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COMMUNICATION

Rhodium(III)-Catalyzed Cascade Reactions of Benzoic Acids with Dioxazolones: Discovery of 2,5-Substituted Benzoxazinones as AIE Molecules

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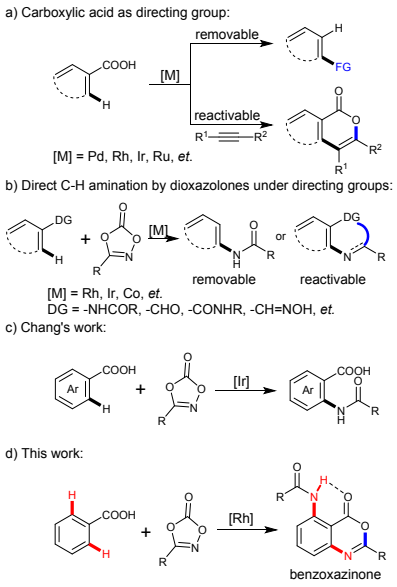
A rhodium-catalyzed cascade reaction of benzoic acids with 1,4,2-dioxazol-5-ones was studied. Carboxyl group enabled a double C–H amidation followed by further intramolecular cyclization to afford 2,5-substituted benzoxazinones which exhibited aggregation-induced emission (AIE) properties with promising excited-state intramolecular proton-transfer (ESIPT) phenomenon.

In the past decade, directing group-assisted transition metal-catalyzed C-H activation has been extensively explored and utilized to convert inert C-H bonds into C-C and C-heteroatom bonds.[1] Although tremendous advancements have been achieved shown by the disclosure of a diversified array of directing groups used in this system, it is still a challenge to transform or remove the installed directing groups later on. The past few years have witnessed the application of modifiable and traceless directing groups to solve this problem, making the transition metal-catalyzed C-H functionalization a more desirable and efficient synthetic method.[2]

Carboxylic acid, bearing both electrophilic carbonyl group and nucleophilic hydroxyl group, is often utilized as functionalizable directing group in metal-catalyzed C-H activation due to its overall simple yet reactive structure. The extrusion of CO_2 in the process allows traceless removal of the directing group[3] while direct intramolecular oxidative alkyne formation by transition metals enables atom-economical and effective routes to construct isocoumarin scaffold (Scheme 1a).[4] Dioxazolones, with their intrinsically high coordination ability, are often employed as amide source to construct nitrogen-containing molecules under the catalysis of transition metals.[5] Continuous exploration led to the discovery of aldehyde, *N*-substituted imine, nitrone, amide and ketone as directing groups facilitating direct *ortho*-C-H amination using dioxazolones (Scheme 1b).[6] Some of these directing groups can be readily removed[7a-c] while others could be further modified by one- or multi-step coupling reaction to give functionalized N-containing heterocycles.[7d-i] In 2017, Chang's team used carboxylic acid as directing group to react with dioxazolones under Ir(III) catalysis and observed single *ortho*-amidated product (Scheme 1c).[8]

Benzoxazinones are privileged scaffolds found in various biologically active molecules. Although their preparation methods have been developed to some extent in the past decade,[9] it remains highly desirable to find direct, simple and efficient synthetic procedures to construct diversified benzoxazinones using easily accessible substrates. It prompted us to explore the possibility of developing rhodium-catalyzed C-H activation of benzoic acid with dioxazolones as effective strategy to produce benzoxazinones with versatile structures.

Herein, we report our success in utilizing the carboxylic acid as functionalizable directing group in the rhodium(III)-catalyzed cascade reactions with dioxazolones (Scheme 1d). Notably, this directing group functioned twice to double amidate C–H



Scheme 1. Directing groups in C-H activation.

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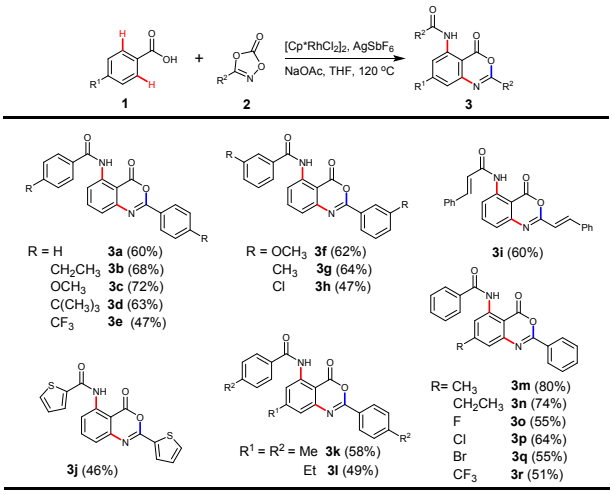
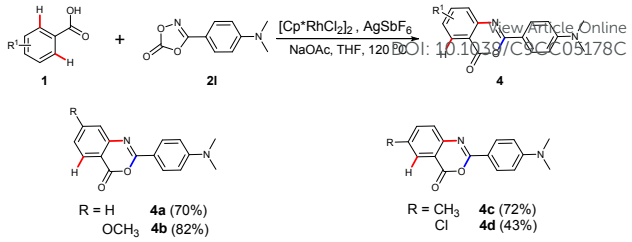
bond, and subsequently participated in the dehydration annulation to give benzoxazinones. The benzoxazinone products were then discovered for the first time to exhibit aggregation-induced emission (AIE) effect, together with excited-state intramolecular proton-transfer (ESIPT) phenomenon.

We embarked on our study with the optimization of reaction conditions using benzoic acid **1a** and 1,4,2-dioxazolone **2a** as the model substrates. The reaction was found to produce the desired benzoxazinones **3a** most efficiently in 5 mol% of $[RhCp^*Cl_2]_2$, 30 mol% of $AgSbF_6$ and 0.2 mmol NaOAc in THF at 120 °C for 12 h (entry 14, Table S1, ESI).

With the optimal conditions in hand, we examined the generality and limitation of this Rh(III)-catalyzed reaction. As shown in Scheme 2, dioxazolones bearing substituent groups at *para*- or *meta*-positions on the phenyl ring were all well tolerated to provide the corresponding N-heterocycles in moderate to good isolated yields (**3a–3h**), wherein substrates with nucleophilic groups on the *para*-position of phenyl ring showed higher yields (**3b–d**, 63–72%), than those with electrophilic group (**3e**, 47%). The similar effect was also observed with the substrates containing *meta*- substituted phenyl ring (**3f–3h**). Styryl and thiophene-substituted dioxazolones were also proven compatible with the reaction and gave moderate product yields of 60% and 46%, respectively (**3i** and **3j**). Also tolerated were dioxazolones and benzoic acids bearing the same *para*-methyl or -ethyl-substituted groups, providing corresponding products **3k** and **3l** in moderate yields. However, no desired product could be formed by substrates **2** hosting alkyl groups, such as methyl, t-butyl, and cyclo-propyl moiety. We then proceeded to investigate the scope of the benzoic acids. All *para*-substituted benzoic acids were amenable to the system, wherein the electron-donating groups showed better yields (**3m** and **3n**, 80% and 74%) than the electron-withdrawing groups (**3o–3r**, 51%–64%). Additionally, benzoic acids with occupied meta- or ortho-position failed to provide desired product,



Scheme 2. Substrate Scope for the Synthesis of **3**. Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (30 mol%), base (0.2 mmol), solvent (2 mL), 120 °C, 12 h. Isolated yields calculated based on the amount of dioxazolones **2**.



Scheme 3. Substrate Scope for the Synthesis of **4**. Reaction conditions: **1** (0.2 mmol), **2l** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (30 mol%), NaOAc (0.2 mmol), THF (2 mL), 120 °C.

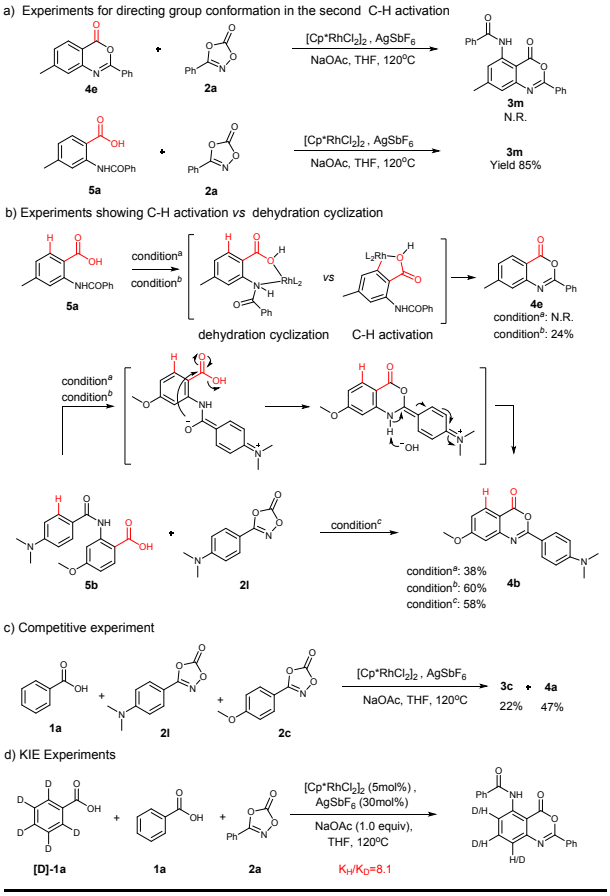
presumably due to the steric hindrance of the substituents which poorly affected the direct amidation process.

It is noteworthy that, when 3-(4-(dimethylamino)phenyl)-1,4,2-dioxazol-5-one **2l** served as amidating agent, single amidation and annulation took place, providing single substituted benzoxazinones product **4** (Scheme 3). Excessive amount of **2l** had no effect on the result wherein **4a** remained as the sole product in isolated yield of 70%. Through the same protocol, product **4b**, **4c and 4d** were also synthesized.

To gain insight into the pathways underlying these reactions (Scheme 2 and 3), we carried on the mechanistic studies to address specifically: (1) What is the function of the directing group in the second amidation of the first scenario? (2) What is the role of Rh(III) in the dehydration annulation and why does **2l** provide only single amidated product? (3) Is C-H activation the rate determining step in these reactions?

To determine whether the second activation during double-amidation reaction was directed by the given carboxylic acid or by the carbonyl group from the newly formed lactone, two parallel experiments were initially carried out as shown in Scheme 4a. Submitting the amidated and cyclized 2-substitued benzoxazinone **4e** to dioxazolone **2a** under the optimal reaction conditions could produce no desired product. Conversely, replacing **4e** with single amidated carboxylic acid **5a** afforded the product **3m** in 85% yield. These results suggest that it is the carboxylic acid that directs the second C-H activation prior to subsequent intramolecular cyclization that ultimately gives 2,5-substitued benzoxazinone product.

As shown in Scheme 4b, the absence of Rh(III) resulted in no formation of desired product **4e**, while 24% yield of **4e** was observed when Rh(III) was applied. The contrasting results showed that Rh(III) plays a key role as dehydrating agent in the cyclization, consistent with the previous report.[9f] However, depleting dioxazolone under the otherwise same reaction conditions resulted in significant lower annulation yield of **5a** than that of product **3m**, indicating that the second C-H activation is preferred than the dehydration cyclization. In the case of *para*-dimethylamino benzamide-substituted **5b**, the intramolecular annulation took place in the absence of dehydrating agent, affording the annulation product **4b** in 38% yield. This might ascribe to the strong electron-donating group of dimethylamino that enhances the nucleophilicity of the produced intermediate oxygen anion under base, prompting the automatic rapid nucleophilic addition and the following annulation. The involvement of Rh(III), on the other hand,

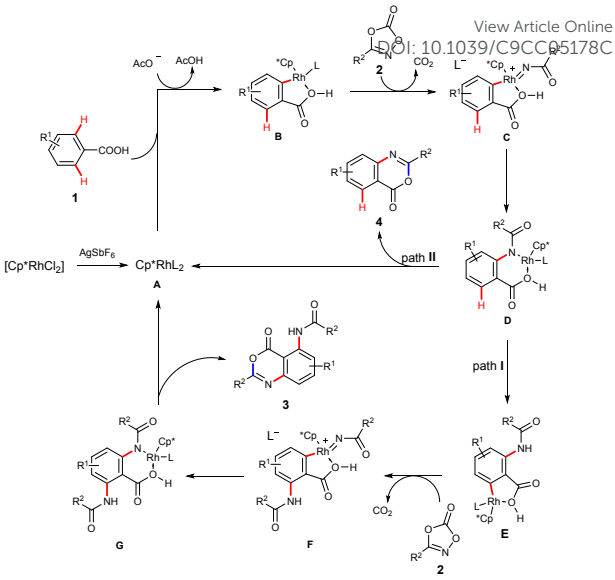


Scheme 4. Mechanistic investigation. Condition[a]: Substrate (0.2 mmol), $AgSbF_6$ (30 mol%), NaOAc (0.2 mmol), THF (2 mL), 120 °C, 12 h, isolated yield. Condition[b]: $[RhCp^*Cl_2]_2$ (5 mol%) was added under reaction condition[a]. Condition[c]: **2l** (0.4 mmol) was added under reaction condition[b].

enhanced the removal of water and therefore increased the yield of **4b** to 60%. Similar outcome was observed when **2l** was added to the reaction system. In this particular case, the strong electron-donating group of *para*-dimethylamino prompted the *in situ* annulation to provide the single amidated **4b** instead of double-amidated product.

Competitive reactions of benzoic acid **1a** with dioxazolones **2l** and **2c** (1 equiv. each) resulted in more turnover of **4a** (Scheme 4c) due to the fast automatic annulation facilitated by the strong electron-donating *para*-dimethylamino group, a finding consistent with the aforementioned observations in Scheme 4b. Additionally, the kinetic isotope effect (KIE) value under the given experimental conditions was found to be 8.1, implicating C–H activation in the rate-determining step (Scheme 4d).

On the basis of our results and the related reports,[6] a plausible catalytic cycle is proposed in Scheme 5. Initially, an active Rh(III) species **A** is generated from the anion exchange between chloride and hexafluoroantimonate. In the presence of acetate ion, **A** reacts with benzoic acid **1** to produce cyclometalated intermediate **B**, which is then coordinated by dioxazolone **2** to give intermediate **C** upon extrusion of CO_2. Subsequent migratory insertion of Rh-aryl bond affords an amidated



Scheme 5. Proposed Reaction Pathways

species **D**. Through path I, a second *ortho*-C–H bond of carboxylic acid is activated by the Rh(III)-catalyzed system to generate immediate **E**, which further reacts with dioxazolone **2** to afford **F**. The following intramolecular migratory insertion gives rise to intermediate **G**. Subsequent protonation of **G** by HOAc followed by tandem dehydration/cyclization sequences leads to the access of 2,5-substitued benzoxazinones **3** and the regeneration of catalyst **A** to continuously drive the reaction cycle. In the special case where (dimethylamino)phenyl-substituted dioxazolone is used, decomposition and subsequent cyclization are preferred by single-amidated intermediate **D**, as shown in short-cut path II, due to the strong electron-donating effect of dimethylamino group, ultimately leading to the formation of the 2-substitued benzoxazinones **4**.

Interestingly, products **3** were found to exhibit AIE behaviors (see Supporting Information for details) which prompted us to study their photophysical properties using **3a** as an example (Figure 1). The PL spectrum of **3a** in THF showed absorption and emission maxima at 372 and 407 nm respectively (Figure 1a), and the fluorescence quantum yield (Φ_f) value was detected to be 40.8% in solid state and 6.7% in THF. Continuous addition of water into the mixture of THF and **3a** induced solute aggregation, a phenomenon well reflected by the uniform increase of photoluminescence of **3a** at an emission wavelength of ~410 nm (Figure 1c). Raising the water fraction from 0 to 99% led to an over eightfold increase of intensity value (Figure 1d, black line) and the wavelength climbed from 407 nm to 452 nm (Figure 1d, red line).

Interestingly, another peak occurred at 507 nm when the water fraction reached 70% (Figure 1c), consistent with the previously observed photoluminescence of **3a** shown in Figure1a (right peak of red line). According to the related reports,[10] the ESIPT phenomenon might ascribe to the intramolecular bond between the amide hydrogen (N-H) and the carbonyl oxygen (C=O) forming a new ring or a twisted

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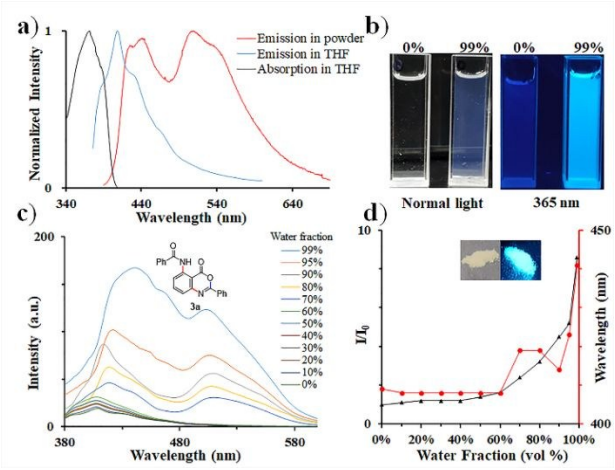

Figure 1. a) Normalized absorption and PL spectra of **3a**. b) Fluorescence photographs of **3a** with 0% and 99% water. c) Emission spectra of **3a** in THF/water mixtures. d) Plots of emission intensity I/I_0 (407 nm, black line) and wavelength (red line) of **3a** in different water fractions. (λ_{ex}= 372 nm, concentration: 10 μM).

conformation in solid state.

In conclusion, an efficient and practical Rh(III)-catalyzed amidation of benzoic acids with dioxazolones has been developed to afford diverse benzoxazinones. The application of carboxylic acid as a functionalizable directing group was successfully expanded in the regioselective amination wherein carboxylic acid directed twice the amidation reactions prior to the annulation to afford 2,5-benzoxazinones. A directed selective single amidation was also observed to deliver 2-benzoxazinones, a process exclusively driven by the dimethylamino group-substituted dioxazolones with strong electron-donating property. The mechanisms underlying these reactions were investigated and the catalytic pathways were proposed. Interestingly, 2,5-substitued benzoxazinones displayed prominent AIE properties with ESIPT phenomenon that can be utilized in various fields.

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Conflicts of interest

There are no conflicts to declare.

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