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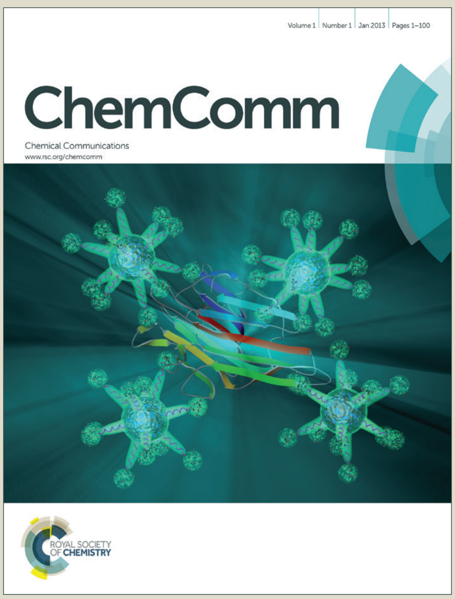

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Rhodium(III)-Catalyzed C–H Activation/[4+3] Annulation of *N*-Phenoxyacetamides and α,β-Unsaturated Aldehydes: an Efficient Route to 1,2-Oxazepines at Room Temperature†

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An efficient Rh(III)-catalyzed coupling reaction of *N*-phenoxyacetamides with α,β-unsaturated aldehydes to 1,2-oxazepines via C–H activation/[4+3] annulation has been developed. This transformation does not require oxidants and features C-C/C-N bond formation to seven-membered oxazepine rings at room temperature. Further derivation of the 1,2-oxazepines leads to important chroman derivatives.

Rhodium-catalyzed chelation-assisted C–H activation–annulation reaction has emerged as a powerful tool for the construction of diversified complex molecules.[1] [Cp*Rh^{III}] is a well-known catalyst for the C–H bond activation thanks to its high efficiency, mild reaction conditions and excellent functional group compatibility. The direct insertion of unsaturated molecules has been developed in Rh^{III}-catalyzed direct aryl C–H functionalization.[2] While various examples have been reported on the formation of five- and six-membered ring scaffolds, the studies using [Cp*Rh^{III}] complex to form seven-membered rings lag behind and the examples are rare.[3] Notably, there are three reports highlighting a [4+3] annulation strategy via Cp*Rh^{III}-catalyzed C–H functionalization. Glorius and co-workers pioneered a Rh-catalyzed reaction between amides and

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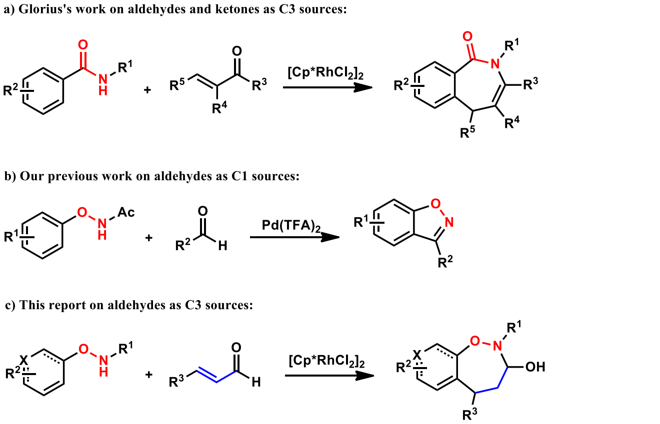
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all new compounds. CCDC1003334 (**3aa**), CCDC1003335 (**3oa**), CCDC1003336 (**4**) and CCDC 1011647 (**6**). For ESI and crystallographic data in CIF or other electronic format see DOI:10.1039/b000000x/



Scheme 1 Heterocycle synthesis through oxyacetamide-directed C–H activation/annulation.

unsaturated aldehydes and ketones to yield azepinones (Scheme 1a).[3a] Cui and co-workers reported two ingenious synthetic designs to azepinones via Rh-catalyzed coupling of amides with methylenecyclopropanes and vinylcarbenoids.[3b,3c] Considering the importance of the seven-membered ring scaffolds and the difficulties of their quick assembly using conventional methods, there is a great need to expand their synthetic repertoire.

Recently, our group reported a palladium-catalyzed intermolecular [4+1] annulation reaction from *N*-phenoxyacetamides and aldehydes to form 1,2-benzisoxazoles. This development suggested that the aldehyde could serve as an excellent C1 component in C–H functionalization (Scheme 1b).[4a] Herein we hypothesized that α,β-unsaturated aldehydes could serve as C3 components in C–H activation/[4+3] annulation. If realized, this reaction would provide a convenient entry to oxazepines from simple oxyamides and widely available α,β-unsaturated aldehydes (Scheme 1c).

1,2-Oxazepine and its derivatives are an important class of seven-membered heterocycles that have been found in pharmaceuticals with potential biological and medicinal activities.[5] With our continued interest in C–H activation/ annulation, we report oxyacetamide-directed Rh^{III}-catalyzed C–

H activation/[4+3] annulations between *N*-phenoxyacetamides and α,β-unsaturated aldehydes to access 1,2-benzoxazepines. The atom-economic synthetic protocol features mild reaction conditions and good to excellent yields.

At the outset of this study, we chose *N*-phenoxyacetamide (**1a**) and acrolein (**2a**) as the starting materials (ESI,† Table S1). The reaction took place in the presence of 3 mol% $[Cp^*RhCl_2]_2$, 10 mol% Ag_2CO_3 and 2 equiv AcOH in CH_3CN at room temperature, affording 1,2-benzoxazepine **3aa** in 71% yield (Table 1, entry 1). The structure of **3aa** was confirmed by X-ray crystallographic analysis (Figure 1). The reaction did not proceed in the absence of Ag_2CO_3 (entry 2). To our pleasant surprise, use of pivalic acid (2 equiv) dramatically improved the yield to 98% (entry 3). A series of silver salts were also tested and we found that Ag_2CO_3 was the best choice (entry 4–6). Finally, a variety of solvents were screened and they all gave slightly lower yields than CH_3CN (entry 7–12). Omission of $[Cp^*RhCl_2]_2$ catalyst completely shut down the reaction (entry 13). Replacing of $[Cp^*RhCl_2]_2$ with $Cp^*Rh(OAc)_2$ avoided the need of silver additives and the results indicated that acids promoted the reaction and PivOH was superior to AcOH (entry 14–16).

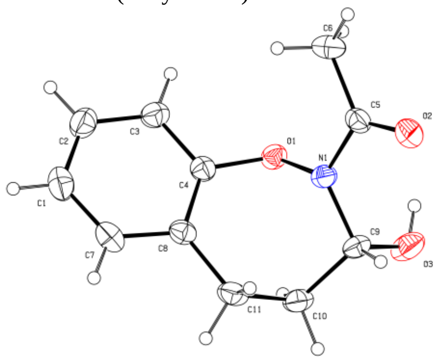
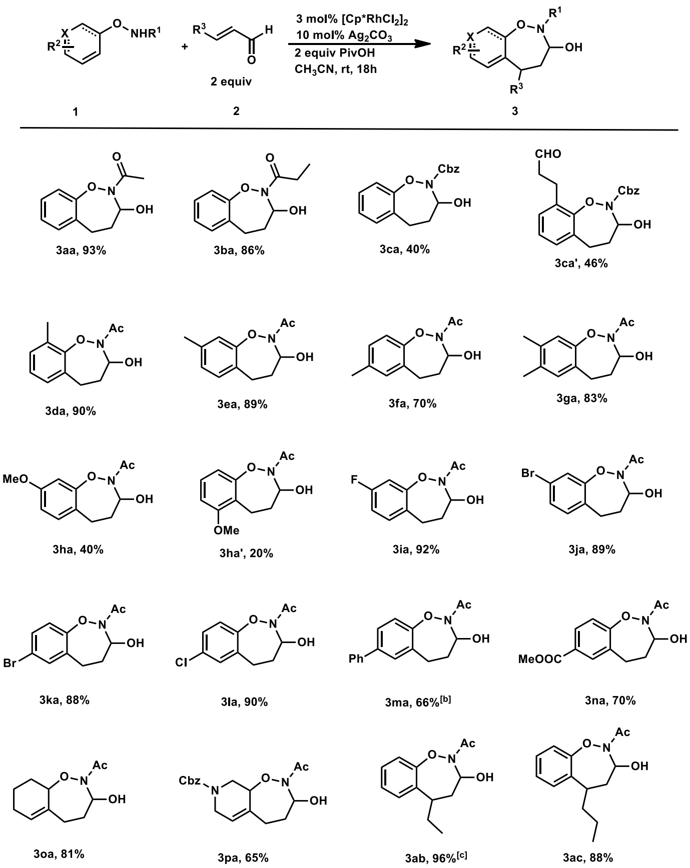


Figure 1 Crystal structure of 1-(3-hydroxy-4,5-dihydrobenzo[*f*][1,2]oxazepin-2(3*H*)-yl)ethanone (**3aa**)

With the optimized conditions in hand, we first explored the scope of *N*-phenoxyacetamides. The substituents on nitrogen were first examined. Replacing of the acetyl group with propionyl group gave **3ba** in 86% yield. Benzyloxycarbonyl group was also a suitable protecting group for this reaction, although we obtained the desired product **3ca** in 40% yield in addition to the aliphatic aldehyde derivative **3ca**' in 46% yield. The substituents on *N*-phenoxyacetamides were also investigated. The electron-donating substituents such as methyl (**1d**, **1e**, **1f**), dimethyl (**1g**) and methoxyl (**1h**) and electron-withdrawing groups such as fluorine (**1i**), bromine (**1j**, **1k**), chlorine (**1l**) and phenyl (**1m**), ester (**1n**) all proceeded smoothly to afford the corresponding products in moderate to high yields. It was worth noting that we obtained the mixture of regioisomers **3ha** and **3ha**' in 2:1 ratio from substrate **1h** bearing methoxyl substituent in the *meta*-position. It occurred with significantly altered regioselectivity as compared to other *meta*-substituted *N*-methoxybenzamide, such as **1e**, **1i** and **1j**.[2a] Substrate **1i** was annulated only at the less hindered *ortho* position with complete regiospecificity even though the fluorine atom is small. More excitingly, the reaction also proceeded well for nonaromatic substrates (**1o**, **1p**), affording the products in 81% and 65% yields, respectively. Crystal structure of **3oa** was shown in SI. We also examined the scope of unsaturated aldehydes, and found that (*E*)-pent-2-enal (**2b**) and (*E*)-hex-2-enal (**2c**) could successfully proceed in 96% and 88% yields, respectively. However, when the alkyl chain was displaced by aryl group, such as cinnamaldehyde, the reaction

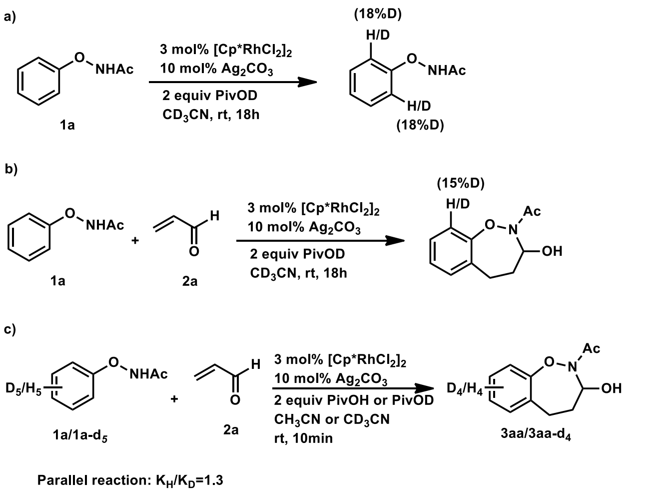
Table 2 Rh^{III}-catalyzed annulation of *N*-phenoxyacetamides **1** with α,β-unsaturated aldehydes **2**[a]



[a]Conditions: **1** (0.4 mmol), **2** (0.8 mmol), $[Cp^*RhCl_2]_2$ (3 mol%), Ag_2CO_3 (10 mol%) in the CH_3CN (2 mL) at rt under nitrogen atmosphere for 18 h, unless otherwise noted. isolated yields [b]Using **2** (3.0 equiv), the product containing an additional aliphatic aldehyde in the 9-position was also obtained in 33% yield. [c]Using **2** (3.0 equiv).

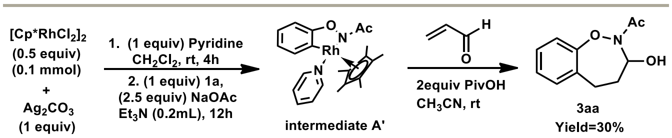
failed. Attempts to install a methyl group at the α-position of unsaturated aldehydes resulted in no reaction.

To probe the catalytic reaction mechanism, isotope experiments were carried out (Scheme 2). Exposure of substrate **1a** to $PivOD/CD_3CN$ afforded the substrate by 18% H/D scrambling *ortho* to the oxyacetamide group (Scheme 2a). We also conducted the reaction using PivOD as the acid and CD_3CN as the solvent, affording the desired product with 15% deuterium incorporation observed at the C-9 position (Scheme 2b). These results demonstrated that the C–H activation step was reversible.[6] Parallel experiments using equimolar amounts of d_5-**1a** and *N*-phenoxyacetamide **1a** were conducted independently to assess the rates of reaction for *ortho*-C–H vs. C–D. It gave a K_H/K_D ratio of 1.3, indicating that C–H bond cleavage could not be the rate-determining step (Scheme 2c).[7]

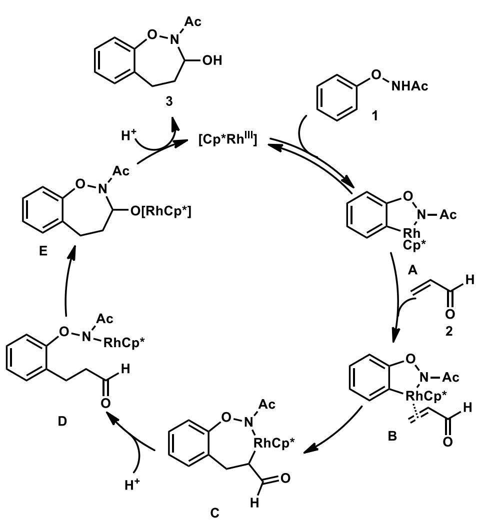


Scheme 2 Deuteration experiments.

To further explore the catalytic cycle, we carried out the synthesis and analysis of the possible intermediate. The substrate (**1a**) was treated with the active catalyst [Cp*Rh^{III}Py] species, prepared *in situ* from stoichiometric quantity of [Cp*RhCl$_2$]$_2$, Ag_2CO_3 and pyridine (Py) in CH_2Cl_2 at rt in the presence of NaOAc and Et_3N. The cyclometalated intermediate **A'** was obtained with 90% yield. Then it was treated with acrolein (**2a**) under our standard reaction conditions, affording the corresponding product **3aa** in 30% yield (Scheme 3). Pyridine was used to stabilize the cyclometalated intermediate,[8] but it suppressed the [4+3] annulation reaction to some extent as a controlled experiment in the presence of 15mol% pyridine afforded the desired product in 44% NMR yield, much lower than the 98% NMR yield for **3aa**. .



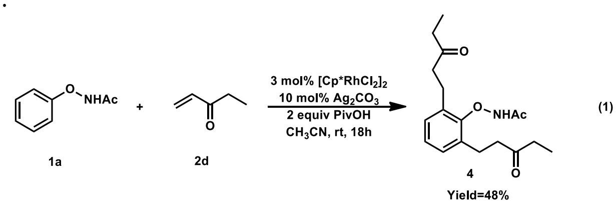
Scheme 3 Synthesis of the cyclometalated intermediate and transformation.

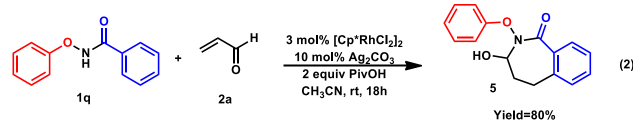


Scheme 4 Plausible mechanism.

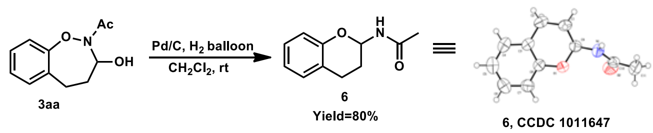
On the basis of these observations and literature precedence, a plausible mechanism was proposed, as shown in Scheme 4. First, an active catalyst [Cp*Rh^{III}] was generated from [Cp*RhCl$_2$]$_2$ and Ag_2CO_3. Then coordination of substrate **1** to [Cp*Rh^{III}] species went through cyclorhodation step, affording intermediate **A**. Intermediate **C** was obtained via alkene insertion. And then it produced the alkylated species **D** with the aid of acid. Lastly, the seven-membered ring intermediate **E** was formed via intramolecular nucleophilic attack,[4a,9] which was then protonated to produce the desired product **3** and regenerate the [Cp*Rh^{III}] species.

Interestingly, when unsaturated ketone such as pent-1-en-3-one (**2d**) was used as the coupling partner, we only obtained the di-alkylated product **4** in 48% yield with no cyclized products [Eq. (1)].[10] The structure of **4** was confirmed by X-ray crystallography (see SI). Furthermore, we examined the influence of both the oxyacetamide and amide directing groups with compound **1q**. Compound **1q** is interesting in that it has two directing groups to compete for sites of C-H activation. The reaction occurred regiospecifically at the position *ortho* to the amide group in Rh-catalyzed C–H activation, affording product **5** in 80% yield [Eq. (2)].[11]





We also explored the synthetic transformation of the obtained 1,2-oxazepines. The product **3aa** underwent the reduction reaction with a H_2 balloon, affording the unexpected benzo-fused oxygen heterocycle chroman derivative **6** in 80% yield.[12] Chromans are important building blocks in a number of biologically important molecules.[13]



Scheme 5 Synthetic transformation of the seven-membered ring product.

In summary, we have developed an efficient Rh(III)-catalyzed intermolecular [4+3] annulation method for the synthesis of 1,2-oxazepines from *N*-phenoxyacetamides and α,β-unsaturated aldehydes. This atom-economic protocol features mild reaction conditions, good to excellent yields, and no need for oxidants. Deuteration experiments suggested that C-H activation step is reversible and not rate-determining. The cyclometalated intermediate was synthesized and analysed. A mechanism involving C-H activation, alkene insertion, and intramolecular nucleophilic attack from a Rh amide was proposed. Reduction of the coupled 1,2-oxazepine product generated biologically important chroman derivatives. Investigations on developing new annulation methods based on O-NHAc moiety are underway and will be reported in due course.

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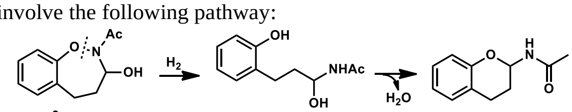

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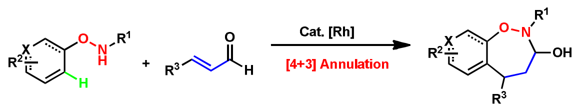

Rhodium-catalyzed C-H bond functionalization led to a [4+3] annulation strategy to access 1,2-oxazepine rings.