Organic LETTERS

Letter

pubs.acs.org/OrgLett

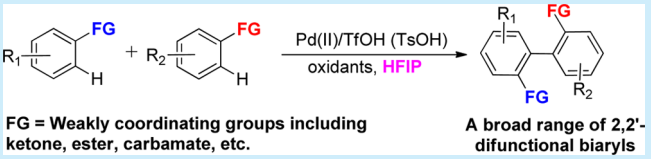
Weak Coordination Promoted Regioselective Oxidative Coupling Reaction for 2,2′-Difunctional Biaryl Synthesis in Hexafluoro-2-propanol

Chao Zhang and Yu Rao*

MOE Key Laboratory of Protein Sciences, Department of Pharmacology and Pharmaceutical Sciences, School of Medicine and School of Life Sciences, Tsinghua University, Beijing 100084, China

Supporting Information

ABSTRACT: An unprecedented weak coordination promoted dehydrogenative cross-coupling reaction has been developed by palladium catalysis, which provides a convenient access to a wide range of 2,2′-difunctional biaryls from easily accessible substrates. Both HFIP solvent and oxidants serve as the critical factors in this new reaction. A plausible mechanism involving Pd(II)/Pd(IV) is proposed. The reaction demonstrates excellent reactivity, broad functional-group tolerance and high yields.

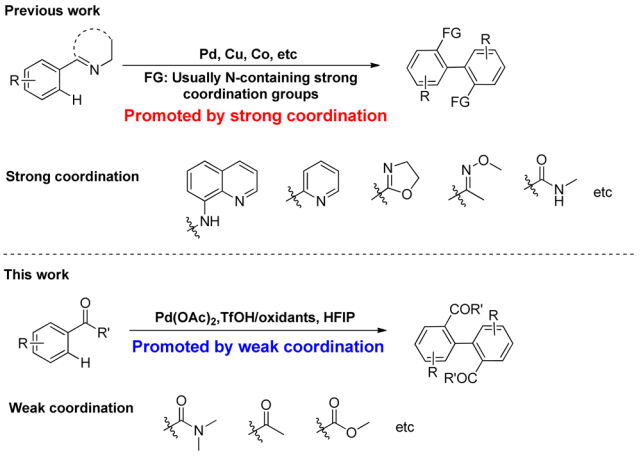


The 2,2′-difunctional biaryl scaffold serves an important structural motif in natural products and bioactive compounds.[1] Because of its significance, the development of general, efficient, and mild methods for aryl−aryl bond formation remains an area of tremendous research efforts. The most common method for 2,2′-difunctional biaryl construction is metal-catalyzed cross-coupling between two functionalized arenes.[2] Compared with classic cross-coupling with preinstalled functional groups, direct dehydrogenative arene coupling[3] by activating two C−H bonds represents the most efficient method for the formation of 2,2′-difunctional biaryls.

Over the past decade, direct C−H bond cleavage by weak coordination[4] of metal catalysts with nearby common functional groups has been well studied by Yu and co-workers and has led to the discovery of a number of powerful C−H functionalization reactions. However, the application of this strategy in dehydrogenative cross-coupling to access 2,2′-difunctional biaryls is still surprisingly under-developed. Currently, the majority of studies of 2,2′-difunctional biaryl synthesis by dehydrogenative cross-coupling have relied on the use of strong coordinating groups like pyridine,[5] amide,[6] oxazoline or imidazole,[7] etc.[8] (Scheme 1). In contrast, the application of ester, ketone, or carbamate functionality as the directing group in transition-metal-catalyzed dehydrogenative cross-coupling has not yet been achieved, despite ester, ketone, or carbamate functional groups being readily available and also easily converted to alcohols, amines, amides, and other carbonyl compounds.

Here, we report the first example of Pd(II)-catalyzed dehydrogenative cross-coupling assisted by weak coordination, which can now readily provide a broad range of 2,2′-difunctional biaryl compounds (Scheme 1). We envisioned that under proper acidic conditions palladium(II) catalysts might promote *o*-C−H bond cleavage by weak coordination with the carbonyl oxygen of aromatic ketones or benzoates. Moreover, with suitable ligands

Scheme 1. Oxidative C−H Dehydrogenative Coupling



and co-oxidants, a Pd(II) complex can be converted into a Pd(IV)[9] intermediate stabilized by a potential dual-coordination with two weakly coordinating groups. Finally, a C−C bond formation would be made possible via a reductive elimination from Pd(IV) to afford corresponding dehydrogenated cross-coupling arenes. Our aim was to identify suitable weak coordination-promoted dehydrogenative cross-coupling conditions via a Pd(II)/Pd(IV) cycle for preparation of unique 2,2′-difunctional biaryls (Scheme 2).

Herein, as briefly shown in Table 1, a model investigation was initiated with benzophenone **1**, which contains a carbonyl group as the weakly coordinating group to test our idea. We evaluated numerous conditions that varied combinations of Pd(II) catalysts, external oxidants, and acid additives. After many

Received: July 22, 2015

DOI: 10.1021/acs.orglett.5b02115
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Proposed Reaction Process

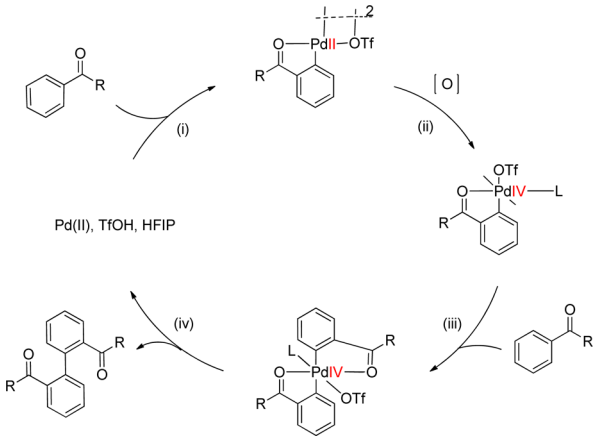
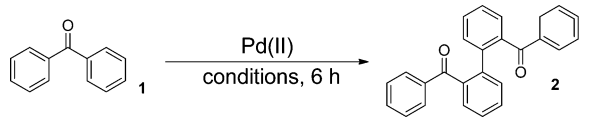


Table 1. Optimization of the Reaction Conditions



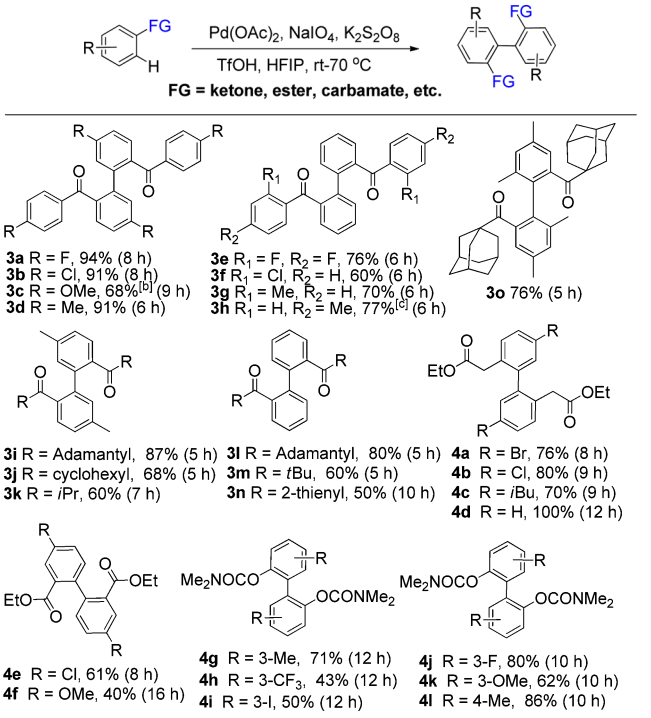
entry	conditions	yield[a] (%)
1	$Pd(OAc)_2$, $K_2S_2O_8$ (1.1 equiv), AgOTf (1.0 equiv), TfOH (1.0 equiv), DCE 70 °C	30
2	$Pd(OAc)_2$, $K_2S_2O_8$ (1.1 equiv), TfOH (2.0 equiv), DCE 70 °C	48
3	$Pd(OAc)_2$, $NaIO_4$ (1.1 equiv), TfOH (2.0 equiv), DCE 70 °C	11
4	$Pd(OAc)_2$, $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), DCE 70 °C	50 (41)[b]
5	$Pd(OAc)_2$, $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), TFE 70 °C	25
6	$Pd(OAc)_2$, $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), ethanol 70 °C	NR
7	$Pd(OAc)_2$, $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), 2-propanol 70 °C	NR
8	$Pd(OAc)_2$, $K_2S_2O_8$ (1.1 equiv), TfOH (2.0 equiv), HFIP 70 °C	70[b]
9	$Pd(OAc)_2$, $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), HFIP 70 °C	86 (83)[b]
10	$Pd(OAc)_2$, $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), HFIP 50 °C	93 (89)[b]
11	$NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), HFIP 70 °C	NR
12	$Pd(OAc)_2$, TfOH (2.0 equiv), HFIP 70 °C	NR
13	$Pd(OAc)_2$, $PhI(OAc)_2$ (1.1 equiv), TfOH (2.0 equiv), HFIP 70 °C	10
14	$Pd(OAc)_2$, Oxone (1.1 equiv), TfOH (2.0 equiv), HFIP 70 °C	18
15	other metals [Ru(II), Rh(III), Cu(II)], $NaIO_4$ (0.6 equiv), $K_2S_2O_8$ (0.5 equiv), TfOH (2.0 equiv), HFIP 70 °C	NR or trace

[a]Conversion. [b]Isolated yield.

fruitless attempts, to our delight, the desired 2,2′-dibenzoyl biaryl compound **2** was observed in 30% yield after stirring for 6 h at 70 °C in the presence of $Pd(OAc)_2$, potassium persulfate,[10] triflic acid (TfOH), and AgOTf (entry 1). The following study revealed that AgOTf was not necessary for the reaction (entry 2). It also was found that $NaIO_4$ could be used as the oxidant to promote the reaction as effectively as potassium persulfate (entry 3). Different solvent systems were screened as well. Among them, no products were observed with other common solvents such as DMSO, DMF, and ethanol, etc. In contrast, TFE[11] (trifluoroethanol) provided **2** in a moderate yield of 40%, which is similar to that of DCE (entry 5). Gratifyingly and interestingly, in the presence of HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol),[12] the yield was significantly improved to 70% (entry 8). We think that HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) may work as an effective ligand for palladium to promote this reaction. Compared with other solvents, HFIP could serve not only as a solvent system but also as a suitable ligand because of its acidity (pK_a = 9.3), which might account for its critical role in this reaction. Notably, it was found that optimizations with the combination of $K_2S_2O_8$ and $NaIO_4$ could increase the yield up to 89% (entry 10). Further investigations confirmed that both a palladium catalyst and an oxidant were essential for the reaction (entries 11−12). Other oxidants such as $PhI(OAc)_2$, oxone, and metal catalysts including Cu, Ru, and Rh, etc., cannot promote the transformation under the reaction conditions (entries 13−15).

Having identified these optimal conditions, we set out to explore the scope for this new reaction. As displayed in Table 2, a

Table 2. Homo-dehydrogenative Cross Coupling of Aryl Ketones, Esters, and Carbamates[a]



[a]Isolated yield. [b]DCE as solvent; only $NaIO_4$ used as oxidant. [c]Overall yield of three regioisomers.

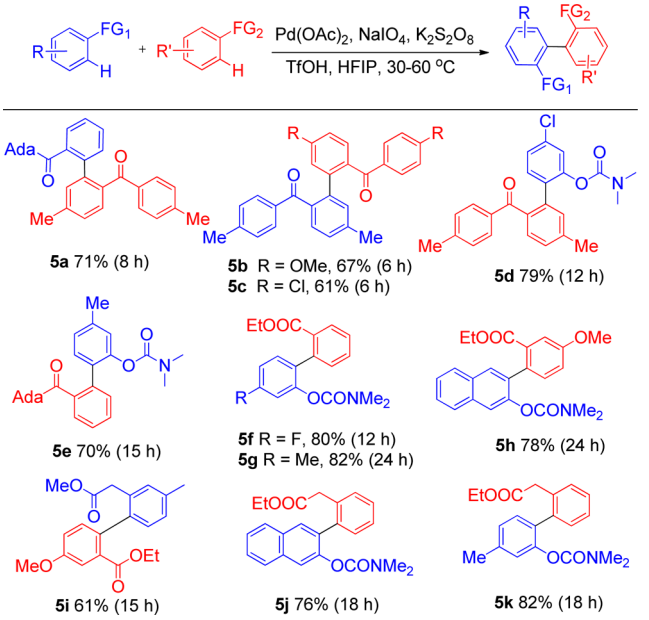
variety of substituted benzophenones were surveyed. The scope of the benzophenone was found to be broad, and various benzophenones were smoothly converted into the corresponding dimers (**3a**−**o**) in moderate to excellent yields. Different substituted aryl groups, as well as the electron-rich (**3a**,**b**,**f**) and electron-deficient (**3c**,**d**,**h**) aryl groups, were well tolerated. For unsymmetrical diaryl ketone substrates, the more electron-rich or less sterically hindered parts coupled preferentially (**3e**,**g**). Besides aromatic groups, alkyl groups (**3i**−**m**) were also compatible with the reaction conditions. Notably, when ketones containing easily oxidizable α-protons were attempted, we found that these ketones could be effectively transformed into the desired products (**3j**,**k**) with excellent chemoselectivity. The

DOI: 10.1021/acs.orglett.5b02115
Org. Lett. XXXX, XXX, XXX−XXX

sterically demanding cross-coupling product **3o** could be formed in a good yield of 76%. It was notable to find that a substrate with a heteroaryl functional group was suitable for providing the corresponding dimer product, **3n**, which contained a 2-thienyl group. As shown in Table 2, besides aromatic ketones, the optimized conditions were further applied to other types of substrates including benzyl acetates (**4a**–**d**), ethyl benzoates (**4e**–**f**), and phenyl carbamates (**4g**–**l**), etc. To our delight, the new reaction demonstrated the compatibility of all these functional groups by generating the desired dimer products in good yields.

As illustrated in Table 3, after our study of this reaction for homo-dimer synthesis, we tried to apply the conditions to prepare hetero-dimers, and for the reaction of systems with two different weak coordinating functional groups as well. To our delight, two types of hetero-dimer products (**5a**–**c**) and (**5d**–**k**) could be obtained in good yield by using an excess of one substrate, with excess starting material usually being readily recovered (for details, see the Supporting Information). It is noteworthy to point out that these results represent an unprecedented mechanistic example of weak coordination promoted hetero-dehydrogenative cross-coupling reactions. Additionally, in comparison with traditional methods which normally need three or more steps with relatively low overall yields (20–30%), our new method can arrive at the target products in only one step in higher yield.

Table 3. Hetero-dehydrogenative Cross-Coupling of Ketones, Esters, and Carbamates.[a]

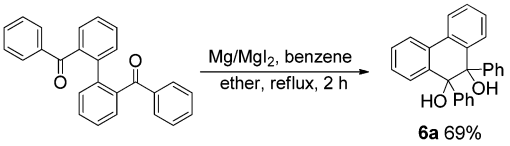


[a]Isolated yield. The red part represented the substrate excess, while the blue showed the substrate is 1 equiv.

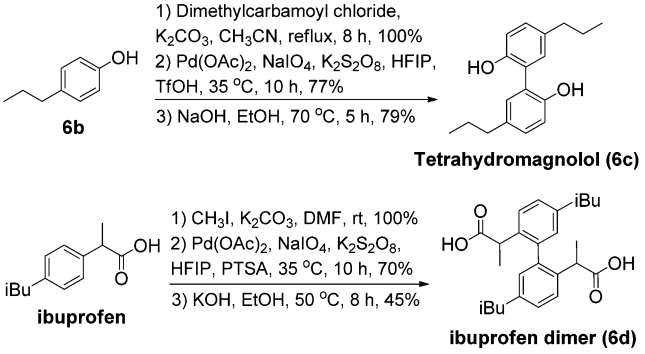
The synthetic utility of this reaction can be further demonstrated by preparation of a variety of biologically important compounds and synthons, which is shown in Scheme 3. For instance, 2,2′-dibenzoyl biaryl **2** can be efficiently converted into **6a**[13] via reduction by a mixture of magnesium and magnesium iodide in 69% yield. Tetrahydromagnolol **6g**[14] is a potent cannabinoid (CB) receptor agonist. Delightfully, we found **6c** could be easily constructed by a three-step chemical manipulation in an overall yield of 62% from simple 4-propylphenol **6b**. This new strategy can serve as a highly efficient way of preparing **6c** and related structural analogues. Interestingly, a novel drug dimer **6d** was also synthesized from ibuprofen,[15] which is a representative nonsteroidal anti-inflammatory drug (NSAID) used for relieving pain, helping with fever, and reducing inflammation. Our procotol can be employed to build up a variety of profen drug dimers, which can be screened for early drug discovery.

Scheme 3. Applications of the CDC reaction

1. Transformation of 2,2'-dibenzoyl biaryls



2. Important scaffolds in natural product or bioactive compound synthesis



In conclusion, we have developed a unique Pd(II)-catalyzed ortho to ortho dehydrogenative cross-coupling reaction. The method provides a novel and convenient access to a broad range of highly valuble 2,2′-difunctional biaryls from readily accessible substrates. Both the oxidants and HFIP solvent play critical roles in this reaction. A possible Pd(II)/Pd(IV) mechanism may be involved. The reaction demonstrates broad functional group tolerance, excellent reactivity, and high yields. Further studies into the scope, mechanism, and synthetic applications of this reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02115.

Material and methods, general procedures, and additional data (PDF)

NMR spectra of obtained compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yrao@mail.tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National "973" Foundation (Grant No. 2011CB965300), the National Natural Science Foundation of China (Grant No. 21302106), and the Tsinghua University Initiative Scientific Research Program.

DOI: 10.1021/acs.orglett.5b02115
Org. Lett. XXXX, XXX, XXX–XXX

REFERENCES

(1) (a) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (d) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (e) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (f) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(2) (a) Percec, V.; Bae, J.—Y.; Zhao, M. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1066. (b) Wang, L.; Zhang, Y. H.; Liu, L. F.; Wang, Y. G. *J. Org. Chem.* **2006**, *71*, 1284. (c) Perissutti, E.; Frecentese, F.; Lavecchia, A.; Fiorino, F.; Severino, B.; De Angelis, F.; Santagada, V.; Caliendo, G. *Tetrahedron* **2007**, *63*, 12779. (d) Schmidt, B.; Riemer, M. *J. Org. Chem.* **2014**, *79*, 4104. (e) Postikova, S.; Sabbah, M.; Wightman, D.; Nguyen, I. T.; Sanselme, M.; Besson, T.; Brière, J.-F.; Oudeyer, S.; Levacher, V. *J. Org. Chem.* **2013**, *78*, 8191.

(3) (a) Van Helden, R.; Verberg, G. *Recl. Trav. Chim. Pays. Bas.* **1965**, *84*, 1263. (b) Fujiwara, Y.; Moritani, I.; Ikegami, K.; Tanaka, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 863. (c) Mukhopadhyay, S.; Rothenberg, G.; Lando, G.; Agbaria, K.; Kazanci, M.; Sasson, Y. *Adv. Synth. Catal.* **2001**, *343*, 455. (d) Li, R. S.; Jiang, L.; Lu, W. J. *Organometallics* **2006**, *25*, 5973. (e) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (f) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456. (g) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2011**, *13*, 276. (h) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (i) Li, B. − J.; Tian, S. − L.; Fang, Z.; Shi, Z. − J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (j) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (k) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (l) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(4) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (d) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (e) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134. (f) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (g) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (h) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215. (i) Li, G.; Wan, L.; Zhang, G. F.; Leow, D. S.; Spangler, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 4391. (j) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (k) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (l) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468. (m) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (n) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440. (o) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (p) Rao, Y.; Shan, G.; Yang, X. L. *Sci. China: Chem.* **2014**, *57*, 930.

(5) (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (b) Chen, X.; Dobereiner, G.; Hao, X.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009**, *65*, 3085. (c) Guo, X. Y.; Deng, G. J.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 2071. (d) Stephens, D. E.; Lakey-Beitia, J.; Chavez, G.; Ilie, C.; Arman, H. D.; Larionov, O. V. *Chem. Commun.* **2015**, *51*, 9507.

(6) (a) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 5713. (b) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2015**, *17*, 1204.

(7) Oi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2008**, *10*, 1823.

(8) Carboxylic acids have also been employed in a rhodium-catalyzed CDC reaction. Gong, H.; Zeng, H. Y.; Zhou, F.; Li, C.-J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5718.

(9) (a) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (b) Racowski, J. M.; Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18022. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Xu, L. M.; Li, B. J.; Yang, Z.; Shi, Z. J. *Chem. Soc. Rev.* **2010**, *39*, 712. (e) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (f) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70.

(10) (a) Shan, G.; Yang, X. L.; Ma, L. L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (b) Dai, H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134. (c) Yang, Y. Q.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874.

(11) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 5713.

(12) HFIP can be a weakly coordinating solvent: (a) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245. (b) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (c) Zhang, F. Z.; Tian, Y.; Li, G.-X.; Qu, J. *J. Org. Chem.* **2015**, *80*, 1107.

(13) Avinir, D.; Blum, J. *J. Heterocycl. Chem.* **1980**, *17*, 1349.

(14) Rempel, V.; Fuchs, A.; Hinz, S.; Karcz, T.; Lehr, M.; Koetter, U.; Müller, C. E. *ACS Med. Chem. Lett.* **2013**, *4*, 41.

(15) (a) Adams, S. S.; McCullough, K. F.; Nicholson, J. S. *Arch. Int. Pharmacodyn. Ther.* **1969**, *178*, 115. (b) Huskisson, E. C.; Hart, F. D.; Shenfield, G. M.; Taylor, R. T. *Practitioner* **1971**, *207*, 639.

DOI: 10.1021/acs.orglett.5b02115
Org. Lett. XXXX, XXX, XXX−XXX