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# Intramolecular Palladium-Catalyzed Direct Arylation of Alkenyl Triflates

**Ana C. F. Cruz,[†] Neil D. Miller,[‡] and Michael C. Willis*[,§]**

*Department of Chemistry, University of Bath, Bath, BA2 7AY, U.K., Department of Chemistry, Chemical Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K., and GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, U.K.*

*michael.willis@chem.ox.ac.uk*

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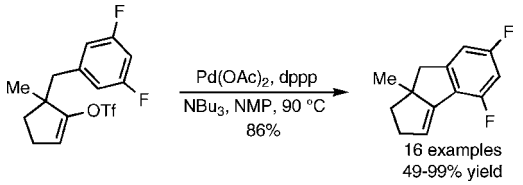
## ABSTRACT




**A catalyst generated from $Pd(OAc)_2$ and dppp is effective for the direct intramolecular arylation of alkenyl triflates. Conjugated alkene–arene-containing carbocycles are produced in good yield. The process tolerates a variety of aryl substituents as well a simple heteroaryl groups. Electron-deficient aryl rings deliver faster reactions.**

Palladium-catalyzed cross-coupling reactions are some of the most reliable and widely used transformations available to synthetic chemists and, in particular, represent a standard method for biaryl synthesis.[1] Traditional cross-coupling reactions rely on the union of two activated aryl units, usually an aryl halide together with an aryl organometallic. However, recent reports have described how one of the two activating groups, usually the organometallic component, can be replaced with a simple C−H unit of an arene.[2,3] These direct functionalization methods offer significant advantages, not least the far simpler preparation of the C−H-containing arene.[4] Although originally limited to the use of electron-rich arenes and heteroarenes,[5] more recent reports have shown that electron-poor[6] and neutral[7] arenes can also be effective in direct arylation reactions.[8] Activated alkenes, in the form of alkenyl halides (or pseudohalides), are also used extensively in cross-coupling chemistry,[1] although to date, reports of their use in direct functionalization methods are limited.[9] Given the diverse range of transformations available with alkene-containing compounds, the direct arylation of activated alkenes would provide an attractive entry to these synthetically valuable products. In this Letter, we detail an

[†] University of Bath.
[‡] GlaxoSmithKline.
[§] University of Oxford.

(1) General reviews: (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: New York, 2002. (b) *Metal-Catalysed Cross-Coupling Reactions*; de Meijere, A., Deidrich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(2) For general reviews on C−H functionalization, see: (a) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(3) For recent examples of Pd-catalyzed cross-coupling processes in which both activating groups are absent, see: (a) Stuart, D. R.; Fagnou, K, *Science* **2007**, *316*, 1172. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

(4) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2005**, 1253.

(5) Selected examples: (a) Ames, D. E.; Opalko, A. *Synthesis* **1983**, 234. (b) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2. (c) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.: Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. (d) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979.

(6) (a) LaFrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) LaFrance, M.; Shore, D.; Fagnou *Org. Lett.* **2006**, *8*, 5097.

(7) (a) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) LaFrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

(8) Directed arylation reactions have been achieved with a variety of electronically varied arenes. For a discussion of directed arylation systems, as well as the use of alternative metal catalysts, see ref 4a.

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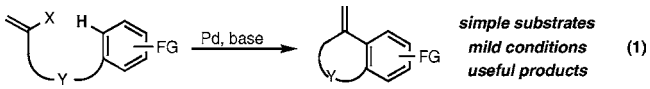
efficient intramolecular direct arylation of alkenyl triflates. The process employs readily available substrates, uses relatively low loadings of a palladium catalyst, and delivers synthetically useful alkene-containing carbocyclic products (eq 1).

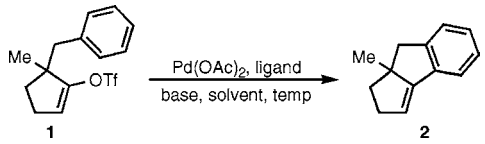



(1)

We focused reaction development on the cyclization of the triflate **1** (Table 1).[10] Our choice of reaction conditions was guided by a related study we had undertaken[11] and involved treatment of triflate **1** with $Pd(OAc)_2$, $PPh_3$, and $NBu_3$ in DMF. We were pleased to observe quantitative conversion to the desired product when the reaction was performed at 60 °C for 24 h using a 5 mol % loading of palladium (entry 1). When the catalyst loading was reduced to 3 mol %, the conversion fell to 82% (entry 2). A number of alternative phosphine ligands were evaluated using this loading, and although several, including both mono- and diphosphines, were successful, the use of dppp proved to be most effective (entries 3−6). The high reaction efficiency combined with the low cost of dppp prompted us to further explore this system. Alternative bases were explored; although $NEt_3$ and Hünigs base delivered product, they were less effective than $NBu_3$ (entries 7 and 8). The strong inorganic base, NaO$^t$Bu, delivered the ketone corresponding to triflate **1** as the only product, while the weaker $Cs_2CO_3$ was poorly effective (entries 9 and 10). Finally, the use of nonpolar or protic solvents proved to be ineffective; however, the use of the polar nonprotic solvent NMP provided quantitative conversion to product after only 8 h reaction (entries 11−13). These last seven experiments were all performed using 2 mol % of palladium.

With efficient conditions for the conversion of **1** into **2** established, we explored the scope of the method (Table 2).

**Table 1.** Reaction Development for the Conversion **1** → **2**[a]

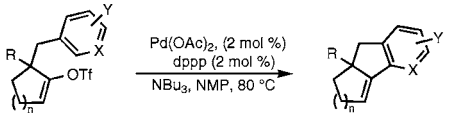


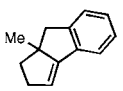
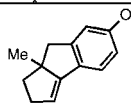
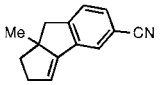
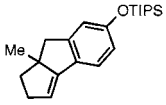
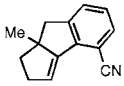
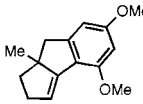
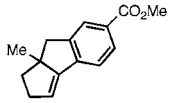
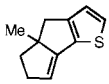
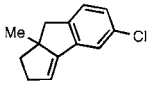
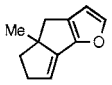
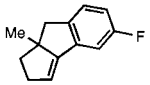
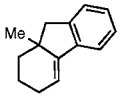
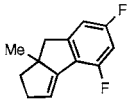
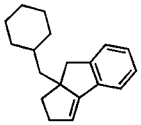
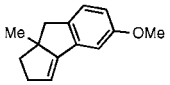
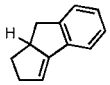

**1** **2**

| entry | ligand | catalyst | base | solvent | time (h) | conversion[b] |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | 5 mol % | $NBu_3$ | DMF | 24 | 99% |
| 2 | $PPh_3$ | 3 mol % | $NBu_3$ | DMF | 48 | 82% |
| 3 | dppb | 3 mol % | $NBu_3$ | DMF | 48 | 90% |
| 4 | dppp | 3 mol % | $NBu_3$ | DMF | 48 | 99% |
| 5 | DPEphos | 3 mol % | $NBu_3$ | DMF | 48 | 89% |
| 6 | $PCy_3$ | 3 mol % | $NBu_3$ | DMF | 48 | 88% |
| 7[c] | dppp | 2 mol % | $NEt_3$ | DMF | 30 | 81% |
| 8[c] | dppp | 2 mol % | N$^i$Pr$_2$Et | DMF | 24 | 16% |
| 9[c] | dppp | 2 mol % | NaO$^t$Bu | DMF | 2 | 0%[d] |
| 10[c] | dppp | 2 mol % | $Cs_2CO_3$ | DMF | 25 | 21% |
| 11[c] | dppp | 2 mol % | $NBu_3$ | PhMe | 48 | 4% |
| 12[c] | dppp | 2 mol % | $NBu_3$ | $^t$BuOH | 24 | 14% |
| 13[c] | dppp | 2 mol % | $NBu_3$ | NMP | 8 | 99% |

[a] Conditions: triflate **1** (1.0 equiv), base (3.0 equiv), 60 °C. [b] Measured using $^1$H NMR. [c] At 80 °C. [d] Ketone corresponding to only product **1**, 99%.

**Table 2.** Scope of the Intramolecular Palladium-Catalyzed Direct Functionalization of Alkenyl Triflates[a]




| entry | product | time/yield | entry | product | time/yield |
|---|---|---|---|---|---|
| 1 |  | 8 h<br>69% | 9 |  | 24 h<br>86%[d,e] |
| 2 |  | 6 h<br>86% | 10 |  | 24 h<br>70%[d,f] |
| 3 |  | 6 h<br>85%[c] | 11 |  | 24 h<br>87%[d] |
| 4 |  | 6 h<br>80% | 12 |  | 6 h<br>90%[d] |
| 5 |  | 8 h<br>80% | 13 |  | 24 h<br>51% |
| 6 |  | 8 h<br>81% | 14 |  | 60 h<br>85% |
| 7 |  | 6 h<br>86% | 15 |  | 6 h<br>93% |
| 8 |  | 24 h<br>86%[d] | 16 |  | 8 h<br>84% |

[a] Conditions: triflate **1** (1.0 equiv), base (3.0 equiv), 80 °C. [b] Isolated yields. [c] A 1.7:1 mixture of regioisomers; major shown. [d] With 5 mol % of Pd and dppp employed. [e] A 2.5:1 mixture of regioisomers; major shown. [f] A 10:1 mixture of regioisomers; major shown.

All of the cyclization substrates were readily prepared by alkylation of the parent ketone followed by triflate formation.[10] Although the conversion for triflate **1** to carbocycle **2** was excellent, the isolated yield was poor due to volatility (entry 1). Adding substituents to the aryl ring remedied this

(9) (a) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569; *Angew. Chem., Int. Ed.* **2002**, *41*, 2227 (erratum). (b) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675. (c) Fishwick, C. W. G.; Grigg, R.; Sridharan, V.; Virica, J. *Tetrahedron* **2003**, *59*, 4451. (d) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627.

(10) See Supporting Information for details.

(11) (a) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. *Angew. Chem., Int. Ed.* **2004**, *42*, 1249. (b) Willis, M. C.; Claverie, C. K.; Mahon, M. F. *Chem. Commun.* **2002**, 832.

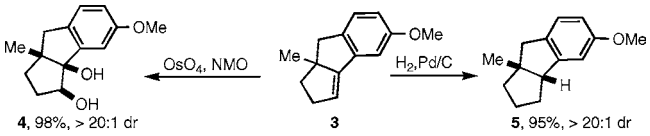
problem and also allowed the effect of electronically different groups to be explored.

Both resonance and inductively electron-withdrawing substituents resulted in smooth conversion to the desired products (entries 2−7). The introduction of electron-donating substituents resulted in significantly slower reactions, and in order to achieve good yields, in reasonable reaction times, the catalyst loading was increased to 5 mol %. Using these conditions, both methoxy and silyloxy substituents were tolerated well (entries 8−11). The use of the *O*-TIPS substrate demonstrated that good levels of regioselection (10:1) could be achieved by steric control (entries 9 and 10). The aryl group could also be exchanged for simple heteroaryl variants without adversely effecting the process and provides a further class of functionalized products (entries 12 and 13). Entries 14, 15, and 16 demonstrate that the starting substrates are not limited to cyclopentene systems, that the second alkyl substituent can be varied from methyl, and finally, that the presence of a second alkyl substituent is not necessary to achieve efficient cyclization.

A number of mechanistic models have been proposed to rationalize the efficiencies and selectivities observed in direct functionalization biaryl syntheses.[12] An electrophilic aromatic substitution ($S_EAr$) mechanism is most often invoked for electron-rich substrates,[13] and either $\sigma$-bond metathesis[14] or proton-abstraction pathways[15] are attributed to the more recently reported electron-poor substrates. The rate differences we observed with variation of the substituents in the substrates used in Table 2 seem to rule out a $S_EAr$ mechanism in the present system, as the electron-rich substrates displayed consistently slower rates. We also compared the reactivity of unfunctionalized triflate **1** and its pentadeuterated counterpart and measured an intermolecular kinetic isotope effect $k_H/k_D = 5.0$ (80 °C).[10] Although we have not performed a detailed mechanistic study, these results are consistent with either $\sigma$-bond metathesis or proton-abstraction mechanisms.

One of the drivers for this study was that an efficient route to synthetically useful alkene-containing products would be achieved. The reactions shown in Scheme 1 serve to demonstrate the potential utility of the products; both dihydroxylation and hydrogenation of alkene **3** proceeded efficiently and with high levels of diastereocontrol to deliver diol **4** and bicyclic alkane **5**, respectively. The latter transformation demonstrates that the net result of an alkenyl triflate direct arylation−alkene hydrogenation combination is the formation of an alkyl-substituted arene, a sequence equivalent to direct alkyl functionalization of the arene.

**Scheme 1.** Functionalization of alkene **3**




**4**, 98%, > 20:1 dr **3** **5**, 95%, > 20:1 dr

In conclusion, we have demonstrated that the Pd-catalyzed direct functionalization of alkenyl triflates represents an efficient route to a variety of conjugated bicyclic alkene−arene systems. The process tolerates a variety of electronically varied aryl substituents and simple heteroarenes. A full mechanistic study of these transformations is underway and will be reported in due course.

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**Noted Added after ASAP Publication.** There were errors in the structures in the Abstract graphic and entries 5 and 6 of Table 2 in the version published ASAP September 13, 2007; the revised version was published ASAP September 18, 2007.

**Supporting Information Available:** Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, Ó. *Synlett* **2003**, 58. See also ref 4a.

(13) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.

(14) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

(15) (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (b) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. See also ref 7c.