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Silver-Promoted, Palladium-Catalyzed Direct Arylation of Cyclopropanes: Facile Access to Spiro 3,3′-Cyclopropyl Oxindoles

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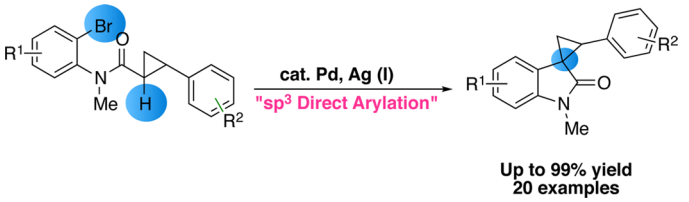
ABSTRACT



The Pd-catalyzed, Ag(I)-mediated intramolecular direct arylation of cyclopropane C−H bonds is described. Various spiro 3,3′-cyclopropyl oxindoles can be obtained in good to excellent yields from easily accessible 2-bromoanilides. The kinetic isotope effect was determined and epimerization studies were conducted, suggesting that the formation of a putative Pd-enolate is not operative and that the reaction proceeds via a C−H arylation pathway.

The spiro 3,3′-cyclopropyl oxindole core is a recurring structural motif present in several agrochemically and pharmaceutically active compounds,[1] including herbicides,[2] inhibitors, and antagonists for treating cancer,[3] mood disorders,[4] and HIV.[5] In addition, spiro 3,3′-cyclopropyl oxindoles have demonstrated synthetic utility as intermediates toward accessing relevant oxindole alkaloids.[6] Given the biological and synthetic potential of these compounds, it is not surprising that the number of reports regarding spirooxindole synthesis has increased over the past decade, suggesting a demand for novel and more efficient routes for preparing these architectures.[7]

Common routes to obtain spiro 3,3′-cyclopropyl oxindoles involve functionalization of enolizable 2-oxindoles via alkylation strategies such as Michael-initiated ring closure (Scheme 1).[8] 3-Alkylidene oxindoles can also be functionlized via the addition of sulfur[9] or phosphorus ylides.[10] Other disclosed methods involve Rh(II)-catalyzed decomposition of carbene precursors such as diazo species and subsequent formal [2 + 1] cycloaddition with alkenes to form cyclopropanes.[11,12] Some drawbacks to these

(1) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem.—Eur. J.* **2011**, *17*, 2842.
(2) Condon, M.; Karp, G. EP 0 549 892 A1, 1993.
(3) Wurster, J. WO 2007/008664 A1, 2007.
(4) (a) Atkinson, B.; Beattie, D.; Culshaw, A.; Dale, J.; Devereux, N.; McKenna, J. WO 2011/092293 A2, 2011. (b) Schmidt, C.; Sobolov-Jaynes, S. EP 1 186 318 A2, 2002.
(5) (a) He, Y.; Jiang, T.; Kuhen, K.; Ellis, D.; Wu, B.; Wu, T.; Bursulaya, B. WO 2004/037247 A1, 2004. (b) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105. (c) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109.
(6) (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694. (c) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 1498. (d) Lerchner, A.; Carreira, E. M. *Chem.—Eur. J.* **2006**, *12*, 8208. (e) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (f) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175.
(7) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165.
(8) (a) Stevens, F. C.; Bloomquist, W. E.; Borel, A. G.; Cohen, M. L.; Droste, C. A.; Heiman, M. L.; Kriauciunas, A.; Sall, D. J.; Tinsley, F. C.; Jesudason, C. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6270. (b) Jaegli, S.; Vors, J.-P.; Neuville, L.; Zhu, J. *Tetrahedron* **2010**, *66*, 8911. (c) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem.—Eur. J.* **2011**, *17*, 2842.
(9) Forrest, G.; Hamilton, H. WO 2004/037820 A1, 2004.
(10) Eberle, M. K.; Kahle, G. G.; Shapiro, M. J. *J. Org. Chem.* **1982**, *47*, 2210.
(11) He, Y.; Jiang, T.; Kuhen, K.; Ellis, D.; Wu, B.; Wu, T.; Bursulaya, B.WO 2004/037247 A1, 2004.

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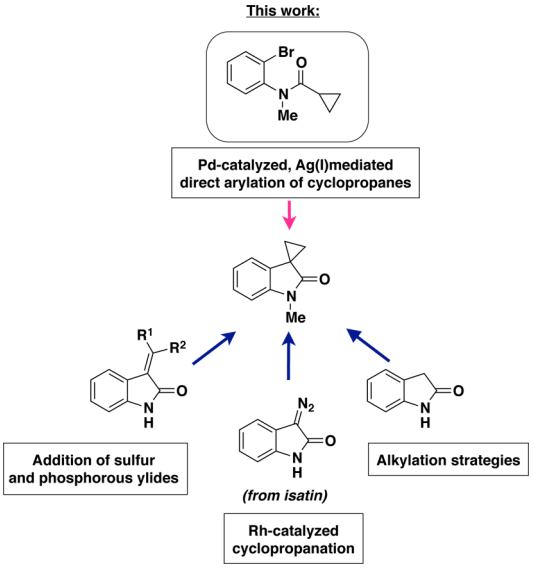
methods involve hazardous reagents such as diazo compounds and extra synthetic steps to access the required precursors. Alternatively, an intramolecular arylation strategy involving a direct functionalization of α-(sp^3)-H from cyclopropyl anilides would permit exploitation of readily accessible, easier to handle starting materials, thus, circumventing the use of the above-mentioned reagents.

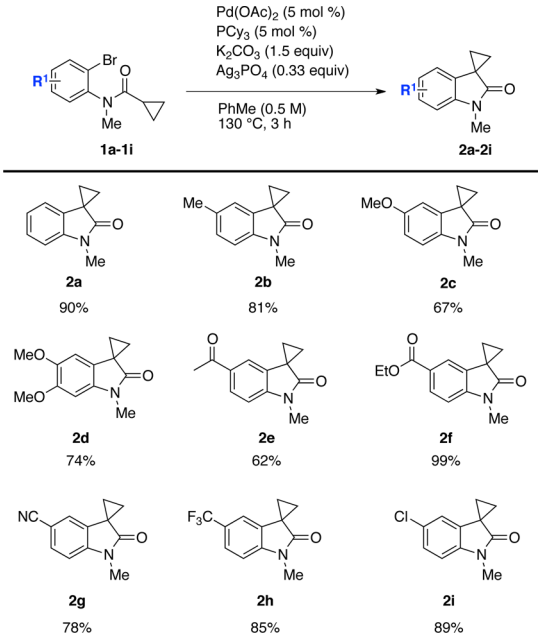
Scheme 1. Routes To Access Spiro 3,3′-Cyclopropyl Oxindoles



Progress within the field of direct C−H functionalization has contributed new synthetic pathways, leading to more streamlined chemical syntheses.[13] Earlier work by our group has focused on the direct functionalization of various arenes, providing facile access to relevant heterocyclic and nonheterocyclic compounds.[14] For example, we reported the direct benzylic arylation of *N*-iminopyridinium ylides with aryl chlorides.[15] Considering the prevalence of C(sp^3)−H bonds, we directed our interests to targeting other direct functionalizations involving these bonds.[16]

Cyclopropanes have been established as key alkene isosteres in various pharmacologically active compounds. They are also present in natural products and have been applied as valuable synthetic precursors en route to the

Scheme 2. Effect of Aromatic Substitution[a]



[a] Reactions were performed on 0.5 mmol scale. Isolated yields.

preparation of numerous other relevant compounds.[17] Cognizant of this, our group has been actively involved in developing novel cyclopropanation methodologies.[18] With this interest, in conjunction with our experience in the direct arylation of C(sp^3)−H centers, we turned our attention to developing methods for functionalizing cyclopropane C−H bonds. The potential for direct functionalization methods for cyclopropanes remains largely untapped, despite the pseudo sp^2 nature of these bonds and their pK_a, which is highly suited for insertion.[19] Herein, we disclose a novel intramolecular Pd-catalyzed arylation of 2-bromoanilides, producing spiro 3,3′-cyclopropyl oxindoles in the presence of Ag(I) salts. Additionally, mechanistic studies were performed to eliminate the possibility of the arylation proceeding via enolate pathways, supporting a direct arylation scaffold.

Our initial optimization of the arylation of 2-bromoanilide **1a** revealed that $Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), and K_2CO_3 (1.5 equiv) were optimal. Only 1 equiv of cationic Ag was required, and this could also be delivered using Ag_3PO_4.[20,21] Aryl bromides proved optimal, as chloro

(12) Kumari, G.; Nutan; Modi, M.; Gupta, S. K.; Singh, R. K. *Eur. J. Med. Chem.* **2011**, *46*, 1181.

(13) For selected reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Daugulis, O.; Do, H.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

(14) (a) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412. (b) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010**, *49*, 1115. (c) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (d) Mousseau, J. J.; Bull, J. A.; Ladd, C. L.; Fortier, A.; Sustac Roman, D.; Charette, A. B. *J. Org. Chem.* **2011**, *76*, 8243.

(15) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641.

(16) For selected reviews, see: (a) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.

(17) (a) Lebel, H.; Marcoux, J.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.

(18) For recent examples: (a) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972. (b) Beaulieu, L. P.; Zimmer, L. E.; Gagnon, A.; Charette, A. B. *Chem.—Eur. J.* **2012**, *18*, 14784. (c) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970. (d) Goudreau, S. R.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15633.

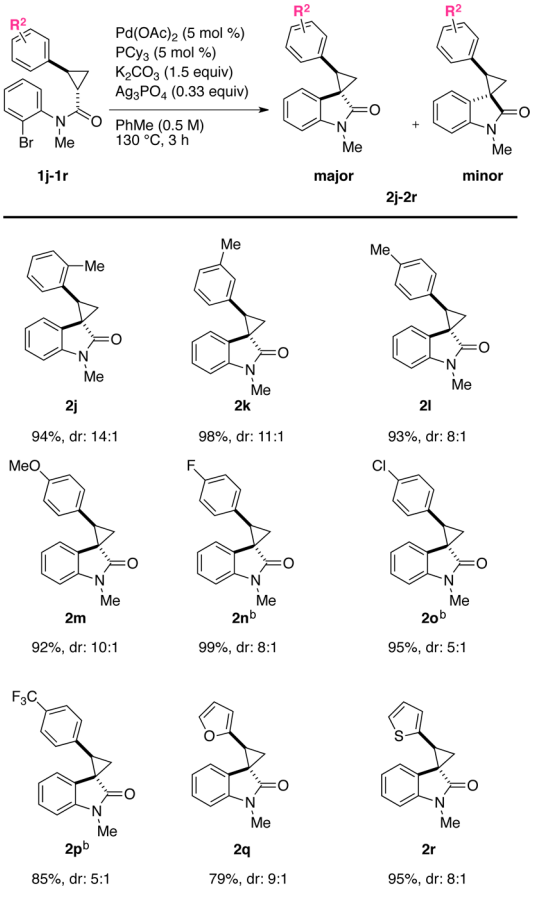
(19) (a) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J. Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (b) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. (c) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (d) Kubota, A.; Sanford, M. S. *Synthesis* **2011**, 2579. (e) Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (f) Ackermann, A.; Kozhushkov, S. I.; Yufit, D. S. *Chem.—Eur. J.* **2012**, *18*, 12068.

(20) The reaction was both hindered by the excess and lack of 1.0 equiv of cationic Ag.

derivatives gave no product and the more costly iodo analogues furnished modest yields.[22] A catalyst-to-ligand ratio of 1:1 was identified, and good yields (80%) could still be achieved upon decreasing the catalyst and ligand loading from 5 to 2.5 mol %, although 5 mol % was optimal for maximum yield. Finally, we found the process to be rapid, as full conversion required only 3 h.

Using optimized conditions, we explored the effect of substitution on the aryl ring containing the halide (Scheme 2). A range of functional groups were tolerated. Electron-donating substituents furnished the desired products in good yield (**2b**–**2d**). Improved results were noted with substrates bearing electron-withdrawing groups (**2e**–**2i**), presumably due to the increased ease of oxidative insertion to the aryl halide bond. Notably, chloro-substituted **2i** was also viable, allowing for further potential structural modifications.

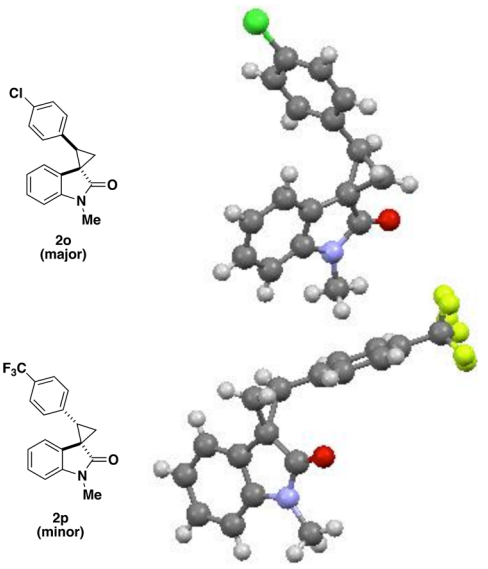
Scheme 3. Effect of Cyclopropane Substitution[a]



[a] Reactions were performed on 0.5 mmol scale. Isolated yields. Major diastereomer is shown. [b] Diastereomers were separated.

Our next step was to investigate the effect of aromatic substitution on the cyclopropane unit (Scheme 3). *Ortho*- and *meta*-substitution provided the spiro 3,3′-cyclopropyl oxindole in high yield (**2j**–**2k**), suggesting that steric hindrance does not negatively impact the process. In addition, *para*-substituted electron-donating (**2l**–**2m**) and electron-withdrawing substrates (**2n**–**2p**) were both tolerated, producing excellent yields, although electron-donating groups gave slightly better diastereoselectivities. Heterocyclic substitution (**2q**–**2r**) could also be achieved. The configuration for both diastereomers was confirmed via X-ray crystallography (Scheme 4).

Scheme 4. X-ray Structures of Diastereomers

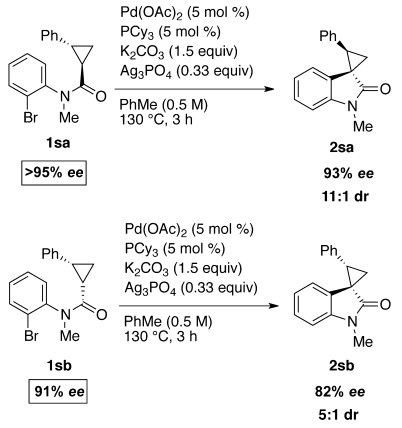


To probe whether the cyclization proceeds via an enolate-like mechanism or direct arylation scaffold, we performed the reaction using enantioenriched **1sa** and **1sb**.[23] In both cases, the reaction proceeded with little erosion of % ee (Scheme 5), supporting the possibility of a direct arylation mechanism.[24] We also determined the KIE to be 3.9, identifying C–H cleavage as the rate-determining step, and providing further evidence against enolate arylation where oxidative insertion is typically the rate-limiting step.[25,26]

We next considered the role of CO_3^{2-}, OAc^-, and Ag(I) in the catalytic cycle. Unlike our previous accounts, OAc^- is not required; $PdBr_2$ still gave **2a** in 81% yield.[27] CO_3^{2-} could then function as an external base, facilitating a

(21) See Supporting Information for full optimization.
(22) 48% yield was obtained for the aryl iodide substrate.
(23) *Trans-rac* **1sa** and **1sb** gave isolated yields of 90% and 93% respectively and diastereoselectivities of 6:1 and 1:5 respectively.
(24) See Supporting Information for more details.
(25) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. For a review on Pd-α arylation methods, see: Bellini, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.
(26) (a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066. (b) Garcia-Cuadrado, D.; Braga, A.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Sun, H. Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L. C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.
(27) Mousseau, J. J.; Vallée, F.; Lorion, M.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 14412.
(28) No conversion occurs without both Ag(I) and base. This differs from literature examples where modest yields are still achieved without Ag(I). For examples, see: (a) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Bryan, C.; Lautens, M. *Org. Lett.* **2008**, *10*, 4633.

Scheme 5. Epimerization Studies[a]



[a] Enantiomeric excess determined via SFC. **1sb** was inseparable via SFC; % ee determined from its carboxylic acid precursor.

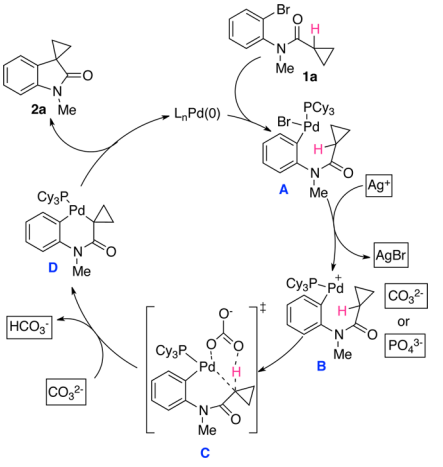
concerted metalation−deprotonation pathway. Ag(I) salts are known halide sequestration agents.[28] However, Ag(I) can also mediate halide abstraction from Pd-complexes, generating reactive cationic Pd-species with counterions such as CO_3^{2-} and PO_4^{3-}.[29]

Based on these findings, we propose the following mechanism (Scheme 6). Oxidative addition of Pd(0) into the Ar−Br bond of **1a** generates intermediate **A**. Ag(I) abstracts bromide, forming cationic Pd-species **B**. CO_3^{2-} serves as the external base, resulting in irreversible deprotonation to form six-membered palladacycle **D**, which undergoes reductive elimination to regenerate Pd(0) and yield **2a**.

In conclusion, we report a novel example of the direct arylation of cyclopropanes via a Pd-catalyzed, Ag-mediated process. This methodology provides an efficient process to access valuable spiro 3,3′-cyclopropyl oxindoles in excellent yields and enhances the collection of C−H

(29) (a) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2010**, *65*, 5342.

Scheme 6. Proposed Mechanistic Pathway



activation reactions targeting cyclopropanes. Work is currently underway to determine the full extent of the reaction and to deepen our mechanistic understanding.

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Supporting Information Available. Experimental procedures, sample spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.