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Synthesis of unsymmetrical biaryls via palladium-catalyzed coupling reaction of aryl halides

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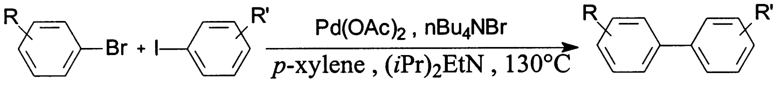
Abstract

Unsymmetrical biaryls bearing electron-donating and electron-withdrawing functional groups have been obtained in an efficient manner by Pd-catalyzed coupling of aryl halides. Aryl bromides react with aryl iodides to yield unsymmetrical biaryls with marked selectivity. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aryl halides; biaryls; Ullmann reaction; coupling reaction.

The development of synthetic methods for the construction of unsymmetrical biaryls has been of interest due, in part, to their presence in many important natural products,[1] in organic materials such as organic semiconductors.[2] Unsymmetrical biaryls, having donor and acceptor groups, can be used as materials for nonlinear optics.[3] Biaryls are usually prepared from aryl iodides, bromides or triflates, either by Ullmann coupling[4] or by Ni- or Pd-catalyzed cross-coupling reactions of arylboranes (the Suzuki reaction),[5] organotins (the Stille reaction)[6] and Grignard reagents.[7] The use of stoichiometric amounts of organometallic intermediates remains an important drawback for these methods. Previously, we reported a catalytic alternative of the Ullmann reaction for the synthesis of symmetrical functionalized biaryls and biheterocycles by using $Pd(OAc)_2$ as the catalyst.[8–11] This method was compatible with sensitive functional groups such as aldehyde or nitro. Here we report that, in the presence of a catalytic amount of $Pd(OAc)_2$, unsymmetrical biaryls have been obtained with good selectivity (Scheme 1).



Scheme 1. Cross-coupling of aryl bromide with aryl iodide catalyzed by palladium

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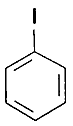
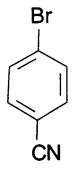
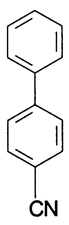
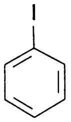
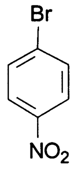
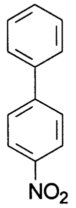
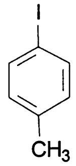
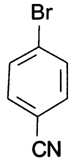
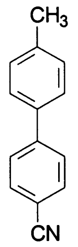
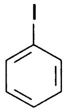
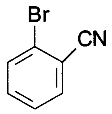
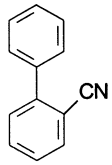
Several substrates having different functional groups have been successively coupled and the results are summerized in Tables 1 and 2.[12] In order to evaluate the scope and limitations of the unsymmetrical coupling reaction, the coupling of iodobenzene with 4-bromobenzonitrile has been studied (entry 1, Table 1).

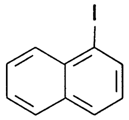
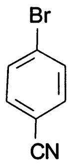
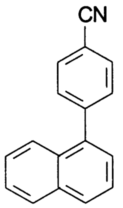
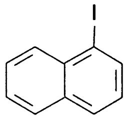
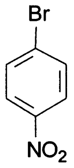
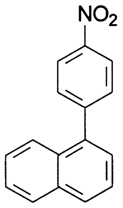
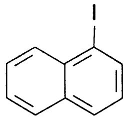
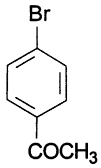
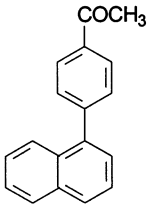
Table 1
Unsymmetrical coupling of various aryl iodides and aryl bromides catalyzed by palladium

Entry	Ar–I	Ar–Br	Time (h)	Product	Ref.[a]	Chemical yield[b] Ar–Ar′	Homocoupling yield[c] GLC (%)
1			24		13	95 (35)	5
2			24		14	79 (32)	21
3			24		4	78 (53)	18
4			68		15	85 (54)	15

[a] All products have been characterized and comparisons with already published data are in agreement.
[b] The value in parentheses indicates isolated yield.
[c] The homocoupling product of aryl iodide.

An excess of 4-bromobenzonitrile has to be used in order to improve the yield of unsymmetrical compounds instead of the competitive Ullmann reactions. Suzuki and colleagues[16] have reported a similar Ullmann cross-coupling between nitro-substituted iodobenzoates and an

Table 2
Unsymmetrical coupling of 1-iodonaphthalene and aryl bromides catalyzed by palladium

Entry	Ar–I	Ar–Br	Time (h)	Product	Ref.[a]	Chemical yield[b] Ar–Ar′	Homocoupling yield[c] GLC (%)
1			24		17	87 (20)	13
2			68		18	100 (35)	0
3			23		17	100 (22)	0

[a] All products have been characterized and comparisons with already published data are in agreement.

[b] The value in parentheses indicates isolated yield.

[c] The homocoupling product of aryl iodide.

excess of iodonaphtalenes to yield poly-nitrobenzanthrones but this method requires stoichiometric amounts of copper and high reaction temperature. In our synthetic route, the reaction temperature is also crucial, higher temperatures seem to specifically accelerate the unsymmetrical coupling reaction. Therefore, *p*-xylene has been used and is more efficient than DMF for unsymmetrical coupling reactions. In all cases, diisopropylethylamine appears to be the most efficient and selective base.

Regarding the mechanism of the reaction, the reaction most likely proceeded via the oxidative addition of aryl iodide onto palladium(0). The second step could be either another oxidative addition onto aryl bromide or a nucleophilic substitution. A good selectivity of the unsymmetrical cross-coupling is observed for each case, relatively low homocoupling of the iodoaryl occurred. Moreover little or no homocoupling of the arylbromide is observed. We note relatively low isolated yields of the desired products, which fall in the range of 12–53% because of the difficulty to purify coupling product. High isolated yields could be obtained by using high molecular mass aryl iodides. As shown in Tables 1 and 2, the coupling reaction is efficient with aryl bromides substituted by various electron-withdrawing groups such as cyano and nitro. In the case of 2-bromobenzonitrile (entry 4, Table 1), the coupling reaction was carried out with high selectivity in spite of a steric hindrance. Finally, the 1-iodonaphthalene was tested (entries 1, 2 and 3, Table 2) and led to the unsymmetrical products with marked selectivity.

In conclusion, the cross-coupling reactions of aryl iodides and aryl bromides catalyzed by palladium complex provides a direct method to prepare unsymmetrical biaryls.

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12. **General Procedure**: A mixture of diisopropylethylamine (8 mmol), palladium acetate (0.4 mmol), tetra-*n*-butylammonium bromide (8 mmol), aryl iodide (8 mmol) and aryl bromide (32 mmol) in *p*-xylene (5 ml) was stirred under nitrogen atmosphere. The mixture was retained for a period of time, as indicated in Table 1. After cooling to room temperature water and ether were added. The organic phase was washed with water and dried over $MgSO_4$. The solvent was evaporated under vacuum. The mixture was distilled to eliminate unreacted aryl bromide, and then the unsymmetrical product was purified either by thin layer chromatography or through a silica gel column.
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