Synthesis of Diaryl Ethers: A Long-Standing Problem Has Been Solved

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Until quite recently the synthesis of diaryl ethers has not been an easy task unless the target molecule was not sensitive to the very harsh reaction conditions employed. The diaryl ether structural unit (Figure 1) is found in natural products

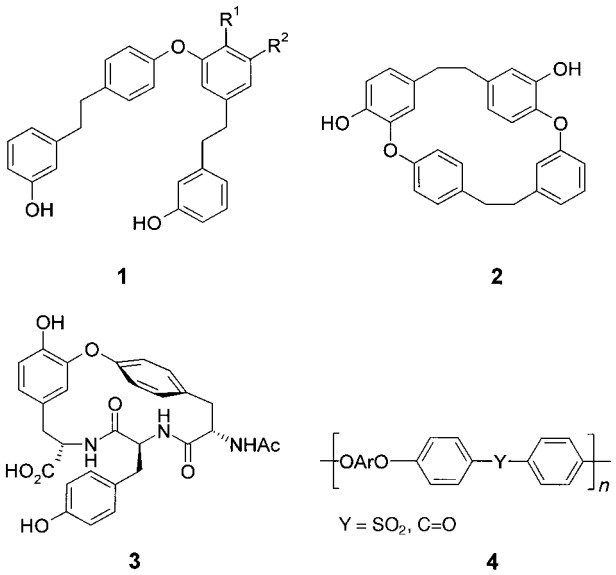
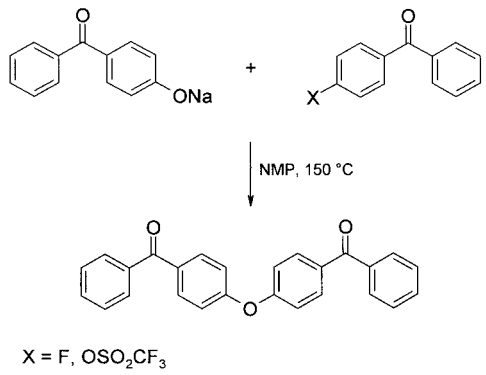


Figure 1. Examples of the diaryl ether function in natural products and synthetic polymers. R^1,R^2 in **1** = H, OH, OMe.

such as perrottetines (**1**),[1] their cyclic analogues,[1b] riccardin B (**2**),[2] and a variety of more complex molecules containing sensitive functional groups and stereogenic centers[3] to which for example the cyclic peptide K 13 (**3**)[3] and vancomycin belong.[4, 5] The diaryl ether formation in cyclic peptides was reviewed by Rama Rao et al.[6] in 1995. Furthermore, poly(aryl ethers) such as **4** are important commercial polymers used as engineering thermoplastics.[7] Both the synthesis of highly functionalized molecules and the large-scale preparation of polymers are challenging tasks for synthetic organic chemists.

However, the classical arylation procedure of phenols with aryl halides under Ullmann conditions[8] using copper powder or copper salts requires harsh reaction conditions as a result of the poor nucleophilicity of the phenoxide and the low reactivity of the aryl halides involved. The reactions have to be carried out in a temperature range of 120–250 °C by using high boiling solvents or neat reagents over an extended period of time. These conditions have been applied to the synthesis of relatively simple diaryl ethers such as riccardin B (**2**), which lacks sensitive functional groups, by using a copper phenoxide and an aryl bromide in refluxing pyridine for twenty hours. For the preparation of poly(aryl ethers) aryl fluorides and triflates are the most reactive electrophiles towards sodium phenoxides. In a model reaction complete conversion has been achieved at 150 °C in *N*-methyl-2-pyrrolidinone (NMP) within four hours if both the haloarene and the phenol are activated by a *para*-carbonyl group (Scheme 1).[9]



Scheme 1. Diaryl ether formation from *para*-carbonyl-activated phenolates and aryl fluorides or triflates.

The structural relevance of diaryl ethers and the lack of a convenient, mild, and general method for their preparation has resulted in increased efforts towards filling this gap in the synthetic methodology during the past decade. Yamamura et al.[10] developed a method that encompasses the oxidative coupling of 2,6-dihalophenols with $Tl(NO_3)_3$ to afford a 2-substitued quinone, which subsequently is reduced to the corresponding diaryl ether. This procedure has been applied by the Evans group[11] for the synthesis of the orienticin C aglycone. Despite the fact that this reaction is conducted under mild conditions, it is nevertheless a two-step procedure that requires a specific type of substituted phenol and a highly toxic thallium salt. These requirements preclude it from being a general user-friendly method.

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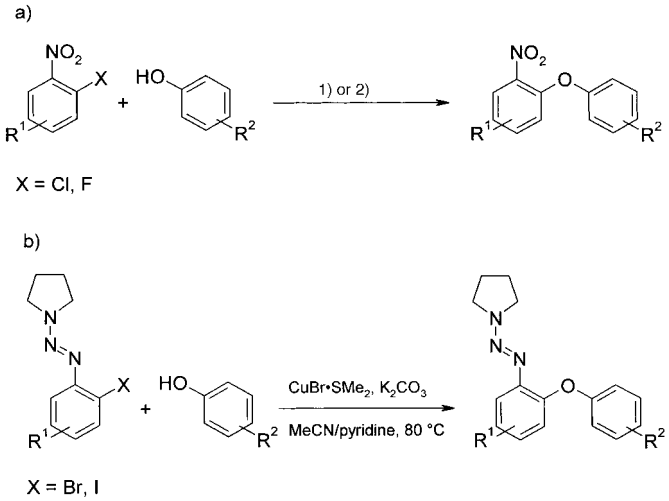
The recent development directed towards the synthesis of diaryl ethers in a milder and more efficient manner was mainly driven by the synthesis of complex natural products.

Eicher and Walter[1] introduced an activating *ortho*-nitro group in their synthesis of diaryl ethers (Scheme 2a), thus increasing the reactivity of aryl halides towards phenoxides



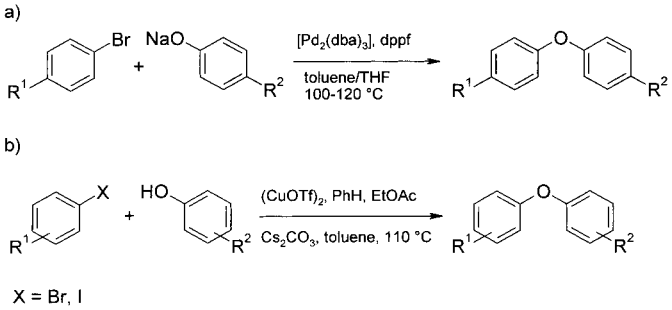
Scheme 2. Diaryl ether formation by *ortho*-activation of haloarenes. a) Methods of Eicher et al. and Zhu, (R^1 = 4-CHO, 4-CO_2Me, 4-$CH_2CH(NHBoc)CO_2Me$; R^2 = 2-OMe-4-CHO, 2,3-$(OMe)_2$-4-CO_2Me, 4-$CH_2CH(NHBoc)CO_2Me$), b) Method of Nicolaou et al. (R^1 = 3-Me, 5-Me, 3,5-Me_2; R^2 = 2-Cl, 4-Cl, 2-Cl-4-Me). 1) NaH, DMF, 125 °C (X = Cl); 2) Na_2CO_3 or CsF, DMF, 25 °C (X = F).

significantly such that a reaction temperature of 125 °C for less than one hour was required. By using this coupling procedure perrottetines (**1**),[1a] and very recently their cyclic analogues[1b] under even milder conditions, have been synthesized. As reported by Zhu[3] phenoxides react smoothly at room temperature when *ortho*-nitrofluoro arenes are used as electrophiles. This approach has been applied to the synthesis of a variety of macrocyclic diaryl ethers[3] including vancomycin[4a,b] and its subunits.[12] However, this method requires subsequent reduction and deamination steps in order to remove the nitro group unless the target molecule bears this functional group.

The approach by Nicolaou et al.[13] is similarly based on the activation of an aryl halide. Aryl bromides and iodides substituted with *ortho*-triazene react smoothly with phenols at 80 °C in the presence of K_2CO_3 and $CuBr \cdot Me_2S$ to afford diaryl ethers in good yields (Scheme 2b). The use of this procedure requires the preformation of the requisite triazenes and the subsequent removal or transformation of this functional group.

Alternatively, chloroarenes can be activated through the formation of manganese, iron, or ruthenium π complexes that react at low temperature with phenoxides to yield diaryl ethers.[14] Higher temperatures (DMF, 90 °C) requires the formation of diaryl ethers from iodonium salts and phenoxides[15] and the coupling of bromo benzoquinones with phenoxides (DMF, 100–110 °C) followed by a subsequent reduction with dithionite.[16]

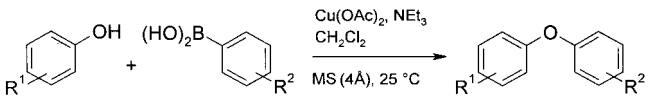
A palladium-catalyzed coupling between sodium phenoxides and electron-deficient aryl bromides has been reported by Mann and Hartwig[17] based on an in-situ ligand exchange of dibenzylideneacetone (dba) with 1,1′-diphenylphosphanylferrocene (dppf; Scheme 3a). The reaction still needs rela-



Scheme 3. Palladium- and copper triflate-catalyzed diarylether synthesis. a) R^1 = CN, CHO, $COCF_3$, COPh; R^2 = Me, OMe; b) R^1 = 4-Cl, 4-CO_2Et, 4-Me, 4-*t*Bu, 4-OMe, 4-NMe_2, 4-CN, 4-COMe, 2,5-Me_2, 3,5-Me_2; R^2 = 2-Me, 4-Me, 2-*i*Pr, 4-Cl, 3,4-Me_2.

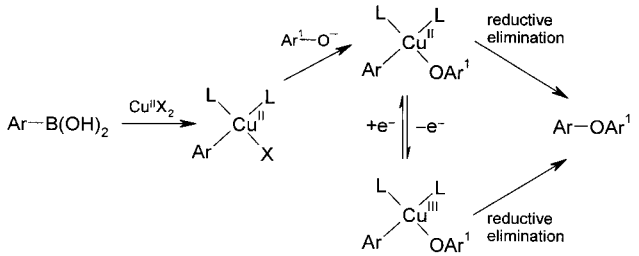
tively high temperatures and long reaction times. Another phenoxide-activating approach published by Buchwald et al.[18] is based on the reaction of cesium phenoxides with aryl bromides or iodides in the presence of catalytic amounts of copper(I) triflate and ethyl acetate in refluxing toluene (Scheme 3b). In certain cases equimolar amounts of 1-naphthoic acid have been added to increase the reactivity of the phenoxide. The authors assume the formation of a cuprate-like intermediate of structure $[(ArO)_2Cu]^-Cs^+$ as the reactive species.

Finally, the remarkably simple resolution came from Evans et al.[19a] and researchers at DuPont[19b] simultaneously. Their method allows the coupling of structurally and electronically diverse phenols and aryl boronic acids in the presence of copper(II) acetate, triethylamine, or pyridine, and molecular sieves at ambient temperature (Scheme 4). Even phenolic



Scheme 4. Copper(II)-promoted coupling of boronic acids with phenols. R^1 = 4-Me, 2-Cl, 2-I, 2-OMe, 4-$CH_2CH(NHBoc)CO_2Me$, 3,5-*t*Bu_2; R^2 = 4-Me, 4-F, 4-OMe, 3-OMe, 3-NO_2, 2-Me, 2-OMe, 3-Cl-4-F.

amino acid derivatives react smoothly without racemization. The only limitation has been observed with *ortho*-heteroatom-substituted boronic acids, which result in lower product yields. The initial step in the assumed pathway (Scheme 5) is



Scheme 5. Proposed mechanism for the copper(II)-promoted coupling of boronic acids with phenols.

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the transmetalation of the boronic acid residue with the copper salt.

The solution of this long-standing problem has been achieved by application of this general method that allows for the coupling of diverse phenols with a variety of aryl boronic acids, many of which are commercially available. It overcomes problems associated with procedures used before and offers significant advantages such as a broad substrate variety, mildness, and avoids the use of highly toxic materials. In addition, N-arylation of different types of N-nucleophiles has been achieved under the reaction conditions employed.[19b]

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