Phosphazene P_4-Bu^t base for the Ullmann biaryl ether synthesis

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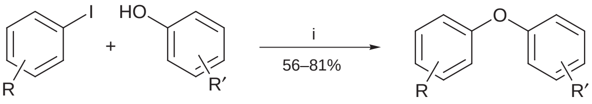
In the presence of phosphazene P_4-Bu^t base and CuBr, aryl halides couple with phenols to give biaryl ethers at *ca.* 100 °C

The reaction of aryl halides with sodium or potassium aryloxides promoted by copper additives results in the formation of aryl ethers, the classical Ullmann biaryl ether synthesis.[1] The major problems of this reaction are the competitive reduction of the aryl halide to the dehalogenated arene[2] and the requirement for extremely harsh conditions, *i.e.* 200–300 °C, long reaction times and strong polar and often toxic solvents.[3] These reaction conditions probably account for an additional problem, namely the formation of isomeric biaryl compounds *via* substitution through an elimination-addition mechanism. On the other hand, the reductive homocoupling of the aryl halide component is also another inherent problem of this reaction.[4] Despite considerable success to date, these efforts have identified the same solution to these problems, namely, the preactivation of the aryl halide component *via*, for instance, the use of transition metals[5] or by placing an electron-withdrawing substituent *ortho* or *para* to the leaving group.[6] Although these variants have a prevalent position in the synthesis of complex macrocyclic peptides,[6,7] there exists no general solution for the direct coupling of aryl halides with phenols.[8]

Recently Buchwald *et al.*[9] described the first case of biaryl ether synthesis with unactivated aryl halides. The reaction occurs at *ca.* 110 °C using Cs_2CO_3 as the key reaction element.

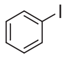
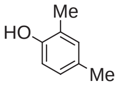
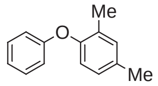
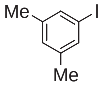
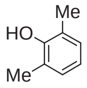
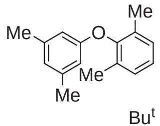
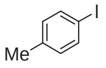
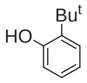
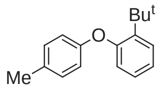
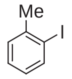
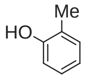
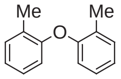
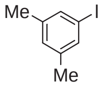
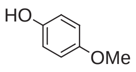
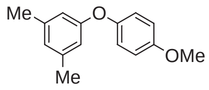
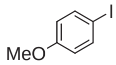
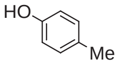
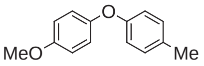
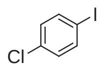
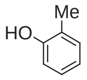
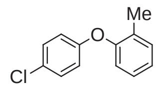
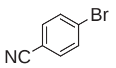
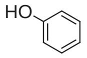
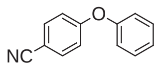
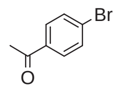
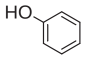
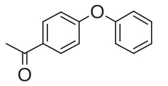
We describe here an efficient method for the direct coupling of aryl halides with phenols that is based on the so-called 'naked anion' phenomenon.[10] Our procedure‡ combines this concept with the use of Schwesinger's phosphazene bases.[11] The synthesis and properties of these bases have been described recently.[12] We have found that P_4-Bu^t base in combination with Cu^I salts in either dioxane or toluene effects the Ullmann reaction of electron-rich, electron-neutral and electron-poor aryl halides with a variety of phenols (Scheme 1). For example, iodobenzene reacted with 2,4-dimethylphenol to produce the corresponding biaryl ether in 81% isolated yield under conditions where the use of other conceptually different bases produced only traces of the expected product, if at all.§ Other copper salts such as CuCl, CuI and $(CuOTf)_2$–benzene were also effective, but Cu^{II} salts did not give the coupling product. As shown in Table 1, the best results were attained using stoichiometric quantities of CuBr, although in some cases the reaction also proceeded well under CuBr catalysis (entries 1, 4, 5 and 8). The method is particularly suitable for electron-neutral aryl halides and *ortho*-substituted phenols. For example 2,6-dimethylphenol (entry 2) provided the corresponding biaryl ether in good yield and even the *o-tert*-butyl phenol (entry 3) coupled with *p*-iodotoluene to give the desired biaryl ether in 56% yield. The coupling reaction of *o*-iodotoluene and *o*-cresol (entry 4) also proceeded well to afford the corresponding biaryl ether in 69% yield. In these two latter cases, once again, no coupling reaction was observed when either DBU or TBD§ were used. Under the established reaction conditions, both electron-rich (entry 6) and electron-poor (entries 7–9) aryl halides also were effective in their coupling with phenols.



Scheme 1 *Reagents and conditions:* i, P_4-Bu^t, CuBr, toluene, reflux

On the other hand, from the examples in Table 1 it also seems that the reaction conditions used are compatible with various functional groups. Nevertheless, neither the amino or the amido functionalities were inert under these reaction conditions. In fact, treatment of 3,5-dimethyliodobenzene with both aniline and *p*-toluidine afforded, under the above reaction conditions, the corresponding biaryl amines in 78 and 71% yield,

Table 1 The Ullmann reaction promoted by P_4-Bu^t base in combination with CuBr^a

Entry	Halide	Phenol	Product	Yield (%)^b
1				81^c (73)
2				72^d (54)
3				56
4				69 (69)
5				81^c (72)^e
6				70^e (25)
7				80^f
8				76 (80)
9				61

[a] Reactions conducted on a 1 mmol scale; aryl halide:phenol:CuBr = 1:2:2 in toluene as solvent unless otherwise stated. [b] Yields in parentheses refer to the reaction under catalytic conditions for Cu^I (20 mol% of CuBr). [c] Dioxane as solvent. [d] Reaction carried out in the presence of DMF (10% v/v). [e] Reaction carried out in the presence of galvinoxyl radical (10 mol%); in the absence of this radical inhibitor undesired byproducts were dominant. [f] Under catalytic conditions a mixture of isomeric biaryl ethers was formed.

respectively.[13] Although the precise role played by the phosphazene P$_4$-Bu^t base in the outcome of the reaction is not clear at present, two observations may give some clue: (i) the well-known ability of such a base to form highly nucleophilic 'naked' anions and, (ii) the complete solubility that the otherwise insoluble CuBr exhibits in the presence of P$_4$-Bu^t. Both factors may facilitate the formation of the reactive intermediate aryloxycopper species,[14] which can then react with the aryl halide under essentially homogeneous conditions. In any case, the use of this phosphazene base appears to be critical for performing the coupling reaction under reaction conditions that are unsuitable for conventional bases.

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Notes and References

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‡ General procedure: A mixture of the aryl halide (1 mmol), the corresponding phenol (2 mmol), P$_4$-Bu^t (2 mmol) and CuBr (2 mmol or 0.2 mmol for the catalytic version) in dry, deoxygenated toluene or dioxane (3 ml) was refluxed under a nitrogen atmosphere until the aryl halide was consumed as determined by GC analysis (typically 16–20 h). The reaction mixture was then allowed to cool to room temperature, diluted with EtOAc and washed sequentially with saturated aq. NH$_4$Cl (25 ml), 0.1 M NaOH (25 ml) and water (25 ml). The organic layer was dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel using hexane afforded the analytically pure product.

§ Among the bases tested, Na$_2$CO$_3$, K$_2$CO$_3$ and 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene (PMDBD) were completely uneffective; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (TBD) afforded the coupling product in less than 20% yield along with the starting material and unidentified side products.

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