Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Free-Radical-Promoted Site-Specific Cross-Dehydrogenative-Coupling of *N*-Heterocycles with Fluorinated Alcohols

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

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

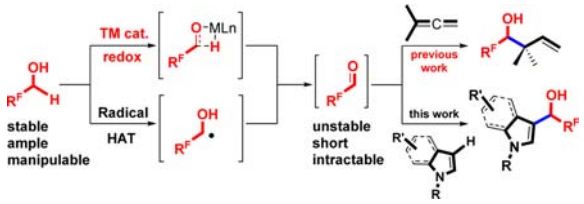
Supporting Information

ABSTRACT: A C−C formation of an electron-rich *N*-heterocycle with fluorinated alcohol is developed. Through this radical-triggered cross-dehydrogenative coupling strategy, a wide range of useful building blocks such as C3 hydroxyfluoroalkylated indoles and pyrroles can be site-specifically synthesized. Mechanistic studies indicate a single-electron-transfer initiated radical cycle would be involved.

The carbon−carbon bond formation using alcohols as hydroxyalkylating reagents is of particular interest in synthetic chemistry.[1] In recent decades, considerable advances in this area have been made through two main pathways. One is transition-metal-catalyzed C−C bond construction with alcohols, which has been extensively studied by Krische,[2] Carreira,[3] and Yi,[4] et al.[5] The other is free-radical-initiated hydroxyalkylation of alkenes, alkynes, and heteroarenes, which has been well-explored by Tu,[6] Han and Pan,[7] us,[8] et al.[9] However, a long-recognized challenging problem is that both strategies are not amenable to trifluoroethanol (TFE) and polyfluorinated alcohols. Although it would be undeniably important and valuable for simultaneous introduction of the hydroxyl and trifluoromethyl or polyfluoroalkyl groups into organic molecules, direct C−C bond construction using TFE and polyfluorinated alcohols has very rarely been achieved. Thirty years ago, a first example of direct C−C bond formation of quinoline with TFE by γ-irradiation was reported by Sugimori and co-workers (yields <9%).[10] The second C−C formation was accomplished by reaction of styrene with supercritical TFE (only one example, yield: 26%).[11] Both examples suffered from extremely harsh reaction conditions and very low yields. Very recently, an efficient Ru-catalyzed cross-coupling of allenes with fluorinated alcohols has been developed by Krische and co-workers, which represents the latter example.[12] Nevertheless, this strategy is limited to primary alcohols and those fluorinated alcohols with at least two β-hydrogen atoms. Moreover, selective functionalization of the α-OH−C(sp^3)−H bond in TFE and polyfluorinated alcohols has remained a great challenge to date.

It is well-known that TFE and polyfluorinated alcohols are often stable, ample, and manipulable while the corresponding fluorinated aldehydes are generally unstable, short, and intractable. Two main reasons make fluorinated alcohols more difficult than others in dehydrogenation. One is the larger endothermic (over 250 °C) and reversibility,[13] and the other is the strong electron-withdrawing effect of the CF_n group which enhances the energetic barrier in β-hydride elimination (ca. 15 kcal/mol).[14] Of particular interest are free-radical-initiated α-OH−C(sp^3)−H bond functionalizations in alcohols/ethers. We hypothesize that a radical-promoted hydrogen-atom-transfer (HAT) strategy would be feasible for dehydrogenation of fluorinated alcohols under relatively mild conditions (Scheme 1).

Scheme 1. Dehydrogenation of Fluorinated Alcohols



Herein, we report a first example of a free-radical-initiated cross-dehydrogenative-coupling (CDC)[15] reaction of fluorinated alcohols with *N*-heterocycles such as indoles and pyrroles. This method provides an efficient and regiospecific access to a wide range of hydroxypolyfluoroalkylated indoles and pyrroles.

To test our hypothesis, we initially chose indole and trifluoroethanol (TFE) as the model compounds (Table 1). Gratifyingly, 2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethan-1-ol was isolated in 37% yield while using dicumyl peroxide (DCP) as the radical initiator in TFE solvent (entry 1). It is interesting that the ratio of TFE and *tert*-butanol was found to be an important factor that critically affects the reaction efficiency (Table 1, entries 1−5). Furthermore, we found that DCP was more efficient than *tert*-butyl hydroperoxide (TBHP) and di-*tert*-butyl peroxide (DTBP). Finally through a series of optimized reaction conditions (see Supporting Information (SI)), the desired product can be isolated in a yield of 74% under the following conditions: indole (1 equiv, 0.2 mmol), peroxide (2 equiv, 0.4 mmol), *t*-BuOH/TFE (3/2, 5 mL), CuBr (5 mol %, 0.01 mmol), 140 °C, 12 h.

With the optimized conditions in hand, we investigated the substrate scope with an array of heterocycles such as indole, pyrrole, and their derivatives (Scheme 2). First, the steric effect is investigated (**1**−**5**). As a result, the effect of hindrance is not

Received: August 2, 2016
Published: August 26, 2016

DOI: 10.1021/acs.orglett.6b02274
Org. Lett. 2016, 18, 4662−4665

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

entry	peroxide	solvent (mL)	t (°C)[b]	yield (%)[c]
1	DCP	TFE (5)	130	37
2	DCP	*t*-BuOH/TFE (1/4, 5)	130	51
3	DCP	*t*-BuOH/TFE (2/3, 5)	130	56
4	DCP	*t*-BuOH/TFE (3/2, 5)	130	69
5	DCP	*t*-BuOH/TFE (4/1, 5)	130	20
6	**DCP**	***t*-BuOH/TFE (3/2, 5)**	**140**	**74**
7	TBHP	*t*-BuOH/TFE (3/2, 5)	140	21
8	DTBP	*t*-BuOH/TFE (2/3, 5)	140	15

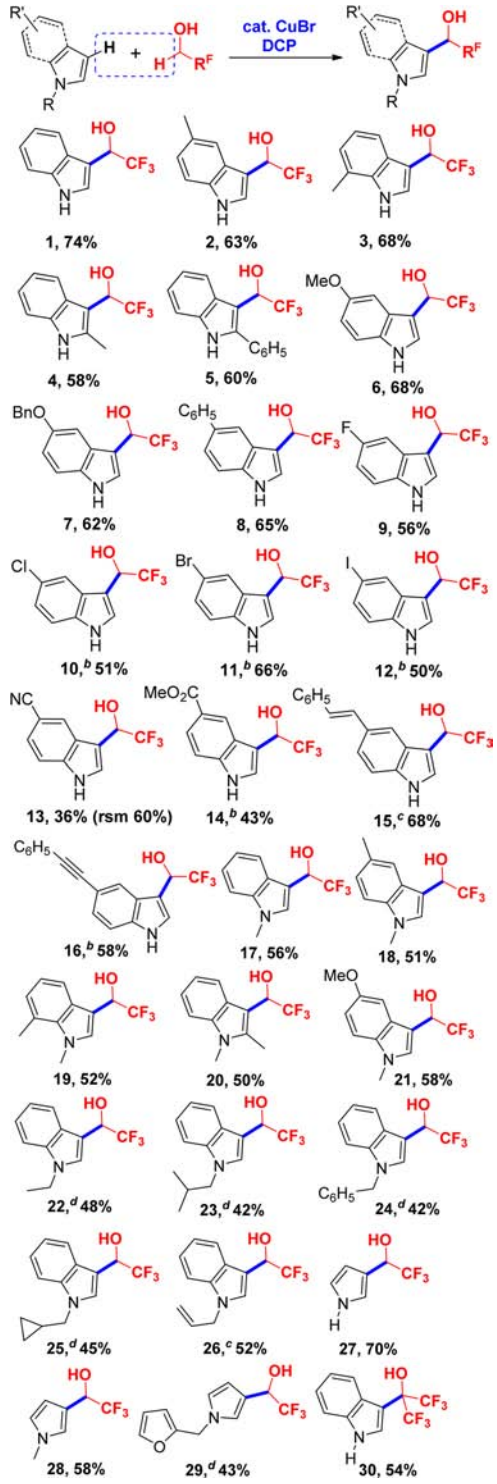
[a]Reaction conditions: indole (1 equiv, 0.2 mmol), peroxide (2 equiv, 0.4 mmol), CuBr (5 mol %, 0.01 mmol), TFE (2 mL), *t*-BuOH (3 mL), 140 °C, 12 h, sealed tube. [b]Measured temperature of the oil bath. [c]Isolated yields.

remarkable. However, while 3-methyl-1*H*-indole was used as the substrate, the target molecule is not detected. It indicates that not a radical process but a polar reaction pathway might be involved in the C−C formation step. Second, the electronic effect and functional group tolerance are studied (**6**−**16**). Electron-rich indoles gave moderate to good yields of products (**6**−**8**). In addition, halogenated indoles also afforded the desired products in good yields (**9**−**12**). Gratifyingly, indoles bearing electron-withdrawing groups such as −CN and −COOMe are also amenable to this system (**13** and **14**). Moreover, both alkenyl and alkynyl groups can be well-tolerated in this reaction (**15** and **16**). Next we examined indoles with substituents on the nitrogen atom (**17**−**26**). And we found that a variety of alkyl-, benzyl, and allyl-substitued indoles all gave the desired products in moderate yields under the typical conditions. Nevertheless, no product was observed by using 1-phenyl-1-*H*-indole. Gratifyingly, pyrrole and its derivatives are also effective substrates (**27**−**30**). It is noteworthy that C−C bond construction occurred selectively on the pyrrole core while using 1-(furan-2-ylmethyl)-1*H*-pyrrole as the substrate (**29**). Finally, other fluorinated alcohols are also investigated. For example, 1,1,1,3,3,3-hexafluoro-2-(1*H*-indol-3-yl)propan-2-ol was isolated in moderate yield with 1,1,1,3,3,3-hexafluoropropan-2-ol (**30**). Overall, the features of direct dehydrogenative C−C formation, versatile functional group tolerance, and site-specificity make this strategy very attractive to synthetic organic chemists.

In addition, large scale experiments and functional group transformations are carried out. It was found that this synthetic method can be conveniently scaled-up to the gram level without loss of efficiency. Furthermore, diverse trasformations from hydroxyfluoroalkylated heterocycles to various useful building blocks can also be smoothly achieved (Figure 1).

As initially hypothesized, HAT from fluorinated alcohol would generate α-OH C-centered radical, which then adds to heterocycle yielding C2 hydroxyalkylated product. However, it is not C2 but C3 alkylated product that is obtained, which indicates that a Friedel−Crafts pathway might be involved in the last step. Therefore, a series of control experiments were carried out (eqs 1 and 2). And we found that both CF_3CHO and 1-ethoxy-2,2,2-trifluoroethan-1-ol gave the corresponding products in excellent yields. As expected, the hemiacetal 1-(*tert*-butoxy)-2,2,2-trifluoroethan-1-ol was also detected by GC-MS (see SI). Next, an array of spin trapping experiments combined with electron paramagnetic resonance (EPR) detections were

Scheme 2. Site-Specific Radical CDC Reaction of Indole/Pyrrole with Fluorinated Alcohols[a]



[a]Reaction conditions: heterocycle (1 equiv, 0.2 mmol), DCP (2 equiv, 0.4 mmol), CuBr (5 mol %), TFE (2 mL), *t*-BuOH (3 mL), 140 °C, 12 h, isolated yield, unless otherwise noted. [b]160 °C. [c]DTBP (3 equiv, 0.6 mmol), CuBr (5 mol %), TFE (3 mL), *t*-BuOH (2 mL), 140 °C, 15 h. [d]DTBP (3 equiv, 0.6 mmol), CuBr (5 mol %), TFE (3 mL), *t*-BuOH (2 mL), 130 °C, 15 h.

carried out to trap the key radical intermediate. Nevertheless, the α-OH C-centered radical was not observed even though various spin trapping reagents were screened. It suggests that this radical

DOI: 10.1021/acs.orglett.6b02274
Org. Lett. 2016, 18, 4662−4665

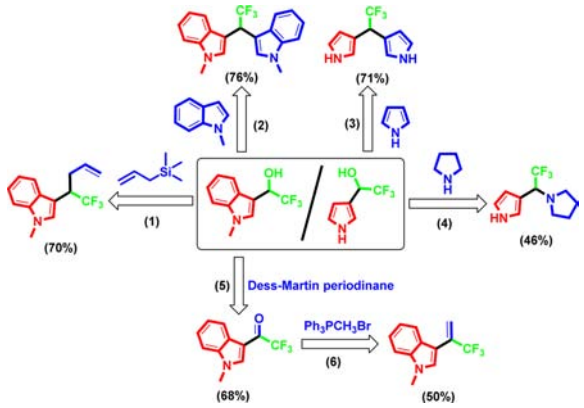


Figure 1. Versatile transformations of hydroxyfluoroalkylated heterocycles. Reaction conditions: (1) $Y(OTf)_3$ (10 mol %), allyltrimethylsilane (5 equiv), CH_2Cl_2, rt; (2) $Y(OTf)_3$ (10 mol %), indole (1.5 equiv), toluene, 90 °C; (3) $Sc(OTf)_3$ (10 mol %), indole (1.5 equiv), toluene, 80 °C; (4) $P(Ph)_3$ (2 equiv), DEAD (2 equiv), pyrrolidine (2 equiv), THF, rt; (5) Dess-Martin periodinane (3.7 equiv), CH_2Cl_2, rt; (6) *n*-BuLi (0.8 equiv), PPh_3CH_3Br (0.8 equiv), THF, rt.

might be very unstable, which would be immediately converted to the corresponding aldehyde under the present conditions.[16] Surprisingly, a β-OH C-centered radical (CF_2CH_2OH, g = 2.0065, a_N = 7.59 G, a_H = 13.72 G) was observed by EPR with 2-methyl-2-nitroso-propane (MNP) as the spin-trapping reagent (see SI). Furthermore, the signal of Cu(II) ($g_{\|}$ = 2.1028, $g_{\perp}$ = 2.0522) was also recorded by EPR (Figure 2).

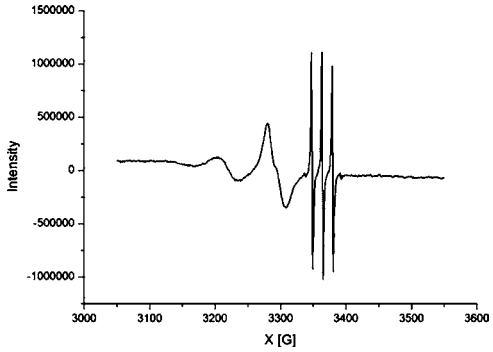
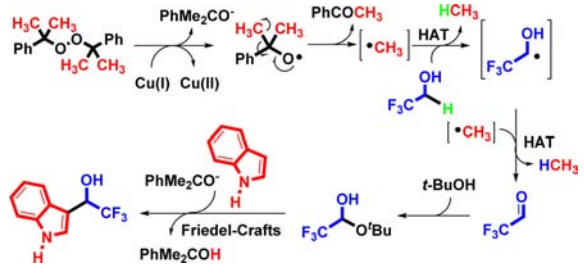


Figure 2. EPR signal of Cu(II) and di-*tert*-butyl nitroxide radical.

A plausible mechanism for this transformation is proposed in Scheme 3 with the experimental data and precedent literatures. One electron transfer from Cu(I) to DCP gives the Cu(II), $PhMe_2CO$ anion, and radical. β-Cleavage of the alkoxyl radical produces acetophenone and a methyl radical. Subsequently, a two-step hydrogen-atom transfer (HAT) from fluorinated alcohol to methyl radical leads to methane and CF_3CHO, which is quickly transferred to the hemiacetal in solvent *t*-BuOH. Finally, Friedel–Crafts reaction of hemiacetal with an electron-rich heterocycle affords the final product.

Scheme 3. Suggested Mechanism



In conclusion, a free radical promoted dehydrogenative C–C coupling of *N*-heterocycle with fluorinated alcohol is developed. Through this strategy, a variety of useful building blocks such as C3 hydroxyfluoroalkylated indoles and pyrroles can be site-specifically synthesized on a large scale. Furthermore, this radical-triggered hydrogen-atom-transfer strategy would open the door to selective functionalization of the inert α-OH–(sp^3)-C–H in fluorinated alcohol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02274.

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 selective functionalization of 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. (b) Shang, X.; Liu, Z.-Q. *Huaxue Xuebao* **2015**, *73*, 1275. For selected reviews on sp^3-C–H functionalization, see: (c) Bergman, R. G. *Nature* **2007**, *446*, 391. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (e) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (f) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (h) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (i) White, M. C. *Science* **2012**, *335*, 807. (j) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (k) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2. For selected recent reviews on general C–H functionalization, see: (l) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (m) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (n) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (o) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (p) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (q) Shang, X.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253. (r) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (s) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (t) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (u) Zheng, Q.-Z.; Jiao, N. *Chem. Soc. Rev.* **2016**, *45*, 4590.

(2) For selected reviews, see: (a) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *34*, 107. (b) Moran, J.; Krische, M. J. *Pure Appl. Chem.* **2012**, *84*, 1729. (c) Dechert-Schmitt, A. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504. (d) Perez, F.; Oda, S.; Geary, L. M.; Krische, M. J. *Top. Curr. Chem.* **2016**, *374*, 1.

DOI: 10.1021/acs.orglett.6b02274
Org. Lett. 2016, 18, 4662–4665

(3) (a) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532. (b) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994. (c) Jeker, O. F.; Kravina, A. G.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12166. (d) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (e) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3020. (f) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3006. (g) Hamilton, J. Y.; Hauser, N.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10759. (h) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363.

(4) (a) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613. (b) Kim, J.; Lee, D.-H.; Kalutharage, N.; Yi, C. S. *ACS Catal.* **2014**, *4*, 3881. (c) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (d) Kalutharage, N.; Yi, C. S. *Org. Lett.* **2015**, *17*, 1778.

(5) (a) Liu, Y.; Hua, R.; Sun, H.-B.; Qiu, X. *Organometallics* **2005**, *24*, 2819. (b) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (c) Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638.

(6) (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. (b) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Shi, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8761.

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

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

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

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

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

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

(13) Mimura, H.; Watanabe, A.; Kawada, K. *J. Fluorine Chem.* **2006**, *127*, 519.

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

(15) For selected recent reviews on CDC reactions, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (d) Jia, F.; Li, Z. *Org. Chem. Front.* **2014**, *1*, 194.

(16) (a) Tokuhashi, K.; Nagai, H.; Takahashi, A.; Kaise, M.; Kondo, S.; Sekiya, A.; Takahashi, M.; Gotoh, Y.; Suga, A. *J. Phys. Chem. A* **1999**, *103*, 2664. (b) Morozov, I.; Gligorovski, S.; Barzaghi, P.; Hoffmann, D.; Lazarou, Y. G.; Vasiliev, E.; Herrmann, H. *Int. J. Chem. Kinet.* **2008**, *40*, 174.

DOI: 10.1021/acs.orglett.6b02274
Org. Lett. 2016, 18, 4662−4665