A High-Yield, General Method for the Catalytic Formation of Oxygen Heterocycles

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Several years ago we reported on the intramolecular cyclization of tertiary alcohols to form five- and six-membered oxygen heterocycles (Scheme 1).[1,2] The optimal cyclization conditions involved the use of either DPPF or Tol-BINAP as the bidentate ligand, K_2CO_3 or NaO*t*-Bu as the base, and toluene as the solvent at 80−100 °C. Application of this method for the cyclization of primary and secondary alcohol substrates was largely unsuccessful due to the formation of the debrominated ketone or aldehyde **B**. For example, efforts to cyclize 2-bromophenethyl alcohol under these conditions resulted in the formation of phenylacetaldehyde as the major product. To overcome this problem it was necessary to discover a new ligand that would interchange the relative rates of reductive elimination and β-hydride elimination of the key intermediate **A**.

We recently showed that bulky, electron-rich *o*-biphenyl phosphines were effective in a variety of Pd-catalyzed cross-coupling reactions.[3] Attempts were made to apply these and related ligands to cyclize 2-bromophenethyl alcohol and it was found that the ligands containing a di-*tert*-butylphosphino moiety tended to be much more effective than others. The most general catalyst system found was the binaphthyl ligand **1**. In addition, both a novel phenanthrene-based ligand **2** and dimethylamino-phosphine **3** were found to be useful in many cases. Our previously reported ligand, commercially available 2-di-*tert*-butylphosphinobiphenyl (**4**), could be successfully employed in several instances, but catalysts based on it were less generally effective than the others.

Scheme 1

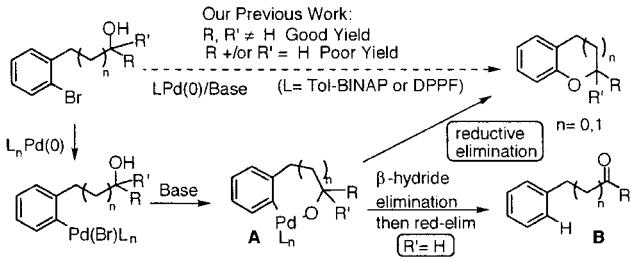
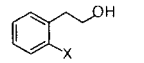
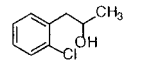
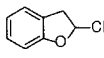
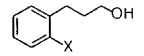
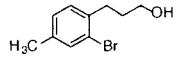
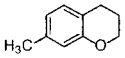
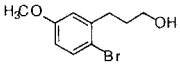
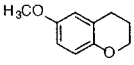
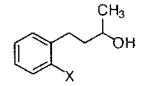
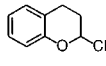
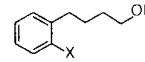
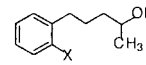
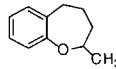
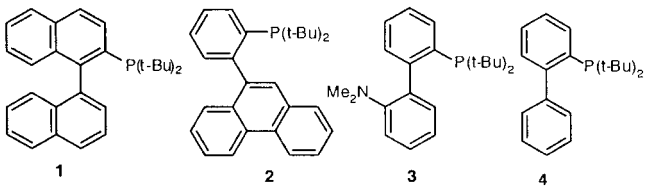


Table 1. Palladium-Catalyzed Synthesis of Cyclic Aryl Ethers

Entry	Substrate		mol% Pd[a]	Temp. (°C)	Product	Yield[b]
1		X = Br	2	50		85 (82)
2		X = Cl	2	50		71
3			3	60		71 (75)
4		X = Br	2	50		85 (72)
5		X = Cl	2	65		85
6			2	50		83
7			2	50		71
8		X = Br	3	65		79 (83)
9		X = Cl	3	80		78 (82)
10		X = Br	2	70		73
11		X = Cl	2	70		74
12		X = Br	3	80		71
13		X = Cl	3	80		65

[a] Reaction conditions: 2−3 mol % $Pd(OAc)_2$, 1.5 equiv of Cs_2CO_3, 2.5−3.5 mol % ligand **1** in toluene. Yields in parentheses were obtained by using **4** and were carried out at 80 °C. [b] Yields refer to average isolated yields of 2 runs.



As shown in Table 1, five-, six- and seven-membered oxygen heterocycles were formed in good yield. Both aryl bromides and aryl chlorides were effectively transformed, although reactions of aryl bromides were more rapid and proceeded more cleanly than those of the corresponding aryl chlorides. Primary alcohols cyclized more easily than secondary alcohols which required higher temperatures and higher quantities of catalyst to go to completion.

The most general catalyst system was that derived from the novel binaphthyl ligand, **1**. Reactions using **1** also proceeded at consistently lower temperatures than when other ligands were employed. While **4** was efficient for the cyclization of primary and secondary alcohols to five- and six-membered heterocycles, its use for the cyclization to seven-membered oxocycles was ineffective.

(1) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333−10334.

(2) For recent reports on palladium-catalyzed C−O bond formation, see: (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (b) Mann, G.; Incarvito, C.; Rheingold, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (c) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (d) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005−8008. (e) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110. For examples of copper-catalyzed C−O bond formation, see: (f) Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011−4014 and references therein. (g) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051 and references therein. (h) Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837−8840 and references therein. (i) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540 and references therein. (j) Lee, S.; Frescas, S. P.; Nichols, D. E. *Synth. Commun.* **1995**, *25*, 2775−2780 and references therein.

(3) For C−N coupling reactions employing these ligands, see: (a) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327−5333. (b) Zhang, X. X.; Sadighi, J. P.; Mackewitz, T. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7606−7607. (c) Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148−7149. (d) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403−1406. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (f) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (g) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. For C−O coupling reactions employing these ligands, see ref 2a. For α-arylation of ketones employing these ligands, see: (h) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370. For C−C coupling reactions employing these ligands, see: (i) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (j) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. For the synthesis of these ligands, see: (k) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334−5341.

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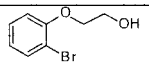
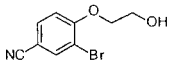
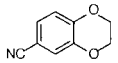
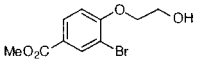
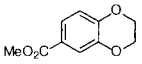
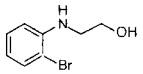
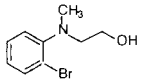
Table 2. Palladium-Catalyzed Synthesis of Heterocycles

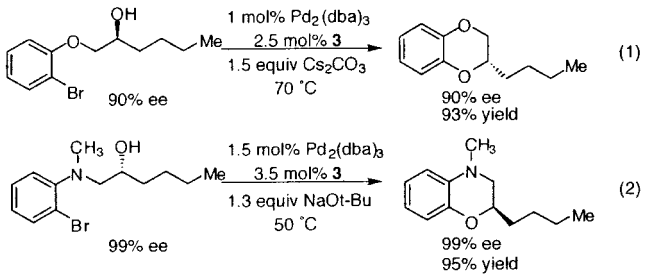
Entry	Substrate	Ligand[a]	Temp (°C)	Product	Yield[b]
1		**3**	70		81
2		**2**	50		82
3		**2**	50		67
4		**1**	50		84
5		**2**	70		74

[a] Reaction conditions: 2 mol % $Pd(OAc)_2$, 1.5 equiv of Cs_2CO_3, 2.5 mol % ligand in toluene. [b] Yields refer to average isolated yields of 2 runs.

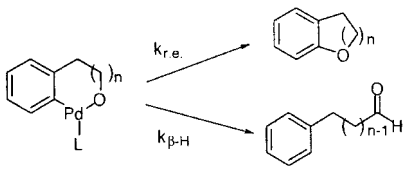
A major incentive for this work was the preparation of heterocycles that contain multiple heteroatoms in the ring that is undergoing construction. The importance of such compounds is apparent from their numerous applications.[4,5] As such, we undertook a study to ascertain whether our newly developed process could be applied to the synthesis of this type of heterocycle. As is evident from the results presented in Table 2, the method is effective in a number of instances.

In addition, as shown in Scheme 2, we were able to cyclize optically active alcohols to optically active cyclic ethers with complete conservation of enantiomeric purity. In the case of reaction 2, the use of higher temperatures or less catalyst led to formation of product with a decreased ee. Presumably this occurs by a pathway analogous to the situation in the related C−N bond-forming process.[6]

Scheme 2



Scheme 3



An important issue in this work was the development of ligands for which $k_{r.e.} \gg k_{\beta-H}$ (Scheme 3). It is interesting to note that with L = **4** for $n = 1$, 2 this requirement is met, but not when $n = 3$. In the latter case the intermediate is an eight-membered palladacycle. These results are in accord with previous work in which β-hydride elimination shows a strong dependence on the ring size of the metallacycle.[7] In the case of larger metallacycles, the energy price paid to achieve the necessary conformation for β-hydride elimination is considerably reduced.

In conclusion, we have developed a palladium-catalyzed synthesis of aryl ethers involving primary and secondary alcohols. In addition, cyclization of enantiopure alcohols results in cyclization without racemization under these reaction conditions. Further studies are underway to extend the scope of these and related metal-catalyzed processes and to ascertain the reasons for the special efficacy of catalyst systems employing **1**.

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Supporting Information Available: Complete experimental procedures and spectral data for ligands **1** and **2** and the compounds listed in Tables 1 and 2 and Scheme 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For recent reports involving 1,4-benzoxazine derivatives, see: (a) Matsumoto, Y.; Uchida, W.; Nakahara, H.; Yanagisawa, I.; Shibanuma, T.; Nohira, H. *Chem. Pharm. Bull.* **2000**, *48*, 428−432. (b) Kuroita, T.; Marubayashi, N.; Sano, M.; Kanzaki, K.; Inaba, K.; Kawakita, T. *Chem. Pharm. Bull.* **1996**, *44*, 2051−2060. (c) Largeron, M.; Lockhart, B.; Pfeiffer, B.; Fleury, M. *J. Med. Chem.* **1999**, *42*, 5043−5052. (d) Buon, C.; Chacun-Lefevre, L.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2000**, *56*, 605−614. (e) Bourlot, A.; Sánchez, I.; Dureng, G.; Guillaumet, G.; Massingham, R.; Monteil, A.; Winslow, E.; Pujol, M. D.; Mérour, J. *J. Med. Chem.* **1998**, *41*, 3142−3158.

(6) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.

(7) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6521−6528.