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Ruthenium(II)-Catalyzed C–H Activation/Annulation of Aromatic Hydroxamic Acid Esters with Enamides Leading to Aminal Motifs

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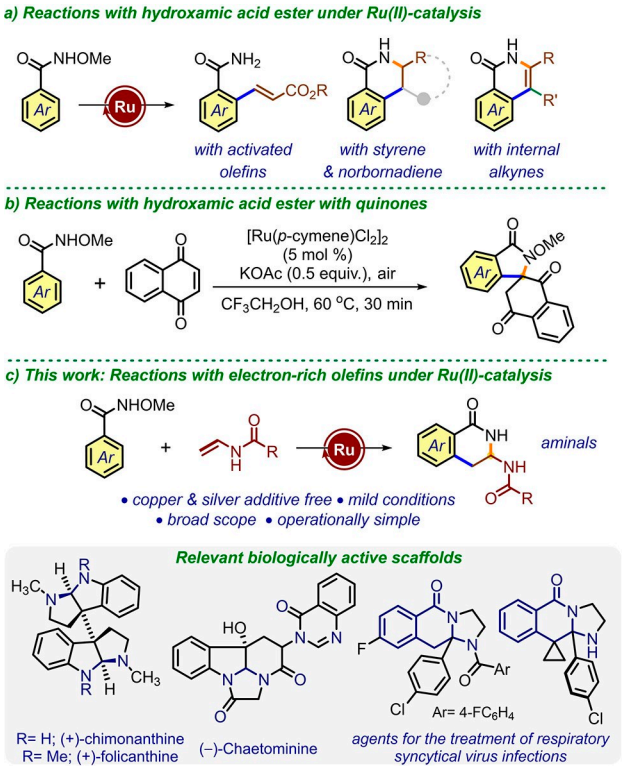
Hydroxamic acid ester directed C(sp^2)–H activation/annulation strategy has been reported employing electron-rich enamides under Ru(II)-catalysis to access aminal frameworks. Both *N*-vinyl acetamide and *N*-vinyl formamide delivered aminals bearing dihydroisoquinolinone motif in good yields. Under modified reaction conditions, vinyl acetate bestowed the selective formation of 3,4-unsubstituted isoquinolones. The protocol operates under mild conditions, where the C–H ruthenation step is reversible and apparently not the rate-determining step.

In the past two decades, the advancement in the transition-metal catalyzed C–H activation/annulation strategies have fetched dramatic influence in the field of organic synthesis, offering a wide range of synthetic transformations that could readily generate important carbocyclic and heterocyclic architectures from relatively simplified progenitors.[1] Particularly, the use of cheap and bench-stable Ru(II)-catalysts have exhibited tremendous potential, wherein various weakly coordinating common functional groups have been harnessed as directing groups to govern the reaction efficacy along with the regioselectivity.[2,3] In this regard, owing to the unique reactivity profile of NH–OMe functionality, C–H bond activation of aromatic hydroxamic acid esters have been extensively leveraged.[4,7] While the available N–O bond efficiently serves as an internal oxidant, obviating the need for stoichiometric metallic and nonmetallic oxidant additives, the increased nucleophilicity of the nitrogen-center could be judiciously engaged for annulation reactions under mild conditions. In 2012, Li and Wang employed aromatic hydroxamic acid esters for *ortho*-olefination with activated olefins under Ru(II)-catalysis (Scheme 1a).[5] The treatment of relatively unactivated olefins such as styrene and norbornadiene as well as internal alkynes bestowed annulated products with ruthenium catalyst (Scheme 1a).[5–6] Recently, we have also reported a spirocyclization reaction with quinones to access diverse spiroisoindolinones in a straightforward manner (Scheme 1b).[7] Despite these advancements, C–H activation/functionalization reaction of



Scheme 1. Hydroxamic acid ester directed C–H activation reactions under Ru(II)-catalysis.

arene hydroxamic acid esters with electron-rich olefins under ruthenium catalysis remained elusive.

Aminals embedded heterocycles are privileged frameworks present in numerous natural products and bioactive molecules (Scheme 1c).[8] They are also widely used as surrogates of imines in diverse organic reactions.[9] Consequently, developing succinct synthetic routes to access functionalized aminals is highly desirable. We envisioned that an annulative coupling of aromatic hydroxamic acid esters with electron-rich olefins such as enamides would be a straightforward method (Scheme 1c). Herein, we report the successful enactment of this approach under ruthenium catalysis leading to aminal frameworks embracing dihydroisoquinolinone motif.

It is worth noting that enamides were previously employed as coupling partners in C–H activation/annulation processes under Rh-catalysis.[10] With benzoic acids, Fu and Chen reported an annulation where *N*-vinyl formamide delivered isoquinolones and *N*-vinyl acetamide produced 3-acetaminoisochromanone

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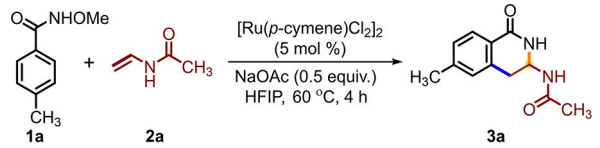
derivatives.[10a] They also observed a self-dimerization reaction in the case of *N*-vinyl benzamides in presence of Ag_2O oxidant and LiO^{t}Bu base.[10b] However, to the best of our knowledge, the reactivity of enamides has never been studied with Ru(II)-catalyzed C–H bond activation reactions.

We began our investigation utilizing *p*-toluic acid-derived hydroxamic acid ester **1a** and commercially available *N*-vinyl acetamide **2a** as model substrates (Table 1). Delightfully, when they were exposed to 5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$ in the presence of NaOAc (0.5 equiv.) in HFIP solvent at 60 °C, the desired annulated product **3a** was obtained in 83% isolated yield after 4 h (Table 1, entry 1). Further experimentation revealed that the solvent plays a crucial role in product formation.[11] While trifluoroethanol (TFE) delivered 16% yield of **3a** (entry 2), methanol and *iso*-propanol were found ineffective for this transformation (entry 3). Other common organic solvents such as 1,2-dichloroethane (DCE) and tetrahydrofuran (THF) were also incompetent to produce **3a** even after prolonged reaction time (entries 4 and 5). Next, the role of the base was examined. While KOAc displayed comparable reactivity (entry 6), other inorganic bases such as K_3PO_4 and K_2CO_3 gave inferior results (entry 7 and 8). Increasing the loading of NaOAc could not improve the yield (entry 9), whereas the

Table 1. Optimization of reaction conditions.[a]



Entry	Deviation from final conditions	Yield [%][b]
1	none	83%
2	trifluoroethanol instead of HFIP	16
3	methanol or *iso*-propanol instead of HFIP	NP[c]
4	DCE instead of HFIP	NP[c]
5	THF instead of HFIP	trace
6	KOAc instead of NaOAc	79
7	K_3PO_4 instead of NaOAc	57
8	K_2CO_3 instead of NaOAc	51
9	1.0 equiv. NaOAc	81
10	without NaOAc	trace
11	without Ru(II)-catalyst	NR[d]
12	$Pd(OAc)_2$ instead of Ru(II)-catalyst	NP[c]

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), NaOAc (0.5 equiv.), HFIP (0.5 mL), 60 °C, 4 h (reaction was set up under air atmosphere). [b] Isolated yields. [c] NP = no product formation with the recovery of **1a**. [d] NR = no reaction with the recovery of **1a**.

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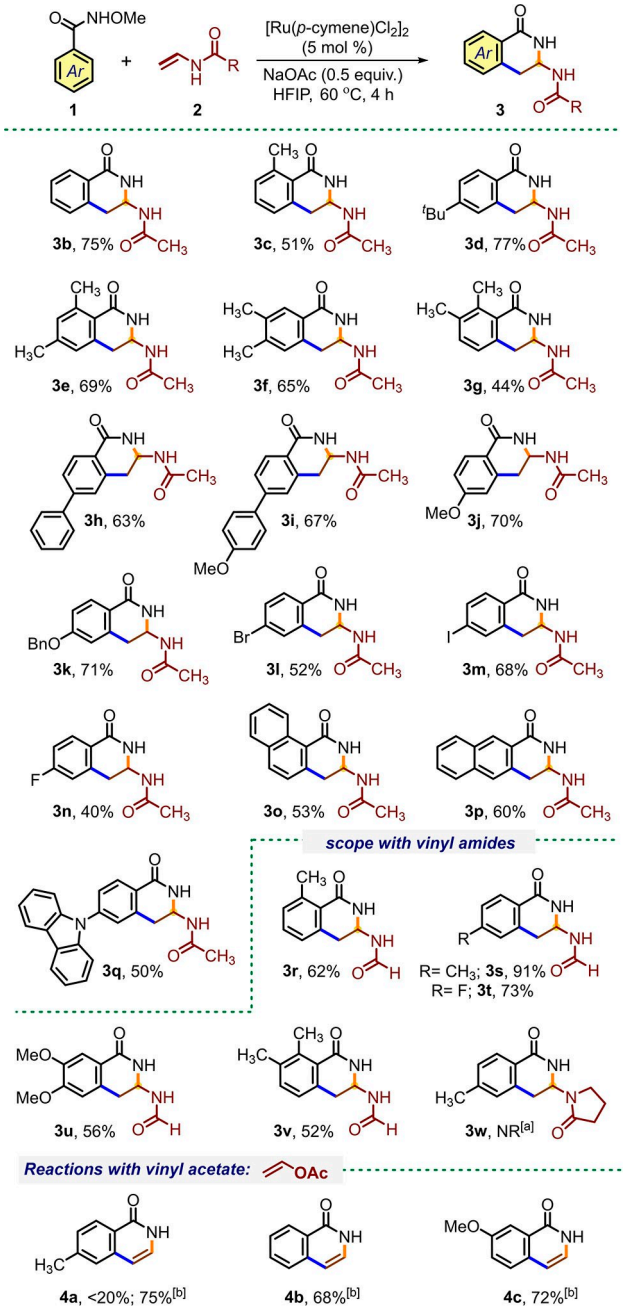
absence of the acetate base completely inhibited the reactivity (entry 10). The reaction was unproductive in the absence of Ru(II)-catalyst (entry 11). Altering the catalyst to $Pd(OAc)_2$ also could not deliver the desired product (entry 12).

Having acquired the standard reaction conditions, we next sought to unravel the substrate compatibility of this method (Scheme 2). The reaction was quite general for a variety of electronically and sterically distinct hydroxamic acid esters.



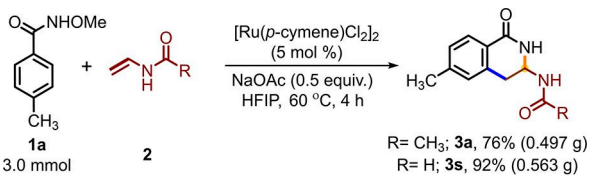
Scheme 2. Scope of substrates. Yields of Isolated products are given. Reaction conditions: **1a** (0.15 mmol), **2** (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), NaOAc (0.5 equiv.), HFIP (0.5 mL), 60 °C, 4 h (reaction was set up under air atmosphere). [a] NR = no reaction. [b] Reaction conditions: **1a** (0.3 mmol), vinyl acetate (**2d**) (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), K_3PO_4 (0.5 equiv.), HFIP (1.5 mL), 60 °C, 36 h.

Unsubstituted benzamide and benzamides consisting of alkyl substituents in various positions of the arene ring delivered corresponding aminals in moderate to good yields (**3b**–**3g**). The protocol also accommodated biphenyl derived amides to generate the aminal products **3h** and **3i** in 63% and 67% yields, respectively. Arenes consisting of electron-donating substituents were also effective substrates, offering aminal products in high yields (**3j**–**3k**). Synthetically useful halogen functionalities such as bromo (**3l**) and iodo (**3m**) were also sustained under the catalytic conditions, whereas electronegative fluoro-substituent (**3n**) resulted in reduced yield. Irrespective of the position of the amide functionality, polyaromatic naphthoic acid-derived amides offered aminals **3o** and **3p** in good yields. Notably, a biologically relevant carbazole derivative containing a benzamide moiety produced the corresponding aminal **3q** in 50% yield.

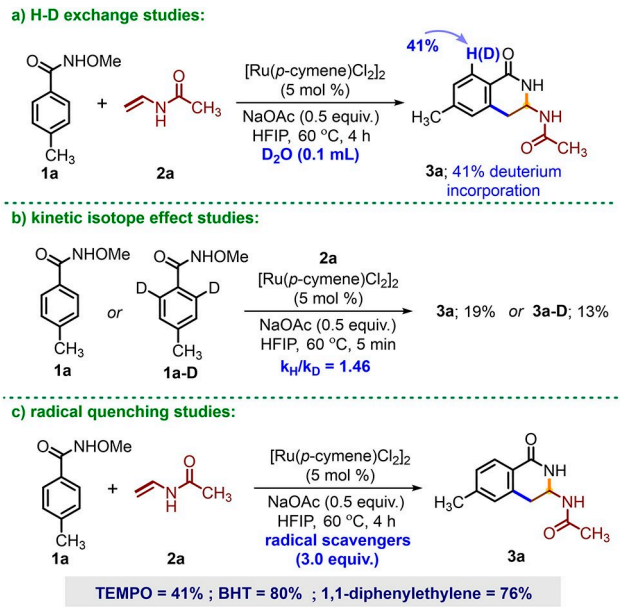
After successfully exploring the scope of the reaction with *N*-vinyl acetamide, other electron-rich olefins were examined under the standard reaction conditions. Similar to *N*-vinyl acetamide, *N*-vinyl formamide was also a fitting coupling partner with diverse aromatic hydroxamic acid esters, forging aminals **3r**–**3v** in good to excellent yields (Scheme 2). However, *N*-vinyl pyrrolidone failed to construct the desired aminal product **3w** and unreacted **1a** was recovered. Next, we wondered whether vinyl acetate can also be employed in this transformation. Accordingly, when we assessed vinyl acetate as a coupling partner under the developed catalytic conditions, we observed the formation of isoquinolone **4a** in poor yield (< 20%, Scheme 2). Reaction yield could be improved up to 75% after slight modification of reaction conditions (employing K_3PO_4 base) and further prolongation of reaction time. Under the modified reaction conditions, 3,4-unsubstituted isoquinolones **4b** and **4c** were also prepared in 68% and 72% yields, respectively (Scheme 2).

To showcase the synthetic utility, we examined the scalability of this process with *N*-vinyl acetamide as well as *N*-vinyl formamide (Scheme 3). To our delight, the efficacy of small-scale reactions was retained upon scale-up, producing **3a** and **3s** in 76% and 92% yields, respectively.

To gain insights into the mode of action of the catalytic system, we next performed a set of control experiments (Scheme 4). The addition of D_2O in the reaction mixture led to significant incorporation (~41%) of deuterium in the product, implicating a reversible C–H metalation process (Scheme 4a). The kinetic isotope effect (KIE) studies resulted in a value of ~1.46, which in combination with the earlier findings suggested that the C–H bond cleavage is probably not the rate-limiting



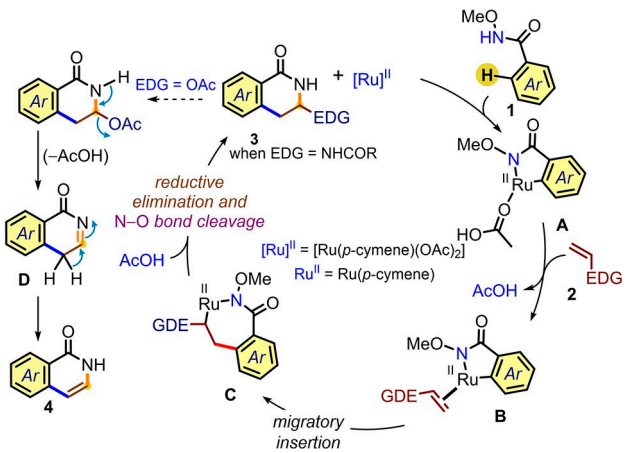
Scheme 3. Scaled-up reaction.



Scheme 4. Control experiments for mechanistic insights.

step (Scheme 4b).[7] The presence of superstoichiometric amounts of radical scavengers did not inhibit the reactivity, justifying the involvement of an organometallic pathway in the process without having any single electron transfer event (Scheme 4c).

Following the literature precedents[12] and above mechanistic experiments, a plausible reaction mechanism of this transformation is depicted in Scheme 5. First, amide **1** undergoes carboxylate-assisted C–H bond activation with Ru(II)-catalyst to form metallacycle **A**. It then coordinates with the olefin **2** and realizes a selective migratory insertion to generate metallacycle **C**, which upon reductive elimination and a facile N–O bond cleavage produces product **3** and regenerates the active Ru(II)-catalyst. At this juncture, we observed two distinct selectivity profiles with *N*-vinyl amides and vinyl acetate. When the



Scheme 5. Plausible mechanism.

electron-donating substituent is a poor leaving group such as acetamido or formamido functionality, the formation of **3** was observed as an exclusive product after the reductive elimination. If the olefin contains a good leaving group such as acetate, then compound **3** experiences a facile elimination of the acetate functionality leading to the formation of intermediate **D**, which upon tautomerization forms the 3,4-unsubstituted isoquinolone **4**.

In conclusion, we have demonstrated the annulative coupling of hydroxamic acid esters and enamides, constructing dihydroisoquinolinone derived aminal scaffolds in good yields. The reaction is operationally simple, air- and moisture-tolerant, and compatible with diverse common organic functionalities. Under modified conditions, the Ru-catalyzed strategy was also well-suited to utilize vinyl acetate as a coupling partner, where 3,4-unsubstituted isoquinolones were formed in high yields. Preliminary mechanistic studies suggested a reversible C–H metalation process to be involved in this reaction, where C–H bond cleavage is perhaps not the kinetically relevant step. Further exploration of hydroxamic acid ester directed C–H bond activation/annulation strategies are ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aminals · Annulation · C–H Activation · Homogeneous catalysis · Ruthenium

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