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Solvent-free palladium-catalyzed C–O cross-coupling of (hetero)aryl halides with primary alcohols

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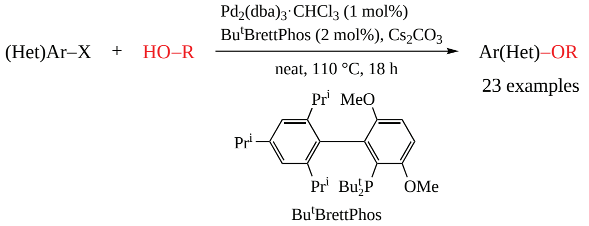
A new efficient solvent-free procedure for the C–O cross-coupling between (hetero)aryl halides with phenols, primary alkanols, or (hetero)arylmethanols using $Pd_2(dba)_3$/Bu^{t}BrettPhos catalytic system is proposed using 23 examples.



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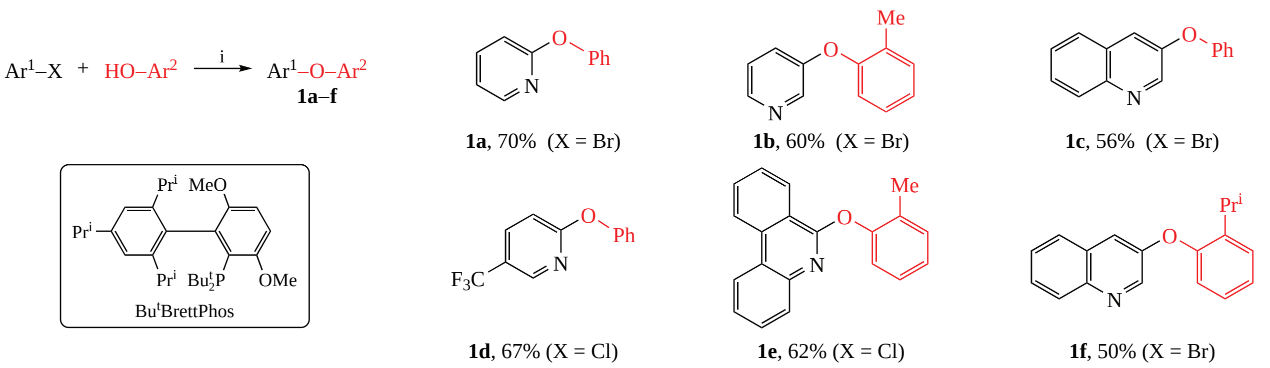
Aryl ethers of primary and secondary aliphatic alcohols are of particular interest as important structural components in many natural compounds, pharmaceuticals, macrocyclic ligands, fragrances and polymers.[1] Traditionally alkyl aryl ethers are synthesized by the Ullman coupling,[2] the Williamson ether synthesis,[3] the Mitsunobu reaction[4] or nucleophilic aromatic substitution.[5] However, these methods have their own substrate limitations due to the harsh reaction conditions, and/or hindered functional group compatibilities. Copper-catalyzed cross-coupling reactions often may be sensitive to the steric hindrance of the reactants.[2(a),(g)] In this regard, Pd-catalyzed C–O cross-coupling between (hetero)aryl halides and primary alcohols has become the subject of the recent efforts and proved to be particularly useful.[6] In turn, the C–O cross-coupling has restrictions related to difficulties in cases of unactivated (electron-rich) or sterically hindered aryl bromides and especially aryl chlorides along with the competition of reductive elimination with undesired β-hydride elimination leading to reduction of aryl halide.[7] Therefore, the search for the efficient, high yielding and selective catalytic system for the Pd-catalyzed C–O cross-coupling between aryl and heteroaryl halides and primary alcohols remains topical.

We have previously shown that 'non-solvent' approach has not only the 'green chemistry' advantage over the traditional coupling using different solvents, but also helps to achieve better yields and to extend the reactant scope in a variety of reactions.[8] Recently, we have studied the solvent-free Pd-catalyzed C–O cross-coupling of aryl bromides with phenols.[8(g)] In this work, we report the C–O cross-coupling of (hetero)aryl halides with phenols and particularly primary alkanols including (hetero)arylmethanols under solvent-free conditions using $Pd_2(dba)_3 \cdot CHCl_3$/Bu^{t}BrettPhos system, which proved to be optimal in our previous study.[8(g)]

Herein, we have started our work with application of these efficient conditions to the C–O cross-coupling of different heteroaryl halides with phenols (Scheme 1). Halo-substituted pyridine (products **1a**,**b**,**d**), quinolone (**1c**,**f**) and phenanthridine (**1e**) derivatives were tested. The $Pd_2(dba)_3$/Bu^{t}BrettPhos catalytic system has shown its versatility under the solvent-free conditions:



1a, 70% (X = Br)
1b, 60% (X = Br)
1c, 56% (X = Br)
1d, 67% (X = Cl)
1e, 62% (X = Cl)
1f, 50% (X = Br)

Scheme 1 *Reagents and conditions*: i, $Pd_2(dba) \cdot CHCl_3$ (1 mol%), Bu^{t}BrettPhos (2 mol%), Cs_2CO_3 (2 equiv.), neat, 110 °C, 18 h.

$$\text{Ar–Br} + \text{HO–R} \xrightarrow{\text{i}} \text{Ar–O–R}$$

2a–l

a Ar = 4-MeC$_6$H$_4$, R = Hex, 65%
b Ar = 4-MeC$_6$H$_4$, R = Pr^i(CH$_2$)$_2$, 64%
c Ar = 4-MeC$_6$H$_4$, R = 4-Pr^{i}C$_6$H$_4$CH$_2$, 62%
d Ar = 4-MeC$_6$H$_4$, R = Bn, 60%
e Ar = 4-MeC$_6$H$_4$, R = 2-furylmethyl, 65%
f Ar = 4-MeC$_6$H$_4$, R = 2-thienylmethyl, 78%
g Ar = 4-MeC$_6$H$_4$, R = 3-pyridylmethyl, 90%
h Ar = 4-MeC$_6$H$_4$, R = 4-pyridylmethyl, 55%
i Ar = 3-pyridyl, R = 3-pyridylmethyl, 70%
j Ar = 3-pyridyl, R = 2-thienylmethyl, 75%
k Ar = 2-pyridyl, R = 3-pyridylmethyl, 81%
l Ar = 4-methylpyridin-2-yl, R = 2-FC$_6$H$_4$CH$_2$, 88%

$$\text{Ar–Cl} + \text{HO–R} \xrightarrow{\text{i}} \text{Ar–O–R}$$

2m–o

m Ar = 3-pyridyl, R = Bn, 53%
n Ar = 2-pyrazinyl, R = 3-pyridylmethyl, 52%
o Ar = 3-(trifluoromethyl)pyridin-2-yl, R = Bn, 38%

Scheme 2 *Reagents and conditions*: i, Pd$_2$(dba)$_3$·CHCl$_3$ (1 mol%), Bu^{t}BrettPhos (2 mol%), Cs$_2$CO$_3$ (2 equiv.), neat, 110 °C, 18 h.

not only heteroaryl bromides (products **1a**,**b**,**d**,**g**), but also heteroaryl chlorides (products **1d**,**e**) reacted with phenols with good yields. In our experiments, ether **1b** was obtained in 60% yield, whereas reported yield for similar reaction in solvent was 69%.[9]

Further on, this procedure was applied to the C–O cross-coupling between (hetero)aryl halides and primary alcohols (Scheme 2). The corresponding aryl **2a–h** and heteroaryl **2i–o** ethers were thus obtained.

Coupling of heteroaryl chlorides is usually a challenge. Luckily, we succeeded in obtaining ethers **2m–o** with 38–53% yields for some of chlorides (see Scheme 2). As for bromides, the good yields were acieved not only in the cases of reactions between *p*-TolBr and primary alkanols or benzylic alcohols (products **2a–d**), but also with primary (hetero)arylmethanols (products **2e–h**). Regarding these results, the C–O coupling was also accomplished for heteroaryl halides and heteroarylmethanols resulting in products **2i–o** with the reasonable yields.

In conclusion, the possibility of Pd-catalyzed C–O cross-coupling under the solvent-free conditions was demonstrated for the different heteroaryl halides reacting with phenols, and also a variety of primary alcohols and aryl and heteroaryl halides.

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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.2022.03.035.

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