Organic LETTERS

Letter

pubs.acs.org/OrgLett

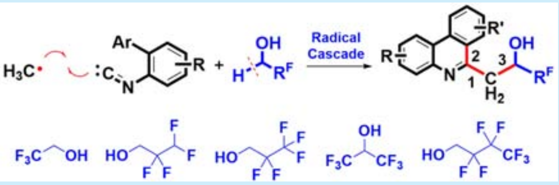
Free-Radical Triggered Ordered Domino Reaction: An Approach to C−C Bond Formation via Selective Functionalization of α-Hydroxyl-(sp^3)C−H in Fluorinated Alcohols

Zhengbao Xu, Zhaojia Hang, and Zhong-Quan Liu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

Ⓢ *Supporting Information*

ABSTRACT: A free-radical mediated highly ordered radical addition/cyclization/(sp^3)C−C(sp^3) formation domino reaction is developed. Three new C−C bonds are formed one by one in a mixed system. Furthermore, it represents the first example of cascade C−C bond formation via selective functionalization of α-hydroxyl-C(sp^3)−H in fluorinated alcohols.

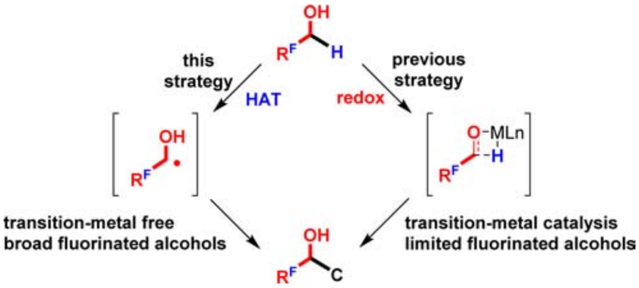


A biosystem usually utilizes domino or cascade reactions constructing multiple bonds in one single step.[1] A well-known example is that lanosterol is efficiently prepared from 2,3-oxidosqualene via a cyclase-catalyzed cyclization/rearrangement/hydride shift cascade.[2] In light of the efficiency and step economy of this strategy, increasingly more bioinspired domino methodologies by transition-metal catalysis as well as organocatalysis have been developed in the past decades.[3] Of particular interest are free-radical-initiated cascade reactions, which had been extensively studied in the past century.[4] However, most of these systems are rarely applied in the synthesis of natural products and pharmaceuticals because of stoichiometric transition metals and overdependence on highly toxic organotins. To overcome these limitations, some tin-free systems have been explored.[5] Recently several peroxide-mediated radical addition/cyclization cascade reactions by selective functionalization of (sp^3)C−H bonds have been achieved. These strategies have been successfully used to form various bioactive heterocycles such as phenanthridines[6] by using simple alkanes, alcohols, and ethers.

Among them, radical-initiated selective sp^3-α-C−H functionalization of simple aliphatic alcohols are of great interest to synthetic chemists.[7] In the past several years, a series of radical C−C bond formations using alcohols have been developed by Tu,[8] Han and Pan,[9] us,[10] and others.[11] However, a long-standing challenging problem is how to simultaneously introduce the hydroxyl and trifluoromethyl or polyfluoroalkyl groups into organic molecules through direct functionalization of α-hydroxyl-(sp^3)C−H in trifluoroethanol (TFE) and polyfluorinated alcohols. Although the corresponding fluorinated aldehydes have been engaged in C−C formation,[12] these aldehydes are generally unstable, scarce, and volatile. In contrast, polyfluorinated alcohols are used as solvent quite often due to its high stability, commercial availability, and abundance. Therefore, direct C−C bond construction using TFE and polyfluorinated alcohols is highly desirable. Unfortunately, this transformation has very rarely been investigated in recent years. The first example of direct C−C bond formation of quinoline with TFE by γ-irradiation was reported by Sugimori and co-workers 30 years ago.[13] The second example was accomplished by reaction of styrene with supercritical TFE.[14] Both cases are suffered from harsh reaction conditions and very low yields. The last, also the most closely successful, method was developed by Krische and co-workers very recently.[15] They achieved an efficient Ru-catalyzed cross-coupling of allenes with fluorinated alcohols. However, only those fluorinated alcohols with at least two β-hydrogen atoms and primary alcohols are effective in this system.

Although the bond dissociation energy (BDE) of the C−H in TFE (92.5 kcal/mol) is only 1 kcal/mol higher than that in ethanol (91.5 kcal/mol),[16] redox-promoted dehydrogenation of fluorinated alcohols is usually difficult. It should be due to the high energetic barrier of β-hydride elimination and reversibility in the dehydrogenation step.[17] Considering the efficiency of radical domino reactions and our previous studies,[18] we hypothesized whether C−C formation could occur with TFE and polyfluorinated alcohols by using a radical cascade strategy (Scheme 1). Fortunately, we successfully achieved a metal-free radical methylation/cyclization/(sp^3)C−C(sp^3) formation

Scheme 1. Strategies for C−C Formation with Polyfluorinated Alcohols



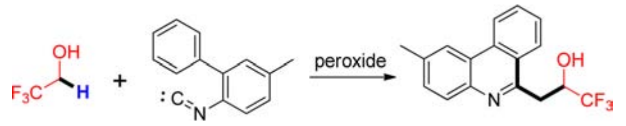
Received: July 5, 2016
Published: August 25, 2016

DOI: 10.1021/acs.orglett.6b01946
Org. Lett. 2016, 18, 4470−4473

domino reaction of isonitriles with TFE and polyfluorinated alcohols. The present method is the first, to the best of our knowledge, broadly practical and applicable C−C bond formation with TFE and polyfluorinated alcohols.

Initially, in continuation of our studies on radical cascade reactions of biarylisonitriles with alcohols, the reaction of TFE and 2-isocyano-5-methyl-1,1′-biphenyl was carried out (Table 1).

Table 1. Modification of the Typical Reaction Conditions[a]



entry	peroxide	solvent (mL)	yields (%)
1	TBHP	*t*-BuOH/TFE (4/1, 5)	–
2	DTBP	*t*-BuOH/TFE (4/1, 5)	18
3	DCP	*t*-BuOH/TFE (4/1, 5)	48
4	DCP	*t*-BuOH/TFE (2/1, 3)	35
5	DCP	*t*-BuOH/TFE (5/1, 6)	48
6	DCP	*t*-BuOH/TFE (4/1, 2.5)	28
7	DCP	*t*-BuOH/TFE (4/1, 10)	51
8[b]	DCP	*t*-BuOH/TFE (3/1, 4)	38
9[b]	**DCP**	***t*-BuOH/TFE (3/1, 8)**	**53**

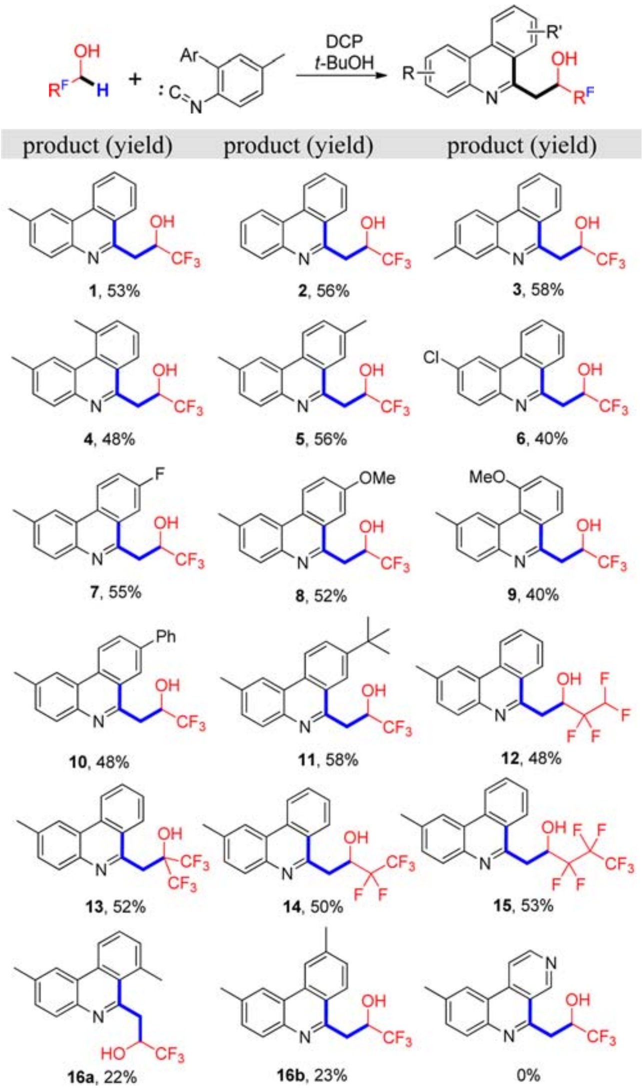
[a]Reaction conditions: isonitrile (1 equiv, 0.2 mmol), peroxide (2 equiv, 0.4 mmol), 130 °C, 24 h, unless otherwise noted. [b]Reaction conditions: isonitrile (1 equiv, 0.1 mmol), peroxide (3 equiv, 0.3 mmol), 130 °C, 24 h, unless otherwise noted. [c]Isolated yields.

No reaction occurred using TBHP (*tert*-butyl hydroperoxide, in decane) as the radical initiator (entry 1). Surprisingly, 1,1,1-trifluoro-3-(2-methylphenanthridin-6-yl)propan-2-ol was isolated in 18% yield while using DTBP (di-*tert*-butyl peroxide) (entry 2). Considering the methylene group should come from either peroxide or *t*-BuOH, other peroxides as well as solvent were screened. Over 100 optimizing reactions were carried out (see Supporting Information (SI)). Finally, DCP (dicumyl peroxide) and a mixture of *t*-BuOH/TFE were chosen as the radical initiator and solvent, respectively.

Next, we studied the scope of this radical cascade reaction (Table 2). As depicted in Table 2, a variety of biaryl isocyanides and polyflorinated alcohols are amenable to this system (**1**−**15**). The aryl substituents such as alkyl, halides, and methoxyl groups can be well-tolerated (**1**−**12**). Gratifyingly, an array of polyflorinated alcohols except for TFE, such as 1,1,1,3,3,3-hexafluoropropan-2-ol, 2,2,3,3,3-pentafluoropropan-1-ol, 2,2,3,3-tetrafluoropropan-1-ol, and 2,2,3,3,4,4,4-heptafluorobutan-1-ol also gave the corresponding products in moderate yields (**13**−**15**).

Inspired by these results and the previous radical cascade methylation of oxindoles and phenanthridines,[19] we began to question whether 6-methylated phenanthridines also can be formed with the (sp^3)C−C(sp^3) bond using TFE and polyfluorinated alcohols. As we expected, an array of 1,1,1-trifluoro-3-(phenanthridin-6-yl)propan-2-ols can be conveniently synthesized via 6-methylated phenanthridines with TFE and polyfluorinated alcohols under the typical reaction conditions (Table 3). As demonstrated in Table 3, various 6-methylated phenanthridines and fluorinated alcohols gave the desired products in good yields (**1**−**17**). However, 2-methylquinaline and 1-methylisoquinoline are not amenable to this system.

Table 2. Metal-Free Radical Reaction of Isonitriles with TFE and Polyfluorinated Alcohols[a,b]

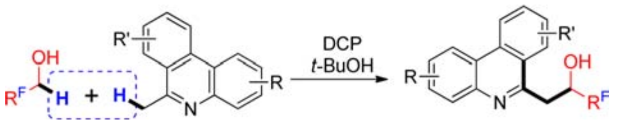


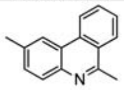
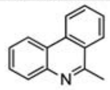
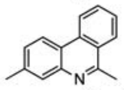
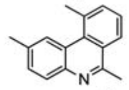
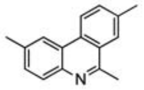
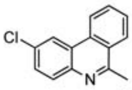
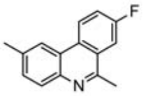
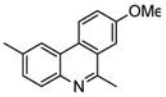
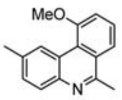
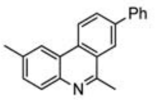
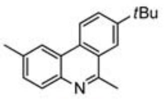
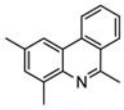
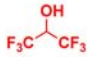
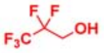
[a]Reaction conditions: isonitrile (1 equiv, 0.1 mmol), DCP (3 equiv, 0.3 mmol), *t*-BuOH (6 mL), polyfluorinated alcohol (2 mL), 130 °C, 24 h. [b]Isolated yields.

In order to investigate the mechanism, a series of control experiments and mechanistic studies have been carried out. As demonstrated in our previous research on methylation of biaryl isonitriles, it is believed to proceed via a radical-mediated addition/cyclization cascade process. We consider that the C−C formation of 6-methylated phenanthridines with fluorinated alcohols might be a Friedel−Crafts pathway. Therefore, CF_3CHO (75 wt % solution in H_2O) and 1-ethoxy-2,2,2-trifluoroethan-1-ol were chosen to test this hypothesis (eqs 1−6). As shown below, the desired products were obtained in good yields by using these surrogates. Gratifyingly, we also detected the 1-(*tert*-butoxy)-2,2,2-trifluoroethan-1-ol by GC-MS analysis (SI), which further confirms the mechanism. In addition, an array of radical trapping experiments through electron paramagnetic resonance (EPR) were also done. However, the corresponding α-OH−C-centered radical in TFE has not been detected by EPR, which might be due to the instability of this radical intermediate.

Based on the literature[20] and our analysis, a suggested mechanism is shown in Scheme 2. Homolysis of DCP followed

Table 3. Metal-Free Radical Reaction of 6-Methylated Phenanthridines with TFE and Polyfluorinated Alcohols[a]

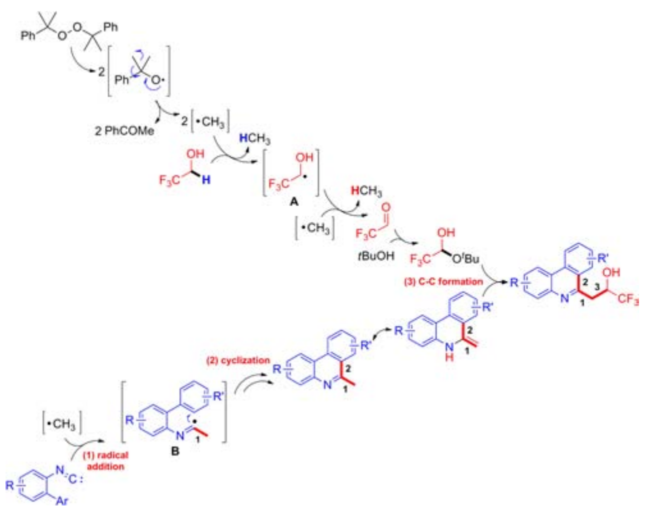


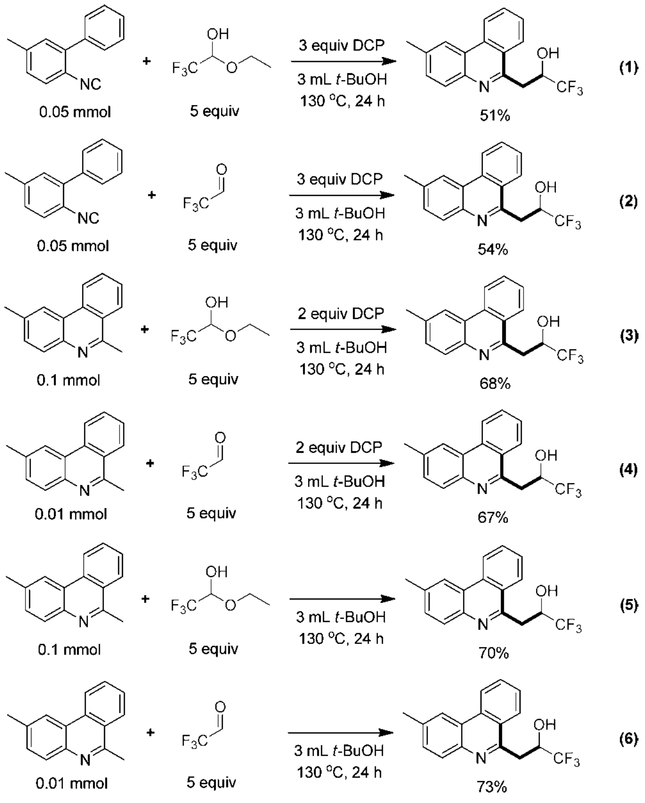
substrate	yield (%[b])	substrate	yield (%[b])
	1 (70)		2 (72)
	3 (73)		4 (71)
	5 (72)		6 (50)
	7 (63)		8 (69)
	9 (68)		10 (64)
	11 (68)[c]		17 (69)[c]
	12 (69)		13 (84)
	14 (77)		15 (70)

[a] Reaction conditions: 6-methylated phenanthridines (1 equiv, 0.1 mmol), DCP (3 equiv, 0.3 mmol), *t*-BuOH (3 mL), polyfluorinated alcohol (1 mL), 130 °C, 24 h. [b] Isolated yields.

by β-cleavage would form the methyl radical and byproduct acetophenone. Subsequently, hydrogen abstraction of the α-hydroxy-C−H of TFE by the methyl radical forms radical intermediate **A**, which is quickly converted to CF_3CHO by the methyl radical. Then the hemiacetal 1-(*tert*-butoxy)-2,2,2-trifluoroethan-1-ol is produced. On the other hand, addition of the methyl radical to biaryl isonitrile gives radical **B**, which cyclizes to the aromatic core followed by hydrogen atom transfer generating 6-methyl phenanthridine. Isomerization of phenanthridine leads to an active enamine. Reaction of hemiacetal with the enamine gives the final product, which joins the two pathways together. The reason why this reaction is described as a highly ordered tandem process is because there are at least two possible competing pathways. One is the radical addition to isonitrile by radical **A** which would compete with the methyl radical. The concentrate of the radical intermediates would be responsible for the priority. The other is condensation of hemiacetal with acetophenone. This system being nearly neutral might be the possible reason.

Scheme 2. Suggested Mechanism





In summary, a highly ordered metal-free radical methylation/cyclization/(sp^3)C−C(sp^3) formation domino reaction of isonitriles with TFE and/or polyfluorinated alcohols has been developed. It provides an efficient method to construct a C−C bond by selective functionalization of α-hydroxyl-C(sp^3)−H in polyfluorinated alcohols. Additionally, the extremely high order in this case indicates that facile access to pharmaceuticals could be well-controlled by a radical triggered domino strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01946.

Full experimental details and characterization data for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuzhq@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project is supported by the National Science Foundation of China (Nos. 21272096, 21472080, 21672089), the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT15R28), and the Fundamental Research Funds for the Central Universities (lzujbky-2016-50, lzujbky-2016-ct02).

■ REFERENCES

(1) For reviews on bioinspired domino reactions, see: (a) Katz, L. *Chem. Rev.* **1997**, *97*, 2557−2576. (b) Mayer, S. F.; Kroutil, W.; Faber, K. *Chem. Soc. Rev.* **2001**, *30*, 332−339.

(2) (a) Chen, N.; Wang, S.; Smentek, L.; Hess, B. A., Jr.; Wu, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 8693−8696. (b) Corey, E. J.; Russey, W. E. *J. Am. Chem. Soc.* **1966**, *88*, 4751−4752. (c) Gao, D.; Pan, Y.-K.; Byun, K.; Gao, J. *J. Am. Chem. Soc.* **1998**, *120*, 4045−4046.

(3) For selected recent reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993−3009. (d) Ruiz, M.; López-Alvarado, P.; Giorgi, G.; Menéndez, J. C. *Chem. Soc. Rev.* **2011**, *40*, 3445−3454. (e) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390−2431. (f) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442−524. (g) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832−1844. (h) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278−1293. (i) Sears, J. E.; Boger, D. L. *Acc. Chem. Res.* **2016**, *49*, 241−251. (j) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. *Chem. Soc. Rev.* **2016**, *45*, 1557−1569.

(4) For an excellent review on the free-radical cascade process, see: McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248.

(5) For a review on tin-free radical reactions, see: Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082.

(6) For reviews on synthesis of phenanthridine via a radical cascade, see: (a) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505−3521. (b) Wang, H.; Xu, B. *Youji Huaxue* **2015**, *35*, 588−602.

(7) For reviews on selective functionalization of the sp^3-α-C−H bond in simple aliphatic alcohols, see: (a) Zhang, S.; Zhang, F.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937−1949. (b) Shang, X.; Liu, Z.-Q. *Huaxue Xuebao* **2015**, *73*, 1275−1282. For selected reviews on sp^3C−H functionalization, see: (c) Bergman, R. G. *Nature* **2007**, *446*, 391−393. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780−1824. (e) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857−1869. (f) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374. (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802. (h) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911−922. (i) White, M. C. *Science* **2012**, *335*, 807−809. (j) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743.

(8) (a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10836−10837. (b) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Shi, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8761−8765.

(9) (a) Zhao, J. C.; Fang, H.; Zhou, W.; Han, J. L.; Pan, Y. *J. Org. Chem.* **2014**, *79*, 3847−3855. (b) Zhou, W.; Qian, P.; Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Org. Lett.* **2015**, *17*, 1160−1163. (c) Zhou, W.; Ni, S.; Mei, H.; Han, J.; Pan, Y. *Org. Lett.* **2015**, *17*, 2724−2727.

(10) (a) Li, Z.; Fan, F.; Yang, J.; Liu, Z.- Q. *Org. Lett.* **2014**, *16*, 3396−3399. (b) Cui, Z.; Shang, X.; Shao, X.-F.; Liu, Z.-Q. *Chem. Sci.* **2012**, *3*, 2853−2858. (c) Liu, Z.-Q.; Sun, L.; Wang, J.; Han, J.; Zhao, Y.; Zhou, B. *Org. Lett.* **2009**, *11*, 1437−1439. (d) Liu, Z.-Q.; Zhang, Y.; Zhao, L.; Li, Z.; Wang, J.; Li, H.; Wu, L.-M. *Org. Lett.* **2011**, *13*, 2208−2211.

(11) (a) Correia, C. A.; Yang, L.; Li, C.-J. *Org. Lett.* **2011**, *13*, 4581−4583. (b) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *13*, 5016−5019. (c) Liu, Y.; Jiang, B.; Zhang, W.; Xu, Z. *J. Org. Chem.* **2013**, *78*, 966−980. (d) Bohman, B.; Berntsson, B.; Dixon, R. C. M.; Stewart, C. D.; Barrow, R. A. *Org. Lett.* **2014**, *16*, 2787−2789. (e) Neubert, T. D.; Schmidt, Y.; Conroy, E.; Stamos, D. *Org. Lett.* **2015**, *17*, 2362−2365. (f) Jin, J.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565−1569. (g) Amaoka, Y.; Nagatomo, M.; Watanabe, M.; Tao, K.; Kamijo, S.; Inoue, M. *Chem. Sci.* **2014**, *5*, 4339−4345. (h) Hamilton, J. Y.; Hauser, N.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10759−10762. (i) Niu, B.; Zhao, W.; Ding, Y.; Bian, Z., Jr.; Pittman, C. U.; Zhou, A.; Ge, H. *J. Org. Chem.* **2015**, *80*, 7251−7257. (j) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540−7542. (k) Cheng, J.-K.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 42−45. (l) Hu, W.; Sun, S.; Cheng, J. *J. Org. Chem.* **2016**, *81*, 4399−4405.

(12) (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16. (b) McBee, E. T.; Pierce, O. R.; Higgins, J. F. *J. Am. Chem. Soc.* **1952**, *74*, 1736−1737. (c) McBee, E. T.; Pierce, O. R.; Meyer, D. D. *J. Am. Chem. Soc.* **1955**, *77*, 83−86. (d) Steves, A.; Oestreich, M. *Org. Biomol. Chem.* **2009**, *7*, 4464−4469. (e) Ishikawa, N.; Moon, G. K.; Kitazume, T.; Sam, K. C. *J. Fluorine Chem.* **1984**, *24*, 419−430. (f) Wu, J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6983−6987.

(13) Sugimori, A.; Yamada, T.; Ishida, H.; Nose, M.; Terashima, K.; Oohata, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3905−3909.

(14) Kamitanaka, T.; Hikida, T.; Hayashi, S.; Kishida, N.; Matsuda, T.; Harada, T. *Tetrahedron Lett.* **2007**, *48*, 8460−8463.

(15) Sam, B.; Luong, T.; Krische, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5465−5469.

(16) (a) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2002. (b) Song, K.-S.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2004**, *60*, 9909−9923.

(17) (a) Gellman, A. J.; Dai, Q. *J. Am. Chem. Soc.* **1993**, *115*, 714−722. (b) Gellman, A. J.; Buelow, M. T.; Street, S. C. *J. Phys. Chem. A* **2000**, *104*, 2476−2485. (c) Li, X.; Gellman, A. J.; Sholl, D. S. *J. Mol. Catal. A: Chem.* **2005**, *228*, 77−82.

(18) (a) Zhang, L.; Liu, D.; Liu, Z.-Q. *Org. Lett.* **2015**, *17*, 2534−2537. (b) Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013**, *15*, 406−409. (c) Zhang, L.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 3688−3691.

(19) (a) Xu, Z.; Yan, C.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 5670−5673. (b) Tan, F.-L.; Song, R.-J.; Hu, M.; Li, J.-H. *Org. Lett.* **2016**, *18*, 3198−3201. (c) Kubo, T.; Chatani, N. *Org. Lett.* **2016**, *18*, 1698−1701. (d) Xia, Q.-Q.; Liu, X.-L.; Zhang, Y.-J.; Chen, C.; Chen, W.-Z. *Org. Lett.* **2013**, *15*, 3326−3329. (e) Zhang, Y.-H.; Feng, J.-Q.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900−2901. (f) Guo, S.-T.; Wang, Q.; Jiang, Y.; Yu, J.-T. *J. Org. Chem.* **2014**, *79*, 11285−11289. (g) Zhu, Y.; Yan, H.; Lu, L.-H.; Liu, D.-F.; Rong, G.-W.; Mao, J.-C. *J. Org. Chem.* **2013**, *78*, 9898−9905.

(20) (a) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650−3651. (b) Qian, B.; Xie, P.; Xie, Y.; Huang, H. *Org. Lett.* **2011**, *13*, 2580−2583. (c) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070−1082. (d) Vanjari, R.; Singh, K. N. *Chem. Soc. Rev.* **2015**, *44*, 8062−8096. (e) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468−3517. (f) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138−12204.