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Palladium-Catalyzed Regioselective Halogenation of Aromatic Azo Compounds

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Abstract: A highly regioselective halogenation reaction of symmetrical and unsymmetrical aromatic azo compounds has been developed at room temperature or at 50 °C. In the presence of 5 mol% palladium diacetate and 0.5 equiv. of *p*-toluenesulfonic acid, a range of symmetrical aromatic azo compounds smoothly undergo monobromination with *N*-bromosuccinimide to give the corresponding unsymmetrical aromatic azo compounds in good to excellent yields with >99:1 *ortho*-selectivity. This chemistry has been successfully extended to unsymmetrical aromatic azo compounds, whose electron-richer aryl groups prefer to be monobrominated. Moreover, replacing *N*-bromosuccinimide with *N*-iodosuccinimide in the reaction allows the synthesis of monoiodinated aromatic azo compounds with >99:1 regioselectivity.

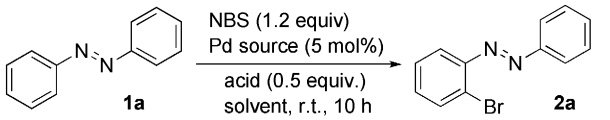
Keywords: aromatic azo compounds; bromination; iodination; palladium; regioselectivity

Owing to their unique structure, aromatic azo compounds are able to serve as food additives, therapeutic agents, indicators, dyes, pigments, and light-responsive functional materials.[1] In this context, much attention has been paid to the synthesis of aromatic azo compounds. In general, symmetrical aromatic azo compounds are readily accessible through reduction of nitroarenes and oxidation of aromatic amines, and the unsymmetrical ones are prepared by diazo coupling and the Mills reaction, which, however, require reactive intermediates (diazonium salts and nitroso compounds) and suffer from a narrow substrate scope due to their intrinsic reaction mechanisms.[2] Although the oxidative cross-dimerization of aromatic amines[3] and the cross-coupling of nitroarenes with aromatic amines[4] have recently been developed for the synthesis of unsymmetrical aromatic azo compounds, they require high temperature, high pressure, excess reactants/reagents, and/or strong bases, and moreover, suffer from a narrow substrate scope.

Since symmetrical aromatic azo compounds are readily accessible, their monofunctionalization would constitute a promising strategy for the synthesis of unsymmetrical aromatic azo compounds. Early studies have shown that treatment of aromatic azo compounds with a stoichiometric amount of palladium leads to the formation of carbon-palladium bonds, which can be further transformed into carbon-carbon and carbon-heteroatom bonds.[5] Although in recent years palladium,[6] ruthenium,[7] and rhodium[8] have been found to catalyze the monofunctionalization of two symmetrical aromatic azo compounds, diphenyldiazene and di(*m*-tolyl)diazene, the reactions require a temperature equal or higher than 100 °C and the yields are unsatisfactory ($\leq$62%). Particularly, a single example for the monoiodination of di(*m*-tolyl)diazene has been reported by Sanford and coworkers to proceed at 100–120 °C and give the *ortho*-iodinated product in 41% yield.[6b] Here we report an efficient palladium-catalyzed regioselective halogenation reaction of symmetrical and unsymmetrical azo compounds at room temperature or at 50 °C.[9] Importantly, this study provides an easy access to functionalized unsymmetrical azo compounds from readily accessible starting materials under mild reaction conditions.

Initially, the model reaction of diphenyldiazene (**1a**) with *N*-bromosuccinimide (NBS) did not occur in the presence of 5 mol% $Pd(OAc)_2$ in acetonitrile at room temperature (Table 1, entry 1). We attempted to promote the reaction with Brønsted acids that were reported previously to be capable of changing the electrophilicity of the palladium(II) catalyst[10] and render NBS a more effective source of Br^+ *via* proto-

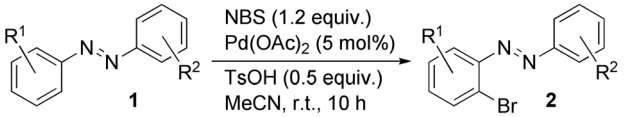
Table 1. Optimization of the reaction conditions.[a]



Entry	Pd source	Acid	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	none	MeCN	0
2	$Pd(OAc)_2$	CH_3CO_2H	MeCN	0
3	$Pd(OAc)_2$	CF_3CO_2H	MeCN	0
4	$Pd(OAc)_2$	HBF_4	MeCN	32
5	$Pd(OAc)_2$	TsOH	MeCN	90
6	$Pd(OTs)_2$	TsOH	MeCN	89
7	$Pd(OTs)_2$	none	MeCN	72
8	$PdCl_2$	TsOH	MeCN	18
9	$[Pd(allyl)Cl]_2$	TsOH	MeCN	14
10	$Pd(PPh_3)_4$	TsOH	MeCN	0
11	$Pd(OAc)_2$	TsOH	acetone	27
12	$Pd(OAc)_2$	TsOH	DMF	60
13	$Pd(OAc)_2$	TsOH	DMSO	0
14	$Pd(OAc)_2$	TsOH	$MeNO_2$	35
15	$Pd(OAc)_2$	TsOH	THF	trace
16	$Pd(OAc)_2$	TsOH	EtOAc	11
17	$Pd(OAc)_2$	TsOH	DCE	34
18	$Pd(OAc)_2$	TsOH	toluene	46

[a] *Reaction conditions:* aromatic azo compound **1a** (0.30 mmol), NBS (0.36 mmol), Pd source (5 mol%), acid (if any, 0.5 equiv.), solvent (1.0 mL), room temperature, 10 h.
[b] Isolated yield.

Table 2. Regioselective monobromination of aromatic azo compounds.[a]



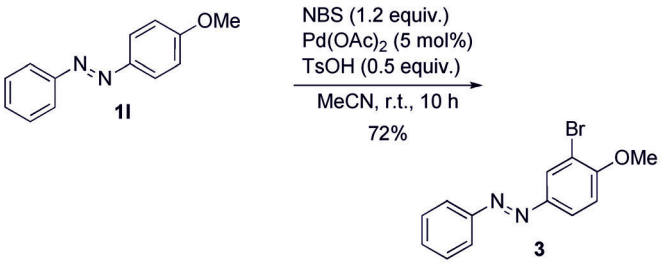
Entry	1	R^1	R^2	2	Yield [%][b]
1	**1a**	H	H	**2a**	90
2	**1b**	4-Me	4-Me	**2b**	90
3[c]	**1c**	4-F	4-F	**2c**	85
4[d]	**1d**	4-Cl	4-Cl	**2d**	58
5[d]	**1e**	4-Br	4-Br	**2e**	58
6[e]	**1f**	4-CO_2Et	4-CO_2Et	**2f**	82
7	**1g**	3-Me	3-Me	**2g**	63
8	**1h**	3,5-Me_2	3,5-Me_2	**2h**	84
9	**1i**	2-Me	2-Me	**2i**	71
10[f]	**1j**	2-F	2-F	**2j**	70
11	**1k**	H	4-Cl	**2k**	87

[a] *Reaction conditions:* aromatic azo compound **1** (0.30 mmol), NBS (0.36 mmol), $Pd(OAc)_2$ (5 mol%), TsOH (0.15 mmol), acetonitrile (1.0 mL), room temperature, 10 h.
[b] Isolated yield.
[c] The reaction was run at 50 °C.
[d] The reaction was run in toluene at 50 °C.
[e] The reaction was run in 1,2-dichloroethane for 20 h.
[f] The reaction was run with 1.0 equiv of NBS in nitromethane.

nation of the carbonyl group.[9h,11] Indeed, the reaction was dramatically affected by the structure of the Brønsted acids (Table 1, entries 2–5) and, to our delight, the use of *p*-toluenesulfonic acid (0.5 equiv.) led to the formation of aromatic azo compound **2a** as a single regioisomer in 90% yield (Table 1, entry 5). Since $Pd(OTs)_2$ (with two solvent molecules of MeCN) could be formed as the actual catalyst from $Pd(OAc)_2$ and excess *p*-toluenesulfonic acid,[9h,l,12] we examined this palladium source and found that the reaction gave a comparable yield (89%, Table 1, entry 6). In sharp contrast to $Pd(OAc)_2$, $Pd(OTs)_2$ itself was capable of catalyzing the reaction in the absence of *p*-toluenesulfonic acid to give the desired product in 72% yield (Table 1, entry 7). Replacing $Pd(OAc)_2$ with other palladium sources such as $PdCl_2$, $[Pd(allyl)Cl]_2$, and $Pd(PPh_3)_4$ gave much lower yields or even resulted in no desired product at all (Table 1, entries 8–10). Moreover, no better yield was obtained by employing a common organic solvents other than acetonitrile (Table 1, entries 11–18).

In the presence of 5 mol% $Pd(OAc)_2$ and 0.5 equiv. of *p*-toluenesulfonic acid, a range of symmetrical aromatic azo compounds smoothly underwent monobromination with NBS in acetonitrile at room temperature or at 50 °C to give the corresponding unsymmetrical aromatic azo compounds in good to excellent yields with >99:1 *ortho*-selectivity (determined by ^{1}H NMR spectroscopic analysis) (Table 2, entries 1–10). It is noteworthy that the reaction tolerated a variety of functional groups such as fluoro, chloro, bromo, and ester. In a few cases acetonitrile was replaced with 1,2-dichloroethane, toluene, and nitromethane in order to provide better solubility for the starting aromatic azo compounds (Table 2, entries 4–6 and 10). Relatively lower yields were obtained in some cases owing to dibromination (Table 2, entries 4, 5, 7, 9, and 10). This chemistry was successfully extended to unsymmetrical aromatic azo compounds, whose electron-richer aryl groups preferred to undergo monobromination with >99:1 regioselectivity. For example, the phenyl group in unsymmetrical aromatic azo compound **1k** was preferentially monobrominated to give product **2k** as a single regioisomer in 87% yield (Table 2, entry 11).

The regioselectivity could be switched when a strong electron-donating group was introduced into the aromatic ring of an aromatic azo compound. For example, the 4-methoxyphenyl group in unsymmetrical aromatic azo compound **1l** was preferentially monobrominated to give product **3** as a single regioisomer in 72% yield (Scheme 1).[13] A control experiment was performed without $Pd(OAc)_2$ and the same product was obtained in 78% yield. These results indicate that



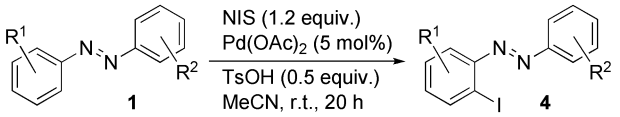
Scheme 1. Monobromination of aromatic azo compound **1l**.

the methoxy group in substrate **1l** completely overrides the azo group with regard to the ability to direct monobromination under the standard reaction conditions.

Replacing NBS with *N*-iodosuccinimide (NIS) in the aforementioned reaction allowed us to obtain a range of monoiodinated aromatic azo compounds in good to excellent yields with >99:1 *ortho*-selectivity (Table 3).[14] A variety of functional groups such as fluoro, chloro, and ester could be introduced into the unsymmetrical aromatic azo compounds. Moreover, the monoiodination with an unsymmetrical aromatic azo compound occurred readily at the unsubstituted phenyl ring rather than at the phenyl ring bearing an electron-withdrawing substitutent (Table 3, entries 7 and 8).

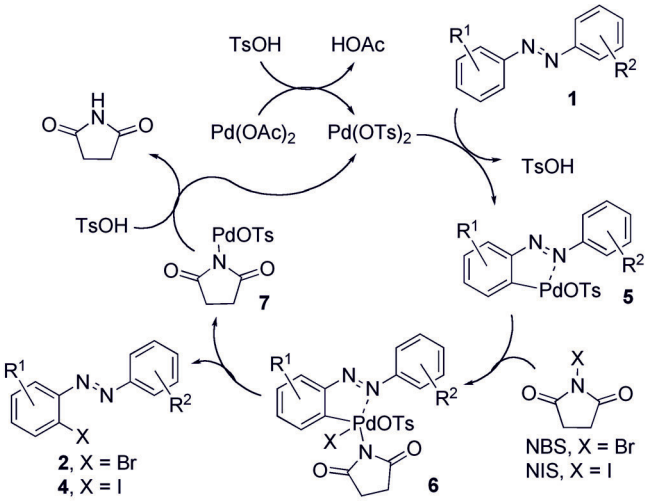
Based on our results and previous studies on the palladium-catalyzed *ortho*-halogenation of aromatic compounds,[6b,9c,i,l] we propose the catalytic cycle depicted in Scheme 2 for the *ortho*-halogenation of aromatic azo compounds. Displacement of $Pd(OAc)_2$ by

Table 3. Regioselective monoiodination of aromatic azo compounds.[a]



Entry	1	R^1	R^2	4	Yield [%][b]
1	**1a**	H	H	**4a**	90
2	**1b**	4-Me	4-Me	**4b**	90
3[c]	**1c**	4-F	4-F	**4c**	60
4	**1g**	3-Me	3-Me	**4d**	67
5	**1h**	3,5-Me_2	3,5-Me_2	**4e**	59
6	**1i**	2-Me	2-Me	**4f**	62
7	**1k**	H	4-Cl	**4g**	77
8[d]	**1m**	H	4-CO_2Et	**4h**	75

[a] *Reaction conditions:* aromatic azo compound **1** (0.30 mmol), NIS (0.36 mmol), $Pd(OAc)_2$ (5 mol%), TsOH (0.15 mmol), acetonitrile (1.0 mL), room temperature, 20 h.
[b] Isolated yield.
[c] The reaction was run at 50 °C.
[d] The reaction was run in nitromethane at 50 °C.



Scheme 2. Proposed catalytic cycle.

p-toluenesulfonic acid results in the formation of the actual catalyst, $Pd(OTs)_2$,[12a] which is attacked by aromatic azo compound **1** to give palladacycle **5**. Oxidative addition of NBS (or NIS), activated by *p*-toluenesulfonic acid,[9h,11] to palladacycle **5** leads to the formation of Pd(IV) complex **6**,[9c,15] which undergoes reductive elimination to give product **2** (or **4**) and meanwhile release Pd(II) species **7**. Displacement of Pd(II) species **7** by *p*-toluenesulfonic acid regenerates $Pd(OTs)_2$ to continue the catalytic cycle.

In summary, we have provided an easy access to functionalized unsymmetrical aromatic azo compounds from readily accessible starting materials under mild reaction conditions. In the presence of 5 mol% $Pd(OAc)_2$ and 0.5 equiv. of *p*-toluenesulfonic acid, a range of symmetrical aromatic azo compounds smoothly undergo monobromination with *N*-bromosuccinimide at room temperature or at 50 °C to give the corresponding unsymmetrical aromatic azo compounds in good to excellent yields with >99:1 *ortho*-selectivity. This chemistry has been successfully extended to unsymmetrical aromatic azo compounds, whose electron-richer aryl groups prefer to be monobrominated. Moreover, replacing *N*-bromosuccinimide with *N*-iodosuccinimide in the reaction allows the synthesis of monoiodinated aromatic azo compounds with >99:1 regioselectivity.

Experimental Section

General Procedure for the Palladium-Catalyzed Regioselective Halogenation of Aromatic Azo Compounds

A mixture of aromatic azo compound **1** (0.30 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), NXS (X = Br or I,

0.36 mmol), and $TsOH \cdot H_2O$ (28.5 mg, 0.15 mmol) in acetonitrile (1.0 mL) was stirred at room temperature or 50 °C for 10 or 20 h as specified in Table 2 and Table 3. The mixture was purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (0~10:1), to give compound **2** or **4**.

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