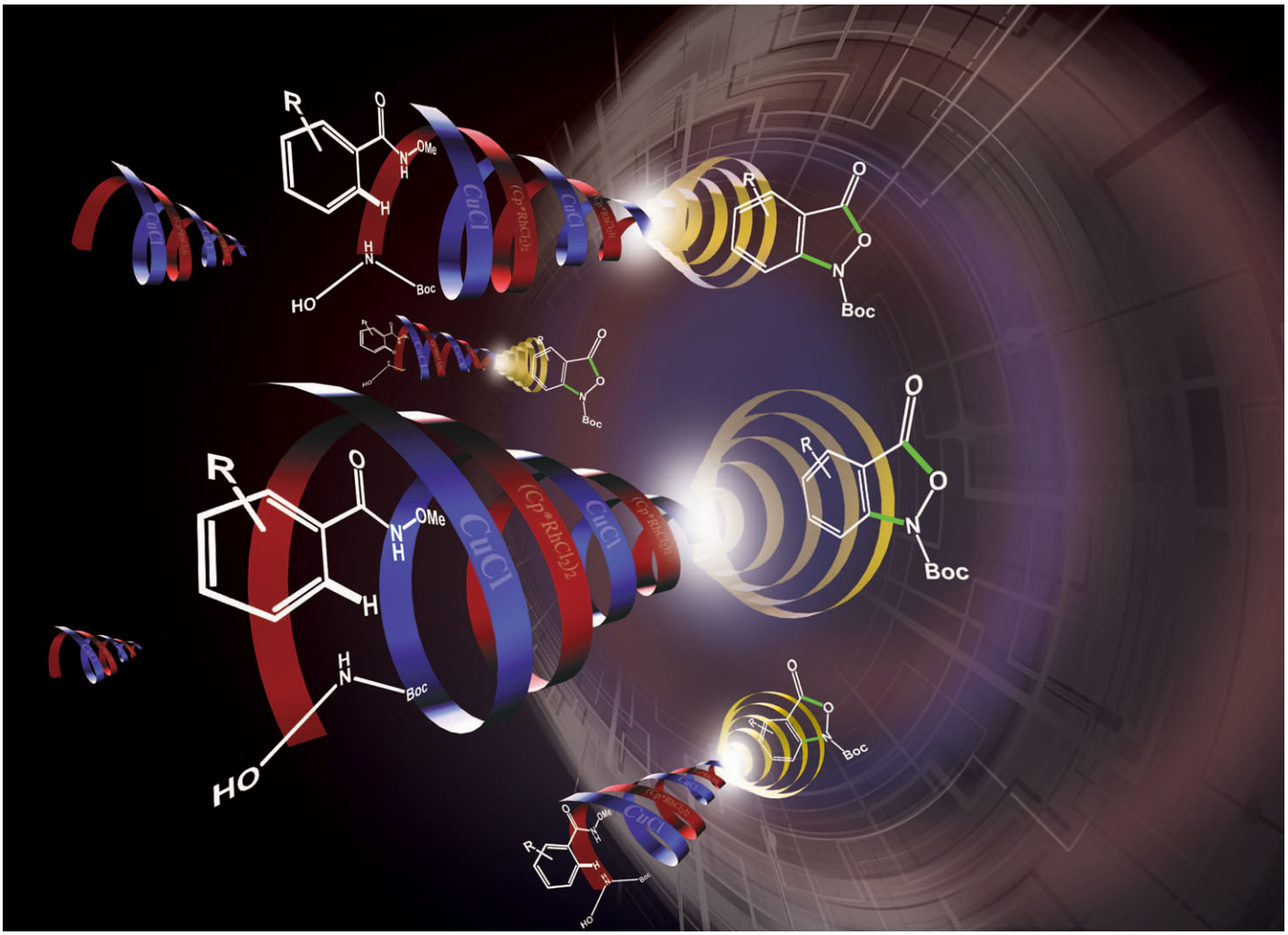

Showcasing research from Prof. Xianxiu Xu and Qian Zhang's Laboratory/ Key Laboratory of Design and Synthesis of Functional Organic Molecules of Jilin, Northeast Normal University, Changchun, China.

A novel synergistic rhodium and copper catalyzed C–H activation/hydroamination reaction for the synthesis of benzo[*c*]isoxazol-3(1*H*)-ones

A novel hydroamination of aryl C–H bonds has been accomplished using *N*-Boc-hydroxyamine *via* synergistic combination of rhodium and copper catalysis. The merger of two robust catalytic systems has allowed for the development of a mild and sustainable protocol for the direct formation of benzo[*c*]isoxazol-3(1*H*)-ones.

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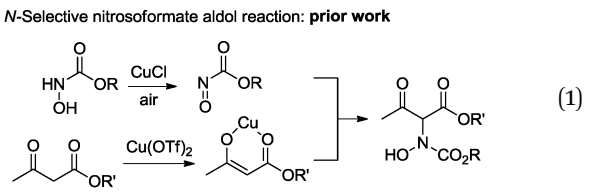
Hydroxyamination of aryl C–H bonds with *N*-hydroxycarbamate by synergistic Rh/Cu catalysis at room temperature†

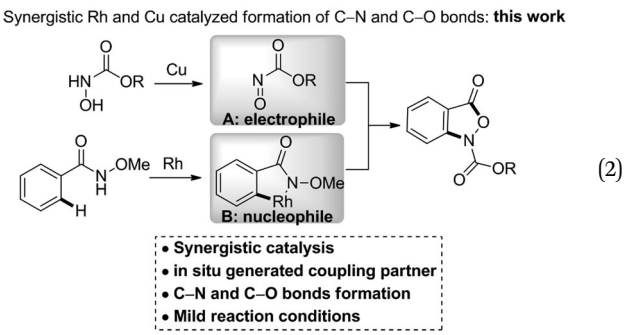
Wei Yang, Jiaqiong Sun, Xianxiu Xu,* Qian Zhang* and Qun Liu

A novel hydroamination of aryl C–H bonds has been accomplished using *N*-Boc-hydroxyamine *via* synergistic combination of rhodium and copper catalysis. The merger of two robust catalytic systems has allowed for the development of a mild and sustainable protocol for the direct formation of benzo[*c*]isoxazol-3(1*H*)-ones.

Synergistic catalysis, a synthetic strategy wherein both the nucleophile and the electrophile are simultaneously activated by two distinct catalysts, has attracted increasing interest in the design of new chemical reactions for improving efficiency and selectivity of a known reaction in organic chemistry.[1] During the past few years, various co-catalyst systems, such as a combination of transition-metal and organocatalysis,[1,2] transition-metal and photoredox catalysis,[1,3] and other bimetal catalysis,[1,4] have been extensively investigated. However, despite their high synthetic potential, the success of synergistic catalysis is still immature and there is a need to develop new synergistic catalysis, especially for the sustainable chemical process.

Nitrosocarbonyl compounds are very unstable and highly reactive species and have attracted considerable attention in organic synthesis.[5–7] They are generally produced *in situ* as transient intermediates and have been studied quite extensively in hetero-Diels–Alder and ene reactions.[7] Recently, Read de Alaniz and co-workers extended the synthetic utility of nitrosocarbonyl to α-hydroamination of reactive β-ketoesters by *N*-hydroxycarbamates using synergistic CuCl/$Cu(OTf)_2$ catalysis, during which nitrosoformate intermediates were generated *in situ* by aerobic oxidation (eqn (1)).[8] In addition, Maruoka reported an enantioselective α-hydroxyamination of aldehydes with nitrosocarbonyl compounds.[9] Yamamoto developed a catalytic enantioselective *O*-nitrosocarbonyl aldol reaction of β-dicarbonyl compounds with nitrosocarbonyl compounds.[10] On the other hand, Rh(III) complexes have stood out as efficient catalysts for atom- and step-economical C–C and C–heteroatom bond formation through C–H functionalization.[11] Among the various coupling partners employed in the Rh(III)-catalyzed C–H bond activation reaction, some electrophiles, such as imines,[12] aldehydes[13] and isocyanates,[14] have been successfully explored. Since nitrosocarbonyl compounds are reactive electrophiles, it is reasonable that they may be good coupling partners in the Rh-catalyzed C–H activation reactions.[15] Thus, as part of our continuing interest in the development of Rh(III)-catalyzed C–H activation,[16] we envisioned that the nitrosocarbonyl compounds **A** could be trapped by the rhodacycle intermediate **B** if they can be formed compatibly *in situ* (eqn (2)). Herein we present the successful development of a synergistic Rh and Cu catalytic system applicable to the hydroamination of aryl C–H bonds by commercially available *N*-Boc-hydroxylamine using O_2 as an oxidant at room temperature. This synergistic catalysis provides a new sustainable process for the preparation of benzo[*c*]isoxazole derivatives, which are the subunits of natural products, parnafungins A and B[17] and other bioactive compounds.[18]





Initially, the reaction of *N*-methoxy benzamides **1a** with *N*-Boc-hydroxylamine **2a** was employed to screen catalysts and reaction

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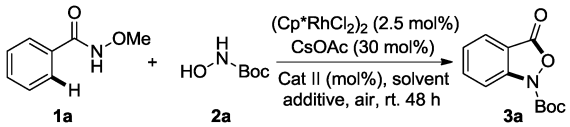
† Electronic supplementary information (ESI) available: Experimental details and spectral data for **3**. See DOI: 10.1039/c3cc49496a

Table 1 Optimization of reaction conditions[a]



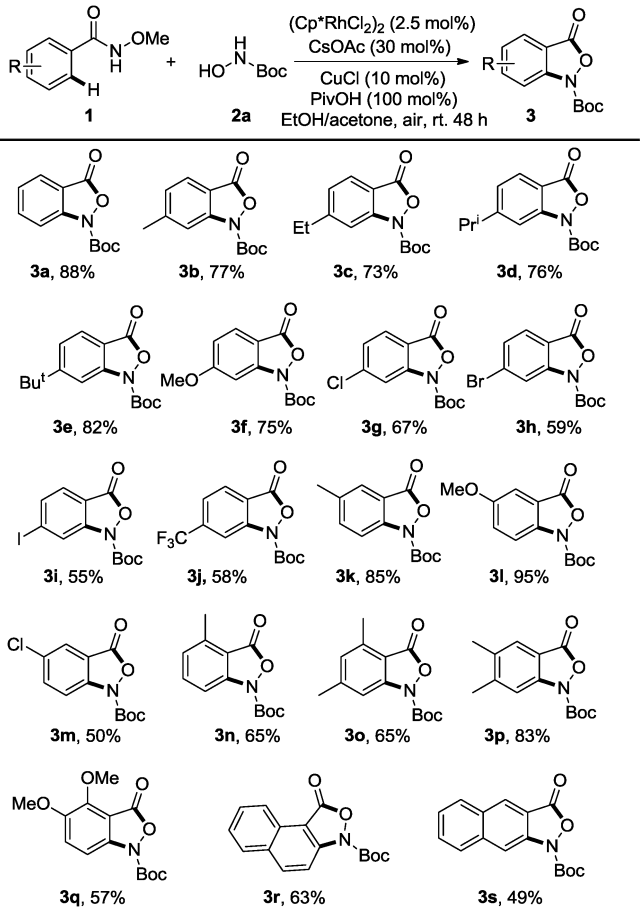
Entry	Solvent	Catalyst II (mol%)	Additive (100 mol%)	Yield[b] (%)
1	MeOH	CuCl (10)	HOAc	11
2	EtOH	CuCl (10)	HOAc	35
3	*t*-AmOH	CuCl (10)	HOAc	Trace
4	Acetone	CuCl (10)	HOAc	32
5	Acetone–EtOH[c]	CuCl (10)	HOAc	70
6	Acetone–EtOH	CuBr (10)	HOAc	42
7	Acetone–EtOH	CuI (10)	HOAc	40
8	Acetone–EtOH	CuOAc (10)	HOAc	60
9	Acetone–EtOH	CuOTf (10)	HOAc	0
10	Acetone–EtOH	—	HOAc	0
11	Acetone–EtOH	CuCl (50)	HOAc	53
12	Acetone–EtOH	CuCl (10)	HCOOH	17
13	Acetone–EtOH	CuCl (10)	PivOH	72
14	**Acetone–EtOH**	**CuCl (10)**	**PivOH**	**88**[d]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), additive (0.2 mmol), solvent (2 mL). [b] Isolated yields. [c] The ratio of acetone and EtOH is 1 : 1 (v : v). [d] 2 Equiv. of **2a** was used, 1 equiv. was added at the beginning of the reaction, the other 1 equiv. was added after 24 h.

conditions for the hydroamination of aryl C–H bonds (Table 1). Because copper salt is compatible with $(Cp^*RhCl_2)_2$,[11] Read de Alaniz's copper-catalyzed aerobic oxidation conditions[8,19] were employed to produce nitrosocarbonyl compounds. Fortunately, benzo[*c*]isoxazol-3(1*H*)-one **3a** was obtained in a 11% isolated yield, when the reaction was conducted in methanol in the presence of $(Cp^*RhCl_2)_2$ (2.5 mol%), CuCl (10 mol%) and 1.0 equivalent of acetic acid in the open air (Table 1, entry 1). Solvent screening revealed that ethanol and acetone gave moderate product yields (Table 1, entries 2 and 4) when a mixture of ethanol and acetone (1 : 1) was used as solvent, and to our delight, the yield of **3a** was improved to 70% (Table 1, entry 5). Among the copper salts tested, CuCl was the most favorable with respect to product yield (Table 1, entries 5–9). Product **3a** could not be detected in the absence of CuCl (Table 1, entry 10), whereas **3a** was obtained in a low yield upon increasing the amount of CuCl to 50 mol% (Table 1, entry 11). Different additives were also screened (Table 1, entries 5, 12 and 13) and it was found that PivOH was as effective as HOAc (Table 1, entry 13). More importantly, the yield of product **3a** could be improved to 88% when 2 equivalents of **2a** were employed (1 equivalent was added to the reaction mixture at the beginning and the other was added after 24 h; Table 1, entry 14). It should be noted that the reaction was performed under very mild conditions, such as at room temperature and in the open air and gave the benzo[*c*]isoxazole derivatives with exclusively *N*-selectivity of the nitrosocarbonyl compounds.

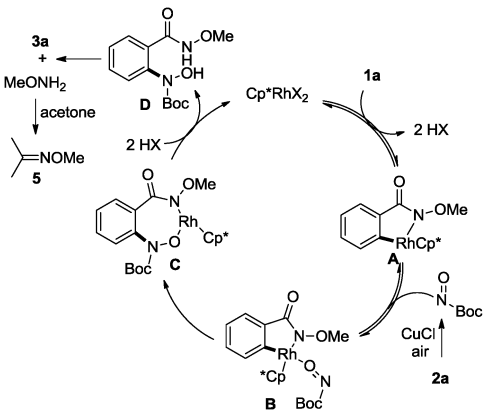
With the optimal conditions in hand, we surveyed various substrates to determine the scope of the reaction. Catalyzed by Rh and Cu system, the reactions proceeded smoothly to afford benzo[*c*]-isoxazol-3(1*H*)-ones in good to excellent yields (Table 2). Substrates with both electron-donating and electron-withdrawing groups at the *para* position of aryl groups participated in this reaction (**3a–j**). *meta*-Substituted benzamides reacted smoothly to give the corresponding benzo[*c*]isoxazol-3(1*H*)-ones in good to excellent yields and in a

Table 2 Synthesis of benzo[*c*]isoxazol-3(1*H*)-ones **3**



highly regioselective manner (**3h–m**). Reactions with *ortho*-substituted and disubstituted benzamides also proceeded smoothly to give the corresponding products in good to high yields (**3n–q**). α- and β-naphthamide also produced the corresponding naphtho-[2,1-*c*]isoxazol-1(3*H*)-one **3r** and naphtho[2,3-*c*]isoxazol-3(1*H*)-one **3s** regioselectively and in good yields. It is worth mentioning that a wide range of important functional groups on the aryl moieties of benzamides **1**, such as methoxy, chloro, bromo, iodo and trifluoromethyl groups, were well tolerated under the reaction conditions (**3f–j**).

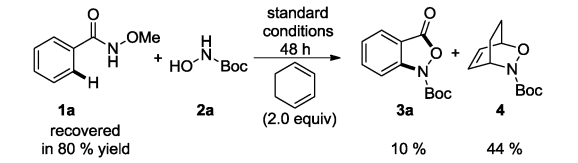
To shed light on the reaction mechanism of this synergistic catalysis process, firstly, a routine Diels–Alder trapping for the nitrosocarbonyl compound[20] was performed to determine whether this unstable and transient intermediate was involved. When cyclohexa-1,3-diene (2.0 equiv.) was added to the reaction mixture of **1a** and **2a** under the standard conditions, the Diels–Alder product **4** was obtained in 44% yield along with product **3a** only in 10% yield (eqn (3)). Then, deuterium-labeling experiments were further carried out to gain some insights into the catalytic mechanism. When the reaction of **1a** was conducted in deuterated acetone and methanol in the absence of **2a**, 94% deuterium incorporation was observed at the two *ortho* positions (eqn (4)). If the same reaction was conducted in the presence of **2a**, 89 and 94% deuterium incorporation into the product **3a** and the recovered starting material **1a** were observed respectively (eqn (4)). These results indicate that the C–H bond metalation step is reversible under the reaction conditions.



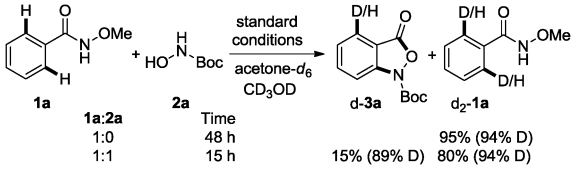
Scheme 1 Proposed mechanism for the formation of **3a**.

Moreover, a competition reaction between protio and deutero **1a** was conducted at early conversion, and ^{1}H NMR spectroscopic analysis of the product mixture gave a kinetic isotope effect (KIE) of 1.5 (eqn (5)).

On the basis of the above results, a mechanistic pathway is proposed (Scheme 1). First, a reversible C–H bond cleavage of **1a** occurs to produce a five-membered rhodacycle intermediate **A**. Next, coordination of the nitrosocarbonyl compound (produced by copper-catalyzed aerobic oxidation of *N*-Boc-hydroxylamine **2a**)[8,19,20] affords intermediate **B**, which undergoes nucleophilic addition to form seven-membered rhodacycle **C**. Protonolysis gives a hydroxyamination intermediate **D**. Metal or acid catalyzed nucleophilic substitution reaction occurs to furnish the final product **3a** with the release of a *O*-methyl hydroxamine (the propan-2-one *O*-methyl oxime **5** was detected using GC-MS).



(3)



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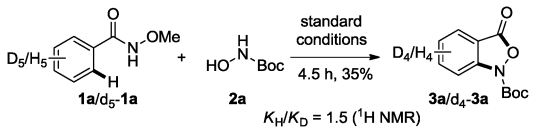

(5)

In summary, we have developed a novel aryl C–H bond hydroamination using *N*-Boc-hydroxyamine *via* synergistic combination of rhodium and copper catalysis for the convenient synthesis of benzo[*c*]isoxazol-3(1*H*)-ones. In this process, the unstable and transient nitrosocarbonyl compounds were generated *in situ* by aerobic oxidation and used as coupling partner to form both C–N and C–O bonds. The reaction features mild reaction conditions (room temperature and in the open air), broad substrate scope and good functional-group tolerance. Additional mechanism studies and more transformations by synergistic catalysis are being carried out in our laboratory.

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