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To be cited as: *ChemSusChem* 10.1002/cssc.201801287

Link to VoR: http://dx.doi.org/10.1002/cssc.201801287

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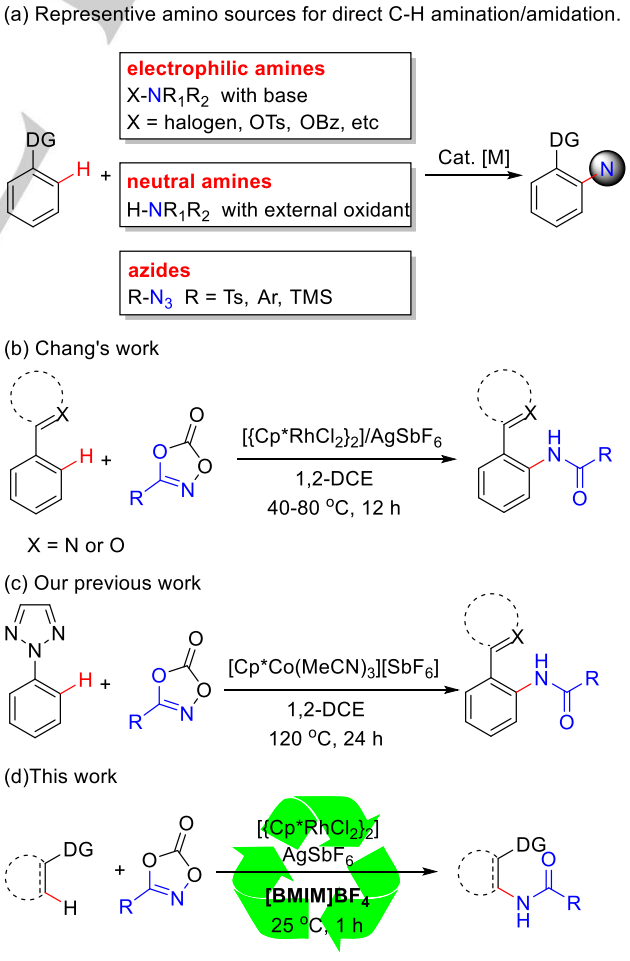
Cp*Rh(III)/Ionic Liquid as a Highly Efficient and Recyclable Catalytic Media for C-H Amidation

Qiang Ma[+], Xinling Yu[+], Ruizhi Lai, Songyang Lv, Weiyang Dai, Chen Zhang, Xiaolong Wang, Qiantao Wang* and Yong Wu*

Abstract: A novel protocol of Cp*Rh(III)-catalyzed direct C-H amidation in ionic liquid is established. Both C(sp^2)-H bonds of (hetero)-arenes, alkenes and unactivated C(sp^3)-H bonds can be easily amidated with high functional group tolerance and excellent yields under this condition. Particularly, using Cp*Rh(III)/[BMIM]BF_4 as the green and recyclable media is environmentally benign due to its peculiar characteristics such as (i) reuse of an expensive rhodium catalytic system, (ii) avoiding the use of highly toxic organic solvents, (iii) mild reaction conditions as well as short reaction time.

Nitrogen-containing molecules are important for natural products, pharmaceuticals and agrochemicals.[1] For this reason, many research efforts have been directed towards the construction of carbon-nitrogen bonds.[2] In the past few years, transition-metal-catalyzed C-H bond functionalization of the unreactive C-H bonds has been established as a potent tool to generate a wide range of new carbon-carbon, carbon-heteroatom bonds and heterocyclic scaffolds by the use of suitable Lewis basic directing group.[3] Generally, the directing group possesses a lone pair which coordinates to the transition-metal catalyst to direct *ortho* functionalization via a five- or six-membered metallacycle thus enabling regiospecific introduction of the other group. Along this line, various coupling partners have been used as efficient aminating or amidating sources to construct carbon-nitrogen bonds. And these nitrogen sources could be summarized into three categories: electrophilic amines,[4] neutral amines[5] and azides (Scheme 1a).[6] Compared with traditional coupling reactions, like Ullmann and Buchwald-Hartwig couplings,[2a-c] the major advantage of C-H amination or amidation is avoiding the prefunctionalization of the substrates, which greatly simplifies the synthetic procedures. Dioxazolone was applied as a new type of amidating reagent firstly by Chang (Scheme 1b).[7] Carbon dioxide is the only byproduct generated during the reaction. Consequently, this user-friendly reagent has come to the fore for the high atomic economy and safety.[8]

Solvent is generally the largest component in most reactions and plays an important role in organic synthesis. Many low polar but toxic solvents, for example 1,2-dichloroethane (DCE),[3m,4b,4d,8a-g] 1,2-dichlorobenzene (DCB),[3l,9] tetrahydrofuran (THF),[4c,10] chlorobenzene (PhCl),[11] xylene[5b,12] are the most common solvents for C-H amination. Therefore, replacement of those harmful organic solvents with an eco-friendly medium is one of the major focus of green chemistry. In this regard, polyethylene glycol and water were recently investigated and successfully employed as solvents for the transformation.[13] But their applications are restricted by their low solubility of many lipophilic organic reagents and catalysts. Ionic liquids (ILs) generally consisting of an organic cation (such as an imidazolium or pyridinium core) and a weakly nucleophilic anion, have drawn the great attention of scientific and industrial communities due to its outstanding merits of low toxicity, nonflammability, recyclability, excellent chemical and thermal stability, negligible vapor pressure as well as good solubility of organic and inorganic compounds.[14] Since these liquids are able to dissolve several transition metal complexes, in recent years, they have often been employed in several catalytic organic reactions to enhance reaction rates and selectivity. [15]



Scheme 1. Strategies for direct C–H amidation.

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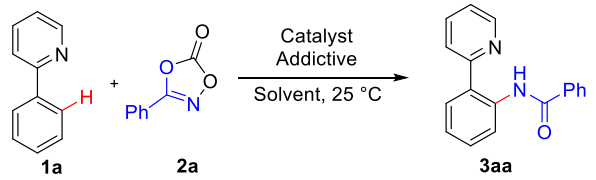
Supporting information for this article can be found under:.
DOI: 10.1002/anie.2016XXXXX

However, as far as we know, it is rarely employed for transition-metal-catalyzed C–H activation.[16] Our group previously reported 1,2,3-triazole-assisted C−H amidation by cobalt(III) catalysis (Scheme 1c).[8k] In order to develop more efficient and selective C−N bond-forming reactions, we herein report a rapid and green method for the amidation of various C(sp^2)−H and C(sp^3)−H bonds by using Cp*Rh(III)/ionic liquid as a highly efficient and recyclable catalytic media (Scheme 1d).

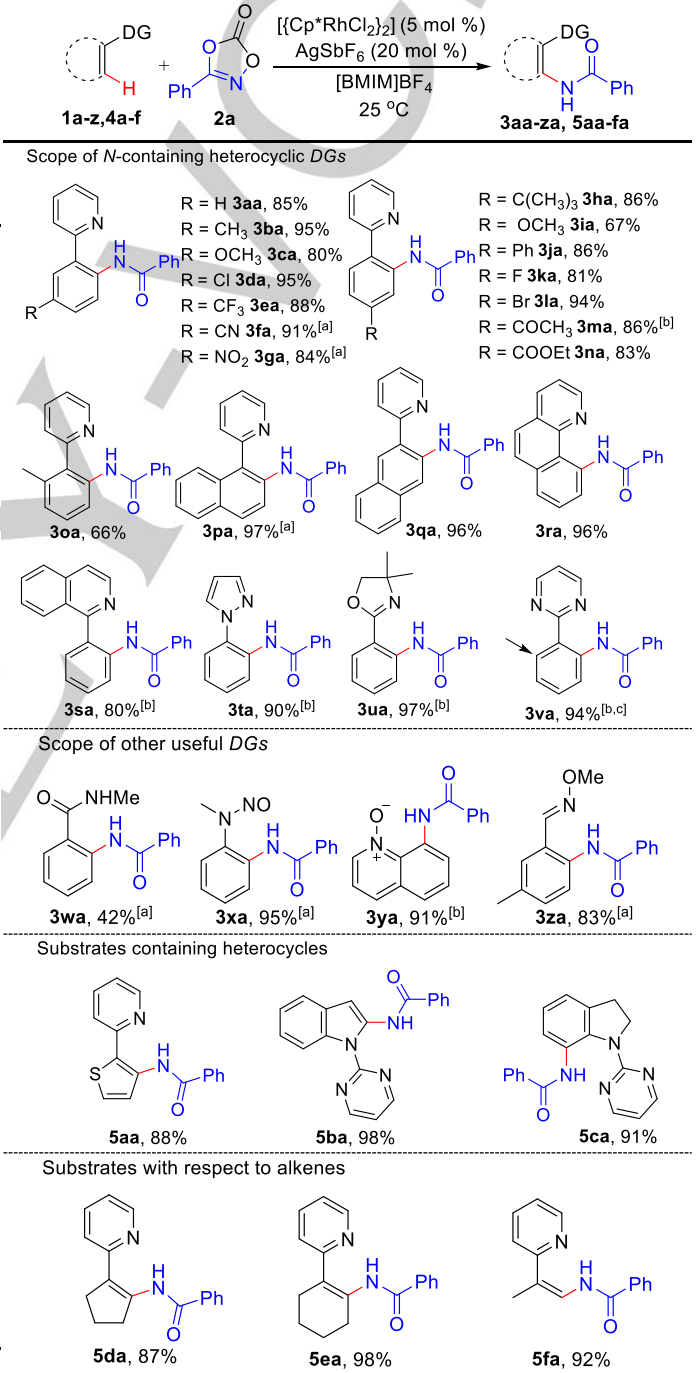
At the outset of our studies, we explored the feasibility of the envisioned Rh(III)-catalyzed C-H amidation of 2-phenylpyridine (**1a**) with 3-phenyl-1,4,2-dioxazol-5-one (**2a**). To our surprise, using [{Cp*$RhCl_2$}$_2$]/$AgSbF_6$ as a catalyst system, coupling occurred in 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) at room temperature afforded the product **3aa** in 85% yield (Table 1, entry 1). To optimize the yield of the orthoamidated derivative, we screened several parameters, and the results were shown in Table 1. It was found that transition metals, such as ruthenium,[6b,6d,13d] palladium[3a,3e,3q,11a] and cobalt complexes,[3i,8a,8b,8g,8h] which are known to be effective in direct C-H bond functionalization, were intolerable in this transformation (entries 4-6). Control experiment also confirmed that the rhodium-catalyst was essential for this reaction (entry 7).

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (5 mol %)	Addictive (20 mol %)	Solvent	Time (h)	Yield [%][b]
1	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]BF_4	12	85
2	$RhCl_3·3H_2O$	$AgSbF_6$	[BMIM]BF_4	12	-
3	$Rh_2(OAc)_4$	$AgSbF_6$	[BMIM]BF_4	12	-
4	[{Ru(*p*-cymene)Cl_2}$_2$]	$AgSbF_6$	[BMIM]BF_4	12	< 5
5	$Pd(OAc)_2$	$AgSbF_6$	[BMIM]BF_4	12	-
6	[Cp*Co(CO)I_2]	$AgSbF_6$	[BMIM]BF_4	12	-
7	-	$AgSbF_6$	[BMIM]BF_4	12	-
8	[{Cp*$RhCl_2$}$_2$]	-	[BMIM]BF_4	12	-
9	[{Cp*$RhCl_2$}$_2$]	AgOAc	[BMIM]BF_4	12	73
10	[{Cp*$RhCl_2$}$_2$]	$AgNTf_2$	[BMIM]BF_4	12	81
11	[{Cp*$RhCl_2$}$_2$]	AgOTf	[BMIM]BF_4	12	77
12	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]NTf_2	12	84
13	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]PF_6	12	78
14	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]OTf	12	39
15	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BDMIM]BF_4	12	81
16	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BPy]BF_4	12	-
17	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BTMG]BF_4	12	-
18	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]BF_4	5	84
19[c]	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]BF_4	6	83
20[d]	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]BF_4	4	85
21[e]	[{Cp*$RhCl_2$}$_2$]	$AgSbF_6$	[BMIM]BF_4	1	85

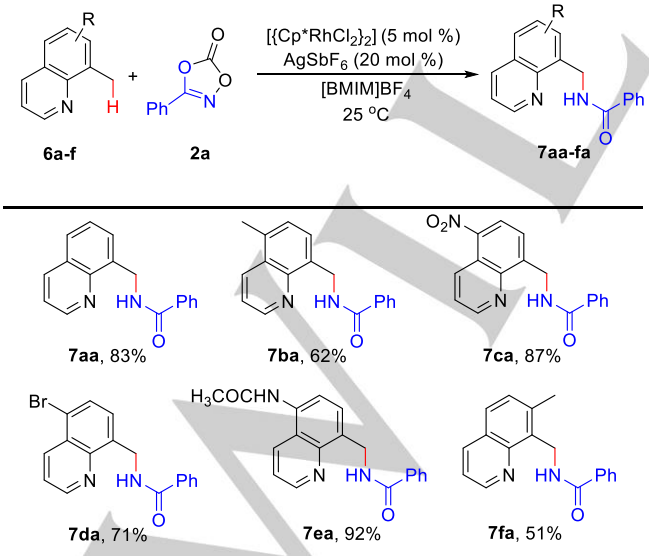
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), addictive (20 mol %) and catalyst (5 mol %) in solvent (0.1 M of **1a**) were used at 25 °C under air. [b] Yield of product isolated after column chromatography. [c] 0.05 M of **1a**. [d] 0.25 M of **1a**. [e] 0.5 M of **1a**. Cp* = pentamethylcyclopentadienyl; [BMIM] = 1-butyl-3-methylimidazolium; [BDMIM] = 1-butyl-2,3-dimethylimidazolium; [BPy] = 1-butylpyridinium; [BTMG] = 2-butyl-1,1,3,3-tetramethylguanidinium.



Scheme 2. Reaction scope of C(sp^2)−H Amidation. Reaction conditions: **1** or **4** (0.2 mmol), **2a** (0.24 mmol), [{Cp*$RhCl_2$}$_2$] (5 mol %), and $AgSbF_6$ (20 mol %) in [BMIM]BF_4 (0.4 mL) were used at 25 °C for 1 h under air. Yield is that of product isolated after column chromatography. [a] Reaction was performed for 5 h. [b] Reaction was performed for 3 h. [c] **2a** (0.48 mmol).

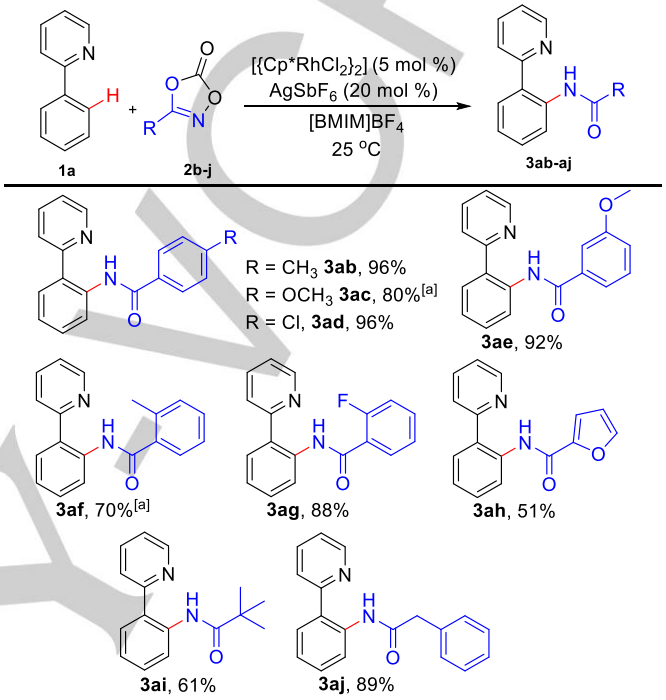
Furthermore, $AgSbF_6$ could promote this reaction and other silver salts, such as AgOAc, $AgNTf_2$ and AgOTf also displayed some activity, but proved to be less effective (entries 8-11). Then we focused our attention on the solvent. $[BMIM]BF_4$, $[BMIM]PF_6$, $[BMIM]NTf_2$, 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ($[BDMIM]BF_4$) could afford the product in good to excellent yield, but other type of ILs were ineffectual (entries 12-17). $[BMIM]BF_4$ was chosen as the best solvent. Based on the above results, we then investigated the concentration of the substrates. It was surprising that the reaction rate was greatly improved by increasing the concentration of the substrates (entries 18-21). And the reaction time could be shortened to 1 hour with a 0.5 mol/L concentration of **1a.**

With the optimized conditions in hand, we set out to explore the feasibility and generality of this coupling system (Scheme 2). A wide range of phenylpyridine derivatives with various electron-donating (**1b**, **1c**, **1h**, **1i**) and electron-withdrawing (**1d-g, 1j-n**) groups on different positions of the phenyl ring were well tolerated. It needs to be mentioned that amidation only occurred at the *ortho* position relative to the 2-pyridyl moiety in the presence of other potential directing groups such as ketone and ester (**1m**, **1n**). Besides pyridine, other *N*-containing heterocycles, such as quinoline (**1s**), pyrazole (**1t**), oxazole (**1u**) and pyrimidine (**1v)** could also act as viable chelating groups in this amidation reaction, providing the corresponding products in 80% to 97% yields. For instance, 1-phenyl-1*H*-pyrazole (**1t**) gave the desired product **3ta** in 90% yield by prolonging reaction time to 3 hours. We were also interested in the replacement of *N*-heterocycles with other more synthetically useful moieties. Commonly used amide (**1w**), *N*-nitrosoaniline (**1x**), *N*-oxide (**1y**) and ketoxime (**1z**) were all found to facilitate *ortho*-selectivity efficiently (**3wa−za**), and only monoamidation product was observed. To further evaluate the scope of this process, heteroarenes such as thiophene (**4a**), indole (**4b**) and indoline (**4c**) were also found to be suitable substrates and afforded the products in great yields. More importantly, this reaction was not limited to direct (hetero)arenes functionalizations, alkenes were identified as amenable substrates as well, delivering the desired products in high yields (**5da-fa**).

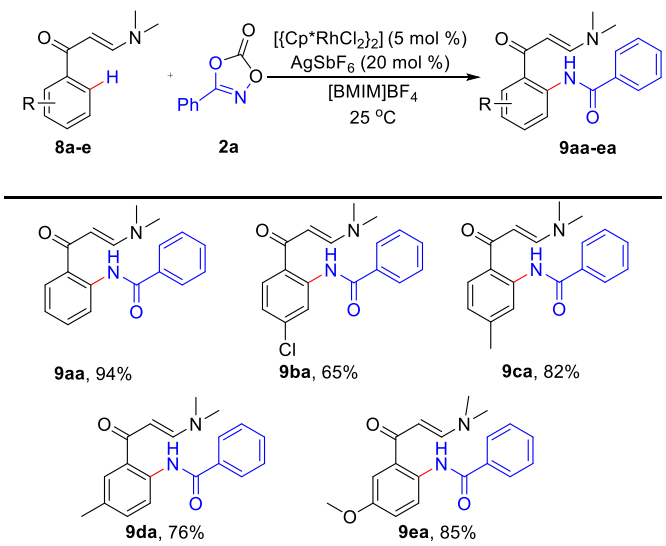


Scheme 3. Reaction scope of C(sp^3)–H Amidation. Reaction conditions: **6** (0.2 mmol), **2a** (0.24 mmol), $[\{Cp^*RhCl_2\}_2]$ (5 mol %), and $AgSbF_6$ (20 mol %) in $[BMIM]BF_4$ (0.4 mL) were used at 25 °C for 2 h under air. Yield is that of product isolated after column chromatography.

Transformations of C(sp^2)-H bonds are favored by precoordination of the arene π system, and the resulting aryl-metal bonds are typically stronger than the corresponding alkyl-metal bonds. Whereas, metal-catalyzed functionalizations of unactivated C(sp^3)-H bonds are considered to be particularly challenging for both kinetic and thermodynamic reasons.[17] Nevertheless, the amidation of 8-methylquinoline derivatives (**6a-f**) proceeded smoothly under the standard condition, and the corresponding amidation products **7aa-fa** were isolated in 51-



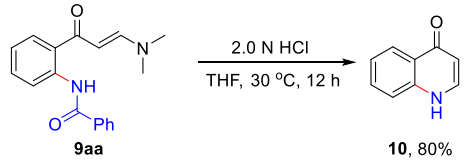
Scheme 4. Reaction scope of dioxazolones. Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $[\{Cp^*RhCl_2\}_2]$ (5 mol %), and $AgSbF_6$ (20 mol %) in $[BMIM]BF_4$ (0.4 mL) were used at 25 °C for 1 h under air. Yield is that of product isolated after column chromatography. [a] Reaction was performed for 3 h.



Scheme 5. Reaction scope of enaminones. Reaction conditions: **9** (0.2 mmol), **2a** (0.24 mmol), $[\{Cp^*RhCl_2\}_2]$ (5 mol %), and $AgSbF_6$ (20 mol %) in $[BMIM]BF_4$ (0.4 mL) were used at 25 °C for 1 h under air. Yield is that of product isolated after column chromatography.

92% yields by prolonging reaction time to 2 hours (Scheme 3). Additionally, the scope of dioxazolones was examined under the established conditions (Scheme 4). Amidating reagents bearing various electron-donating (**2b**, **2c**, **2e,** **2f**) and electron-withdrawing groups (**2d**, **2g**) on the different positions of the phenyl ring were fully tolerated. Heterocycle-containing dioxazolone (**2h**) was also smoothly amidated by this catalytic system. In addition, dioxazolones having alkyl substituents at the 3-position were highly facile to afford the desired products (**3ai**, **3aj**) in moderate to good yields ranging from 61% to 89%.

The resulting amidation derivatives are not only common subunits in many molecules, but also served as important intermediates of synthesis many heterocycle structures. The quinolin-4(1*H*)-one moiety has been shown to exhibit a broad spectrum of pharmacological and biological activities such as antibiotic,[18] antidiabetic,[19] antimalarial,[20] anticancer,[21] and antiviral properties.[22] In 2017, a new two-stage synthetic strategy to access 4-quinolone derivatives using enaminone as a weakly coordinating directing group has been developed by Li and Zhu respectively.[8e,8l] Consequently, we were curious whether similar directing effects can also be displayed under our reaction system. Fortunately, a number of enaminones were successfully employed under the above catalytic system (Scheme 5). The representative hydrolysis−cyclization of the amidated product (**9aa**) with 2.0 N hydrochloric acid solutions smoothly gave the quinolone derivative **10** in 80% yield (Scheme 6).



Scheme 6. Synthesis of NH quinolone.

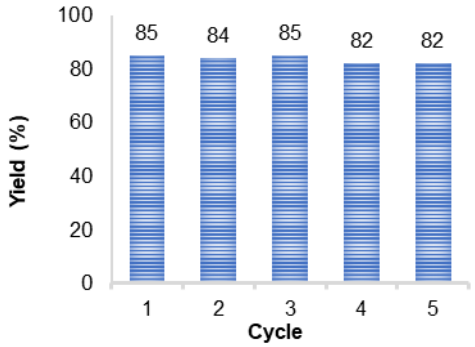
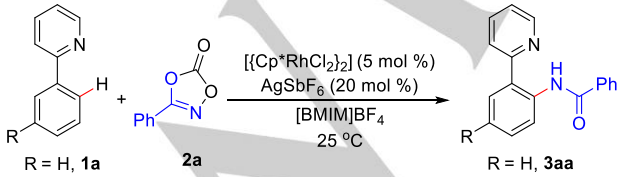


Figure 1. Recyclability of Cp*Rh(III)/[BMIM]BF_4 in the C-H amidation between phenylpyridine **1a** and dioxazolone **2a**.

Table 2. Recyclability of Cp*Rh(III)/[BMIM]BF_4 in the C-H amidation between dioxazolone **2a** and phenylpyridine **1a** or *m*-methylphenylpyridine **1b**.[a]

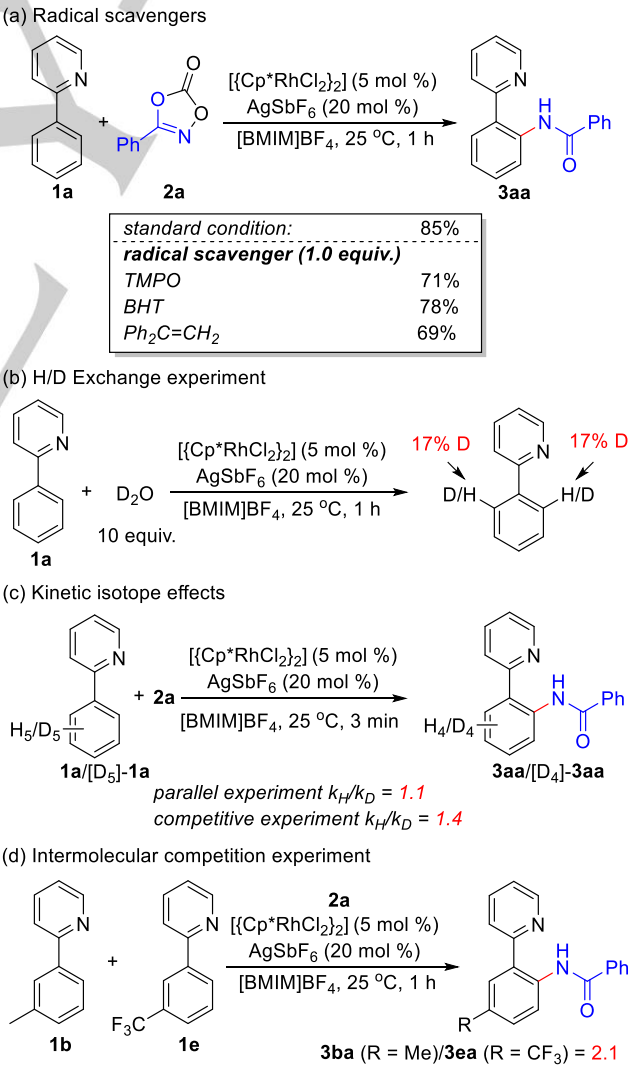


Cycle	Phenylpyridine	Yield [%]
1	**1a**	85
2	**1b**	94
3	**1a**	85

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), [{Cp*RhCl$_2$}$_2$] (5 mol %), and $AgSbF_6$ (20 mol %) in [BMIM]BF_4 (0.4 mL) were used at 25 °C for 1 h under air. Recycling was performed as stated in the main text.

To investigate the reusability of the catalyst and solvent, the recycling of the Cp*Rh(III)/[BMIM]BF_4 system was investigated under the optimized conditions (Figure 1). After the reaction was complete, diethyl ether was added and shaken. The upper layer of diethyl ether contains a product mixture directly used for purification and the lower layer contains [BMIM]BF_4 with a catalytic system. The Cp*Rh(III)/[BMIM]BF_4 medium was further subjected to vacuum to remove the rest of diethyl ether before it was reused in subsequent reactions. It was observed that this system was utilized repeatedly five times without much loss in its activity and the slight decrease in yield might be lost during workup.

To further verify the recovery and practicability of this catalyst system, we next decided to carry out recycling experiments in which substrate changed after each catalytic run. Thus, after setting up a reaction between 2-phenylpyridine (**1a**) and dioxazolone **2a** (Table 2, cycle 1), Cp*Rh(III)/[BMIM]BF_4 system were recovered as stated in the previous paragraph. The so-recycled material was then treated with *m*-methylphenylpyridine (**1b**) and dioxazolone **2a**, being the mixture vigorously stirred for

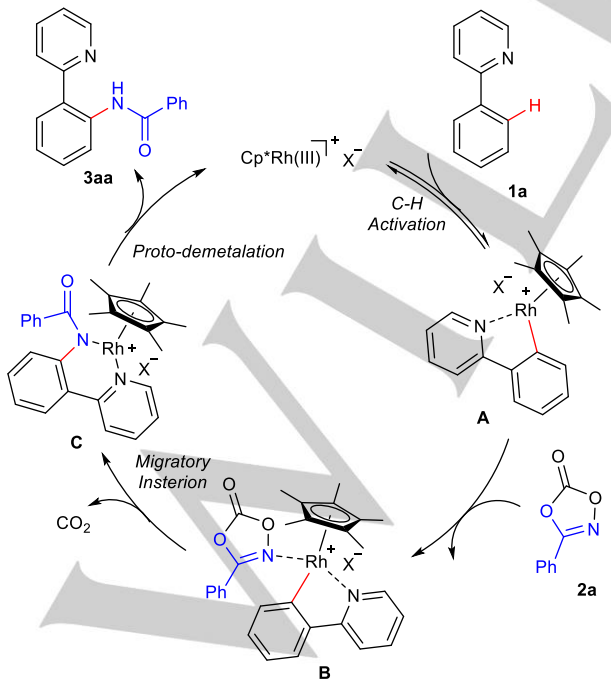


Scheme 7. Mechanistic findings.

1 hour, to render amidated product **3ba** in excellent yield (cycle 2), without any product **3aa** coming from the previous run. After recycling Cp*Rh(III)/[BMIM]BF_4 system from the second cycle, a third reaction could be run within the same medium employing 2-phenylpyridine (**2a**, cycle 3). Gratifyingly, the desired amide **3aa** was produced with comparable selectivity as those of Figure 1, entry 3, and Table 2, entry 1, which refer to the same product. And **3ba** was not detected as a contaminant.

We next conducted preliminary mechanistic studies to gain insight into the present reactions (Scheme 7). First, C−H functionalizations performed in the presence of typical radical scavengers gave the amidated product **3aa** with only a minor loss in catalytic activity, which indicated that a radical-based mechanism is unlikely (Scheme 7a). Then, H/D exchange experiment has been performed. ^{1}H NMR analysis of the recovered (96% yield) 2-phenylpyridine revealed slight H/D exchange (17% D) at both *ortho* positions, and no exchange at any other position has been observed, which indicated that the C-H bond cleavage is reversible (Scheme 7b). What's more, the parallel reactions (k_H/k_D = 1.1) and intermolecular competition (k_H/k_D = 1.4) using **1a** and [D_5]-**1a** consistently gave a relatively small value, which indicated that cleavage of the C−H bond is likely not involved with the ratedetermining step (Scheme 7c). Moreover, intermolecular competition experiments with differently substituted arenes revealed that an electronrich substrate showed slightly higher reactivity (Scheme 7d).

Based on the mechanistic studies and the relevant reports,[7a,8a,8d,8f,8h,23] a plausible mechanistic pathway is depicted in Scheme 8 with **1a** and **2a** as model substrates. A cationic [Cp*Rh(III)] complex is generated in the presence of $AgSbF_6$ in situ as an active catalyst, which is followed by C-H activation to give the corresponding five-membered rhodacycle intermediate **A**. Coordination of **2a** leads to intermediate **B**, which may undergo release of CO_2 followed by an intermolecular migratory insertion to furnish six-membered intermediate **C**. Finally, *proto*-demetalation of **C** delivers the orthoaminated product **3aa** and regenerate the rhodiumacycle species.



Scheme 8. Proposed catalytic cycle.

In summary, we have developed the first general procedure for direct C-H amidation under ambient reaction conditions using Cp*Rh(III)/[BMIM]BF_4 as a highly efficient, green and sustainable system. Various kinds of *DG*-containing substrates, including synthetically useful *N*-containing hetereocycles, amide, ketoxime, and *N*-oxide were selectively amidated with high regio-stereoselectivity and excellent functional group compatibility. Specifically, this strategy allows direct amidation of both C(sp^2)−H and inert C(sp^3)−H bonds to yield monoamidation products without additionally heating and in shorter reaction time than in organic solvents. A range of quinolone precursors can be easily synthetized by this newly developed method. Most importantly, this system is very easy to handle and can be recycled and reused for at least four runs without showing a significant loss of activity. We believe that this facile and environmentally friendly protocol has opened up the applications of ionic liquids in C–H bond activation.

Experimental Section

General procedure for C−H amidation (3aa as an example)

To a test tube with a magnetic stir bar was added 2-phenyl pyridine (**1a**, 31.0 mg, 0.2 mmol, 1.0 equiv), 3-phenyl-1,4,2-dioxazol-5-one (**2a**, 39.2 mg, 0.24 mmol, 1.2 equiv), [{Cp*$RhCl_2$}$_2$] (6.9 mg, 0.01 mmol, 5 mmol %), $AgSbF_6$ (13.7 mg, 0.04 mmol, 20 mmol %) and [BMIM]BF_4 (0.4 mL) under atmospheric conditions for 1 hour. Afterward, the mixture was extracted with diethyl ether (5 × 1 mL). The organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (gradient of Petroleum ether/EtOAc) to give the desired product **3aa** (46.6 mg, 85%) as a white solid.

Acknowledgements

We are grateful for support from the National Natural Science Foundation of China (NSFC) (grant number 81573286, 81773577 & 81602954) and the Fundamental Research Funds for the Central Universities (grant number YJ201561).

Keywords: C-H amidation • dioxazolones • directing groups • rhodium • ionic liquids

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10.1002/cssc.201801287

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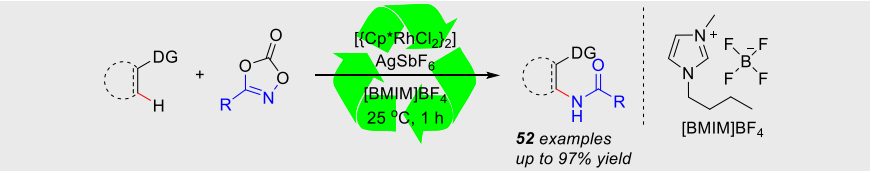

Qiang Ma[+], Xinling Yu[+], Ruizhi Lai, Songyang Lv, Weiyang Dai, Chen Zhang, Xiaolong Wang, Qiantao Wang and Yong Wu**

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Cp*Rh(III)/Ionic liquid as a Highly Efficient and Recyclable Catalytic Media for C-H Amidation

Cp*Rh(III)/[BMIM]BF_4 medium was used as a highly efficient, green and sustainable system for both C(sp^2)-H and C(sp^3)-H amidation under ambient reaction conditions. Various kinds of *DG*-containing substrates were selectively amidated with high regio-stereoselectivity and excellent functional group compatibility. Most importantly, this system is very easy to handle and can be recycled and reused for at least four runs without showing a significant loss of activity.