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COMMUNICATION

Rhodium(III)-Catalysed Carboxylate-Directed C-H Functionalizations of Isoxazoles with Alkynes

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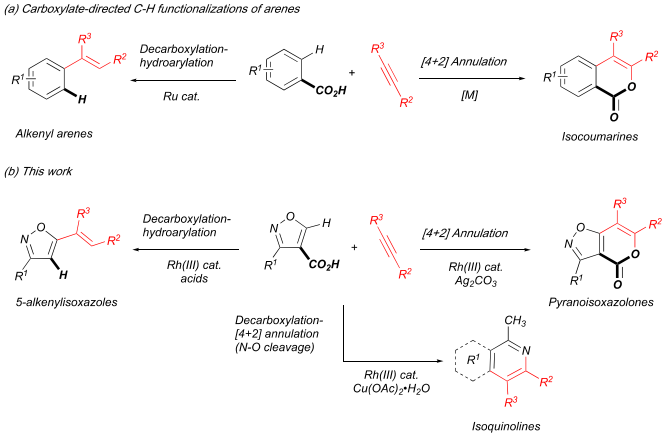
An efficient oxidative [4+2] annulation of isoxazolyl-4-carboxylic acids with internal alkynes proceeded in the presence of $[Cp^*RhCl_2]_2$ catalyst. Oxidants control the formation of pyranoisoxazolones and isoquinolines. Decarboxylative approach for hydroarylation of alkynes with isoxazolyl-4-carboxylic acids was also achieved in the presence of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ catalyst.

Transition metal-catalyzed direct C-H functionalization of arenes has gained much attention in organic synthesis for making C-C and C-heteroatom bonds, without pre-functionalization of the starting materials because these reactions are highly step and atom economy.[1] A directing group (DG) is able to facilitate C-H activation by enhancing the effective coordination with catalysts, resulting in both high reactivity and selectivity. Although various DGs have been reported for the direct C-H activation,[2] removal of these DGs from the products is not easy task and always requires additional chemical transformations.[3] In this regard, the carboxylate has been focused as a simple DG.

Miura et al., reported the first oxidative [4+2] annulation of benzoic acids with alkynes using Rh(III) catalysts for the synthesis of isocoumarins,[4] where the DG is involved as a component in a newly formed ring system in the reaction. After their report, other groups have also reported the synthesis of isocoumarin derivatives using various transition metals such as Pd(II) (acrylic acids),[5] Ru(II),[6] Ir(III)[7] and recently Co(III)[8] complexes for this annulation (Scheme 1a; right). In contrast, a decarboxylative approach for hydroarylation of akynes with benzoic acids also proceeded under the Ru(II)-catalyzed conditions (Scheme 1a; left).[9,10] A carboxylate acts as a DG to induce hydroarylation to alkynes and then decarboxylation takes place to afford *ortho*-alkenyl benzenes, although the strategy of a carboxylate as a removable *ortho*-directing group has been reported in tandem or separate manners.[11]

Isoxazole, as a heteroaromatic arene, is an important five-membered heteroaromatic ring system exhibiting various biological activities and applications in pharmaceuticals and agrochemicals, and also it acts as a masked 1,3-dicarbony intermediates in organic synthesis.[12,13] Conventional synthetic approaches of functionalized isoxazoles are based on ring construction with pre-functionalized linear components[12] and the direct C-H coupling on isoxazole ring is a still challenging task.[14] Recently, we succeeded in the generation of an 4-isoxazolyl anion species to introduce various functional groups including a carboxylate into C-4 of isoxazoles.[15] In this paper, we demonstrated the first carboxylate-directed C-H functionalizations of isoxazoles (Scheme 1b). Rh(III) catalysts enabled the direct C-H activation of isoxazolyl-4-carboxylic acids to react with alkynes for systematic synthesis of pyranoisoxazolones ([4+2] annulation), isoquinolines (N-O cleavaged decarboxylative [4+2] annulation), and 5-alkenylisoxazoles (hydroarylation of alkynes).



Scheme 1 (a) Carboxylate-direct functionalizations of arenes (known) vs. (b) carboxylate-direct functionalizations of isoxazoles with alkynes (this work).

We first examined the reaction of isoxazolyl-4-carboxylic acids **1a** (1.0 equiv.) and diphenylacetylene **2a** (1.2 equiv.), $[Cp^*RhCl_2]_2$ (5 mol %) as a catalyst and Ag_2CO_3 (0.5 equiv.) as an oxidant in DMF at 100 °C for 16 h. As shown in Table S1 in the supporting information, the expected pyranoisoxazolone **3aa** was obtained in 27% yield (entry 1). The molecular structure of **3aa** was further confirmed by single-crystal X-ray analysis (CCDC

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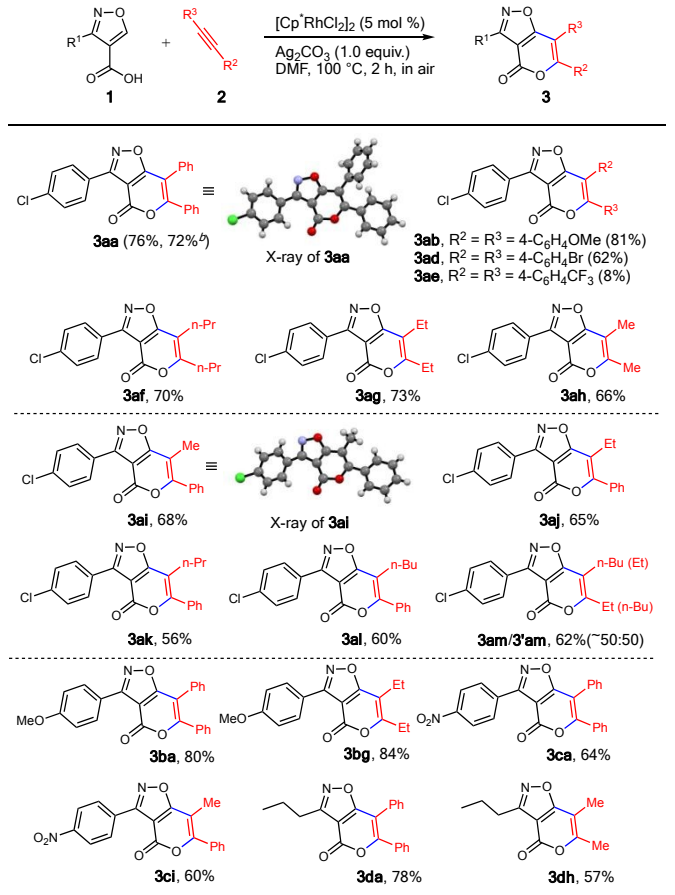
1870838; also see Table 1). The increase of the amount of oxidant Ag_2CO_3 afforeded the desired pyranoisoxazolone **3aa** in 72% yield (entry 2). Although other oxidants, such as $K_2S_2O_8$ and $AgNTf_2$ were not effective, AgOAc gave **3aa** in 53% yield (entries 3-5). Further, solvents and other additives have been examined to improve the yields, however **3aa** was observed in moderate to poor yields (eitries 6-11). The best result was observed when the reaction carried out under open air and **3aa** was obtained in 76% yield (entry 12). In the absence of Ag_2CO_3, **3aa** was observed in 8% yield, revealing the importance of oxidant in this transformation (entry 13). Interestingly, when $Cu(OAc)_2•H_2O$ was used as an oxidant instead of Ag_2CO_3, **3aa** was not observed and the product found to be isoquinoline **4aa** (entry 14). The structure of **4aa** was further confirmed by single-crystal X-ray analysis (CCDC 1870841; also see Table 3). However, **4aa** was not observed in presence of CuO or in the absence of Rh(III) catalyst (entries 17 and 18, respectively).

Table 1 Scope of Alkynes[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp*RhCl_2]_2$ (5 mol %), Ag_2CO_3 (1 equiv.), DMF (1 mL) under open air atmosphere. [b] Isolated yield in 1 mmol scale.

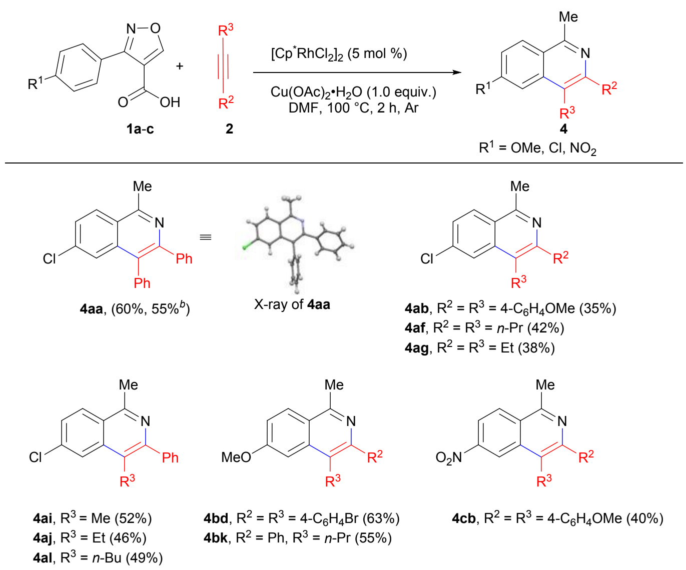
We next evaluated the generality and scope of these protocols for the introduction of various substituents in **3** and **4** (Tables 1 and 2). We first examined the reaction of **1a** with different symmetrical and unsymmetrical alkynes **2** for the synthesis of pyranoisoxazolones **3** (Table 1). Symmetrical alkynes **2b** and **2d**, having different *para*-substituents such as electron donating (-OMe) and electron withdrawing (-Br), respectively, on aryl ring underwent the oxidative annulation with **1a** to provide **3ab** and **3ad** in high yields. Similarly, electron rich alkynes such as **2f-h** also provided the corresponding pyranoisoxazolones **3af-ah** in good yields. When we used unsymmetrical alkynes **2i-l**, surprisingly single regioisomer of pyranoisoxazolones **3ai-al** was obtained exclusively. The regioisomer of pyranoisoxazolone **3ai** was confirmed by single-crystal X-ray analysis (CCDC 1870840). However, unsymmetrical aliphatic-disubstituted alkyne **2m**, gave a mixture of inseparable regioisomers of pyranoisoxazolone (**3am** and **3'am**) (~1:1) in 62% yield. We also examined the scope of isoxazolyl-4-carboxylic acids **1**. We have introduced different *para*-substituents such as electron donating (-OMe) and electron withdrawing ($-NO_2$) groups on aryl ring at 3-position of isoxazolyl-4-carboxylic acids **1b** and **1c**, respectively. Interestingly, these substrates underwent the oxidative annulation with both symmetrical and unsymmetrical alkynes (**2a**, **2g** and **2i**) to provide the corresponding pyranoisoxazolones, **3ba**, **3bg**, **3ca** and **3ci**, in high yields. The synthetic utility of this reaction was further extended by introducing alkyl (*n*-propyl) group at 3-position of 4-isoxazolyl carboxylic acid **1d** and the corresponding pyranoisoxazolones **3da** and **3dh** could also be obtained in 78% and 57% yields, respectively.

As mentioned earlier, we have observed the isoquinoline **4aa** exclusively instead of pyranoisoxazolone **3aa**, when we used $Cu(OAc)_2•H_2O$ as an oxidant and $[Cp*RhCl_2]_2$ as a catalyst. Thus, we next utilized for the synthesis of various substituted isoquinolines **4** through the oxidative annulation of isoxazolyl-4-carboxylic acids **1** and alkynes **2** as shown in Table 2. Various 3,4-substituted isoquinolines **4ab, 4af-ag**, **4bd** and **4cb** were obtained in moderate to good yields. Similarly, the reaction proceeded highly regioselectively with unsymmetrical alkynes **2i-l** to provide a single regioisomer of isoquinolines **4ai**, **4aj**, **4al** and **4bk** respectively, in good yields. However, the reaction of simple isoxazolyl-4-carboxylic acid with **2a** resulted in decomposition of the isoxazole ring.

In the substrate scope of pyranoisoxazolens **3**, we observed the formation of **5ae** i.e., hydroarylation of alkynes as a major product over **3ae** (Table 1). Intrigued by these results, we were further interested in the investigation of hydroarylation of alkynes using Rh(III)catalyst. We have tried various reaction conditions for the formation of **5** using $[Cp*RhCl_2]_2$, and other catalysts, additives, bases and solvents (Tables S2-S4). Finally, we found that 2.5 mol% of Rh(III) catalyst with the combination of $AdCO_2H$ (1.0 equiv.) and 0.3 equiv. of K_2CO_3 in mesitylene at 120 °C gave the best yield of **5aa** in 78 % (Table 3). The *E*-regioselectivity of **5aa** and **5ae** was further confirmed by single-crystal X-ray analysis (CCDC 1899700 and 1899699) respectively. With this optimized reaction conditions, we observed various hydroarylations of alkynes with isoxazolyl-4-carboxylic acids **1** in good yields. Unsymmetrical alkynes also provided excellent regioselectivity **5ai-ak** and **5cl**. Surprisingly, with aliphatic alkynes we have not observed the formation of **5af** and **5ag**, instead only annulated products were observed (**3af** and **3ag**). However, terminal alkynes did not provide **5** under these reaction conditions. The plausible mechanism for

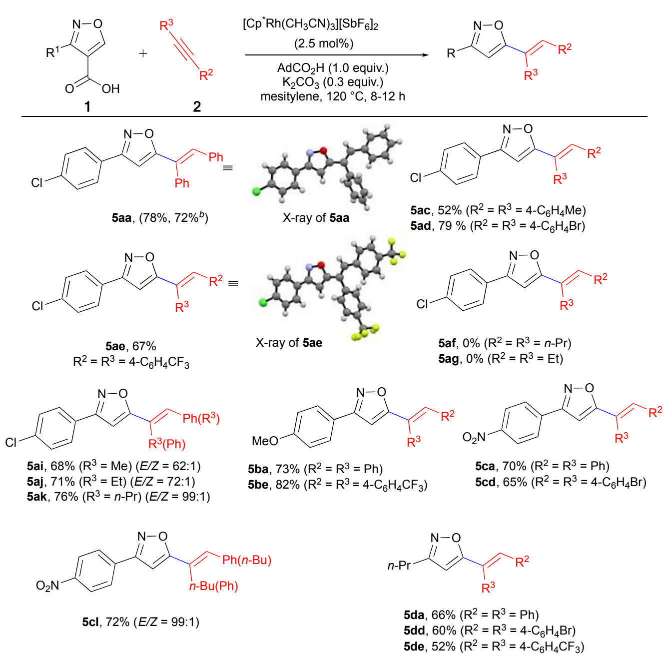
formation of pyranoisoxazolones **3** and decarboxylative hydroarylation products **5** is shown in Scheme S1 in the supporting information.

Table 2 Synthesis of Isoquinolines[a]



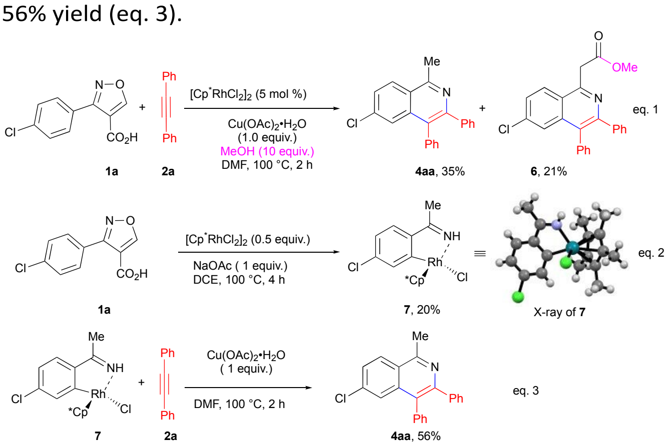
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2$•H_2O (1 equiv.), DMF (1 mL) under Ar atmosphere. [b] Isolated yield in 1 mmol scale.

Table 3 Hydroarylation of alkynes from isoxaolyl-4-carboxylic acids **1** and alkynes **2**[a]

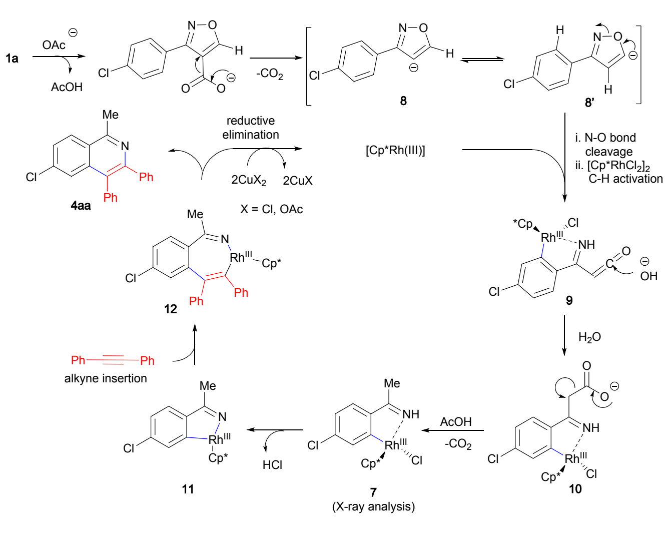


[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (2.5 mol %), $AdCO_2H$ (1 equiv.), K_2CO_3 (0.3 equiv.), mesitylene (0.5 mL). [b] Isolated yield in 1 mmol scale.

To clarify the mechanism for the formation of isoquinolines **4** in presence of Rh(III) catalyst, further experiments were conducted. Since the decarboxylation was observed in the reaction, we performed a reaction of 3-(4-chloropheny)isoxazole with **2a** to confirm whether the carboxylic acid group of **1** is required or not for the transformation. The reaction proceeded very slowly (48 h) to afford **4aa** in 18% yield along with 44% of starting material recovered, suggesting that the carboxylic acid group is necessary to accelerate the reaction rate to provide the product **4aa** in good yields. Further, the reaction of **1a** and **2a** in the presence of MeOH (10 equiv.) under the isoquinoline formation condition afforded the ethyl ester **6** in 21% yield in addition to **4aa** (Scheme 2; eq. 1). Finally, the rhodacyle intermediate **7** was able to be isolated by treating of stoichiometric amount of $[Cp^*RhCl_2]_2$ with **1a** as a possible reactive intermediate and its structure was confirmed by single-crystal X-ray analysis (CCDC 1870842; eq. 2). The reaction of the intermediate **6** with **2a** in the presence of $Cu(OAc)_2$•H_2O provided the isoquinoline **4aa** in 56% yield (eq. 3).



Scheme 2 Mechanistic Studies for the formation of **4**



Scheme 3 Plausible mechanism for the formation of **4**

Based on these observations, the plausible mechanism for the formation of isoquinolines **4** is shown in Scheme 3. Isoxazolyl-4-carboxylic acid **1a** undergoes decarboxylation in the presence of an acetate anion generated from $Cu(OAc)_2$•H_2O to generate the isoxazole anion **8**. There is an equilibrium between **8** and **8'** which undergoes N-O bond cleavage[17] followed by C-H activation by Rh(III)-catalyst to provide the intermediate **9**. The hydroxide anion attacks ketene in intermediate **9** to afford the corresponding product **10** which

undergoes decarboxylation and protonation to give isolable rhodacycle **7**. The generation of **10** was supported by the formation of **6** in the presence of MeOH (Scheme 2; eq. 1). Finally, HCl elimination of **7** forms five membered rhodacyle **11**, and then alkyne insertion followed by reductive elimination of **12** provides **4aa** (Scheme 2). Under the $[Cp^*RhCl_2]_2$ catalysed conditions, the decarboxylation of isoxazolyl-4-carboxylic acid **1a** (in the absence of alkyne **2a**) was observed in the presence of Ag_2CO_3, whereas the decomposition of **1a** was observed in the presence of $Cu(OAc)_2 \bullet H_2O$. These observations suggest that $Cu(OAc)_2 \bullet H_2O$ not only acts as an oxidant but also assists N-O cleavage to generate intermediate **9** in the catalytic cycle.

In conclusion, we have developed an efficient Rh(III)-catalyzed oxidative couplings of isoxazolyl-4-carboxylic acids **1** with internal alkynes **2** for the synthesis of pyranoisoxazolones **3** and isoquinolines **4** in good to excellent yields. Choice of oxidizing agents is essential to control both transformations of pyranoisoxazolones and isoquinolines. We have also developed decarboxylative approach for hydroarylation of alkynes **5** using Rh(III) catalyst, where carboxylic group acts as deciduous group/traceless directing group after C-H functionalization. This is the first to report for the synthesis of pyranoisoxazolones **3** and hydroarylation of alkynes **5** from isoxazolyl-4-carboxylic acids and alkynes. The broad substrate scope, high efficiency and good regioselectivity make these reactions more useful in the drug discovery process of isoxazole containing fused heterocycles and isoquinolines.

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Conflicts of interest

The authors declare no conflict of interest.

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