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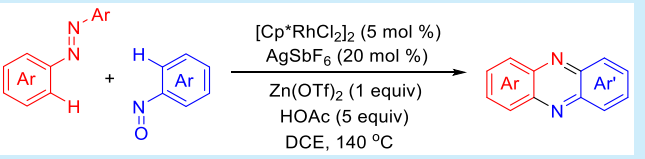
Rhodium-Catalyzed Reaction of Azobenzenes and Nitrosoarenes toward Phenazines

Yan Xiao, Xiaopeng Wu, Hepan Wang, Song Sun, Jin-Tao Yu, and Jiang Cheng*

School of Petrochemical Engineering, and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou 213164, P.R. China

Supporting Information

ABSTRACT: A rhodium-catalyzed annulative reaction between azobenzenes and nitrosoarenes has been developed, leading to a series of phenazines in moderate to good yields. This procedure proceeds with sequential chelation-assisted addition of aryl C−H to nitrosoarenes and ring closure by electrophilic attack of azo group to aryl. During this transformation, the azo group served as not only a traceless directing group but also a building block in the final products.



Phenazines are ubiquitous in natural products[1] and bioactive compounds, which show antibacterial,[2] antifungal,[3] antiviral,[4] and antitumor[5] activities (Scheme 1). The synthetic pathways starting from *ortho*-difunctionalized substrates, such as the Beirut reaction,[6] the Buchwald−Hartwig amination,[7] and Chen's procedure,[8] allow facile access to phenazine frameworks. However, they often suffer from a multistep process to prepare the starting material in the case of accessing polysubstituted phenazines. Alternatively, the annulation between 2 equiv of monofunctionalized starting material features rapid construction of products with chemical diversity and complexity. However, the traditional Wohl−Aue reaction required harsh reaction conditions.[9] Recently, Ellmann reported an efficient method toward phenazine by the rhodium-catalyzed annulation of aldehydes and azides.[10]

Nitrosoarenes are versatile building blocks in organic synthesis.[11] Previously, we developed a Rh(III)-catalyzed bilateral cyclization of aldehydes with nitrosoarenes toward unsymmetrical acridines proceeding with C−H functionalization enabled by a transient directing group.[12] Herein, we report the rhodium-catalyzed reaction of nitrosoarenes and azobenzenes[13,14] toward phenazines, proceeding with the

Scheme 1. Representative Phenazines Compounds

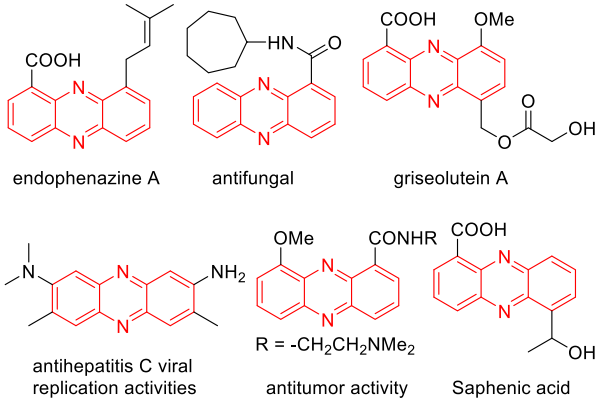
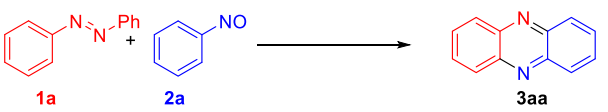


Table 1. Selected Results for Screening the Optimized Reaction Conditions[a]



entry	catalyst	additive (equiv)	solvent	yield[b] (%)
1	$[Cp^*RhCl_2]_2$		MeOH	23
2	$[RuCl_2(p\text{-cymene})_2]_2$		MeOH	nr
3	$[Cp^*Co(CO)I_2]$		MeOH	nr
4	$[Cp^*Rh(OAc)_2]_2$		MeOH	14
5[e]	$[Cp^*Rh(MeCN)_3X_2]$		MeOH	18[c]
6	$[Cp^*RhCl_2]_2$		DMF	25
7	$[Cp^*RhCl_2]_2$		CH_3CN	41
8	$[Cp^*RhCl_2]_2$		THF	nr
9	$[Cp^*RhCl_2]_2$		dioxane	nr
10	$[Cp^*RhCl_2]_2$		DCE	55
11	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (1)	DCE	63
12	$[Cp^*RhCl_2]_2$	$Zn(OTf)_2$ (1) CF_3SO_3H (1)	DCE	nr
13	$[Cp^*RhCl_2]_2/AgSbF_6$	$Zn(OTf)_2$ (1) AcOH (5)	DCE	50[c],68, 71[d]
14	$[Cp^*RhCl_2]_2/AgSbF_6$	$Cu(OAc)_2$ (1) AcOH (5)	DCE	45
15	$[Cp^*RhCl_2]_2/AgSbF_6$	$MgSO_4$ (1)AcOH (5)	DCE	50

[a]Reaction conditions: azobenzene **1a** (0.1 mmol), nitrosobenzene **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), AcOH (5 equiv), other indicated additives (0.1 mmol), solvent (2.0 mL), N_2 (1.0 atm.), at 120 °C for 24 h, in a sealed Schlenk tube. [b]Isolated yield. [c]100 °C. [d]140 °C. [e]X = SbF_6.

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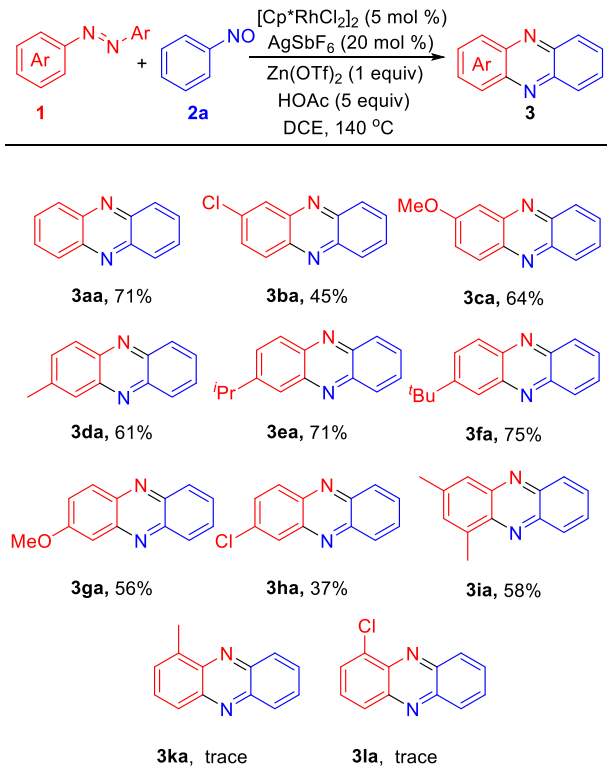


Figure 1. Scope of substituted azobenzenes. (a) Reaction conditions: substituted azobenzenes **1** (0.1 mmol), nitrosobenzene **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Zn(OTf)_2$ (1 equiv), AcOH (5 equiv), DCE (2.0 mL), N_2 (1.0 atm.), at 140 °C for 24 h, in a sealed Schlenk tube. (b) Isolated yield.

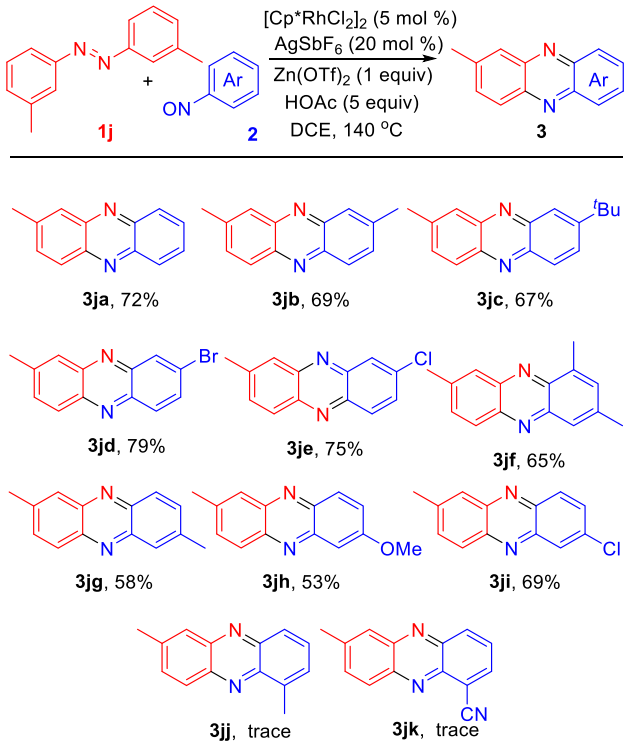
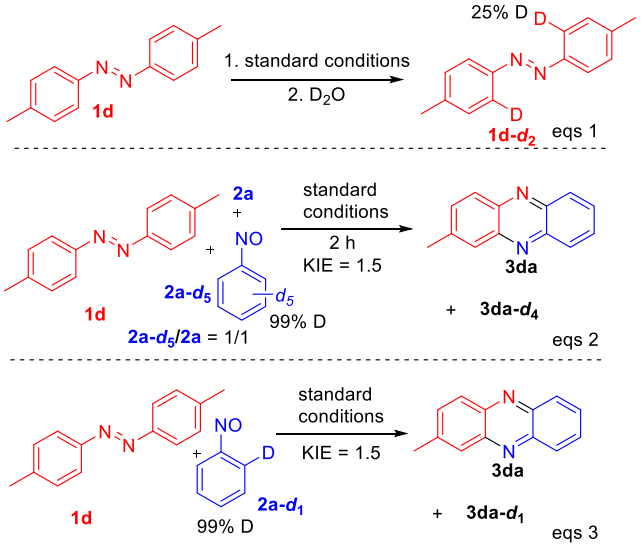


Figure 2. Scope of substituted nitrosobenzenes. (a) Reaction conditions: (*E*)-1,2-di-*m*-tolyldiazene **1j** (0.1 mmol), substituted nitrosobenzenes **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Zn(OTf)_2$ (1 equiv), AcOH (5 equiv), DCE (2.0 mL), N_2 (1.0 atm), at 140 °C for 24 h, in a sealed Schlenk tube. (b) Isolated yield.

sequential directing group-assisted C−H functionalization and catalytic annulation.

We initiated our work by exploring the reaction of azobenzene **1a** (0.1 mmol) and nitrosobenzene **2a** (0.15 mmol) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %) in MeOH at 120 °C in a sealed tube for 24 h (Table 1). To our delight, the annulation product phenazine **3aa** was isolated in 23% yield (entry 1). On the contrary, the reaction resulted in poor or no conversion in the absence of either $AgSbF_6$ or $[RhCp^*Cl_2]_2$. $[RuCl_2(p\text{-cymene})_2]_2$ and $[Cp^*Co(CO)I_2]$ were ineffective for this transformation (entries 2 and 3), while $[Cp^*Rh(OAc)_2]_2$ (14%) and $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ (18%) decreased the reaction efficiency (entries 4 and 5). During the solvent screening, dichloroethane (DCE, 55%) was superior to MeOH (23%), DMF (25%), and MeCN (41%, entries 6, 7, and 10). However, THF and dioxane inhibited the reaction (entries 8 and 9). The yield was improved in the presence of $Zn(OTf)_2$ (63%, entry 11). Moreover, in the presence of $Zn(OTf)_2$ (1 equiv) and AcOH (5 equiv), the yield further improved to 68% (entry 13). When AcOH was replaced by triflic acid, the product could not be detected (entry 12). Therefore, AcOH plays an important role in this transformation. Meanwhile, $Cu(OAc)_2$ and $MgSO_4$ along with AcOH had little effect on the reaction (entries 14 and 15). The reaction temperature had some effect on the reaction efficiency (71%, 140 °C; 50%, 100 °C). Finally, the optimized reaction conditions were selected as follows: azobenzene **1** (0.1 mmol), nitrosobenzenes **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Zn(OTf)_2$ (0.1 mmol), and AcOH (5 equiv) in DCE (2.0 mL) at 140 °C for 24 h under an inert atmosphere (N_2).

Scheme 2. H/D Exchange of Azobenzenes and Kinetic Isotopic Experiments



To study the scope of the C−H activation bilateral cyclization process, we initially conducted the reactions of various azobenzenes **1** with nitrosobenzene **2a** under the optimized conditions (Figure 1). Notably, some azobenzenes with electron-donating groups such as methyl (**3da**, 61%), isopropyl (**3ea**, 71%), *tert*-butyl (**3fa**, 75%), and methoxy (**3ga**, 56%) at the *para*-position worked in good to moderate yields. However, azobenzenes possessing electron-withdrawing groups

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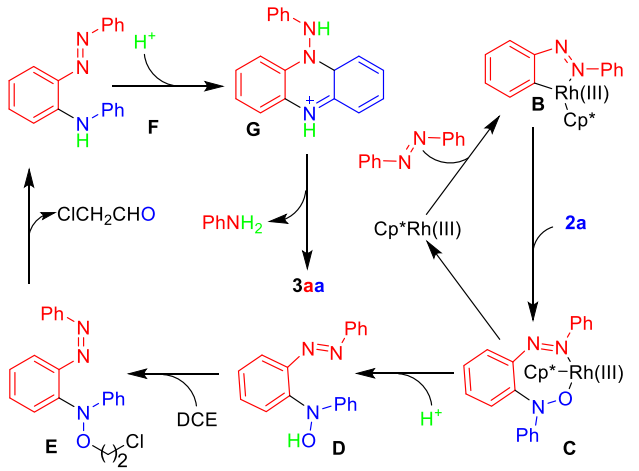
Scheme 3. Tentative Mechanism



provided the corresponding products in relatively low yields (**3ba**, 45%; **3ha**, 37%). Meanwhile, this procedure was also applicable for multisubstituted azobenzenes (**3ia**, 58%). Disappointingly, the *ortho*-substituted analogues (**3ka** and **3la**) did not work under the reaction conditions.

Next, the substrate scope of nitrosobenzenes **2** was investigated by the reaction of substituted nitrosobenzenes with **1j** (Figure 2). Various nitrosobenzenes **2** including those bearing both electron-donating (methyl, *tert*-butyl and methoxy) and electron-withdrawing groups (chloro, bromo) were all well tolerated, affording the corresponding products **3ja**–**ji** with yields ranging from 53% to 79%. Notably, some nitrosobenzenes with electron-withdrawing groups such as bromo (**3jd**, 79%) and chloro (**3je**, 75%) at the *para*-position proceeded in good yields, while those with methyl (**3jb**, 69%) and *tert*-butyl (**3jc**, 67%) provided the products in relatively low yields. Typically, the compatibility of halogen-containing substrates provided facile handles for potentially further functionalizations. Moreover, multisubstituted nitrosobenzenes also access phenazine analogues (**3jf**, 65%). In the cases of *meta*-substituted nitrosobenzenes, **3jg** and **3ji** were isolated in moderate yields (53–69%). Disappointingly, the *ortho*-substituted analogues (**3jj** and **3jk**) failed to work under the reaction conditions.

The test of KIE on azobenzenes was failed since the H/D exchange of azobenzenes was confirmed (Scheme 2, eqs 1). This result indicated the cleavage of *ortho*-C–H in azobenzenes was reversible. Meanwhile, the inter- and intramolecular KIE for nitrosobenzene were both found to be 1.5 (Scheme 2, eqs 2 and 3). Thus, the cleavage of the C–H bond in nitrosobenzene was unlikely to be the rate-determining step during this transformation.

A proposed mechanism is outlined in Scheme 3. First, azobenzene undergoes directed *ortho* C–H bond cleavage leading to metallacycle **B**. Then, the coordination and migratory insertion of newly formed Rh–C bond into the N=O group takes place to form rhodacycle **C**. Second, the protonolysis of rhodacycle **C** produces hydroxylamine **D**, along with the regeneration of Rh(III) species to enter the catalytic cycle. Third, intermediate **F** is formed via the sequential alkylation of **D** by DCE and release of chloroethanal.[15] Finally, in the presence of proton, the intramolecular electrophilic aromatic substitution of **F** forms **G**, which encounters the aromatization leading to phenazine **3aa** and aniline.

In summary, we have demonstrated a facile procedure starting from azobenzenes and nitrosobenzenes to access phenazine analogues. This procedure allowed the rapid access of a series polysubstituted phenazine. Preliminary mechanistic studies indicated that a sequential chelation-assisted addition of aryl C–H to nitrosobenzenes and the ring closure by electrophilic attack of azo group to aryl and aromatization process was involved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00502.

Experimental procedures along with copies of spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jiangcheng@cczu.edu.cn.

ORCID

Song Sun: 0000-0002-9974-6456
Jin-Tao Yu: 0000-0002-0264-9407
Jiang Cheng: 0000-0003-2580-1616

Notes

The authors declare no competing financial interest.

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