One-Pot Homo- and Cross-Coupling Reactions of Arenediazonium Tosylate Salts for the Synthesis of Biaryls and Polyaryls[†]

Vaishali Vajpayee, Young Ho Song, Jeong Soo Ahn, and Ki-Whan Chi[*]

Department of Chemistry, University of Ulsan, Ulsan 680-749, Korea
[*]*E-mail: kwchi@ulsan.ac.kr*
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One-pot homo- and cross-coupling reactions of arenediazonium tosylate salts bearing a halogen group have been exploited for the synthesis of biaryls and polyaryls under mild conditions. Pd(OAc)$_2$ has proven to be an efficient catalyst for the successful dual transformation of diazonium salts into *p*-quaterphenyl (**3**).

Key Words : Arenediazonium tosylates, Biaryl and polyaryl synthesis, Homo- and cross-coupling reactions, One-pot reaction

Introduction

There is a vast literature demonstrating the importance of biaryls and polyaryls as building blocks for natural products, pharmaceuticals, optoelectronics and advanced materials.[1-3] Polyphenyls are also important structural elements in liquid crystals[4] and fluorescent compounds.[5] Traditionally, the Ullmann reaction[6] is one of the most important methods for the synthesis of polyaryls, but its requirement of high temperature has motivated the development of a number of milder Pd and Ni mediated procedures[7-14] starting from aryl halides and aryl sulphonates. In addition, symmetrical biaryls are also accessible through the Pd catalyzed homo-coupling of arylboronic acids.[15,16]

In the literature of Pd catalyzed cross-coupling reactions, the generation of homo-coupled by-products is often report-ed.[17] This observation led us to investigate the feasibility of preparing homo-coupled aryls by optimizing the disproportiona-tion and reductive elimination steps in these reactions. Despite an increased awareness of the synthetic advantages of arenediazonium salts in cross-coupling reactions, they have continued to be underutilized in organic synthesis, and in particular, the synthesis of polyaryls starting from arenediazonium salts has been explored only rarely. Recently, a few reports on the homo-coupling of arenediazonium salts have appeared, but the scope of these reactions was limited to biaryl synthesis.[18,19] Only few reports described the use of cross-coupling reaction to generate polyphenyls.[20-22]

Since methods for the synthesis of polyaryls from arenediazonium salts under Pd catalysis have infrequently been studied, we attempted to find a Pd catalyzed route for this transformation. Recently, our group has reported the synthesis of unusually stable arenediazonium tosylate salts[23] which have proven to be excellent synthetic precursors to aryl halides.[24, 25] As part of a broader project aimed at exploring the synthetic potential of arenedizonium tosylate

salts, we have focused our attention on the salts, **1**, in homo- and cross-coupling reactions. Due to the high reactivity of these salts, the short reaction times, mild reaction conditions, and broad substrate scope, such reactions should be readily applicable to a variety of materials.

Results and Discussion

Recent reports concerning the palladium catalyzed synthesis of biaryls[26-28] prompted our design of a scheme that combines homo- and cross-coupling reactions (Scheme 1) of arenediazonium tosylate salts for a short and efficient synthetic route to polyaryls. We began our study with the homo-coupling reaction of arenediazonium tosylate and bisulfate salts. We were pleased to discover that when a methanolic solution of *p*-bromophenyldiazonium salt was refluxed in the presence of Pd(OAc)$_2$ (15 mol%), 4,4'-dibromobiphenyl was collect-ed in 54% yield (Table 1). Significantly, excellent selectivity was observed for reaction with the diazo group in the homo-coupling reaction with halogenated arenediazonium tosylate salts, and no evidence for competing electrophilic reactivity of Cl, Br or even the highly reactive I atom was observed. The diazonium salt counter ion does not affect the reaction as almost identical results were achieved with either diazonium salt. The homo-coupling reaction also worked well with -
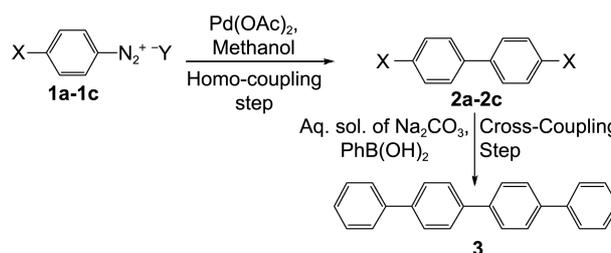
Scheme 1. One-Pot Homo- and Cross-Coupling Reactions of Arenediazonium Salts.

NO_2 or -CN substituted arenediazonium tosylate salts and produced the respective homo-coupled products in 60 ~ 62% yields.

The high chemoselectivity for the diazonium group allowed us to make *p*-quaterphenyl in reasonable yield in a one-pot transformation by adding base and phenylboronic acid in a second step after the initial homo-coupling reaction had completed. Such multiple transformations performed in a single vessel are very practical and economically cost effective considering the savings in catalyst, solvent, purification, and time. Results are compiled in Table 1.

After successfully demonstrating the effectiveness of the one-pot reaction, further refinement of the reaction parameters was carried out by varying the catalyst loading, palladium source, solvent, reaction time, temperature, and base.

With the aim of testing other catalyst systems (Table 2), we screened various catalysts that are known to promote C-C bond formation. However, none of these other Pd catalysts gave improved results as only low yields were obtained. Interestingly, although Pd/C has been successfully applied to cross-coupling reactions it gave only a sluggish reaction with our protocol.

The activity of $Pd(OAc)_2$ as a catalyst for one-pot multiple transformations was also in doubt; however, after a few optimization studies, we determined that $Pd(OAc)_2$ was an efficient catalyst for promoting two C-C bond formations in the same reaction vessel. We then focused our attention on catalyst loading and observed the best results with 15 mol% of $Pd(OAc)_2$. Lowering the amount of catalyst resulted in decreased yields and increased reaction times; addition of an increased amount of catalyst, 20 mol %, did not improve the product yield (Table 3).

An observation from the literature, that alcohols act as reducing agents for $Pd(OAc)_2$ as well as solvent, allowed us to choose an inexpensive and stable source of Pd for this scheme. The use of other added reducing agents such as

Table 1. Homo- and Cross- Coupling of Arenediazonium Salts

Entry	X	HY	Reaction Temp (°C)	Reaction Time (h)	Isolated Yield (%)	
					2	**3**
1	4-Cl(**1a**)	*p*-TsOH	60	20	62(**2a**)	49
2	4-Br(**1b**)	NaHSO$_4$	60	20	54(**2b**)	45
3	4-Br(**1b**)	*p*-TsOH	60	20	52(**2b**)	47
4	4-I(**1c**)	*p*-TsOH	60	20	66(**2c**)	51

Table 2. Optimization of Catalyst

Entry	Catalyst	Isolated Yield (%)	
		2b	**3**
1	Pd(OAc)$_2$	52	47
2	Pd$_2$(dba)$_2$	20	9
3	Pd(PPh$_3$)$_4$	5	0
4	Pd/C	14	5
5	Pd/Al$_2$O$_3$	8	0

Table 3. Catalyst Loading Optimization

Entry	Pd(OAc)$_2$ (mol %)	Isolated Yield (%)	
		2b	**3**
1	10	40	30
2	15	52	47
3	15^a	50	42
4	20	51	47
5	20^a	51	46

^{a} K$_2$CO$_3$ used as base.

Table 4. Optimization of Solvent and Base

Entry	Base	Solvent	Temp.	Isolated Yield (%)	
				2b	**3**
1	Na$_2$CO$_3$	Methanol	60	52	47
2	K$_2$CO$_3$	Methanol	60	50	42
3	Na$_2$CO$_3$	Ethanol	60	45	39
4	Na$_2$CO$_3$	Isopropanol	60	48	44
5	K$_2$CO$_3$	Isopropanol	60	45	40
6	Na$_2$CO$_3$	DMF	60	13	0
7	Na$_2$CO$_3$	Acetone	60	19	18
8	Na$_2$CO$_3$	Acetone:Water(0.5:0.5)	60	23	13
9	Na$_2$CO$_3$	Acetone:Water(0.4:0.6)	60	12	5

PPh_3 caused side reactions.

Other solvents were tested, but the reaction did not initiate and reaction substrates were recovered unchanged or decomposed after heating the reaction mixture at 60 °C for up to 36 h. Methanol proved to be the most appropriate reaction solvent functioning as both initial and terminal reducing agent, and the reaction required no additional reducing agent. In addition, the concentration also played a role in facilitating the reaction, with a higher concentration favoring a higher yield of the desired product. This effect can be explained as methanol acting as the reducing agent to produce the active Pd catalyst leading to the biaryl Pd complex.

Recognizing that a base would be required for the cross-coupling reaction, we found that the second step (Suzuki cross-coupling reaction) proceeded smoothly in the presence of Na_2CO_3 or K_2CO_3 (Table 4).

Finally the reaction time was optimized. We observed that the homo-coupling reaction is quite fast, delivering biaryls after 1 h refluxing at 60 °C, but the second step takes more time for completion as the polyphenyl was attained after 20 h refluxing at 60 °C. At room temperature the reaction did not initiate and unconverted starting materials were recovered.

Conclusion

In conclusion, we have developed a new application of arenediazonium tosylate salts as electrophiles in coupling reactions. The greater reactivity of the diazonium nucleofuge in comparison to the corresponding halide is advantageous in developing an efficient and practical approach to a single reaction vessel synthesis of polyaryls. In this one-pot, two-

step transformation, it is important to note that a dual catalytic activity of Pd has been exploited to shorten the reaction time and to provide a simplified and more effective experimental procedure.

Experimental Procedures

General. Nuclear magnetic resonance (NMR) spectra were recorded on Varian FT-NMR 300 MHz spectrometer. All starting amines were obtained from commercial suppliers and used without further purification. Diazonium tosylates were synthesized by the reported method.[23] Physical and ^{1}H NMR data of reaction products were identical to those of known compounds.[18,19, 29]

General Synthesis of *p*-Quaterphenyl. A 10 ml flask equipped with a magnetic spin bar and a reflux condenser was charged with Pd(OAc)$_2$ (15 mol%), methanol (1 ml) and arenediazonium salt **1b** (0.1776 g, 0.5 mmol) and then was refluxed with stirring until the arenediazonium tosylate salt was consumed (checked by β-naphthol test) (approximately 1 h). Then phenylboronic acid (0.1225 g, 1.0 mmol) and an aqueous solution of Na$_2$CO$_3$ (0.106 g, 1.0 mmol in 1 ml water) were added and the reaction was refluxed for 20 h at 60 $^{\circ}$C. The course of the reaction was checked by TLC. After completion of the reaction, the mixture was cooled, and the catalyst was filtered and washed with dichloromethane. Finally, the extracted crude products were purified by column chromatography (hexane: dichloromethane = 1:1) to give **3** as a white crystalline solid, mp 322 $^{\circ}$C.[29] ^{1}H NMR (DMSO-d_6) : δ 7.60[m, 8H], 7.43[m, 4H], 7.30[m, 2H], 7.04[m, 4H].

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