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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7687–7690

Palladium-catalyzed homocoupling of arenediazonium salts: an operationally simple synthesis of symmetrical biaryls

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Received 7 August 2007; revised 21 August 2007; accepted 22 August 2007
Available online 29 August 2007

Abstract—A simple procedure for the intermolecular homocoupling of arenediazonium salts in air using a catalytic amount of palladium acetate is described. The optimum conditions were found to be 15 mol % palladium acetate in refluxing methanol, with no additional terminal reducing agent required. These optimized conditions were used to prepare biaryls from several arenediazonium tetrafluoroborate salts, and most examples proceeded in moderate to high yields.

The preparation of biaryls is an important objective in organic synthesis, since the biaryl unit is found in a number of natural products, pharmaceuticals, conducting polymers, and optically active ligands for asymmetric synthesis.[1] Symmetrical biaryls have traditionally been synthesized by the Ullmann reaction,[2] but the high temperatures which are typically required have spawned the development of a number of milder palladium[3,4a]- and nickel[4]-mediated protocols for the synthesis of these compounds from both aryl halides and aryl sulfonates. These methods usually also require the addition of a stoichiometric amount a terminal reducing agent such as zinc powder. Copper[5]- and rhodium[6]-based methods for the homocoupling of aryl halides have been developed, and it has been shown that a system of zinc and trimethylammonium formate will mediate the homocoupling of aryl halides without the need for a nickel or palladium co-catalyst.[7] Symmetrical biaryls are also accessible through the copper-catalyzed homocoupling of organosilicon halides,[8] as well as the homocoupling of arylboronic acids catalyzed by metals such as palladium and gold.[9]

In contrast, transition-metal-catalyzed routes to symmetrical biaryls from arenediazonium salts have not received as much attention although stoichiometric copper-mediated methods are known.[10] Since arenediazonium tetrafluoroborates are easily prepared from the corresponding arylamines,[11] which are often more readily available than the corresponding aryl halides or phenols, we became interested in developing a transition-metal-catalyzed homocoupling protocol for the synthesis of symmetrical biaryls from these compounds. Very recently, Cepanec and coworkers reported the copper(I) triflate catalyzed homocoupling of arenediazonium salts using stoichiometric copper bronze as the terminal reducing agent.[12] Their protocol was carried out in acetonitrile and required the exclusion of oxygen and water. Electron-rich substrates were homocoupled in good yield under these conditions, although electron-poor substrates were more efficiently homocoupled using stoichiometric amounts of copper(I) triflate. Since similar palladium-catalyzed methods have not been studied, we embarked on an attempt to develop a viable palladium-catalyzed route to symmetrical biaryls from arenediazonium salts.

When we considered the generally accepted mechanism for the Pd-catalyzed homocoupling of aromatic electrophiles (Scheme 1),[3a] it became clear to us that a palladium-catalyzed approach to the homocoupling of arenediazonium salts had ample literature precedent. The palladium-catalyzed cross-coupling of arenediazonium tetrafluoroborates with arylboronic acids,[13] potassium organotrifluoroborates,[14] and aryl silanes[15] indicated that oxidative addition of an arenediazonium salt to low-valent palladium (step ii) readily occurs. Furthermore, the observation of products derived from

Keywords: Arenediazonium salts; Symmetrical biaryls; Palladium-catalyzed homocoupling.
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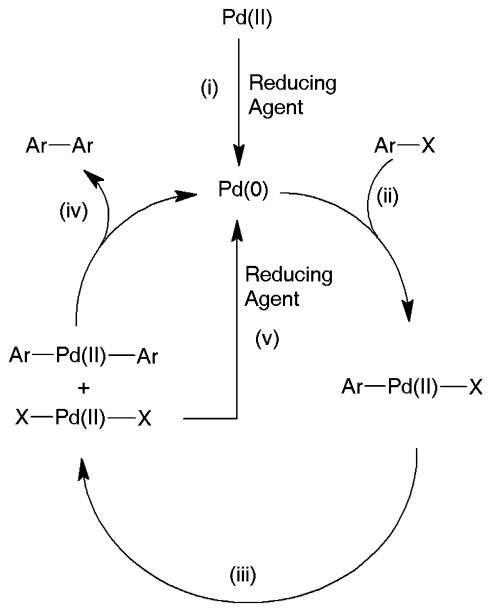
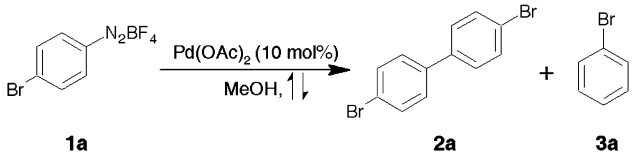
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.083



Scheme 1. Pd-catalyzed homocoupling of aryl electrophiles.

the homocoupling of arenediazonium salts as by-products in palladium-catalyzed cross-coupling reactions[14] showed the feasibility of the disproportionation (step iii) and reductive elimination (step iv) steps. Additional precedent was provided by one early literature report of the homocoupling of an arenediazocyanide mediated by $PdCl_2$.[16] The fact that palladium(II) is known to catalyze the oxidation of alcohols[17] also suggested to us that an alcohol solvent might function as both the initial reducing agent (step i) and the terminal reducing agent (step v) and allow the homocoupling to be carried out in an operationally simple manner without the addition of a zero-valent metal or other terminal reductant.[18] We have indeed found that several arenediazonium tetrafluoroborates can be successfully converted to symmetrical biaryls in good yield using an operationally simple system of palladium acetate in refluxing methanol without the need for an additional terminal reductant and without any special oxygen- or water-exclusion techniques. Herein we report the results of our study.

We chose to begin by looking at the homocoupling of 4-bromobenzenediazonium tetrafluoroborate (Scheme 2, **1a**) in methanol. We were pleased to find that when a 0.1 M methanolic solution of **1a** was refluxed in the presence of palladium acetate (10 mol %), 4,4′-dibromobiphenyl (**2a**) was produced in 45% yield. In addition to the homocoupled product, the reduced product, bromobenzene (**3a**) was also formed in 35% yield. Along with proving the viability of a palladium-catalyzed homocoupling protocol for the synthesis of biaryls from

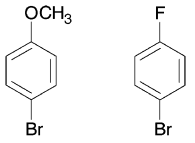


Scheme 2. Pd-catalyzed homocoupling of **1a**.

arenediazonium salts, this result demonstrates the preference for homocoupling of the diazonium group in the presence of a bromo substituent, which could be elaborated further by, for example, a Suzuki coupling.

Encouraged by this result, we began to optimize the conditions of the homocoupling reaction, using the reaction of **1a** as the model system. First, we investigated the effect of concentration on the yield and product distribution. According to the assumed mechanism, the formation of biaryl **2a** requires the formation of the diaryl Pd complex, which arises from the (bimolecular) disproportionation step (step iii, Scheme 1). Therefore, we thought we could increase the rate of diaryl Pd complex formation and improve the yield of **2a** by increasing the concentration of the reaction mass. We did indeed find that higher concentrations favor a higher yield of **2a** and these results are shown in Table 1. The best yields of **2a** were produced within 1 h at **1a** concentrations of 0.5–1.0 M (entries 4 and 5). Because the reaction mass was more fluid at a concentration of 0.5 M, we used this concentration for further optimization studies.

We then turned our attention to the optimization of catalyst precursor loading, and the results are shown in Table 2. As indicated, the best yields of **2a** were seen using 10–15 mol % of $Pd(OAc)_2$. Increasing the amount to 20 mol % did not improve the yield or the product distribution. The reaction was usually complete within 1 h in refluxing methanol, although it could be carried out at room temperature for a longer time period (entry 2). Also, the reaction in the absence of $Pd(OAc)_2$ (entry 8) produced very little biaryl **2a**, confirming that the homocoupling pathway is catalyzed by the palladium salt. Instead this reaction led primarily to reduced product **3a** along with 4-bromoanisole (**4a,** derived from reaction of **1a** with methanol) and 4-fluorobromobenzene (**5**, derived from the Schiemann reaction of **1a**).



4a **5**

Our supposition that methanol is the terminal reductant is supported by the fact that the formation of palladium black is observed during the reaction. Furthermore,

Table 1. Concentration effect on the homocoupling of **1a** (Scheme 2)[a]

Entry	[**1a**] (M)	Yield[b] (%)	
		2a	**3a**
1	0.05	40	45
2	0.1	45	35
3	0.25	54	19
4	0.5	59	12
5[c]	1.0	59	3

[a] All reactions were performed in refluxing methanol in the presence of $Pd(OAc)_2$ (10 mol %).
[b] Determined by GC analysis using an internal standard.
[c] $Pd(OAc)_2$ of 15 mol %. 4-Bromoanisole (**4a**, 1%) was also detected in this reaction.

Table 2. Effect of $Pd(OAc)_2$ loading on the homocoupling of **1a**[a]

Entry	$Pd(OAc)_2$ (mol %)	Yield[b] (%)	
		2a	**3a**
1	20	62	10
2[c]	20	65	9
3	15	66	13
4[d]	15	15	10
5	10	59	12
6	5	54	14
7	1	34	25
8[e]	0	5	61

[a] All reactions were performed at a **1a** concentration of 0.5 M in refluxing methanol.
[b] Determined by GC analysis using an internal standard. Unless otherwise noted, yields reported are an average of at least two experiments.
[c] Reaction mass was stirred at room temperature for three days.
[d] Reaction carried out in the presence of 2,2′-bipyridine (15 mol %). Compounds **4a** (42%) and **5** (10%) were also produced. Results are based on one experiment only.
[e] Compounds **4a** (15%) and **5** (4%) were also detected.

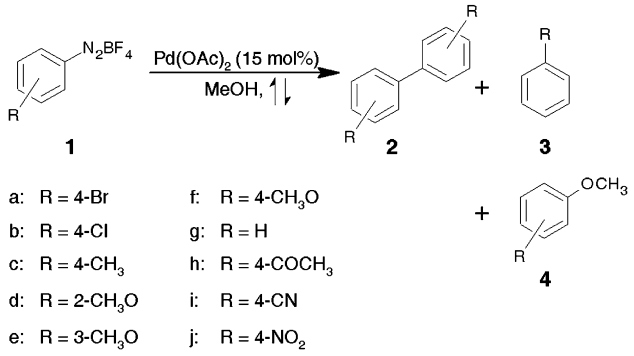
when a molar equivalent of 2,2′-bipyridine (relative to the $Pd(OAc)_2$) was added in an attempt to stabilize the active catalyst species and prevent the formation of palladium black, only a 15% yield of **2a** was observed (entry 4). Since 2,2′-bipyridine is known to inhibit the $Pd(OAc)_2$-catalyzed oxidation of alcohols,[17] we believe this result further supports our hypothesis that methanol is functioning as the terminal reducing agent in this reaction. Based on these results, additional optimization studies were carried out in the presence of 15 mol % $Pd(OAc)_2$.

We next conducted a survey of potential catalyst precursors and the results are shown in Table 3. $Pd(OAc)_2$ and $Pd(O_2CCF_3)_2$ were shown to be the most effective (entries 1 and 4). $PdCl_2$ was somewhat effective, giving a 36% yield of **2a** and a favorable **2a**:**3a** ratio (entry 2). However a significant amount of **4a**, derived from reaction of **1a** with methanol, was also formed. $Pd(PPh_3)_4$ gave a moderate overall yield, but produced **2a** and **3a** in essentially equivalent amounts (entry 5). Other palladium compounds led to much lower amounts of

Table 3. Effect of catalyst precursor on the homocoupling of **1a**[a]

Entry	Catalyst precursor	Yield[b] (%)			
		2a	**3a**	**4a**	**5**
1	$Pd(OAc)_2$	66	13	0	0
2	$PdCl_2$	36	9	21	3
3[c]	$Pd_2(dba)_3$	7	1	1	0
4	$Pd(O_2CCF_3)_2$	60	12	1	0
5	$Pd(PPh_3)_4$	24	25	0	0
6	Pd/C (10%)	5	35	1	0
7	$Pd(acac)_2$	5	5	24	3
8[c]	K_2PdCl_4	0	2	40	0

[a] All reactions were performed at a **1a** concentration of 0.5 M, with 15 mol % catalyst precursor in refluxing methanol.
[b] Determined by GC analysis using an internal standard. Unless otherwise noted, yields reported are an average of at least two experiments.
[c] Results are based on one experiment only.



Scheme 3. Scope and limitations of the homocoupling reaction.

the desired **2a**. Occasionally, a small amount of the Schiemann product **5** was also detected.

With the optimized conditions in hand (0.5 M arenediazonium salt and 15 mol % $Pd(OAc)_2$ in refluxing methanol), we proceeded to study the scope and limitations of the homocoupling reaction using this protocol (Scheme 3). The results are shown in Table 4. In most cases, moderate to high yields were obtained. A 2-methoxy group exhibited some steric effect, leading to a lower yield of homocoupled product from the reaction of **1d** (entry 4) when compared to **1f** (entry 6).

The reaction of the cyano-substituted compound **1i** produced no biaryl **2i**, but gave primarily two products derived from the reaction with the methanol solvent—**4i** and methyl 4-methoxybenzoate (entry 9). We speculate that this may be the result of coordination of the cyano group to $Pd(OAc)_2$ interfering with the reduction of the catalyst precursor, similar to the result in the presence of 2,2′-bipyridine (*vide supra*). Further evidence for this type of effect was provided by an experiment in which diazonium salt **1a** was refluxed in 3:1 acetonitrile–methanol with $Pd(OAc)_2$. This experiment gave only a 16%

Table 4. Scope and limitations of the Pd-catalyzed homocoupling reaction (Scheme 3)[a]

Entry	R	Product	Yield[b] (%)		
			2	**3**	**4**
1	4-Br	**a**	66	13	0
2	4-Cl	**b**	74	11	0
3	4-CH_3	**c**	82	3	—[c]
4	2-CH_3O	**d**	66	6	0
5[d]	3-CH_3O	**e**	25	17	36
6	4-CH_3O	**f**	88	4	0
7	H	**g**	55	5	26
8	4-$COCH_3$	**h**	44	18	9
9[e]	4-CN	**i**	0	4	16
10	4-NO_2	**j**	67	30	0

[a] All reactions were performed at an arenediazonium salt concentration of 0.5 M, with 15 mol % $Pd(OAc)_2$ in refluxing methanol.
[b] Determined by GC analysis using an internal standard. Yields reported are an average of at least two experiments.
[c] Compound **4c** was detected by GC/MS, but was not quantified.
[d] 3-Fluoroanisole was detected by GC/MS, but was not quantified.
[e] Methyl 4-methoxybenzoate, 4-fluorobenzonitrile, and methyl 4-fluorobenzoate were also identified in the reaction mixture by GC/MS. Of these, methyl 4-methoxybenzoate had the largest GC area.

yield of biaryl **2a**, along with a 21% yield of reduced product **3a**. The 3-methoxy diazonium salt **1e** surprisingly gave a very low yield (25%) of biaryl **2e**. The reason for this result is unclear at this time.

In conclusion, we have developed a synthesis of symmetrical biaryls from arenediazonium tetrafluoroborates using a catalytic amount of palladium acetate in refluxing methanol. The reaction is operationally simple, can be carried out with no special oxygen- or water-exclusion techniques, proceeds in moderate to high yield in most cases, and does not require addition of a zero-valent metal or other terminal reductant. In addition, the reaction can be carried out chemoselectively in the presence of bromine and chlorine substituents, allowing the products to be further transformed using, for example, a Suzuki coupling. We believe that this protocol is an effective complement to existing methods for biaryl synthesis. Further study of the scope and mechanism of this reaction is continuing in our laboratory.

General procedure for optimization studies: A 5-mL pear-shaped flask equipped with a spin vane and a reflux condenser was charged with catalyst precursor and methanol as indicated in Tables 1–3. 4-Bromobenzenediazonium tetrafluoroborate[11] (**1a**, 0.5 mmol) was added, and the mixture was stirred at reflux until the reaction mass did not produce a reddish-purple color upon treatment with an alkaline solution of H-acid (4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid), indicating that the diazonium salt had been consumed. The mixture was cooled to room temperature, diluted with 30 mL of methylene chloride, and filtered through a Celite pad. An appropriate internal standard was added, and the resulting solution was analyzed by GC. 4,4′-Dibromobiphenyl (**2a**), bromobenzene (**3a**), 4-bromoanisole (**4a**), and 4-fluorobromobenzene (**5**) were identified by comparison of their GC retention times with authentic samples and by GC/MS.

General procedure for biaryl synthesis: A 5-mL pear-shaped flask equipped with a spin vane and a reflux condenser was charged with methanol (1 mL), $Pd(OAc)_2$ (0.075 mmol), and an appropriate internal standard. The appropriate arenediazonium tetrafluoroborate (0.5 mmol) was then added. The mixture was stirred at reflux until the reaction mass did not produce a reddish-purple color upon treatment with an alkaline solution of H-acid (4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid), indicating that the diazonium salt had been consumed (usually within 1 h). The mixture was cooled to room temperature, diluted with 30 mL of methylene chloride, and filtered through a Celite pad. The resulting solution was analyzed by GC. Products were identified by comparison of their retention times with authentic samples and by GC/MS.

Acknowledgments

We gratefully acknowledge the Winthrop University Department of Chemistry, Physics, and Geology and the Winthrop University Research Council for financial support.

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