



Published in final edited form as:

Org Lett. 2020 July 17; 22(14): 5369–5374. doi:10.1021/acs.orglett.0c01668.

An Improved Process for the Palladium-Catalyzed C–O Cross-Coupling of Secondary Alcohols

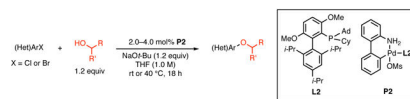
Hong Zhang, Paula Ruiz-Castillo, Alexander W. Schuppe, Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Abstract

An improved protocol for the Pd-catalyzed C–O cross-coupling of secondary alcohols is described. The use of biaryl phosphine **L2** as the ligand was key to achieving efficient cross-coupling of (hetero)aryl chlorides with only a 20% molar excess of the alcohol. Additionally, we observed an unusual reactivity difference between an electron-rich aryl bromide and the analogous aryl chloride, and deuterium-labeling suggested that currently unidentified pathways for reduction play an important role in explaining this disparity.

Graphical Abstract



The synthesis of alkyl aryl ethers has seen significant advances in the past decade.¹ Traditional approaches, such as the Williamson ether synthesis,² the Mitsunobu reaction,³ and nucleophilic aromatic substitution,⁴ often require specific and limited classes of substrates to achieve efficient C–O bond formation. Transition-metal-catalyzed C–O cross-coupling reactions, including Pd,⁵ Cu⁶ and Ni⁷ catalysis, have also been improving to operate on an increasingly broad scope of (hetero)aryl halides and aliphatic alcohols. Alternative metal-free approaches involving sulfonate esters^{8a} or diaryliodonium salts^{8b, 8c, 8d} also show great promise.

The Pd-catalyzed *O*-arylation of aliphatic alcohols has been widely explored by our group and by others.⁵ As depicted in Scheme 1, the slow rate of reductive elimination from intermediate [L_nPd^{II}(Ar)(alkoxide)] (**IV**) is generally believed to account for the diminished efficiency of C–O bond formation, compared to the analogous C–N cross-coupling processes.⁹ As a result, competitive β-hydride elimination can lead to the overall reduction

*Corresponding Author: sbuchwal@mit.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

The authors declare the following competing financial interest(s): MIT has or has filed patents on ligands/precatalysts that are described in the paper from which S.L.B. and former coworkers receive royalty payments.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for new compounds (PDF)

of the aryl halide and the formation of undesired carbonyl side products. Between the two classes of aliphatic alcohols bearing β -hydrogens, secondary alcohols are typically considered more challenging coupling partners. Previously, the coupling reaction of primary alcohols has been shown to proceed with higher yields and less reduction of aryl halide, compared to that of the corresponding secondary alcohols under the same reaction conditions.^{5c, 5g, 5i, 5n} The most recent report from our group on the coupling reaction of secondary alcohols introduced the use of a bulky biaryl phosphine ligand RockPhos (**L1**, Figure 1) to facilitate C–O bond formation.⁵ⁱ This method required the use of two equivalents of alcohol substrate at somewhat elevated temperature (90 °C) to provide moderate yields with a restricted scope of alcohol substrates (Scheme 2A).

Two recent reports from the groups of Ma^{6a} and Stradiotto^{7a} demonstrated great potential for utilizing Cu- and Ni-catalyzed methods, respectively, to prepare secondary alkyl aryl ethers. The use of two oxalic diamide ligands and sodium *tert*-butoxide enabled Cu-catalyzed C–O cross-coupling of secondary alcohols with aryl chlorides, bromides and iodides with excellent efficiency.^{6a} Compared to that of more reactive aryl bromides and iodides, the coupling reaction of aryl chlorides still required higher catalyst loading (10 mol % Cu) as well as elevated temperature (100 °C). Ni-catalyzed C–O cross-coupling of secondary alcohols with aryl halides was achieved with the use of (Cy)PAd-DalPhos-based precatalysts,^{7a} proving the feasibility of such transformation in the absence of photoredox catalysts.^{7b} Although the Ni-catalyzed coupling of aryl chlorides with secondary alcohols was first achieved in this report, the method was limited to activated substrates and also required elevated temperature (110 °C). Additionally, all three metal-catalyzed methods necessitated the use of 100% or more molar excess of alcohols (i.e., more than two equivalents of alcohol, with two exceptions^{7a}) to ensure successful C–O bond formation. Therefore, the development of a method that operates under mild conditions, preferably at room temperature, and that utilizes a smaller excess of alcohol (i.e., less than two equivalents of alcohol) for the coupling reactions of (hetero)aryl chlorides and secondary alcohols, remains a desirable goal.

We recently disclosed a catalyst system that employs one of two ligands for Pd-catalyzed C–O cross-coupling reactions of (hetero)aryl halides with primary alcohols.^{5b} In particular, the use of a new (now commercially available, CAS No.: 2197989-24-3) hybrid biaryl phosphine ligand **L2** (Figure 1) allowed the effective coupling of challenging electrophiles, including unactivated aryl chlorides (e.g., electron-rich (hetero)aryl chlorides). Herein, we report the Pd-catalyzed C–O cross-coupling of secondary alcohols, facilitated by the use of **L2**, with a diverse range of (hetero)aryl chlorides under improved reaction conditions: more than half of the reactions proceeded at room temperature, while only requiring a 20% molar excess of alcohols. Additionally, we present examples of the *O*arylation of secondary alcohols with aryl bromides and the observation of an unusual difference in reactivity between an electron-rich aryl bromide and the corresponding aryl chloride.^{5b, 5i, 10}

Following the conditions previously reported for the cross-coupling of primary alcohols,^{5b} we employed palladacycle **P2** (Figure 1) as the precatalyst and 1,4-dioxane as the solvent. Electron-rich aryl chloride **1**, containing a *para*-morpholino substituent, and *sec*-butanol (*s*-BuOH) were chosen as model coupling partners. Lowering the number of equivalents of *s*-

BuOH from 3 to 1.2 resulted in a decline in the efficiency of the reaction: the conversion of the starting aryl chloride **1** decreased by 50%, and the ratio of the reduction side product **4** to the coupling product **3** increased substantially (Table 1, entries 1–3). However, when the solvent was changed to THF, lowering the number of equivalents of *s*-BuOH to 1.2 had a negligible effect on the efficiency of the reaction (Table 1, entries 4–6). Therefore, THF was selected as an appropriate solvent for further exploration of the substrate scope.

Although it is widely accepted that aryl bromides exhibit higher reactivity in cross-coupling reactions than aryl chlorides,^{5b, 5i, 10} we observed an opposite trend between electron-rich aryl chloride **1** and aryl bromide **2**. First, under the same set of reaction conditions (Table 1, entries 6 and 9), while the reaction of **1** provided a 90% yield of desired aryl ether **3**, along with 9% reduction product **4**, that of **2** only provided a 63% yield of **3**, with a notable increase in the amount of **4** (33%) that was formed. Although this difference could be partially ameliorated by adjusting the quantity of *s*-BuOH to 2 equivalents, a further increase of the amount of alcohol utilized did not lead to an additional improvement in the yield of **3** (Table 1, entries 7 and 8).

A variety of (hetero)aryl chlorides and secondary alcohols were surveyed to examine the generality of this method (Scheme 3). The C–O cross-coupling reactions took place under mild conditions, using only a 20% molar excess of alcohols. Many traditionally-challenging substrates, including unactivated aryl chlorides (**3**, **5**, **7**) and five-membered heterocycles (**9**, **10**, **11**) readily underwent C–O bond formation at room temperature. Various heterocycles, such as a quinoline (**7**), a pyridazine (**8**), a pyrazole (**8**), a thiadiazole (**9**), a benzisothiazole (**10**), a benzimidazole (**11**), a pyrazine (**12**), a quinazoline (**13**), a pyrazolopyrimidine (**14**), and a pyridine (**15**) were tolerated as structural components in the electrophiles. Functional groups such as an unprotected tertiary hydroxyl group (**6**), a carbamate group (**7**), and a lactone (**14**) were also compatible with the reaction conditions. While sterically accessible alcohols proved to be good coupling partners at room temperature, secondary alcohols with moderate steric encumbrance at either the α -carbon (**12**, **13**) or the β -carbon (**14**, **15**) required moderate heating (40 °C) to react with activated heteroaryl chlorides and afford corresponding heteroaryl ethers in 80% yields.

The coupling reactions between electron-rich aryl chlorides and more sterically-demanding nucleophiles, however, remained challenging, as demonstrated in the reactions of aryl chloride **1** (Table 2). As the steric congestion around the α -carbon of the alcohol increased (Table 2, entries 1 and 2), both the conversion and the yield of desired product decreased by approximately 40%, while a small increase in reduction product **4** was observed. We hypothesize that increasing the steric bulk around the α -carbon could negatively impact the binding tendency of alcohol nucleophiles to the oxidative-addition complex **II** (Scheme 1), thus accounting for the less efficient C–O bond formation. Although heteroaryl ethers **9**, **12**, and **13** were prepared and isolated in >80% yields, benzylic alcohols proved to be more difficult coupling partners for electron-rich aryl chloride **1** (Table 2, entries 3 and 4). The steric environment of the benzylic carbon also played an important role in the coupling process, as a change from a methyl to an ethyl group led to a 60% decrease in conversion, and only a trace amount of desired product was detected (Table 2, entries 3 and 4).

As we continued to examine the scope of C–O cross-coupling reactions of aryl bromides, we noticed that the difference in reaction efficiency between the cross-coupling of aryl bromides and aryl chlorides was greatest for highly electron-rich substrates, such as **2** vs **1** (to prepare **3** in Schemes 4 and 3, respectively). In contrast, for weakly electron-rich, electron-neutral and electrondeficient aryl bromides (to prepare **5**, **16** and **17**, respectively), the cross-coupling reactions proceeded with comparable levels of efficiency (>80% yield, Scheme 4).

To gain an understanding of the difference in reactivity between aryl halides **1** and **2**, we performed experiments to examine the cause of increased reduction in the cross-coupling reaction of aryl bromide **2**. In order to ascertain whether reduction product **4** resulted solely from β -hydride elimination, we prepared α -deutero-alcohol **18-d** (98% d_1 , see Supporting Information) and examined its reaction with aryl bromide **2**. When **2** and protio-alcohol **18** were subjected to the standard cross-coupling conditions, the desired product **19** and the reduction product **4** were observed in 47% and 54% yield, respectively as determined by ^1H NMR analysis, while ketone **20** was formed in 31% yield, as judged by GC analysis (Scheme 5A). Ketone **20** is believed to result from β -hydride elimination from the intermediate $[\text{L}_n\text{Pd}^{\text{II}}(\text{Ar})(\text{alkoxide})]$ (**IV**, Scheme 1), and should theoretically be formed in a 1:1 ratio with **4**. Therefore, these results indicate that β -hydride elimination only accounts for a fraction of the formation of **4**. When **2** and **18-d** were subjected to the cross-coupling conditions, the desired product **19-d** was formed in 65% yield and contained the same amount of deuterium (98%) as in **18-d** (estimated by ^1H NMR analysis, Scheme 5B). Reduction product **4-d** was formed in 36% yield (by ^1H NMR analysis) and was 80% d_1 (by HRMS analysis). Ketone **20** was detected in 20% yield by GC analysis. Taken together, these experiments demonstrate that not all reduction side product arises from β -hydride (deuteride) elimination, and some stems from (as yet) unidentified processes. It is conceivable that the reduction byproduct may arise from protodemetalation of the oxidative addition complex $[\text{L}_n\text{Pd}^{\text{II}}(\text{Ar})\text{X}]$ (**II**, Scheme 1). Similar findings have been reported by Hartwig, in his studies of the Pd-catalyzed amination of aryl bromides in the presence of bidentate ligands.¹¹

In conclusion, we have developed a significantly improved procedure for the Pd-catalyzed C–O cross-coupling of secondary alcohols. This protocol employs a previously disclosed hybrid biaryl phosphine ligand **L2**, while using THF as the reaction solvent in lieu of 1,4-dioxane as in our previous report. A variety of (hetero)aryl ethers were obtained in higher yields from the corresponding (hetero)aryl halides under more user-friendly reaction conditions than in our earlier method. For instance, a 20% molar excess of alcohols sufficed to allow the cross-coupling reaction of (hetero)aryl chlorides at room temperature or 40 °C. An interesting but unconventional reactivity difference between an electron-rich aryl bromide **2** and chloride **1** was discovered. A deuterium-labeling study suggested the possibility of as yet unidentified pathways responsible for the greater reduction of aryl bromide **2**, indicating the need for further studies to establish a better detailed understanding of the mechanism of the Pd-catalyzed C–O coupling under these conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Research reported in this publication was supported by the National Institutes of Health (R35-GM122483) and Arnold and Mabel Beckman Foundation for a postdoctoral fellowship to A.W.S. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We acknowledge MilliporeSigma (formerly Aldrich) for the generous donation of 1-adamantylzinc bromide solution, and Ryan King (MIT) for one batch of 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl used in this work. We thank Dr. Jeffrey Yang (MIT) and Dr. Bryan Ingoglia (MIT) for helpful discussions. We thank Dr. Scott McCann (MIT), Dr. Richard Liu (MIT), and Dr. Christine Nguyen (MIT) for their assistance with the preparation of this manuscript.

REFERENCES

1. Mandal S; Mandal S; Ghosh SK; Sar P; Ghosh A; Saha R; Saha B, A review on the advancement of ether synthesis from organic solvent to water. *RSC Adv.* 2016, 6, 69605–69614.
2. (a)Wang Z, Williamson Ether Synthesis. In *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc.: John Wiley & Sons, Inc.: Hoboken, 2010; pp 3026–3030;(b)Fuhrmann E; Talbiersky J, Synthesis of Alkyl Aryl Ethers by Catalytic Williamson Ether Synthesis with Weak Alkylation Agents. *Org. Process Res. Dev* 2005, 9, 206–211.
3. (a)Fletcher S, The Mitsunobu reaction in the 21st century. *Org. Chem. Front* 2015, 2, 739–752; (b)Swamy KCK; Kumar NNB; Balaraman E; Kumar KVPP, Mitsunobu and Related Reactions: Advances and Applications. *Chem. Rev* 2009, 109, 2551–2651; [PubMed: 19382806] (c)Manivel P; Rai NP; Jayashankara VP; Arunachalam PN, Base catalyzed Mitsunobu reactions as a tool for the synthesis of aryl sec-alkyl ethers. *Tetrahedron Lett.* 2007, 48, 2701–2705.
4. (a)Caron S; Ghosh A, Nucleophilic Aromatic Substitution. In *Practical Synthetic Organic Chemistry*, John Wiley & Sons, Inc.: Hoboken, 2011; pp 237–253;(b)Henderson AS; Medina S; Bower JF; Galan MC, Nucleophilic Aromatic Substitution (S_NAr) as an Approach to Challenging Carbohydrate–Aryl Ethers. *Org. Lett* 2015, 17, 4846–4849. [PubMed: 26379123]
5. (a)Laffoon SD; Chan VS; Fickes MG; Kotecki B; Ickes AR; Henle J; Napolitano JG; Franczyk TS; Dunn TB; Barnes DM; Haight AR; Henry RF; Shekhar S, Pd-Catalyzed Cross-Coupling Reactions Promoted by Biaryl Phosphorinane Ligands. *ACS Catal.* 2019, 9, 11691–11708;(b)Zhang H; Ruiz-Castillo P; Buchwald SL, Palladium-Catalyzed C–O Cross-Coupling of Primary Alcohols. *Org. Lett* 2018, 20, 1580–1583; [PubMed: 29474078] (c)Sawatzky RS; Hargreaves BKV; Stradiotto M, A Comparative Ancillary Ligand Survey in Palladium-Catalyzed C–O Cross-Coupling of Primary and Secondary Aliphatic Alcohols. *Eur. J. Org. Chem* 2016, 2016, 2444–2449;(d)Rangarajan TM; Brahma R; Ayushee; Prasad AK; Verma AK; Singh RP, Mild and efficient palladium/BrettPhos-catalyzed methoxylation and deuteriomethoxylation of activated aryl bromides. *Tetrahedron Lett.* 2015, 56, 2234–2237;(e)Rangarajan TM; Singh R; Brahma R; Devi K; Singh RP; Singh RP; Prasad AK, BrettPhos Ligand Supported Palladium-Catalyzed C–O Bond Formation through an Electronic Pathway of Reductive Elimination: Fluoroalkoxylation of Activated Aryl Halides. *Chem. Eur. J* 2014, 20, 14218–14225; [PubMed: 25236851] (f)Cheung CW; Buchwald SL, Mild and General Palladium-Catalyzed Synthesis of Methyl Aryl Ethers Enabled by the Use of a Palladacycle Precatalyst. *Org. Lett* 2013, 15, 3998–4001; [PubMed: 23883393] (g)Maligres PE; Li J; Krska SW; Schreier JD; Raheem IT, C–O Cross-Coupling of Activated Aryl and Heteroaryl Halides with Aliphatic Alcohols. *Angew. Chem. Int. Ed* 2012, 51, 9071–9074;(h)Gowrisankar S; Neumann H; Beller M, A Convenient and Practical Synthesis of Anisoles and Deuterated Anisoles by Palladium-Catalyzed Coupling Reactions of Aryl Bromides and Chlorides. *Chem. Eur. J* 2012, 18, 24982502; (i)Wu X; Fors BP; Buchwald SL, A Single Phosphine Ligand Allows Palladium-Catalyzed Intermolecular C–O Bond Formation with Secondary and Primary Alcohols. *Angew. Chem. Int. Ed* 2011, 50, 9943–9947;(j)Enthaler S; Company A, Palladium-catalysed hydroxylation and alkoxylation. *Chem. Soc. Rev* 2011, 40, 4912–4924; [PubMed: 21643619] (k)Gowrisankar S; Sergeev AG; Anbarasan P; Spannenberg A; Neumann H; Beller M, A General and Efficient Catalyst for Palladium-Catalyzed C–O Coupling Reactions of Aryl Halides with Primary Alcohols. *J. Am. Chem. Soc* 2010, 132, 11592–11598; [PubMed: 20672810] (l)Milton EJ; Fuentes JA; Clarke ML, Palladium-catalysed synthesis of aryl-alkyl ethers using alkoxy silanes as nucleophiles. *Org. Biomol. Chem* 2009, 7, 26452648;(m)Withbroe GJ; Singer RA; Sieser JE, Streamlined Synthesis of the Bippyphos Family of Ligands and Cross-Coupling Applications. *Org. Process Res. Dev* 2008, 12,

- 480–489;(n)Vorogushin AV; Huang X; Buchwald SL, Use of Tunable Ligands Allows for Intermolecular Pd-Catalyzed C–O Bond Formation. *J. Am. Chem. Soc* 2005, 127, 8146–8149. [PubMed: 15926842]
6. (a)Chen Z; Jiang Y; Zhang L; Guo Y; Ma D, Oxalic Diamides and tert-Butoxide: Two Types of Ligands Enabling Practical Access to Alkyl Aryl Ethers via Cu-Catalyzed Coupling Reaction. *J. Am. Chem. Soc* 2019, 141, 3541–3549; [PubMed: 30688450] (b)Bhunia S; Pawar GG; Kumar SV; Jiang Y; Ma D, Selected Copper-Based Reactions for C–N, C–O, C–S, and C–C Bond Formation. *Angew. Chem. Int. Ed* 2017, 56, 16136–16179;(c)Lam PYS, Chapter 7 Chan-Lam Coupling Reaction: Copper-promoted C-Element Bond Oxidative Coupling Reaction with Boronic Acids. In *Synthetic Methods in Drug Discovery: Volume 1*, The Royal Society of Chemistry: 2016; Vol. 1, pp 242–273;(d)Lin H; Sun D, Recent Synthetic Developments and Applications of the Ullmann Reaction. A Review. *Org. Prep. Proced. Int* 2013, 45, 341–394;(e)Niu J; Zhou H; Li Z; Xu J; Hu S, An Efficient Ullmann-Type C–O Bond Formation Catalyzed by an Air-Stable Copper(I)–Bipyridyl Complex. *J. Org. Chem* 2008, 73, 7814–7817; [PubMed: 18771324] (f)Altman RA; Shafir A; Choi A; Lichtor PA; Buchwald SL, An Improved CuBased Catalyst System for the Reactions of Alcohols with Aryl Halides. *J. Org. Chem* 2008, 73, 284–286; [PubMed: 18044928] (g)Zhang H; Ma D; Cao W, N,N-Dimethylglycine-Promoted Ullmann-Type Coupling Reactions of Aryl Iodides with Aliphatic Alcohols. *Synlett* 2007, 2007, 0243–0246;(h)Wolter M; Nordmann G; Job GE; Buchwald SL, Copper-Catalyzed Coupling of Aryl Iodides with Aliphatic Alcohols. *Org. Lett* 2002, 4, 973–976. [PubMed: 11893199]
7. (a)MacQueen PM; Tassone JP; Diaz C; Stradiotto M, Exploiting Ancillary Ligation To Enable Nickel-Catalyzed C–O Cross-Couplings of Aryl Electrophiles with Aliphatic Alcohols. *J. Am. Chem. Soc* 2018, 140, 5023–5027; [PubMed: 29601188] (b)Terrett JA; Cuthbertson JD; Shurtleff VW; MacMillan DWC, Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* 2015, 524, 330–334; [PubMed: 26266976] (c)Mann G; Hartwig JF, Nickel- vs Palladium-Catalyzed Synthesis of Protected Phenols from Aryl Halides. *J. Org. Chem* 1997, 62, 5413–5418.
8. (a)Sach NW; Richter DT; Cripps S; Tran-Dubé M; Zhu H; Huang B; Cui J; Sutton SC, Synthesis of Aryl Ethers via a Sulfonyl Transfer Reaction. *Org. Lett* 2012, 14, 3886–3889; [PubMed: 22799458] (b)Lindstedt E; Stridfeldt E; Olofsson B, Mild Synthesis of Sterically Congested Alkyl Aryl Ethers. *Org. Lett* 2016, 18, 42344237.(c)Sundalam SK; Stuart DR, Base Mediated Synthesis of Alkyl-aryl Ethers from the Reaction of Aliphatic Alcohols and Unsymmetric Diaryliodonium Salts. *J. Org. Chem* 2015, 80, 64566466.(d)Lindstedt E; Ghosh R; Olofsson B, Metal-Free Synthesis of Aryl Ethers in Water. *Org. Lett* 2013, 15, 6070–6073. [PubMed: 24228788]
9. (a)Hartwig JF, Electronic Effects on Reductive Elimination To Form Carbon–Carbon and Carbon–Heteroatom Bonds from Palladium(II) Complexes. *Inorg. Chem* 2007, 46, 1936–1947; [PubMed: 17348724] (b)Widenhoefer RA; Buchwald SL, Electronic Dependence of C–O Reductive Elimination from Palladium (Aryl)neopentoxide Complexes. *J. Am. Chem. Soc* 1998, 120, 6504–6511.
10. (a)Ingoglia BT; Wagen CC; Buchwald SL, Biaryl monophosphine ligands in palladium-catalyzed C–N coupling: An updated User’s guide. *Tetrahedron* 2019, 75, 4199–4211; [PubMed: 31896889] (b)Ruiz-Castillo P; Blackmond DG; Buchwald SL, Rational Ligand Design for the Arylation of Hindered Primary Amines Guided by Reaction Progress Kinetic Analysis. *J. Am. Chem. Soc* 2015, 137, 3085–3092; [PubMed: 25651374] (c)Barrios-Landeros F; Carrow BP; Hartwig JF, Effect of Ligand Steric Properties and Halide Identity on the Mechanism for Oxidative Addition of Haloarenes to Trialkylphosphine Pd(0) Complexes. *J. Am. Chem. Soc* 2009, 131,8141–8154; [PubMed: 19469511] (d)Littke AF; Fu GC, Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. *Angew. Chem. Int. Ed* 2002, 41, 4176–4211;(e)Grushin VV; Alper H, Transformations of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev* 1994, 94, 1047–1062.
11. Hamann BC; Hartwig JF, Systematic Variation of Bidentate Ligands Used in Aryl Halide Amination. Unexpected Effects of Steric, Electronic, and Geometric Perturbations. *J. Am. Chem. Soc* 1998, 120, 3694–3703.

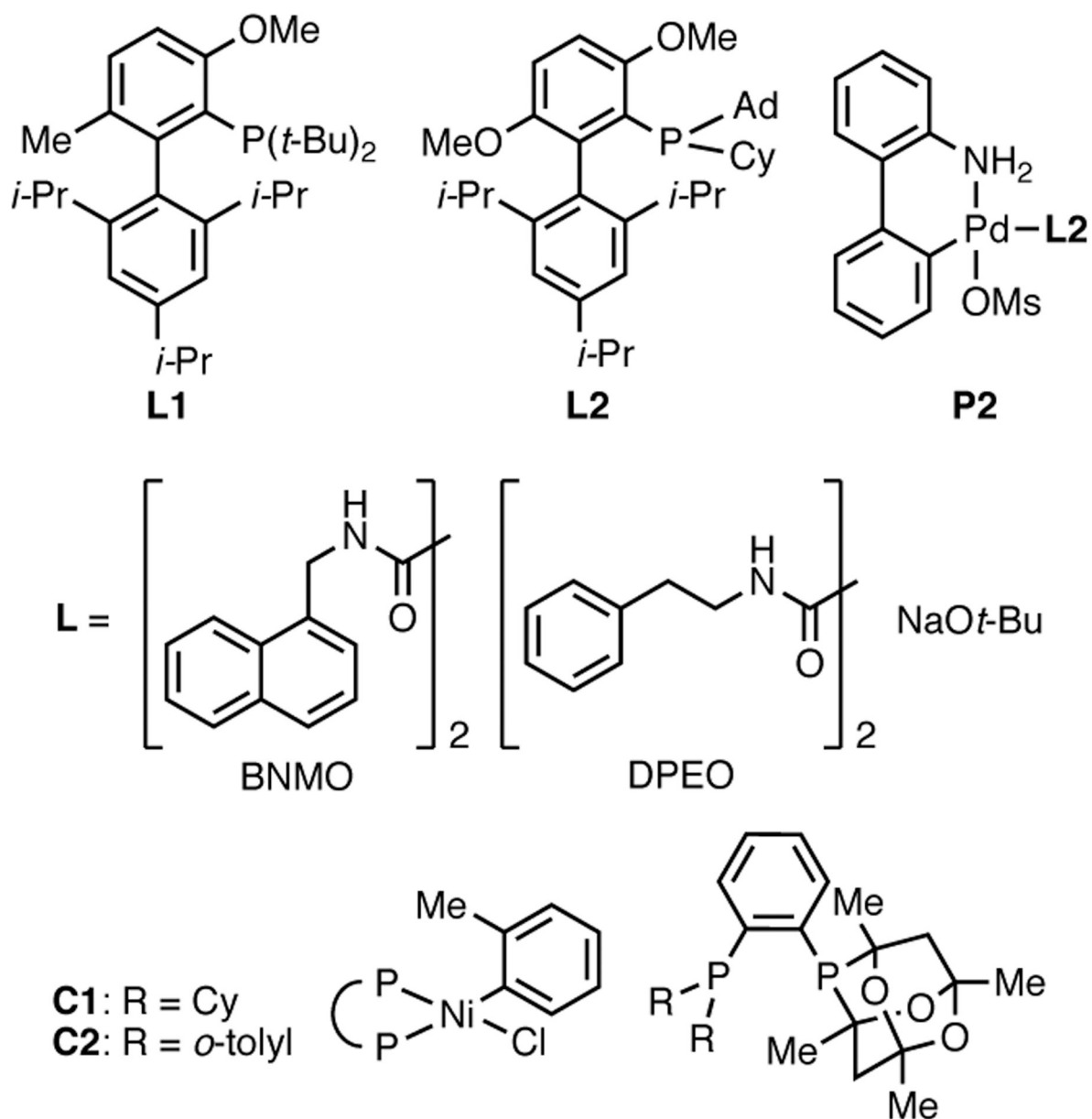
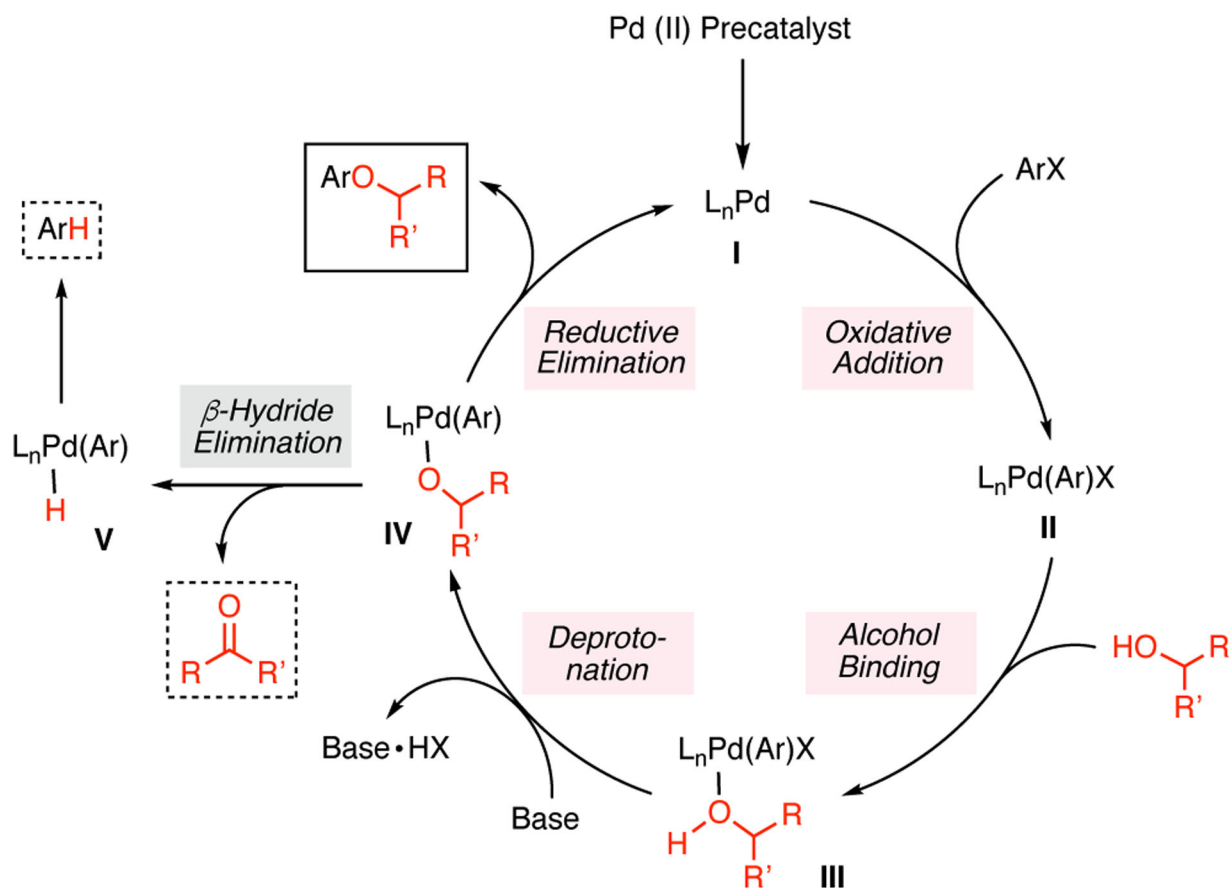
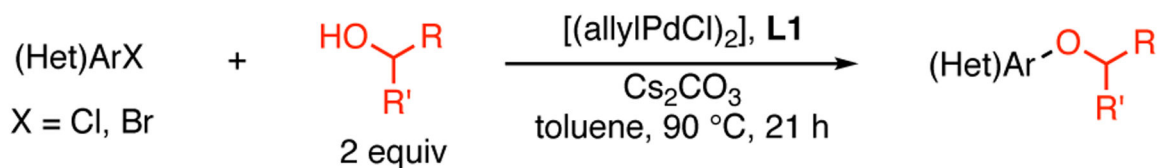
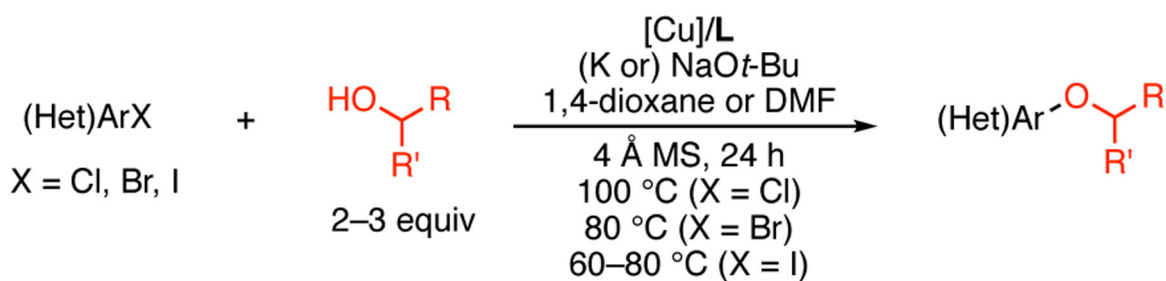
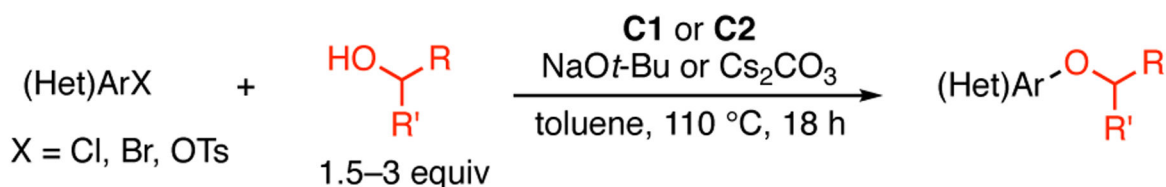


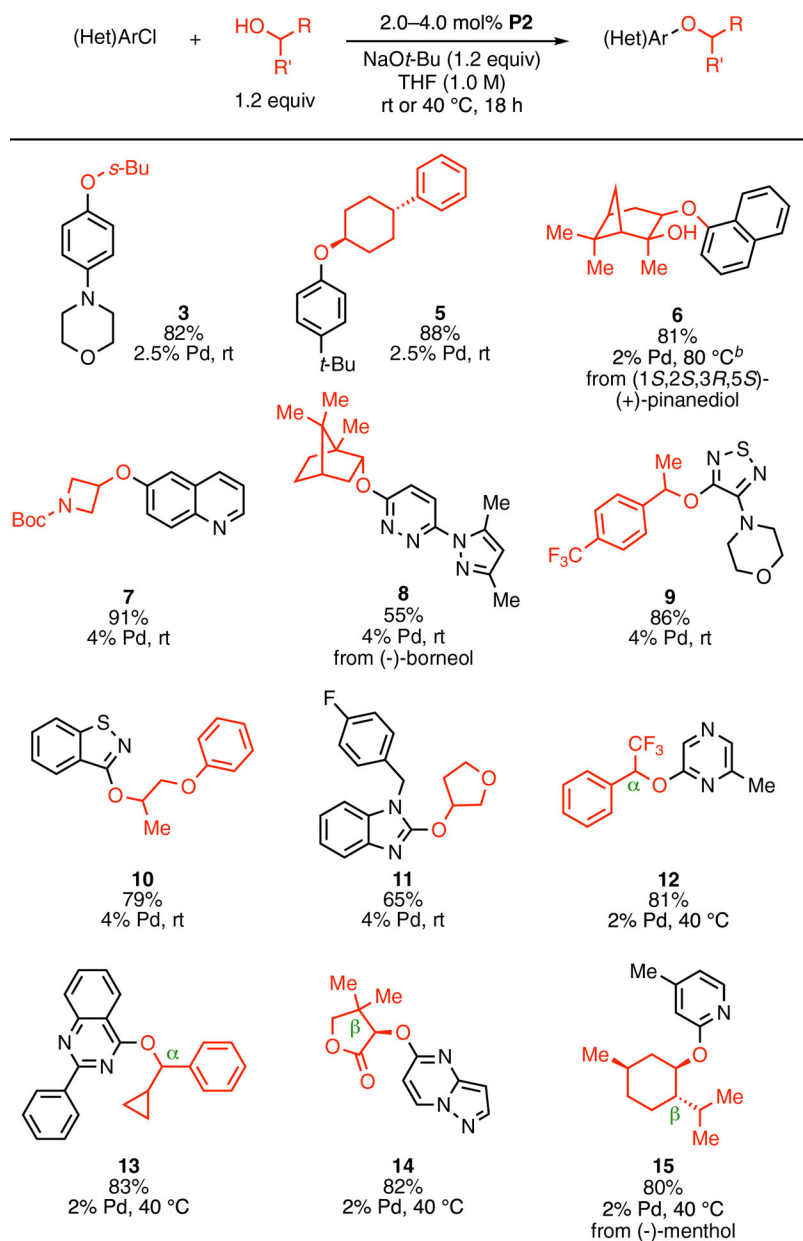
Figure 1. Ligands and precatalysts employed in Pd-, Cu- and Ni-catalyzed C–O cross-coupling of secondary alcohols.



Scheme 1.
General catalytic cycle of Pd-catalyzed C–O cross-coupling of aryl halides with secondary alcohols.

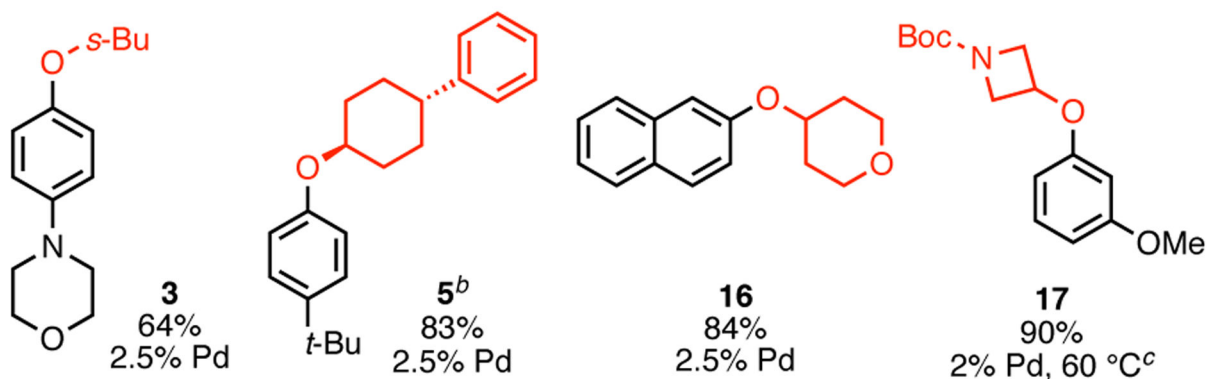
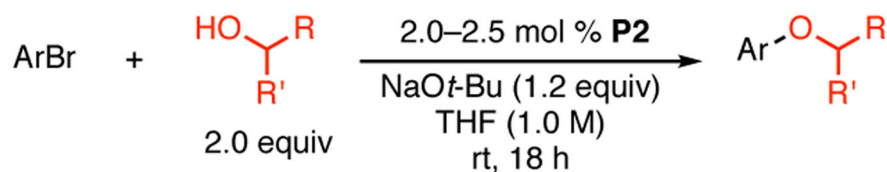
A) Pd-catalyzed C–O cross-coupling of secondary alcohols (Buchwald, 2011)**B) Cu-catalyzed C–O cross-coupling of secondary alcohols (Ma, 2019)****C) Ni-catalyzed C–O cross-coupling of secondary alcohols (Stradiotto, 2018)****Scheme 2.**

Literature precedents of transition-metalcatalyzed C–O cross-coupling of secondary alcohols.



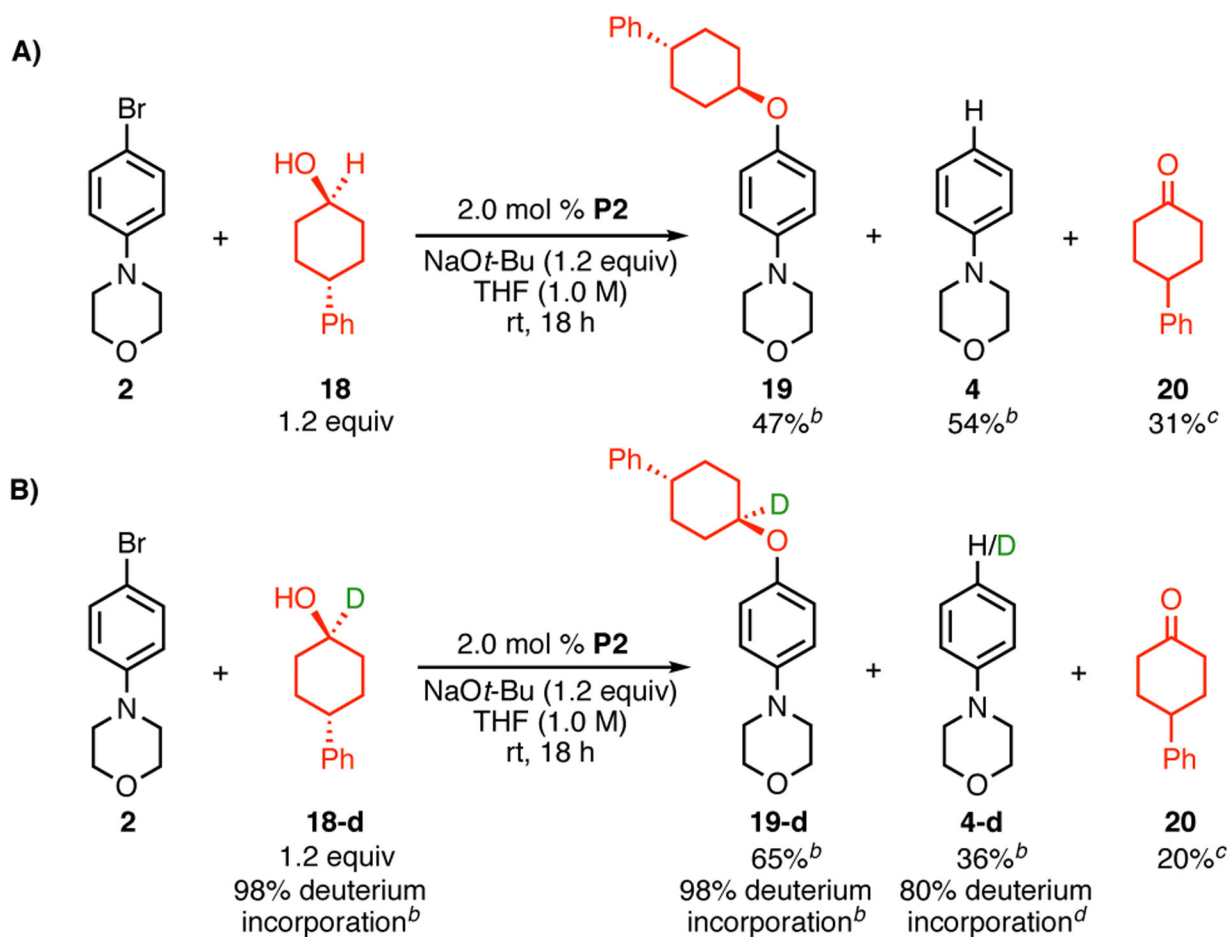
Scheme 3. Pd-catalyzed C–O cross-coupling of (hetero)aryl chlorides with secondary alcohols.^a

^aReaction conditions: ArCl (1.0 mmol), alcohol (1.2 mmol), NaO*t*-Bu (1.2 mmol), **P2** (2.0–4.0 mol %), THF (1.0 mL, 1.0 M), rt–40 °C, 18 h. Isolated yields represent the average result of two runs. ^bTHF (7.0 mL) and higher temperature were used due to the poor solubility of the combination of aryl chloride, alcohol and NaO*t*-Bu under standard reaction conditions.



Scheme 4. Pd-catalyzed C–O cross-coupling of aryl bromides with secondary alcohols.^a

^aReaction conditions: ArBr (1.0 mmol), alcohol (2.0 mmol), NaOt-Bu (1.2 mmol), **P2** (2.0–2.5 mol %), THF (1.0 mL, 1.0 M), rt, 18 h. Isolated yields represent the average result of two runs. ^b1.5 equiv of alcohol. ^cTHF (5.0 mL) and higher temperature were used due to the poor solubility of the combination of aryl chloride, alcohol and NaOt-Bu under standard reaction conditions.

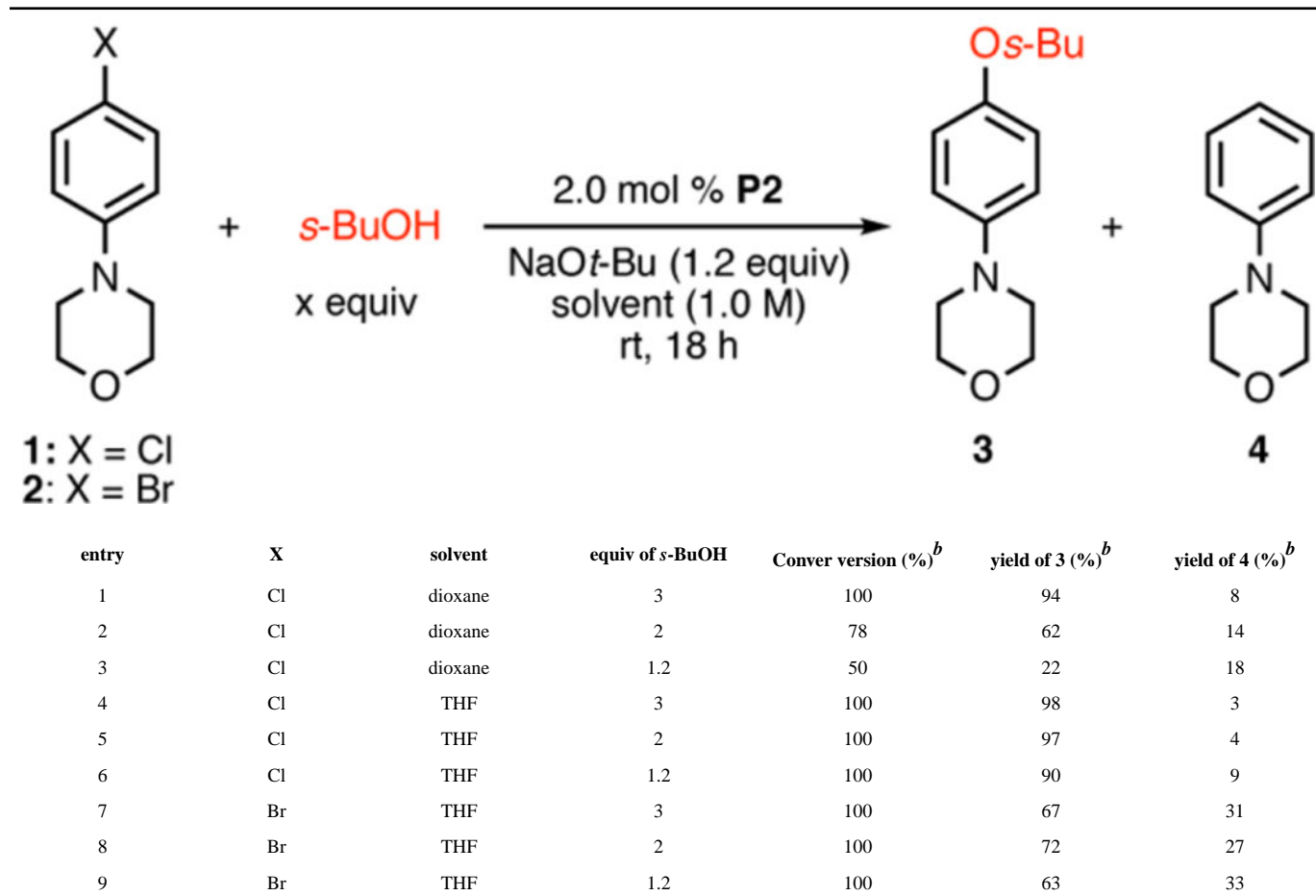


Scheme 5. Pd-catalyzed C–O cross-coupling of aryl bromide **2** with A) cyclohexanol **18**, and B) deuterocyclohexanol **18-d**.^a

^aReaction conditions: **2** (0.5 mmol), **18** or **18-d** (0.6 mmol), NaOt-Bu (0.6 mmol), **P2** (2.0 mol %), THF (0.5 mL, 1.0 M), rt, 18 h. ^bDetermined by ¹H NMR analysis using an internal standard. ^cDetermined by GC analysis using an internal standard. ^dDetermined by HRMS analysis.

Table 1.

Evaluation for Pd-catalyzed C–O cross-coupling of electron-rich aryl halides with different equivalents of *s*-BuOH in 1,4-dioxane and THF.^a



^aReaction conditions: ArX (0.5 mmol), *s*-BuOH (x mmol), NaOt-Bu (0.6 mmol), **P2** (2.0 mol %), solvent (0.5 mL, 1.0 M), rt, 18 h. dioxane = 1,4-dioxane. THF = tetrahydrofuran.

^bDetermined by GC analysis using an internal standard. All yields presented are not normalized. In certain cases, the sum of yields being over 100% is a result of the error in the analytical method used.

Table 2.

Alcohol evaluation for Pd-catalyzed C–O cross-coupling of electron-rich aryl chloride 1.^a

entry	alcohol	Conversion (%) ^b	yield of P (%) ^c	yield of 4 (%) ^c
1		100	90	9
2		68	53	20
3		100	64	29
4		40	5	15

^aReaction conditions: ArCl (0.5 mmol), alcohol (0.6 mmol), NaOt-Bu (0.6 mmol), **P2** (2.0 mol %), THF (0.5 mL, 1.0 M), rt, 18 h.^bDetermined by GC using an internal standard.^cDetermined by ¹H NMR using an internal standard.