DOI: 10.1002/cjoc.201400868

$Pd(OAc)_2/PPh_3$-Catalyzed Desulfonylative Homocoupling of Arylsulfonyl Chlorides

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The Pd-catalyzed homodimerization with respect to arylsulfonyl chlorides as an efficient method for the synthesis of biaryls has been developed. This desulfonylative reaction which was performed at reflux in 1,4-dioxane for 4 h under air afforded the desired products in good to excellent yields.

Keywords biaryls, arylsulfonyl chlorides, desulfonylative, palladium-catalyzed

Introduction

Biaryls have attracted considerable attention recently owing to their extensive applications in the areas of organometallic catalysis,[1] asymmetric synthesis,[2] functional materials,[3] supramolecular chemistry[4] as well as bioactive natural products,[5] pharmaceuticals and agrochemicals.[6] Coupling reactions were one of the most studied and applied areas of synthetic methodology. Typical procedures for the preparation of dimeric compounds began with the Ullmann coupling[7] more than 100 years ago and evolved into one of the most investigative carbon-carbon bond forming reactions afterwards.[8] Inspired by the homocoupling reaction of organohalides,[8b-8f] a number of researches were conducted in the synthesis of biaryls, involving self-coupling of arylmetal reagents,[9] dimerization of arylboronic acids,[10] dehydrogenative homocoupled reaction of arenes,[11] decarboxylative homocoupling of arylcarboxylic acid or decarbonylative homodimerization of aromatic aldehydes[12] as well as desulfitative dimerization of sodium arylsulfinates.[13]

Arenesulfonyl chlorides constitute a large family of inexpensive and widely available organic compounds that have been used for more than a century in materials science and medicinal chemistry;[14] however, self-coupling reaction regarding to arenesulfonyl chlorides was less investigated. Miura and co-workers offered the first attempt in transition metal-catalyzed homocoupling reaction of arenesulfonyl chlorides involving desulfonylation, but rigorous reaction condition restricted its application.[15a] Subsequently, the work was explored further by Tanaka and co-workers with hexamethyldisilane being used. However, relatively high temperature (140 ℃) as well as $Pd_2dba_3 \cdot CHCl_3$ catalyst was required.[15b] Therefore, a better synthetic approach for coupling of arylsulfonyl chlorides was desired. Herein, we reported a $Pd(OAc)_2/PPh_3$-catalyzed homocoupling reaction, which was conducted at reflux in 1,4-dioxane for 4 h under air.

Experimental

To a 25-mL Schlenk tube equipped with a magnetic bar was added CuI (0.5 mmol, 94.9 mg), Ag_2CO_3 (0.5 mmol, 137.9 mg), $NaHCO_3$ (0.5 mmol, 42.0 mg), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), PPh_3 (0.05 mmol, 13.1 mg), and arylsulfonyl chlorides (0.5 mmol). Then 1,4-dioxane (2 mL) was added in the tube and the reaction mixture was stirred at reflux for about 4 h. After the starting material disappeared monitored by TLC, the reaction mixture was filtered and concentrated to dryness. The crude material was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent to give the desired homocoupling products.

Results and Discussion

From starting point of view, *p*-toluenesulfonyl chloride, an inexpensive and readily available starting material, was chosen as a model substrate to screen suitable reaction conditions. Based on previous coupling reaction reports,[15,16] we initiated the preliminary reaction

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Received December 18, 2014; accepted January 28, 2015; published online March 30, 2015.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201400868 or from the author.

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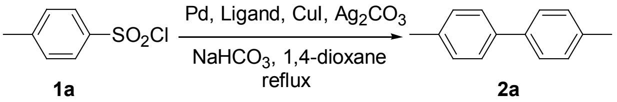
condition study (see Table S1). It was found that the reaction was catalyzed by $Pd(OAc)_2$ with the ligand of PPh_3 and promoted by Ag_2CO_3 and CuI in the presence of $NaHCO_3$, affording the desired product **2a** in 90% yield (see Table S1, Entry 6). Encouraged by this result, a systematic study was conducted to further enhance yield. Firstly, various common ligands and palladium catalysts were examined as summarized in Table 1. After screening ligands carefully (Table 1, Entries 1—8), PPh_3 was a very suitable ligand from both the economic and high-yield point of view. Furthermore, palladium catalysts such as $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_2$ and Pd_2dba_3•$CHCl_3$ failed to improve yield of corresponding product (Table 1, Entries 9—13).

Table 1 Screening of palladium catalysts in homocoupling of *p*-toluenesulfonyl chloride[a]

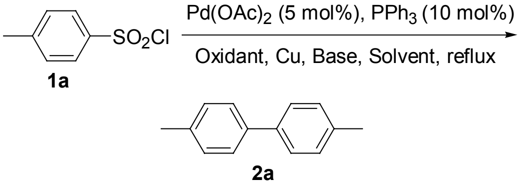


Entry	Cat./mol%	Ligand/mol%	Yield[b]/%
1	$Pd(OAc)_2$ (5)	PPh_3 (10)	90
2	$Pd(OAc)_2$ (5)	PCy_3 (10)	36
3	$Pd(OAc)_2$ (5)	$P(^tBu)_3$•HBF_4 (10)	43
4	$Pd(OAc)_2$ (5)	dppb (10)	81
5	$Pd(OAc)_2$ (5)	dppp (10)	90
6	$Pd(OAc)_2$ (5)	dppe (10)	92
7	$Pd(OAc)_2$ (5)	dppm (10)	83
8	$Pd(OAc)_2$ (5)	1,10-phenanthroline (10)	56
9	$PdCl_2$ (5)	PPh_3 (10)	55
10	$PdCl_2(PPh_3)_2$ (5)	—	80
11	$Pd(PPh_3)_4$ (5)	—	74
12	$Pd_2(dba)_2$ (5)	—	54
13	Pd_2dba_3•$CHCl_3$ (5)	—	85

[a] Reaction conditions: **1a** (0.5 mmol), Pd catalyst (5 mol%), ligand (10 mol%), CuI (0.5 mmol), Ag_2CO_3 (0.5 mmol), $NaHCO_3$ (0.5 mmol), 1,4-dioxane (2 mL), reflux for 4 h under air. [b] Yields of isolated products.

Next, evaluation with other oxidants identified Ag_2CO_3 as the most efficient one (Table 2, Entries 1—6). Various copper salts were sequentially investigated (Table 2, Entries 7—9) because negligible product was detected in the absence of copper salt (see Table S1, Entry 3). To our delight, all copper salts delivered fair yields of 72%—88%. In addition, further modification of the reaction condition revealed that $NaHCO_3$ was the best base compared with KH_2PO_4, K_3PO_4, Na_2CO_3, Cs_2CO_3, Et_3N and NaOH (Table 2, Entries 10—15); 1,4-dioxane was found to be a more suitable solvent (Table 1, Entries 1, 16—21). However, when the reaction was conducted at lower temperature, the isolated yield for symmetric biaryl was obviously decreased.

Table 2 Screening of other reaction conditions in homocoupling of *p*-toluenesulfonyl chloride[a]

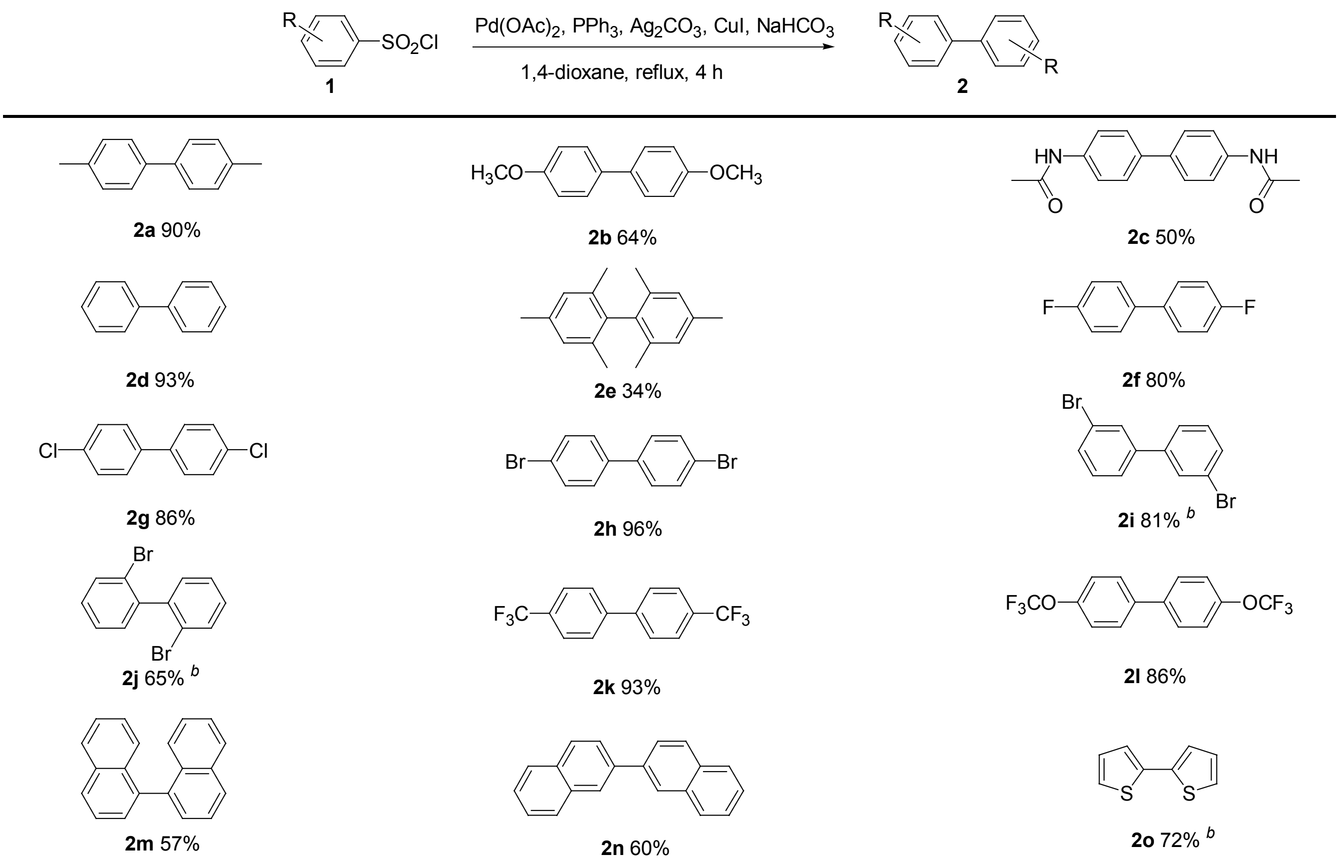


Entry	Oxidant	Copper salt	Base	Solvent	Yield[b]/%
1	Ag_2CO_3	CuI	$NaHCO_3$	1,4-dioxane	90
2	Ag_2O	CuI	$NaHCO_3$	1,4-dioxane	76
3	AgOAc	CuI	$NaHCO_3$	1,4-dioxane	45
4	$AgNO_3$	CuI	$NaHCO_3$	1,4-dioxane	43
5	BQ	CuI	$NaHCO_3$	1,4-dioxane	36
6	$K_2S_2O_8$	CuI	$NaHCO_3$	1,4-dioxane	67
7	Ag_2CO_3	CuBr	$NaHCO_3$	1,4-dioxane	82
8	Ag_2CO_3	CuCl	$NaHCO_3$	1,4-dioxane	88
9	Ag_2CO_3	CuTC	$NaHCO_3$	1,4-dioxane	72
10	Ag_2CO_3	CuI	KH_2PO_4	1,4-dioxane	75
11	Ag_2CO_3	CuI	K_3PO_4	1,4-dioxane	67
12	Ag_2CO_3	CuI	Na_2CO_3	1,4-dioxane	74
13	Ag_2CO_3	CuI	Cs_2CO_3	1,4-dioxane	48
14	Ag_2CO_3	CuI	Et_3N	1,4-dioxane	65
15	Ag_2CO_3	CuI	NaOH	1,4-dioxane	37
16	Ag_2CO_3	CuI	$NaHCO_3$	DMF	70
17	Ag_2CO_3	CuI	$NaHCO_3$	Toluene	36
18	Ag_2CO_3	CuI	$NaHCO_3$	DCE	34
19	Ag_2CO_3	CuI	$NaHCO_3$	CH_3CN	67
20	Ag_2CO_3	CuI	$NaHCO_3$	^{i}PrOH	58
21	Ag_2CO_3	CuI	$NaHCO_3$	THF	85

[a] Reaction conditions: **1a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), oxidant (0.5 mmol), copper salt (0.5 mmol), base (0.5 mmol), solvent (2 mL), reflux for 4 h under air. BQ=benzoquinone. [b] Yields of isolated products.

To demonstrate the efficiency and scope of the present method, we applied the optimum reaction conditions to a variety of arylsulfonyl chlorides (Table 3). In general, the reaction proved successful for arenesulfonyl chlorides with electron-poor or electron-neutral groups on the phenyl rings, affording the corresponding products in good to excellent yields, whereas symmetrical biaryls bearing electron-rich groups were obtained in slightly lower yields. For example, products with methoxyl, acylamino substituents at the aryl moiety were isolated in 64% and 50% yields, respectively (**2b**, **2c**). By contrast, 4,4'-dimethylbiphenyl and biphenyl were observed with distinct increased yields (90% and 93%, **2a** and **2d**). Substrates with halogen, trifluoromethyl, trifluoromethoxy-substituents at the *para*-position of the benzene ring (F, Cl, Br, CF_3, OCF_3) furnished desired biaryls in good to excellent yields (80%—96%, **2f**, **2g**, **2h**, **2k**, **2l**), especially for bromo-substituent (96%). Apparently, the *ortho*- substituents gave a relatively

Table 3 The homocoupling scope of arylsulfonyl chlorides[a]

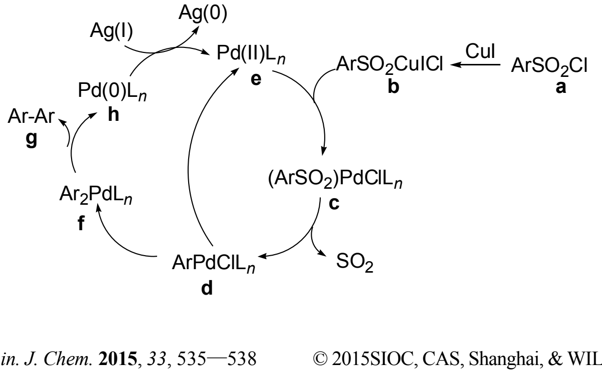


[a] Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (0.5 mmol), Ag_2CO_3 (0.5 mmol), $NaHCO_3$ (0.5 mmol), 1,4-dioxane (2 mL), reflux for 4 h under air. [b] Ag_2O (0.5 mmol) was employed as oxidant.

lower product yield than the *para*- or *meta*- ones due to steric hindrance (**2e**, **2h**, **2i**, **2j**). It is noteworthy that the starting materials with naphthyl and heteroaryl structures delivered the desired products in moderate to good yields (**2m**, **2n**, **2o**).

A plausible mechanism is outlined in Scheme 1. The first step of the reaction is insertion of the copper iodide into the S—Cl bond,[17] and then CuI/Pd(II)L_n exchange occurs to form the Pd(II) species **c**.[18] Subsequently, SO_2 group is lost from Pd(II) intermediate promoted by the thermal conditions,[19] and intermediate **d** disproportionation to Pd(II) species **e** and diarylpalladium **f** which undergoes reductive elimination to generate the product **g** and Pd(0) species **h**.[15b] Finally reoxidation of Pd(0) by Ag(I) regenerats the catalytically active Pd(II) species to finish the catalytic cycle.[20]

Scheme 1 Plausible mechanism



Conclusions

In conclusion, a new method allowing for the synthesis of various symmetrical biaryl units via homocoupling of arylsulfonyl chlorides has been developed. Additionally, high-yield biaryls, which are core motifs and important building blocks in the construction of complex molecules, are achieved. Combined with other coupling reactions, this approach could be applied in the synthesis of pharmaceuticals, functional materials, and coordination compounds.

Acknowledgement

The work was supported by the National Natural Science Foundation of China (Nos. 21272069, 20672035), the Fundamental Research Funds for the Central Universities, and the Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

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