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One-Pot Synthesis of Benzofurans via Palladium-Catalyzed Enolate Arylation with *o*-Bromophenols

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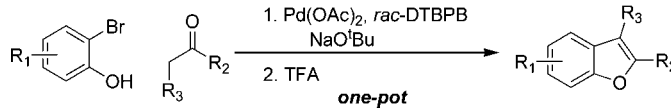
ABSTRACT



A one-pot synthesis of benzofurans which utilizes a palladium-catalyzed enolate arylation is described. The process demonstrates broad substrate scope and provides differentially substituted benzofurans in moderate to excellent yields. The utility of the method is further demonstrated by the synthesis of the natural product eupomatenoid 6 in three steps.

The benzofuran scaffold is ubiquitous in the realms of pharmacologically active agents and in isolated natural products. Prescribed agents featuring this nucleus include the antidepressant (−)-BPAP[1] and the antiarrythmic Amiodarone.[2] Some benzofuran derivatives are also known as 5-lipoxygenase inhibitors,[3] angiotensin II inhibitors,[4] calcium entry blockers,[5] and antitumor agents.[6] Benzofuran-containing natural products include frondosin B[7] and the eupomatenoid family.[8] Thus synthetic access to benzofurans is of considerable interest, and numerous approaches to this scaffold have been disclosed in the literature.[9] Many of these methods rely on harsh conditions with limited functional group tolerability. Recent approaches have focused on the use of relatively mild, transition-metal-catalyzed processes such as the Heck[10] and Sonagashira[11] reactions. In general, however, these approaches require multiple steps and yield benzofurans of limited structural diversity. Herein we disclose a one-pot approach to benzofurans using readily available ketones and *o*-bromophenols as starting materials.

The palladium-catalyzed enolate arylation reaction pioneered by Buchwald and Hartwig is a powerful method for the construction of α-aryl ketones that has demonstrated excellent substrate scope.[12] Recently, Willis and co-workers have used this reaction for the construction of benzofurans using *o*-bromoiodobenzene as the electrophilic reaction partner. In this case, ring closure is accomplished by a palladium-catalyzed O-arylation of the enol.[13] While this process could occur in theory via a sequential one-pot process, this was only possible for a single ketone; all other

(1) Shimazu, S.; Takahata, K.; Katsuki, H.; Tsunekawa, H.; Tanigawa, A.; Yoneda, F.; Knoll, J.; Akaike, A. *Eur. J. Pharmacol.* **2001**, *421*, 181–189.

(2) Singh, B. M.; Vaughan Williams, E. M. *Br. J. Pharmacol.* **1970**, *139*, 255–264.

(3) Ohemeng, K. A.; Apollina, M. A.; Nguyen, V. N.; Schwender, C. F.; Singer, M.; Steber, M.; Ansell, J.; Argentieri, D.; Hageman, W. *J. Med. Chem.* **1994**, *37*, 3663–3667.

(4) Kiyama, R.; Homna, T.; Hayashi, K.; Ogawa, M.; Hara, M.; Fujimoto, M.; Fujishita, T. *J. Med. Chem.* **1995**, *38*, 2728–2741.

(5) Kozikowsky, A. P.; Ma, D.; Du, L.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 6666–6672.

(6) Gangjee, A.; Devraj, R.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **1995**, *38*, 3798–3805.

(7) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. *Tetrahedron* **1997**, *53*, 5047–5060.

(8) Bowden, B. F.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1972**, *25*, 2659–2669.

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(10) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144–6148.

(11) (a) Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334–3341. (b) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.

(12) (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.

(13) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513–11520.

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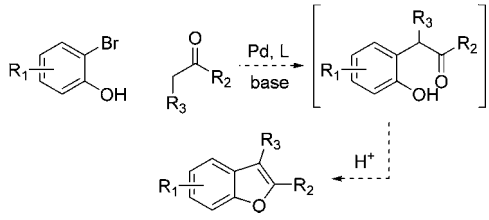
cases required ring closure in a separate operation. Further, only bromoiodobenzene was used as the electrophilic partner, thus limiting structural diversity of the benzenoid portion of the benzofurans accessible by this method. While related, our approach (Scheme 1) is fundamentally different in that

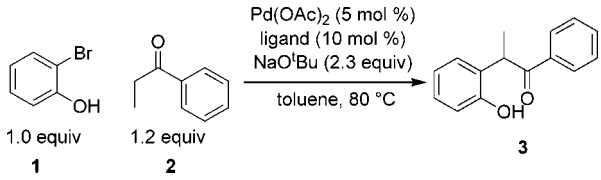
Scheme 1. One-Pot Approach to Benzofurans

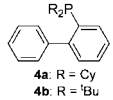
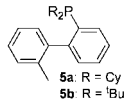
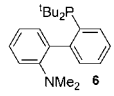
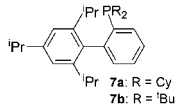
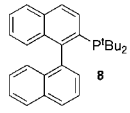


cyclization will occur via an acid-catalyzed process. The broad availability of *o*-bromophenols should allow access to benzofurans of wide structural diversity.[14]

For optimization of the arylation process, unsubstituted *o*-bromophenol and propiophenone were selected as the reaction partners. An initial ligand screen was carried out (Table 1), and

Table 1. Optimization of Phosphine Ligand



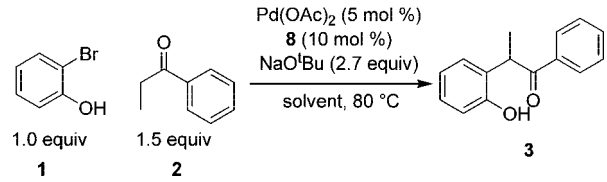
entry	ligand	conversion[a]
1	 **4a**: R = Cy **4b**: R = ^{t}Bu	R = Cy: 0%
2		R = ^{t}Bu: 30%
3	 **5a**: R = Cy **5b**: R = ^{t}Bu	R = Cy: 62%
4		R = ^{t}Bu: 42%
5	 **6**	0%
6	 **7a**: R = Cy **7b**: R = ^{t}Bu	R = Cy: 58%
7		R = ^{t}Bu: 17%
8	 **8**	64%

[a] Measured by HPLC analysis; see Supporting Information for further details.

it was found that the reaction was quite sensitive to the steric constraints of the phosphine ligand. As with several of the Buchwald examples, aryldialkylphosphines were preferred,[15] and in this case *rac*-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl **8** (*rac*-DTBPB) was the optimal ligand. Conversion could be increased to 97% by the use of 1.5 equiv of ketone and 2.7 equiv of base.

Optimization of solvent (Table 2) revealed that the reaction could be carried out in a variety of higher boiling ethereal

Table 2. Optimization of Reaction Solvent



entry	solvent	conversion (%)[a]
1	toluene	97
2	THF	85
3	DME	78
4	dioxane	84
5	DMF	54
6	DMA	37
7	^{t}BuOH	45
8	DCE	0

[a] Measured by HPLC analysis; see Supporting Information for further details.

solvents (DME, THF, dioxane) in addition to toluene, although in slightly diminshed conversions. Polar aprotic solvents, such as DMF and DMA, or protic solvents (^{t}BuOH) resulted in significantly diminished conversion, and dichloroethane was not acceptable.

A reaction temperature screen was then undertaken from room temperature to 110 °C. It was found that at temperatures lower than 80 °C, reaction times were exceedingly long. At temperatures above 80 °C, conversion rates were increased, but several unidentified minor side products were formed.

Finally, a variety of bases other than sodium *tert*-butoxide were tested in this process, such as inorganic (K_2CO_3, K_3PO_4, NaH, CsOH), hindered pyridyl (2,6-di-*tert*-butyl-4-methylpyridine), and amide (NaHMDS) bases. Unfortunately, no conversion to the desired product was observed in all cases.

With an optimal set of catalysis conditions selected, we were then poised to test the one-pot process and to evaluate the substrate scope of this reaction. Gratifyingly, treatment of the reaction mixture from the arylation process with a 1:1 mixture of CH_2Cl_2 and trifluoroacetic acid (TFA) at room temperature cleanly provided the desired benzofurans, which could then be isolated by simple filtration through a plug of silica. Further, it was found that the arylation process could be run under microwave irradiation without a reduction in

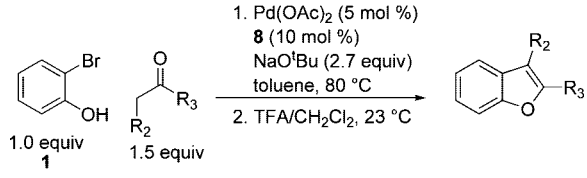
(14) A recent ACD search revealed >1300 commercially available *ortho*-bromophenols.

(15) PPh_3, BINAP and dppf provided no conversion to the desired aryl ketone.

yield, which has the added benefit of shorter reaction times (30 min versus 22 h).

To investigate the scope of the process, the reaction between *o*-bromophenol and a series of ketones was investigated. As can be seen in Table 3, the process allows

Table 3. Ketone Substrate Scope



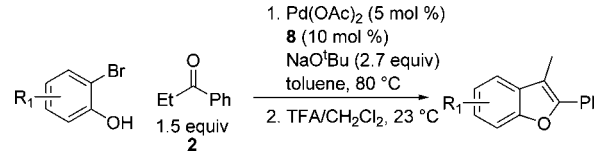
entry	ketone	benzofuran	isolated yield[a]
1	**9**	**10**	76% (73%)
2	**11**	**12**	59% (59%)
3	**13**	**14**	73% (71%)
4	**15**	**16**	(65%)
5	**17**	**18**	84% (72%)
6	**19**	**20**	70% (75%)
7	**21**	**22**	(41%)
8	**23**	**24**	(75%)[b]
9	**25**	**26**	84% (80%)[b]
10	**27**	**28**	85% (78%)

[a] Yields in parentheses are for microwave reactions; for further details see Supporting Information. [b] Single regioisomer by NMR.

a wide variety of substrate classes: aryl alkyl ketones (entries 1−5), heteroaryl alkyl ketones (entry 6), dialkyl ketones (entries 8−10), and cyclic ketones (entries 5, 7−10). Interestingly, for cases in which two regioisomers are possible (entries 8 and 9) the reaction is completely regioselective, providing only a single benzofuran by NMR. One of these examples (entry 5) was scaled up to preparative scale (10 mmol) without a significant decrease in yield (see Supporting Information).

Table 4 outlines the bromophenol substrate scope. As can be seen from entries 1−6, electron-donating, halogen, and

Table 4. Bromophenol Substrate Scope



entry	phenol	benzofuran	yield[a]
1	**29**	**30**	58% (64%)
2	**31**	**32**	(34%)
3	**33**	**34**	57% (54%)[b]
4	**35**	**36**	58% (50%)[b]
5	**37**	**38**	(49%)[b]
6	**39**	**40**	(42%)
7	**41**	---	0%
8	**42**	---	0%
9	**43**	---	0%

[a] Yield in parentheses are for microwave reactions; for further information see Supporting Information. [b] Reactions performed at 100 °C.

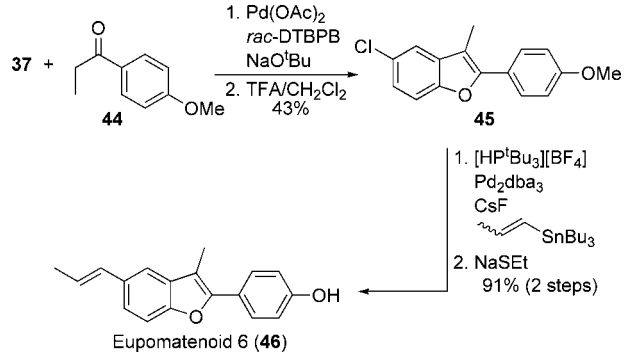
aryl substitution is tolerated, although in general yields are only moderate. Entry 6 also indicates that increased steric hindrance adjacent to the cross-coupling site is acceptable. Entries 7−9 demonstrate limitations to the current protocol: electron-poor bromophenols, hydroxypyridines, and free anilines are not successful in the palladium-catalyzed arylation process and are recovered unreacted.

Eupomatenoid **6**, first isolated in 1969 from the bark of *Eupomatia laurina R.*, shows a wide range of biological activities.[8] It was first synthesized in seven steps by Stevenson,[16] and subsequently two five-step syntheses followed from Bach (25% overall yield)[17] and Naito (52% overall yield).[18] Using the ketone arylation approach, we

(16) Stevenson, R.; McKittrick, B. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 475–482.
(17) Bach, T.; Bartels, M. *Synthesis* **2003**, 925–939.

were able to complete a four-step, three-pot approach to this natural product (Scheme 2). Subjection of 2-bromo-4-chlorophenol (**37**) and 4′-methoxypropiophenone (**44**) to our optimized conditions provided benzofuran **45** in 45% yield for the one-pot process. Stille reaction with a 1-propenylstannane using conditions developed by Fu,[19] followed by demethylation with ethanethiolate provided eupomatenoid **6** in 39% overall yield. Interestingly, although a commercially available 1:1 *cis*:*trans* mixture of stannanes was used (in excess), a 9:1 mixture of olefins was isolated, indicating the *trans*-stannane couples at a significantly higher rate.

Scheme 2. Total Synthesis of Eupomatenoid **6**



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

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