

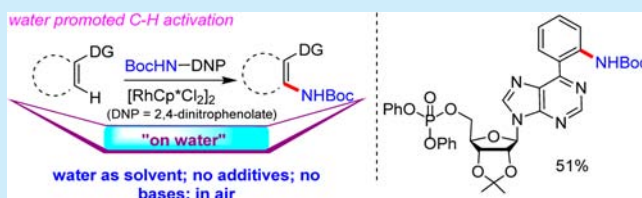
[RhCp*Cl₂]₂-Catalyzed Directed *N*-Boc Amidation of Arenes “on Water”

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S Supporting Information

ABSTRACT: Rhodium(III) catalysis “on water” is effective for directed C–H amidation of arenes. The catalytic process is promoted by OH groups present on the hydrophobic water surface and is inefficient in all (most) common organic solvents investigated so far. In the presence of easily prepared *tert*-butyl 2,4-dinitrophenoxycarbamate, a new and stable nitrene source, the “on water” reaction can efficiently provide the desired *N*-Boc-aminated products with good functional group tolerance.



Water is the most ubiquitous solvent in biological systems, and being abundant, nontoxic, nonflammable, and environmentally benign, it could be regarded as the *solvent of Nature*.¹ In comparison with common organic solvents, the unique and unusual physical and chemical properties of water, such as amphiphilicity and hydrogen-bonding capability, can deliberately influence the selectivity and reactivity of chemicals.² Although the role of water is often unclear, many explanations, such as stabilization of transition states by hydrophobic hydration,^{3a–d} hydrogen bonding,^{3e,f} or hydrophobic interactions^{3g} and high cohesive energy density of water,^{3h} are available to explain enhanced rates of reaction in aqueous media. Despite limited aqueous solubility of organic reactants, water has been widely used as a solvent in organic reactions such as pericyclic reactions, multicomponent reactions, Wittig reaction, and olefin metathesis.¹ Aqueous heterogeneous reactions have been reinvestigated since Sharpless and co-workers reported a number of “on water” reactions.⁴ It has been postulated that the hydrophobic surface structures of water contain “dangling OH groups” (OH groups which are not involved in intermolecular hydrogen bonding) at the reactant–water interfaces^{5–7} and stabilize the transition states by hydrogen-bonding interactions to accelerate reaction rates.^{4a,b,5}

In recent years, direct metal-catalyzed C–H functionalization using water as a solvent has emerged as a research field of immense interest.^{1f,8} The difficulties associated with such reactions are the stability of the metal catalysts and ligands in water. Metal catalysts may form complexes with water molecules, and ligands such as phosphines are not tolerated in water.^{1f} Therefore, the scope for selection of suitable reactants and catalysts is limited.^{1f} Despite these challenges, metal-catalyzed C–H activation/C–C, C–halogen, or C–O bond formation methods have been developed for use in aqueous systems.⁸ However, C–H activation/C–N bond formation protocols with water as a solvent have not been developed so far, even though it is one of most efficient methods for the preparation of aminated

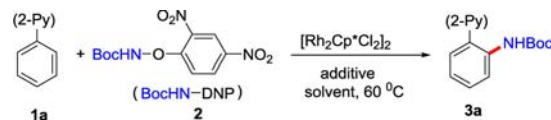
compounds.⁹ As a part of our ongoing research on C–H amination reactions,¹⁰ herein we report the first Rh(III)-catalyzed, directed sp² C–H activation/C–N bond formation “on water” under neutral and nonoxidative conditions. This process uses the easily accessible and bench-stable *tert*-butyl 2,4-dinitrophenoxycarbamate (**2**)¹¹ as a nitrene source. Water plays a unique role, including two key functions: promoting the C–H activation and assisting the absorption of the acidic side products. The removal of the acidic side products and activation of metal catalyst are generally achieved by adding bases and silver salts as additives in organic solvents.^{9,12}

We commenced our investigation by the reaction of 2-phenylpyridine (**1a**) and the nitrene source **2** in the presence of 4 mol % of [RhCp*Cl₂]₂ “on water” at 60 °C and found that the reaction proceeded smoothly to provide the desired *ortho* *N*-Boc-aminated product (**3a**) with 88% conversion (82% isolated yield, Table 1, entry 1). It should be noted that the reaction provided 70% conversion after only 10 min of reaction time (entry 2). In the presence of a decreased amount of catalyst, a longer reaction time was required to achieve acceptable levels of conversion (entries 3 and 4). Additives such as AgSbF₆ (entry 5) and NaHCO₃ (entry 6) failed to increase the yield. The rhodium(III) catalyst was found to be ineffective for C–H bond amidation in common organic solvents such as ClCH₂CH₂Cl, toluene, CH₃CN, THF, DMSO, *i*-PrOH, hexane, and DMF (entries 7–14). In all these cases, the observed conversions were less than 11%. Additionally, the reactions with a catalytic or excess amount of water as an additive in organic solvents failed (entries 15–18). Finally, the reaction attempted without solvent was also inefficient (entry 19).

With these optimized conditions, we explored the substrate scope for the C–H amidation “on water” (Scheme 1). Various

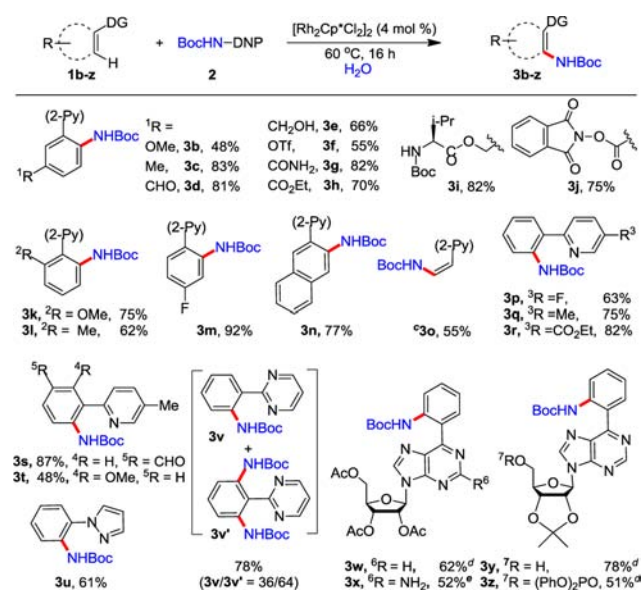
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Table 1. Optimization of Reaction Conditions^a


entry	catalyst loading (mol %)	additive	solvent	time	conv ^b (%)
1	4		H ₂ O	3 h	88 (82)
2	4		H ₂ O	10 min	70
3	2		H ₂ O	16 h	83
4	1		H ₂ O	16 h	65
5	4	AgSbF ₆ (8 mol %)	H ₂ O	3 h	85
6	4	NaHCO ₃ (1.0 equiv)	H ₂ O	3 h	90
7–12	4		organic ^c	3 h	<5
13	4		hexane	3 h	8
14	4		DMF	3 h	11
15–17	4	H ₂ O ^d	ClCH ₂ CH ₂ Cl	3 h	<5
18	4	H ₂ O (10 equiv)	iPrOH	3 h	8
19	4			16 h	25

^a1a (0.15 mmol), 2 (0.18 mmol), [RhCp*Cl₂]₂ (4 mol %), and additive in solvent (1 mL). ^bConversion was calculated based on crude ¹H NMR; isolated yield in parentheses. ^cClCH₂CH₂Cl, PhMe, CH₃CN, THF, DMSO, or iPrOH was used as solvent. ^d0.2, 1.0, or 10 equiv of H₂O was used as additive.

Scheme 1. Substrate Scope^{a,b}

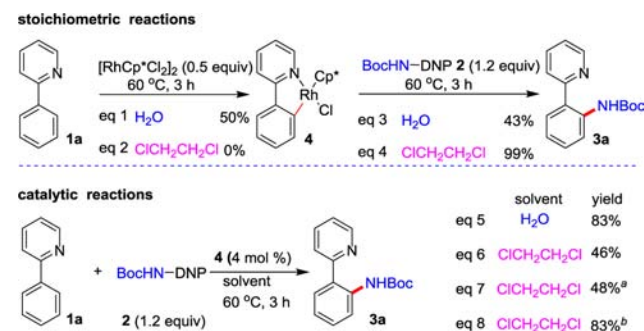
^a1 (0.2 mmol), 2 (0.24 mmol), [RhCp*Cl₂]₂ (4 mol %), and H₂O (1 mL) were stirred at 60 °C for 16 h. ^bIsolated yield. ^cReaction time 1 h. ^d1 (0.15 mmol), 2 (0.30 mmol), [RhCp*Cl₂]₂ (4 mol %), and H₂O (1 mL) were stirred at 60 °C for 24 h. ^eThe reaction was performed at 80 °C with 8 mol % of catalyst and 3.0 equiv of starting material 2.

substrates with substituents in the 2-phenyl ring (1b–m) readily underwent reaction with the nitrene source 2 to give the desired products in good to high yield. For example, *meta*-substituted 2-phenylpyridines which contain functional groups commonly used in organic synthesis, such as aldehyde, primary alcohol, O-Tf, primary amide, and ester, were also converted to the desired products (3d–h) with good yield. Furthermore, substrates containing a Boc-protected amino acid ester (3i) and a weak N–O bond (3j) were also tolerated, suggesting that the reaction conditions are mild and highly selective. Likewise, compounds with *ortho*- and *para*-substituents in the phenyl ring were successfully *N*-Boc aminated (3k–m). Substrates such as 2-

pyridynaphthalene and 2-vinylpyridine could also be converted to the desired products 3n and 3o, respectively. Similarly, substrates bearing pyridine ring substituents such as fluoro, methyl, and ester also gave the *N*-Boc-aminated products (3p–t) in good yield. Furthermore, substrates with directing groups other than pyridine, such as 1-phenyl-1*H*-pyrazole, were tolerated to give the desired product (3u) in good yield, and 2-phenylpyrimidine provided both the mono- and di-*N*-Boc-amino products 3v and 3v' in a 64:36 ratio, respectively.

Inspired by the high selectivity and functional group tolerance of this reaction, we further intended to examine some bioactive substrates such as 6-arylpyriminyl nucleosides which are known for their anti-HCV, antimycobacterial, and cytostatic activities.¹³ The reaction proceeded smoothly with such substrates, providing the mono-*N*-Boc-amino products in good yield. Functional groups such as hydroxyl, phosphate ester, and amino (3w–z) were also well tolerated.

To understand the unique role of water, we performed a series of parallel experiments “on water” and in 1,2-dichloroethane (ClCH₂CH₂Cl) (Scheme 2). The five-membered rhodocyclic compound (4) can be prepared in 50% yield “on water” (eq 1) and was able to catalyze the C–H amidation efficiently “on water” (eq 5), while in the case of ClCH₂CH₂Cl no product formation was observed (eq 2). This observation suggests that

Scheme 2. Reactions “on Water” or in ClCH₂CH₂Cl

^aReaction time 12 h. ^bAdditional NaHCO₃ (1.0 equiv) was used.

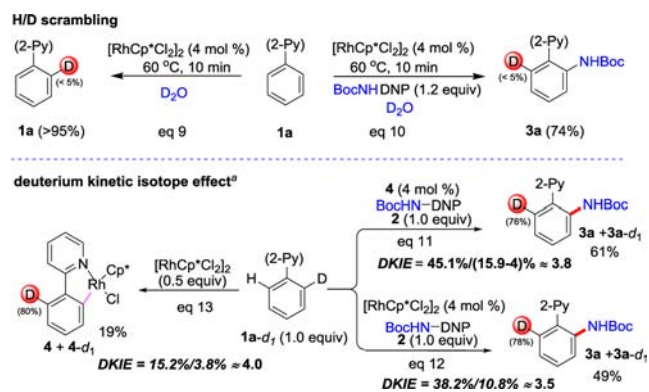
complex **4** is involved in the catalytic cycle and is generated through C–H activation with the assistance of water, but the organic solvent $\text{ClCH}_2\text{CH}_2\text{Cl}$ failed to assist the process. Next, we treated complex **4** “on water” with 1.2 equiv of the nitrene source **2** at 60 °C for 3 h and observed 43% formation of desired product **3a** “on water” but, surprisingly, 99% in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (eqs 3 and 4). The higher yield obtained in $\text{ClCH}_2\text{CH}_2\text{Cl}$ than “on water” may possibly be due to the side product 2,4-dinitrophenol, which could act as an acid ($\text{p}K_{\text{a}} = 4.09$).¹⁴ In this regard, 2,4-dinitrophenol may provide a proton to release the product from the rhodium complex intermediate (see complex **8** in Figure 2B) in $\text{ClCH}_2\text{CH}_2\text{Cl}$.^{9j,q} The higher conversion achieved in the catalytic reaction (eq 5) than in the stoichiometric reaction (eq 3) suggests that the proton in the H-transfer step of the catalytic reaction probably comes from 2-pyridylpyridine **1a**^{9o} rather than 2,4-dinitrophenol (Figure 2B). Meanwhile, less than 50% conversion even with a longer reaction time (eqs 6 and 7) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ indicates that half of **1a** may act as a base. The reaction performed in the presence of 1 equiv of base (NaHCO_3) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (eq 8) provided 83% of the desired product, while the same reaction “on water” gave a yield similar to that in the absence of any base (Scheme 2, eq 5). This is because in $\text{ClCH}_2\text{CH}_2\text{Cl}$ the pyridine functional group of the product **3a** cannot act as a base, possibly due to an intramolecular H-bonding interaction with the amide group. Intermolecular H-bonding between water and the amide group of product **3a** helps to regenerate the starting material **1a** from $[\mathbf{1a}\cdot\text{H}]^+$ “on water” (Figure 1). Therefore, water has been shown to play two key roles, promoting the formation of the active species **4** and activating the product **3a** to serve as a base.



Figure 1. Water-promoted regeneration of **1a** from $[\mathbf{1a}\cdot\text{H}]^+$.

Next, we investigated the H/D scrambling and deuterium kinetic isotope effects (DKIE) (Scheme 3). A negligible amount of H/D exchange was observed in the presence or absence of the nitrene source **2** (eqs 9 and 10), indicating that the amidation process is faster compared to H/D exchange. In an intra-

Scheme 3. Kinetic Experiments



^aUsing $\text{D}_2\text{O}/\text{H}_2\text{O}$ (0.5 mL/0.5 mL) as the solvent at 60 °C for 10 min.

molecular competition reaction of **1a-d**₁ with rhodocycle **4** or $[\text{RhCp}^*\text{Cl}_2]_2$ as catalyst (eqs 11 and 12), the DKIE of 3.8 and 3.5, respectively, were observed after consideration of the effect of the catalyst (five-membered rhodocycle **4**, 4 mol %, which could form 4% of **3a** directly). We have also observed the DKIE of 2.6 for parallel reactions (see the Supporting Information for details). This suggests that the C–H activation step is possibly one of the rate-limiting steps,¹⁵ and the complex **4** is involved in the catalytic cycle. The conversion was higher with 4 mol % of species **4** than with 4 mol % of $[\text{RhCp}^*\text{Cl}_2]_2$ (equal to 8 mol % mono rhodium catalyst), possibly due to the comparatively slow formation of rhodocycle **4** from $[\text{RhCp}^*\text{Cl}_2]_2$ under these reaction conditions (eqs 11 and 12). A DKIE of 4.0 for the formation of species **4** was also obtained (eq 13).

To understand such unusual activation of $[\text{RhCp}^*\text{Cl}_2]_2$ “on water”, we tested whether or not the water can activate the catalyst under homogeneous conditions, but the results were negative (Table 1, entries 15–18). Hydrophobic water surfaces have been reported to contain 25% dangling OH groups protruding into the hydrophobic phase,^{5–7} and this finding has been used to explain the enhanced rate of “on water” reactions.^{4a,5} Considering this phenomenon as an explanation of our observations, we suggest that dangling OH groups protruding into the hydrophobic phase activate $[\text{RhCp}^*\text{Cl}_2]_2$ by hydrogen bonding and, thus, support the formation of five-membered rhodocyclic complex **4** which is the active species^{9h} (Figure 2A). The complex **4** may convert to **5** by removal of a Cl[–]

A. proposed mechanism of H_2O promoted to generate active species



B. proposed catalytic cycle

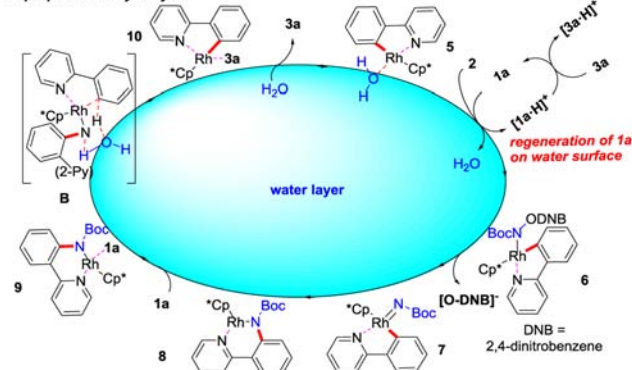


Figure 2. Possible Reaction Pathway.

ion by H_2O . Complex **5** then may react with **1a** and the nitrene source **2** to generate the intermediate **6**, which then may be converted to **7** via valence expansion of Rh(III) to Rh(V) (Figure 2B). The intermediate **7** may be converted to **8** by stepwise nitrenoid transfer,¹⁶ which was observed in the ESI mass spectrum (see the Supporting Information). The intermediate **8** may coordinate with **1a** to give the intermediate **9**, which then may undergo C–H activation and then rearrange to intermediate **10** through a transition state **B**. The intermediate **10** will react with water to give the product **3a** and the intermediate **5**, thus completing the catalytic cycle. The pyridinium ion $[\mathbf{1a}\cdot\text{H}]^+$ generated during the formation of intermediate **6** regenerates

1a in a reaction promoted by water in the presence of the product 3a as shown in Figure 1, and in this way, the reaction can proceed “on water” without any additional base.

In conclusion, we report the first C–H amidation “on water” with $[\text{RhCp}^*\text{Cl}_2]_2$ catalyst activated by dangling OH groups present on hydrophobic water surfaces. The reaction works well, resulting in *N*-Boc-amidated products of a variety of substrates bearing different active functional and biologically important groups. We have also introduced *tert*-butyl 2,4-dinitrophenoxycarbamate as a new, easily accessible, stable *N*-Boc amine source. The reaction conditions are simple and do not require oxidants, ligands, acids, or bases.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for the products, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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