Organic LETTERS

Letter

pubs.acs.org/OrgLett

Palladium-Catalyzed Asymmetric Arylation of C(sp^3)–H Bonds of Aliphatic Amides: Controlling Enantioselectivity Using Chiral Phosphoric Amides/Acids

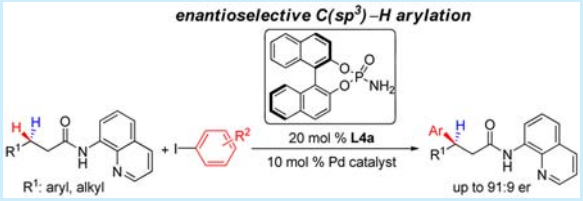
Shao-Bai Yan,[†] Song Zhang,[‡] and Wei-Liang Duan*[,†]

[†]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

[‡]School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

Supporting Information

ABSTRACT: Enantioselective arylation of secondary β-C(sp^3)–H bonds of 8-aminoquinoline amides was realized with a palladium catalyst. Chiral phosphoric amides and acids were used for the first time to control the stereoselectivity at the C–H bond cleavage step in the C–H activation reactions.



Transition-metal-catalyzed direct functionalization of unreactive C–H bonds has been extensively investigated in recent years. Numerous synthetic methods have been developed to build diverse complex compounds from simple and nonfunctionalized molecules.[1] By contrast, enantioselective C–H activation has not received much attention probably because of the absence of suitable ligands to control the stereoselectivity in the C–H activation reaction. Chiral phosphine or nitrogen ligands, which are widely used in asymmetric catalysis, have also been applied to C–H activation reactions but with limitations. Successful examples have only appeared recently.[2] The most frequently used strategies to generate enantioenriched products are monoprotected amino acids in combination with a Pd catalyst,[3] chiral phosphine/NHC ligand-promoted Pd(0)-catalyzed cyclization,[4] and a chiral Cp* Rh catalyst.[5] Despite great progress, developing new protocols is still highly desirable for enantioselective C–H activation reactions.

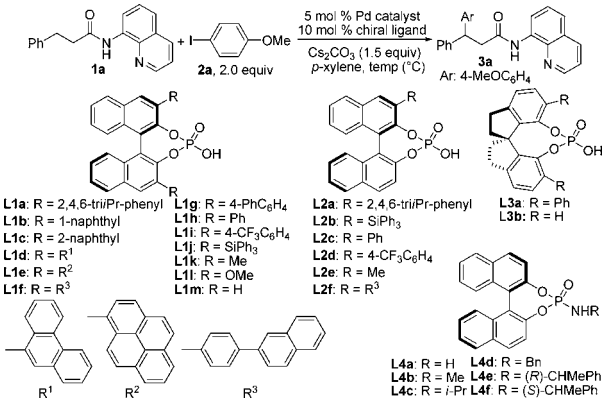
Carboxylic acids, such as pivalic acid, are frequently involved in C–H activation reactions[6] because these acids can facilitate the cleavage of the unreactive C–H bond. This process is known as the concerted metalation deprotonation mechanism.[7] Consequently, chiral carboxylic acids have been utilized to control enantioselectivity in Pd(0)-catalyzed intramolecular cyclization reactions with moderate enantiomeric excess.[4d,f] Chiral phosphoric acids (CPAs), as the prominent catalysts, have been extensively applied in catalytic reactions with excellent enantioselectivities.[8] Although phosphoric acids have recently been reported as additives in C–H activation reactions,[9] the detailed roles of these acids remain ambiguous.[10] The use of CPAs in C–H activation reactions to control stereoselectivity at the C–H bond cleavage step has not been reported.[11] Considering the high basicity of the P═O function in the phosphoric acid[8d,g] and good chiral environment induced by the binaphthyl skeleton of BINOL-based CPAs, we envisioned whether CPAs can serve as ligands to control stereoselectivity in the C–H activation reaction, consequently generating a chiral center. To realize our hypothesis, we attempted to apply CPAs for the enantioselective β-arylation reactions of aliphatic carboxylic amides bearing an 8-aminoquinoline[12,13] moiety (equation in Table 1). The direct enantioselective β-functionalization of such monosubstituted carboxylic amides with flexible carbon chains has not been realized yet.[14−16]

Carboxylic amide **1a** was reacted with 4-iodoanisole **2a** in the presence of Pd(OAc)$_2$ catalyst to examine an array of CPAs[17] in *p*-xylene at 140 °C. The use of 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **L1a** only generated a racemic product (Table 1, entry 1). The use of CPAs (**L1b** and **L1c**) bearing 1- or 2-naphthyl groups at the 3,3′-position of the binaphthyl skeleton generated products with 61.5:38.5 and 54:46 er, respectively (entries 2 and 3), which proved the feasibility of our initial hypothesis. Furthermore, various CPAs (**L1d**–**L1l**) were examined (entries 4–12), and up to 71:29 er of product was obtained when the catalyst with a 3,3′-bis(SiPh$_3$) moiety was tested (entry 10). The simplest CPA **L1m** without any substituents unexpectedly generated products with 83:17 er (entry 13). To further examine the substituent effects of CPAs on the er of products, several CPAs (**L2a**–**L2f**) that only bear monosubstituents at the 3-position of the binaphthyl skeleton were prepared and examined. The mono-3-substituted CPAs **L2** generally induced an er (entries 14–19) higher than that of the corresponding 3,3′-disubstituted CPAs, but still inferior to **L1m**. To further improve the er, CPAs with a spiro skeleton, **L3a** and **L3b**, were also examined, but a racemic product was generated (entries 20 and 21). However, examining several bases and solvents with CPAs **L1m** did not further improve the er (see Supporting Information for details). Given that the different binding energies and bond distances between nitrogen and

Received: April 3, 2015
Published: May 4, 2015

DOI: 10.1021/acs.orglett.5b00968
Org. Lett. 2015, 17, 2458–2461

Table 1. Palladium-Catalyzed Enantioselective Arylation of Carboxylic Amide 1a with 4-Iodoanisole



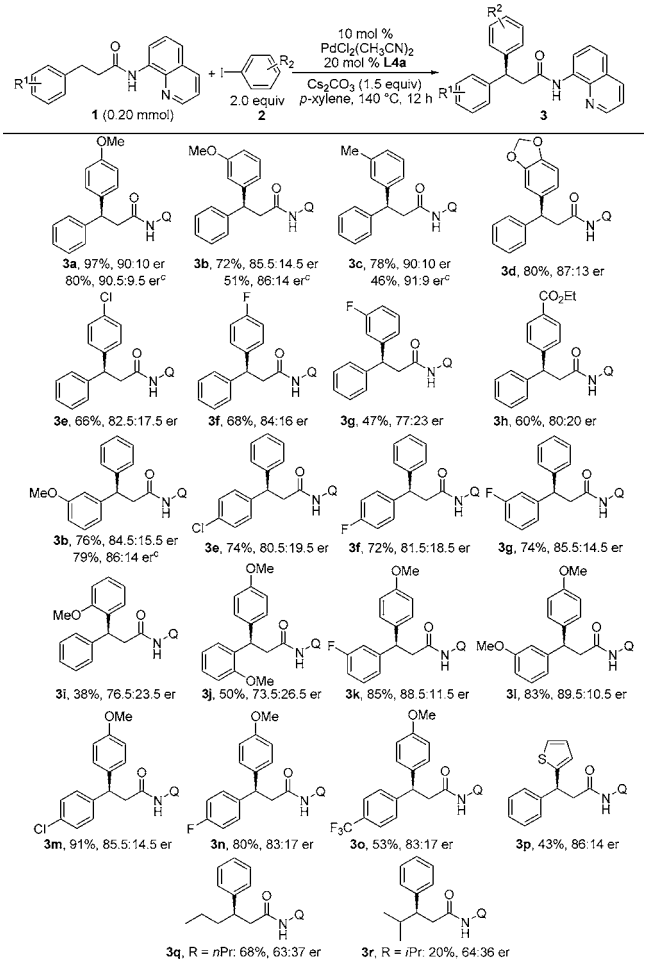
entry	ligand	Pd salt	temp (°C)/time (h)	yield (%)[a]	er[b]
1	**L1a**	$Pd(OAc)_2$	140/7	40	racemic
2	**L1b**	$Pd(OAc)_2$	140/10	55	61.5:38.5
3	**L1c**	$Pd(OAc)_2$	140/12	54	54:46
4	**L1d**	$Pd(OAc)_2$	140/10	69	54:46
5	**L1e**	$Pd(OAc)_2$	140/12	71	67:33
6	**L1f**	$Pd(OAc)_2$	140/10	52	71:29
7	**L1g**[c]	$Pd(OAc)_2$	140/10	53	59:41
8	**L1h**	$Pd(OAc)_2$	140/10	38	53.5:46.5
9	**L1i**	$Pd(OAc)_2$	140/5	47	67.5:32.5
10	**L1j**	$Pd(OAc)_2$	140/10	70	71:29
11	**L1k**	$Pd(OAc)_2$	140/5	48	60:40
12	**L1l**	$Pd(OAc)_2$	140/8.5	24	55.5:44.5
13	**L1m**	$Pd(OAc)_2$	140/12	64[d]	83:17
14	**L2a**	$Pd(OAc)_2$	140/10	23	53.5:46.5
15	**L2b**	$Pd(OAc)_2$	140/5	86	70:30
16	**L2c**	$Pd(OAc)_2$	140/5	33	63:37
17	**L2d**	$Pd(OAc)_2$	140/11	91	75:25
18	**L2e**	$Pd(OAc)_2$	140/12	50	75:25
19	**L2f**	$Pd(OAc)_2$	140/10	58	77:23
20	**L3a**	$Pd(OAc)_2$	140/8	38	racemic
21	**L3b**	$Pd(OAc)_2$	140/6	31	racemic
22	**L4a**	$Pd(OAc)_2$	140/8.5	80	86.5:13.5
23[e]	**L1m**	$PdCl_2(MeCN)_2$	140/12	83[d]	88.5:11.5
24[e]	**L4a**	$PdCl_2(MeCN)_2$	140/7.5	97[d]	90:10
25[e]	**L4a**	$PdCl_2(MeCN)_2$	120/7.5	80[d]	90.5:9.5

[a]Yields were determined by ^{1}H NMR analysis of the crude product. [b]The er was determined with chiral HPLC using hexane/isopropyl alcohol. [c](*S*)-**L1g** was used. [d]Isolated yields. [e]10 mol % of Pd catalyst and 20 mol % of ligand were used.

oxygen with Pd metal often exhibit varying results in the reactions, whether chiral phosphoric amides **L4** could enhance stereoselectivity was also determined. The use of the chiral phosphoric amide **L4a** enhanced the er of products to 86.5:13.5 (entry 22), which is better than the results derived from **L4b**−**L4f** bearing different substituents on the nitrogen atom (see Supporting Information for details). Carboxylic acids have certain accelerated effects on the C−H activation reaction.[6] Thus, different Pd sources were investigated, and the use of $PdCl_2(MeCN)_2$ with ligand **L1m** or **L4a** increased the er to 88.5:11.5 and 90:10 (entries 23 and 24), respectively. Others ($Pd(OTFA)_2$, $PdCl_2$, and $Pd(acac)_2$) afforded inferior er (see Supporting Information for details). Decreasing the temperature to 120 °C slightly enhanced the er to 90.5:9.5 but with a decreased 80% yield (entry 25).[18]

With the established conditions, the substrate scope of the reaction was examined, and the results are shown in Scheme 1.[19]

Scheme 1. Substrate Scope[a,b]



[a]Isolated yields; er was determined with chiral HPLC using hexane/isopropyl alcohol. [b]The absolute configuration of **3** was deduced from the configuration of **3a**, which was determined by comparison of the specific optical rotation of a **3a** derivative with the value reported in literature (see Supporting Information). [c]Reactions were run at 120 °C for 12 h.

Substrates bearing various substituents on the iodoarene rings, such as methyl, alkoxy, fluoro, chloro, and ester groups, were well-tolerated, and the corresponding products were generated in good yields and moderate to good enantiomeric ratio (Scheme 1, **3a**−**3h**). In terms of the substituent effects on the aliphatic carboxylic amides, the substrates also contained different moieties, such as methyl, methoxy, trifluoromethyl, and halogen under the standard conditions, and moderate to good er of products was formed. A sterically hindered *ortho*-methoxy group on the phenyl ring of substrate **1** or iodoarene **2** was tolerated, and the desired products **3i** and **3j** were generated with decreased yield and er (76.5:23.5 and 73.5:26.5). Coupling of substituted amides with 4-iodoanisole yielded various *β*,*β*-diaryl-functionalized carboxylic amides (**3k**−**3o**) in moderate to good er. Notably, the heterocycle 2-iodothiophene was also used in the reaction, and the *β*-functionalized product was isolated in 86:14 er. Finally, challenging substrates with alkyl substituents, such as *n*-propyl and isopropyl, were examined, and the desired products

DOI: 10.1021/acs.orglett.5b00968
Org. Lett. 2015, 17, 2458−2461

3q and **3r** were produced with relatively low enantioselectivities and yields.

Considering the observed important effects of phosphoric acid/amide in the reaction, we conducted a series of experiments to compare their effects on the reaction rate (Figure 1). The

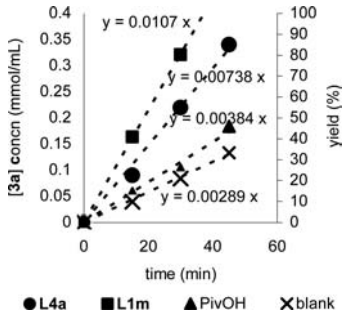
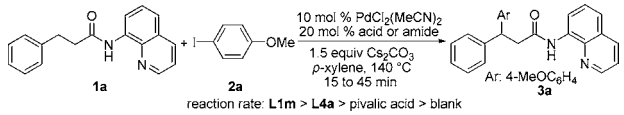


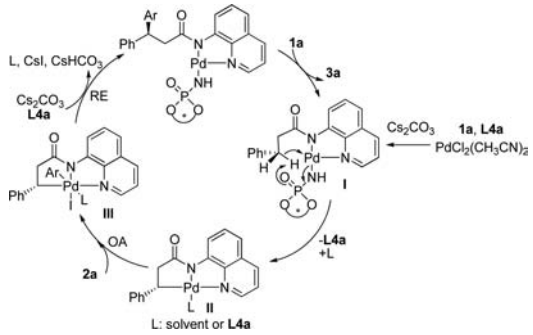
Figure 1. Additive effects on the reaction rate.

reaction rate with **L4a** was increased by 2.6 times compared with that in the blank reaction. More acidic CPA **L1m** had a stronger acceleration effect (3.7 times) than **L4a**. Meanwhile, widely used pivalic acid exhibited an acceleration effect (1.3 times) inferior to that of **L1m** and **L4a**. Then, the deuterium-labeled substrate was used to examine the kinetic isotope effects, and k_H/k_D = 3.9 was observed (see Supporting Information for details). This value indicates that the C−H bond cleavage is the rate-limiting step in this reaction,[20] which is consistent with the reported data for a similar reaction by Shi et al.[13e]



Based on the observed experimental results and published examples,[9,12,13] a tentative catalytic cycle is proposed in Scheme 2. First, the ligand exchange of $PdCl_2(CH_3CN)_2$ with substrate

Scheme 2. Proposed Catalytic Cycle



1a in the presence of Cs_2CO_3 and chiral phosphoric amide **L4a** affords a Pd(II) intermediate **I** bearing an amide anion. Selective cleavaging of one of the C−H bonds over another at the β-position of **1a** with the assistance of chiral amide **L4a** generates an enantioenriched intermediate **II**. The oxidative addition of iodoarene **2a** to the Pd(II) atom affords a Pd(IV) intermediate **III**. Finally, reductive elimination from the Pd(IV) center, followed by a ligand exchange with substrate **1a**, releases the corresponding product **3a**.

In summary, we have described a Pd-catalyzed enantioselective C(sp^3)−H functionalization of aliphatic carboxylic amides. This process effectively generated an array of β,β-diaryl carboxylic derivatives in moderate to good enantiomeric ratios. Chiral phosphoric amides and acids have been found to have prominent effects on the control of enantioselectivity and the acceleration of the reaction rate. Further improvement on the stereoselectivity of the current reaction and extending the utility of chiral CPAs in C−H bond activation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00968.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wlduan@mail.sioc.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by NSFC (20902099, 21172238, and 21472218). We thank Prof. Qi-Lin Zhou and Prof. Shou-Fei Zhu at Nankai University for kindly donating ligand **L3a**, and Prof. Tamio Hayashi at IMRE, Singapore, for helpful suggestions.

■ REFERENCES

(1) For selected reviews on C−H activation, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, *7*, 949. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (f) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (g) *C−H Activation.*; Yu, J.-Q., Shi, Z., Eds.; Topics in Current Chemistry; Springer: Berlin, 2010; Vol. *292*. (h) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (i) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (j) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (k) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421.

(2) For reviews on enantioselective C−H activation, see: (a) Wencel-Delord, J.; Colobert, F. *Chem.—Eur. J.* **2013**, *19*, 14010. (b) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927. (c) Zheng, C.; You, S.-L. *RSC Adv.* **2014**, *4*, 6173.

(3) For selected examples of Pd-catalyzed enantioselective C−H activation using chiral amino acid as the ligand, see: (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (c) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (d) Musaev, D. G.; Kaledin, A.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 1690. (e) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 1236. (f) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344. (g) Chu, L.; Xiao, K.-J.; Yu, J.-Q. *Science* **2014**, *346*, 451. (h) Xiao, K.-J.; Lin, D.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138. (i) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042.

(4) (a) Albicker, M. R.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 9139. (b) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7261. (c) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (d) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*,

DOI: 10.1021/acs.orglett.5b00968
Org. Lett. 2015, 17, 2458−2461

11483. (e) Katayev, D.; Nakanishi, M.; Bürgi, T.; Kündig, E. P. *Chem. Sci.* **2012**, *3*, 1422. (f) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238. (g) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. *Chem.—Eur. J.* **2012**, *18*, 4480. (h) Shintani, R.; Otomo, H.; Ota, K.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 7305. (i) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (j) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 7865. (k) Katayev, D.; Jia, Y.-X.; Sharma, A. K.; Banerjee, D.; Besnard, C.; Sunoj, R. B.; Kündig, E. P. *Chem.—Eur. J.* **2013**, *19*, 11916. (l) Larionov, E.; Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Chem. Sci.* **2013**, *4*, 1995. (m) Trost, B. M.; Thaisrivongs, D. A.; Donckele, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1523. (n) Deng, R.; Huang, Y.; Ma, X.; Li, G.; Zhu, R.; Wang, B.; Kang, Y.-B.; Gu, Z. *J. Am. Chem. Soc.* **2014**, *136*, 4472. (o) Gao, D.-W.; Yin, Q.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2014**, *136*, 4841. (p) Ma, X.; Gu, Z. *RSC Adv.* **2014**, *4*, 36241. (q) Liu, L.; Zhang, A.-A.; Zhao, R.-J.; Li, F.; Meng, T.-J.; Ishida, N.; Murakami, M.; Zhao, W.-X. *Org. Lett.* **2014**, *16*, 5336. (r) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 9064.

(5) (a) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (b) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504. (c) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636. (d) Ye, B.; Donets, P. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 507. (e) Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896. (f) Zheng, J.; You, S.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13244.

(6) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(7) (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

(8) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Xu, F.-X.; Huang, D.; Han, C.; Shen, W.; Lin, X.-F.; Wang, Y.-G. *J. Org. Chem.* **2010**, *75*, 8677. (d) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569. For selected reviews, see: (e) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (f) Terada, M. *Chem. Commun.* **2008**, 4097. (g) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (h) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047 and references therein.

(9) (a) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.-S.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (b) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (c) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (d) Chen, K.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 11950. (e) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531.

(10) The phosphoric acids were proposed to act as the phase transfer catalyst to silver salt or facilitate the dissociation of Pd(II) from Pd-bound functionalized products in C−H activation reactions; see refs 9a, 9c, and 9e.

(11) For an example of CPA-mediated enantioselective cross-dehydrogenative coupling reactions, see: Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044.

(12) For pioneering works utilizing 8-aminoquinoline in C−H activation by the Daugulis group, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209 and their previous reports cited therein.

(13) For a review on AQ-directed C−H bond functionalization, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. For selected reports on Pd-catalyzed AQ-directed C−H functionalizations, see: (b) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (c) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (d) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (e) Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang, X.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 4758. (f) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899. (g) Chen, K.; Li, Z.-W.; Shen, P.-X.; Zhao, H.-W.; Shi, Z.-J. *Chem.—Eur. J.* **2015**, *21*, 7389.

(14) An enantioselective arylation of cyclobutanecarboxylic amides was reported by Yu et al. recently; see ref 3h.

(15) For a digest paper on direct β-C−H functionalization of carbonyl compounds, see: Huang, Z.; Dong, G. *Tetrahedron Lett.* **2014**, *55*, 5869 and references therein.

(16) For Yu's seminal works on Pd-catalyzed substituted amines directed β-arylation, see: (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (b) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570.

(17) For selected reports involving organic phosphate ligands in Pd-catalyzed reactions, see: (a) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (b) Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471. (c) Chai, Z.; Rainey, T. J. *J. Am. Chem. Soc.* **2012**, *134*, 3615. (d) Yu, S.-Y.; Zhang, H.; Gao, Y.; Mo, L.; Wang, S.; Yao, Z.-J. *J. Am. Chem. Soc.* **2013**, *135*, 11402. (e) Zhang, D.; Qiu, H.; Jiang, L.; Lv, F.; Ma, C.; Hu, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 13356. (f) Wang, P. S.; Lin, H.-C.; Zhai, Y.-J.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 12218. (g) Tao, Z.-L.; Li, X.-H.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 4054.

(18) The reaction afforded <10% yield of product at 100 °C.

(19) Due to the catalyst deactivation at high temperature, the reactions in Scheme 1 were run for 12 h, although 2 h of the reaction time is enough for some substrates.

(20) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

DOI: 10.1021/acs.orglett.5b00968
Org. Lett. 2015, 17, 2458−2461