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Palladium Catalyzed C–O Coupling of Amino Alcohols for the Synthesis of Aryl Ethers

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Abstract. Amine containing aryl ethers are common pharmacophore motifs that continue to emerge from drug discovery efforts. As amino alcohols are readily available building blocks, practical methodologies for incorporating them into more complex structures are highly desireable. We report our efforts to explore the application of Pd-catalyzed C-O coupling methods to the arylation of 1,2- and 1,3-amino alcohols. We established general and reliable conditions, under which we explored the scope and limitations of the transformation. The insights gained have been valuable in employing this methodology within a fast-moving drug discovery environment, which we anticipate will be of general interest to the synthesis and catalysis communities.

Keywords: amino alcohols; C-O coupling; aryl alkyl ethers; bippyphos; palladium catalysis

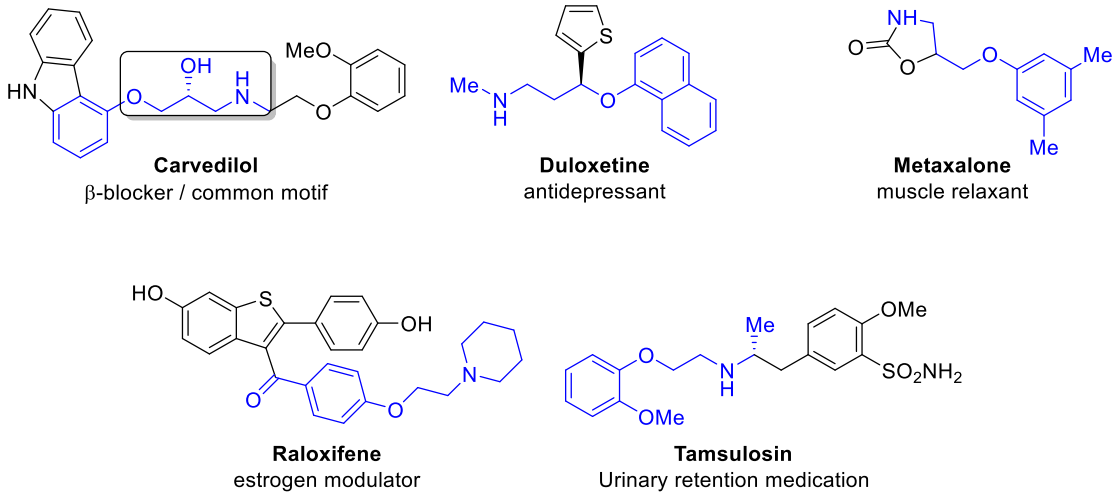
Introduction.

Due to their presence in a large number of biologically active natural products, amino alcohols have found significant application as essential pharmacophores and structural motifs in modern drug design,[1] and as highly effective stereocontrol elements in the field of asymmetric catalysis.[2] Consequently, a diverse number of practical methodologies that render them readily accessible have been developed in addition to chiral pool sources,[3] making them ideal building blocks to be used in the design and optimization of novel pharmaceuticals. For example, nearly the entire class of beta-blocker drugs such as Carvedilol (Scheme 1) contain a common 1-aminopropan-2,3-diol motif variable only in the aromatic ether of the primary hydroxyl and the substitution on the amine. Given this historical success (Scheme 1),[4] aryl ether derivatives of amino alcohols continue to emerge from the drug discovery process and practical

10.1002/adsc.201901302

methodologies that render them readily accessible are sought after in the pharmaceutical industry. For the synthesis of aryl ethers, methods such as S_NAr/S_N2, Ullman or Mitsunobu reactions have been traditionally employed,[5] while more efficient catalytic methods, including the Cu-[6] and Pd-catalyzed[7] coupling of aryl halides with alcohols, continue to evolve. More recently, Ni-promoted coupling reactions, including those utilizing photoredox catalysis, have also been shown to be effective for the synthesis of aryl ethers.[8] While all these methods have different strengths and weaknesses, our highest priority was the expedient development of general and reliable conditions for the scalable production of aryl ethers starting with readily available amino alcohols in support of a swiftly moving drug discovery project.

In this context, we rapidly found that the established Pd-catalyzed C-O coupling methdologies could be effectively applied to amino alcohol substrates despite few precedented examples in the literature.[9] Included among the potential reasons for the paucity of amino alcohol examples are the issue of N- vs. O-selectivity, the relative propensity for these substrates to undergo β-hydride elimination, and the potential for these substrates to sequester the catalyst through chelation.[10] While there have been studies of Cu-promoted coupling reactions of amino alcohols and amino acids (e.g. derivatives of serine and threonine),[11] to the best of our knowledge this substrate class has yet to be thoroughly explored in Pd catalysis. In this communication, we detail our experiences exploring the Pd-catalyzed C-O coupling of this important and under-represented class of alcohol substrates.



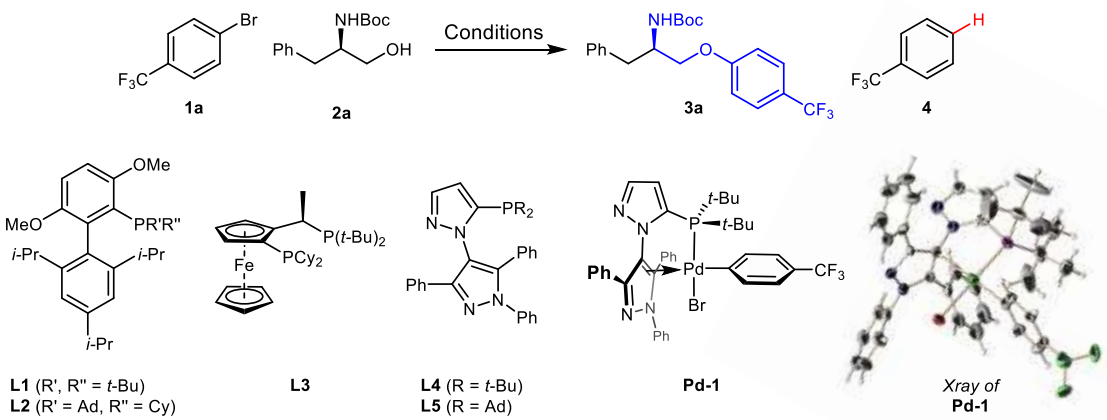
Scheme 1. Selected examples of pharmaceuticals containing amino aryl ethers

Results and Discussion. In our search for robust and scaleable conditions, we began by evaluating the optimized conditions reported by the Beller[7f] and Buchwald[7l] groups, as well as a process group from Merck,[7g] to the coupling of **1a** and **2a** (Table 1, entries 1-5). We found the bippyphos ligands **L4** and **L5** gave the highest yield of the desired product **3a**, with **L5** giving slightly better results. We further optimized

10.1002/adsc.201901302

around ligand **L4** since it is more generally available in larger quantities, and, except where noted, the differences between **L4** and **L5** were negligible (<5% difference in isolated yield). Variation of the stoichiometry between the aryl halide and alcohol substrate showed no significant impact on either the yield of the ether product or the formation of the reduced arene **4** (entries 6-10), which results from competitive β-hydride elimination of the intermediate Pd-alkoxide followed by reductive elimination. This alternate pathway highlights one of the main challenges in this chemistry. In order to obtain consistent results, it was beneficial to premix the phosphine ligand, base and aryl halide in the reaction solvent with heating until oxidative addition was observed (indicated by a distinct color change) prior to addition of the amino alcohol substrate.[12] Following this premixing procedure, ^{19}F-NMR spectroscopy revealed that a species was formed with an identical CF_3 chemical shift to that observed for the independently synthesized oxidative addition complex **Pd-1**.[13] The performance of complex **Pd-1** in the reaction was similar to that of the *in situ* generated species (Table 1, entry 11).[14]

Table 1. Evaluation of published optimal reaction conditions.[15]



Entry	Ligand	Base	Solvent	T (°C)	**1a**:**2a**	Yield[a] **3a** (%)	Yield[a] **4** (%)
1	**L1**	NaO*t*-Bu	Dioxane	75	1:2	<5	nd
2	**L2**	NaO*t*-Bu	Dioxane	75	1:2	14	nd
3	**L3**	Cs_2CO_3	THF	75	1:1	5	nd
4	**L4**	Cs_2CO_3	Toluene	75	1:1	77 (67)[b]	15
5	**L5**	Cs_2CO_3	Toluene	75	1:1	89 (76)[b]	6
6	**L4**	Cs_2CO_3	Toluene	85	1:1	82 (68)[b]	14
7	**L4**	Cs_2CO_3	Toluene	85	1:1.5	80	16
8	**L4**	Cs_2CO_3	Toluene	85	1:2	81	16
9	**L4**	Cs_2CO_3	Toluene	85	1.5:1	81	20
10	**L4**	Cs_2CO_3	Toluene	85	2:1	74	19
11	**Pd-1**[c]	Cs_2CO_3	Toluene	85	0.95:2	80	15

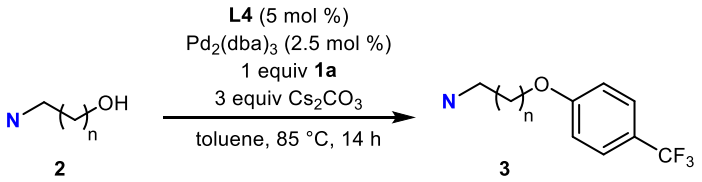
10.1002/adsc.201901302

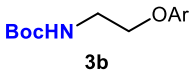
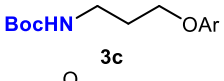
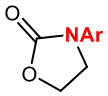
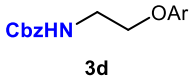
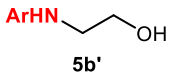
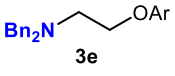
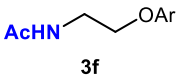
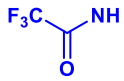
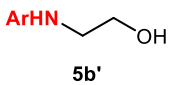
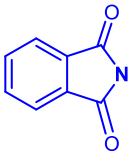
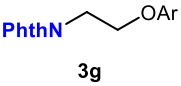
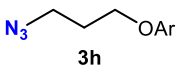
[a] Values represent NMR yield determined by ^{19}F NMR of unpurified mixtures versus 1,3,5-$(CF_3)_3C_6H_3$ as internal standard. [b] Values in parenthesis represent isolated yield of purified products. [c] The reaction was run using complex **Pd-1** in place of ligand and $Pd_2(dba)_3$, and the alcohol was added directly without preheating.

With general reaction conditions identified, a range of common amine protecting groups were next evaluated in order to better define the scope and limitations of the method (Table 2). As expected, unprotected amines gave predominant formation of N-coupled products indicating that the potential for chelation shutting down catalysis was not observed, even with 1,2 amino alcohols.[16,9] Electronic deactivation of the amine by Boc protection effectively reversed the chemoselectivity of the reaction, affording **3b** and **3c** in 66% and 68% yield respectively (entries 1-2). Boc protection proved to be the most general, as Cbz protection resulted in cyclization to the oxazolidinone and arylation on nitrogen (entry 3). However, switching from Cs_2CO_3 to the less basic CsF allowed the desired product to be isolated in 59% yield (entry 4). The Fmoc group was rapidly deprotected under the reaction conditions with either base, leading to a complex mixture with N-arylated species as the major products (entry 5). As with previous examples containing tertiary amines,[9] the dibenzylamine product **3e** was obtained in 80% yield (entry 6), thereby allowing facile revelation of the primary amine by hydrogenolysis. Amide protection as the acetate gave product **3f** in moderate yield despite the potential for either direct N-coupling or dehydration to form the oxazoline, while the trifluoroacetamide proved insufficiently stable to the reaction conditions, yielding mixtures of N- and O-coupled products (entries 7-8 respectively). Common groups used to introduce protected amine functionality (phthalimide and azide) were also found to be sufficiently stable to obtain products **3g** and **3h** in moderate yields (entries 9-10).

10.1002/adsc.201901302

Table 2. Evaluation of substitution on nitrogen on chemoselectivity and reaction efficiency.



Entry	N	n	Major Product[a]	Yield (%)[b]
1	NHBoc	1	 **3b**	66
2	NHBoc	2	 **3c**	68
3	NHCbz	1	 **5b**	63[c]
4	NHCbz	1	 **3d**	59[d]
5	NHFmoc	1	 **5b'**	37[e]
6	NBn_2	1	 **3e**	80
7	NHAc	1	 **3f**	55[f]
8		1	 **5b'**	41[f,g]
9		1	 **3g**	46
10	N_3	2	 **3h**	46

[a] Ar refers to the 4-(CF_3)-C_6H_4- fragment introduced. [b] Yields are for purified products. [c] Corrected yield after isolation as an inseparable mixture with compound **5b'**. Pure product could be isolated by slurrying in heptanes. [d] CsF used in place of Cs_2CO_3. [e] The N,O-diarylated species was also isolated in 19% isolated yield (**5c** in supporting information). [f] The reactions were run in 1,4-dioxane due to low solubility of the amide alcohols in toluene. [g] The desired O-coupled product was isolated in 11% yield as a 9:1 mixture with the N,O-diarylated species.

Exploring the scope of aryl halides and amino alcohols, we next investigated the coupling of various aryl bromides and chlorides with several Boc-protected 1,2- and 1,3-amino alcohols (Scheme 2). Choosing aryl

10.1002/adsc.201901302

bromide **1a** as coupling partner, we compared a variety of cyclic and acyclic amino alcohols. As seen in Table 2 (entries 1-2), the 1,2-product (**3b**) and 1,3-product (**3c**) were obtained in similar yield. This trend was also observed in the case of cyclic amino alcohols, as products **3i** and **3j** were also obtained in nearly identical yield. However, the ring size clearly plays a significant role in the efficiency of the reaction, as the 6- and 7-membered ring substrates gave products in <60% yield (**3i-j**, **3m**), while the 4- and 5-membered ring substrates gave products **3k** and **3l** in 85% and 87% yield respectively. In addition, increasing substitution around the reacting alcohol center had a significantly detrimental effect with acyclic substrates (cf. **3n** and **3o** vs **3c**), leading to N-arylation of the Boc carbamate as a competing pathway (predominant in case of **3o**). On the other hand, secondary alcohols on cyclic structures showed little detriment relative to primary alcohols when the nitrogen was contained in the ring (cf. **3k** vs **3p**), suggesting secondary alcohols are competent substrates in the absence of an NH carbamate.[16] In the case of **3q** where a sterically hindered NH carbamate is present, both O- and N-coupling are similarly impaired, yielding the desired product in only 20% yield.[17] However, coupling ethyl 4-bromobenzoate more than doubled the yield of the desired O-coupled product (**3r**), presumably due to the electronic nature of the aromatic ring facilitating reductive elimination. Taken together, these data suggest that reduced steric congestion around the alcohol is a crucial factor in reaction efficiency, with the geometric constraints of the cyclic systems reinforcing these factors relative to acyclic systems. Moreover, **3a**, **3k** and **3q** were isolated with no significant erosion in enantio- or diastereomeric purity, highlighting the utility of the method to incorporate chiral substrates.[16,7m]

Varying substituents on the aryl halide partner shows that several common functional groups are amenable to the conditions, such as nitrile (**3s** and **3t**), ester (**3r** and **3w**), ketone (**3x**), and xanthene (**3y**). As with the alcohol substrates, increasing the steric bulk ortho to the halide carbon hinders the efficiency of the reaction, as the ortho isopropyl containing **3v** was isolated in only 49% yield. In addition, several electron-poor heteroaromatics yielded products in 63-97%, including 7-bromoquinoline (**3u**), 2-chlorobenzoxazole (**3z**), 2-chloropyridine (**3aa**), and 2-bromo-5-methylpyrazine (**3ab**).

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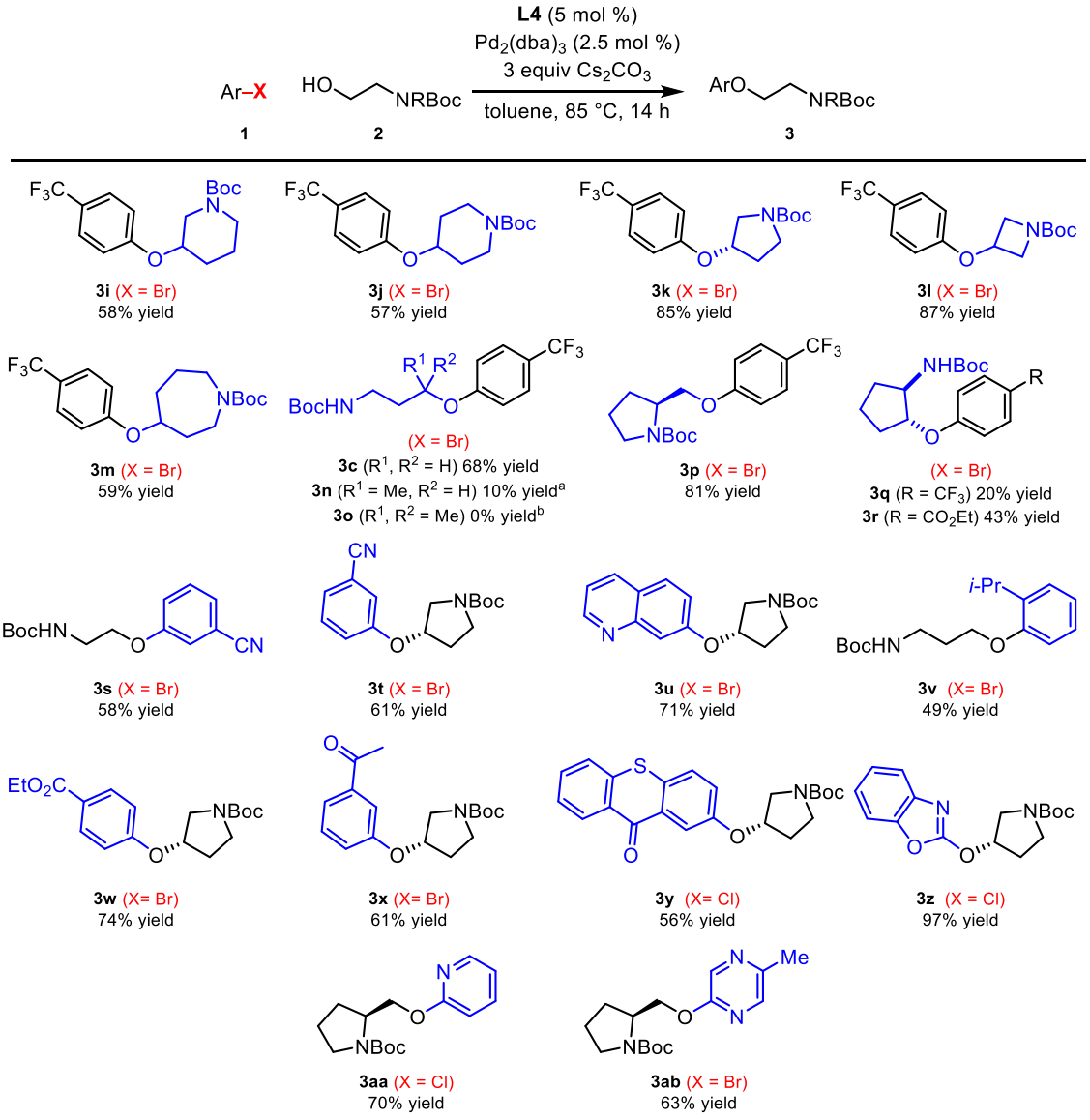
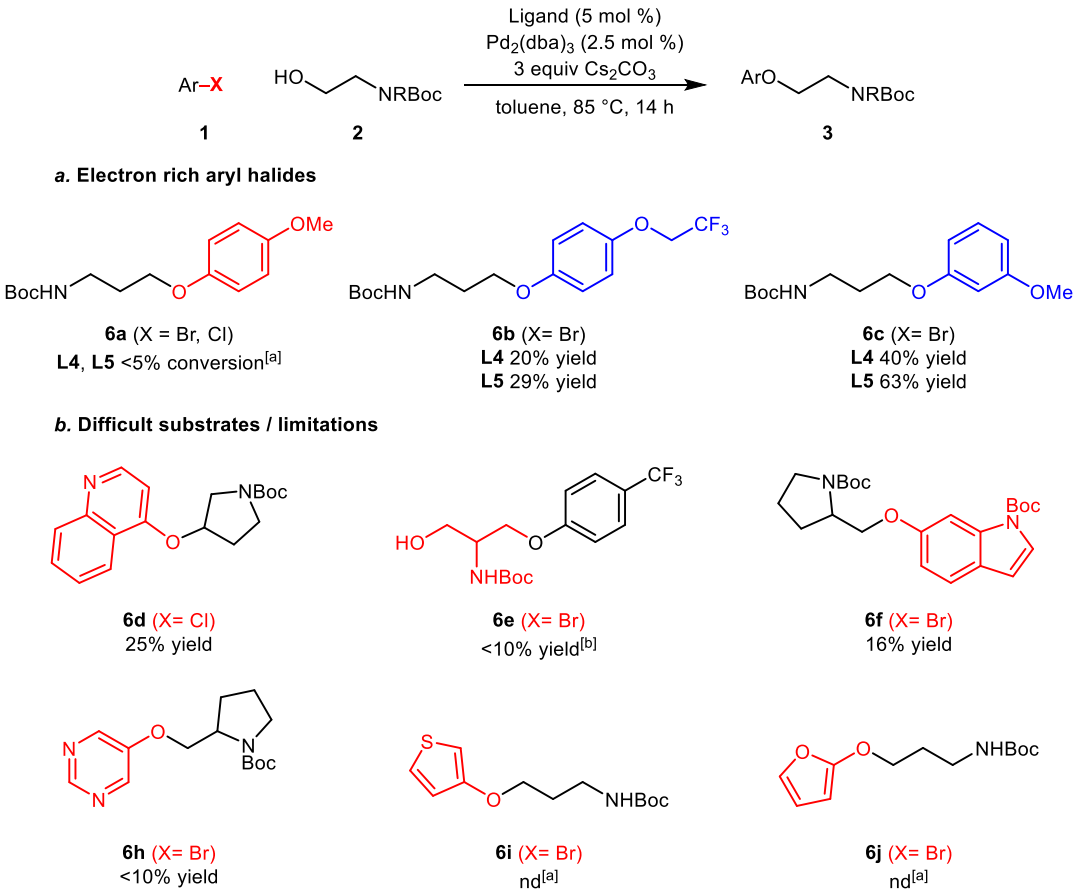


Scheme 2. Substrate scope of amino alcohols and aryl halides. [a] A mixture of O- and N-arylated products was formed (see supporting information for details). [b] The N-arylated carbamate product was isolated in 77% yield (see supporting information for details).

A common challenge in Pd promoted coupling reactions are electron rich aryl halides.[18] As shown in Scheme 3, the formation of para methoxy **6a** was not observed, rather a complex mixture of side products was formed. We did find that the less electron rich p-OCH_2CF_3 **6b** could be isolated in 20% yield. As described by Beller,[7f] the use of the bis(adamantyl)phosphine ligand **L5** resulted in a significant increase in reaction efficiency with electron rich substrates, as **6b** was isolated in 29% yield (~50% increase in yield over the use of **L4**). Similarly, *m*-methoxy substituted **6c** was isolated in 63% yield (vs 40% when **L4** was employed). Other limitations of the current methodology include the coupling of electron-rich

10.1002/adsc.201901302

heteroaromatics such as 4-chloroquinoline, 5-bromopyrimidine, and 1-Boc-6-bromoindole, which gave products **6d**, **6h** and **6f** in <25% yield, while 3-bromothiophene and 2-bromofuran leading to **6i** and **6j** were not stable to the reaction conditions. Further limitations around the alcohol substrate include protected serine and threonine derivatives (acid and esters), as well as glycol type substrates with or without protection of the pendant alcohol (**6e**).



Scheme 3. Challenging substrates and limitations of the reaction. [a] Conversion was assessed by LC/MS analysis. [b] Formation of a mixture of N-, O- and bis-arylated products was observed.

Conclusion

In this study, we have found that established conditions for Pd-catalyzed C-O coupling have proven reliable to provide scalable access to 1,2- and 1,3 amino aryl ethers. While several amine protecting groups were tolerated in the coupling reaction, Boc protection of non-tertiary amines was demonstrated as the most general means to not only reverse the inherent chemoselectivity of the reaction, but to also prevent reaction of the alcohol with the carbamate group. Our results showed comparable substrate scope and reactivity

patterns as simple alcohol substrates, leading to a number of products in good to excellent yield utilizing a variety of readily available amino alcohol building blocks. The robustness of this methodology has enabled rapid application up to kilogram scale both internally and with external CRO partners. In addition, with a well-defined scope, we anticipate this methodology will find ready application to parallel and library synthesis platforms to enable access to diverse chemical space containing this historically rich pharmacophore motif. Our current efforts are aimed towards expanding the substrate scope by developing a deeper understanding of some of the ligand effects observed with challenging substrates.

Experimental Section

Under a nitrogen atmosphere, an oven-dried 50 mL two-neck flask equipped with a magnetic stir bar was charged with cesium carbonate (977 mg, 3 mmol, 3 equiv), $Pd_2(dba)_3$ (22.9 mg, 0.025 mol, 2.5 mol %) and ligand **L4** (25.3 mg, 0.05 mmol, 5 mol %). The flask was sealed with a septum and then purged by performing two vacuum-to-nitrogen cycles with a manifold. A solution of aryl bromide in anhydrous toluene (4 mL) was added via syringe, followed by another purge cycle with the manifold.[19] The dark red suspension was then allowed to stir at 85 °C (external) until a color change indicating oxidative addition was observed (usually within 10-15 minutes). At this point, a solution of the amino alcohol derivative (2 mmol) in anhydrous toluene (1 mL) was added via syringe, and the reaction allowed to stir for 14h. The reaction mixture was allowed to cool to room temperature, and the dark suspension was filtered through a pad of Celite and washed through with EtOAc. The filtrate was concentrated by rotary evaporation under reduced pressure. The dark oil residue was subjected to silica gel chromatography, eluting with heptanes and EtOAc gradients, to afford the aryl ether product after removal of solvents.

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References

[1] In addition to common pharmaceuticals such as epinephrine and beta–blockers, see: a) E. F. Nemeth, B. C. Van Wagenen, M. F. Balandrin, in *Progress in Medicinal Chemistry, 1st ed., Vol. 57* (Eds.: D. Witty, B. Cox), Elsevier, San Diego, **2018**, pp. 1–86; b) H. A. Kirst, N. E. Allen, in *Comprehensive Medicinal Chemistry II, 1st ed., Vol. 7* (Eds.: J. B. Taylor, D. J. Triggle), Elsevier, Amsterdam, **2007**, pp. 629–652; For selected examples, see: c) R. A. Duffy, C. Morgan, R.Naylor, G. A. Higgins, G. B. Varty, J. E. Lachowicz, E. M. Parker, *Pharmacol. Biochem. Behav.*, **2012**, *102*, 95–100; d) J. Y. Gauthier, N. Chauret, W. Cromlish, W. C. Black, *et al.*, *Bioorg. Med. Chem. Lett.*, **2008**, *2*, 218–222.

[2] a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.*, **1996**, 96, 835–876; b) J. Vicario, D. Badia, L. Carrillo, E. Reyes and J. Etxebarria, *Curr. Org. Chem.*, **2005**, 9, 219–235; c) S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767–796; d) H. C. Kolb, K. B. Sharpless, in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, (Eds. M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**; e) A. G. Myers, M. G. Charest,

Myers, Pseudoephedrine. In e-Encyclopedia of Reagents for Organic Synthesis, **2003**, (Ed.), doi:10.1002/047084289X.rn00136; f) M. R. Morales, K. T. Mellem, and A. G. Myers, *Angewandte Chemie International Edition*, **2012**, 51(19), 4568–4571; g) Singh, R., Deng L. in *Asymmetric Organocatalysis 2*, (Ed., Maruoka, K.), Science of Synthesis, Georg Thieme Verlag KG: New York, **2012**, pp. 41–117.

[3] For reviews on the synthesis of amino alcohols, see: a) S. C. Bergmeier, *Tetrahedron*, **2000**, *56*, 2561–2576; b) M. Zaidlewicz, M. Sokol, A. Wolan, J. Cytarska, A. Tafelska-Kaczmarek, A. Dzielendziak, A. Prewysz-Kwinto, *Pure Appl. Chem.* **1996**, *68*, 663; c) cf 2a; d) C. Anaya de Parrodi, E. Juaristi, *Synlett*, **2006**, 2699–2715; e) T. J. Donohoe, C. K. A. Callens, A. Flores, A. R. Lacy, A. H. Rathi, *Chem. Eur. J.*, **2011**, *17*, 58–76, f) H.-T. Chang, K.B. Sharpless, *Tetrahedron Lett.*, **1996**, 37, 3219; g) J. A. Birrell, E. N. Jacobsen, *Org. Lett.*, **2013**, *15*, 2895–2897; S. E. Shaus, J. F. Larrow, E. N. Jacobsen, *J. Org. Chem.*, **1997**, *62*, 4197–4199.

[4] a) D. T. Wong, D. W. Robertson, F. P. Bymaster, J. K. Krushinski, L. R. Reid, *Life Sci.* **1988**, *43*, 2049–2057; b) J. F. Kurtzke, J. Gylfe, *Neurology* **1962**, *12*, 343; c) C. D. Jones, M. G. Jevnikar, A. J. Pike, M. K. Peters, L. J. Black, A. R. Thompson, J. F. Falcone, J. A. Clemens, *J. Med. Chem.* **1984**, *8*, 1057–1066; d) T. Takenaka, K. Honda, T. Fujikura, *J. Pharm. Pharmacol.* **1984**, *36*, 539–542.

[5] For a representative overview, see: a) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458; for relevant publications, see: b) J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456; c) G. Chauviere, C. Viode, J. Perie, *J. Heterocycl. Chem.* **2000**, *37*, 119–126; d) J. Zilberman, *Org. Process Res. Dev.* **2003**, *7*, 303–305; e) E. Fuhrmann, J. Talbiersky, Org. Process Res. Dev. **2005**, *9*, 206–211. For a relevant recent study, see: f) E. E. Kwan, Y. Zeng, H. A. Besser, E. N. Jacobsen, *Nat. Chem.* **2018**, *10*, 917–923.

[6] For relevant reviews, see: a) Q. Cai, H. Zhang, B. Zou, X. Xie, W. Zhu, G. He, J. Wang, X. Pen, Y. Chen, Q. Yuan, F. Liu, B. Lu, D. Ma, *Pure Appl. Chem.* **2009**, *81*, 227–234; b) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev*. **2014**, *43*, 3525–3550; For relevant studies, see: c) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973–976; d) A. Shafir, P. A. Lichtor, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491; e) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 284–286; f) D. Maiti, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 17423-17429; g) D. Ma, Q. Cai, *Org. Lett.* **2003**, *5*, 3799–3802; h) Z. Chen, Y. Jiang, L. Zhang, Y. Guo, D. Ma, *J. Am. Chem. Soc.* **2019**, *141*, 3541-3549.

[7] a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; b) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; c) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378; d) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149; e) G. J. Withbroe, R. A. Singer, J. E. Sieser, *Org. Process Res. Dev.* **2008**, *12*, 480–489; f) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598; g) P. E. Maligres, J. Li, S. W. Krska, J. D. Schreiner, I. T. Raheem, *Angew. Chem., Int. Ed.* **2012**, *51*, 9071–9074; h) S. Gowrisankar, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 2498–2502; i) C. W. Cheung, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 3998–4001; j) T. M. Rangarajan, R. Singh, R. Brahma, K. Devi, R. P. Singh, R. P. Singh, A. K. Prasad, *Chem. Eur. J.* **2014**, *20*, 14218–14225; k) T. M. Rangarajan, R. Brahma, Ayushee, A. K. Prasad, A. K. Verma, R. P. Singh, *Tetrahedron Lett.* **2015**, *56*, 2234–2237; l) H. Zhang, P. Ruiz-Castillo, S. L. Buchwald, *Org. Lett.* **2018**, *20*, 1580–1583; m) I. S. Young, E. M. Simmons, M. D. B. Fenster, J. J. Zhu, K. R. Katipalli, *Org. Process Res. Dev.*, **2018**, *22*, 585–594.

[8] For Ni promoted synthesis of alkyl-aryl ethers, see: a) P. M. MacQueen, J. P. Tassone, C. Diaz, M. Stradiotto, *J. Am. Chem. Soc.* **2018**, *140*, 5023-5027. For coupling reactions utilizing photo-redox catalysis, see: b) J. A. Terrett, J. D. Cuthbertson, V. W. Shurtleff, D. W. C. MacMillan, *Nature*, **2015**, *524*, 330–334; c) Q.-Q. Zhou, F.-D. Lu, D. Liu, L.-Q. Lu, W.-J. Xiao, *Org. Chem. Front.* **2018**, *5*, 3098–3102.

[9] All of the examples utilize amino alcohols containing tertiary amines in which the substituents are incorporated into the final molecule. See: refs. 7f, 7g, and 7m.

[10] For a recent study exploring catalyst sequestration in Pd catalyzed C-N coupling, see: a) N. A. Strotman, M. C. Soumeillant, K. Zhu, C. E. Markwalter, C. S. Wei, Y. Hsiao, M. D. Eastgate, *J. Org. Chem.* **2019**, *84*, 4653–4660. For further studies, see: b) ref. 6d. For studies discussing the issue of beta-hydride elimination in Pd promoted C-O coupling, see: refs. 7b and 7m.

[11] a) See ref. 6h; b) M. E. Khatib, G. A. Molander, *Org. Lett.* **2014**, *16*, 4944–4947; c) M. Al Masum, L. Quinones, L. T. Cain, *Int. J. Org. Chem.* **2016**, *6*, 100–106.
[12] For a discussion of the importance of premixing reagents and establishing the initial oxidative addition occured in absence of alcohol, see: ref 7g.
[13] a) For procedures for the preparation of complex **Pd-1**, see: B. T. Ingoglia, S. L. Buchwald, *Org. Lett.* **2017**, *19*, 2853–2856. See supporting information for details. b) CCDC-1959277 (**Pd-1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
[14] Although not extensively considered for this work, a screening of typical Pd sources in our reaction of interest revealed $Pd_2(dba)_3$ to give the best results, but most other common sources were also effective in addition to the specific methodologies in ref. 7. For a relevant discussion, see: a) B. Schlummer, U. Scholz, *Adv. Synth. Catal.*, **2004**, *346*, 1599–1626.
[15] Not shown in the table, a comparison of typical solvents and bases confirmed best results when employing cesium carbonate and toluene, although the differences were not substantial. In cases where one of the substrate partners was poorly soluble in toluene and could not be added neat, 1,4-dioxane was substituted with nearly identical results.
[16] See supporting information for details.
[17] The product of β-hydride elimination of the alcohol substrate was also isolated in 26% yield, but coupling of the secondary NH carbamate was not significantly observed. Similar results were observed in the reaction to produce **3r**.
[18] R. A. Widenhoefer, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511
[19] In cases where the alcohol substrate was insufficiently soluble in toluene, the entire 5 mL volume was added with the aryl bromide and the alcohol was added as a solid through the second neck. No significant differences in reaction performance were observed, highlighting the robustness of the reaction.

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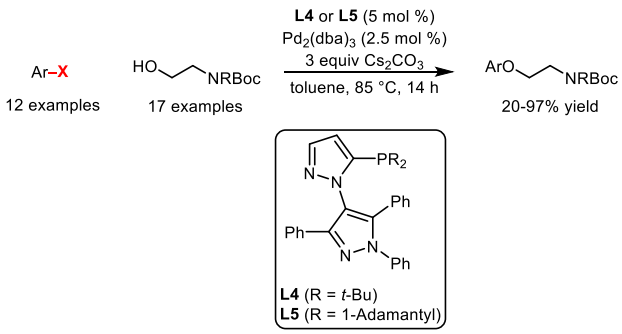
UPDATE

Palladium Catalyzed C–O Coupling of Amino Alcohols for the Synthesis of Aryl Ethers



Adv. Synth. Catal. **2020**, *Volume*, Page – Page

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2