Organic LETTERS

Letter

pubs.acs.org/OrgLett

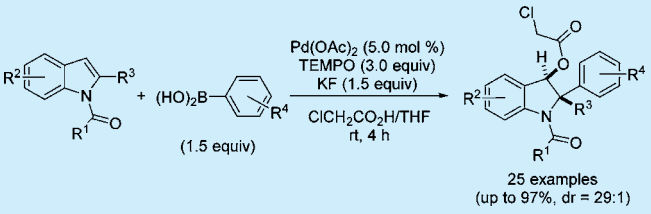
Palladium-Catalyzed Diastereoselective Oxyarylation of 2-Alkylindoles

Vincenzo Ramella, Zhiheng He, Constantin G. Daniliuc, and Armido Studer*

Organic Chemistry Institute, Westfälische Wilhelms-University, Corrensstraße 40, 48149 Münster, Germany

Supporting Information

ABSTRACT: Diastereoselective oxyarylation of N-protected 2-alkylindoles with commercially available boronic acids and TEMPO as a mild oxidant to give N-protected 2-aryl-2-alkyl-3-(2-chloroacetoxy)indolines is described. Reactions are easy to conduct, and product indolines containing a fully substituted C-center are obtained in good yields with good to excellent selectivities.



The indoline substructure can be found in many biologically active natural products and pharmaceutically relevant compounds (Figure 1).[1] Therefore, development of novel and simple synthetic methods for their preparation from readily available starting materials is important. Considering the structure of these natural products in particular, methods for the construction of indolines with fully substituted C-centers at the C2 and/or C3 positions are valuable. Established approaches include tandem reactions of arynes,[2] Fischer indolizations,[3] Diels–Alder-cyclizations,[4] epoxidation/cyclization reactions,[5] Heck cyclizations,[6] functionalization of oxindoles,[1b,7] and oxidative dearomatizations of indoles.[8] Despite great achievements in this area, it is still of importance to develop novel and efficient approaches to access this compound class.

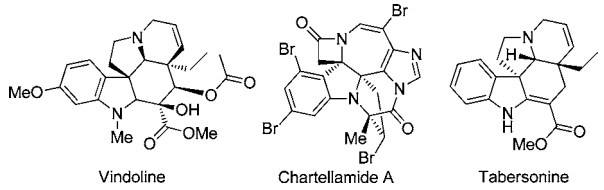
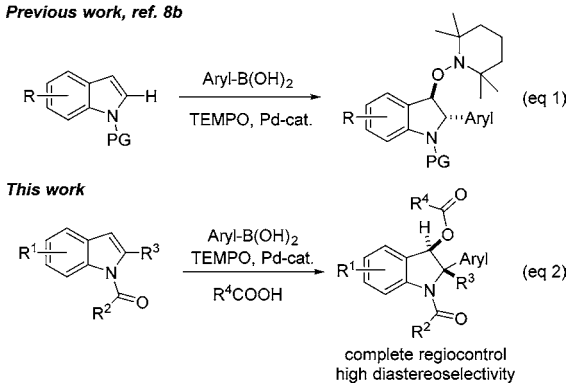


Figure 1. Indoline-based natural products.

Carbooxygenation of carbon–carbon double bonds allows the vicinal incorporation of an O-substituent and an alkyl/aryl group in one sequence, thereby ensuring a fast and easy access to valuable structures in a single operation. Intramolecular carbooxygenations of alkenes have been intensively studied.[9] On the other hand, the intermolecular variant is less well developed but has recently emerged as a highly active research field with great potential.[10] Along these lines, we have developed protocols for intermolecular oxyarylation of indenes,[11] indoles,[8b] and benzofurans[11] with arylboronic acids and TEMPO.[12] In the reported indole oxyarylation,[8b] reactions provided TEMPO-trapped indolines, and formation of fully substituted C-centers was not achieved (Scheme 1, eq 1).[13] Herein, we disclose a highly diastereoselective intermolecular Pd-catalyzed oxyarylation of 2-substituted indoles providing N-protected 2-aryl-2-alkyl-3-(acyloxy)indolines with complete regiocontrol and high stereocontrol (Scheme 1, eq 2).

Scheme 1. Intermolecular Oxyarylation of Indoles

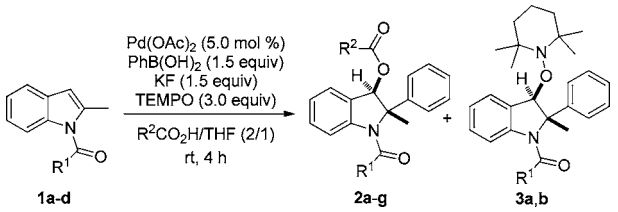


For reaction optimization, we used phenylboronic acid, various N-protected 2-methylindoles, and $Pd(OAc)_2$ (5 mol %) as a catalyst mostly in combination with TEMPO as an oxidant. Solvent and the N-protecting group were systematically varied, and reactions were conducted at room temperature for 4 h (Table 1). The first experiment was conducted with 2-methyl-*N*-acetylindole (**1a**) in neat acetic acid, and as the major product we isolated the oxyarylated indoline **2a** with high diastereoselectivity (Table 1, 17:1, entry 1). The corresponding TEMPO-trapping product **3a** was isolated in 32% yield with complete diastereocontrol. In order to suppress TEMPO trapping, we tested various standard oxidants, like $Cu(OAc)_2$, AgOAc, $FeCl_3$, 1,4-benzoquinone, $PhI(OAc)_2$, and oxygen, but with these oxidants oxyarylation did not work. By switching the protecting group from acetyl to methyloxycarbonyl, yield for the carboacyloxy product **2b** increased to 79% and also diastereoselectivity further increased (Table 1, entry 2). However, the TEMPO-trapping derivative **3b** was still formed in 21%.

Received: December 22, 2014
Published: January 26, 2015

DOI: 10.1021/ol503689r
Org. Lett. 2015, 17, 664–667

Table 1. Reaction Optimization



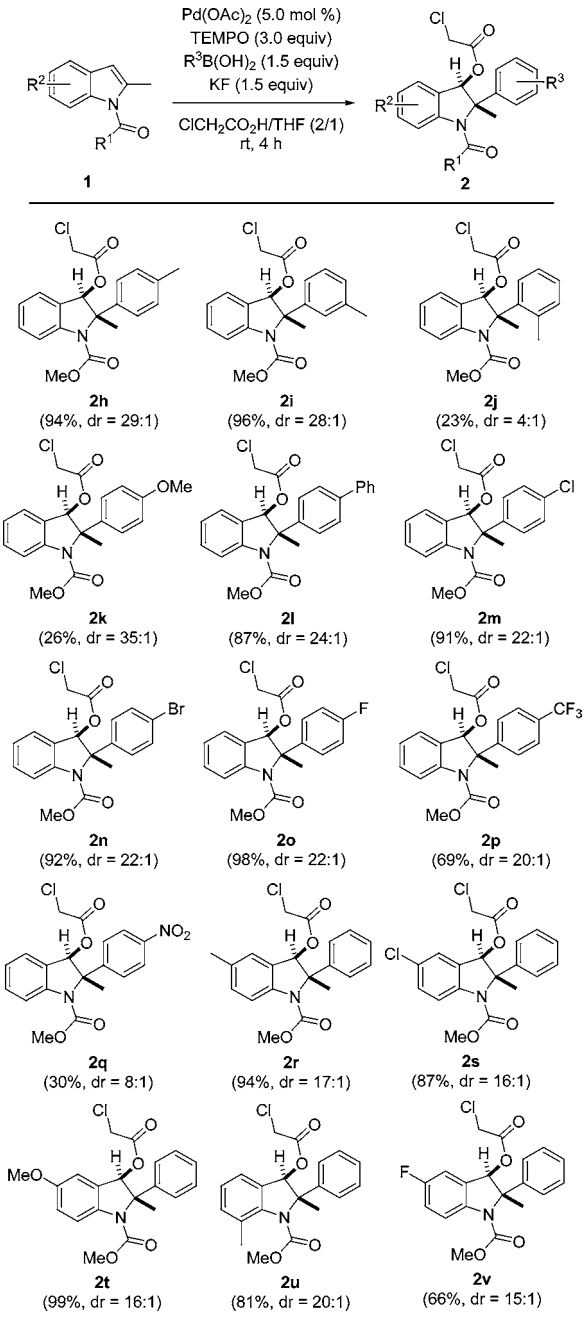
entry	R^1	R^2	yield (%), dr (*trans*/*cis*)[a]	yield (%), dr (*trans*/*cis*)[a]
1	Me	Me[b]	51 (17:1, **2a**)	32 (>98:2, **3a**)
2	OMe	Me[b]	79 (21:1, **2b**)	21 (>98:2, **3b**)
3	OMe	Et[b]	12 (45:1, **2c**)	46 (>98:2, **3b**)
4	OMe	Me[c]		
5	OMe	$ClCH_2$[d]	94 (25:1, **2d**)	
6	OMe	Cl_2CH[d]		
7	OMe	$ClCH_2$	97 (29:1, **2d**)	
8	OMe	$ClCH_2$[e]	97 (22:1, **2d**)	
9	O*t*Bu	$ClCH_2$	93 (17:1, **2e**)	
10	Ph	$ClCH_2$	84 (25:1, **2f**)	
11	Me	$ClCH_2$	82 (>98:2, **2g**)	
12[f]	OMe	$ClCH_2$	87 (8:1, **2d**)	
13[g]	OMe	$ClCH_2$	78 (11:1, **2d**)	
14[h]	OMe	$ClCH_2$	93 (25:1, **2d**)	
15[i]	OMe	$ClCH_2$	94 (27:1, **2d**)	
16[j]	OMe	$ClCH_2$	52 (28:1, **2d**)	
17[k]	OMe	$ClCH_2$	87 (29:1, **2d**)	

[a]Isolated yield; dr determined by ^{1}H NMR. [b]Conducted in neat acid. [c]With MeOH as cosolvent (1/1). [d]Acid/THF (1/1). [e]$ClCH_2COOH$/THF (3/1). [f]$TEMPO^+BF_4^-$ used as oxidant. [g]Benzoyl peroxide used as oxidant. [h]TEMPO (2.5 equiv) was used. [i]$PhB(OH)_2$ (1.2 equiv) and KF (1.2 equiv) were used. [j]$Pd(OAc)_2$ (1.0 mol %) was used. [k]Reaction time: 1 h.

To further improve selectivity toward the targeted acyloxyarylation, the acid and organic cosolvent were varied. We found that subtle changes in the solvent mixture dramatically influenced the reaction outcome. MeOH was not a suitable cosolvent (Table 1, entry 4), and $Cl_2CHCOOH$ as the acid component also shut down reactivity (Table 1, entry 6). Interestingly, the less acidic chloroacetic acid turned out to be optimal (Table 1, entries 5, 7, and 8), and the best result was achieved upon use of a 2:1 mixture with THF to give indole **2b** with high diastereoselectivity and excellent yield (Table 1, entry 7). The corresponding TEMPO-trapping product was not identified. With the *tert*-butyloxycarbonyl-protected indole, diastereoselectivity slightly dropped to 17:1 (see **2e**) (Table 1, entry 9). With the benzoylated indole as substrate to afford **2f** and the acetylated derivative to provide **2g**, yields slightly dropped (Table 1, entries 10 and 11). Notably, the acetylated indole showed the highest diastereoselectivity. We also tested whether $TEMPOBF_4$ and benzoyl peroxide can be applied as oxidants. However, in both cases, yield and selectivity were lower as compared to the TEMPO-mediated reaction (Table 1, entries 12 and 13). Lowering the amount of boronic acid, KF, TEMPO, or $Pd(OAc)_2$ or shortening the reaction time led to reduced yields (Table 1, entries 14−17).

With optimized conditions in hand (Table 1, entry 7), we examined the substrate scope by studying electronic and steric effects. The indole substrate and the boronic acid component were systematically varied (Scheme 2). As expected, 4-methyl- and 3-methylphenylboronic acid reacted efficiently with **1b**,

Scheme 2. Scope of the Pd-Catalyzed Oxyarylation of 2-Methyl-N-Protected Indoles

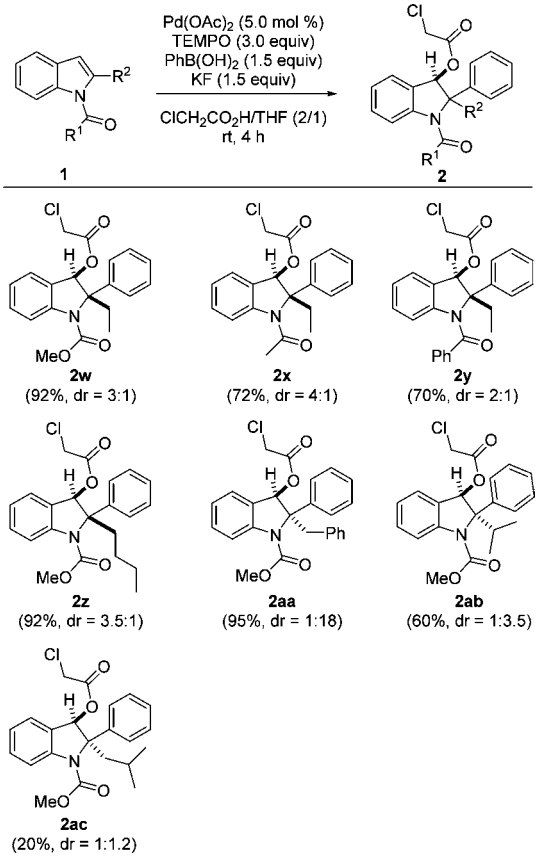


providing the indolines **2h** and **2i** in excellent yields and selectivities. However, the sterically more hindered 2-methylphenylboronic acid afforded **2j** in a significantly lower yield and lower selectivity. The lower yield is a result of increased steric hindrance, and protodeborylation starts to compete. 4-Biphenylboronic acid worked well (**2l**). The more electron-rich 4-methoxyphenylboronic acid gave a low yield (see **2k**), and also the electron-poor *p*-nitro congener provided a moderate result (see **2q**). However, all other *para*-substituted phenylboronic acids bearing electron-withdrawing halide or trifluoromethyl substituents gave the corresponding indolines **2m**−**p** in excellent yields and diastereoselectivities. Electron-donating and -withdrawing substituents at the C5 and C7 position of the indole core were well tolerated, and the oxyarylation products **2r**−**v** were isolated in good to high yields and high selectivities.

DOI: 10.1021/ol503689r
Org. Lett. 2015, 17, 664−667

Next, the effect of the alkyl group at the C2 position of the starting indole on the reaction outcome was investigated. To this end, various 2-alkyl N-protected indoles were prepared (see the Supporting Information) and reacted with phenylboronic acid under optimized conditions (Scheme 3). Changing the alkyl

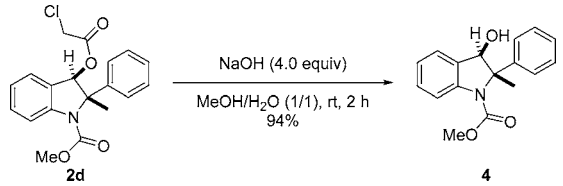
Scheme 3. Scope—Variation of the 2-Alkyl Substituent in the Indole (Major Isomer Drawn)



group from methyl to ethyl resulted in a significant drop of diastereoselectivity, although the yield remained high (**2w**). In order to improve selectivity, the *N*-acetyl- and *N*-benzoyl-protectected 2-ethylindoles were tested. In both cases, the yield slightly dropped and selectivity remained moderate (**2x**, **2y**). The 2-butyl-substituted indole gave a similar yield and selectivity as the ethyl congener (see **2z**). Surprisingly, the 2-benzyl derivative showed reversed selectivity. The *syn*-oxyarylation product **2aa** was formed in excellent yield and selectivity. In addition, the isopropylindole gave the *syn*-product as major isomer, although yield and selectivity dropped (**2ab**). The indole bearing the isobutyl group at the C2 position was not a good substrate in terms of yield and selectivity (**2ac**).

As a first follow-up reaction which further documents the value of our new method, the ester in compound **2d** (major isomer) was hydrolyzed under mild conditions to the corresponding alcohol **4**, which was isolated in 94% yield (Scheme 4). The relative configuration of 3-hydroxyindoline **4** was unambiguously assigned by X-ray analysis (Figure 2). The relative configuration of all other *anti*-products was assigned on the basis of compound **4**. The *syn*-products showed characteristic NMR signatures, and *syn*-configuration of the major isomer of **2aa** was confirmed by X-ray analysis (Figure 3).

Scheme 4. Hydrolysis of 2d



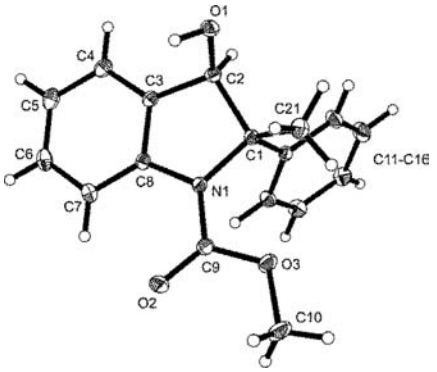


Figure 2. Crystal structure of compound **4** (thermal ellipsoids are shown with 15% probability).

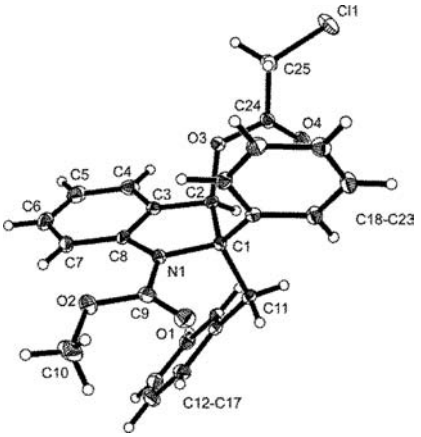
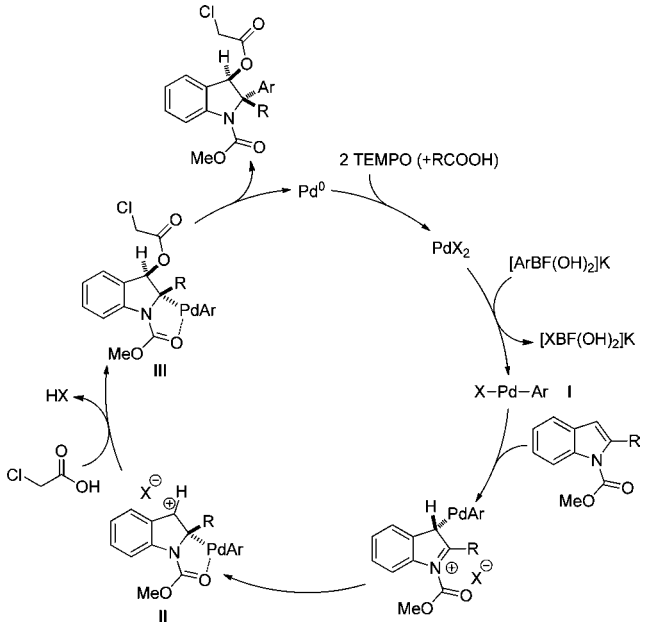


Figure 3. Crystal structure of compound **2aa** (thermal ellipsoids are shown with 15% probability).

To explain the reaction outcome we suggest the following mechanism. First, the boron $[ArBF(OH)_2]K$ species reacts with PdX_2 salt to form an aryl—Pd complex of type **I** (Scheme 5). This palladium species undergoes an electrophilic palladation of the indole at the most activated C3 position. Under the acidic conditions applied, the ArPdX species might be dissociated and react as a cationic ArPd complex. A 1,2-Pd migration then generates intermediate **II**. C3-Palladation followed by metallotropic 1,2-migration in indoles is well investigated, and it was shown that in particular under acidic conditions this migration is faster over direct reductive elimination.[14] The C2-metalated species is likely further stabilized by interaction with the protecting group. The carbeniumion is then stereoselectively *anti*-trapped[15] by chloroacetic acid to generate intermediate **III**. Direct trapping with the bulky TEMPOH as a nucleophile is probably suppressed for steric reasons due to the neighboring fully substituted C-center. Although we cannot fully exclude, we currently assume that the TEMPO trapping product is not an intermediate which further reacts to the indoline. We showed that TEMPO-trapping product **3b** is stable toward acetic acid

DOI: 10.1021/ol503689r
Org. Lett. 2015, 17, 664—667

Scheme 5. Proposed Catalytic Cycle for the Oxyarylation of 2-Substituted Indoles



and does only react very slowly with $ClCH_2CO_2H$ in THF (2/1 mixture) at room temperature, where we observed only 13% conversion to **2d** in 4 h. Reductive elimination in **III** eventually provides the product indoline. Oxidation of Pd[0] with 2 equiv of TEMPO regenerates the Pd[II] species PdX_2 (X^- = AcO^- or TEMPO$^-$ or $ClCH_2COO^-$).

In conclusion, we have developed a highly diastereoselective palladium-catalyzed oxyarylation of 2-substituted indoles with commercially available arylboronic acids and TEMPO as a mild oxidant to give indolines, which are biologically interesting building blocks. Reactions occur at room temperature in a short time (4 h). Hydrolysis of the ester gives the corresponding alcohol, which allows for further functionalization. All reactions shown deliver racemic indolines. We are currently working on an enantioselective version of this type of reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for the products, and supplementary crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: studer@uni-muenster.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Chinese Scholarship Council (stipend to Z.H.) and the Deutsche Forschungsgemeinschaft (DFG).

■ REFERENCES

(1) (a) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519−1522. (b) Pinder, J. L.; Weinreb, S. M. *Tetrahedron Lett.* **2003**, *44*, 4141−4143. (c) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151−161. (d) Sasaki, Y.; Kato, D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 13533−13544.

(2) Pian, J.-X.; He, L.; Du, G.-F.; Guo, H.; Dai, B. *J. Org. Chem.* **2014**, *79*, 5820−5826.

(3) Martínez, A.; Webber, M. J.; Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 9486−9490.

(4) (a) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035−6041. (b) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606−13607.

(5) Han, L.; Liu, C.; Zhang, W.; Shi, X.-X.; You, S.-L. *Chem. Commun.* **2014**, *50*, 1231−1233.

(6) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368−5377.

(7) Yasui, Y.; Kinugawa, T.; Takemoto, Y. *Chem. Commun.* **2009**, 4275−4277.

(8) (a) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886−10887. (b) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235−4238.

(9) (a) Wolfe, J. P. *Synlett* **2008**, 2913−2937. (b) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052−2053. (c) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474−1475. (d) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870−7871. (e) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149−12156. (f) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462−12465. (g) Cahard, E.; Bremeyer, N.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9284−9288.

(10) (a) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494−16495. (b) Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885−8887. (c) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Chem.—Eur. J.* **2012**, *18*, 2931−2937. (d) Hartmann, M.; Li, Y.; Studer, A. *J. Am. Chem. Soc.* **2012**, *134*, 16516−16519. (e) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808−9812. (f) Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 2794−2800. (g) Itoh, T.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 2736−2739. (h) Zhang, Y.-C.; Jiang, F.; Wang, S.-L.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2014**, *79*, 6143−6152.

(11) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 6877−6880.

(12) (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979−1993. (b) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034−5068. (c) Wertz, S.; Studer, A. *Green Chem.* **2013**, *15*, 3116−3134.

(13) For an intermolecular variant on the benzofuran series, see: Hata, K.; He, Z.; Daniliuc, C. G.; Itami, K.; Studer, A. *Chem. Commun.* **2014**, *50*, 463−465.

(14) (a) Focante, F.; Camurati, I.; Nanni, D.; Leardini, R.; Resconi, L. *Organometallics* **2004**, *23*, 5135−5141. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125−3129.

(15) In case of *syn*-trapping, the Pd-aryl group shields the face less efficiently than the R group.

DOI: 10.1021/ol503689r
Org. Lett. 2015, 17, 664−667