ORGANIC LETTERS

2013
Vol. 15, No. 6
1354–1357

Synthesis of Functionalized Spiroindolines *via* Palladium-Catalyzed Methine C–H Arylation

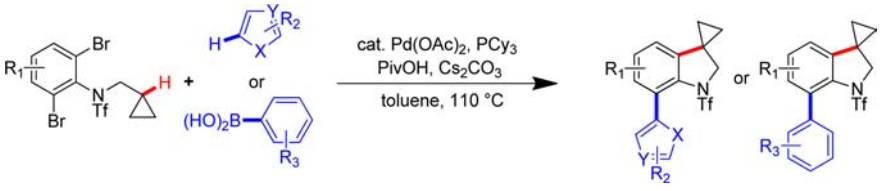
Tanguy Saget, David Perez, and Nicolai Cramer*

Laboratory of Asymmetric Catalysis and Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSA, BCH 4305, CH-1015 Lausanne, Switzerland

nicolai.cramer@epfl.ch

Received February 7, 2013

ABSTRACT



The synthesis of cyclopropyl spiroindolines is described using an intramolecular palladium(0)-catalyzed C–H functionalization of a methine C(sp^3)–H bond. This transformation can be coupled with intermolecular Suzuki couplings or direct arylations of heteroaromatics to access functionalized indoline scaffolds in a single step.

The indoline scaffold is a ubiquitous structural motif found in many alkaloid natural products and bioactive molecules.[1] Cyclopropanes and spirocyclopropanes are design elements in medicinal chemistry due to their increased metabolic stability and their favorable properties to constrain molecular conformation rigidifying structural scaffolds.[2] In particular, compounds with a spirocyclopropyl oxindole motif display interesting biological properties (Figure 1).[3] Furthermore, they serve as substrates for ring-expansion reactions to oxindole alkaloids.[4] However, the corresponding and chemically more stable cyclopropyl spiroindolines remain less explored despite their application potential. By and large, they are synthetically accessed by the reduction of oxindole precursors.

Among others,[5] most methods for indoline synthesis are based on C–N bond formation.[6] Complementary strategies to access indolines by constructing of C–C bonds were reported.[7] In particular, these methods are based on palladium(0)-catalyzed direct functionalization of C(sp^3)–H bonds[8] occurring *via* a concerted metalation–deprotonation

(1) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

(2) (a) Armstrong, P. D.; Cannon, G. J.; Long, J. P. *Nature* **1968**, *220*, 65. (b) Stammer, S. H. *Tetrahedron* **1990**, *46*, 2231. (c) Shimamoto, K.; Ofune, Y. *J. Med. Chem.* **1996**, *39*, 407. (d) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284. (e) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305.

(3) (a) Schwartz, R. E.; Hirsch, C. F.; Springer, J. P.; Pettibone, D. J.; Zink, D. L. *J. Org. Chem.* **1987**, *52*, 3704. (b) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntlan, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109. (c) Pan, G.; Mason, J. M.; Wei, X.; Fher, M. WO 201200103, 2012. (d) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013**, *15*, 42.

(4) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (c) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.

(5) (a) Lui, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447.

(6) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (c) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311. (d) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (e) Neumann, J. J.; Rakshit, S.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (f) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (g) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312. (h) Nguyen, Q.; Sun, K.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *134*, 7262. (i) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944.

(7) (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (b) Nakanishi, M.; Katayev, D.; Besnard, C.; Kundig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (c) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483. (d) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238. (e) Katayev, D.; Nakanishi, M.; Bürgi, T.; Kündig, E. P. *Chem. Sci* **2012**, *3*, 1422. (f) Guyonnet, M.; Baudoin, O. *Org. Lett.* **2012**, *14*, 398. (g) Donets, P. A.; Saget, T.; Cramer, N. *Organometallics* **2012**, *31*, 8040.

10.1021/ol400380y
Published on Web 03/01/2013

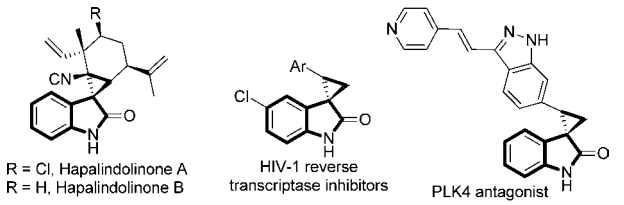


Figure 1. Natural products and pharmaceuticals comprising a spirocyclopropane indoline motif.

(CMD) pathway.[9] Whereas the activation of aromatic, methyl, and methylene C−H bonds recently underwent significant progress,[8,10] tertiary C(sp^3)−H bond functionalizations with palladium catalysis remain largely elusive.[11] The increased steric shielding and the decreased acidity of the methine C−H bond are key factors rendering functionalization reactions by discrete C−Pd intermediates inherently difficult (Figure 2).

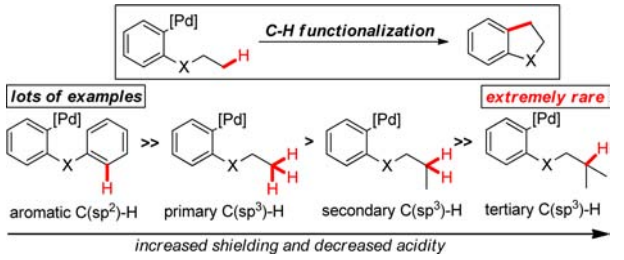
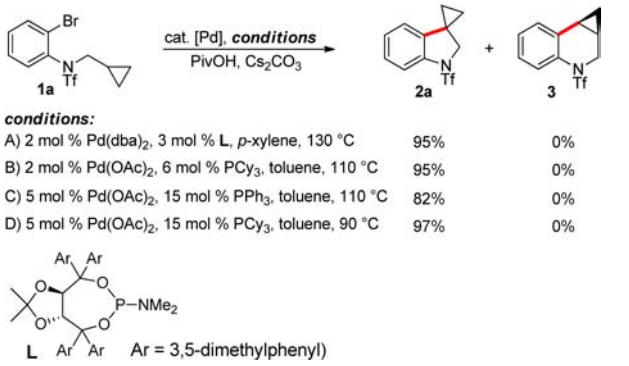


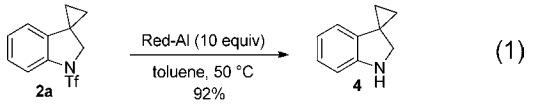
Figure 2. Reactivity trends in palladium-catalyzed C−H functionalization.

During the development of enantioselective C−H functionalizations,[12] we discovered a very rare Pd-catalyzed methine C−H arylation giving spiroindoline **2a** rather than the expected product **3** (Scheme 1).[13] Although formation of **2a** is favored by a smaller palladacycle (six-membered over seven-membered), we were surprised that methine C−H activation dominates methylene activation completely. With a range of conditions and as low as a 2 mol % catalyst loading, the reaction provides reliably excellent yields of **2a** (Scheme 1). The enhanced reactivity can be attributed to the enhanced s-character and acidity of the cyclopropane C−H bonds[14] rendering them attractive for functionalizations.[15]

Scheme 1. Selective Methine C−H Functionalization for the Synthesis of Spiroindoline **2a**



We then explored the potential and generality of this activation (Scheme 2). Common electron-donating and -withdrawing groups are well tolerated in the *ortho*-, *meta*-, and *para*-position. Aryl chlorides can be employed as well, though slightly higher reaction temperatures are required (**2a**). The *N*-triflyl group of the indolines is readily removed with Red-Al (eq 1). Alternatively, the process works as well for substrates with a carbamate group, e.g. **1n** with a methyl carbamate.



However, with the current set of conditions, the unsubstituted oxygen analog **1p** did not undergo cyclization. In contrast, the carbon analog **1o** with a malonyl group gives rise to the congested dihydroindene **2o**. More sterically demanding substituted cyclopropanes are also smoothly activated and cyclized. Noteworthy, the stereochemistry of both *cis*- and *trans*-cyclopropanes is completely transferred to the indolines. As shown for **2l** and **2m**, this reaction characteristic allows substituted spiroindolines to be prepared in a stereodefined and programmed manner.

2,6-Dibromoaniline **1k** was not a competent substrate, and most of the starting material was recovered after the reaction. Presumably, after indoline formation, oxidative

(8) For reviews about metal-catalyzed C(sp^3)−H functionalizations, see: (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack- Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (b) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

(9) (a) Garcia-Cuadrado, D.; Braga, A.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(10) For selected reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(11) For two isolated examples with Pd-catalysis, see: (a) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. (b) Ren, Z.; Mo, F.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 16991.

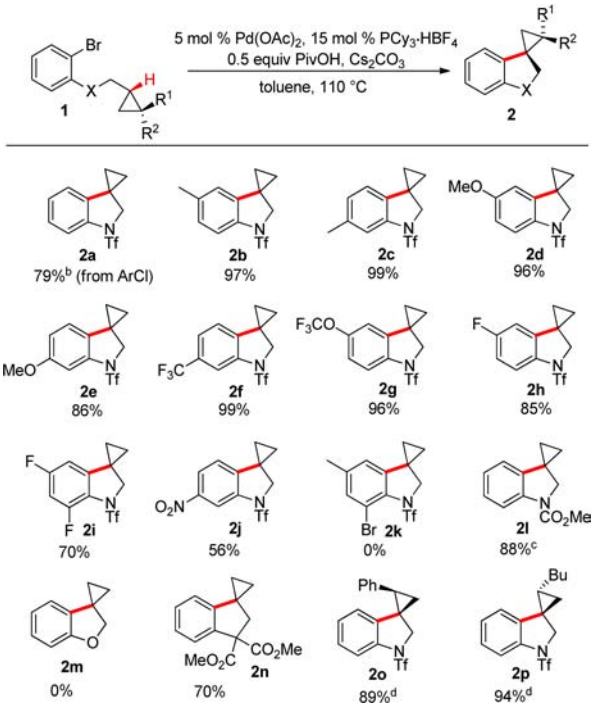
(12) (a) Albicker, M. R.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 9139. (b) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320. (c) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11098. (d) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504. (e) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636.

(13) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842.

(14) (a) de Meijere, A. *Angew. Chem., Int. Ed.* **1979**, *18*, 809. (b) Exner, K.; Schleyer, P. V. R. *J. Phys. Chem. A* **2001**, *105*, 3407.

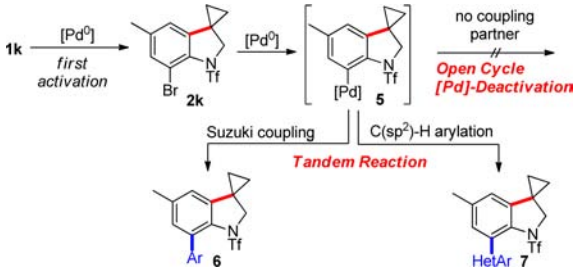
(15) (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (c) Kubota, A.; Sanford, M. S. *Synthesis* **2011**, 2579.

Scheme 2. Scope of the Indoline **2** by Methine C−H Arylation[a]

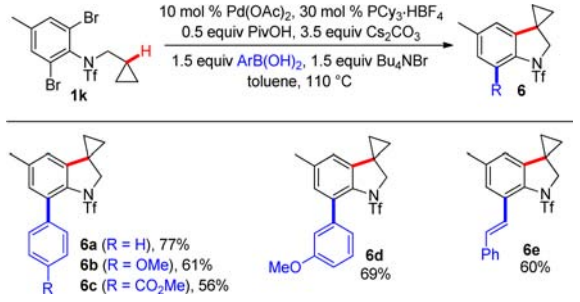


[a] Reaction conditions: **1** (0.10 mmol), PivOH (50.0 μmol), Cs_2CO_3 (0.20 mmol), $Pd(OAc)_2$ (5.00 μmol), $PCy_3 \cdot HBF_4$ (15.0 μmol), 0.30 M in toluene at 110 °C for 12 h; yield of isolated product **2**. [b] From Ar−Cl instead of Ar−Br, in *p*-xylene at 130 °C. [c] In mesitylene at 130 °C. [d] With PPh_3 (15.0 μmol).

Scheme 3. Tandem Strategy to Access More Complex Indolines



Scheme 4. Domino Methine C−H Arylation and Intermolecular Suzuki Coupling[a]



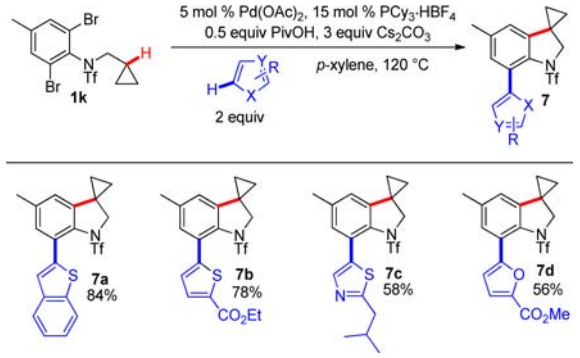
[a] Reaction conditions: **1** (0.10 mmol), PivOH (50.0 μmol), Cs_2CO_3 (0.35 mmol), Bu_4NBr (0.15 mmol), $Pd(OAc)_2$ (10.0 μmol), $PCy_3 \bullet HBF_4$ (30.0 μmol), 0.10 M in toluene at 110 °C for 12 h; isolated yields.

addition of the remaining aryl bromide irreversibly forms aryl Pd(II) intermediate **5** hence sequestering the palladium catalyst (Scheme 3).[16] This results in an open catalytic cycle, deteriorating over time all of the palladium catalyst. We reasoned that a suitable coupling partner for **5** would allow the catalytic cycle to be closed. In this respect, one could exploit the dual functionality of **1k** to induce versatile complexity in tandem processes. We chose Suzuki cross-couplings and intermolecular C−H functionalizations of heteroaromatics as two promising reactions. Both are known to proceed under very similar conditions as required for the methine functionalization.[17]

At first, we tried to combine our methine C−H arylation with Suzuki couplings (Scheme 4). The addition of Bu_4NBr[18] was critical for the reaction success. Both electron-rich and -poor arylboronic acids react well and provide arylated indolines **6a**−**6d**. Vinylated product **6e** is obtained in good yield with (*E*)-styrylboronic acid as the coupling partner. No trace of product arising from a double Suzuki coupling was observed, suggesting that the intramolecular C−H functionalization is faster than the intermolecular transmetalation.

Replacing the stoichiometric aryl boronic acids with cheap and widely available heteroarenes, we aimed for an intramolecular methine $C(sp^3)$−H/intermolecular arene $C(sp^2)$−H functionalization tandem.[19] As the utilized

Scheme 5. Domino Methine C−H and Intermolecular C−H Arylation[a]



[a] Reaction conditions: **1** (0.10 mmol), PivOH (50.0 μmol), Cs_2CO_3 (0.35 mmol), HetAr (0.20 mmol), $Pd(OAc)_2$ (5.00 μmol), $PCy_3 \cdot HBF_4$ (15.0 μmol), 0.30 M in *p*-xylene at 120 °C for 12 h; isolated yields.

(16) (a) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679. (b) Leclerc, J.-P.; André, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711.

(17) (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(18) Nicolaus, N.; Franke, P. T.; Lautens, M. *Org. Lett.* **2011**, *13*, 4236.

conditions are similar to Fagnou's general protocol for the arylation of heteroaromatics,[14b] we first evaluated thiophenes for this tandem process (Scheme 5). The reaction afforded indolines **7a** and **7b** in high yields. Thiazoles and furanes are also competent coupling partners providing indolines **7c** and **7d** in a regioselective manner.

In conclusion, we have reported an intramolecular palladium(0)-catalyzed methine C−H arylation which provided a convenient access to conformationally constrained spiroindolines. The employed reaction conditions are well suited for consecutive Suzuki couplings or intermolecular C−H arylations to give well functionalized indoline scaffolds.

(19) For a related tandem sequence, see: Pierre, C.; Baudoin, O. *Org. Lett.* **2011**, *13*, 1816.

Supporting Information Available. Experimental procedures, analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgment. This work is supported by the European Research Council under the European Community's Seventh Framework Program (FP7 2007−2013)/ ERC Grant Agreement No. 257891 and the EPFL.

The authors declare no competing financial interest.