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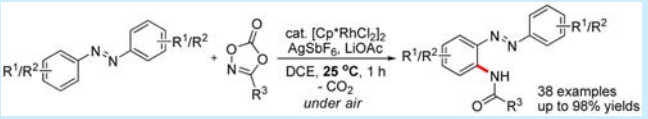
Selective Rhodium-Catalyzed C−H Amidation of Azobenzenes with Dioxazolones under Mild Conditions

Bomi Jeon, Uiseong Yeon, Jeong-Yu Son, and Phil Ho Lee*

Department of Chemistry, Kangwon National University, Chuncheon 24341, Republic of Korea

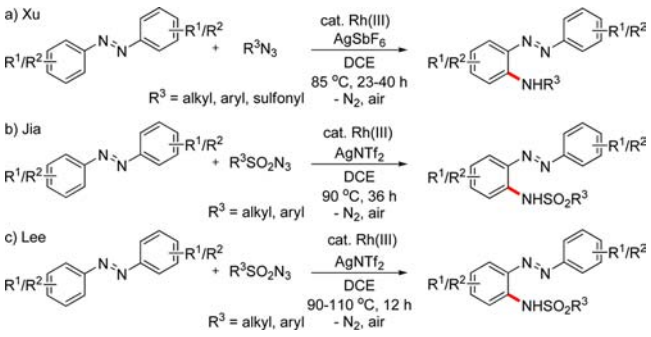
Supporting Information

ABSTRACT: A synthetic method for a wide range of amidated azobenzenes is developed from the selective rhodium-catalyzed C−H amidation reaction of symmetrical as well as unsymmetrical azobenzenes with alkyl-, aryl-, and heteroaryl-substituted dioxazolones under mild conditions. Diamidation of azobenzenes and amidation of monoamidated azobenzenes were also demonstrated.

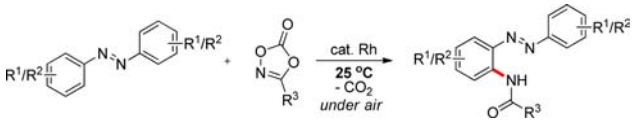


Azobenzenes are a significant class of compounds in many fields, such as organic dyes, food additives, and material science. Thus, development of streamlined synthetic methods for their derivatives is greatly needed.[1] Although the introduction of a wide range of functional groups onto a symmetrical azobenzene ring has been reported, selective introduction of substituents onto unsymmetrical azobenzenes still represents a formidable challenge. In recent years, C−H activation of azobenzenes using azo group as a directing group has gained reasonable attention for the functionalization of azobenzenes including the following reactions: acylation,[2] alkoxylation,[3] nitration,[4] halogenation,[5] olefination,[6] alkylation,[7] arylation,[8] phosphorylation,[9] amination,[10] cyanation,[11] aminocarbonylation,[12] and tandem cyclization.[13] Regardless of the successes that have been achieved with respect to C−H activation of azobenzenes, the formation of a C−N bond through C−H activation of azobenzenes has been scarcely reported. Recently, the Xu, Jia, and Lee groups independently reported Rh-catalyzed C−H amidation of azobenzenes with azides (Scheme 1a, b, and c, respectively).[10,13d,14] However, these methods are achieved under harsh conditions, and symmetrical azobenzenes are mainly used. In our continuing efforts in C−H activation,[15] we have been interested in the development of direct and selective C−N bond formation using both symmetrical and unsymmetrical azobenzenes under mild conditions. Chang and co-workers recently reported the usefulness of dioxazolones as excellent amidation reagents in C−H activation.[16] Accordingly, we envisioned the C−H amidation reaction of azobenzenes with dioxazolones. Herein, we demonstrate selective C−H amidation reactions of symmetrical as well as unsymmetrical azobenzenes with a large number of dioxazolones through decarboxylation under mild conditions (Scheme 2).

Scheme 1. Previously Reported Methods for the C−H Amidation of Azobenzenes



Scheme 2. Selective Rh-Catalyzed C−H Amidation of Azobenzenes with Dioxazolones



First, we began our investigation by examining the reaction of azobenzene (**1a**) with 3-phenyl-1,4,2-dioxazol-5-one (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) with a variety of silver additives (10.0 mol %), bases (10.0−30.0 mol %), and solvents (Table 1). Among the additives investigated, such as $AgNTf_2$, AgOTf, and $AgSbF_6$, $AgSbF_6$ provided the amidated azobenzene **3aa** in 83% yield (entry 3). LiOAc (30.0 mol %) as a base was superior to NaOAc and CsOAc. DCE was the solvent of choice (entry 3); other reaction media such as MeOH, EtOAc, THF, and $PhCH_3$ were less effective (entries 7−10). Since the desired product **3aa** was obtained in 74% yield without base (entry 6), a reduced amount (10.0 mol %) of LiOAc was used, resulting in the formation of **3aa** in 84% yield (entry 11). The use of $[Cp^*CoCl_2]_2$ catalyst was not effective. Azoxybenzene and *N*-methyl-*N*-nitrosoaniline did not react with **2a** under the optimum conditions.

To demonstrate the scope and limitations of the present method, we applied this catalytic system to a wide range of

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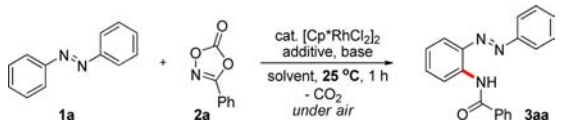
Table 1. Reaction Optimization[a]

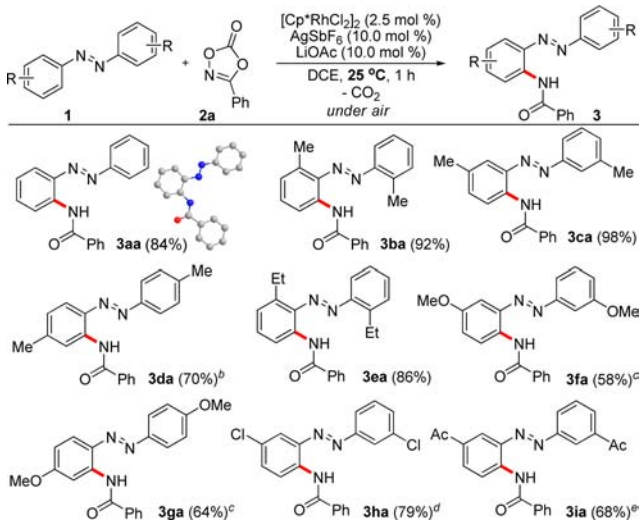


entry	additive	base (mol %)	solvent	yield[b] (%)
1	$AgNTf_2$	LiOAc (30)	DCE	77
2	AgOTf	LiOAc (30)	DCE	38
3	$AgSbF_6$	LiOAc (30)	DCE	83
4	$AgSbF_6$	NaOAc(30)	DCE	74
5	$AgSbF_6$	CsOAc (30)	DCE	66
6	$AgSbF_6$		DCE	74
7	$AgSbF_6$	LiOAc (30)	MeOH	0
8	$AgSbF_6$	LiOAc (30)	EtOAc	31
9	$AgSbF_6$	LiOAc (30)	THF	42
10	$AgSbF_6$	LiOAc (30)	$PhCH_3$	40
11	$AgSbF_6$	LiOAc (10)	DCE	86 (84)[c]

[a]Conditions: **1a** (2 equiv), **2a** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), additive (10.0 mol %), and base (10.0−30.0 mol %) in solvent (1.0 mL) were used under air. [b]NMR yield using dibromomethane as an internal standard. [c]Isolated yield.

symmetrical azobenzenes **1** in reactions with 3-phenyl-1,4,2-dioxazol-5-ones (**2a**) (Scheme 3). When methyl-substituted

Scheme 3. Substrate Scope of Symmetrical Azobenzenes[a]

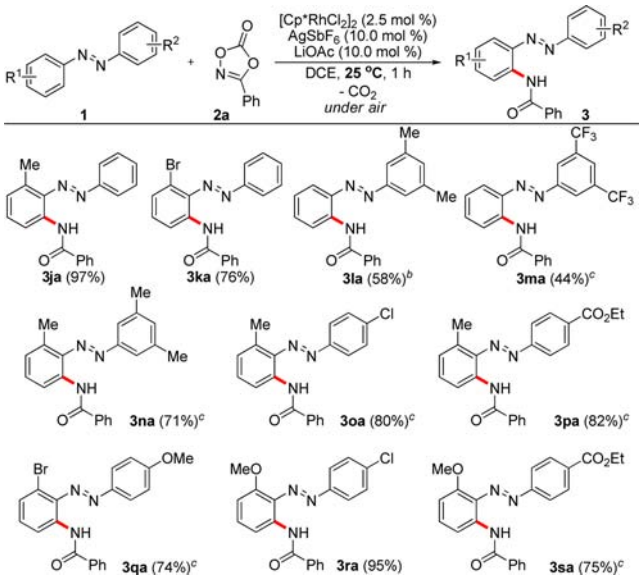


[a]Conditions: **1** (2 equiv), **2a** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), and LiOAc (10.0 mol %) in DCE (1.0 mL) were used at 25 °C for 1 h under air. [b]12 h. [c]$[Cp^*RhCl_2]_2$ (4.0 mol %) and $AgSbF_6$ (16.0 mol %) were used. [d]**1** (0.2 mmol, 1 equiv) and **2a** (2 equiv) were used for 24 h. [e]60 °C.

azobenzenes were treated with **2a** in the presence of a Rh catalyst at 25 °C, the desired amidation products (**3ba**, **3ca**, and **3da**) were produced in good to excellent yields. In particular, it is noteworthy that 3-methyl-substituted azobenzene **1c** was quantitatively amidated to provide 2-amidated azobenzene **3ca** in 98% yield. In this case, no compound amidated at the 2-position was detected due to steric hindrance. 2-Ethyl-substituted substrate **1e** was also transformed to the amidated azobenzene **3ea** in 86% yield. The strongly electron-donating 3- and 4-methoxy substituents slightly influenced the amidation reaction, and the desired products **3fa** and **3ga** were produced in 58% and 64% yields, respectively. 3-Chloro-substituted azbenzene **1h** is applicable to the present method, providing the desired azobenzene **3ha** in a good yield. However, 3-acetylazobenzene **1i** was less reactive, and the desired product **3ia** was obtained in 68% yield at 60 °C.

Encouraged by these results, we investigated the selectivity of the Rh-catalyzed C−H amidation reaction using unsymmetrical azobenzenes by modification of the steric and/or electronic environment (Scheme 4). When 2-methylazobenzene **1j** was

Scheme 4. Substrate Scope of Unsymmetrical Azobenzenes[a]



[a]Conditions: **1** (2 equiv), **2a** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), and LiOAc (10.0 mol %) in DCE (1.0 mL) were used at 25 °C for 1 h under air. [b]60 °C. [c]$[Cp^*RhCl_2]_2$ (4.0 mol %) and $AgSbF_6$ (16.0 mol %) were used.

treated with the Rh catalyst, C−H amidation reaction selectively took place on the methyl-substituted aryl ring under mild conditions, and the desired amidated azobenzene **3ja** was obtained in 97% yield. In the case of 2-bromoazobenzene **1k**, the C−H amidation reaction also occurred on the bromo-substituted aryl ring. In these cases, no diamidated compounds were detected. These results indicate that the selectivity of the C−H amidation reaction in unsymmetrical azobenzenes is governed by steric effects rather than by electronic effects. Although 3,5-dimethyl- and 3,5-di(trifluoromethyl)azobenzene were less reactive, the amidation reaction selectively occurred on the phenyl ring. 2-Methyl along with 3,5-dimethyl-, 4-chloro-, and 4-(ethoxycarbonyl)-substituted azobenzenes (**1n**, **1o**, and **1p**) selectively underwent a C−H amidation reaction on the phenyl ring having a 2-methyl group. Azobenzene **1q** bearing 2-bromo and 4′-methoxy groups was selectively transformed to 6-amidated azobenzene **3qa** due to steric congestion. 2-Methoxy- along with 4′-chloro- and 4′-(ethoxycarbonyl)azobenzenes (**1r** and **1s**) were subjected to a selective C−H amidation reaction on the phenyl ring having a 2-methoxyl group.

To further investigate the generality of the present method, alkyl-substituted dioxazolones **2** were examined in a reaction with **1c** under the optimum conditions (Scheme 5). C−H amidation reactions using 3-methyl-1,4,2-dioxazol-5-one (**2b**) led to the corresponding product **3cb** in 98% yield. To our

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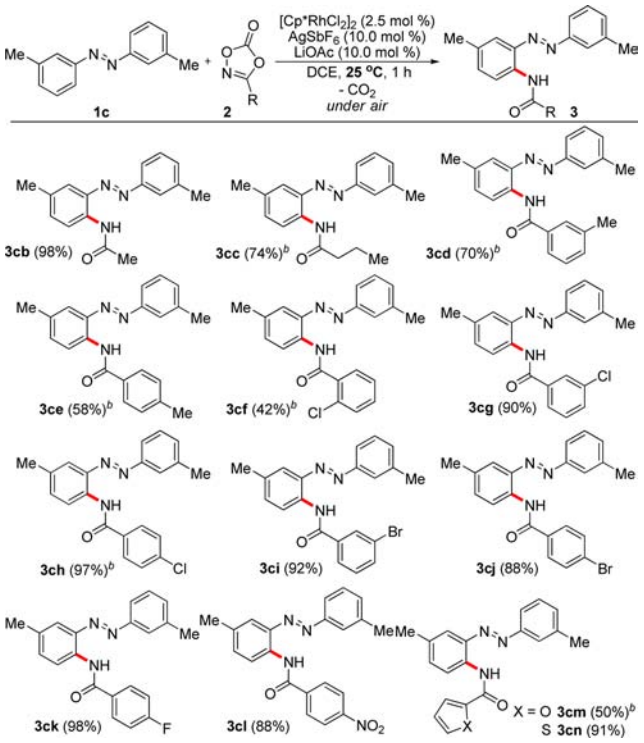
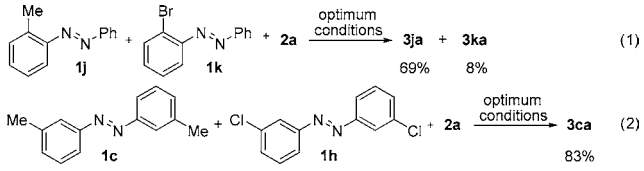
Scheme 5. Substrate Scope of Dioxazolones[a]



[a]Conditions: **1c** (2 equiv), **2** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), and LiOAc (10.0 mol %) in DCE (1.0 mL) were used at 25 °C for 1 h under air. [b]$[Cp^*RhCl_2]_2$ (4.0 mol %) and $AgSbF_6$ (16.0 mol %) were used.

delight, the amidation reaction of 3,3′-dimethylazobenzene (**1c**) with *n*-propyl-1,4,2-dioxazol-5-one (**2c**) under the slightly modified reaction conditions (4.0 mol % of Rh catalyst and 16.0 mol % of $AgSbF_6$) afforded the desired product **3cc** in 74% yield. We next focused on the C−H amidation reaction of **1c** with a large number of aryl- and heteroaryl-substituted dioxazolones **2**. Dioxazolones (**2d** and **2e**) having a methyl group on the phenyl ring were reacted with **1c** to give **3cd** and **3ce** in moderate to good yields. Aryl dioxazolones **2** having electron-withdrawing groups (Cl, Br, F, and NO_2) on the aromatic ring also underwent the amidation reaction to afford the desired products **3cg−cl** in good to excellent yields ranging from 88% to 98%. However, 2-chlorophenyl-substituted dioxazolone (**2f**) was less reactive due to steric effects. Although 3-(2-furyl)-1,4,2-dioxazol-5-one (**2m**) reacted with **1c** to provide **3cm** in 50% yield under the modified conditions, 3-(2-thiophenyl)-1,4,2-dioxazol-5-one (**2n**) gave the desired amidation product **3cn** in 91% yield under the optimum conditions.

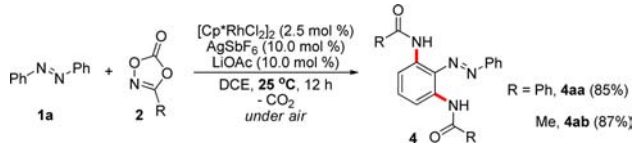
Competitive reactions between various azobenzenes were performed. Dioxazolone (**2a**) was simultaneously reacted with **1j** and **1k** (1 equiv each), which led to the formation of **3ja** as the major product (eq 1). Similarly, simultaneous C−H



amidation with **1c** and **1h** (1 equiv each) resulted in the selective production of **3ca** (eq 2). These results indicate that the electron-rich azobenzenes are more reactive than the electron-deficient ones.

Next, we are interested in the diamidation reaction of azobenzenes due to selectivity on the two aryl rings after the first amidation (Scheme 6). When **1a** (1 equiv) was treated

Scheme 6. Diamidation of Azobenzenes[a]

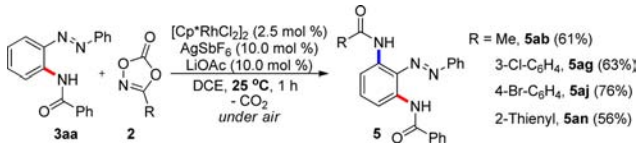


[a]Conditions: **1a** (0.2 mmol, 1 equiv), **2** (3 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), and LiOAc (10.0 mol %) in DCE (1.0 mL) were used at 25 °C for 12 h under air.

with **2a** (3 equiv) under the optimum conditions, the first as well as second amidation reactions occurred on the same phenyl ring, providing **4aa** in 85% yield. 3-Methyl-1,4,2-dioxazol-5-one (**2b**) turned out to have the same tendency toward a 2-fold Rh-catalyzed diamidation reaction.

On the basis of these results, the Rh-catalyzed amidation reaction of monoamidated azobenzene **3aa** was examined (Scheme 7). When **3aa** was treated with methyl- and aryl-

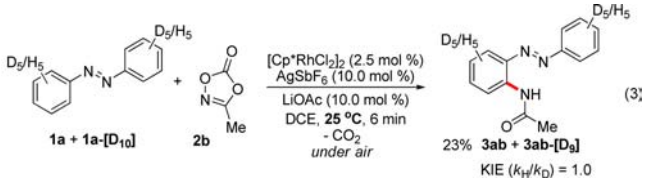
Scheme 7. Amidation of Monoamidated Azobenzenes[a]



[a]Conditions: **3aa** (2 equiv), **2** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), and LiOAc (10.0 mol %) in DCE (1.0 mL) were used at 25 °C for 1 h under air.

substituted dioxazolones (**2b**, **2g**, **2j**, and **2n**) under the optimum conditions, the amidation reaction proceeded smoothly, providing the corresponding amidated azobenzenes (**5ab−an**) in moderate to good yields ranging from 56% to 76%.

Next, we conducted KIE studies to obtain insight into the reaction mechanism (eq 3). A KIE was not observed (k_H/k_D = 1.0), indicating that the C−H bond cleavage at the *ortho* position of azobenzene is not involved with the rate-determining step.



A plausible reaction mechanism is described in Scheme 8.[17] First, exposure of $[Cp^*RhCl_2]_2$ to $AgSbF_6$ and LiOAc provides the cationic Rh(III) catalyst, which undergoes C−H activation with **1** to afford a five-membered rhodacycle **I**. Subsequent coordination of dioxazolones **2** with rhodacycle **I** generates intermediate **II**, which upon decarboxylation and amidation of

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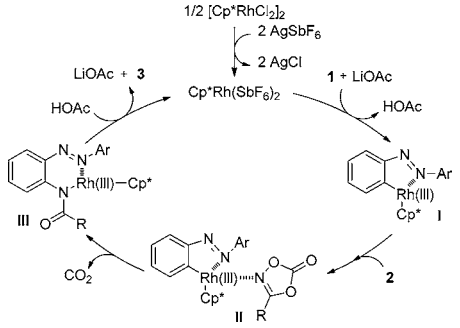
Scheme 8. Plausible Mechanism



the C–Rh bond furnishes complex **III**. Finally, protoderhodation of **III** delivers the desired product **3** and the regeneration of the active Rh(III) catalyst.

In summary, we have developed an efficient synthetic method for a wide range of amidated azobenzenes through the selective Rh-catalyzed C–H amidation reaction of symmetrical as well as unsymmetrical azobenzenes with alkyl-, aryl-, and heteroaryl-substituted dioxazolones under mild conditions. In addition, diamidation of azobenzenes and amidation of monoamidated azobenzenes were developed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02250.

Experimental procedures, characterization data, X-ray crystallographic data (**3aa**), and NMR spectra for all of the products (PDF)

X-ray data for compound **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: phlee@kangwon.ac.kr.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Naoto Chatani (Osaka University) on the occasion of his 60th birthday.

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