

Solvent-free palladium-catalyzed C–O cross-coupling of aryl bromides with phenols

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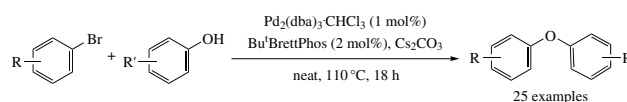
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A new solvent-free procedure for C–O cross-coupling between phenols and aryl bromides comprising of Pd₂(dba)₃/Bu^tBrettPhos catalytic system is efficient for substrates bearing donor or acceptor, as well as bulky substituents.



Keywords: cross-coupling, phenols, arylation, solvent-free reactions, Pd-catalysis, aryl bromides, diaryl ethers.

Compounds containing diaryl ether and aryl alkyl ether moieties prevalent in wide array of naturally occurring and medicinal substances.¹ Palladium- and copper-catalyzed cross-coupling methodologies have become an efficient tool for formation of C–O bond in these molecules both in academic and industrial laboratories.² Since Buchwald’s studies³ a lot of different protocols were discovered by testing of ligands and reaction conditions.⁴ Unfortunately, the best results were obtained for activated (*i.e.* electron-deficient) aryl halides, and in many cases elevated temperatures and high Pd loadings (over 1 mol%) were required. The most challenging Pd-catalyzed C–O cross-coupling reactions typically require inactivated, electron-rich and sterically hindered aryl halides.

It is of high importance to develop not only efficient, selective and high yielding but also ‘green’, environmentally friendly and safe protocols for cross-coupling reactions.⁵ Solvent-free cross-coupling procedures were developed in the last decades.⁶ Among them, there are Buchwald–Hartwig C–N,⁷ Suzuki,⁸ Miyaura,⁹ Sonogashira,¹⁰ Heck,¹¹ Hiyama¹² and Stille¹³ reactions. To the best of our knowledge, nothing on solvent-free C–O cross-coupling has been documented yet. We have previously shown that solvent-free approaches are not only ‘greener’ than traditional procedures using solvents, but, in some cases, provide additional benefits such as higher product yields, stronger selectivity, and wider substrate scope.^{13,14} Thus, it was of particular interest to utilize solvent-free approach to overcome the problems of Pd catalyzed C–O cross-coupling reactions.

Herein, we report on the development of a catalytic system for C–O cross-coupling of aryl bromides with phenols based on Pd/Bu^tBrettPhos **L1** system under solvent-free conditions.

We started our search for optimal conditions for solvent-free cross-coupling by testing catalytic systems known to be active in solvents. We used *p*-TolBr and phenol as the model substrates, Pd₂(dba)₃·CHCl₃ as a palladium source, and K₃PO₄ (2 equiv.) as a base.¹⁵ Catalytic tests were conducted in toluene at 110 °C for 18 h. A series of conventional bulky phosphine ligands were

tested, namely, Bu^tBrettPhos **L1**, Bu^tXPhos **L2**, RuPhos **L3**, Bu^tP **L4** (Table 1, entries 1, 5–7). We have also tested an NHC based catalytic system (6-Dipp)Pd(cinn)Cl (Pd·**L5**)/Bu^tOK which is highly active in solvent-free C–N coupling reactions (entry 8).^{14(d),16} The highest yield of 70% was achieved in case of Bu^tBrettPhos **L1** at 110 °C.¹⁷ Temperature decrease has led to significant drop in yield down to zero at room temperature (entries 2–4).

Further, Pd₂(dba)₃·CHCl₃/Bu^tBrettPhos **L1** was tested in the absence of a solvent. Base, ligand loading, and reaction temperature were varied to find optimal conditions (see Table 1, entries 9–22). Eventually, we reached the highest yield of 88% using 2 equiv. of Cs₂CO₃ as a base and 1 : 2 palladium to ligand ratio at 110 °C (entry 14). Notably, the obtained yields were lower for *p*-TolCl or *p*-TolI as coupling partners.

We investigated the activity of thus found solvent-free procedure on a variety of substrates (Scheme 1).[†] Compounds bearing various electron-withdrawing groups at *ortho*-, *meta*-,

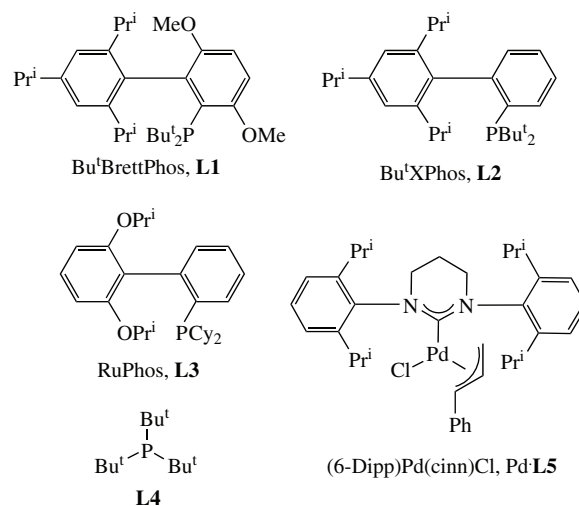
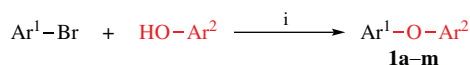


Table 1 Optimization of the C–O cross-coupling with *p*-TolBr and PhOH as the model substrates.^a

Entry	Solvent	Ligand	Ligand amount/mol%	Base	<i>T</i> /°C	Yield (%)
1	toluene	L1	1	K ₃ PO ₄	110	70
2	toluene	L1	1	K ₃ PO ₄ ^b	90	45
3	toluene	L1	1	K ₃ PO ₄	60	traces
4	toluene	L1	1	K ₃ PO ₄	20	–
5	toluene	L2	1	K ₃ PO ₄	110	traces
6	toluene	L3	1	K ₃ PO ₄	110	–
7	toluene	L4	1	K ₃ PO ₄	110	30
8	toluene	Pd- L5	1	Bu ^t OK	110	–
9	–	L1	1	K ₃ PO ₄	110	50
10	–	L1	1	K ₃ PO ₄	90	22
11	–	L1	1	K ₃ PO ₄	60	traces
12	–	L1	1	Cs ₂ CO ₃	110	79
13	toluene	L1	1	Cs ₂ CO ₃	110	75
14	–	L1	2	Cs ₂ CO ₃	110	88 ^c
15	–	L1	3	Cs ₂ CO ₃	110	85
16	–	L1	0.5	Cs ₂ CO ₃	110	72
17	–	L1	2	Cs ₂ CO ₃	90	81
18	–	L1	2	Cs ₂ CO ₃	130	77
19	–	L1	2	Bu ^t ONa	110	32
20	–	L1	2	K ₃ PO ₄	110	67
21	–	L1	2	K ₂ CO ₃	110	23
22	–	L1	2	Cs ₂ CO ₃ ^b	110	69

^a Reaction conditions: *p*-TolBr (1 mmol), phenol (1.2 mmol), Pd₂(dba)₃·CHCl₃ or (6-Dipp)Pd(cinn)Cl (1 mol%), ligand, base (2 mmol), neat (or toluene (0.3 M) for entries 1–8 and 13), 100 °C, 18 h. ^b 1.2 equiv. ^c *p*-TolCl yield 40%, *p*-TolI yield 57%.

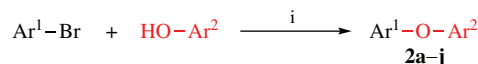
and *para*-positions were systematically tested, namely, NO₂ (products **1b–d**), CN (products **1e–h**) and CF₃ (products **1i–m**).



- a** Ar¹ = 4-MeC(O)C₆H₄, Ar² = 4-NCC₆H₄; 48%
b Ar¹ = 2-O₂NC₆H₄, Ar² = Ph; 71%
c Ar¹ = 3-O₂NC₆H₄, Ar² = Ph; 68%
d Ar¹ = 4-O₂NC₆H₄, Ar² = Ph; 65%
e Ar¹ = 4-NCC₆H₄, Ar² = Ph; 59%
f Ar¹ = 4-NCC₆H₄, Ar² = 4-ClC₆H₄; 55%
g Ar¹ = 2-NCC₆H₄, Ar² = 2-MeC₆H₄; 53%
h Ar¹ = 4-NCC₆H₄, Ar² = 2-PrⁱC₆H₄; 53%
i Ar¹ = 4-F₃CC₆H₄, Ar² = Ph; 79%
j Ar¹ = 2-F₃CC₆H₄, Ar² = Ph; 78%
k Ar¹ = 4-F₃CC₆H₄, Ar² = 2-MeC₆H₄; 82%
l Ar¹ = 2-F₃CC₆H₄, Ar² = 2-MeC₆H₄; 74%
m Ar¹ = 3,5-(F₃C)₂C₆H₃, Ar² = Ph; 72%

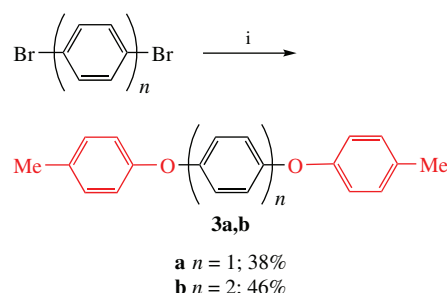
Scheme 1 Reagents and conditions: i, Pd₂(dba)₃·CHCl₃ (1 mol%), Bu^tBrettPhos **L1** (2 mol%), Cs₂CO₃ (2 equiv.), neat, 110 °C, 18 h.

[†] *General procedure.* An oven-dried screw-cap tube was cooled to room temperature under argon pressure and was charged with aryl halide (1.0 mmol), phenol (1.2 mmol), the ligand (2 mol%) and Pd₂(dba)₃·CHCl₃ (10 mg, 1 mol%). The mixture was well homogenized followed by addition of Cs₂CO₃ (650 mg, 2.0 mmol). The tube was sealed and placed in a pre-heated oil bath at 110 °C and stirred for 18 h. The mixture was then allowed to cool to room temperature, and the resulting dark heterogeneous mixture was treated with water (10 ml) and ethyl acetate (10 ml). The organic phase was collected, filtered through a small pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.



- a** Ar¹ = 4-MeC₆H₄, Ar² = Ph; 88%
b Ar¹ = 3,5-Me₂C₆H₃, Ar² = Ph; 86%
c Ar¹ = 3,5-Me₂C₆H₃, Ar² = 4-MeC₆H₄; 68%
d Ar¹ = 4-MeC₆H₄, Ar² = 2-MeC₆H₄; 86%
 or Ar¹ = 2-MeC₆H₄, Ar² = 4-MeC₆H₄; 71%
e Ar¹ = 4-Bu^tC₆H₄, Ar² = 2-MeC₆H₄; 82%
f Ar¹ = 4-MeC₆H₄, Ar² = 2-Bu^tC₆H₄; 85%
g Ar¹ = 4-MeOC₆H₄, Ar² = Ph; 65%
h Ar¹ = 2-MeOC₆H₄, Ar² = 2-MeC₆H₄; 48%
i Ar¹ = 3-MeOC₆H₄, Ar² = Ph; 80%
j Ar¹ = 4-MeOC₆H₄, Ar² = 2-PrⁱC₆H₄; 54%

Scheme 2 Reagents and conditions: i, Pd₂(dba)₃·CHCl₃ (1 mol%), Bu^tBrettPhos **L1** (2 mol%), Cs₂CO₃ (2 equiv.), neat, 110 °C, 18 h.



Scheme 3 Reagents and conditions: i, 4-MeC₆H₄OH (2 equiv.), Pd₂(dba)₃·CHCl₃ (2 mol%), Bu^tBrettPhos **L1** (4 mol%), Cs₂CO₃ (4 equiv.), neat, 110 °C, 18 h.

Coupling of donor group-substituted aryl bromides is usually a challenge. To our delight, we were able to obtain diaryl ethers in yields over 80% for a series of substrates (Scheme 2) including cases with sterically hindered *ortho*-substituted substrates (products **2d,h,j**). Dibromides could be also subjected to such C–O cross-coupling to afford diethers **3a,b** (Scheme 3).

In conclusion, we have revealed the possibility of efficient coupling of aryl bromides with phenols under solvent-free conditions. The Pd₂(dba)₃·CHCl₃/Bu^tBrettPhos **L1** catalytic system in the presence of Cs₂CO₃ is the optimal choice for obtaining good to high yields of the coupling products. The scope of aryl bromides includes substrates bearing electron-withdrawing and electron-donating groups. *ortho*-Substituted bromides are suitable coupling substrates as well. Finally, solvent-free protocol can be used as a basis for further development of environmentally friendly methods of synthesis of fine chemicals both in laboratory and in industry.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.042.

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