

Rhodium-Catalyzed Direct Addition of Aryl C–H Bonds to Nitrosobenzenes at Room Temperature

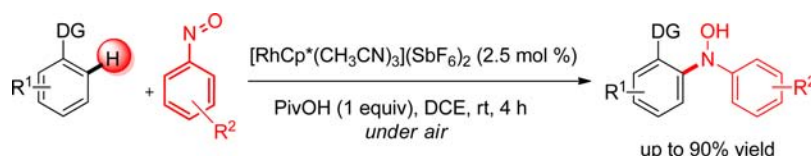
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ABSTRACT



An unprecedented Rh-catalyzed direct addition of aryl C–H bonds to nitrosobenzenes has been developed under very mild reaction conditions (room temperature). The reaction is highly step-, atom-, and redox-economic and compatible with air and water to *N*-selectively provide a variety of *N*-diarylhydroxylamines in good to excellent yields. More importantly, this process may provide a new direction for C–N bond formation through direct C(sp²)–H functionalization.

Catalytic site-selective C–H bond functionalizations have emerged as a powerful tool for the atom-economical formation of C–C and C–heteroatom bonds.¹ While transition-metal-catalyzed arylations of alkene and alkyne derivatives have been well studied,² analogous additions across polar multiple bonds are rare.

Recently, nitrosobenzene has emerged as an attractive electrophilic source of nitrogen or oxygen in nitroso-aldol reactions to afford aminoxylation or hydroxyamination products.³ However, to the best of our knowledge, no example of direct addition of aryl C–H bond to nitrosobenzene (N=O bonds) has been reported, although this is an attractive and direct method for installing nitrogen or oxygen into aromatic rings. In recent years, {Cp*RhIII} complexes have been recognized as a promising catalyst for

aryl C–H bond activation and subsequent addition to polar C=N and C=O groups.⁴ Inspired by these works and other Rh(III)-catalyzed arene C–H bond functionalizations,^{2,5–7} herein we report the first example of Rh-catalyzed direct addition of aryl C–H bond to N=O bonds without any undesirable waste under very mild reaction conditions (room temperature). Compared with traditional addition of organometallic reagents, such as Grignard reagents, to nitrosobenzenes, this process is highly step-, atom- and redox-economic, and compatible with air and water to *N*-selectively afford synthetically important *N*-arylhydroxylamines.⁸

2-Phenylpyridine (**1a**) and methyl 4-nitrosobenzoate (**2a**) were selected as model substrates (Table 1). While no coupling occurred when [RhCp*Cl₂]₂ (2.5 mol %) was used as a catalyst, addition of a halide abstractor (10 mol %), AgSbF₆, for example, could catalyze the reaction to give the hydroxyl amine **3a** in 20% yield (entry 2). The prepared RhIII precursor [RhCp*(CH₃CN)₃](SbF₆)₂ gave higher yields (entry 3). The presence of base completely inhibited the addition reaction (entries 4 and 5), whereas the addition of an acid such as PivOH and 1-AdCO₂H can significantly effect this addition reaction (entries 8 and 9), affording **3a** in good yield. A screen of the solvents gave DCE as an optimal one (entry 10), and the best result for **3a** was obtained by using [RhCp*(CH₃CN)₃](SbF₆)₂ catalyst,

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PivOH and DCE solvent at room temperature for 4 h (entry 14). A control experiment revealed that no product was observed in the absence of rhodium(III) complex (entry 15). Notably, this catalytic addition reaction can be performed with excellent efficiency in the presence of a lower catalyst loading (1 mol %) by simply lengthening the reaction time to 12 h (entry 16). The regioselectivity of this addition reaction was confirmed by the single-crystal X-ray crystallography of compound **3a**.⁹

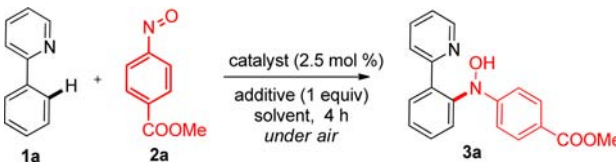
With the optimized reaction conditions, the scope of this amination reaction was investigated (Scheme 1). Evaluation of substituted 2-arylpyridines showed that introduction of various electron-rich, electron-poor, and halogen groups at the para (**3b–g**), meta (**3h** and **3i**), and ortho (**3j**) positions of the phenyl ring were all well tolerated. For 3-substituted derivatives, functionalization occurred exclusively para to the substitutions to afford products **3h** and **3i** in high yields. In particular, the 2-Me derivative (**3j**)

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Table 1. Optimization of Rh-Catalyzed Direct Addition Reaction^a



entry	catalyst (2.5 mol %)	additive	solvent	3a (%)
1	(Cp*RhCl ₂) ₂		PhCl	0
2	(Cp*RhCl ₂) ₂ /AgSbF ₆		PhCl	20
3	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂		PhCl	35
4	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	CS ₂ CO ₃	PhCl	0
5	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOK	PhCl	0
6	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	Cu(OAc) ₂	PhCl	27
7	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	AcOH	PhCl	45
8	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	PhCl	72
9	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	1-AdCO ₂ H	PhCl	60
10	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	DCE	82
11	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	THF	54
12	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	PhMe	65
13	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	CH ₃ OH	44
14 ^b	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	DCE	90
15		PivOH	DCE	0
16 ^c	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PivOH	DCE	87

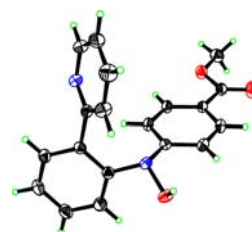
^a **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (0.005 mmol), additive (0.2 mmol), and solvent (1 mL) at 40 °C for 4 h. Yield of isolated product. 1-AdCO₂H = 1-adamantanecarboxylic acid. ^b The reaction is carried out at room temperature. ^c 1.0 mol % of catalyst was used; reaction time = 12 h.

also showed excellent reactivity, thus showing high tolerance for steric hindrance. Moreover, the present addition reaction showed excellent functional group tolerance. For

(7) For Rh(III)-catalyzed C–N bond forming reactions, see: (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (b) Shi, J.; Zhou, B.; Yang, Y.; Li, Y. *Org. Biomol. Chem.* **2012**, *10*, 8953. (c) Yu, D. G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (d) Zhou, B.; Yang, Y.; Shi, J.; Feng, H.; Li, Y. *Chem.—Eur. J.* **2013**, *19*, 10511. (e) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904. (f) Lian, Y.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 12548. (g) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2013**, *125*, 8189. (m) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272. (h) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (i) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869. (j) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014. (k) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706. (l) Zhao, H.; Shang, Y.; Su, W. *Org. Lett.* **2013**, *15*, 5106.

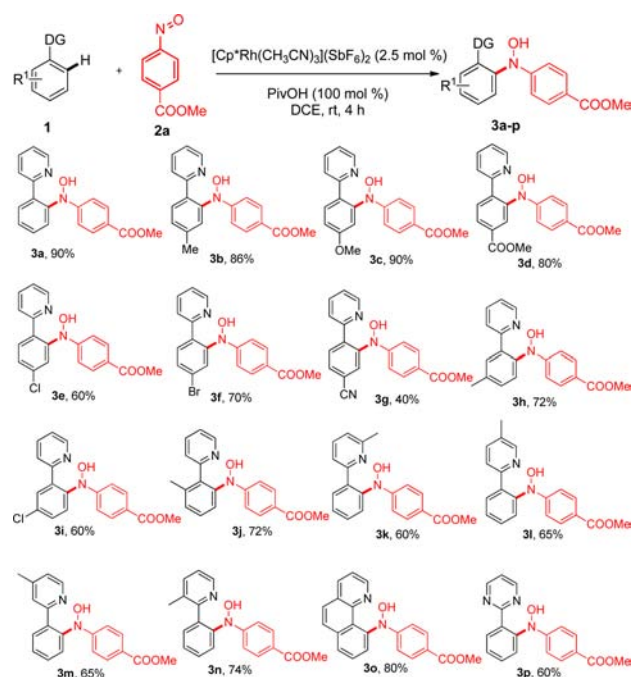
(8) In addition to their synthetic application, *N*-diarylhydroxylamines are important antioxidant stabilizers for various substrates including polyolefins, polyesters, and polyurethanes; see: Ravichandran, R.; Yonkers, N. Y.; Pastor, S. D.; Basel, S. US patent 5021479, 1991 and references cited therein.

(9) CCDC 958066 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. X-ray structure of **3a**:



example, the ester (**3d**) and halogen (**3e**, **3f** and **3i**) groups were highly compatible with this amination reaction, enabling further synthetic manipulations. The 4-CN derivative gave a relatively low yield of **3g** (40%), presumably because the CN group competitively coordinates to the Rh(III) center.^{4a} The substrate scope was further extended to other directing groups, and a variety of pyridinyl directing groups were investigated first. The steric bulkiness on the pyridine ring had quite a limited effect on this addition reaction (**3k–n**). Significantly, the tricyclic benzo-*[h]*quinolone (**3o**) and other N-based heterocycles such as pyrimidine (**3p**) also worked well as efficient directing groups for this addition reaction.

Scheme 1. Substrate Scope for the Rh-Catalyzed Addition Reaction^a

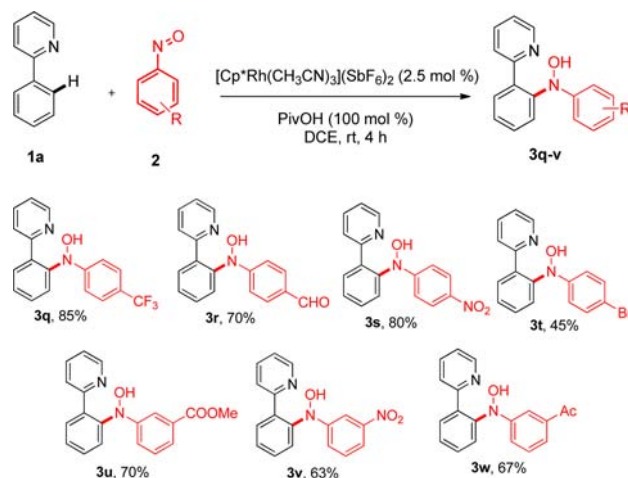


^aThe reactions were performed by heating [RhCp*(CH₃CN)₃](SbF₆)₂ (2.5 mol %), substrate **1** (0.2 mmol), **2a** (0.24 mmol), PivOH (0.2 mmol), and DCE (1 mL) for 4 h at room temperature. Isolated yields.

The scope of nitrosobenzenes was then examined (Scheme 2). Other different electron-poor nitrosobenzenes showed excellent activities (**3q–v**). A variety of functional groups (e.g., trifluoromethyl (**3q**), nitro (**3s** and **3v**), bromo (**3t**), ester (**3u**), acetyl (**3w**), and even the electrophilic carboxaldehyde (**3r**) groups)¹⁰ were well-compatible with this addition reaction. However, similar to previous results,^{4d,e} no desired product was observed when electron-rich nitrosobenzenes were used. Further efforts are being made in our laboratory to approach such a goal. Notably, to date, this is the first example of direct addition of aryl C–H bonds to nitrosobenzenes, thus providing

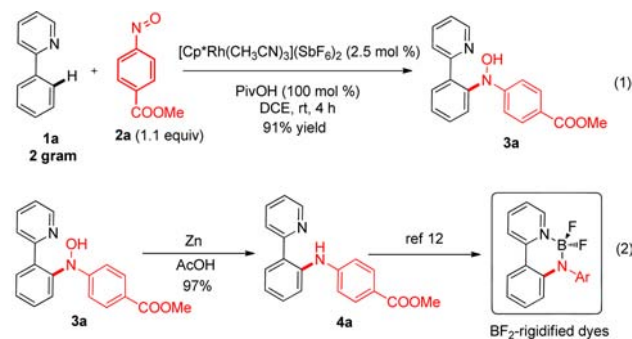
(10) No any byproduct involving the addition of C–H bond to aldehydes was observed (**3r**).

Scheme 2. Substrate scope of nitrosobenzenes.^a



^aThe reactions were performed by heating [RhCp*(CH₃CN)₃](SbF₆)₂ (2.5 mol %), substrate **1a** (0.2 mmol), **2** (0.24 mmol), PivOH (0.2 mmol) and DCE (1 mL) for 4 h at room temperature. Isolated yields.

insights for further work on intermolecular C–N bond-forming reactions.



To our delight, the present addition reaction is potentially applicable in large-scale synthesis, and the product was easily isolated by a simple recrystallization process (eq 1). Treatment of **3a** with Zn/AcOH gave the valuable diarylamine product **4a** in 97% yield.¹¹ Notably, the diarylamine product has utility as dyes and functional materials, as exemplified by Piers's group as important fluorenes dyes with large Stokes shifts and high photostability.¹²

To obtain more mechanistic insight, we carried out several preliminary mechanistic experiments. First, a cyclometalated Rh(III) complex **5** successfully catalyzed the addition reaction to provide the hydroxylamine product **3a** in 90% yield, indicating the relevancy of C–H activation

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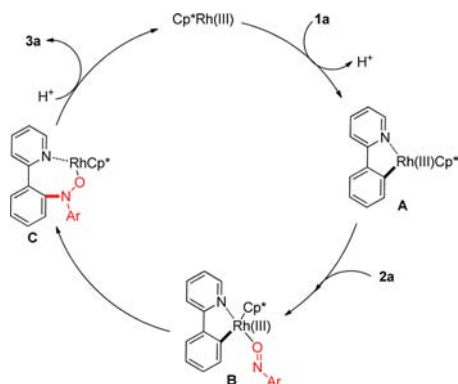
(12) Araneda, J. F.; Piers, W. E.; Heyne, B.; Parvez, M.; McDonald, R. *Angew. Chem., Int. Ed.* **2011**, 50, 12214.

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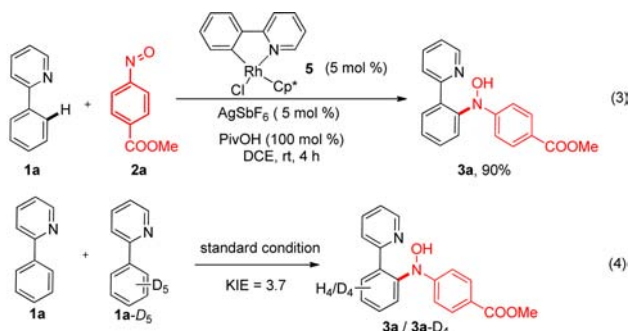
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Scheme 3. Proposed Mechanism (Ar = 4-COOMe-phenyl)



(eq 3). An intermolecular competitive coupling of **2a** with a 1:1 mixture of **1a** and **1a-d₅** revealed a significant primary kinetic isotope effect (KIE) of 3.7 at a low conversion. This KIE value of 3.7 is typical for the C–H activation processes (eq 4).¹³



Based on the above experiment, we tentatively propose the following mechanism (Scheme 3). 2-Phenylpyridine undergoes Rh-catalyzed *ortho*-directed C–H bond activation to provide a rhodacycle **A**,¹⁴ followed by coordination and the subsequent nucleophilic addition (or migratory insertion of N=O) to give O–Rh species **C**. Protonation of **C** delivers the hydroxylamine **3a** and the Rh(III) catalyst.¹⁵

In summary, we have developed an unprecedented rhodium-catalyzed addition of aryl C–H bonds to nitrosobenzenes. The reaction is highly step-, atom-, and redox-economic and can be readily scaled up. Moreover, this procedure can be carried out under very mild conditions in the atmospheric environment, providing a variety of *N*-arylhydroxylamines in good to excellent yields. The hydroxylamine products can be easily reduced to provide valuable diarylamines in excellent yield. More importantly, this process may provide a new direction for C(sp²)–H activation/C–N bond formation involving the use of nitrosobenzenes as the nitrogen source. Studies to expand this methodology to a wider range of substrates are currently underway in our laboratories.

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Supporting Information Available. Experimental procedures, characterization of products, and copies of ¹H and ¹³C NMR spectra are provided. The material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.