Organic LETTERS

Letter

pubs.acs.org/OrgLett

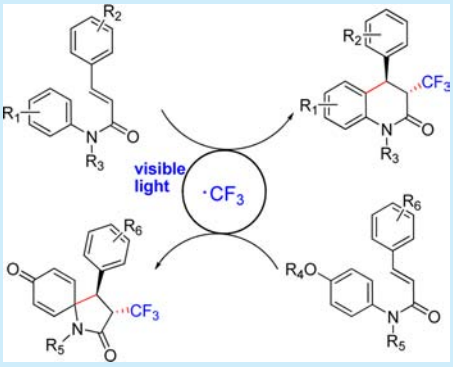
Visible-Light Induced Trifluoromethylation of *N*-Arylcinnamamides for the Synthesis of CF_3-Containing 3,4-Disubstituted Dihydroquinolinones and 1-Azaspiro[4.5]decanes

Fei Gao, Chao Yang, Guo-Lin Gao, Lewei Zheng, and Wujiong Xia*

State Key Lab of Urban Water Resource and Environment, The Academy of Fundamental and Interdisciplinary Sciences, Harbin Institute of Technology, Harbin 150080, China

Supporting Information

ABSTRACT: The visible-light induced trifluoromethylation of *N*-arylcinnamamides with Togni's reagent has been explored. This method allows for an efficient and practical synthesis of a variety of CF_3-containing dihydroquinolin-2(1*H*)-ones and 1-azaspiro[4.5]decanes bearing various functional groups under mild conditions.

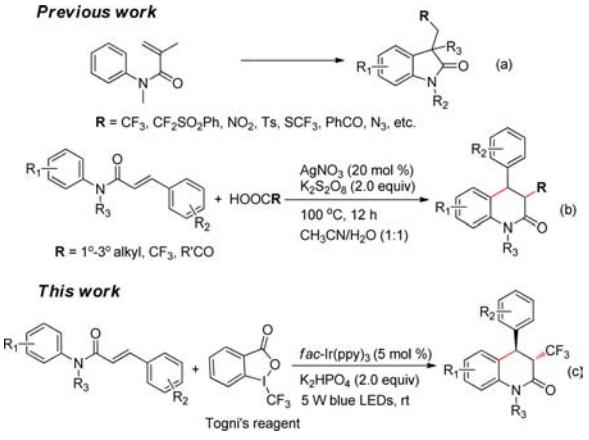


The trifluoromethyl group plays an important role in pharmaceutical chemistry, agrochemistry, and materials science due to its unique properties such as increased electronegativity, metabolic stability, hydrophobicity, and bioavailability.[1,2] Hence, the research of selectively introducing a trifluoromethyl group into organic molecules has become a hot topic in modern organic chemistry.[3] Over the past decade, all kinds of practical methods have been developed to synthesize CF_3-containing compounds with "CF_3^+", "CF_3^-", or "$CF_3^\bullet$" reagents through nucleophilic, electrophilic, or radical trifluoromethylation.[4] Among these methods, visible-light-promoted carbotrifluoromethylation reactions have been proven to be a powerful and ecofriendly strategy to introduce the CF_3 group into aromatic compounds.[5]

Recently, difunctionalization of alkenes to prepare substituted oxindoles has attracted special attention from chemists due to the importance of alkenes in the pharmaceutical industry (Scheme 1a).[6,7] In the last year, the silver catalyzed tandem decarboxylation and C−H functionalization of *N*-arylcinnamamides in aqueous solution under heating to synthesize dihydroquinolinones has also been found by Mai's group (Scheme 1b).[8] Despite these advances, there is still room for inspiration in developing efficient and benign methods to prepare CF_3-containing 3,4-dihydroquinolinones. Herein, we present a novel visible-light-promoted tandem trifluoromethylation of *N*-arylcinnamaide derivatives in the presence of Togni's reagent (Scheme 1c).

Our initial study was carried out by use of *N*-methyl-*N*-phenylcinnamamide **1a** as the model substrate (Table 1). Irradiation of the mixture of *N*-methyl-*N*-phenylcinnamamide **1a**, K_2HPO_4, and Togni's reagent in anhydrous acetonitrile by 5 W blue LEDs with **3a** as a catalyst gave the desired product **2a** in

Scheme 1. Reported Difunctionalization of Alkenes and Our Strategy

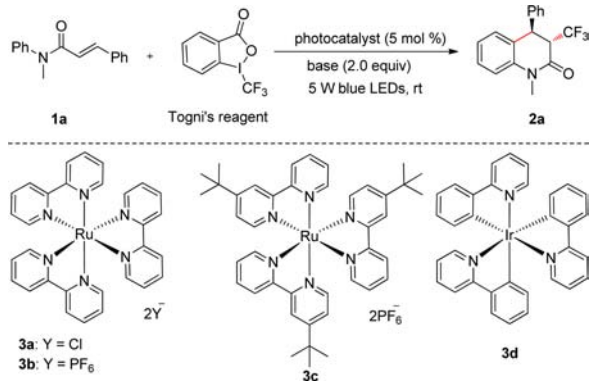


62% yield after 4 days (entry 1). The change of photocatalyst did not improve the yield; however, the reaction time was reduced to 40 h when **3d** was used as catalyst (entries 2−4). In comparison with K_2HPO_4 as the additive, other bases such as NaOH, pyridine, K_2CO_3, DBU, and imidazole led to lower yields (entries 5−9). Subsequently, different solvents were also tested (entries 10−13) and anhydrous acetonitrile was found to be the best choice (entry 1). Further experiments showed that both light and photocatalyst were essential for the reaction (entries 14−15).

Received: May 26, 2015
Published: July 1, 2015

DOI: 10.1021/acs.orglett.5b01530
Org. Lett. 2015, 17, 3478−3481

Table 1. Optimization of Reaction Conditions[a]



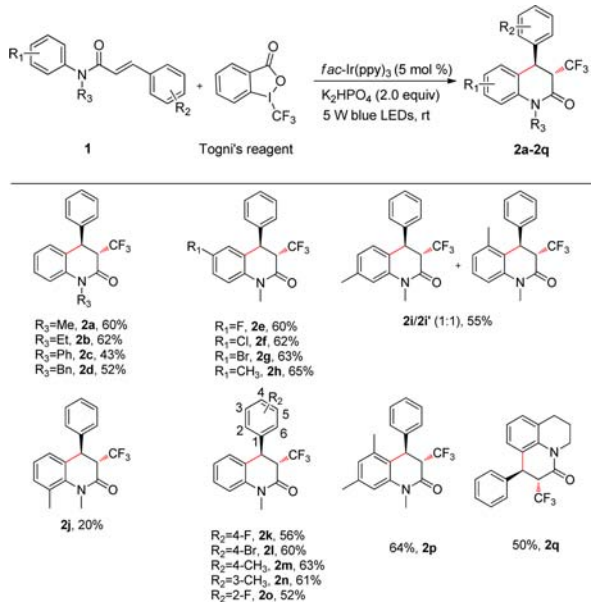
entry	photocatalyst	base	solvent	yield [%][b]
1[c]	**3a**	K_2HPO_4	CH_3CN	62
2	**3b**	K_2HPO_4	CH_3CN	0
3	**3c**	K_2HPO_4	CH_3CN	0
4[d]	**3d**	K_2HPO_4	CH_3CN	60
5	**3d**	NaOH	CH_3CN	46
6	**3d**	pyridine	CH_3CN	trace
7	**3d**	K_2CO_3	CH_3CN	43
8	**3d**	DBU	CH_3CN	26
9	**3d**	imidazole	CH_3CN	51
10	**3d**	K_2HPO_4	DMSO	trace
11	**3d**	K_2HPO_4	DMF	33
12	**3d**	K_2HPO_4	CH_2Cl_2	48
13	**3d**	K_2HPO_4	THF	trace
14[e]	**3d**	K_2HPO_4	CH_3CN	0
15	-	K_2HPO_4	CH_3CN	0

[a]Reaction conditions: **1a** (0.1 mmol), Togni's reagent (0.2 mmol), base (0.2 mmol), photocatalyst (5 mol %), solvent (anhydrous, 1.5 mL), 5 W blue LEDs light, rt, under N_2 atmosphere. [b]Isolated yield. [c]Four days. [d]Forty hours. [e]In the dark.

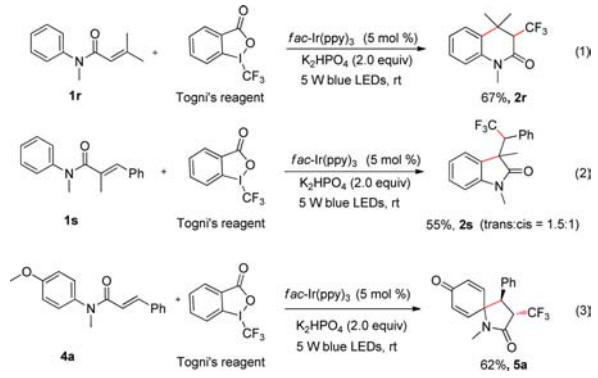
Having the optimized reaction conditions in hand, we turned our attention to explore the substrate scope with a range of different *N*-arylcinnamamide derivatives (Scheme 2). Substrates with different *N*-protecting groups were suitable for the reaction conditions and provided the desired products in moderate to good yields (**2a**−**d**). The para-position of anilines substituted with different groups such as F, Cl, Br, and Me are still tolerant with the reaction conditions (**2e**−**2h**). When the meta-position of the aniline ring was substituted with a Me group, a mixture of **2i** and **2i′** was obtained in a ratio of 1:1. As the substrate bears an ortho-substituent, a lower yield was observed (**2j**). The electron-donating or -withdrawing group on the aromatic ring that was located at the beta-position of double bonds had no influence on the reaction, and corresponding products were obtained in good yields (**2k**−**2o**). Disubstituted aniline substrate was also compatible with the reaction conditions to give the desired product **2p**. Moreover, the cyclic substrate reacted smoothly to afford the desired product **2q** in moderate yield, which provided an easy access to the preparation of the polycyclic quinolines.

To examine the effect of substitution on the double bond, α,β-unsaturated compounds **1r** and **1s** were prepared and submitted to the reaction conditions, respectively. When the beta-position of olefin was disubstituted with methyl groups, the desired product was obtained in 67% yield (eq 1). While the Alfa-position of the olefin was substituted, an oxindole product was preferably formed (eq 2). Such results suggest that the stability of the radical intermediate formed from the addition of

Scheme 2. Scope of Substrates 1[a]



[a]Reaction conditions: **1a** (0.1 mmol), Togni's reagent (0.2 mmol), K_2HPO_4 (0.2 mmol), *fac*-Ir(ppy)$_3$ (5 mol %), CH_3CN (anhydrous, 1.5 mL), 5 W blue LEDs light, rt, under N_2 atmosphere.



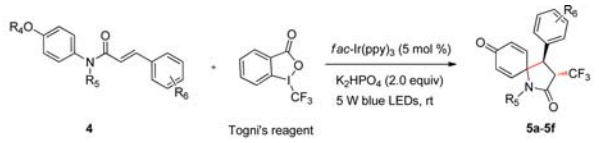
trifluoromethyl radical plays an important role in the product distribution. Interestingly, when the para-position of the aniline ring was replaced by a methoxy group, a spiro product **5a** was obtained instead of the corresponding six-membered ring product (eq 3), which, to our knowledge, presents the first example of photoredox catalytic synthesis of trifluoromethylated azaspiro compounds under benign conditions and encouraged us to explore it in more detail.[9]

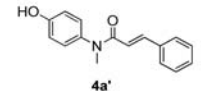
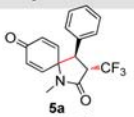
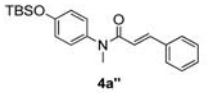
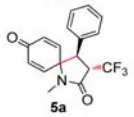
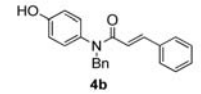
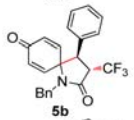
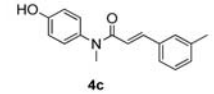
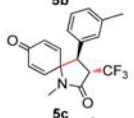
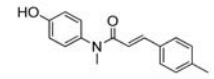
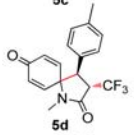
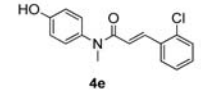
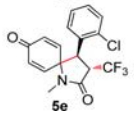
The scope study showed that when the methoxy group was replaced by the hydroxyl or *tert*-butyldimethylsilanoxy group, the desired product **5a** could be obtained in good yields (Scheme 3, entries 1−2). When the hydrogen on the nitrogen atom was substituted with a benzyl group instead of a methyl one, the substrate was tolerant with the reaction conditions to form the desired product in little decreased yield (entry 3). Cinnamamides with methyl or Cl group on the aromatic ring were also suitable for the optimal conditions to give the product in good yields (entries 4−6). It is worth noting that when the beta-position of the olefin was disubstituted with methyl groups, the desired product **5f** was obtained in 65% yield (eq 4).

On the basis of the above results, a plausible mechanism is described in Scheme 4.[10−13] Initially, [*fac*-^{III}Ir(ppy)$_3$] was excited

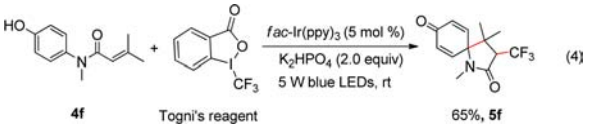
DOI: 10.1021/acs.orglett.5b01530
Org. Lett. 2015, 17, 3478−3481

Scheme 3. Scope of Substrate 4[a]

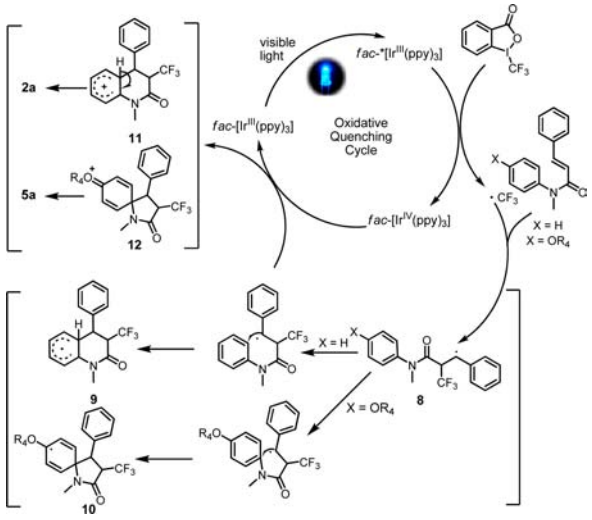


entry	substrate	product	yield/ %[b]
1	 4a'	 5a	70
2	 4a''	 5a	67
3	 4b	 5b	58
4	 4c	 5c	70
5	 4d	 5d	72
6	 4e	 5e	68

[a]Reaction conditions: **4** (0.1 mmol), Togni's reagent (0.2 mmol), K_2HPO_4 (0.2 mmol), *fac*-Ir(ppy)$_3$ (5 mol %), CH_3CN (anhydrous, 1.5 mL), 5 W blue LEDs light, rt, under N_2 atmosphere. [b]Isolated yield.



Scheme 4. Proposed Reaction Mechanism



to [*fac*-^{III}Ir(ppy)$_3$]* under the irradiation of visible light. Then, [*fac*-^{III}Ir(ppy)$_3$]* was oxidatively quenched by Togni's reagent to generate a relatively stable CF_3 radical along with *fac*-Ir^{IV}(ppy)$_3$. Subsequently, the CF_3 radical underwent a selectively radical addition of the double bond, leading to radical intermediate **8** after formation of a new C(sp^3)−CF_3 bond. When X was H, intramolecular cyclization of **8** formed intermediate **9**. For X = R_4O, cyclization of the benzyl radical intermediate **8** led to spirocyclic intermediate **10**. Then, **9** or **10** was oxidized by *fac*-Ir^{IV}(ppy)$_3$ to obtain the key cation **11** or **12**, respectively. Finally, the desired product **2a** or **5a** was obtained.

In summary, we have developed a highly efficient and practical approach for the preparation of CF_3-containing 3,4-disubstituted dihydroquinolin-2(1*H*)-one derivatives as well as 1-azaspiro[4.5]-decanes by visible-light-induced trifluoromethylation of an *N*-arylcinnamamide reaction with Togni's reagent under mild conditions. The method described in this Letter represents one of the most powerful routes for its operational simplicity, low catalyst loading, and less additives, and further extends the application of photochemistry in the realm of organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01530.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiawj@hit.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from China NSFC (Nos. 21002018, 21072038, 21472030, and 21302029), SKLUWRE (No. 2015DX01), the Fundamental Research Funds for the Central Universities (Grant No. HIT.BRETIV.201310), and HLJNSF (B201406).

■ REFERENCES

(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(2) For reviews for trifluoromethylation, see: (a) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475.

(3) (a) Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2745. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. - Asian J.* **2012**, *7*, 1744. (d) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (e) Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 585.

(4) (a) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (b) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (c) Zhao, Y.; Zhu, J.; Ni, C.; Hu, J. *Synthesis* **2010**, *2010*, 1899. (d) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (e) Hu, M.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 15257. (f) Prakash, G. K.

DOI: 10.1021/acs.orglett.5b01530
Org. Lett. 2015, 17, 3478−3481

S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324. (g) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 16167. (h) Prakash, G. K. S.; Zhang, Z.; Wang, F.; Munoz, S.; Olah, G. A. *J. Org. Chem.* **2013**, *78*, 3300. (i) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (j) Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955. (k) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (l) Zhang, L.-S.; Chen, K.; Chen, G.; Li, B.-J.; Luo, S.; Guo, Q.-Y.; Wei, J.-B.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 10. (m) He, Z.; Zhang, R.; Hu, M.; Li, L.; Ni, C.; Hu, J. *Chem. Sci.* **2013**, *4*, 3478. (n) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3944.

(5) (a) Xu, Pan.; Xie, Jin.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem. - Eur. J.* **2013**, *19*, 14039. (b) Tang, X.-J.; Thomoson, C. S.; Dolbier, W. R. *Org. Lett.* **2014**, *16*, 4594. (c) Straathof, N. J.W.; Tegelbeckers, B. J. P.; Hessel, V.; Wang, X.; Noel, T. *Chem. Sci.* **2014**, *5*, 4768. For the Tognis' reagent, please see: (d) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579.

(6) (a) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (b) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (c) Egami, H.; Shimizu, R.; Sodeoka, M. *J. Fluorine Chem.* **2013**, *152*, 51.

(7) (a) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (b) Shen, T.; Yuan, Y.; Jiao, N. *Chem. Commun.* **2014**, *50*, 554. (c) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343. (d) Yin, F.; Wang, X.-S. *Org. Lett.* **2014**, *16*, 1128. (e) Zheng, L.; Huang, H.; Yang, C.; Xia, W. *Org. Lett.* **2015**, *17*, 1034.

(8) (a) Mai, W.-P.; Wang, J.-T.; Yang, L.-R.; Yuan, J.-W.; Xiao, Y.-M.; Mao, P.; Qu, L.-B. *Org. Lett.* **2014**, *16*, 204. (b) Mai, W.-P.; Sun, G.-C.; Wang, J.-T.; Song, G.; Mao, P.; Yang, L.-R.; Yuan, J.-W.; Xiao, Y.-M.; Qu, L.-B. *J. Org. Chem.* **2014**, *79*, 8094.

(9) Han, G.; Wang, Q.; Liu, Y.; Wang, Q. *Org. Lett.* **2014**, *16*, 5914.

(10) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

(11) (a) Janson, P. G.; Ghoneim, I.; IIchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (b) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462. (c) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 5687. (d) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655. (e) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (f) Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem. - Eur. J.* **2013**, *19*, 6209.

(12) (a) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1881. (b) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841. (c) Lin, J.-S.; Xiong, Y.-P.; Ma, C.-L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Chem. - Eur. J.* **2014**, *20*, 1332.

(13) (a) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480. (b) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. (c) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 10202.

DOI: 10.1021/acs.orglett.5b01530
Org. Lett. 2015, 17, 3478−3481