *J. Fluorine Chem.* **2015**, *179*, 77. (c) Kowalczyk, R.; Wierzba, A. J.; Boratynski, P. J.; Bakowicz, J. *Tetrahedron* **2014**, *70*, 5834. (d) Lian, X.; Guo, S.; Wang, G.; Lin, L.; Liu, X.; Feng, X. *J. Org. Chem.* **2014**, *79*, 7703. (e) Li, J.; Zhang, Y.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2014**, *50*, 6672.

(12) For a review, see: (a) Janecka, A.; Wyrebska, A.; Gach, K.; Fichna, J.; Janecki, T. *Drug Discovery Today* **2012**, *17*, 561. For selected examples, see: (b) Companyó, X.; Geant, P.-Y.; Mazzanti, A.; Moyano, A.; Rios, R. *Tetrahedron* **2014**, *70*, 75. (c) Pan, F.; Chen, J.-M.; Zhuang, Z.; Fang, Y.-Z.; Zhang, S. X.-A.; Liao, W.-W. *Org. Biomol. Chem.* **2012**, *10*, 2214. (d) Companyó, X.; Mazzanti, A.; Moyano, A.; Janecka, A.; Rios, R. *Chem. Commun.* **2013**, *49*, 1184. (e) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rózalski, M. *J. Med. Chem.* **2005**, *48*, 3516. (f) Zhu, Y.; Li, X.; Chen, Q.; Su, J.; Jia, F.; Qiu, S.; Ma, M.; Sun, Q.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2015**, *17*, 3826. (g) Xu, J.; Chen, J.; Yang, Q.; Ding, L.; Liu, X.; Xu, D.; Zhao, B. *Adv. Synth. Catal.* **2014**, *356*, 3219.

DOI: 10.1021/acs.orglett.5b03566
Org. Lett. XXXX, XXX, XXX–XXX