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Letter

The Direct Rh(III)-Catalyzed C−H Amidation of Aniline Derivatives Using a Pyrimidine Directing Group: The Selective Solvent Controlled Synthesis of 1,2-Diaminobenzenes and Benzimidazoles

Shrikant M. Khake and Naoto Chatani*

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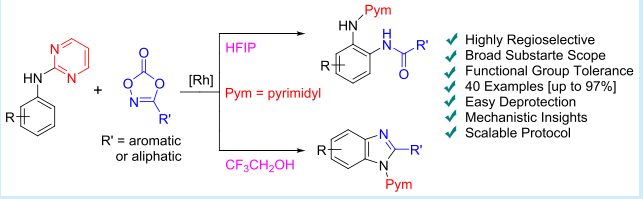
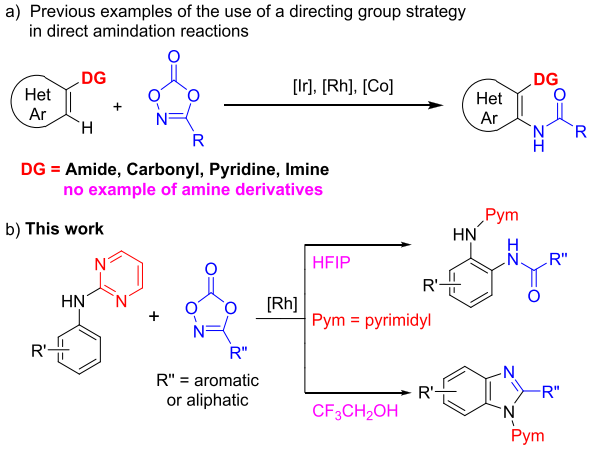
ABSTRACT: The regioselective Rh(III)-catalyzed C−H amidation of aniline derivatives with dioxazolones as an amidating reagent with a pyrimidine as a directing group leading to the production of 1,2-diaminobenzene derivatives or benzimidazole derivatives is described. The product distribution is controlled by the nature of solvent used. The reaction provides a broad substrate scope for aniline derivatives with various important functional groups including dioxazolones.



Because nitrogen-containing heteroarenes are fundamental units of a variety of naturally occurring compounds, biologically active compounds, agricultural products, pharmaceutical drug molecules, and polymers, C−N bond forming reactions are of great importance in synthetic chemistry.[1] Traditional reactions for the formation of C−N bond include the Ullmann−Goldberg reaction, Chan−Lam coupling, and the Buchwald−Hartwig amination reaction, but these reactions have drawbacks in that a stoichiometric amount of metal species is required, resulting in the formation of a stoichiometric amount of byproducts such as hydrogen halides or their base salts.[2] Transition metal catalyzed C−N bond formation reactions via C−H bond activation are currently the most powerful and versatile synthetic tool in synthetic chemistry.[3] Direct C−H bond amidation by transition metal catalysis would be highly desirable because it is highly atom-economical and is an efficient alternative route to conventional cross-coupling reactions. Various amidating reagents such as *N*-tosylates,[4] *N*-carboxylate,[5] *N*-fluorobenzenesulfonimide,[6] organic azides,[7] and others[8] have been used in C−H amidation reactions. Dioxazolones have recently been explored as amidating reagents because they are easily handled and strongly coordinate to a metal, and only CO_2 is produced as a byproduct.[9] In 2015, Chang used dioxazolones as an amidating reagent for the Rh-catalyzed C−H amidation of 2-phenylpyridines, and a DFT study showed dioxazolones strongly coordinate to rhodium compared to sulfonyl azide as amidating reagent. Since then, a number of reports have appeared on the use of Ir(III), Rh(III), and Co(III) catalysts in C−H amidation reactions with dioxozolones via a directing group strategy (Scheme 1a).[9b−x] Various substrates, such as 2-arylpyridines, azobenzene, indole derivatives, benzamides, azoles, and arylpyrozolopyrimidine, have been used, but aniline derivatives have been less explored for use in amidation reactions, although the amidation of aniline derivatives is an attractive route to the synthesis of 1,2-aminobenzene derivatives.

Scheme 1. Transition Metal Catalyzed C−H Bond Amidation with Dioxazolones



While the use of a pyrimidine directing group in C−H bond alkylation,[10] alkynylation,[11] and sulfenylation[12] of aniline derivatives has been widely explored, C−H bond amidation has been less explored. In 2017, Cui developed the Ir(III)-catalyzed C−H amidation of anilines with sulfonyl azides as an amidating reagent.[13] This method, however, involves the use of a

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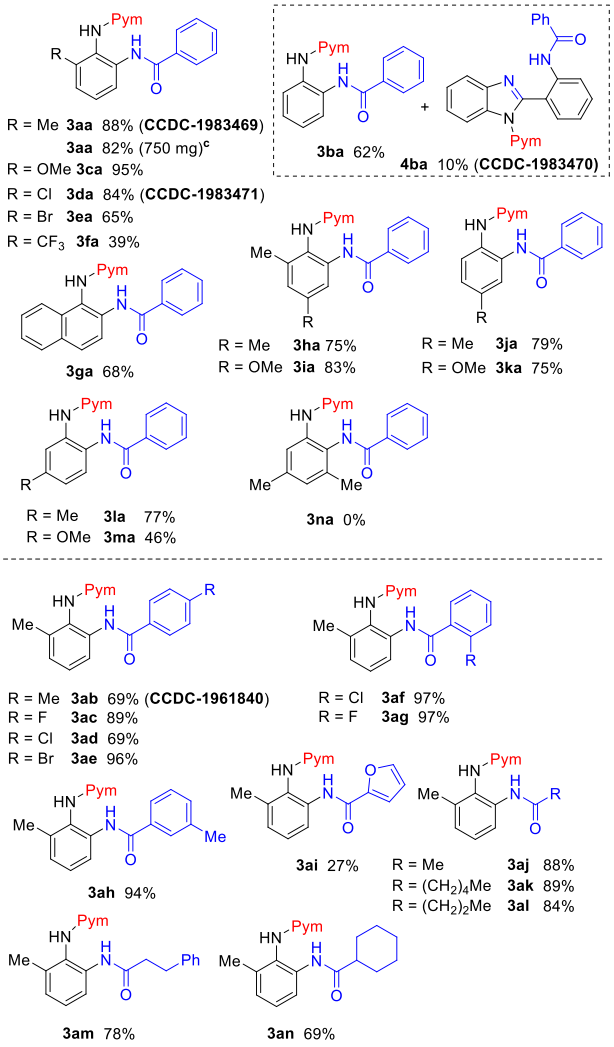
hazardous and heat-sensitive amidating reagent, and the reaction has only a limited scope. In the same year, Li reported the Ir(III)-catalyzed synthesis of benzimidazole via C−H amidation of aniline derivatives using a pyridine as directing group wherein the first step is amidation which upon cyclization forms benzimidazole.[9o] We herein report the Rh(III)-catalyzed C−H amidation of various aniline derivatives with dioxazolones using a pyrimidine directing group (Scheme 1b). It should be noted that this protocol can be used for the amidation of various aniline derivatives with aromatic as well as aliphatic dioxazolones as amidating reagents with functional groups. Most importantly, the product distribution between 1,2-diaminobenzene derivatives or benzimidazole derivatives can be controlled by the nature of solvents used.

We started optimizing the reaction conditions for C−H bond amidation using *N*-(2-tolyl)pyrimidin-2-amine (**1a**) as a model substrate with 3-phenyl-1,4,2-dioxazol-5-one (**2a**) as an amidating reagent (see Table S1 in Supporting Information (SI)). The optimal reaction conditions were determined to be as follows: **1a** (0.15 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), and $AgSbF_6$ (10 mol %) in HFIP (1 mL) at 100 °C for 8 h (entry 12 in Table S1).

Having the optimized conditions in hand, we employed this method for the C−H amidation of substituted aniline derivatives **1** (Scheme 2). The reaction of an aniline substrate without any substituent **1b** afforded the expected monoamidated product **3ba** as a major product. While a diamidating product was not formed, instead, **4ba** was formed, the structure of which was confirmed by X-ray diffraction. The reaction path for **4ba** will be discussed below. Important functional groups, such OMe, Cl, Br, and CF_3 substituents, were tolerated in the backbone of the aniline substrates to give the corresponding products **3ca**−**3fa**. In the case of 1-naphthylaniline **1g**, the C−H bond at the 2-position was exclusively amidated to give **3ga** and no C−H amidation at the 8-position was detected. The reaction of *meta*-substituted aniline **1l** gave the expected product **3la** exclusively in 77% yield, in which the less hindered C−H bond was selectively amidated. The reaction of the 3,5-dimethyl-substituted aniline **1n** did not give the desired amidated product **3na** because of the steric hindrance at the *ortho*-position. We further extended the scope of the reaction with respect to the amidating reagent. Various dioxazolones **2** bearing alkyl, aryl, and heteroaryl substituents were examined for the C−H bond amidation of **1a**. Dioxazolone bearing a methyl group **2b** on the phenyl ring efficiently afforded **3ab** in 69% yield. In addition, aryl dioxazolones **2** having electron-withdrawing groups such as F, Cl, and Br substituents at the *para*-position of the phenyl ring gave the desired products **3ac**, **3ad**, and **3ae**, respectively. Similarly, a substituent at the *ortho*-position of a phenyl ring of dioxazolone derivatives afforded excellent yields of **3af** and **3ag**. The alkyl substituted dioxazolone **2j**−**2m** reacted efficiently with **1a** to afford **3aj**−**3am** in high yields. The cyclohexyl-substituted dioxazolone **2n** also participated in the reaction.

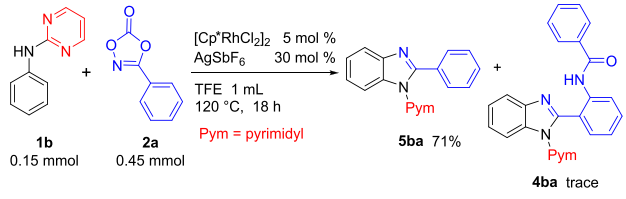
As shown in Scheme 2, we observed that the benzimidazole derivative **4ba** was formed as a minor product. The formation of **4ba** could occur through monoamidation followed by cyclization and further C−H amidation. If it were possible to stop the reaction at the cyclized product stage, this would be a convenient route to prepare C2-arylated benimidazole derivatives, which are a fundamental unit of many pharmaceutical compounds as well as naturally occurring heterocycles.[14] We therefore screened various solvents in attempts to obtain the cyclized product and avoid further amidation (Scheme 3).

Scheme 2. Scope of Aniline Derivatives and Dioxazolones for the C−H Amidation[a,b]



[a]Reaction conditions: **1** (0.15 mmol), dioxazolone **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (10 mol %) in HFIP (1 mL) at 100 °C for 8 h under N_2 atmosphere. [b]Isolated yield. [c]3 mmol scale synthesis.

Scheme 3. Selective Formation of Cyclized Product



Gratifyingly, the use of trifluoroethanol (TFE) as a solvent gave **5ba** as a single product in 71% isolated yield, while other solvents, such 1,4-dioxane (20%), DCE (35%), and toluene (32%), gave **4ba** selectively, along with a trace amount of **5ba**. TFE has a more acidic nature than HFIP which makes carbonyl groups more electrophilic in nature by donating a proton to a carbonyl group. Because of this, it would facilitate an intramolecular nucleophilic attack of NH to the amide carbonyl group and the subsequent elimination of water would result in the formation of the cyclized product **5**. This is a possible reason

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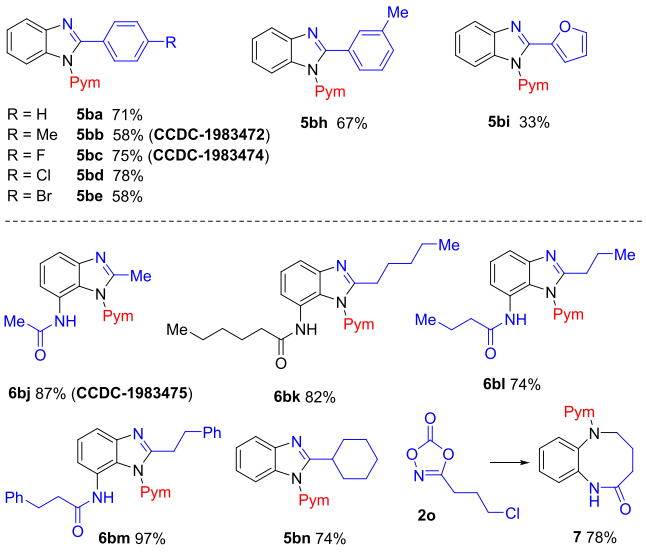
for why changing the solvent from HFIP to TFE changes the selectivity for product formation.

With the optimized conditions for the cyclized product **5** in hand, we then employed this method for the C−H amidation/cyclization of the aniline derivative **1b** with various aryl-substituted dioxazolones (Scheme 4). The reaction shows broad substrate scope for dioxazolone derivatives bearing halides, such as F, Cl, and Br. The heteroaryl substituted dioxazolone **2i** also gave **5bi**.

Scheme 4. Scope of Cyclized Products 5 and 6[a,b]

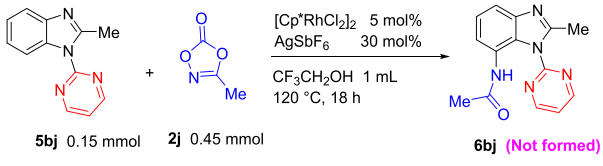


[a]Reaction conditions: **1b** (0.15 mmol), **2a** (0.45 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (30 mol %) in CF_3CH_2OH (1 mL) at 120 °C for 18 h. [b]Isolated yield.

When the alkyl-substituted dioxazolone **2j** was used for the C−H amidation/cyclization of **1b**, the double amidated and cyclized product **6bj** was selectively formed (Scheme 4). In the case of the cyclohexyl-substituted dioxazolone **2n**, the reaction stopped at monoamidation/cyclization stage to give **5bn** due to steric hindrance. The use of 3-(3-chloropropyl)-1,4,2-dioxazol-5-one (**2o**) gave **7**, the formation of which occurs through C−H amidation followed by a nucleophilic attack of the free NH to the alkyl chloride to form an eight-membered ring.

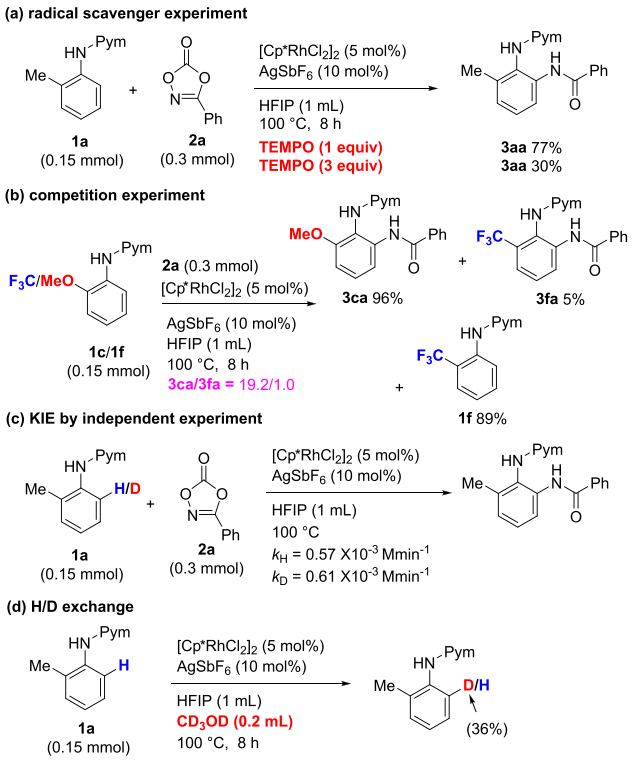
There are two possible paths for the formation of **6**: (i) **1b** undergoes diamidation followed by cyclization or (ii) **1b** undergoes monoamidation and cyclization to give benzimidazole **5** which undergoes further C−H amidation at the 7-position. To examine the operative reaction pathway, we examined the C−H amidation reaction of **5bj** with **2j** (Scheme 5). However, no C7 amidation took place, indicating that the diamidation of **1b** at both the 2- and 6-positions occurs, followed by cyclization to form product **6**. In the monoamidation product from alkyl-substituted dioxazolone, the presence of an electron-rich alkyl group decreases the electrophilic nature of a carbonyl group, which disfavors or slows down the nucleophilic attack of the NH group to the amide carbonyl, resulting in a pyrimidine group for directing the second C−H amidation.

Scheme 5. Control Experiment



Some control experiments were performed to gain some insights into the reaction mechanism (Scheme 6; see also SI for details). When the reaction was performed in the presence of a radical scavenger TEMPO (1 and 3 equiv), **3aa** was formed in 77% and 30% yields, respectively (Scheme 6a). This observation ruled out the involvement of free-radical species in the present reaction. Intermolecular competition experiments were carried out between the electron-rich aniline **1c** and the electron-deficient aniline **1f** with **2a** (Scheme 6b). The ratio of product distribution between **3ca** and **3fa** was 19.2/1, indicating that an electron-donating group facilitates the reaction. This finding suggests that a cationic rhodium species acts as an electrophile during the catalytic cycle.[13] To gain additional information regarding the initial rates of the reaction, reactions using substrate **1a** and [D]-**1a** were conducted, and the kinetic isotope effect $k_H/k_D = 0.93$ was determined (Scheme 8c; see Figure S1 in SI), which indicates that C−H activation is not involved in the rate-determining step. When **1a** was treated with HFIP/CD_3OD under the standard reaction conditions in the absence of **2a**, a 36% D-incorporation was observed only at the *ortho*-position, which indicates that C−H bond metalation is a reversible step (Scheme 6d).

Scheme 6. Control Experiments



Based on the experimental data obtained from control experiments and previous reports on Rh-catalyzed C−H bond amidation reactions reported thus far,[3d,5a,9a,l,n,o,3d,5a,9a,l,n,o,v−x,10h,15] a plausible catalytic cycle for the present amidation reaction is shown in Scheme 7. First, the reaction of $[Cp^*RhCl_2]_2$ with $AgSbF_6$ forms a cationic Rh(III)-complex **A**. The coordination of a $N(sp^2)$ atom of the aniline

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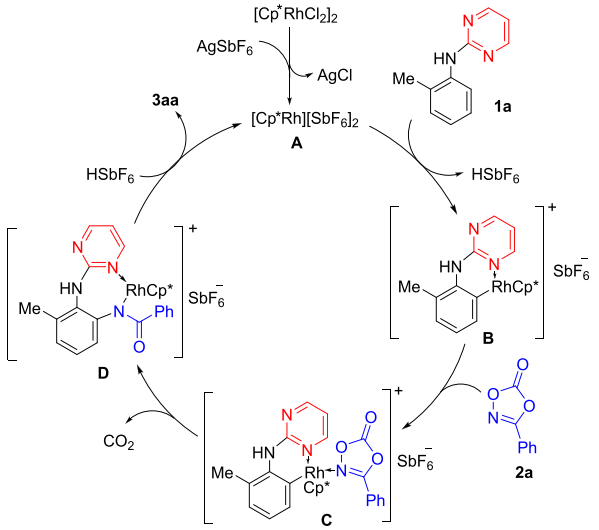
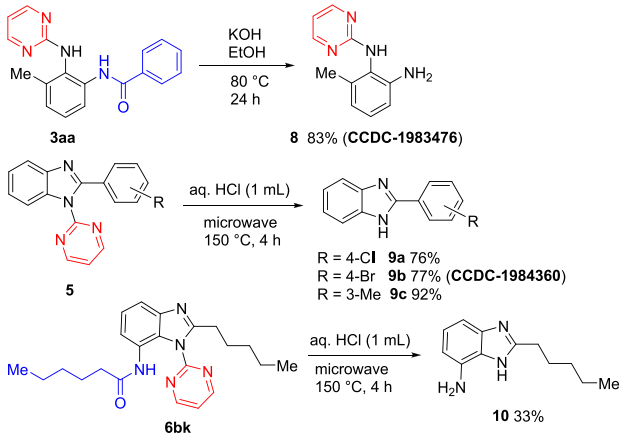
Scheme 7. Proposed Catalytic Cycle



substrate **1a** to **A** then undergoes reversible C−H activation to give the six-membered rhodacycle **B**. The coordination of dioxazolone **2a** to the rhodacycle **B** generates intermediate **C**, which, upon migratory insertion, forms complex **D** with the concomitant generation of CO_2. Complex **D** upon proto-derhodation in the presence of $HSbF_6$ affords the desired product **3aa** and with the regeneration of the cationic Rh(III) species **A**.

The chemoselective deprotection of amide **3aa** was accomplished by treating it with KOH in ethanol, which gives the free amine **8** (Scheme 8). Further, the treatment of **5bd**, **5be**, and **5bh** with aqueous HCl provided the free benzimidazoles **9a**, **9b**, and **9c**. The treatment of **6bk** with aqueous HCl results in the deprotection of both the amide and the pyrimidinyl group to give **10**.

Scheme 8. Chemoselective Deprotection



In summary, we report the Rh(III)-catalyzed C−H bond amidation of aniline derivatives with dioxazolones using a pyrimidine directing group. The reaction shows a tolerance of various functional groups that are attached to aniline derivatives as well as dioxazolones. The product distribution between 1,2-diaminobenzene derivatives or benzimidazole derivatives is controlled by the nature of solvents used. Notably, the chemoselective deprotection of the amide and the pyrimidinyl group of the amidated products afforded 1, 2-diaminobenzene and benzimidazole derivatives which are important scaffolds in synthetic chemistry. Preliminary mechanistic studies ruled out the involvement of a free-radical species in the reaction. A deuterium scrambling experiment indicated that C−H bond metalation is a reversible process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01126.

Experimental procedures and characterization data of all new compounds (PDF)

Accession Codes

CCDC 1961840, 1983469−1983472, 1983474−1983476, and 1984360 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Naoto Chatani − *Department of Applied Chemistry, Faculty of Engineering, Suita, Osaka 565-0871, Japan;* orcid.org/0000-0001-8330-7478; Email: chatani@chem.eng.osaka-u.ac.jp

Author

Shrikant M. Khake − *Department of Applied Chemistry, Faculty of Engineering, Suita, Osaka 565-0871, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01126

Notes

The authors declare no competing financial interest.

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