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Rhodium Carbenoid Initiated O−H Insertion/Aldol/Oxy-Cope Cascade for the Stereoselective Synthesis of Functionalized Oxacycles

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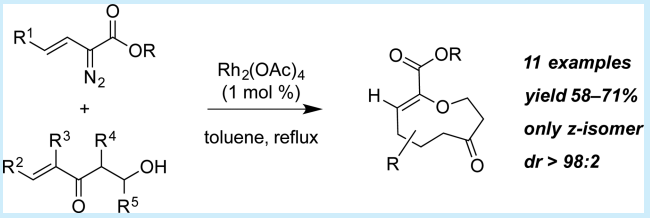
Supporting Information

ABSTRACT: A novel diazo-cascade approach has been developed for the synthesis of nine-membered oxacycles utilizing readily accessible β-hydroxy vinyl ketones and vinyl diazo esters. The Rh(II)-catalyzed cascade reaction begins with carbene O−H insertion followed by an intramolecular aldol cyclization to provide a substituted tetrahydrofuran intermediate that undergoes an oxy-Cope rearrangement to provide functionalized nine-membered oxacycles with complete stereoselectivity.



Cascade reactions are valuable tools for installing complex molecular designs with high efficiency, selectivity, and atom economy.[1] Other than being synthetically appealing, cascade transformations allow for price efficiency in terms of reagents, catalysts, solvents, and waste management as well as in time and efforts.[2] One of the biggest advantages of cascade reactions over classical synthetic reactions is the ability to carry out two or more transformations in a single step under the same reaction conditions.[3] These advantages together make them ideal to be considered for green chemistry synthesis.[4]

In continuation of our interest in cascade reactions initiated by carbene O−H insertion,[5] we now report a new approach involving β-hydroxy vinyl ketones and vinyl diazo esters for the synthesis of functionalized nine-membered oxacycles, which are important structural motifs found in many bioactive natural products.[6] There have been several reports in literature for the synthesis of oxacycles through cyclization of an appropriate linear precursor (Figure 1a).[7] The cyclization step often poses challenges due to entropic barriers and also requires high dilution conditions to avoid polymerization.[8] Ring expansion reactions that are insensitive to substrate conformational effects provide an alternative to the conventional cyclization strategy.[9] However, the synthesis of an appropriate precursor for the ring expansion reactions requires multiple steps and limits the synthetic utility.

To overcome this chemical challenge, we envision a cascade approach for the synthesis of oxacycles that utilizes readily accessible starting materials (Figure 1b). The cascade begins with carbene O−H insertion followed by an intramolecular aldol cyclization to provide a substituted tetrahydrofuran intermediate, which undergoes an oxy-Cope rearrangement to provide functionalized oxacycles.

Our hypothesis was inspired by our recently developed $Rh_2(esp)_2$-catalyzed chemoselective carbene O−H insertion

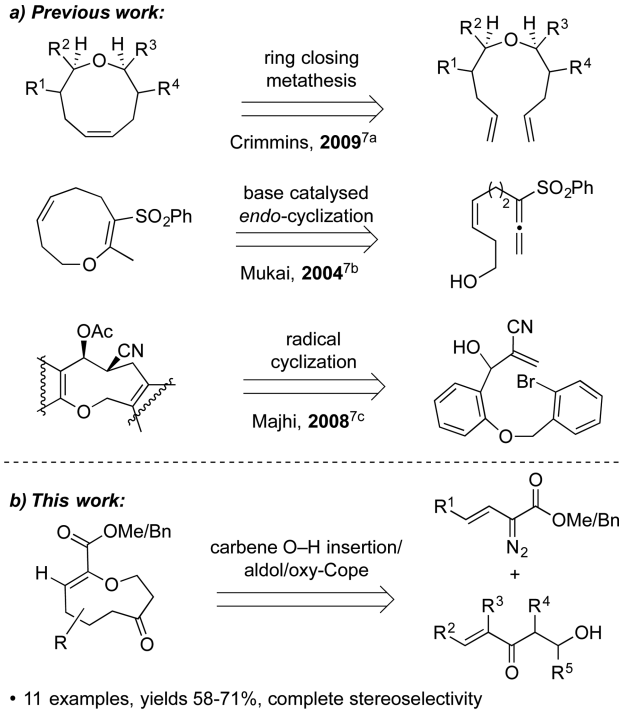


Figure 1. Synthetic approaches toward nine-membered oxacycles.

that accommodates varying functionalities including alkenes, alkynes, and substituted aromatics.[10] Additionally, cascade

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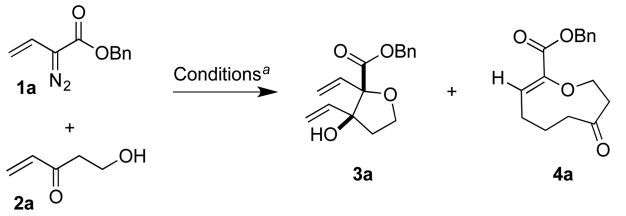
reactions initiated by carbene O−H insertion have been utilized for the synthesis of substituted tetrahydrofurans.[11] Furthermore, there have been reports of rhodium carbenoid initiated sigmatropic rearrangements in literature.[12]

For the initial optimization, vinyl diazo benzoate **1a** and *β*-hydroxy vinyl ketone **2a** were selected as model substrates and exposed to $Rh_2(esp)_2$ in CH_2Cl_2 at room temperature (rt), and under refluxing conditions (Table 1, entries 1, 2). To our

Table 1. Efficiency of Metal Salts in Carbene O−H Insertion/Aldol/Oxy-Cope Cascade[a]



entry	reagent	solvent, temp (°C)	product yield (%)[b]
1	$Rh_2(esp)_2$	CH_2Cl_2, rt	**3a**, 45
2	$Rh_2(esp)_2$	CH_2Cl_2, reflux	**3a**, 72
3	$Rh_2(esp)_2$	DCE, reflux	**3a**, 71
4	$Rh_2(esp)_2$	toluene, reflux	**4a**, 42
5	$Rh_2(OAc)_4$	toluene, reflux	**4a**, 68
6	$Rh_2(TFA^c)_4$	toluene, reflux	**4a**, 26
7	$Rh_2(HFB^d)_4$	toluene, reflux	**4a**, 29
8	$Cu(acac)_2$	toluene, reflux	CM[e]
9	$Cu(OAc)_2$	toluene, reflux	CM
10	Cu(OTf)	toluene, reflux	CM
11	$Rh_2(OAc)_4$	trifluorotoluene, reflux	**4a**, 67
12	$Rh_2(OAc)_4$	chlorobenzene, reflux	**4a**, 68

[a]All optimization reactions were performed by adding a 0.38 M solution of **1a** (1.5 equiv) into a 0.17 M solution of **2a** (1 equiv) with catalyst (1 mol %) over 3 h via a syringe pump; after the addition of a diazo compound, all reactions were refluxed for an additional 1 h. [b]Isolated yields after column chromatography. [c]TFA = trifluoroacetate. [d]HFB = heptafluorobutyrate. [e]CM = complex mixture.

expectations, diazo **1a** underwent a chemoselective O−H insertion followed by an aldol cyclization to yield **3a**, but did not proceed to oxy-Cope rearrangement to complete the third step of our envisioned cascade sequence. Since the oxy-Cope rearrangement could be thermally driven[13] we focused our attention toward identifying an appropriate solvent and temperature that would allow for the oxy-Cope rearrangement to proceed after yielding **3a** to generate the desired nine-membered oxacycle **4a**.

In order to initiate the cascade process at higher temperatures, we first attempted 1,2-dichloroethane (DCE, boiling point 84 °C) as a solvent, but met with a similar outcome to afford **3a** exclusively (entry 3). To our delight, toluene (boiling point 110 °C) at reflux obtained the desired oxacycle **4a**, albeit in low conversion (entry 4). Encouraged by this findings, we then screened other Rh(II)-salts to attain nine-membered oxacycle **4a** (entries 5−7). Among them, $Rh_2(OAc)_4$ was found to be the most efficient catalyst for the cascade sequence (entry 5). With hope to achieve the cascade sequence with earth abundant transition metal catalysts known to effectively form carbenoid intermediates, we also screened various Cu-salts,[14] but observed a complex mixture of different products without any trace of desired product **3a** or **4a** (entries 8−10).

Lastly, we also screened the effect of solvent polarity and reaction temperature with trifluorotoluene (boiling point 102 °C, entry 11) and chlorobenzene (boiling point 131 °C, entry 12) as a solvent respectively, but did not observe any significant improvement.

With optimized conditions in hand, we then investigated the scope of the carbene O−H insertion/aldol/oxy-Cope cascade sequence using $Rh_2(OAc)_4$ as a catalyst (Figure 2). Both the

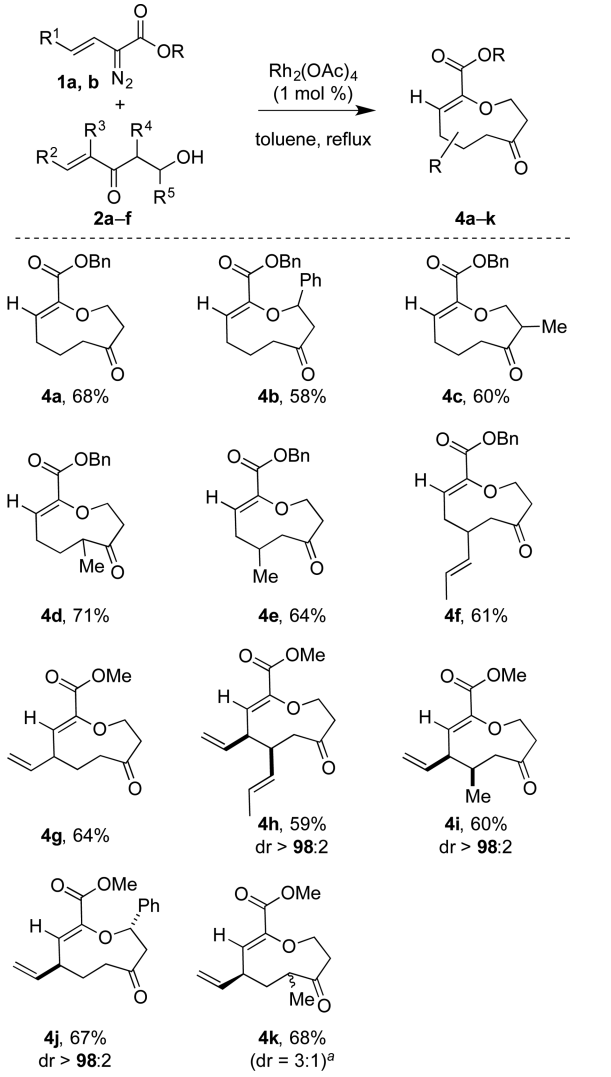


Figure 2. Scope of $Rh_2(OAc)_4$-catalyzed carbene O−H insertion/aldol/oxy-Cope cascade sequence; all reactions were performed by adding a 0.38 M solution of **1** (1.5 equiv) into a 0.17 M solution of **2** (1 equiv) over 3 h via a syringe pump; after the addition of a diazo compound, all reactions were refluxed for an additional 1 h. [a]The isolated compound **4k** was subjected to the reaction conditions $Rh_2(OAc)_4$ in refluxing toluene; no change was observed in the diastereomeric ratio.

primary and secondary alcohols proceeded in good yield with high stereoselectivity providing only *Z*-olefin oxacycles (Figure 2, **4a**, **4b**). We were pleased to find that the cascade sequence worked equally well with the substituted vinyl keto alcohols in good yields (Figure 2, **4c−e**). Notably, the cascade reaction also accommodated additional olefin functionality present in the starting material vinyl keto alcohol **2f** (Figure 2, **4f**) and in the vinyl diazo ester **1b** (Figure 2, **4g**).

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To further explore the generality of this transformation, substituted vinyl diazoesters were examined with the substituted vinyl keto alcohols. Remarkably, vinyl diazoester **1b** on treatment with substituted vinyl keto alcohols underwent the desired cascade sequence smoothly to obtain the corresponding oxacycles in good yields with complete stereoselectivity (Figure 2, **4h–j**). The stereochemical arrangement of substituents and *Z*-configuration of olefin was determined based on the nuclear Overhauser effect (NOE) correlations and was further confirmed by the single crystal structure of **4i** using X-ray crystallography (Figure 3, see the Supporting Information for more details).[15]

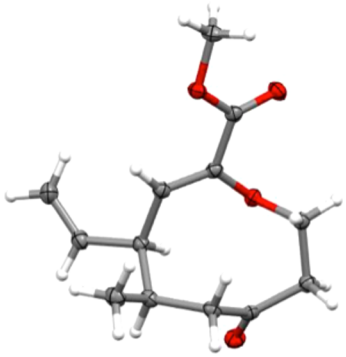
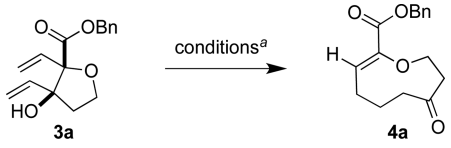


Figure 3. X-ray crystal structure of oxacycle **4i**.

Interestingly, we observed a decrease in diastereoselectivity (dr = 3:1) with vinyl keto alcohol **2d** bearing a substituent at the internal position of the olefin double bond (Figure 2, **4k**). This may be attributed to the transannular interaction present in the enol-form of the nine-membered oxacycle, which rearranges to the thermodynamically more stable keto-form as shown in the plausible mechanism (Figure 4).

For further insights into the reaction mechanism, additional experiments were carried out as shown in Table 2. First, the intermediate aldol product **3a**, which was isolated as as single diastereomer, was exposed to $Rh_2(OAc)_4$ in refluxing toluene. As expected, we observed a clean formation of oxy-Cope rearrangement product **4a** in excellent yield (Table 2, entry 1). Next, **3a** was refluxed in toluene without $Rh_2(OAc)_4$ to rule out the involvement of Rh-metal in the oxy-Cope rearrangement. As expected, the reaction took the same time to afford the compound **4a** suggesting a thermally driven oxy-Cope rearrangement (Table 2, entry 2).

Table 2. Oxy-Cope Rearrangement of Compound 3a into 4a under Thermal, Basic, and Acidic Conditions[a]



3a **4a**

entry	reagent	solvent, temp (°C), *t*	yield (%)[b]
1	$Rh_2(OAc)_4$	toluene, reflux, 2 h	88
2	–	toluene, reflux, 2 h	90
3	KH, 18-crown-6	THF, 0 °C, 5 min	CM[c]
4	LiHMDS	THF, 0 °C, 15 min	CM
5	CSA	toluene, rt to reflux, 2 h	CM

[a]All optimization reactions were performed with 0.1 M solution of **3a**. [b]Isolated yields after column chromatography; CSA = camphor sulfonic acid. [c]CM = complex mixture.

As oxy-Cope rearrangement could be catalyzed under basic conditions,[16] aldol product **3a** was subjected to different bases known to promote anionic oxy-Cope rearrangement. Unfortunately, we observed a complex mixture without any trace of desired oxacycle **4a** (Table 2, entries 3, 4). We also attempted acidic conditions to catalyze oxy-Cope rearrangement, but did not experience success (Table 2, entry 5).

These findings allow us to propose a reaction mechanism as depicted in the Figure 4.

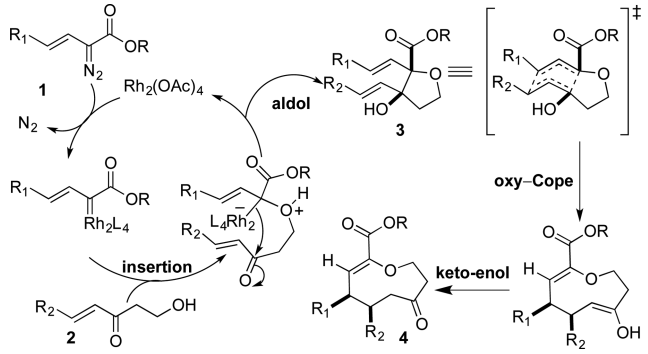


Figure 4. Proposed reaction mechanism for $Rh_2(OAc)_4$-catalyzed carbene O–H insertion/aldol/oxy-Cope cascade.

First, diazo compound **1** is decomposed by the $Rh_2(OAc)_4$ to form a Rh-carbenoid that undergoes a chemoselective O–H insertion reaction with the alcohol **2**. The resulting insertion intermediate then undergoes an aldol cyclization to provide a tetrahydrofuran intermediate **3** with high diastereoselectivity.[11] The tetrahydrofuran intermediate **3** sets the stage for a thermally driven concerted oxy-Cope rearrangement with a boat-type transition state, which results in an enol-form having both the substituents *syn* to each other. The enol-form then rearranges to the thermodynamically more stable keto-form **4**.

In conclusion, the reported rhodium carbenoid initiated O–H insertion/aldol/oxy-Cope cascade sequence is convergent in nature and uses readily accessible starting materials to access functionalized nine-membered oxacycles. An important feature of this transformation is its complete regio- and stereoselectivity. Applications of this chemoselective cascade reaction to the corresponding azacycles are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03229.

Complete experimental details and relevant spectra for all important compounds (PDF)

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Notes

The authors declare no competing financial interest.

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