

Copper-Catalyzed Etherification of Aryl Iodides Using KF/Al₂O₃: An Improved Protocol

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Abstract: A simple and efficient method for the coupling of aryl iodides with aliphatic alcohols and phenols that does not require the use of alkoxide bases is described. This C–O bond forming procedure shows that the combination of air stable CuI and 1,10-phenanthroline in the presence of KF/Al₂O₃ comprises an extremely efficient and general catalyst system for the etherification of aryl iodides. Different functionalized aryl iodides were coupled with alcohols and phenols using this method.

Key words: etherification, aryl iodides, copper iodide, potassium fluoride on alumina, coupling reaction

The development of mild methods for the synthesis of C–O bonds has recently gained increased attention.¹ Formation of carbon-oxygen bonds by transition metal-catalyzed cross-coupling methodology has been the subject of significant interest during recent years.²

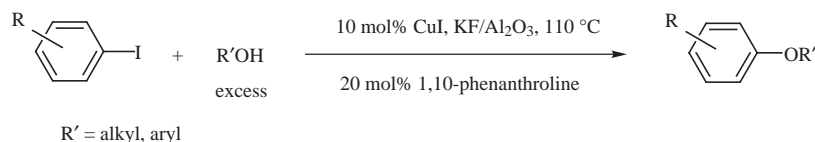
The copper-mediated Ullmann reaction has previously been the method of choice for the synthesis of C–O bonds. However, these reactions often require high temperatures (ca. 200 °C), the use of copper salts in greater than stoichiometric amounts, highly polar aprotic solvents, and a large excess of the alkoxide.^{3–5} The Buchwald and Hartwig research groups have been prominent in developing palladium-based methods for C–O bond synthesis.^{6,7} However, although successful, these protocols have inherent limitations, Pd-based methods can often be relatively sensitive to moisture and require expensive metal catalysts.⁸ Buchwald et al. and others have reported the copper-based protocol for the formation of aryl alkyl and diaryl ethers.^{2b,c,9} Most of these reported methods require Cs₂CO₃ as a base in a sealed tube, but Cs₂CO₃ has a high sensitivity towards moisture and this problem reduces its capability as a base in moisture-sensitive reactions.

The application of KF/Al₂O₃ to organic synthesis has provided new methods for a wide array of organic reactions, many of which are staples of synthetic organic chemistry.¹⁰ Its benefits have been achieved by taking advantage of the strongly basic nature of KF/Al₂O₃ which has allowed it to replace organic bases in a number of reactions.¹¹ In many cases, the use of this base provides milder conditions and simpler procedures than previously reported methods.

We have explored the CuI-catalyzed O-arylation of aryl iodides with excess of alcohol and phenol using 1,10-phenanthroline (20 mol%) as a simple ligand and KF/Al₂O₃ as a suitable base in the presence of CuI (10 mol%; Scheme 1).

The choice of 1,10-phenanthroline as ligand and KF/Al₂O₃ as base in the presence of CuI (10 mol%) was made because we have recently used this system for C–N bond formation in N-amidation.¹² To find the optimum conditions, we chose the cross-coupling reaction of iodobenzene and *n*-butanol in the presence of 1,10-phenanthroline, KF/Al₂O₃ and CuI in toluene, dioxane and excess *n*-butanol as solvents at 100–110 °C. Under these conditions after 15 hours, *n*-butyloxybenzene was obtained in 95% yield, while in toluene or dioxane, *n*-butyloxybenzene was obtained in 30% and 25% yield, respectively.

Using the above protocol, we subjected a series of aryl iodides to these reaction conditions (Table 1). As can be seen in Table 1, primary, benzylic and secondary alcohols were successfully transformed to their corresponding ethers. The reaction between these alcohols with iodobenzene gives excellent yields after 5–14 hours (entries 1–3). Substrates possessing electron-withdrawing groups such as CF₃ in the *meta*-position (entry 8) and bromine in the



Scheme 1

para-position (entries 17–19) and electron-releasing groups such as OMe (entry 7), and Me (entries 10, 13, 15) in the *ortho*- and *para*-positions of the aromatic ring also give excellent yields of the corresponding ethers. On the other hand, substitution in the *ortho*-position of the aromatic ring for the coupling of secondary alcohols (entry 14) afforded lower yields of product, which is probably due to the steric effect of the substituents. It should also be noted that the yield of reaction with alcohols, which dissolve KF, is very low. This is probably due to separation of KF from the alumina surface (entries 11, 12); it having

been reported that KF supported on alumina is more basic than unsupported KF.¹³

We have also used this method for forming diaryl ethers and the products have been achieved with excellent yields (entries 4–6, 9). Reaction of *ortho*-substituted aryl iodides with phenol gives very low yield of the product after 15 hours (entry 16). However, *ortho*-substituted diaryl ethers can be prepared by the reaction of iodobenzene with *ortho*-cresol (entry 6).

Table 1 The Copper-Catalyzed Etherification of Aryl Iodides in the Presence of KF/Al₂O₃

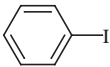
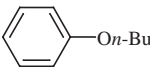
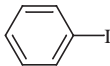
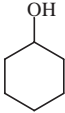
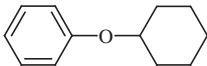
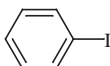
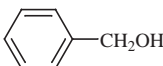
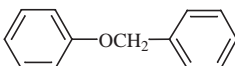
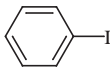
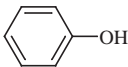
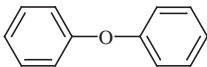
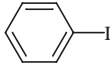
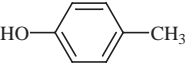
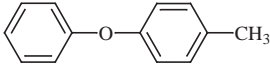
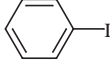
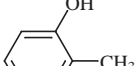
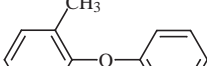
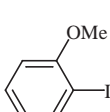
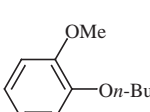
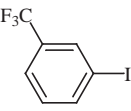
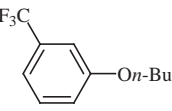
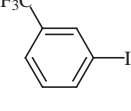
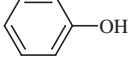
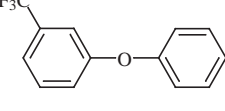
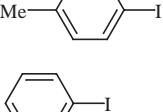
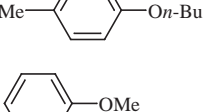
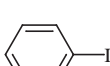
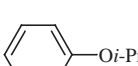


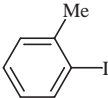
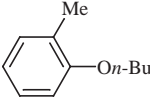
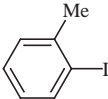
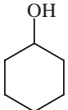
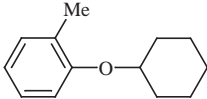
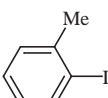
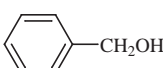
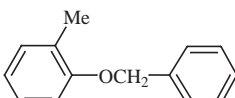
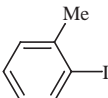
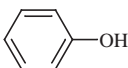
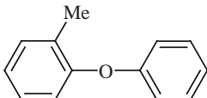
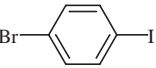
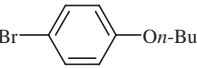
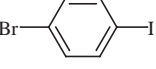
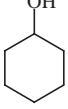
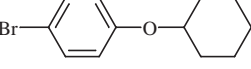
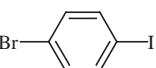
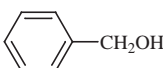
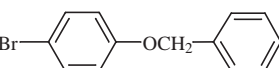
Entry	Aryl iodide	Alcohols and phenols	Time (h)	Product ^a	Yield (%) ^b
1		<i>n</i> -BuOH	12		95
2			14		90
3			5		98
4			13		92
5			14		92
6			14		95
7		<i>n</i> -BuOH	15		70
8		<i>n</i> -BuOH	7.5		98
9			11		98
10		<i>n</i> -BuOH	9		95
11		MeOH	12		30
12		<i>i</i> -PrOH	12		25

Table 1 The Copper-Catalyzed Etherification of Aryl Iodides in the Presence of KF/Al₂O₃ (continued)

Entry	Aryl iodide	Alcohols and phenols	Time (h)	Product ^a	Yield (%) ^b
13		<i>n</i> -BuOH	13		90
14			14		70
15			9		98
16			15		30
17		<i>n</i> -BuOH	12		93
18			13		88
19			6		98

^a Performed using 20 mol% of 1,10-phenanthroline as ligand, 1.0 equiv of aryl iodide, 30 equiv of alcohol or phenol, and 5 equiv of KF/Al₂O₃ as base at 100–110 °C.

^b Isolated yields; products were characterized by ¹H NMR and mp.

In summary, we have developed an experimentally simple and inexpensive catalyst system for the etherification of aryl iodides. We believe that potassium fluoride supported on alumina (KF/Al₂O₃) provides an excellent complement to other bases such as Cs₂CO₃ in copper-catalyzed methodology that has already utilized in a number of applications.

Typical Procedure

To a solution of alcohol or phenol (30 mmol) and aryl iodides (1 mmol) under argon atmosphere were added CuI (19 mg, 10 mol%) and 1,10-phenanthroline (40 mg, 20 mol%) followed by KF/Al₂O₃¹⁴ (5 equiv, 780 mg) and the mixture was stirred at 110 °C for the times specified (Table 1). The progress of the reaction was monitored by TLC. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was separated by column chromatography on silica gel using hexane as eluent to afford the pure coupled product.

Acknowledgment

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