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Synthesis of Polyaromatic Rings: Rh(III)-Catalyzed [5 + 1] Annulation of Enaminones with Vinyl Esters through C–H Bond Functionalization

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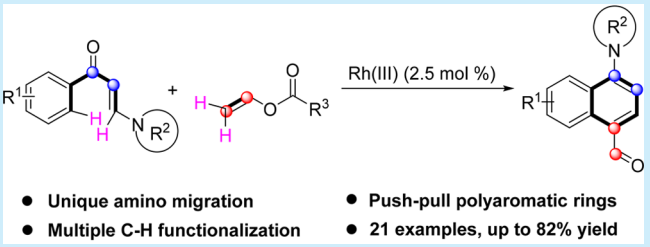
Supporting Information

ABSTRACT: An expedient [5 + 1] annulation method via Rh(III)-catalyzed C–H bond functionalization of enaminones to synthesize polyaromatic rings is described. The reaction tolerates a broad range of functional groups and offers a new entry to construct polycyclic aromatic compounds with amino and formyl substituents. A possible reaction mechanism was proposed based on the results obtained from isotope labeling experiments.



Transition-metal-catalyzed C–H activation has gained widespread applications in the total synthesis of natural products[1] and materials science research.[2] Since the pioneering work by Fagnou and Guimond in 2010 on the use of $[Cp^*RhCl_2]_2$-catalyzed $C(sp^2)$–H functionalization,[3] application of this method utilizing a nitrogen-containing auxiliary as a directing group coupled with annulation of the unsaturated C–C bond to synthesize aza-heterocycles have witnessed remarkable progress.[4] However, it has been a challenging task to construct carbocyclic compounds by this strategy since heteroatoms in the directing group may participate in the reaction to form heterocycles instead.[5] To overcome this problem, a less strong directing group is highly desirable for the Rh(III)-catalyzed $C(sp^2)$–H functionalization.[6]

As part of our continued interest in the C–H bond functionalization of enamines[7] as well as in the development of practical methods to access polyaromatic compounds,[8] we envisioned that using ketones as weak directing groups may be possible to install functionalized carbocyclic compounds via multiple sp^2 C–H functionalizations. Recently, Zhu's group has developed an elegant method to access aromatic rings based on the [4 + 2] annulation of enaminones with either alkynes or diazo compounds.[9] Herein, we demonstrate for the first time a Rh(III)-catalyzed [5 + 1] annulation of enaminones and vinyl esters to construct useful functionalized polyaromatic rings through multiple C–H bond functionalizations (Figure 1).[10] The obtained 1,4-substituted polyaromatic derivatives carrying an electron-donating amino group and an electron-deficient formyl group are located in opposite position of aromatics leading to push–pull electronic structure; this method could potentially be applied to the discovery of efficient fluorescent probes in biological and material science.[11]

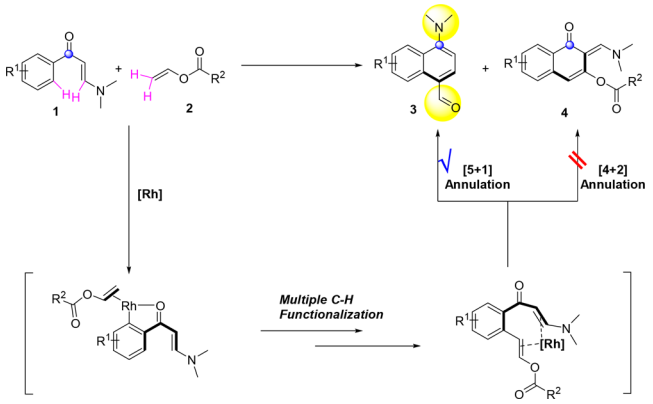


Figure 1. Rhodium-catalyzed C–H functionalization.

We first explored the possibility of annulation of enaminone **1a** with vinyl pivalate **2** in the presence of Rh(III) catalyst and KOAc with different oxidants in DCE at 125 °C (Table 1, entries 1–4). The annulation product 4-(dimethylamino)-1-naphthaldehyde **3a** was obtained when copper oxidants were employed, while other commonly used oxidants such as silver and $PhI(OAc)_2$ failed to promote the reaction. The structure of this product **3** was determined by NMR spectroscopies and further confirmed by a single crystal X-ray analysis of **3m** (CCDC: 1524569) (Scheme 1). Screening other bases found that inorganic bases displayed higher reactivities compared to organic bases in the reaction (Table 1, entries 5–7). Enamines normally are sensitive to acid, and the reaction might generate the

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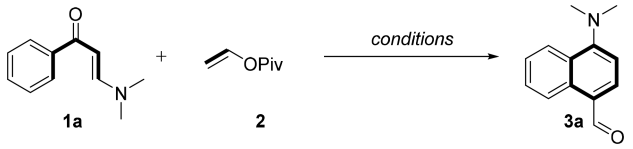
Table 1. Reaction Conditions Optimization[a]



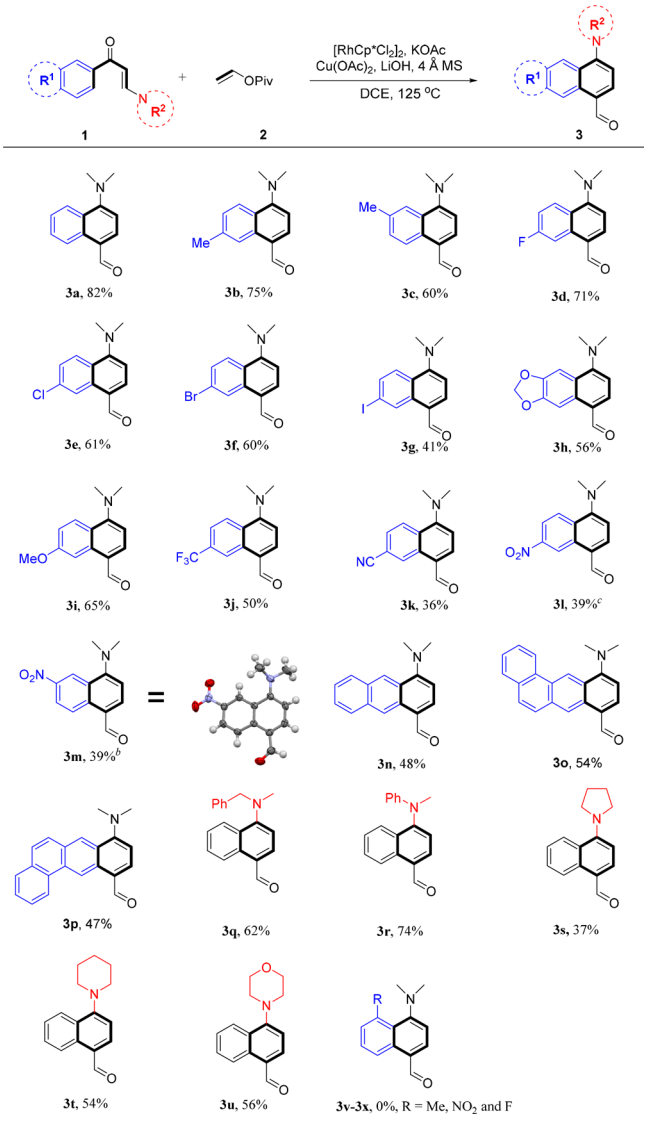
entry	catalyst	oxidant	base	additive	yield[b] (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	KOAc		66
2	$[RhCp^*Cl_2]_2$	CuOAc	KOAc		46
3	$[RhCp^*Cl_2]_2$	AgOAc	KOAc		0
4	$[RhCp^*Cl_2]_2$	PIDA	KOAc		0
5	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	K_2CO_3		45
6	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	KOH		50
7	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	TEA		0
8	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	KOAc	LiOH	71
9	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	KOAc	NaOH	67
10	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	KOAc	KOH	56
11	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	KOAc	LiOH	82[c]
12		$Cu(OAc)_2$	KOAc	LiOH	0
13	$[RhCp^*Cl_2]_2$		KOAc	LiOH	0

[a]Conditions: a mixture of **1a** (0.15 mmol, 1.0 equiv), **2** (0.75 mmol, 5.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (0.225 mmol, 1.5 equiv), KOAc (0.09 mmol, 0.6 equiv), LiOH (0.225 mmol, 1.5 equiv), 4 Å MS (100 mg), and DCE (1.5 mL) was sealed in Schlenk tube under nitrogen atmosphere, and the mixture was stirred until the **1a** was consumed completely. [b]Isolated yield. [c]100 mg 4 Å MS was added.

pivalic acid. Therefore, additional base additives were examined to modify the pH of the catalytic system (Table 1, entries 8−10). Remarkably, LiOH effectively promoted the reaction, and the desired product was obtained in 71% yield (Table 1, entry 8). Finally, the reaction was carried out with 2.5 mol % of $[RhCp^*Cl_2]_2$, 2.0 equiv of $Cu(OAc)_2$, 0.6 equiv of KOAc, 1.5 equiv of LiOH, and 100 mg of 4 Å MS in DCE at 125 °C under N_2 atmosphere, and the desired product **3a** was obtained in the highest yield (82%) (Table 1, entry 11). Control experiments performed in the absence of Rh catalyst or oxidant led to no desired product **3a** (Table 1, entries 12−13).

With the optimized reaction conditions in hand, we proceeded to screen the substrate scope of the reaction (Scheme 1). Overall, a broad range of functional groups was tolerated, and the corresponding products were obtained in moderate to good yields. Enaminones with aryl groups bearing methyl groups both at the *para* and *meta* positions were subjected to the optimized reaction conditions, and the corresponding 4-amino-naphthaldehydes were obtained in 75% and 60% yields, respectively (**3b** and **3c**). Unfortunately, *ortho*-substitued groups failed to react and recovered the starting material completely (**3v−3x**). Halogenic substituents (F, Cl, Br, and I) at the *para*-position of the phenyl groups were well tolerated (**3d−3g**). It is important to note that the bromo and iodo functional groups could be further transformed in many known coupling reactions.[12] Enaminones with aryl groups bearing electron-donating and electron-withdrawing groups were then explored to the standard reaction conditions to examine the electronic effect. The result revealed that substrates containing electron-donating groups (**3h** and **3i**) proceeded more efficiently compared to those containing electron-withdrawing (**3j−3m**) groups. Remarkably, when enaminones with polycyclic aromatic groups as substrates were employed using this new method, it has the potential to afford amino polycyclic aromatic aldehyde compounds, which have

Scheme 1. Substrate Scope[a,b]



[a]Conditions: a mixture of **1** (0.20 mmol, 1.0 equiv), **2** (1.0 mmol, 5.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (0.30 mmol, 1.5 equiv), KOAc (1.2 mmol, 0.6 equiv), LiOH (0.30 mmol, 1.5 equiv), 4 Å MS (135 mg), and DCE (2.0 mL) was sealed in a Schlenk tube under a nitrogen atmosphere, and the mixture was stirred until **1** was consumed completely. [b]Isolated yields.

great applications in material science. Indeed, the corresponding products could be obtained in synthetically useful yields ranging from 47% to 54% (**3n−3p**). Changing *N*-substituents from dimethyl to other alkyl and aryl groups, the desired annulation products were obtained in moderate to good yields, either with acyclic or cyclic amino substitutions (**3q−3u**).

With these encouraging results in hand, we carried out a series of experiments to explore the reaction mechanism (Scheme 2a). Initially, we carried out the experiment using the γ-carbon ^{13}C isotope labeled of enaminone **1a** under the optimized reaction conditions. NMR spectroscopic analysis (DEPT-135, HMQC, and HMBC) indicated that the ^{13}C labeled carbon is directly attached to the nitrogen. This result shows that the nitrogen group of the enaminone has migrated to the γ-carbon. In addition, when we carried out crossover experiments using enaminone **1b** and **1t**, we observed four different products (**3b**,

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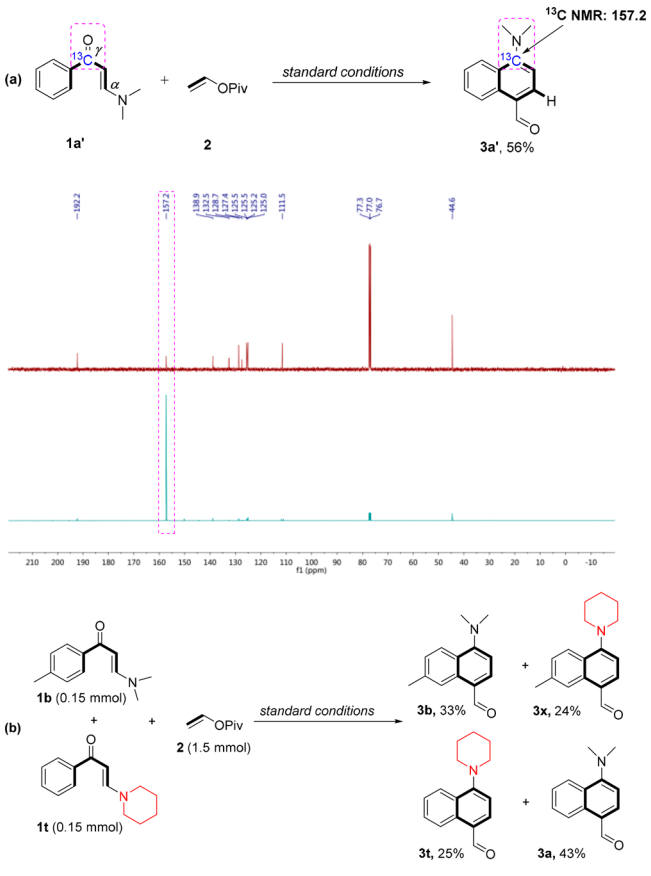
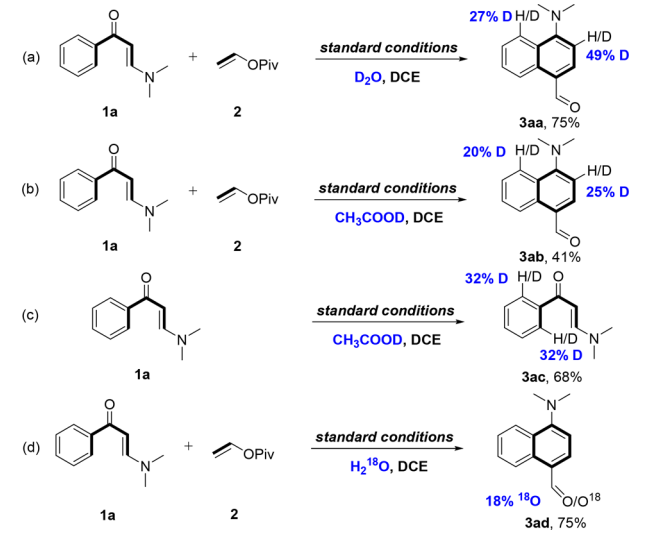
Scheme 2. ^{13}C Labelling and Control Experiments



3x, **3t**, and **3a**), indicating that the migration is an intermolecular reaction (Scheme 2b).

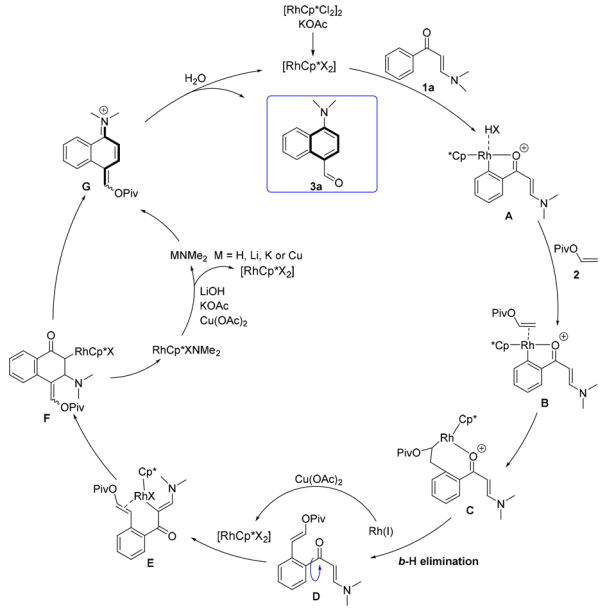
Next, we carried out the reactions in the presence of D_2O and CH_3COOD to probe the sites of the C−H bond functionalization. In this experiment, the obtained the products deuterium labeled at the *ortho*-position of the enaminone's phenyl group **3ab** and **3ac** with 27% and 20% deuterium, respectively (Scheme 3a,b). This result provides evidence of the possibility that the ketone is functioning as a weak directing group to assist the

Scheme 3. Reaction Mechanism Study



rhodium in activation C−H bonds of the phenyl group. Interestingly, we also found that the *β*−C−H bond of the enaminone was deuterated in the presence of either D_2O or CH_3COOD. To rule out the possibility of enaminone reacting with the acid, we carried out the reaction in the absence of vinyl pivalate **2** under the standard conditions (Scheme 3c). No isotope-labeled *β*−C−H bond was observed, indicating that the isotope-labeled product was most probably derived from a C−H bond functionalization assisted by rhodium (Scheme 4,

Scheme 4. Proposed Reaction Mechanism



intermediate **F**). Finally, we employed $H_2{}^{18}O$ under the standard reaction conditions. The ^{18}O labeling product was obtained in the formyl group. It supports the proposed that the formyl group may undergo a hydrolysis process.

On the basis of the above experiments, we propose a possible reaction pathway as depicted in Scheme 4. Initially, $[RhCp^*Cl_2]_2$ activates the *ortho*-position of the phenyl group via a weak keto coordination to generate intermediate **A**. Migratory insertion of vinyl pivatate **2** via intermediate **B** to form rhodium complex **C** followed by *β*-H elimination provides intermediate **D**. After rotation of the C−C bond, a pivalate-mediated C−H activation forms complex **E**. Next, a six-membered cyclic intermediate **F** is generated through reductive elimination. The amino group may then be released with the Rh complex and consequently condense with the keto group to give **G**. The desired product **3a** is finally obtained through hydrolysis and aromatization.

A large scale experiment was explored to investigate the potential applications both in academic and industrial laboratories (Scheme 5). The reaction proceeded efficiently on 5 mmol scale of **1a**, albeit in slightly decreased yield (45%). The obtained 4-(dimethylamino)-1-naphthaldehyde **3a** could be decorated both in the formyl and the amino groups. For example, the formyl group could be condensed with malonate,[13] olefinated with $MePPh_3Br$,[14] and reacted with Grignard reagent[15] (78%, 73%, and 82%). Furthermore, the amino group could also be functionalized to attach NO/NO_2.[16]

In summary, we have described an expedient [5 + 1] annulation method to synthesize polyaromatic rings via Rh-(III)-catalyzed C−H activation of enaminones. The reaction

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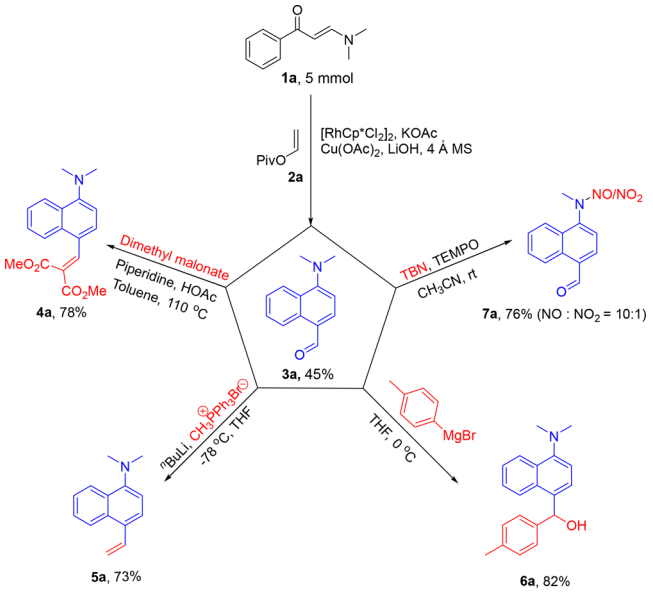
Scheme 5. Transformation of Functional Groups



tolerates a broad range of functional groups and offers a new entry to construct amino- and formyl-substituted polyaromatic compounds. A possible reaction mechanism was proposed based on a series of isotope labeling experiments. The application of this method for the synthesis of new polyaromatic materials is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03284.

Experimental procedures and characterization data for new compounds (PDF)

Accession Codes

CCDC 1524569 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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