

# Mild Rhodium(III)-Catalyzed Cyclization of Amides with $\alpha,\beta$ -Unsaturated Aldehydes and Ketones to Azepinones: Application to the Synthesis of the Homoprotoberberine Framework\*\*

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The synthesis of azaheterocyclic compounds is a topic of continued interest due to the presence of this skeletal motif in countless natural products and synthetic compounds that display important chemical, biological, and medicinal properties.<sup>[1]</sup> Azepine and its derivatives at various oxidation levels fall into this category. Examples are azepinone-based natural products such as the checkpoint kinase 2 (Chk2) inhibitor debromohymenialdisine, the marine sponge constituent CID755673, which is a highly selective inhibitor of protein kinase D (PKD), and the matrix metalloproteinase inhibitor (–)-Cobactin T.<sup>[2]</sup> Benzazepines such as ribasine, isolated from *Fumariaceae* plants in 1983, and homoprotoberberines alkaloids that exhibit antimalarial and antibacterial properties (Figure 1).<sup>[3]</sup> Consequently, extensive research has focused on the development of effective routes towards azepine derivatives.<sup>[4]</sup> Herein, we report a novel method joining simple and readily available amides with  $\alpha,\beta$ -unsaturated aldehydes and ketones to construct azepinones for the

versatile and efficient preparation of numerous seven-membered-ring scaffolds.

Direct C–H activation has advantages over traditional protocols based on substrate preactivation.<sup>[5]</sup> The {Rh<sup>III</sup>Cp\*} fragment is one of the most frequently used catalysts for this transformation<sup>[6]</sup> and a number of novel C–H activation strategies for the synthesis of heterocycles have been explored.<sup>[7]</sup> In particular, the Rh<sup>III</sup>-catalyzed cyclization of benzamides represents a useful contribution to azaheterocycle synthesis. Among these, direct annulations of benzamides with CO, isocyanides, olefins, and aldehydes have been developed for the synthesis of five-membered heterocycles (Scheme 1 a).<sup>[8]</sup> Fagnou's,<sup>[9]</sup> Rovis',<sup>[10]</sup> Cramer's,<sup>[11]</sup> our,<sup>[12]</sup> and

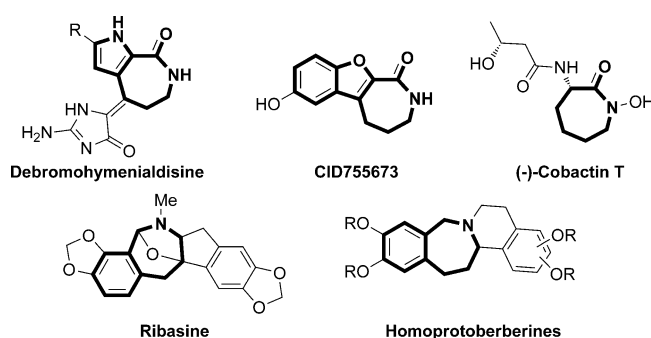
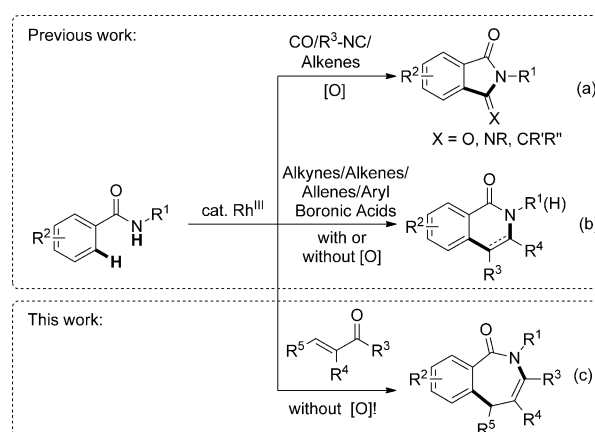


Figure 1. Important compounds containing azepine units.



Scheme 1. Rh<sup>III</sup>-catalyzed cyclization of benzamides to build five- (a), six- (b), and seven-membered rings (c).

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other groups<sup>[13]</sup> have reported the synthesis of isoquinolones and  $\delta$ -lactams by the Rh<sup>III</sup>-catalyzed coupling of benzamides with alkynes, alkenes, and allenes. Very recently, Cheng and co-workers reported the Rh<sup>III</sup>-catalyzed regioselective synthesis of phenanthridinones from benzamides and aryl boronic acids through C–C/C–N bond formation<sup>[14]</sup> in a one-pot transformation (Scheme 1 b). Although these methods have been shown to be highly efficacious in the construction of five- or six-membered azaheterocyclic skeletons, there is no report on the more challenging synthesis of seven-membered nitrogen-containing rings by these Rh-catalyzed transformations.<sup>[15]</sup> The proper choice of a suitable bridging unit is quite challenging due to the requirement of mild reaction conditions and ready availability.

Acrolein is the simplest unsaturated aldehyde, and has been widely utilized as the electrophilic component in Michael addition reactions and Diels–Alder reactions. The initial reaction of *N*-methoxybenzamide (**1a**) and acrolein (**2a**) was carried out in the presence of 2.5 mol % [(Cp\*RhCl<sub>2</sub>)<sub>2</sub>] and 10 mol % AgSbF<sub>6</sub> as the catalyst system, at 80 °C in dioxane under an Ar atmosphere. This set of conditions afforded the desired product **3aa** in 25 % yield after 12 h without additional oxidant (Table 1, entry 1). We

**Table 1:** Development of the reaction.<sup>[a]</sup>

| Entry | Cat. system                                                  | Additive (equiv)         | Solv.          | T [°C]    | Yield [%] <sup>[b]</sup> |
|-------|--------------------------------------------------------------|--------------------------|----------------|-----------|--------------------------|
| 1     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | –                        | dioxane        | 80        | 25                       |
| 2     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | Cu(OAc) <sub>2</sub> (1) | dioxane        | 80        | 30                       |
| 3     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | PivOCs (1)               | dioxane        | 80        | 18                       |
| 4     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | AcOH (2)                 | dioxane        | 80        | 26                       |
| 5     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | PivOH (1)                | dioxane        | 80        | 56                       |
| 6     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | <b>PivOH (2)</b>         | <b>dioxane</b> | <b>60</b> | <b>83</b>                |
| 7     | [RhCp*(MeCN) <sub>3</sub> ](SbF <sub>6</sub> ) <sub>2</sub>  | PivOH (2)                | dioxane        | 60        | 75                       |
| 8     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | PivOH (2)                | dioxane        | RT        | 56                       |
| 9     | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | PivOH (2)                | THF            | 60        | 69                       |
| 10    | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ] + AgSbF <sub>6</sub> | PivOH (2)                | EtOAc          | 60        | 35                       |
| 11    | AgSbF <sub>6</sub>                                           | PivOH (2)                | dioxane        | 60        | 0                        |
| 12    | [(Cp*RhCl <sub>2</sub> ) <sub>2</sub> ]                      | PivOH (2)                | dioxane        | 60        | 0                        |

[a] Conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), 2.5 mol % catalyst, 10 mol % AgSbF<sub>6</sub>, solvent (1.0 mL), 12 h, under Ar. [b] Yield of isolated product.

tested different additives in this system, and observed that PivOH was the most efficient, affording the cyclization product **3aa** in 56 % yield (Table 1, entries 2–5). To our delight, increasing the amount of the acid additive to 2.0 equiv improved the yield, providing 83 % of the product at lower temperature (Table 1, entry 6). Using a cationic rhodium species afforded **3aa** in only slightly lower yield (Table 1, entry 7), suggesting that [Cp\*Rh(SbF<sub>6</sub>)<sub>2</sub>] is the likely catalytically active species. Under these conditions, lowering the reaction temperature or changing the solvent gave lower yields of **3aa** (Table 1, entries 8–10). Control reactions confirmed that the transformation does not occur in the absence of [(Cp\*RhCl<sub>2</sub>)<sub>2</sub>] or AgSbF<sub>6</sub> (Table 1, entries 11 and 12).

With the optimized conditions in hand, we examined the scope of this C–H activation and cyclization process (Table 2). First, the effect of N substituents was examined. We were pleased to find that besides the *N*-methoxy derivative, *N*-alkylbenzamides such as *N*-methyl- (**1b**), *N*-*n*-butyl- (**1c**), and *N*-benzylbenzamides (**1d**) were also suitable substrates for this transformation. However, substrates with other N substituents such as H, phenyl, and OPiv did not afford the corresponding products. Interestingly, when 3.0 equiv of acrolein (**2a**) was used as the reaction partner of **1a**, we selectively obtained the aliphatic aldehyde derivative **3aa'** in 53 % yield by means of double C–H activation. The reaction was found to be tolerant of both electron-

**Table 2:** Rh<sup>III</sup>-catalyzed cyclization of benzamides **1** with  $\alpha,\beta$ -unsaturated aldehydes and ketones **2**.<sup>[a]</sup>

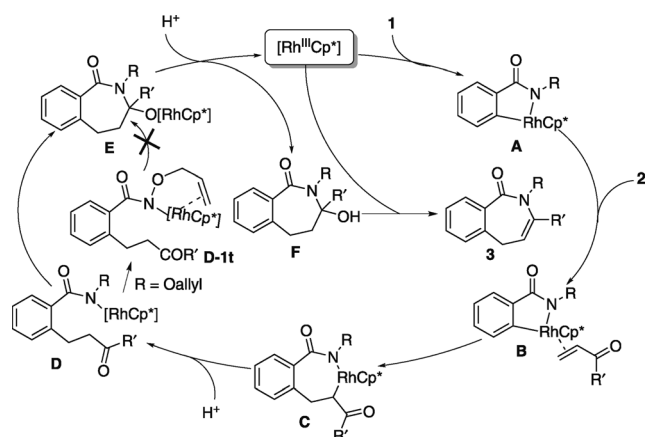
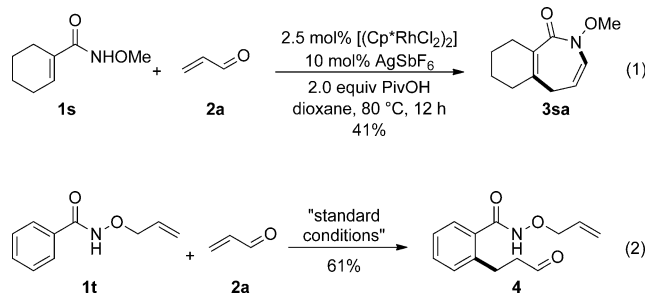
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|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | <p>R<sup>1</sup> = OMe, <b>3aa</b>, 83 %<br/> R<sup>1</sup> = Me, <b>3ba</b>, 67 %<br/> R<sup>1</sup> = <i>n</i>Bu, <b>3ca</b>, 56 %<br/> R<sup>1</sup> = Bn, <b>3da</b>, 64 %<br/> R<sup>1</sup> = H, Ph, OPiv: not detected</p> <p>R<sup>2</sup> = OMe, <b>3ea</b>, 78 %<br/> R<sup>2</sup> = F, <b>3fa</b>, 68 %<br/> R<sup>2</sup> = Cl, <b>3ga</b>, 67 %<br/> R<sup>2</sup> = Br, <b>3ha</b>, 71 %<br/> R<sup>2</sup> = I, <b>3ia</b>, 75 %<br/> R<sup>2</sup> = Ph, <b>3ja</b>, 76 %<br/> R<sup>2</sup> = COOMe, <b>3ka</b>, 71 %<br/> R<sup>2</sup> = NO<sub>2</sub>, <b>3la</b>, 45 %</p> <p>R<sup>2</sup> = Me, <b>3ma</b>, 50 %<br/> R<sup>2</sup> = F, <b>3na</b>, 54 %</p> <p>R<sup>2</sup> = Me, <b>3oa</b>, 79 %<br/> R<sup>2</sup> = CF<sub>3</sub>, <b>3pa</b>, 74 %</p> <p><b>3ab</b>, 63 %<sup>[c]</sup></p> <p>R<sup>4</sup> = Me, <b>3bc</b> + <b>3bc'</b>, 78 % (7 : 1)<sup>[c]</sup><br/> R<sup>4</sup> = Bn, <b>3bd</b>, 61 %</p> <p>R<sup>5</sup> = Me, <b>3be</b>, 32 %<sup>[c]</sup><br/> R<sup>5</sup> = Ph, <b>3bf</b>, 0 %<sup>[c]</sup></p> |

[a] Conditions: **1** (0.20 mmol), **2** (0.24 mmol), 2.5 mol % [(Cp\*RhCl<sub>2</sub>)<sub>2</sub>], 10 mol % AgSbF<sub>6</sub>, PivOH (0.4 mmol) in dioxane (1.0 mL) at 60 °C, 12 h, under Ar. [b] Using **2** (3.0 equiv). [c] Using **2** (2.0 equiv), at 80 °C; like **3aa'**, **3bc'** contains an additional aliphatic aldehyde in the 6-position.

donating groups such as methoxy (**3ea**) and methyl (**3ma** and **3oa**) and electron-withdrawing groups such as phenyl (**3ja**), carboxylate (**3ka**), nitro (**3la**), and trifluoromethyl (**3pa**). Halogen-containing substrates (**3fa–3ia** and **3na**) also reacted efficiently. This transformation also tolerates *ortho* substitution; the corresponding products (**3ma** and **3na**) can be produced under these optimized conditions in moderate yield. The naphthamide substrate **1q** can also be converted into the interesting product **3qa** in 88 % yield as a single regioisomer. Heterocyclic substrates were also tolerated, and the thiophene-annulated product **3ra** was produced in moderate yield.

The scope of other  $\alpha,\beta$ -unsaturated aldehydes and ketones as substrates was also investigated with benzamides as partners. We found the simplest enone, methyl vinyl ketone (**2b**), can also generate the cyclization product **3ab** without any difficulty. Surprisingly, the reaction of *N*-methoxybenzamide (**1a**) with methacrolein (**2c**) and benzylacrolein (**2d**) only gave trace amounts of the corresponding products, but under the same reaction conditions, **2c** and **2d** reacted with *N*-methylbenzamide (**1b**) to afford the desired products **3bc** and **3bd** in good yield. The reaction of crotonaldehyde (**2e**) gave a lower conversion, and cinnamaldehyde (**2f**) did not afford

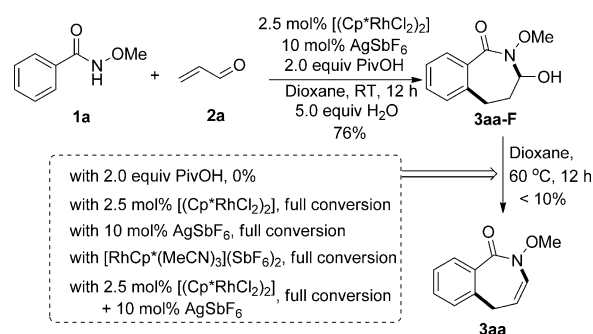
any cyclization product, presumably due to the steric hindrance of the phenyl group. Interestingly,  $\alpha,\beta$ -unsaturated amides such as **1s** can also react with acrolein (**2a**); the corresponding azepinone product **3sa** was obtained in 41% yield [Eq. (1)].<sup>[16]</sup> This finding greatly expands the range of synthetic applications. Interestingly, the subsequent cyclization step can also be suppressed by the choice of the N substituent: the coupling of the *N*-allyloxy derivative **1t** with **2a** under the standard conditions yielded the noncyclized product **4** [Eq. (2)].



Scheme 2. Plausible reaction mechanism.

On the basis of these investigations, a possible mechanism is proposed in Scheme 2. Coordination of the benzamide to a  $\{Rh^{III}Cp^*\}$  species appears to be crucial for the regioselective C–H bond cleavage to afford **A**. This rhodacycle can coordinate one equivalent of **2** to form **B**, which undergoes alkene insertion giving intermediate **C**. Subsequently, protonolysis of **C** delivers the carbonyl intermediate **D**.<sup>[17]</sup> The formed Rh–N bond can add across the carbonyl group affording the cyclorhodated intermediate **E**, which undergoes protonolysis to give the seven-membered-ring hemiaminal **F** and the recovered  $\{Rh^{III}Cp^*\}$  species.<sup>[8c]</sup> When **1t** is used as substrate, the formed Rh species may coordinate with the olefin and thus further cyclization is blocked. Finally,  $\{Rh^{III}Cp^*\}$ -catalyzed dehydration of **F** gives access to the desired enamide product **3**. Strong evidence in support of this step was obtained from the following experiments. Treatment of **1a** and **2a** in dioxane containing 5.0 equiv  $H_2O$  at room temperature afforded the hemiaminal **3aa-F** (isolated in 76%

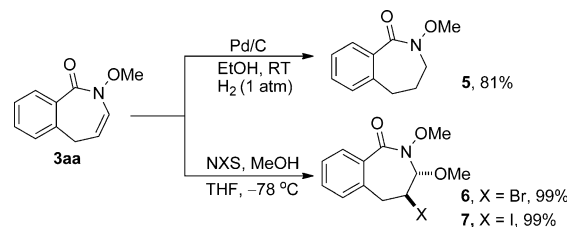
yield), which was stable in the presence of PivOH at 60 °C in dioxane. However, when the reaction was conducted with 2.5 mol%  $[(Cp^*RhCl_2)_2]$  and 10 mol%  $AgSbF_6$ , dehydration yielded product **3aa** with full conversion (Scheme 3). These tests indicate that the catalytically active species  $\{Rh^{III}Cp^*\}$



Scheme 3. Experiments probing the role of the  $\{Rh^{III}Cp^*\}$  species.

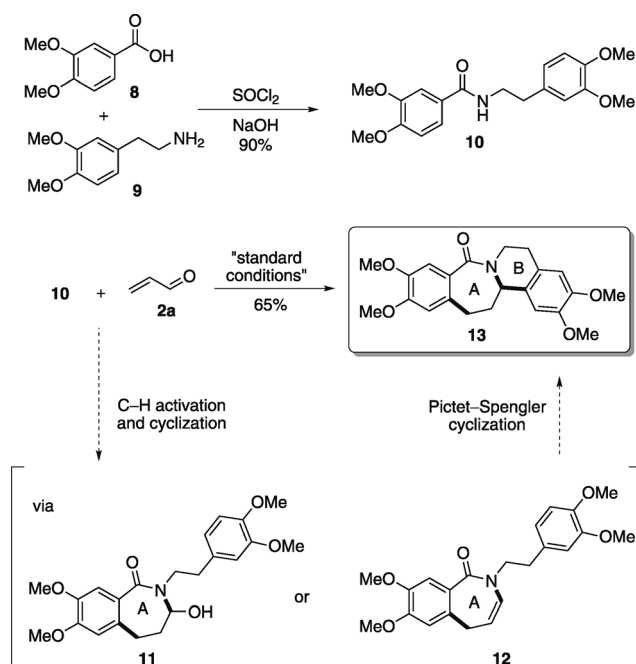
acts simultaneously as a transition-metal catalyst for C–H activation and as a Lewis acid catalyst for dehydration in this transformation.<sup>[18]</sup>

Facile manipulation of the enamine units in these azepinones offers an additional synthetic opportunity. For example, the double bond in **3aa** could be hydrogenated to yield  $\epsilon$ -lactam **5** in good yield. It is known that electrophilic additions to enolactams can provide useful intermediates for the synthesis of a number of nitrogen-containing natural products.<sup>[19]</sup> We employed **3aa** in the reactions with NBS/MeOH and NIS/MeOH systems. Both combinations exclusively produced single diastereomers of the corresponding halomethoxylation products **6** and **7** in almost quantitative yields (Scheme 4).



Scheme 4. Further applications of **3aa**.

The total synthesis of homoprotoberberines as exemplified by compound **13** has been reported by several groups.<sup>[20]</sup> Very recently, Couture and co-workers developed an efficient synthetic approach to **13** in 9 steps from readily available starting materials.<sup>[21]</sup> Since we had a reliable azepine synthesis method in hand, we commenced our synthesis with the preparation of benzamide **10** using the commercially available substrates veratric acid (**8**) and homoveratrylamine (**9**). Fortunately and surprisingly, reaction of **10** with acrolein (**2a**) under the optimized conditions led directly to **13**. This conversion likely involves C–H activation and cyclization for the formation of ring **A** and subsequent Pictet–Spengler cyclization for the formation of ring **B** (Scheme 5).



**Scheme 5.** Synthesis of the homoprotoberberine framework **13** by a reaction cascade consisting of C–H activation, cyclization, and Pictet–Spengler reaction cascade.

In summary, we have developed a novel and efficient method for the synthesis of azepinones utilizing benzamides and  $\alpha,\beta$ -unsaturated aldehydes and ketones as starting materials. This Rh<sup>III</sup>-catalyzed intermolecular annulation procedure involving tandem C–H activation, cyclization, and condensation steps, proceeds under mild conditions, releases H<sub>2</sub>O as the only byproduct, and displays a broad substrate scope with respect to the substituents. Furthermore, the highly efficient construction of the homoprotoberberine framework, involving Rh<sup>III</sup>-catalyzed C–H activation and cyclization as a key step, was accomplished.

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