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Synthesis of Unsymmetrical Aromatic Azoxy Compounds by Silver-Mediated Oxidative Coupling of Aromatic Amines with Nitrosoarenes

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Abstract. A silver(I) oxide-mediated synthesis of unsymmetrical aromatic azoxy compounds has been successfully achieved, wherein oxidative coupling reactions between aromatic amines and nitrosoarenes take place in ethanol under air. This reaction has very high economic value because silver(I) oxide is the only oxidant required and no other additive is needed. The resulted silver particles can be easily recovered, while the only other byproduct is water. This new procedure is compatible with various functional groups and proceeds under mild reaction conditions.

Keywords: Aromatic amines; Nitrosoarenes; Oxidative coupling; Silver oxide; Unsymmetrical azoxybenzenes

Azoxyarenes have been widely applied in dyes, reducing agents, polymerization inhibitors, and chemical stabilizers due to their conjugated system and polar functionality.[1,2] In the light of their importance, the development of azoxyarene derivatives with varied functional groups, such as unsymmetrical azoxyarenes, has become a hot research topic. The direct oxidation of aromatic amines[3] and reduction of nitroarenes[4] are well established methods for the preparation of azoxy compounds. However, only symmetrical azoxyarenes can be obtained.

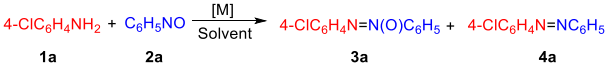
To introduce different functional groups into azoxy compounds, much effort has been directed toward the C–H functionalization of symmetrical azoxyarenes, with o*rtho*-acylation,[5] halogenation,[6] acetoxylation,[7] alkoxylation,[7,8] sulfonamidation,[9] acylamidation,[10] and alkenylation[11] achieved to form unsymmetrical azoxyarenes. Unfortunately, these reactions suffer from the severe drawback that functional groups can only be introduced in the *ortho*-position of the synthesized azoxybenzenes, which limits the scope of functionality. Furthermore, environmentally unfriendly oxidants and relatively low yields and selectivity have limited their real applications. Therefore, developing a low-cost, green, and high atom economy procedure for the synthesis of unsymmetrical azoxybenzenes from simple starting materials remains highly desirable in modern organic synthesis.

We have recently developed a practical and convenient method for the synthesis of unsymmetrical azoxybenzenes through the I_2-mediated oxidative coupling reaction of aromatic amines with nitrosoarenes.[12] However, some shortcomings still need to be addressed, such as the use of large amount of oxidant used, which leads to much waste and post-processing. Meanwhile, the reaction of aromatic amines with strongly electron-withdrawing groups ($–NO_2$, $–CF_3$, $–CO_2Me$) is significantly inhibited by the strong iodination effect. To overcome these problems, appropriate oxidants should be selected. Fortunately, in our studies, we found that silver could promote oxidative coupling reactions between aromatic amines and nitrosoarenes, which would solve the problems encountered previously.[12] Ag(I) oxidants have been found to be generally superior to other common oxidants in various oxidative coupling reactions.[13] Herein, we applied silver(I) as an oxidant for the synthesis of unsymmetrical azoxybenzenes as a green chemistry approach with high atom economy.

We started our investigation by examining the reaction of 4-chloroaniline (**1a**) and nitrosobenzene (**2a**) to obtain optimized reaction conditions (Table 1). An initial attempt, using 0.15 equiv. of silver salt to promote the reaction of **1a** and **2a**, was not efficient. Mills reaction products (**4a**) were formed with specific selectivity in the presence of silver nitrate or silver triflate (Table 1, entries 2 and 6). Oxidative coupling products **3a** were obtained with 13% conversion and 99% selectivity, accompanied by 1% of the oxidative dimerization product (**5a**) of **1a**, when 0.15 equiv. of commercially available silver oxide was added to the reaction mixture (Table 1, entry 4). To achieve a higher yield, an increasing amounts of silver(I) oxide was used (Table 1, entries 7–10). In the presence of 1.0 equiv. of Ag_2O, **1a** and **2a** reacted to give an improved conversion of 91%

with 95% selectivity. The conversion was further increased to 97% by prolonging the reaction time to 48 h (Table 1, entry 9). When the amount of Ag_2O was further increased to 1.1 equiv., the reaction went to completion (Table 1, entry 10). Other metallic oxides were also explored, but a lower efficiency was obtained (see Table S1 in the supporting information (SI)).

Table 1. Optimization of reaction conditions[a].



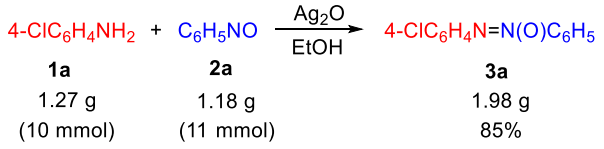
Entry	[M]	Equiv.	Solvent	Conv. (%)[b]	Sel. (%)[b]		
					3a	**4a**	**5a**
1	AgOAc	0.15	Toluene	13	30	70	-
2	$AgNO_3$	0.15	Toluene	35	-	100	-
3	Ag_2CO_3	0.15	Toluene	-	-	-	-
4	Ag_2O	0.15	Toluene	13	99	-	1
5	AgBr	0.15	Toluene	-	-	-	-
6	AgOTf	0.15	Toluene	17	-	100	-
7	Ag_2O	0.5	Toluene	43	95	-	5
8	Ag_2O	1.0	Toluene	91	95	-	5
9[c]	Ag_2O	1.0	Toluene	97	95	-	5
10	Ag_2O	1.1	Toluene	100	94	1	5
11	Ag_2O	1.1	DMSO	99	98	1	1
12	Ag_2O	1.1	DMF	92	98	1	1
13	Ag_2O	1.1	CH_3CN	94	98	1	1
14	Ag_2O	1.1	THF	92	97	1	2
15	Ag_2O	1.1	Dioxane	71	97	1	2
16	Ag_2O	1.1	DCE	92	96	1	3
17	Ag_2O	1.1	EtOH	99	98	1	1
18	Ag_2O	1.1	*n*-hexane	90	86	1	13

[a] All experiments were conducted using *p*-$ClC_6H_4NH_2$ (0.20 mmol), C_6H_5NO (0.22 mmol), [M], and solvent (1.0 mL) at 65 °C under air for 24 h, unless otherwise noted. [b] Conversion and selectivity were measured by monitoring *p*-$ClC_6H_4NH_2$ using GC–MS. [c] Reaction time extended to 48 h.

The solvent effect was then evaluated (Table 1, entries 11–18). Solvents including DMSO, DMF, CH_3CN, THF, DCE ($ClCH_2CH_2Cl$), and EtOH were found to be highly effective media for this transformation. In contrast, 1,4-dioxane and *n*-hexane showed lower reactivity. EtOH was selected as the reaction solvent for subsequent experiments because it was the most green solvent among those tested. The influence of temperature was investigated (Table S2, SI), with complete conversion achieved at room temperature with a prolonged reaction time (120 h). Higher temperatures had nearly no effect on reaction selectivity.

With optimal reaction conditions in hand, we explored the scope and limitations of these oxidative coupling reactions (Table 2). Various aromatic amines bearing different functional groups, including ester, ketone, nitrile, nitro, alkynyl, fluoro, chloro, bromo, and iodo substituents, underwent the oxidative coupling reaction to form azoxyarenes with moderate to excellent yields. We did not observe any steric effect on this reaction, with sterically hindered amines, such as 2-chloro (**3c**), 2-fluoro (**3g**), 2-phenyl (**3m**), 2-methoxy (**3p**), and even 2-tert-butyl aniline (**3k**), showing high reactivity and producing the corresponding azoxyarenes in high yields. However, aromatic amines were observed to have an electronic effect on this transformation. For example, 2-(phenylethynyl)aniline reacted with **2a** at 65 °C to give 2-phenylethynyl product **3ab** in 52% isolated yield with 20% unidentified products. Furthermore, aromatic amines bearing strongly electron-withdrawing substituents, such as –COPh, –CN, –CO_2Me, –NO_2, and –CF_3, exhibited slightly lower reactivity, affording corresponding products **3q**–**3y** in 67%–82% yields using an elevated temperature (80 °C) and longer reaction time (48 h). Heteroaromatic amines, such as pyridin-3-amine and quinolin-3-amine, were also tolerated in the oxidative coupling reaction, affording corresponding unsymmetrical products **3z** and **3aa**, respectively, in moderate yields.

Next, we tested nitrosoarenes bearing an electron-donating or electron-withdrawing group. Nitrosoarenes with a strongly electron-donating group exhibited comparatively lower reactivity, while the reaction of *N*,*N*-dimethyl-4-nitrosoaniline with aromatic amines gave a lower yield than the reactions of chloro, bromo, ester, and methyl-substituted nitrosoarenes. Substrates used in this study were then extended to sterically hindered 1-chloro-2-nitrosobenzene and 1-methyl-2-nitrosobenzene, which produced the corresponding azoxyarenes in good yields. Notably, *ortho*-halogenation products **3au** and **3av**, which are difficult to prepare through the C–H functionalization of azoxyarenes owing to their unavailability, were conveniently synthesized using our method.[6] The limitation of this method was that no reaction occurred between strongly electron-rich nitrosobenzenes and strongly electron-poor aromatic amines. For example, *N*,*N*-dimethyl-4-nitrosoaniline did not react with 4-nitroaniline.



Scheme 1. Gram-scale synthesis.

To demonstrate the scalability and practicality of the above silver-mediated oxidative coupling method, we performed a gram-scale reaction using **1a** and nitrosobenzene as the substrates under the optimized reaction conditions, with unsymmetrical azoxybenzene **3a** obtained in 85% isolated yield after reacting for 24 h in ethanol (Scheme 1). Furthermore, a series of repeat reactions showed that the silver recovery was more than 99% (see SI for details).

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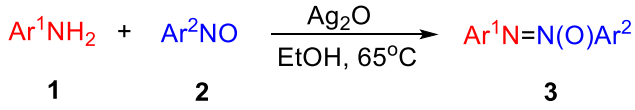
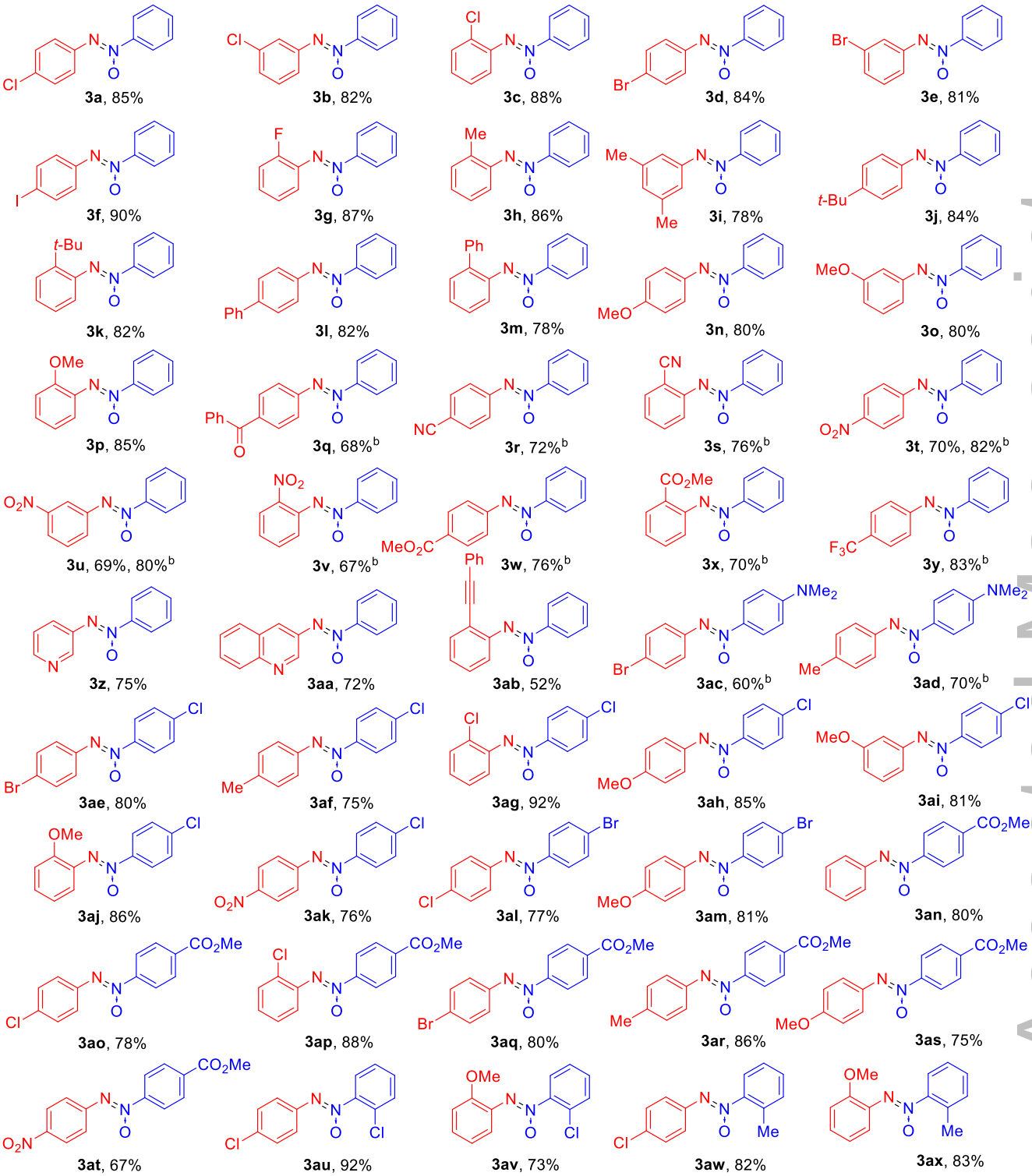
Table 2. Substrate scope.





[a] All experiments were conducted with Ar^1NH_2 (0.20 mmol), Ar^2NO (0.22 mmol), Ag_2O (0.22 mmol), and EtOH (1.0 mL) at 65 °C under air for 24 h, unless otherwise noted. [b] Reacted at 80 °C for 48 h.

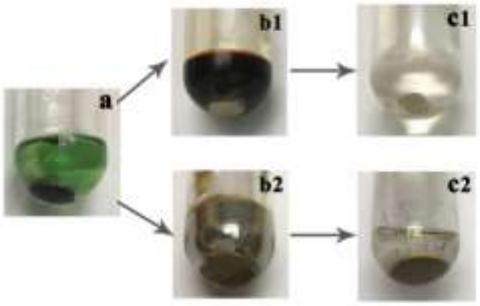


Figure 1. Visual appearance.
(a) Reaction mixture at room temperature before heating. (b1,b2) Reaction mixture turned brown after the reaction, where silver particles were formed. (c1,c2) Silvery or black solids were collected from the reaction mixture by filtration and washed with ultrasonication.

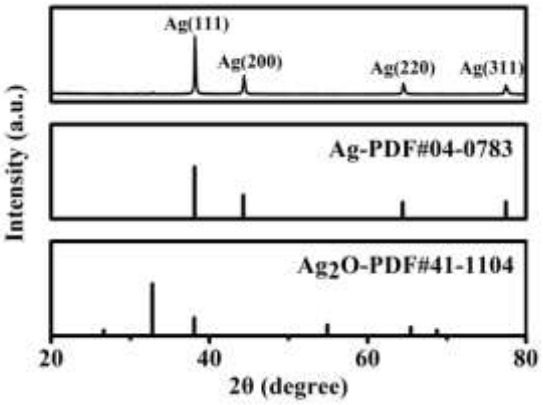
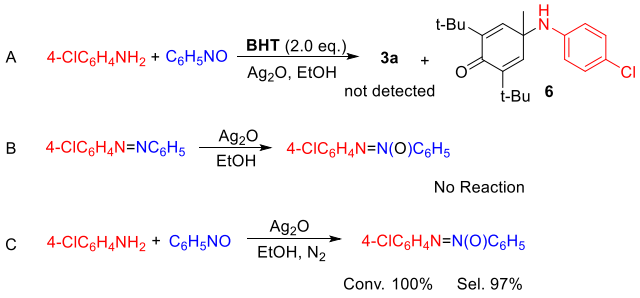


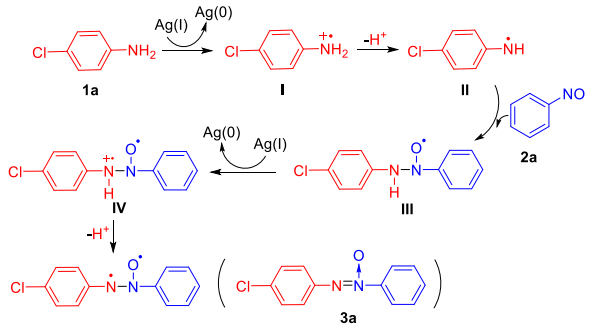
Figure 2. XRD diffraction patterns of the collected silver particles.

We noticed that the black silver oxide had turned silvery when the reaction was finished (Figure 1). The XRD pattern of a silver particle sample collected after reaction completion is shown in Figure 2. The XRD patterns exhibited diffraction peaks at 2θ = 37.9°, 43.9°, 64.3°, and 77.3°, representing (111), (200), (220), and (311) planes of Ag particles, which supported that silver oxide had been reduced to silver particles during the reaction and, therefore, acted as an oxidant in this transformation.

To probe the reaction mechanism, several control experiments were conducted. As shown in Scheme 2A, using butylhydroxytoluene (BHT) as a radical scavenger in the model reaction completely inhibited the formation of **3a**. Instead, corresponding trapping product **6** was detected as a byproduct by GC–MS (Figure S1), suggesting that a radical intermediate was involved in this silver-mediated synthesis of unsymmetrical aromatic azoxy compounds. Furthermore, the oxidation reaction of azobenzene was investigated in the presence of 1.1 equiv. of Ag_2O (Scheme 2B), with no azoxybenzene detected after 24 h. This result indicated that azobenzene was not an intermediate in this transformation. A high GC yield of **3a** was obtained when the reaction was performed under N_2 protection, confirming that oxygen in air was not involved in the reaction, with silver oxide acting as the oxidant (Scheme 2C). To identify whether the oxygen atom in azoxybenzene came from nitrosobenzene or silver oxide, we reacted **1a** and **1b** in the presence of different amounts of silver acetate (Table S3 in SI). During the optimization process, we found that silver acetate promoted the oxidative coupling reaction (Table 1, entry 1). Furthermore, we also found that the yield of **3a** increased with an increasing amount of silver acetate, which clearly demonstrated that silver acetate might also act as the oxidant to produce **3a**. The above study led us to propose that the oxygen atom of **3a** was not derived from silver oxide.

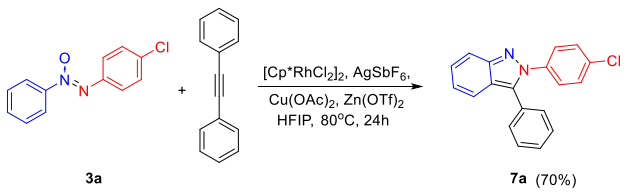


Scheme 2. Control experiments.



Scheme 3. Proposed reaction mechanisms.

Based on the above experimental evidence and existing mechanisms for the oxidative dimerization of aniline,[14] we have proposed a reaction mechanism for this transformation, as shown in Scheme 3. Initially, **1a** reacts with silver(I) oxide to generate radical cation **I.** Subsequent deprotonation affords active radical **II**, which can be trapped by BHT to give **6**. Alternatively, the addition of radical **II** to nitrosoarene **2a** produces radical intermediate **III**. Next, aided by silver(I) oxide, radical intermediate **III** generates species **IV**. Product **3a** is then formed by the deprotonation of intermediate **IV**, accompanied by the formation of Ag(0).



Scheme 4. Synthetic applications.

Finally, using **3a** as a representative sample, we investigated the synthetic potential of this transformation. As shown in Scheme 4, based on a literature procedure,[15] **3a** underwent regioselective C–H activation/cyclization with an alkyne to construct 2H-indazole **7a** in 70% isolated yield, which is recognized as an effective pharmacophore.[16]

In summary, we have developed a simple and efficient approach to the construction of azoxyarenes using a commercially available silver-mediated oxidative coupling reaction of aromatic amines with nitrosoarenes. This reaction takes place in ethanol solution under air without other additives. This new protocol enables a variety of functionalized amines and nitrosoarenes to be transformed into the corresponding products under very mild reaction conditions. This transformation has several advantages, including a high atom economy, simple recovery of silver particles, an environmentally friendly solvent, no use of moisture-sensitive starting materials, and mild reaction conditions with a wide substrate scope. Furthermore, the synthetic utility of this method was demonstrated by a gram-scale reaction and the synthesis of 2H-indazole **7a**. Investigations into the detailed reaction mechanism and potential medicinal activities are underway in our laboratory.

Experimental Section

General remarks

4-Nitrosobenzoate, 1-chloro-4-nitrosobenzene, 1-bromo-4-nitrosobenzene, 1-chloro-2-nitrosobenzene, and 1-methyl-2-nitrosobenzene were synthesized according to the literature.[17] Silver(I) oxide (99%), 2-fluoroaniline (99%), 2-aminodiphenyl (97%), 4-methoxy-phenylamine (99%), (4-aminophenylhenyl)(phenyl)methanone (98%), 4-aminobenzonitrile (98%), 2-aminobenzonitrile (98%), 2-aminobenzoic acid methyl ester (98%), 4-aminobenzotrifluoride (98%), 3-aminoquinoline (97%), nitrosobenzene (97%), and *N*,*N*-dimethyl-4-nitrosoanline (98%) were purchased from Energy Chemical. All other compounds were purchased from Aladdin. All reagents were used without further purification. Melting points were recorded on Digital Melting Point Apparatus WRS-1B and are uncorrected. Crude reaction mixtures were analyzed using an Agilent 7890 GC System with Shimadzu GCMS-QP2010 Plus spectrometer (EI). ^{1}H NMR spectra were recorded on Bruker AVANCE III-500 spectrometers. Chemical shifts (in ppm) were referenced against TMS in $CDCl_3$ (δ 0 ppm). ^{13}C NMR spectra were obtained using the same NMR spectrometers and calibrated with $CDCl_3$ (δ 77.00 ppm). High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer.

General procedure for the synthesis of unsymmetrical aromatic azoxy compounds

A solution of aromatic amines (0.20 mmol, 1.0 equiv.), nitrosoarenes (0.22 mmol, 1.1 equiv.), and Ag_2O (0.22 mmol, 1.1 equiv.) in EtOH (1.0 mL) in a sealed (or open to air) 10-mL Schlenk tube was stirred at 65 °C for 24 h. Reaction progress was monitored by TLC and/or GC–MS. After reaction completion, the crude reaction mixture was cooled to room temperature, filtered to remove silver particles, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel with EtOAc and petroleum ether as eluent to give unsymmetrical aromatic azoxy compounds. Characterization data of the products are provided in the Supporting Information.

Typical procedure for the synthesis of 2-(4-chlorophenyl)-3-phenyl-2H-indazole

To a dried 10-mL round-bottom flask equipped with a magnetic stir bar were added $[Cp^*RhCl_2]_2$ (7.7 mg, 0.0125 mmol), $AgSbF_6$ (17.3 mg, 0.05 mmol), $Cu(OAc)_2$ (90.8 mg 0.5 mmol), $Zn(OTf)_2$ (36.3 mg, 0.1 mmol), 1,2-diphenylethyne (106.9 mg, 0.6 mmol), and 2-(4-chlorophenyl)-1-phenyldiazene oxide (116.0 mg, 0.5 mmol). The vessel was evacuated and backfilled with N_2 before adding 1,1,1,3,3,3-hexafluoro-2-propanol (1.0 mL). The mixture was heated to 80 °C and stirred for 24 h. After reaction completion, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 30:1, v/v) to afford 2-(4-chlorophenyl)-3-phenyl-2H-indazole as a light yellow solid (106.0 mg, 70% yield).

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UPDATE

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