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Water as a green solvent for efficient synthesis of isocoumarins through microwave-accelerated and Rh/Cu-catalyzed C–H/O–H bond functionalization†

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Green chemistry that uses water as a solvent has recently received great attention in organic synthesis. Here we report an efficient synthesis of biologically important isocoumarins through direct cleavage of C–H/O–H bonds by microwave-accelerated and Rh/Cu-catalyzed oxidative annulation of various substituted benzoic acids, where water is used as the only solvent in the reactions. The remarkable features of this "green" methodology include high product yields, wide tolerance of various functional groups as substrates, and excellent region-/site-specificities, thus rendering this methodology a highly versatile and eco-friendly alternative to the existing methods for synthesizing isocoumarins and other biologically important derivatives such as isoquinolones.

Introduction

In recent years, much effort has been devoted towards the development of sustainable reaction media, especially, the use of water as solvent has aroused considerable interest in the field of organic synthesis.[1] Indeed, water as a solvent has many advantages over conventional organic solvents, because it is cheap, readily available, non-toxic, non-polluting, and non-flammable. Thus, the water-mediated organic synthesis is very attractive from both an economical and environmental point of view.[2] As a result, intensive effort has been invested into the development of catalytic processes by employing water as a medium to accomplish greener syntheses of many biologically important pharmacophores.[3] An uncertainty that exists is how far the catalytic processes used the water as the green solvent could be engineered to benefit the synthesis of biologically important pharmacophores. To speak of bioactive molecules, various pharmacophores bearing isocoumarin unit have attracted particular attention because of their broad ranges of interesting biological properties including anti-diabetic, anti-allergic, anti-fungal, anti-bacterial, anti-inflammatory, anti-angiogenic, and differentiation inducing-activities against leukemic cells.[4]

The potential of isocoumarins has led to the development of various synthetic protocols for making these compounds. So far, one of the most general strategies for their synthesis involves palladium-catalyzed annulations of alkynes by *ortho*-halo-substituted carboxylic acids.[5] However, this approach requires pre-functionalized benzoic acids as substrates, which result in formation of stoichiometric amounts of salt wastes as by-products, thus limiting the utility and applicability of this method in practical use. To circumvent these disadvantages, Miura,[6] Jeganmohan[7a] and Ackermann[7b] have recently developed a more atom- and step-economical process, in which transition-metal Rh or Ru/Cu was used to catalyze oxidative annulations of alkynes by non-halogenated carboxylic acids *via* a direct C–H bond cleavage with organic solvent DMF, DCE or *t*-BuOH as the reaction medium. This process improved the reaction conditions but produced environmentally non-compatible solvents that limit its utility. Taking into account this point, Ackermann and co-workers also investigated the Ru/Cu-catalyzed reaction, where the water was used as the solvent. However, the lower reaction yield was found in their catalysis.[7c] In addition, Chiba and co-workers showed that the treatment of Cu^{2+} in DMF resulted in the disappearance of Cu^{2+} band in the UV/vis region, implying that DMF might reduce Cu^{2+} to form Cu^{+}.[8] This result suggests that the use of DMF reduced the synthetic efficiency in the Rh/Cu-catalyzed oxidative annulation

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system. Therefore, it is important to develop economically and environmentally more viable procedures for the synthesis of isocoumarins.

On the other hand, microwave-assisted reaction strategy has now been recognized as one of the most powerful and environmental friendly tools in synthetic chemistry and has attracted much attention due to its specific effects such as efficient atomic utilization, improved temperature and reaction homogeneity, and possible modifications of activation parameters (*e.g.*, $\Delta H\neq$ and $\Delta S\neq$).[9,10] Indeed, many reports have demonstrated that a wide range of metal-catalyzed reactions and cross-coupling reactions benefit strongly from microwave heating, exhibiting faster reaction kinetics.[11]

Thus, we envisioned that the use of microwave-assisted method in combination with water as a solvent could be developed as a versatile and sustainable methodology for expeditious synthesis of biologically important heterocyclic molecules. Here we report a "greener" route to isocoumarins *via* a water-mediated and Rh/Cu-catalyzed coupling reaction of benzoic acids with alkynes under microwave-assisted heating procedures. This method is simple, efficient, and fast, which can be extended to the synthesis of many other biologically important heterocyclic compounds.

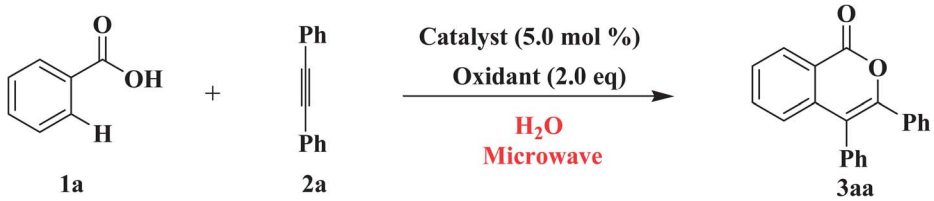
Results and discussion

From "green chemistry" point of view, we initiated our study with the coupling reaction of tolane and carboxylic acid under the microwave heating condition using water as a green solvent. After many trials (Table 1, entries 1–8), we found that treatment of **1a** with **2a** in the presence of 5.0 mol% of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2\cdot H_2O$ in water at 120 °C for 0.5 h gave the desired isocoumarin product **3aa** in the best yield of 85% (Table 1, entry 5). Comparison with the present example (Table 1, entry 8), which resulted in 62% yield of **3aa** for 1 h under the conventional heating conditions, it showed that the use of microwave-assisted heating provided a faster reaction rate and an improved yield of the desired product. Moreover, the reaction could conveniently be scaled up to gram levels (Table 1, entry 9).

It is noteworthy that the addition of copper acetate was essential for the success of the present catalytic reaction, because the acetate anion and the copper cation is critical for the cyclometallation step and the regeneration of the catalyst (see below). No reaction was observed in the absence of the oxidant $Cu(OAc)_2\cdot H_2O$ (Table 1, entry 10). Other anionic copper salts, such as $Cu(BF_4)_2\cdot 6H_2O$ and $CuCl_2\cdot 2H_2O$, gave lower conversion (Table 1, entries 11 and 12). No desired product was formed in the absence of catalyst under otherwise identical conditions (Table 1, entry 13).

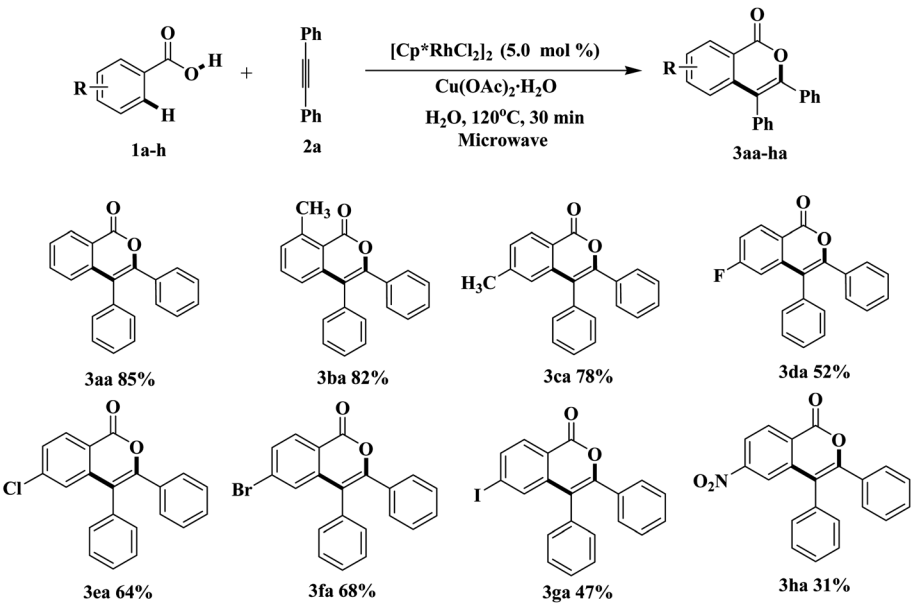
With the optimal "green" conditions in hand, we sought to investigate the scope and generality of this methodology. The results shown in Scheme 1 attest that this methodology is compatible with a wide range of substituents in the carboxylic acids. As shown in Scheme 1, the reaction of various substituted benzoic acids with **2a** proceeded well, which resulted in the corresponding isocoumarin derivatives in good yields. Both electron-rich and electron-deficient benzoic acids were good substrates in this reaction. Many important and valuable

Table 1 Optimization of reaction conditions[a]



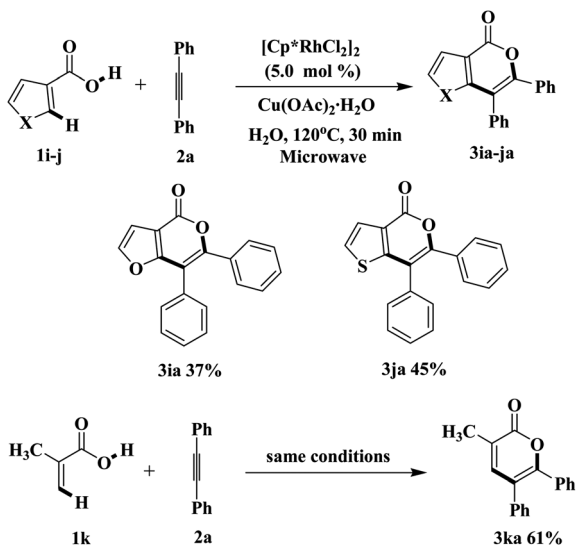
Entry	Catalyst	Oxidant	Temp (°C)	Time (min)	Yield[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	110	30	79%
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2\cdot H_2O$	110	30	40%
3	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	110	30	61%
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	100	30	65%
5	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	120	30	85%
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	130	30	51%
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	120	15	35%
8[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	120	60	62%
9[d]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	120	30	81%
10	$[Cp^*RhCl_2]_2$	—	120	30	0
11	$[Cp^*RhCl_2]_2$	$Cu(BF_4)_2\cdot 6\ H_2O$	120	30	11%
12	$[Cp^*RhCl_2]_2$	$CuCl_2\cdot 2H_2O$	120	30	0
13	—	$Cu(OAc)_2\cdot H_2O$	120	30	0
14[e]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$	120	30	46%

[a] *Reaction conditions*: **1a** (0.25 mmol), **2a** (0.3 mmol), Rh catalyst (5.0 mol%), and $Cu(OAc)_2\cdot H_2O$ (0. 5 mmol), H_2O (1.0 mL). [b] Isolated yields. [c] The reaction was carried out under the conventional heating conditions. [d] The reaction was scaled-up to a gram substrate level. [e] 1 mol% of Rh catalyst was used.



Scheme 1 Scope using symmetrical phenyl disubstituted alkyne **2a**. Isolated yield were given. *Reaction conditions*: **1a–h** (0.25 mmol, 1.0 eq.), **2a** (0.3 mmol, 1.2 eq.), Rh catalyst (5.0 mmol%), and $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol, 2.0 eq.), H_2O (1.0 mL), 120 °C, 30 min.

functional groups in the aromatic ring of carboxylic acids **1b–h**, such as fluoro, chloro, bromo, iodo, methyl, and nitro substituents (**3ba–ha**) were compatible in the present catalytic reaction. Notably, *para*-methyl benzoic acid afforded the isocoumarin product in good yield (**3ca**), whereas *para*-nitro or -iodo benzoic acid showed a slightly decreased efficiency (**3ga** and **3ha**). The result suggested that the introduction of electron-rich groups might be more favorable for the optimal "green" catalytic system.



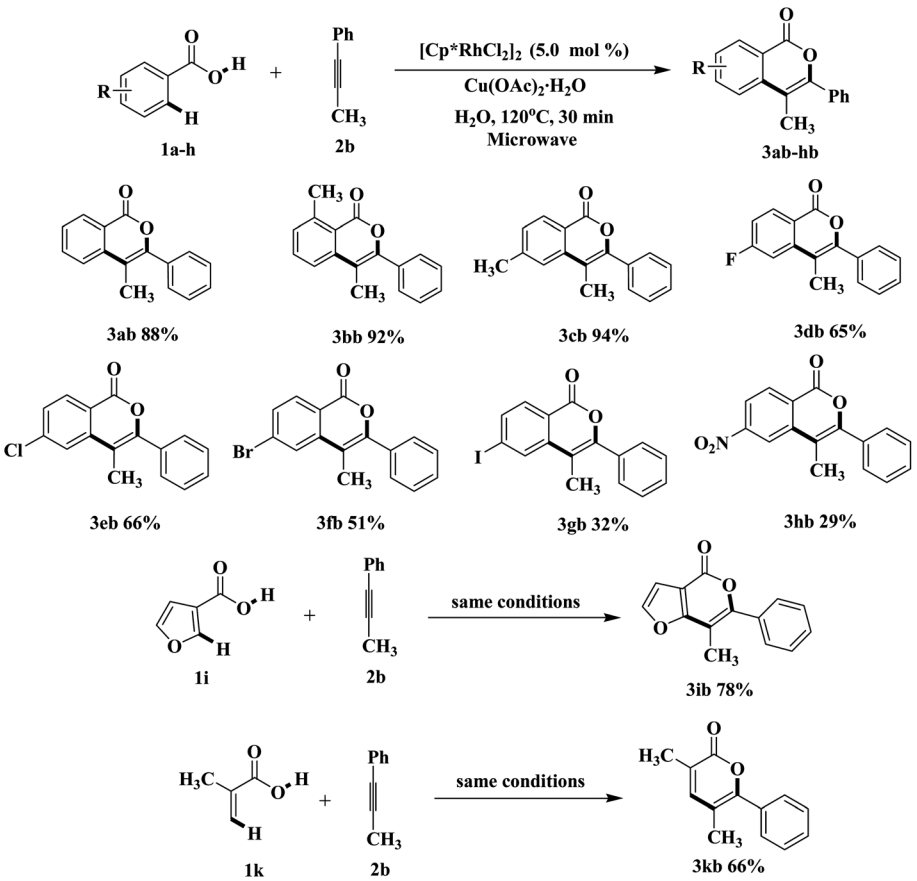
Scheme 2 Oxidative annulations with heteroarenes **1i–j** and 2-methyl acrylic acid **1k**. Isolated yield were given. *Reaction conditions*: **1i–k** (0.25 mmol, 1.0 eq.), **2a** (0.3 mmol, 1.2 eq.), Rh catalyst (5.0 mmol%), and $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol, 2.0 eq.), H_2O (1.0 mL), 120 °C, 30 min.

Interestingly, extension of this reaction to heteroarenes **1i–j** proved to be successful (Scheme 2, **3ia–ja**). Moreover, the cationic rhodium(III) catalyst further allowed the oxidative coupling of acrylic acid derivative **1k** and alkyne **2a**, providing a step-economical access to α-pyrone **3ka**.

It is important to note that when asymmetrical alkynes were employed, the insertion of an aryl alkyl-disubstituted alkyne occurred in remarkably high region-selectivity with the aryl-substituted carbon center being installed at the 3-position (Scheme 3, **3ab–hb**, **3ib** and **3kb**).

Considering the remarkably broad substrate scope displayed by the rhodium(III) catalysis in water, we performed mechanistic studies to delineate its mode of action (Scheme 4). To this end, an intramolecular competition experiment with *meta*-substituted benzoic acid **1l** exclusively delivered product **3la** through the site-selective functionalization, which occurred at the sterically less congested C–H bond and displayed a higher kinetic acidity. This result was in good agreement with that found by Ackermann.[7] Additionally, competition experiments between differently substituted carboxylic acids indicated that electron-rich benzoic acids were converted preferentially, suggesting they were better substrates than electron-poor benzoic acids.

Based on these observations and the known metal-catalyzed C–H bond activation/annulations reactions,[12] we proposed a possible mechanism as illustrated in Scheme 5. The first step is an acetate-assisted irreversible C–H bond activation, which yields a five-membered rhodacycle intermediate **A** coupling with formation of acetic acid. Subsequently the region-selective transfer of alkyne insertion forms seven-membered rhodacycle intermediate **B**, which, upon reductive elimination of C–H/O–H bonds, yields the desired isocoumarin derivative **3** with the reduction of rhodium center



Scheme 3 Scope using asymmetrical phenyl methyl-disubstituted alkyne **2b**. Isolated yield were given. *Reaction conditions*: **1a–h**, **1i** and **1k** (0.25 mmol, 1.0 eq.), **2b** (0.3 mmol, 1.2 eq.), Rh catalyst (5.0 mmol%), and $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol, 2.0 eq.), H_2O (1.0 mL), 120 °C, 30 min.

from Rh(III) to Rh(I). Finally, the resulting Rh(I) may be oxidized by the Cu(II) salts to regenerate Rh(III) complex, which is then released to reinitiate the catalytic cycle.

Developing a "greener" process as a synthetic strategy to make biologically active scaffolds is one major impetus in the field of organic synthesis. We therefore sought to demonstrate the application of our methodology in the synthesis of isoquinolones **5** and **7**, indispensable structural motifs in bioactive compounds of importance to medicinal chemistry.[13] Although two protocols for preparing the isoquinolones were reported by Ackermann that employed Ru(II) as the catalyst and used water as the solvent,[14] which represent important advances, the development of novel catalysts is still necessary to achieve elusive intermolecular reactivity. Therefore, the reactions for synthesizing the isoquinolones **5** and **7** were investigated in our Rh (III)-catalyzed system and typical results were summarized in Scheme 6. We were pleased to find that the green catalytic system worked well on *N*-hydroxybenzamide **4** and acetophenonoxime **6**. In the present cases, the desired products **5** and **7** were produced smoothly through oxidative annulations of the C–H/N–O bonds cleavage in the same conditions and using water as the reaction solvent. All these results further illustrated the remarkable robustness of our "green" catalyst system.

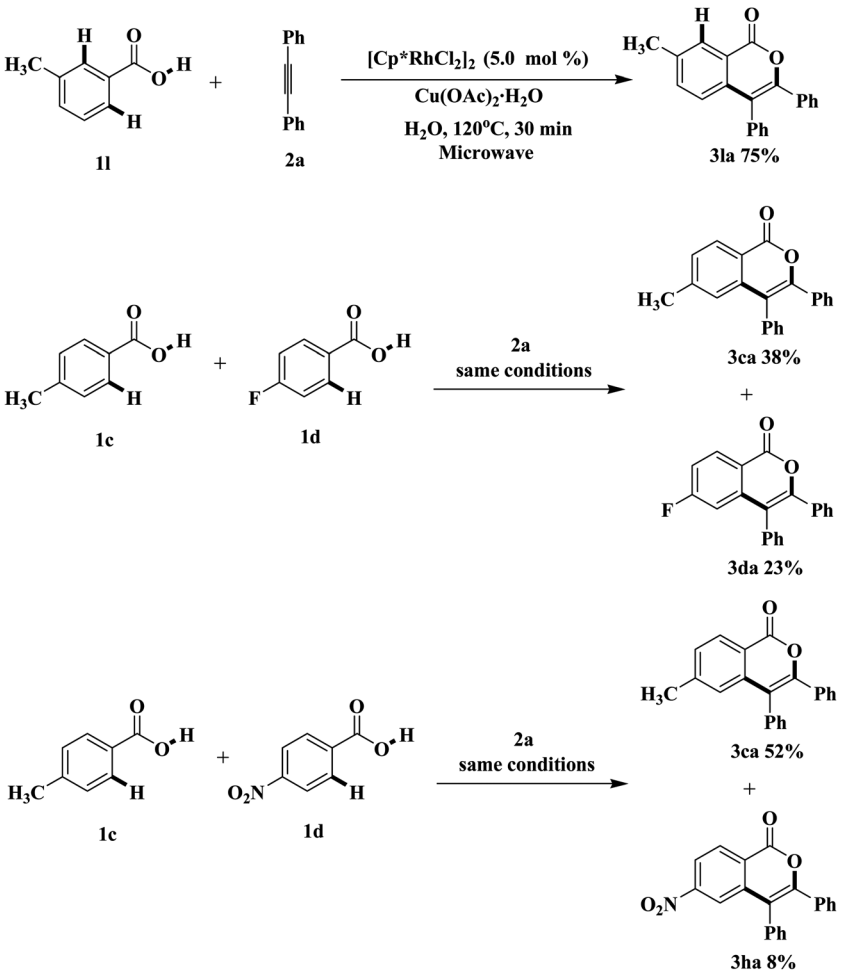
Conclusions

In conclusion, we have developed a simple, versatile, efficient, and high region-/site-selective methodology for the direct synthesis of isocoumarins and their heterocyclic analogs through microwave-accelerated and Rh-catalyzed oxidative C–H/O–H bonds cleavages, where water was used as a green solvent. In the present study, a $Cu(OAc)_2 \cdot H_2O$ co-catalyst was found to be crucial for the C–H bond activation step. A wide range of substrates are compatible with this synthetic method, including both electron-rich and electron-deficient benzoic acids, and other characteristic carboxylic acids. The identical catalytic system was applicable to make biologically important molecules such as isoquinolones. The use of a microwave-accelerated protocol and water as the green reaction medium makes this methodology as a benign alternative to the existing methods.

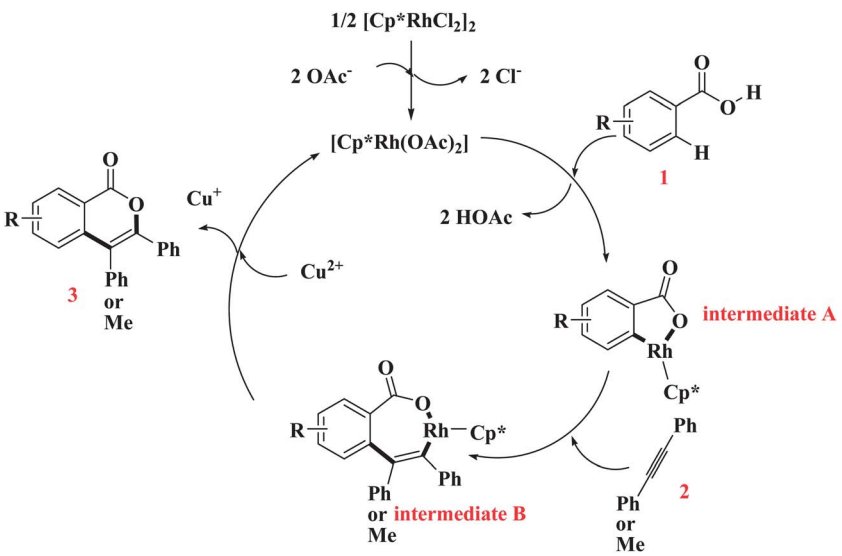
Experimental section

General procedure for activation/annulations reactions

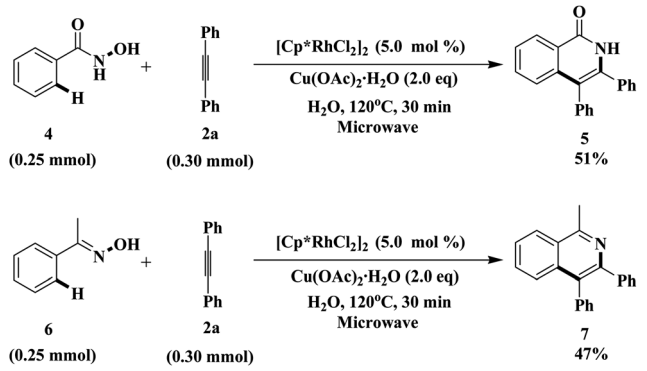
A biotage microwave vial was charged with Rh catalyst (5 mol%) H_2O (1 mL), carboxylic acids (0.25 mmol), alkynes (0.3 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol). The vial was capped and heated



Scheme 4 Intramolecular competition experiment. Isolated yield were given. *Reaction conditions*: **1l**, **1c–d** (0.25 mmol, 1.0 eq.), **2a** (0.25 mmol, 1.0 eq.), Rh catalyst (5.0 mmol%), and $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol, 2.0 eq.), H_2O (1.0 mL), 120 °C, 30 min.



Scheme 5 Proposed mechanism of this "green" catalyst system.



Scheme 6 Isoquinolone synthesis using this "green" catalyst system.

in the microwave reactor at 120 °C for 30 min. A sample of the cool reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was purified by chromatography on a silica gel column to afford the corresponding product.

Acknowledgements

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