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Palladium-Catalyzed Intramolecular *O*-Arylation of Enolates: Application to Benzo[*b*]furan Synthesis

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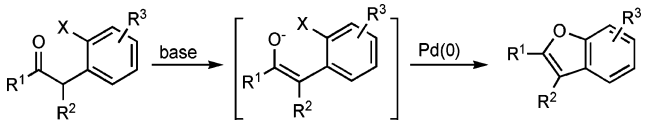
ABSTRACT



A catalyst generated from $Pd_2(dba)_3$ and the ligand DPEphos effects intramolecular C–O bond formation between enolates and aryl halides in the conversion of 1-(2-haloaryl)ketones directly into the corresponding benzofurans. Both cyclic and acyclic ketones are efficient substrates. Thio ketones can also be employed allowing the preparation of the corresponding benzothiophenes.

Palladium-catalyzed C−N and C−O arylation reactions have had a significant impact upon organic synthesis and are now reliable and well-used processes.[1] Intramolecular variants of these reactions, leading to the synthesis of a variety of heterocyclic structures, have also received considerable attention.[1] More recently, the use of palladium catalysis to mediate carbonyl α-arylation reactions (*C*-arylation) has been developed as a useful synthetic procedure and methods for the arylation of ketones,[2] esters,[3,4] amides,[5] and malonates[6] have all been reported. In this paper, we demonstrate that palladium-catalyzed intramolecular *O*-arylation of enolates is an efficient process and can be used to prepare a variety of substituted benzofurans.[7]

The benzo[*b*]furan ring system features in many naturally occurring and designed molecules responsible for a diverse range of biological responses. Accordingly, there exists a wide selection of methods for the synthesis of this important structural motif,[8] including many based on palladium catalysis.[9] Some of the most useful methods for benzo[*b*]furan synthesis are based on the palladium-catalyzed cyclization of appropriately substituted alkenyl[10] or alkynyl phenols;[11]

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(1) For recent reviews on Pd-catalyzed C−O and C−N bond fomation, see: (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; Vol. 2, p 1051. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; Vol. 2, p 1097. (c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.

(2) (a) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(3) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996.

(4) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410.

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(6) Aramendia, M. A.: Borau, V.; Jiménez, C.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Tetrahedron Lett.* **2002**, *43*, 2847.

(7) For an example of this type of cyclization in the context of a tandem reaction, see: Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345.

(8) For reviews dealing with benzofuran synthesis, see: (a) Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2002**, *14*, 139. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (d) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds,; Pergamon Press: New York, 1984; Vol. 4, p 657.

(9) Reviews: (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(10) Reviews: (a) Hosokawa, T.; Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; Vol. 2, p 2169. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

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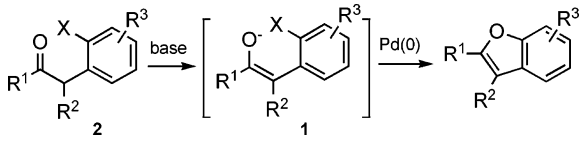


Figure 1. Enolate *O*-arylation route to benzofurans.

these methods can be extended to one-pot tandem reaction sequences that combine alkyne to arene union with cyclization.[12] The key step in these approaches is attack of a nucleophilic phenol oxygen atom onto an activated C−C multiple bond. We wished to develop an alternative palladium-catalyzed cyclization in which the nucleophilic oxygen atom of an enolate **1** is coupled with a halo-substituted arene ring (Figure 1). This would lead to α-aryl-substituted ketones such as **2** being the cyclization substrates; given the wide availability of substituted ketones, this simple disconnection provides access to a useful new class of benzofuran precursor.

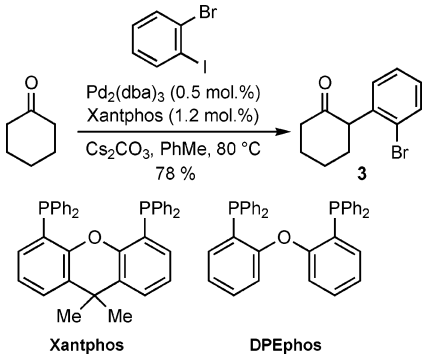
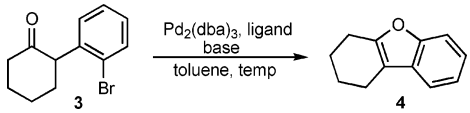


Figure 2. Preparation of ketone **3**.

For the purpose of our study we chose to prepare the required (2-haloaryl)-substituted ketones using a palladium-mediated ketone arylation. For example, treatment of a mixture of cyclohexanone and 2-bromoiodobenzene with $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 delivered arylated ketone **3** in 78% yield (Figure 2).[2] All of the substrates used in the following study were prepared using slight variations of this method.[13]

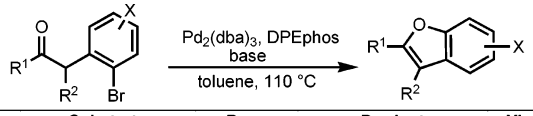
Table 1. Optimization of Benzofuran Synthesis[a]

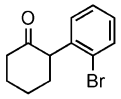
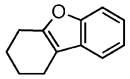
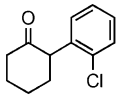
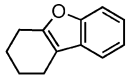
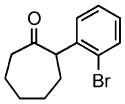
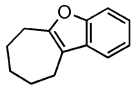
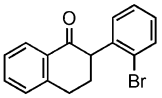
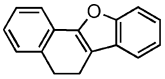
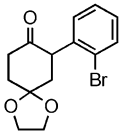
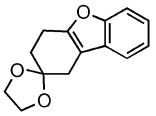
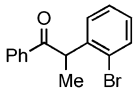
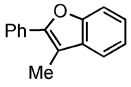
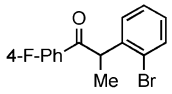
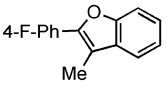
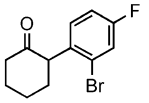
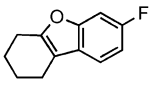
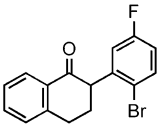
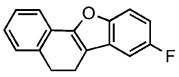
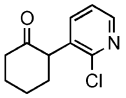
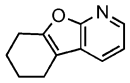


entry	ligand	base	T (°C)	time (h)	yield[b] (%)
1	Xantphos	Cs_2CO_3	110	20	<5
2	Xantphos	NaO^{t}Bu	110	20	0
3	DPEphos	Cs_2CO_3	100	20	95
4	DPEphos	Cs_2CO_3	80	24	52
5	DPEphos	Cs_2CO_3	50	30	0

[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %), base (2.2 equiv). [b] Isolated yields.

Table 2. Scope of Benzofuran Synthesis[a]



	Substrate	Base	Product	Yield[b]
1		Cs_2CO_3		95
2		NaHMDS		94
3		NaHMDS		95
4		NaHMDS		81
5		NaO^{t}Bu		73
6		NaO^{t}Bu		80
7		NaO^{t}Bu		68
8		Cs_2CO_3		81
9		NaO^{t}Bu		74
10[c]		NaO^{t}Bu		86

[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %), base (2.2 equiv). [b] Isolated yields. [c] In the absence of catalyst a 40% conversion is achieved after 20 h.

With access to the required 2-(haloaryl) ketones secured, we turned our attention to the key benzofuran-forming transformation. Substituted cyclohexanone **3** was selected for initial study (Table 1). Although we had detected trace amounts of benzofuran **4** during the preparation of ketone **3**, when we resubjected ketone **3** to a Xantphos[14]-derived catalyst in combination with Cs_2CO_3 we could only isolate small amounts of the benzofuran product (entry 1). The use of the same catalyst system with a stronger base was similarly

unsuccessful (entry 2). However, the use of the ligand DPEphos[14] with Cs_2CO_3 as base at 100 °C provided benzofuran **4** in 95% yield (entry 3). Lowering the reaction temperature simply resulted in poorer conversions (entries 4 and 5).

Table 2 charts the scope of the cyclization reaction. Although some variation in the choice of base was needed, the same catalyst system ($Pd_2(dba)_3$, DPEphos) proved effective for all the substrates studied. Simple cyclic and aryl- and ketal-substituted cyclic ketones were tolerated well (entries 1−5). Entry 2 demonstrates that a Cl-substituted arene ring is also an effective substrate for the cyclization.[15] Acyclic ketones also perform well provided NaO^{t}Bu is used as base (entries 6 and 7). The final three examples demonstrate that variation in the aryl substituent can also be achieved, with monofluoro and pyridyl units being readily incorporated (entries 8−10).

Although examples of palladium-catalyzed C−S bond formation are known,[16] they are much less common than the corresponding C−N and C−O examples. However, we were interested in whether the concept of intramolecular *O*-enolate arylation could be extended to thio ketone *S*-enolate arylation to provide a route to benzothiophenes. Conversion of arylated ketone **3** to the corresponding thio ketone **5** was achieved by treatment with P_4S_{10} (71%). Cyclization of thio ketone **5** could be achieved using identical conditions to that used for the parent ketone, providing the corresponding benzothiophene **6** in 74% yield (Figure 3). This final reaction provides a further example of palladium-catalyzed C−S bond formation.

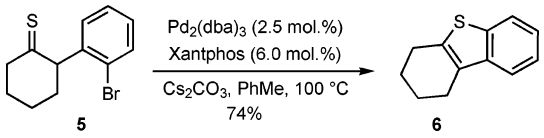


Figure 3. Benzothiophene formation.

In conclusion, we have demonstrated that the combination of $Pd_2(dba)_3$ and DPEphos generates an effective catalyst for the intramolecular *O*-arylation of enolates, allowing 1-(2-haloaryl ketones to be efficiently converted to benzofurans. The scope of the reaction with respect to ketone is good, allowing access to a variety of benzofuran systems. The same catalyst system is also effective for a thio ketone substrate, providing the corresponding benzothiophene in good yield.

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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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(11) For reviews, see: (a) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613. (b) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42. (c) Cacchi, S.; Arcadi, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; Vol. 2, p 2193.

(12) For recent examples, see: (a) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221. (b) Dai, W.-M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377. (c) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, 45, 2670. (d) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387.

(13) See the Supporting Information for details.

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(15) For a review documenting the use of aryl chlorides in Pd catalysis, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(16) For recent examples, see: (a) Moreau, X.; Campagne, J.-M. *J. Organomet. Chem.* **2003**, *687*, 322. (b) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069. (c) See also ref 1.