Organic LETTERS

Letter

pubs.acs.org/OrgLett

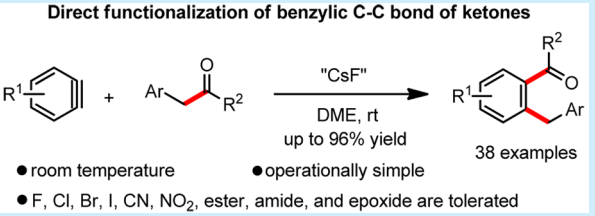
Synthesis of 2-Benzylphenyl Ketones by Aryne Insertion into Unactivated C−C Bonds

Bin Rao, Jinghua Tang, and Xiaoming Zeng*

Center for Organic Chemistry, Frontier Institute of Science and Technology, Xi'an Jiaotong University, Xi'an, Shaanxi 710054, P. R. China

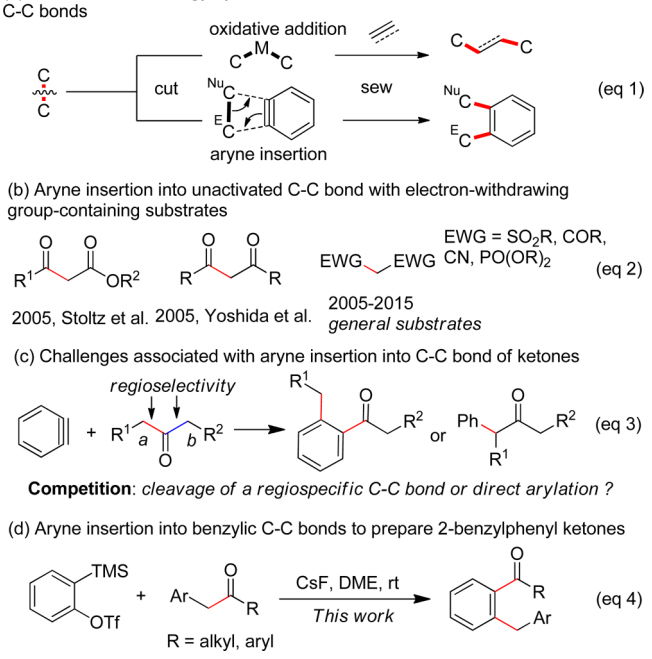
Supporting Information

ABSTRACT: A transition-metal-free procedure to access to functionalized 2-benzylphenyl ketones is described by direct insertion of arynes into benzylic C−C bonds. This reaction was promoted by cesium fluoride at room temperature, allowing the products to form in high selectivity and achieve good functional group tolerance.



The development of efficient strategies to cleave C−C σ-bonds followed by addition across unsaturated C−C bonds has recently attracted broad interests.[1] Such a "cut and sew" method provides a powerful and useful tool for the rapid buildup of complex molecules in high atom economy, but the cleavage of unactivated C−C bonds has long been a formidable challenge. Recent developments in the field mainly focused on transition metal-catalyzed reactions, such as the expansion of strained rings,[2] chelation-assisted transformations,[3] and addition to C−CN bonds[4] (Scheme 1, eq 1). Mechanistically different from the oxidative addition-involving conversions, the direct insertion of arynes into C−C bonds provides an alternative strategy via the formation of a four-membered ring intermediate,[5,6] which was disclosed by Stoltz and Yoshida using β-dicarbonyl precursors.[7] In spite of the considerable progress, strongly electron-withdrawing groups such as cyano, ester, sulfonyl and phosphonate locating at the α position of ketones are often indispensable for the cleavage of C−C bonds (Scheme 1, eq 2).[8] Note that Yoshida demonstrated that trifluoromethyl or 9-fluorenyl-containing ketone undergo the aryne insertion effectively, but suffer from a limited substrate scope.[9] In view of its efficiency in the rapid construction of synthetically appealing structural motifs, further exploration of new procedure with alternative substrates would be particularly attractive.

Scheme 1. Straightforward Functionalization of Unactivated C−C Bonds



2-Benzylphenyl ketones are fundamental building blocks found in various drug molecules and complex natural products.[10] They have often been employed as crucial precursors in preparing blue-emitting molecules,[11] and heterocycles such as isobenzofuran, isobenzothiophene, isoindazole, phthalazine.[12] We assumed that the direct insertion of arynes into benzylic ketones allows these frameworks to form by the cleavage of unactivated C−C bonds. That said, it may suffer from a selectivity issue because of the competitive α-arylation of ketone (Scheme 1, eq 3).[13] Herein, we report a straightforward, selective aryne insertion into benzylic C−C bonds enabled by cesium fluoride, providing access to 2-benzylphenyl ketones at room temperature in a simple operation (Scheme 1, eq 4).

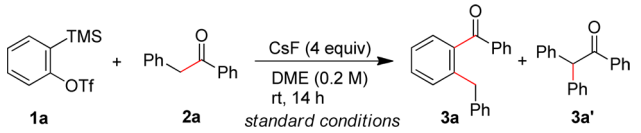
Initially, 2-phenylacetophenone **2a** was treated with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** for optimizing reaction conditions. In the presence of cesium fluoride, we were pleased to find that the resulting benzyne was allowed to direct insert into benzylic C−C bonds in a solution of DME, leading to (2-benzylphenyl) (phenyl)methanone (**3a**) in 67%

Received: February 29, 2016

DOI: 10.1021/acs.orglett.6b00578
Org. Lett. XXXX, XXX, XXX−XXX

yield (Table 1, entry 1). Note that the replacement of DME by THF, toluene, DCE, DCM or ethyl ether completely inhibited

Table 1. Optimizing Reaction Conditions[a,b]



1a 2a 3a 3a'

entry	deviation from the standard conditions	3a (%)	3a/3a'[c]
1	none	72 (67)[d]	20:1
2	toluene, DCE, CH_2Cl_2, THF, or ethyl ether instead of DME	nd	
3	CH_3CN or dioxane instead of DME	<10	
4	70 °C in CH_3CN instead of rt in DME	45	4:1
5	70 °C in THF instead of rt in DME	41	24:1
6	105 °C in THF instead of rt in DME	61 (56)[d]	23:1
7	0.1 M instead of 0.2 M	39	23:1
8	0.3 M instead of 0.2 M	69	12:1
9	KF and 18-C-6 instead of CsF	38	10:1
10	TBAT or TBAF instead of CsF	<20	<12:1
11	**1a** (1.5 equiv) instead of **1a** (2 equiv)	63	20:1

[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), CsF (0.4 mmol), DME (0.5 mL, 0.2 M), rt, 14 h. [b]^{1}H NMR yield was determined using dibromomethane as internal standard. [c]The ratio was determined by ^{1}H NMR analysis of the crude product. [d]Isolated yield in parentheses. DCE = 1,2-dichloroethane, nd = not detected, DME = 1,2-dimethoxylethane, 18-C-6 = 18-crown-6 ether, TBAF = tetrabutylammonium fluoride, TBAT = tetrabutylammonium triphenyldifluorosilicate.

the conversion, and **2a** was recovered in these cases (Table 1, entry 2). While the use of acetonitrile and dioxane led to a low conversion (Table 1, entry 3). Inferior performance was observed when heating the reaction mixture (Table 1, entries 4–6). Other fluoride salts including KF, TBAT and TBAF cannot improve the transformation (Table 1, entries 9 and 10).

Having the optimal conditions, the substrate scope was next investigated (Figure 1). The insertion of benzyne into substituted 2-phenylacetophenone carried out effectively at room temperature. A wide range of functional groups such as alkoxy, cyano, fluoride, chloride, bromide, iodide, and trifluoromethyl were tolerated by the protocol, forming diverse substituted 2-benzylbenzophenones **3c–i** in good to excellent yields (68–96%). Meanwhile, installation of OBoc, OTs, OTf, or amino carbonate onto the scaffold of aromatics has no influence on the benzyne insertion (**3j–m**). The reaction with 1-(1-naphthyl)-2-phenylethanone proceeded smoothly, forming the product **3r** in 75% yield. Introducing a bromo substituent into the *ortho* position of the benzyl scaffold did not hamper the transformation (**3u** and **3v**). 2-Thienylmethyl-substituted benzophenone was formed in 80% yield (**3y**). Furthermore, the extension of this protocol to the preparation of ferrocenyl- and methyl-substituted ketone derivatives **3z–ab** was successful. Interestingly, the use of 1,3-diphenylacetone gave an unexpected product **3ac** by a double aryne insertion into two benzylic C–C bonds. In addition, two-substituted benzynes also underwent the reaction effectively under standard conditions (**3ae** and **3af**).[14] It was noteworthy that a single product of **3ag** was formed with high regioselectivity from an unsymmetric 3,5-dimethoxy-substituted benzyne for the inductive effect of methoxyl groups.[15]

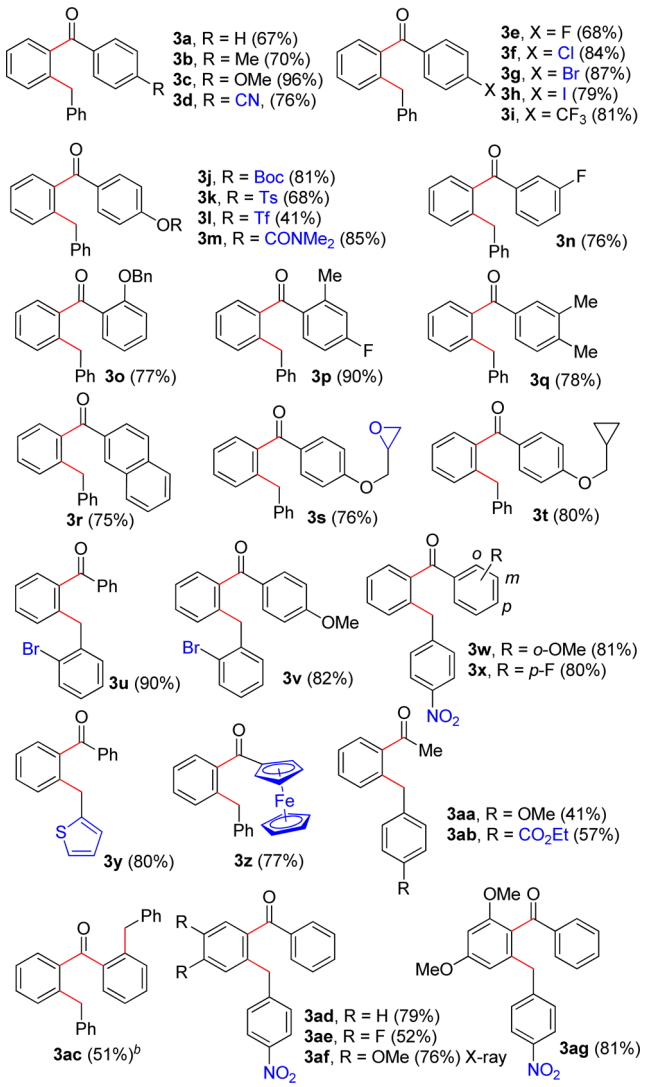
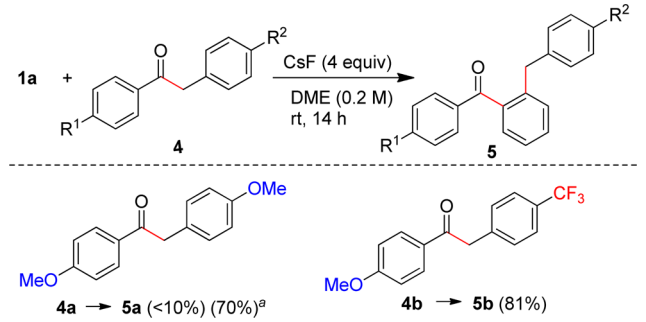


Figure 1. Aryne insertion into C–C bonds for the synthesis of 2-benzylphenyl ketones. (a) Conditions: aryne precursor (0.4 mmol), ketone (0.2 mmol), CsF (0.8 mmol), DME (1 mL), rt, 6–16 h. Isolated yield was given. (b) **1a** (0.8 mmol), 24 h.

Aiming to gain insight into the electronic effect on the transformation, methoxy- or trifluoromethyl-substituted 1-(4-methoxyphenyl)-2-phenylethanone (**4a** or **4b**) was treated with benzyne precursor (Scheme 2). A low conversion was obtained

Scheme 2. Investigation of the Electronic Influence of Benzylic Ketones on the Conversion



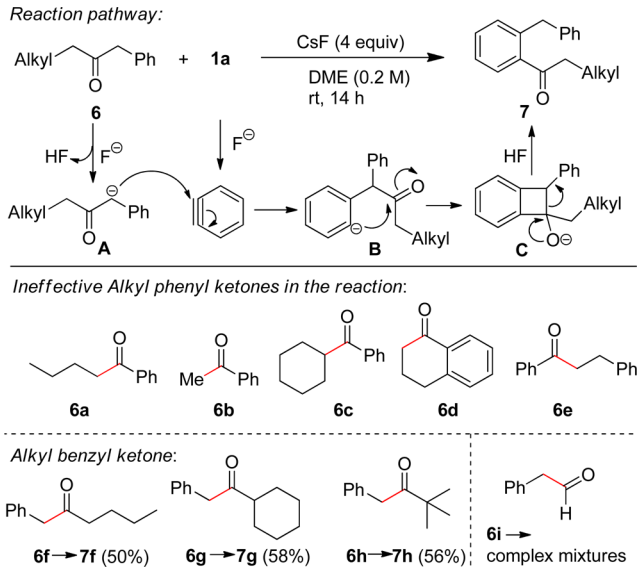
[a]The reaction was performed at 90 °C for 14 h.

DOI: 10.1021/acs.orglett.6b00578
Org. Lett. XXXX, XXX, XXX–XXX

by use of 4-methoxy-containing ketone **4a** (<10%). Conversely, the reaction with **4b** provided the corresponding product **5b** in 81% yield. These results suggest that the electronic properties on the benzyl scaffold affect the transformation, and support an electron-deficient benzyl-favorable transformation because of its facile formation of a carbanion in the transformation.

To explore a plausible mechanism for the aryne insertion, the experiment by reacting alkyl phenyl ketones **6a−e** with benzyne was next carried out (Scheme 3). It was found that the

Scheme 3. Mechanistic Insights



conversion did not proceed, even heating the mixture at 90 °C. Comparing with this, the use of alkyl benzyl ketones (**6f−h**) allows giving the desired products by the cleavage of benzylic C−C bonds combining with some byproducts. These results indicate that forming a carbanion **A** is indispensible for ensuring the reaction to proceed, which can be produced by a deprotonation of methenyl with fluoride salt. Subsequently, a nucleophilic attack on benzyne followed by a process of cyclization/ring-opening may lead to the product.

In summary, we have developed a transition metal-free, operationally simple procedure that allows efficient buildup of 2-benzylphenyl ketones at room temperature. This reaction was enabled by a simple salt of cesium fluoride via the direct insertion of arynes into benzylic C−C bonds. A diverse range of functionalities including fluoride, bromide, iodide, cyano, nitro, ester, amide, epoxide, ferrocenyl, and thienyl groups are well tolerated. Further studies on the application in the preparation of complex molecules are ongoing 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.6b00578.

Detailed optimization data; experimental procedures; characterization data of all new compounds (PDF)

X-ray crstallographic data for **3af** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zengxiaoming@mail.xjtu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this work by XJTU from a start-up fund and the National Natural Science Foundation of China [Nos. 21202128 (X.Z.), 21572175] is gratefully acknowledged. We thank Prof. Yan-Zhen Zheng (XJTU) and Mr. Guojun Zhou (XJTU) for X-ray crystallographic analysis.

■ REFERENCES

(1) (a) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410−9464. (b) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613−8661. (c) Dermenci, A.; Coe, J. W.; Dong, G. *Org. Chem. Front.* **2014**, *1*, 567−581. (d) Dong, G. *Synlett* **2012**, *24*, 1−5. (e) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (f) Perthuisot, C.; Edelbach, B. L.; Zubris, D. L.; Simhai, N.; Iverson, C. N.; Müller, C.; Satoh, T.; Jones, W. D. *J. Mol. Catal. A: Chem.* **2002**, *189*, 157−168. (g) Dong, G.; Cramer, N. *C−C Bond Activation*; Springer, 2014; Vol. *346*.

(2) For selected examples, see: (a) Souillart, L.; Parker, E.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3001−3005. (b) Chen, P.-h.; Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1674−1678. (c) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005−20008. (d) Korotvička, A.; Císařová, I.; Roithová, J.; Kotora, M. *Chem. - Eur. J.* **2012**, *18*, 4200−4207. (e) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502−17504. (f) Tamaki, T.; Ohashi, M.; Ogoshi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12067−12070. (g) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T.-a. *Angew. Chem., Int. Ed.* **2004**, *43*, 5369−5372. (h) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976−13977.

(3) (a) Ko, H. M.; Dong, G. *Nat. Chem.* **2014**, *6*, 739−744. (b) Lutz, J. P.; Rathbun, C. M.; Stevenson, S. M.; Powell, B. M.; Boman, T. S.; Baxter, C. E.; Zona, J. M.; Johnson, J. B. *J. Am. Chem. Soc.* **2012**, *134*, 715−722. (c) Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6121−6123. (d) Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412−413.

(4) (a) Nakao, Y. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 731−745. (b) Nakao, Y.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10024−10026. (c) Hirata, Y.; Yukawa, T.; Kashihara, N.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 10964−10973. (d) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594−12595. (e) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874−12875. (f) Nakao, Y.; Hirata, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7420−7421. (g) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904−13905. (h) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303−3306.

(5) For selected reviews on aryne chemistry, see: (a) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725−1732. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550−3577. (c) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579−3581. (d) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140−3152. (e) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1450−1460. (f) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116−125. (g) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766−3778. (h) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502−528.

(6) (a) Yoshida, S.; Yano, T.; Misawa, Y.; Sugimura, Y.; Igawa, K.; Shimizu, S.; Tomooka, K.; Hosoya, T. *J. Am. Chem. Soc.* **2015**, *137*, 14071−14074. (b) Pawliczek, M.; Garve, L. K. B.; Werz, D. B. *Org. Lett.* **2015**, *17*, 1716−1719. (c) Li, Y.; Chakrabarty, S.; Mück-Lichtenfeld, C.; Studer, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 802−806. (d) Yoshida, H.; Yoshida, R.; Takaki, K. *Angew. Chem., Int. Ed.* **2013**,

DOI: 10.1021/acs.orglett.6b00578
Org. Lett. XXXX, XXX, XXX−XXX

52, 8629−8632. (e) Shen, C.; Yang, G.; Zhang, W. *Org. Lett.* **2013**, *15*, 5722−5725. (f) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168−171. (g) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405−2407. (h) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112−13113. (i) Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2004**, 1980−1981. (j) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052−5055. (k) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247−3249. (l) Rao, B.; Zeng, X. *Org. Lett.* **2014**, *16*, 314−317. (m) Yang, G.; Shen, C.; Quan, M.; Zhang, W. *Tetrahedron* **2016**, *72*, 333−337. (n) Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1612−1614. (o) Yoshida, H.; Morishita, T.; Ohshita, J. *Chem. Lett.* **2010**, *39*, 508−509. (p) Rao, B.; Tang, J.; Wei, Y.; Zeng, X. *Chem. - Asian J.* **2016**, DOI: 10.1002/asia.201600065.

(7) (a) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340−5341. (b) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292−3294. For selected early reports on the insertion of arynes into C−C bonds, see: (c) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509−9525. (d) Shair, M. D.; Yoon, T.-y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1721−1723. (e) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471−9479. (f) Guyot, M.; Molho, D. *Tetrahedron Lett.* **1973**, *14*, 3433−3436.

(8) (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729−6731. (b) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505−1507. (c) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 5691−5694. (d) Zhang, T.; Huang, X.; Xue, J.; Sun, S. *Tetrahedron Lett.* **2009**, *50*, 1290−1294.

(9) Yoshida, H.; Kishida, T.; Watanabe, M.; Ohshita, J. *Chem. Commun.* **2008**, 5963−5965. (b) Yoshida, H.; Ito, Y.; Yoshikawa, Y.; Ohshita, J.; Takaki, K. *Chem. Commun.* **2011**, *47*, 8664−8666.

(10) (a) Jiang, B.; Shi, D.; Cui, Y.; Guo, S. *Arch. Pharm.* **2012**, *345*, 444−453. (b) Wright, N. E.; ElSohly, A. M.; Snyder, S. A. *Org. Lett.* **2014**, *16*, 3644−3647. (c) Buchgraber, P.; Domostoj, M. M.; Scheiper, B.; Wirtz, C.; Mynott, R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519−6534.

(11) (a) Hu, J.-Y.; Pu, Y.-J.; Satoh, F.; Kawata, S.; Katagiri, H.; Sasabe, H.; Kido, J. *Adv. Funct. Mater.* **2014**, *24*, 2064−2071. (b) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7005−7009.

(12) (a) Nishina, Y.; Kida, T.; Ureshino, T. *Org. Lett.* **2011**, *13*, 3960−3963. (b) Ohmura, T.; Kijima, A.; Suginome, M. *Org. Lett.* **2011**, *13*, 1238−1241. (c) Ohmura, T.; Kijima, A.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 6070−6071.

(13) (a) Chen, Q.; Zhang, C.; Chen, L.; Wen, C.; Du, Z.; Chen, H. *Tetrahedron Lett.* **2015**, *56*, 2094−2097. (b) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, *14*, 4686−4689.

(14) CCDC 1443328 (**3af**) contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224−1227.

DOI: 10.1021/acs.orglett.6b00578
Org. Lett. XXXX, XXX, XXX−XXX