## A Single Phosphine Ligand Allows Palladium-Catalyzed Intermolecular C–O Bond Formation with Secondary and Primary Alcohols\*\*

Xiaoxing Wu, Brett P. Fors, and Stephen L. Buchwald\*

Aryl alkyl ethers are present in many naturally occurring and medicinally relevant compounds.<sup>[1]</sup> Copper<sup>[2]</sup>- and palladiumcatalyzed C–O bond-forming reactions have become effective strategies for their preparation. Although reasonably efficient palladium catalysts for the coupling reactions of phenols<sup>[3]</sup> and tertiary alcohols,<sup>[4]</sup> which lack  $\beta$ -hydrogen atoms, have been developed, much less progress in the realization of a practical and general system for the analogous coupling of primary and, especially, secondary alcohols<sup>[5]</sup> has been realized. This deficit is attributed to the competing  $\beta$ hydride elimination pathway from the [L<sub>n</sub>Pd<sup>II</sup>(Ar)(alkoxide)] intermediates that leads to significant amounts of arene formation.

Our first report on palladium-catalyzed intermolecular cross-coupling reactions of primary alcohols with unactivated aryl bromides and chlorides<sup>[6a]</sup> necessitated the presence of an *ortho* substituent or an electron-withdrawing substituent on the aryl halide, both of which increase the rate of reductive elimination, to achieve satisfactory results. In 2005, we disclosed an efficient protocol for the cross-coupling of primary and secondary alcohols with aryl halides that utilized a collection of new (at the time) ligands.<sup>[6b]</sup> The ligands employed were carefully chosen to match the steric properties of the substrate combination. Additionally, the analogous reaction of electron-rich aryl halides with secondary alcohols remained a challenge because of the extensive formation of the reduced arene.

Furthermore, very few examples of palladium-catalyzed cross-coupling reactions of primary and secondary alcohols with heteroaryl halides have been reported to date.<sup>[7]</sup> Most recently, Beller and co-workers disclosed that a single catalyst based on a modified version of Singer's Bippyphos ligand, **L2** (Scheme 1),<sup>[8]</sup> was able to couple primary alcohols with a few types of heteroaryl halides. Examples carried out with this new system were restricted to reactions of primary alcohols with electron-neutral, electron-deficient, or *ortho*-substituted

[\*] Dr. X. Wu, Dr. B. P. Fors, Prof. Dr. S. L. Buchwald Department of Chemistry, Room 18-490, Massachusetts Institute of Technology, Cambridge, MA 02139 (USA) E-mail: sbuchwal@mit.edu

[\*\*] We are grateful to the National Institutes of Health for financial support (grant GM-58160). This activity is supported by an educational donation provided by Amgen. B.P.F. thanks Bristol-Myers Squibb for a graduate fellowship. The Varian 300 MHz instrument used in this work was purchased with funding from the National Institutes of Health (GM 1S10RR13886-01).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104361.



**Scheme 1.** Ligands for palladium-catalyzed C–O cross-coupling reactions.

aryl halides, that is, substrates that contain steric and electronic features that are known to facilitate reductive elimination.<sup>[6a]</sup> No examples with more challenging electronrich aryl halides (e.g., *para-* or *ortho*-halo anisole) were described. Importantly, no examples of the successful coupling reactions of secondary alcohols were reported.

Herein, we report a catalyst based on a new ligand that provides a single general system for the coupling of both primary and secondary alcohols and is applicable to the reactions of formerly inaccessible substrates, such as a wider range of heteroaryl and electron-rich aryl halides.

In light of the aforementioned limitations for the palladium-catalyzed coupling reactions of secondary and primary alcohols with aryl halides, we felt that the development of a more general catalyst system for the preparation of (hetero)aryl alkyl ethers was highly desirable. On the basis of our recent observations that a catalyst based on the sterically demanding di-*tert*-butyl biarylphosphine ligand, **L3** (*t*Bu-BrettPhos), was able to promote the difficult reductive elimination to form Ar–F,<sup>[9a]</sup> Ar–Br,<sup>[9b]</sup> and Ar–O<sup>[9c]</sup> bonds, we postulated that for reactions of secondary alcohols this catalyst may accelerate reductive elimination relative to the rate of  $\beta$ -hydride elimination. By using a catalyst based on **L3** for the coupling of 2-butanol and 4-chloroanisole, only a 20% yield of the desired product **2a** and 63% of the reduced arene by-product **2a'** resulted (Table 1, entry 2).

Previous studies from our group have shown that the substituent in the 3-position of our biarylphosphine ligands helps fix the  $Pd^{II}$  center over the triisopropylphenyl ring,

## Communications

| Table 1: Ligand evaluation. <sup>[a]</sup> [(allyIPdCl) <sub>2</sub> ] (1 mol %)           CI         ligand (3 mol %)         COMe |        |  |   |         |                          |  |  |  |  |
|---|--------|--|---|---------|--------------------------|--|--|--|--|
| MeO   |        | 2-BuOH, Cs <sub>2</sub> CO <sub>3</sub><br>4Å M.S., Bu <sub>3</sub> N<br>90 °C, 21 h | MeO                                     | Me +    | OMe                      |  |  |  |  |
|   | 1a     |  | 2a                                      |         | 2a'                      |  |  |  |  |
| Entry   | Ligand | Conv. [%] <sup>[b]</sup>   | Yield [%] <sup>[b]</sup> ( <b>2 a</b> ) | Yield [ | %] <sup>[b]</sup> (2 a') |  |  |  |  |
| 1   | L1     | 100  | 26                                      | 54      |                          |  |  |  |  |
| 2   | L3     | 100  | 20                                      | 63      |                          |  |  |  |  |
| 3   | L4     | 100  | 70                                      | 19      |                          |  |  |  |  |
| 4   | L5     | 70   | trace                                   | 61      |                          |  |  |  |  |
| 5   | L6     | 67   | 3                                       | 43      |                          |  |  |  |  |
| 6   | L7     | 100  | 66                                      | 26      |                          |  |  |  |  |
| 7   | L8     | 100  | 64                                      | 28      |                          |  |  |  |  |
| 8   | L9     | 100  | 57                                      | 32      |                          |  |  |  |  |
| 9   | L10    | 100  | 54                                      | 31      |                          |  |  |  |  |

[a] Reaction conditions: 4-chloroanisole (1.0 mmol), 2-BuOH

(2.0 mmol), [(allyIPdCl)<sub>2</sub>] (1 mol%), ligand (3 mol%), Cs<sub>2</sub>CO<sub>3</sub>

(1.5 mmol), 4 Å molecular sieves (M.S.; 200 mg), Bu<sub>3</sub>N (1 mL), 90 °C, 21 h. [b] Determined by GC analysis.

which in turn accelerates reductive elimination (Figure 1).<sup>[10]</sup> Furthermore, we have disclosed, for both C–N and C–O cross-coupling reactions, that a ligand bearing a methoxy group in the 3-position led to the most active catalyst systems.<sup>[9c,11]</sup> However, none of our previous studies have focused solely on the effect of the substituent in the 6-position of L3. We previously postulated that the 6-methyl group in L1 provided increased conformational rigidity in the ligated Pd<sup>II</sup> complexes, thus leading to accelerated rates of reductive elimination for cross-coupling reactions of phenols.<sup>[3d]</sup> Therefore, replacing the 6-methoxy group in L3 with a methyl group, as shown in L4, would provide a hybrid of L1 and L3, which we hypothesized would accelerate the rate of reductive elimination and impede that of  $\beta$ -hydride elimination for reactions of secondary alcohols (Figure 1).

In support of this hypothesis, a catalyst based on **L4** was tested for the coupling of 2-butanol with 4-chloroanisole and gave 70% of the desired product 2a and only 19% of the reduced arene 2a' (Table 1, entry 3). This is the first example for the coupling of a secondary alcohol with an electron-rich aryl halide. Moreover, this result reveals that the substituent in the 6-position of the ligand has a profound effect on the reactivity of the catalyst.<sup>[12]</sup>

In an attempt to further probe the effect of the substituents in the 3- and 6-positions of the ligand, catalysts based on



The 6 substituent interacts with the triispropylbenzene ring and provides conformational rigidity.

Figure 1. Rationalizing the substituent effect on reductive elimination.

9944 www.angewandte.org

© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

**L5–L10** were examined for this reaction (Table 1, entries 4–9). When the 6-methyl group in **L4** was removed (**L6**), the activity of the derived catalyst dropped off substantially giving only 3% product (Table 1, entry 5). This result again demonstrates that subtle differences in ligand structure have a dramatic effect on these C–O cross-coupling reactions. Utilizing catalysts based on **L7**, **L8**, **L9**, and **L10**, which contain a 6-ethyl, 6-isopryl, 3-ethoxy, and 3-isopropoxy substituent, respectively, led to a slight reduction in the production of **2a** and a modest increase in that of **2a'** formed (Table 1, entries 6–9). This indicates that the 3-methoxy and 6-methyl groups in **L4** are optimal for promoting reductive elimination and suppressing  $\beta$ -hydride elimination.

We next explored the scope of the cross-coupling reactions of secondary alcohols with aryl halides (Scheme 2). Typically these reactions were carried out at 90 °C using 1 mol % [(allylPdCl)<sub>2</sub>]. In a few cases, Bu<sub>3</sub>N was chosen as the solvent because of its ability to suppress the formation of the reduction by-product.<sup>[6b]</sup> A range of electron-rich aryl halides were found to undergo reactions with cyclic and acyclic secondary alcohols to afford aryl alkyl ethers in moderate to good yields (**2a–2d**, **2f**, **2g**); these yields are the highest reported to date for this difficult process. For a slightly electron-deficient substrate, 3-chloroanisole, only 0.5 mol% [(allylPdCl)<sub>2</sub>] was required to give **2e** in 86% yield. In contrast a 63% yield was obtained with 2 mol% Pd(OAc)<sub>2</sub>





**Scheme 2.** Coupling of aryl halides with secondary alcohols. Reaction conditions: ArX (1 mmol), alcohol (2 mmol),  $Cs_2CO_3$  (1.5 mmol), [(allyIPdCl)<sub>2</sub>] (0.5–2.5 mol%), L4 (1.5–6 mol%), toluene (1 mL), 90°C, 21 h; yields are of isolated products (average of two or more runs). [a] 200 mg of 4 Å molecular sieves was added. [b] in Bu<sub>3</sub>N. [c] cyclohexanol (1.5 mmol) was used. [d] In Et<sub>3</sub>N. [e] 24 h.



and 2.4 mol % **L12**, which was previously the most efficient catalyst system reported for this transformation.<sup>[6b]</sup>

Furthermore, switching to toluene from Bu<sub>3</sub>N as solvent did not affect the efficiency of the coupling with basicnitrogen-containing heteroaryl halides as substrates, thus allowing simplified isolation of the products (2g, 2i-2m). 6-Chloroquinoline, however, was found to be an exception to this trend. In toluene the reaction of 6-chloroquinoline and cyclopentanol resulted in the formation of a significant amount of reduced arene by-product. In this case switching to Et<sub>3</sub>N as the solvent reduced the amount of quinoline formation and resulted in a 62 % yield of the desired product 2h. For the coupling of halopyridines and halopyrimidines, we found it was necessary to premix the [(allylPdCl)<sub>2</sub>], L4, Cs<sub>2</sub>CO<sub>3</sub>, and 2-butanol in toluene at 90 °C for 3 minutes with subsequent addition of the aryl halide (presumably because of the competitive binding of the substrate's nitrogen atom to the Pd center). In this way, 3-chloropyridine and 5-bromopyrimidine were coupled with 2-BuOH in 71% and 76% yields, respectively. Moreover, 5-chlorobenzoisoxazole, and 5chlorobenzothiazole proved to be proficient substrates in these reactions, thus giving the desired products (2m and 2l) in 61% and 63%, respectively. Therefore, this suggests that the N atom of the pyridine rings (and related substrates) interferes with catalyst generation, more than with the catalyst itself.

We next decided to explore the application of L4 for the cross-coupling of primary alcohols (Scheme 3). Excellent yields were obtained for the combination of primary alcohols with electron-rich, electron-neutral, and electron-deficient aryl halides using 0.5 mol % [(allylPdCl)<sub>2</sub>] and 1.5 mol % L4. The high efficiency displayed with L4 as the supporting ligand allowed the reactions to be carried out in toluene, rather than in Bu<sub>3</sub>N as the solvent as in our previous method.<sup>[6b]</sup> For unactivated substrates, the coupling of aryl chlorides with primary alcohols was generally less efficient than that of aryl bromides and resulted in incomplete conversion of the starting material. For instance, the reaction of *n*BuOH with 4-bromoanisole proceeded within 21 hours (see 3a) when using only 1 mol% of palladium. However, the analogous reaction with 4-chloroanisole using 2 mol% of palladium resulted in only approximately 85% conversion within the same time. Interestingly, the less nucleophilic fluorinated primary alcohol was a more efficient coupling partner than nBuOH.<sup>[13]</sup> Thus, the reaction of trifluoroethanol with 4chlorodiphenyl ether afforded an 83% yield of the desired product **3e**.<sup>[14]</sup> Furthermore, the coupling of *N*-Boc-D-prolinol gave the desired product **3g** with no erosion of enantiopurity (86% yield, 98.5% ee). The catalyst combination of Pd- $(OAc)_2$  and the less bulky ligand L3 (*t*BuBrettPhos) was optimal for the reaction of aryl bromides bearing ortho-alkyl substituents to give **3h** and **3i** in comparable yields.<sup>[6b]</sup>

In contrast to a catalyst based on L2,<sup>[8]</sup> whose application was limited to halopyridines and haloquinolines, a variety of aryl alkyl ethers derived from five- and six-membered heteroaryl halides could be accessed under our new conditions (**3j–3o**). For example, 3-bromopyridine, 5-bromopyrimidine, and 3-bromoquinoline were all coupled with *n*BuOH in good to excellent yields (see **3k**, **3l**, and **3m**). The



**Scheme 3.** Coupling of aryl halides with primary alcohols. Reaction conditions: ArX (1 mmol), alcohol (2 mmol),  $Cs_2CO_3$  (1.5 mmol), [(allylPdCl)<sub>2</sub>] (0.5 mol%), L4 (1.5 mol%), toluene (1 mL), 90°C, 5–21 h; yields are of of isolated products (average of two or more runs). [a] 200 mg of 4 Å molecular sieves was added. [b] [(allylPdCl)<sub>2</sub>] (2 mol%) and L4 (4.8 mol%). [c] Alcohol (3 mmol). [d] Pd(OAc)<sub>2</sub> (2 mol%) and L3 (2.4 mol%). [e] [(allylPdCl)<sub>2</sub>] (1 mol%) and L4 (2.4 mol%). Boc = *tert*-butoxycarbonyl.

conversion of 4-bromoisoquinoline into 30 proved more difficult, but could be efficiently accomplished by using 3 equivalents of *n*BuOH and the premixing protocol described above.

To highlight the generality and efficiency of a catalyst based on **L4**, we directly compared it to several of the previous reported systems. For the reaction of 4-bromoquinoline with a secondary alcohol our new catalyst system gave an 88% yield of isolated product, whereas a catalyst based on **L12** (previously the best reported system for reactions of secondary alcohols)<sup>[6b]</sup> gave no desired product (Scheme 4). Furthermore, for the reaction of a primary alcohol with an electron-rich aryl halide, a catalyst based on **L4** gave an 84% yield as determined by GC analysis; for the same reaction a catalyst based on the recently reported **L2**<sup>[8]</sup> afforded no desired product, and a catalyst based on **L1** gave a 73% yield

## Communications



**Scheme 4.** Comparison of catalysts based on L4 and L12 for the coupling of a secondary alcohol.

as determined by GC analysis (Table 2, **4a**). Switching to reactions of primary alcohols with heteroaryl bromides further displayed the superiority of a catalyst based on **L4** compared to previous catalyst systems (Table 2, **4b**–**4d**).

**Table 2:** Comparison of catalysts based on L4 and the previously reported ligands for the C–O cross-coupling reactions of primary alcohols.<sup>[a]</sup>

|           |    | L4          | L2 L11<br>(previous best<br>ligands for coupling<br>primary alcohols) |                     | L1<br>(primary alcohols<br>with electron-rich<br>aryl halides) |
|-----------|----|-------------|---|---------------------|--|
| MeO       | 4a | 84%         | 0%  | n.a. <sup>[d]</sup> | 73%  |
| OnBu      | 4b | <b>96</b> % | 0% <sup>[b]</sup>   | 26%                 | n.a. <sup>[e]</sup>  |
| OnBu<br>N | 4c | <b>98</b> % | 57% <sup>[c]</sup>  | 12%                 | n.a. <sup>[e]</sup>  |
| OnBu      | 4d | 83%         | 29%   | 39%                 | n.a. <sup>[e]</sup>  |

[a] Corrected GC yields. [b] No desired product was obtained under our reaction conditions or the conditions reported by Beller and co-workers.<sup>[8]</sup> [c] Using the conditions reported by Beller and co-workers.<sup>[8]</sup> [d] A catalyst based on this ligand was reported to not be efficient for coupling electron-rich aryl halides. [e] A catalyst based on this ligand was reported to only be efficient for reactions of electron-rich aryl halides. n.a. = not applicable.

In summary, we have developed a general system for the palladium-catalyzed C–O cross-coupling reactions of aryl halides with secondary and primary alcohols. We found that the substituent in the 6-position of the biarylphosphine ligand scaffold has a profound effect on the catalytic activity of these systems and that a catalyst based on L4 (RockPhos, soon to be commercially available), which contains a methyl group in the 6-position, displays the highest reactivity reported to date for these reactions. We postulate that the introduction of 6-methyl group rather than a 6-methoxy group, to the ligand provides increased conformational rigidity in the [LPd(Ar)-(alkoxide)] complexes and, therefore, accelerates the rate of reductive elimination while preventing  $\beta$ -hydride elimination. Thus, the utilization of catalyst based on L4 allows the synthesis of an array of aryl alkyl ethers with unprecedented

substrate scope of both the aryl halide and alcohol coupling partners.

Received: June 23, 2011 Published online: September 12, 2011

Keywords: arenes  $\cdot$  C–O cross-coupling  $\cdot$  ligand design  $\cdot$  palladium  $\cdot$  synthetic methods

- J. Buckingham, *Dictionary of Natural Products*; University Press, Cambridge, MA, **1994**.
- [2] For Cu-catalyzed C-O coupling of aliphatic alcohols, see: a) P. J. Fagan, E. Hauptman, R. Shapiro, A. Casalnuovo, J. Am. Chem. Soc. 2000, 122, 5043; b) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, Org. Lett. 2002, 4, 973; c) R. Hosseinzadeh, M. Tajbakhsh, M. Mohadjerani, M. Alikarami, Synlett 2005, 1101; d) A. Shafir, P. A. Lichtor, S. L. Buchwald, J. Am. Chem. Soc. 2007, 129, 3490; e) H. Zhang, D. Ma, W. Cao, Synlett 2007, 243; f) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, J. Org. Chem. 2008, 73, 284; g) A. B. Naidu, G. Sekar, Tetrahedron Lett. 2008, 49, 3147; h) A. B. Naidu, E. A. Jaseer, G. Sekar, J. Org. Chem. 2009, 74, 3675; i) J. Niu, P. Guo, J. Kang, Z. Li, J. Xu, S. Hu, J. Org. Chem. 2009, 74, 5075.
- [3] For palladium-catalyzed C-O coupling of phenols, see: a) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, J. Am. Chem. Soc. 1999, 121, 4369; b) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, J. Am. Chem. Soc. 1999, 121, 3224; c) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, M. Beller, *Tetrahedron Lett.* 2005, 46, 3237; d) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, Angew. Chem. 2006, 118, 4427; Angew. Chem. Int. Ed. 2006, 45, 4321; e) T. Hu, T. Schulz, C. Torborg, X. Chen, J. Wang, M. Beller, J. Huang, Chem. Commun. 2009, 7330.
- [4] For palladium-catalyzed intermolecular C–O coupling of tertiary alcohols, see: a) G. Mann, J. F. Hartwig, J. Am. Chem. Soc. 1996, 118, 13109; b) M. Watanabe, M. Nishiyama, Y. Koie, Tetrahedron Lett. 1999, 40, 8837; c) Q. Shelby, N. Kataoka, G. Mann, J. F. Hartwig, J. Am. Chem. Soc. 2000, 122, 10718; d) C. A. Parrish, S. L. Buchwald, J. Org. Chem. 2001, 66, 2498.
- [5] For palladium-catalyzed intramolecular C-O coupling of primary and secondary alcohols, see: a) M. Palucki; J. P. Wolfe, S. L. Buchwald, J. Am. Chem. Soc. 1996, 118, 10333; J. P. Wolfe, S. L. Buchwald, J. Am. Chem. Soc. 1996, 118, 10333; b) K. E. Torraca, S.-i. Kuwabe, S. L. Buchwald, J. Am. Chem. Soc. 2000, 122, 12907; c) S.-i. Kuwabe, K. E. Torraca, S. L. Buchwald, J. Am. Chem. Soc. 2001, 123, 12202.
- [6] a) K. E. Torraca, X. Huang, C. A. Parrish, S. L. Buchwald, J. Am. Chem. Soc. 2001, 123, 10770; b) A. V. Vorogushin, X. Huang, S. L. Buchwald, J. Am. Chem. Soc. 2005, 127, 8146.
- [7] Only three examples of palladium-catalyzed C–O coupling of alcohols with heteroaryl halides have been previously described (See Ref. [6]).
- [8] S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, J. Am. Chem. Soc. 2010, 132, 11592.
- [9] a) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S. L. Buchwald, *Science* 2009, 325, 1661;
  b) X. Shen, A. M. Hyde, S. L. Buchwald, *J. Am. Chem. Soc.* 2010, 132, 14076; c) T. J. Maimone, S. L. Buchwald, *J. Am. Chem. Soc.* 2010, 132, 9990.
- [10] a) T. Ikawa, T. E. Barder, M. R. Biscoe, S. L. Buchwald, J. Am. Chem. Soc. 2007, 129, 13001–13007.
- [11] a) K. Dooleweerdt, B. P. Fors, S. L. Buchwald, Org. Lett. 2010, 12, 2350; b) J. D. Hicks, A. M. Hyde, A. M. Cuezva, S. L. Buchwald, J. Am. Chem. Soc. 2009, 131, 16720; c) B. P. Fors,



S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898; d) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552.

- [12] See the Supporting Information for additional studies on the effect of the substituent in the 6-position of the ligand.
- [13] For copper-mediated or copper-catalyzed C–O coupling with fluorinated alcohols, see: a) H. Suzuki, T. Matuoka, I. Ohtsuka,

A. Osuka, *Synthesis* **1985**, 499; b) D. Vuluga, J. Legros, B. Crousse, D. Bonnet-Delpon, *Eur. J. Org. Chem.* **2009**, 3513.

[14] The conversion of 4-chlorodiphenyl ether, which coupled with nBuOH using 2 mol% palladium within 24 hours, was less than 80% (determined by GC) using variety of bases or at elevated temperature.