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Photochemical Synthesis

Metal-Free Synthesis of Sterically Crowded Biphenyls by Direct Ar–H Substitution in Alkyl Benzenes**

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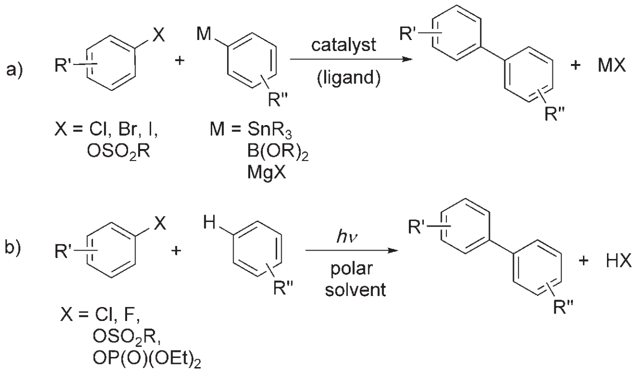
A biaryl moiety is a common structural component of many pharmaceutically and biologically active compounds.[1] Therefore, the synthesis of asymmetric or crowded biaryl compounds is a significant challenge. In recent decades, traditional methods, such as the Ullmann and Gomberg reactions, have been supplanted by novel transition-metal-catalyzed processes.[2] These reactions involve the coupling of a nucleophilic organometallic derivative Ar–M ($M = SnR_3$: Stille reaction; M = MgX: Kumada reaction; $M = B(OH)_2$: Suzuki reaction) with an electrophilic reagent Ar–X (X = halogen or triflate; see Scheme 1 a).



Scheme 1. Synthesis of biaryl compounds by a) metal catalysis and b) the proposed photochemical method.

The main limitation of these methods is that activating groups must be present on both arene coupling partners. The process is therefore inherently unfavorable from the point of view of atom economy. The replacement of one (or both) of these functionalized reagents by a simple Ar–H derivative is thus a key goal in the attempt to develop "greener" methods and of particular appeal with respect to the organometallic reagent, which is often the less stable component and the more difficult to prepare. As the organometallic reagent acts as the nucleophile, electron-rich (hetero)aromatic compounds have been used in this role:[3] One of the first examples was the palladium-catalyzed arylation of isoxazoles.[4] Until now, most reported coupling reactions of this type have been intramolecular reactions. Successful intermolecular coupling required the presence of a group R″ (R″ = OH, CONR2, COR, C=N–R, or a pyridyl nitrogen atom) in the nucleophilic component, placed at a position *ortho* with respect to the attack site that ensured binding to the metal catalyst.[5]

As nonfunctionalized aromatic compounds are deemed to be unreactive, benzene and xylene can be used as solvents for the coupling of functionalized aromatic compounds.[6] To the best of our knowledge, the only exceptions to this rule are a few reactions that occur in moderate yield under severe conditions: the arylation of azulene (at the 1-position) by 4-nitrochlorobenzene under palladium catalysis at 140 °C in a sealed tube[7] and the arylation of benzene both by aryl iodides in the presence of iridium complexes[8a] and by aryl bromides under palladium catalysis in the presence of pivalic acid (30 mol %) at 120 °C.[8b] A novel arylation method that does not involve metal catalysis was described recently.[9] In this method, phenyl cations generated by photoheterolysis of the Ar–X or Ar–O bond of aryl halides (chlorides and fluorides)[10] and esters (mesylates, triflates, and phosphates)[11] with an electron-donating substituent undergo selective addition to π nucleophiles with no interference by the solvent, even when the solvent is a nucleophile, such as an alcohol. The reaction is distinguished by the mild conditions required and in preliminary studies was demonstrated to offer viable access to biphenyl compounds (Scheme 1 b).[9]

The importance of the synthetic target encouraged us to explore the scope of the reaction. The photochemistry of a variety of aryl halides and sulfonate/phosphate esters with an electron-donating substituent ($R'C_6H_4X$, **1**–**11**, Table 1) was investigated in the presence of symmetrical methylbenzenes $C_6H_{6-n}(CH_3)_n$, namely, *p*-xylene, 1,3,5-trimethylbenzene (mesitylene), and 1,2,4,5-tetramethylbenzene (durene). These methyl-substituted benzenes were not only chosen to tune the degree of steric hindrance involved, but also to allow us to assess whether benzylic C–H bond activation competed with Ar–H bond activation under these conditions.[12] The electron-donating group R′ and the leaving group X in the component $R'C_6H_4X$ were varied as much as possible to test the generality of the method.

We found that the desired coupling took place satisfactorily: A variety of bulky biaryl compounds were formed in yields greater than 50 % (mostly > 70 %; Table 1). Direct irradiation at 310 nm was effective for compounds that absorbed sufficiently at this wavelength, whereas sensitization by acetone was successful in the other cases. Arylation yields were higher in the solvent 2,2,2-trifluoroethanol (TFE), but

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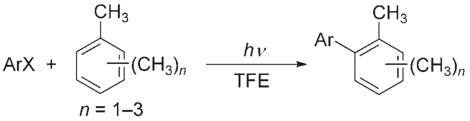
cheaper acetonitrile was a convenient alternative in some cases. A large excess of the methylbenzene (1 M) was used; the concentration of the aryl-cation precursor was 0.05 M. However, reasonable yields were also observed at a lower concentration of the methylbenzene (≤ 0.5 M; see below). Triethylamine (0.05 M) was added in all cases to buffer the acid liberated in the reaction.

Specifically, *p*-xylene was arylated smoothly to give the biphenyl **12** (Table 1, entries 1 and 2) upon irradiation in the presence of the *N*,*N*-dimethylaminophenyl mesylate **1a** or phosphate **1b** in 76 and 52 % yield, respectively. The course of the reaction was not affected by the presence of a methyl group adjacent to X or when the electron-donating group R′ was in the *ortho* position with respect to X. In this way, the 2,2′-disubstituted biphenyls **13** and **14** were obtained from the chloride **2** and triflate **3a**, respectively (Table 1, entries 3 and 4). In the former case, the protection of the OH group in the parent compound as a silyl ether led to a significant improvement in the yield. In the reaction of **3a**, sensitization with acetone was required.

Mesitylene, which is more crowded than *p*-xylene, underwent arylation with the same efficiency. Thus, the irradiation of 4-chlorothioanisole (**4**) in the presence of mesitylene gave the 2,6-dimethylbiphenyl **15** in a yield comparable to those observed with *p*-xylene (Table 1, entry 5; 70 % with 1 M mesitylene, 58 % with 0.5 M mesitylene). The *meta*-methoxy triflate **5** also underwent successful arylation to give **16** in 71 % yield, despite the fact that photosolvolysis has been shown to be effective with this derivative.[13] The more sterically crowded tri-*ortho*-substituted biaryl compounds **17** and **18** were prepared by the irradiation of *ortho*-methoxy mesylate (**3b**) and the methylchloroaniline **6** in 77 and 62 % yield, respectively (Table 1, entries 7 and 8). In the former case, acetonitrile could be used conveniently in place of TFE.

Table 1: Photoarylation of alkyl benzenes.



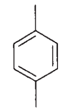
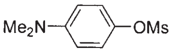
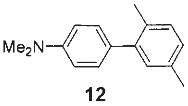
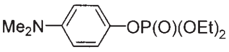
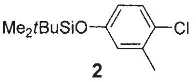
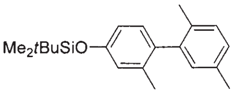
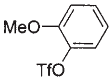
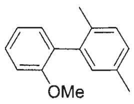
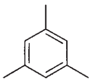
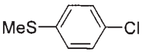
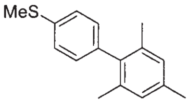
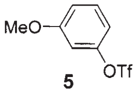
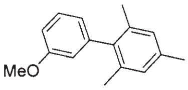
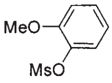
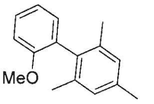
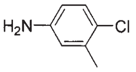
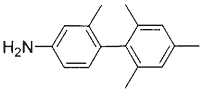
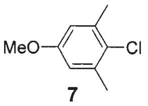
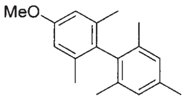
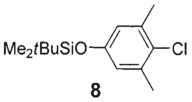
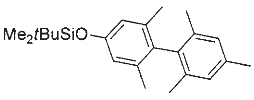
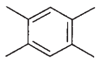
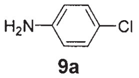
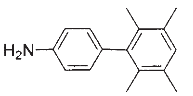
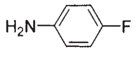
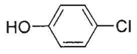
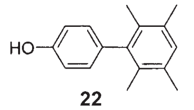
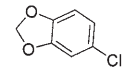
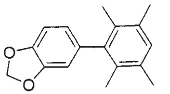
Entry	Alkyl benzene (1 M)	Aryl halide or ester (0.05 M)	t_{irr} [h]	Product	Yield [%][a]
1		 **1a**	7	 **12**	76
2		 **1b**	7		52
3		 **2**	7	 **13**	56
4[b]		 **3a**	7	 **14**	77
5		 **4**	8	 **15**	70
6[b]		 **5**	7	 **16**	71
7[b]		 **3b**	7	 **17**	77[c]
8		 **6**	5	 **18**	62
9[d]		 **7**	7	 **19**	84
10[b,e]		 **8**	1.5	 **20**	77

Table 1: (Continued)

Entry	Alkyl benzene (1 M)	Aryl halide or ester (0.05 M)	t_{irr} [h]	Product	Yield [%][a]
11[f]		 **9a**	4	 **21**	58
12[f]		 **9b**	4		46
13[f,g]		 **10**	7	 **22**	60
14[f,g]		 **11**	7	 **23**	76

[a] Yield of the isolated compound. [b] Acetone (0.9 M) was added as a sensitizer. [c] Compound **17** was formed in 71 % yield with MeCN as the solvent. [d] Cesium carbonate was used as the base. [e] Two equivalents of Et_3N were used. [f] Durene: 0.2 M. [g] Aryl chloride: 0.02 M. Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl.

Most interestingly, the arylation took place smoothly with the aryl halides **7** and **8**, in which two methyl groups flank the leaving chlorine atom (Table 1, entries 9 and 10). The corresponding tetra-*ortho*-substituted biaryl compounds **19** and **20** were formed in high yields of 84 and 77 %, respectively. (Compound **20** was formed in 63 % yield when mesitylene was used at a concentration of 0.5 M.) Cesium carbonate was used in place of triethylamine in the reaction with compound **7**, and the amount of triethylamine used was doubled with **8** to avoid desilylation during the irradiation.

The extension of the coupling reaction to the substrate durene was limited by the low solubility of this aromatic compound in polar solvents. It was necessary to carry out the irradiation at a durene concentration of 0.2 M. Gratifyingly, biaryl compounds were again formed as the main products by far, although the yields were somewhat lower (Table 1, entries 11–14). Thus, the aminobiphenyl **21** was synthesized from both chloro- (**9a**) and fluoroaniline (**9b**) in 58 and 46 % yield, respectively. Despite the moderate yield, the reaction of **9b** is noteworthy because the use of an aryl fluoride in a coupling reaction with a non-activated aromatic compound has no precedent under thermal conditions. Furthermore, 4-chlorophenol (**10**; Table 1, entry 13) underwent successful arylation with durene, as did the benzo[1,3]dioxole **11**, which was transformed into **23** in 76 % yield (Table 1, entry 14). The aryl halide was used at a lower concentration (0.02 M) in these last two reactions.

These results show that direct hydrogen-atom substitution of simple arenes (such as alkyl benzenes) is possible in a metal-free process in which phenyl cations are generated photochemically under mild conditions. Thus, twelve increasingly congested biaryl compounds, from 2,6- or 2,2′-dimethyl-substituted to tetra-*ortho*-methyl-substituted biphenyls, were prepared by photoinduced coupling between an aryl halide (or sulfonate/phosphate ester) $R'C_6H_4X$ and an arene $R''ArH$ by elimination of HX. The functional groups OH, NH_2, OR, NR_2, SR, and $OSiR_3$ were found to be suitable as electron-donating groups R′, mostly in the *ortho* or *para* position. As demonstrated by the experiments with **6**, **9a**,**b**, and **10** (see Table 1), the protection of the acidic hydrogen atoms in anilines and phenols is unnecessary in some cases, despite the fact that the corresponding phenyl cation can undergo deprotonation to give a 4-iminocyclohexa-2,5-dienylidene carbene (in the case of **6** and **9a**,**b**)[14a] or 4-oxocyclohexa-2,5-dienylidene carbene (in the case of **10**).[14b–d] Apparently, the trapping of the phenyl cation by a (sufficiently concentrated) π nucleophile is faster,[15] and deprotonation is a minor process, if it occurs at all: Benzoquinone (the diagnostic product of the trapping of the corresponding carbene by oxygen) was not formed when **10** was irradiated under oxygen.

We can conclude from this series of experiments that this method for the synthesis of biaryl compounds has broad scope and that steric hindrance presents no significant limitation. Products of the type shown in Table 1 can be obtained by metal-mediated syntheses with an activating functional group, such as $SnBu_3$ or $B(OH)_2$.[16] However, for the present method simple aromatic compounds rather than organometallic aromatic compounds are required (see Scheme 1), and mild, practical conditions are used: Moisture has no effect, no labile or toxic reagent is required, there is no metal residue to collect and dispose of after the reaction, and the reactions are carried out at room temperature.

Nevertheless, there is a mechanistic analogy with metal-catalyzed reactions, particularly with respect to the electrophilic component. The present reactions involve the generation of a cation by heterolytic cleavage of the Ar−X bond. This process can be likened to the weakening of such bond by donation from the metal catalyst to the antibonding orbital of the halide:[9a] Thus, the aryl–metal complex has some carbocationic character.[3]

The photochemical arylation reactions were strictly chemoselective. No functionalization was observed at benzylic positions despite the statistical predominance of benzylic hydrogen atoms over aryl hydrogen atoms (6:1 in the case of durene). Furthermore, clean monoarylation was always observed, and other possible competitive pathways, such as the reduction of the starting halides or sulfonate/phosphate esters, were in most cases negligible. (Such by-products were usually formed in 2–5 % yield, except in two cases in which the product of reduction was formed in 9 % yield; see the Supporting Information.) Furthermore, this method is more versatile than traditional methods with respect to the range of possible aryl-cation precursors, as the photochemical reaction is more effective than metal-catalyzed activation of the ArX bond. Indeed, ArX derivatives that are usually less reactive under palladium catalysis,[5b] such as aryl chlorides and even aryl fluorides and phosphates, can be used conveniently. Finally, a large variety of substituents can be present in the *ortho*, *meta*, or *para* position of the aryl-cation precursor. In conclusion, this novel photochemical synthesis of biaryl compounds represents a convenient alternative to organometallic processes.

Experimental Section

General procedure: A solution of an aryl sulfonate ester, phosphate ester, or halide (1.5 mmol, 0.05 M), triethylamine (0.05 M), and a methylbenzene (1 M) in TFE (30 mL) was poured into two quartz tubes and purged with argon for 10 min. The tubes were closed with serum caps and the solution was irradiated with six 15-W phosphor-coated lamps (emission centered at 310 nm). The photolyzed solution was concentrated under reduced pressure and purified by column chromatography (cyclohexane/ethyl acetate). For the reactions of compounds **3a**,**b**, **5**, and **8**, acetone (3 mL, 0.9 M) was added to the reaction mixture.

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[15] The diagnostic reaction for 4-oxocyclohexa-2,5-dienylidene (or 4-iminocyclohexa-2,5-dienylidene) is trapping by oxygen to form a carbonyl oxide[14a,b,d] and ultimately benzoquinone (or benzoquinone imine). The present reactions are affected to only a small extent by oxygen, the presence of which leads to a moderate decrease in the yield (≤20%), at least when the concentration of the nucleophile is 1 M. No benzoquinone is formed.

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