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Homocoupling of aryl iodides and bromides promoted by sulfur-containing palladacycles

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Abstract—Sulfur-containing palladacycles, in particular those derived from the orthometalation of benzylthioethers, effectively promote the homocoupling of aryl iodides and bromides, under relatively mild reaction conditions to furnish symmetrical biphenyls in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

Biaryls possess a large variety of physical and chemical properties and they have a broad range of applications, encompassing various areas such as intermediates for natural product synthesis, monomers for conducting polymers and ligands for organometallic catalysis.[1] These compounds are traditionally prepared by the Ulmann homocoupling reaction, which involves the condensation of two aryl halide molecules in the presence of stoichiometric amounts of copper salts.[2] More recently, symmetrical biphenyls have been prepared from arylboronic acids,[3] arylstannanes[4] and arylzinc[5] reagents. These methods are quite effective for the generation of biphenyls although the necessity for the preparation of these organometallic reagents and their use in stoichiometric amounts are the major drawbacks.

The transition-metal catalyzed homocoupling of aryl halides is a catalytic alternative for the generation of biphenyls starting from commercially available starting materials. Indeed, various nickel[6] and palladium[7] catalyst precursors have been reported to promote the coupling of aryl halides, under relatively mild reaction conditions. Amongst these, palladium acetate associated with phosphines, arsines, tetrabutylammonium bromide and phosphapalladacycles have been successfully used in the aryl halide homocoupling reaction. However, in most of the cases reported, the method is only effective for aryl iodides and activated aryl bromides in the presence of large quantities of the palladium catalyst precursor (2–5%). Moreover, the homocoupling reaction is accompanied by the formation of significant amounts of reduced aryl halide product. Therefore, the development of an effective catalytic protocol for this reaction, in particular involving less reactive bromo arenes, remains a challenge is this area.

We have recently shown that sulfur-containing palladacycles[8] (Fig. 1) are effective catalyst precursors for the Heck, Suzuki and hydro-arylation coupling reactions, under mild reactions.[9] In the case of the Heck reaction of aryl iodides with tetrahydropyrans, a significant amount of arene homocoupling product was observed depending on the reaction conditions, suggesting that palladacycle **1** is a potential catalyst precursor for arene homocoupling reactions.[9c] We wish to disclose herein our preliminary results on the use of the palladacycle **1**, derived from the orthometallation of *t*-butylmethylbenzyl sulfide, on the homocoupling of aryl iodides and bromides (Eq. (1)).

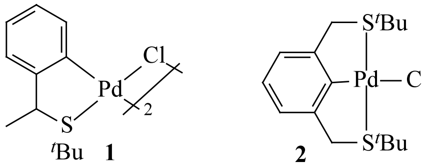
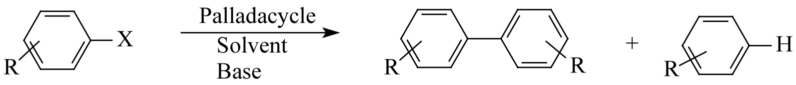


Figure 1. Sulfur-containing palladacycles used as catalyst precursors for C–C coupling reactions.

 (1)

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Initially, we tested the homocoupling of iodobenzene catalyzed by this palladacycle at 130°C for 24 h using different solvents and bases (Table 1).

It is evident from the data in Table 1 (entries 1–8), that for the homocoupling of iodobenzene, the reaction performed in DMF using triethylamine as base gave complete conversion and excellent isolated yields of the biphenyl product (entry 8, Table 1). Moreover, under these reaction conditions the biphenyl was the sole product detected by GC–MS without traces of by-products, such as benzene—the product resulting from the reduction of the iodobenzene—usually observed in most of the palladium-catalyzed homocoupling reactions reported to date.

This experimental protocol has been successfully extended to other *para*, *meta* and *ortho* substituted iodo arenes (entries 9–14, Table 1), giving almost complete conversion and excellent isolated yields of biphenyl products with the exception of the *ortho* substituted aryl iodides.[10] In these cases (entries 13 and 14, Table 1), a substantial amount of the methylbenzoate and naphthalene by-products were formed, indicating that this reaction is sensitive to steric factors. Nonetheless, palladacycle **1** is one of the most effective and selective catalyst precursors for the generation of biphenyls from aryl iodides, reported to date.

Once the protocol was established we turned our attention to the homocoupling of the less reactive aryl bromides. However, attempts to perform the homocoupling of aryl bromides, under the same reaction conditions employed for aryl iodides, have failed and the starting materials were recovered almost quantitatively after catalysis. We have thus reinvestigated the reaction conditions by studying the homocoupling of 4-bromoanisole as a model reaction. The use of K_3PO_4 as a base in DMF at 100°C gave the best results in terms of selectivity and yields of the biphenyl products (Table 2).

However, in all cases significant amounts of reduced bromoarene products were formed. The proportion of these by-products increases with the introduction of *ortho* substituents in the bromo-arene moiety (see entries 5–7, Table 2). In the case of 2-trifluoromethylbromobenzene (entry 5, Table 2), besides the high amount of the reduction product, a mixture of biphenyl isomers was obtained (Eq. (2)). The formation of these isomers is probably related to a side reaction involving benzyne intermediates, analogous to those already reported in other related palladium-catalyzed coupling reactions.[11]

Table 1. Palladacycle **1**-catalyzed homocoupling of aryl iodides[a]

Entry	ArI	Base	Solvent	Conv. (%)	ArH yield (%)[b]	Ar–Ar yield (%)[b]
1	PhI	Cs_2CO_3	DMA	18		2
2	PhI	K_3PO_4	DMA	27		9
3	PhI	NaOAc	DMA	93		68
4	PhI	NEt_3	DMA	96		79
5	PhI	NEt_3	Dioxane	39		10
6	PhI	NEt_3	Toluene	55		3
7	PhI	NEt_3	MeCN	87		34
8	PhI	NEt_3	DMF	100	–	100 (96)
9	4-MeC_6H_4I	NEt_3	DMF	99	–	98 (94)
10	4-MeOC_6H_4I	NEt_3	DMF	93	–	94 (84)
11	4-AcC_6H_4I	NEt_3	DMF	99	–	96 (82)
12	3-FC_6H_4I	NEt_3	DMF	100	–	97 (83)
13	$2\text{-MeO}_2CC_6H_4I$	NEt_3	DMF	100	46	54
14	$1\text{-C}_{10}H_7I$	NEt_3	DMF	100	37	63

[a] *Reaction conditions*: 0.5 mol% palladacycle **1**, 1 mmol of iodo arene, 1.4 mmol of base, 5 mL of solvent, 130°C, 24 h.

[b] GC yields using undecane as internal standard. Isolated yields in parentheses.

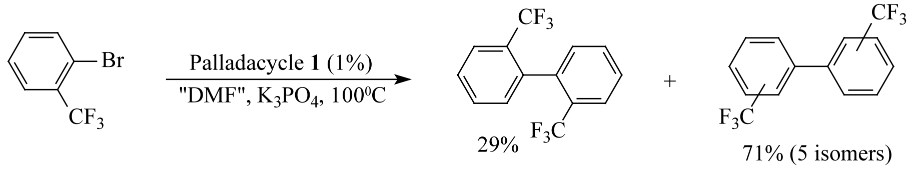
Table 2. Palladacycle **1**-catalyzed homocoupling of aryl bromides[a]

Entry	Ar–Br	Time (h)	Conv. (%)	Ar–H (%)	Ar–Ar (%)[b]
1	4-MeOC_6H_4Br	87	100	30	70 (61)
2	4-AcC_6H_4Br	95	99	13	56 (56)
3	$4\text{-F}_3CC_6H_4Br$	90	85	29	46 (40)
4	$3\text{-F}_3CC_6H_4Br$	90	79	34	35 (35)
5	$2\text{-F}_3CC_6H_4Br$	90	65	50	15[c]
6	$2,5\text{-Me}_2C_6H_3Br$	115	95	74	12
7	$1\text{-C}_{10}H_7Br$	143	100	72	28

[a] *Reaction conditions*: 1.0 mol% palladacycle **1**, 1 mmol of bromo arene, 1.4 mmol of base (K_3PO_4), 5 mL of solvent (DMF), 100°C.

[b] GC yields using undecane as internal standard. Isolated yields in parentheses.

[c] Mixture of six isomers.



(2)

The homocoupling of 2-trifluoromethylbromobenzene catalyzed by palladacycle **1**.

It is interesting to note that all of these reactions employ DMF as solvent and catalytic activity and selectivity were strongly dependent on the DMF source[12]. It is well known that, depending on its source, DMF contains different impurities such as dimethylamine and formate or that such impurities may be generated in situ.[13,14] Moreover, it was proposed earlier that these impurities could react with Pd(II) species to generate Pd–H intermediates, which are reduced to Pd(0) by the action of the base.[13] In our case, the generation of Pd–H intermediates can explain the formation of the Ar–H by-products through a reductive elimination step. We can note that the hydrogen source in the reduction process is not water that may be present in the medium, since reactions performed with 4-bromoanisole in the presence of D_2O indicated no D-incorporation (by GC–MS) in the anisole formed.

In summary, sulfur-containing palladacycles such as **1** are excellent catalyst precursors for the homocoupling of aryl iodides. They are also effective for the homocoupling of aryl bromides. Further work is in progress in our laboratory in order to understand the role of DMF impurities in these reactions.

Acknowledgements

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10. Typical procedure: An oven-dried resealable Schlenk flask was charged with palladacycle **1** (0.005–0.01 mmol). The flask was evacuated and backfilled with argon and then were added aryl halide (1.0 mmol), base (1.5 mmol) and 5 mL of solvent. The reaction mixture was stirred at the desired temperature. The solution was then allowed to cool to room temperature, taken up in ether (20 mL) and washed with aqueous NaOH (1 M, 2×10 mL) and brine (2×10 mL) and then dried over $MgSO_4$. After filtration, the product was isolated by chromatography. All biphenyl products reported in this work are known and have spectroscopic data in accord with those reported (mp, CG–MS, ^1H and ^{13}C NMR).
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12. We have tested DMF from Acros (p.a.), Merck (p.a. or Omnisolv) and Grupo Química (p.a.). The 4-bromoanisole homocoupling reactions performed with these commercial solvents gave the conversions and selectivities presented in Table 2. However, the use of purified (dried over CaH_2) and distilled DMF furnishes the bromoanisole as the main product. GC–MS analysis of these commercial solvents indicated the presence of different amounts of dimethylamine. However, the addition of different amounts of dimethylamine to the purified DMF solvents gave random results.
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