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The Development of Efficient Protocols for the Palladium-Catalyzed Cyclization Reactions of Secondary Amides and Carbamates

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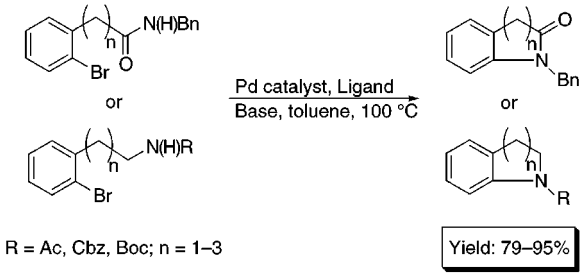
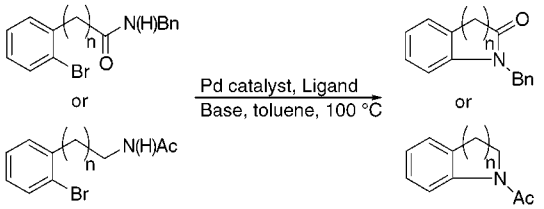
ABSTRACT



With the proper choice of palladium catalyst, ligand, and base, five-, six-, and seven-membered rings are formed efficiently from secondary amide or secondary carbamate precursors, offering significant improvements to currently existing methodology.

We recently reported that aryl bromides with pendant secondary amide groups could be cyclized to form tertiary amides (Scheme 1).[1] Some advantages of this palladium-catalyzed approach were that the cyclization reactions occurred under fairly mild conditions and displayed good functional group tolerance. However, these cyclization protocols typically employed high catalyst loadings and often long reaction times were necessary. Furthermore, while this methodology did allow for the formation of five- and six-membered rings, preparation of seven-membered rings proceeded in low overall yield. Motivated by an increased understanding of Pd-catalyzed C−N bond-forming reactions,[2] we undertook a reinvestigation of this problem.

Scheme 1



The conditions which we previously reported for the cyclization of secondary amides involved the use of $Pd_2(dba)_3$ (10 mol % Pd), $(o\text{-tolyl})_3P$, or $(2\text{-furyl})_3P$ as ligand (20 mol %) and K_2CO_3 or Cs_2CO_3 as base (1.4 equiv) in toluene at 100 °C for 8−91 h.[1] Using, among others, ligands used recently in the corresponding amination chemistry,[3]

(1) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *21*, 7525.

(2) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 121. (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2090.

(3) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

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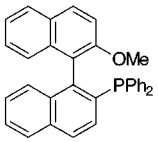
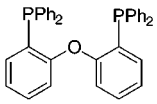
these same transformations can now be achieved in higher yield and with decreased quantities of catalyst (3.3 mol % Pd and 5.0 mol % ligand). For instance, the use of (±)-MOP as ligand and K_2CO_3 as base was effective for the preparation of lactam **5a** (82% isolated yield, Table 1, entry 1) and lactam **5b** (94% yield, entry 2).[4] In conjunction with Cs_2CO_3 as base, the use of (±)-MOP also proved optimal for preparation of the seven-membered lactam **5c** (88% isolated yield, entry 3). These results all compare favorably to our previous report,[1] where **5a** was produced in only 59% yield and the preparation of **5b** required a reaction time of 91 h. In that report, attempted synthesis of seven-membered lactam **5c** proceeded in only 5% yield, affording either unreacted starting material or debrominated material instead.

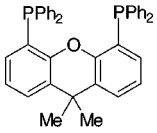
Similar results were obtained for the cyclization of acetamides **2a**−**2c** (entries 4−6).[5] Although excellent yields were reported previously for the cyclization of **2a** using (2-furyl)$_3$P as ligand, high catalyst loadings were necessary (10 mol % Pd).[1] Furthermore, formation of the six-membered ring **6b** was sluggish (44% isolated yield),[1] and no product was detected in the attempted cyclization of **2c**. We have now found that cyclization of **2a** can be readily accomplished using DPEphos (**10**)[4,6] as ligand and Cs_2CO_3 as base (87% isolated yield). Amide **6b** could be prepared in 92% yield using (±)-BINAP as ligand and Cs_2CO_3 as base. And while the preparation of **6c** (90% yield) requires 36 h using Xantphos[6] (**11**) as ligand, the inaccessibility of this product by our previous method[1] makes this an attractive procedure.



MOP (**9**)



DPEphos (**10**)

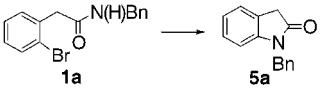
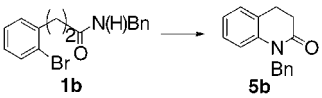
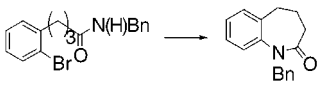
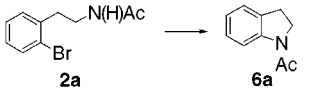
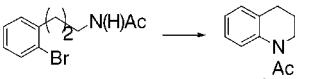
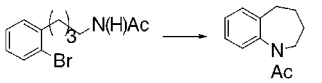
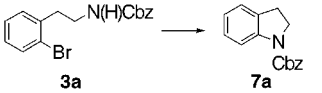
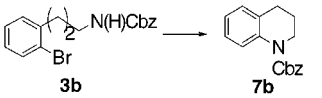
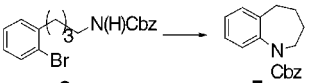
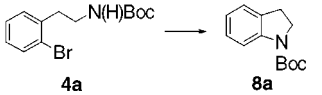
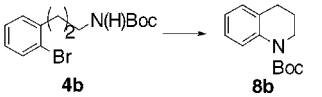
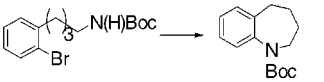


Xantphos (**11**)

The cyclization of secondary carbamates (Table 1, entries 7−12) is not only a logical extension of the intramolecular cyclization of acetamides but it has already been applied in total synthesis.[7] From the same primary amine precursors of acetamides **2a**−**2c**, both the *N*-*tert*-butoxycarbonyl (**3a**−**3c**) and *N*-carbobenzyloxy (**4a**−**4c**) derivatives were prepared. As would be expected, yields for analogous cyclizations (i.e. **3a** → **7a** vs **4a** → **8a**) were comparable when the same ligand/base systems were utilized.[8] Thus the five-membered rings **3a** and **4a** were smoothly formed using Cs_2-

Table 1. Cyclization of Secondary Amides and Secondary Carbamates

Secondary Amide or Secondary Carbamate[a] → $Pd(OAc)_2$ (3.3 mol % Pd), Ligand (5.0 mol %), Base (1.4 equiv), Tol, 100 °C → Cyclized Product

Entry	Transformation	Ligand Base	Time (h)	Isol Yield (%)
1	 **1a** → **5a**	(±)-MOP K_2CO_3	36	82
2	 **1b** → **5b**	(±)-MOP K_2CO_3	24	94
3	 **1c** → **5c**	(±)-MOP Cs_2CO_3	48	88[b]
4	 **2a** → **6a**	DPEphos Cs_2CO_3	23	87
5	 **2b** → **6b**	(±)-MOP Cs_2CO_3	24	87
6	 **2c** → **6c**	Xantphos Cs_2CO_3	24	90
7	 **3a** → **7a**	DPEphos Cs_2CO_3	22	92
8	 **3b** → **7b**	(±)-BINAP Cs_2CO_3	24	95
9	 **3c** → **7c**	(±)-MOP Cs_2CO_3	22	79
10	 **4a** → **8a**	DPEphos Cs_2CO_3	36	82
11	 **4b** → **8b**	(±)-BINAP Cs_2CO_3	24	81
12	 **4c** → **8c**	(±)-MOP Cs_2CO_3	20	85

[a] Unless indicated otherwise, all reactions were conducted at 0.2−0.3 M in starting substrate. [b] Reaction was run at 0.06 M in starting substrate, using 5.0 mol % $Pd(OAc)_2$ and 7.5 mol % ligand.

(4) Optically active MOP, (±)-BINAP, and DPEphos (vide infra) are commercially available from Strem Chemical Co. (±)-MOP is prepared from a literature procedure. See: (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Kurz, L.; Lee, G.; Morgans, D. Jr.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321.

(5) Prepared using the procedures described in ref 1. In each case, the crude primary amine precursor was prepared by lithium aluminum hydride reduction of the corresponding nitrile. Small amounts (2−7%) of debromination can also occur during the reduction step. Substrates **1**−**4** are therefore contaminated with small amounts of the corresponding debrominated material. The debrominated byproduct is not believed to affect the efficiency of the cyclization step, and it is easily removed by flash column chromatography after the cyclization step.

(6) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwan, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

(7) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

CO_3 as base and DPEphos as ligand (entries 7 and 10). Although the use of (±)-BINAP/Cs_2CO_3 was ineffective for the formation of five-membered rings, it is a useful system for the preparation of six-membered rings, affording the corresponding *N*-Cbz compound **7b** in 92% isolated yield and the analogous *N*-Boc substrate **8b** in 81% isolated yield. For formation of the seven-membered ring compounds **7c** and **8c**, (±)-MOP/Cs_2CO_3 is found to be an effective ligand/base combination (79% and 85% yields, respectively).

The superiority of the ligands xantphos and MOP (relative to BINAP and DPEphos) for cyclizations leading to seven-membered rings is of some interest. The second ligating group of both xantphos and MOP is less strongly bound to palladium than that for either BINAP or DPEphos since the OMe group on MOP is only weakly chelating and the increased bite angle of Xantphos (relative to BINAP and DPEphos) should result in an increased Pd−P bond length.[6,9] We suggest that the availability of an open coordination site may be important in the coordination of the secondary amide to the putative Pd(II) oxidative addition complex to form an eight-membered palladacycle intermediate. Since the formation of a six- or seven-membered palladacycle is presumably a more facile process, an open coordination site may not be necessary. This would explain why the more tightly bound ligands BINAP and DPEphos are often suitable for the formation of five- and six-membered ring products but not seven-membered ring products.

In summary, we have shown that ligands capable of chelation (i.e. bisphosphines or ligands with heteroatoms capable of coordination) are in many instances useful ligands for the palladium-catalyzed cyclization of secondary amides and carbamates. Further studies, however, are necessary to elucidate the mechanism of these reactions and to delineate the effect that ligand structure, ligand electronics, and base counterion have on these transformations.

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Supporting Information Available: Characterization data for products **5**−**8** (6 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) A general procedure for amide or carbamate cyclizations: a dry 25-mL sealable Schlenk tube was charged with $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and (±)-BINAP (13.4 mg, 0.022 mmol). The reaction vessel was evacuated and flushed with argon. A solution of **4b** (135 mg, 0.43 mmol) in toluene (1 mL) was added via cannula. The mixture was heated under argon at 100 °C for 2 min to dissolve the solids. The reaction vessel was removed from the oil bath, charged quickly with Cs_2CO_3 (196 mg, 0.60 mmol) and toluene (0.3 mL), sealed with a Teflon screwcap, and heated at 100 °C until the aryl bromide was consumed (24 h). The reaction mixture was cooled to rt, filtered through a short plug of SiO_2, and concentrated. The residue was purified by flash column chromatography (9% EtOAc−hexanes) to afford **8b** (81 mg, 81% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 8.1 Hz), 7.4−6.9 (m, 3H), 3.71 (t, 2H, J = 6.1 Hz), 2.74 (t, 2H, J = 6.6 Hz), 1.90 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 138.6, 129.9, 128.5, 125.7, 124.1, 123.2, 80.7, 44.6, 28.4, 27.5, 23.6; FTIR (neat) 1704 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.15; H, 8.33.

(9) Kranenburg, M.; Delis, J. G. P.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vrieze, K.; Veldman, N.; Spek, A. L.; Goubitz, K.; Fraanje, J. *J. Chem. Soc., Dalton Trans.* **1997**, 1839.