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Rh(III)-catalyzed diastereoselective C-H bond addition/cyclization cascade of enone tethered aldehydes†

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The Rh(III)-catalyzed cascade addition of a C-H bond across alkene and carbonyl π -bonds is reported. The reaction proceeds under mild reaction conditions with low catalyst loading. A range of directing groups were shown to be effective as was the functionalization of alkenyl in addition to aromatic C(sp²)-H bonds. When the enone and aldehyde electrophile were tethered together, cyclic β -hydroxy ketones with three contiguous stereocenters were obtained with high diastereoselectivity. The intermolecular three-component cascade reaction was demonstrated for both aldehyde and imine electrophiles. Moreover, the first X-ray structure of a cationic Cp*Rh(III) enolate with interatomic distances consistent with an η^3 -bound enolate is reported.

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Introduction

Recently, the design and implementation of Rh(III)-catalyzed C-H bond functionalization has led to a diverse array of structural motifs, including many that are present in drugs and natural products.1-3 In particular, Rh(III)-catalyzed C-H bond additions to polarized π -bonds³ provides convergent entry to drug relevant amines,4 amides,5 alcohols,6 and oxygen or nitrogen heterocycles.7 While a variety of methods have been developed for direct $C(sp^2)$ -H bond addition into polarized π bonds, cascade addition sequences would offer an attractive strategy for rapidly building complexity into organic structures. To date, Rh(III)-catalyzed cascade C-H bond functionalization has primarily been reported for 5-membered ring synthesis by additions to an alkene or alkyne followed by cyclization upon the directing group for C-H bond activation.8 However, to the best of our knowledge, Lin and coworkers have reported the only example of Rh(III)-catalyzed C-H bond cascade addition to a π -bond and an electrophile other than the directing group. In their study, Rh(III)-catalyzed C-H bond addition to enones tethered to an alkyne proceeded to give substituted tetrahydrofurans (Fig. 1A). Herein, we demonstrate the Rh(III)-catalyzed cascade addition of a C-H bond across alkene and carbonyl π bonds. When the two electrophiles are tethered together, cyclic β-hydroxy ketone products incorporating three contiguous stereocenters are produced with high diastereoselectivity (Fig. 1B).10,11

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Results and discussion

For our initial exploration of this reaction we employed 2-phenylpyridine and the enone tethered aldehyde 2a based on successful Rh(III)-catalyzed hydroarylation of enones (Table 1). After considerable optimization, we found that β -hydroxy ketone 3a could be obtained in high yield as a single diastereomer with only 2.5 mol% of Rh precatalyst and 10 mol% of AgSbF₆ (entry 1). A 3:2 dioxane/H₂O reaction solvent at 50 °C was found to be effective. Lower conversion was observed at 30 °C (entry 2). Solvents commonly used in Rh(III)-catalyzed C–H functionalization such as dichloroethane (entry 3) and dioxane (entry 4) provided lower yields, and reducing the amount of H₂O also was detrimental (entry 5). In contrast, acetic acid as

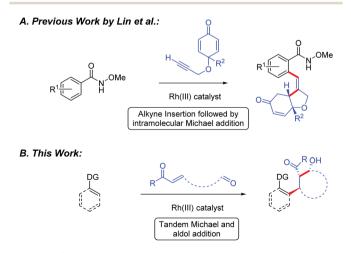


Fig. 1 Rh(III)-catalyzed cascade C–H bond addition across two different $\pi\text{-bonds}.$

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Table 1 Optimization conditions for the Rh(III)-catalyzed cascade addition/cyclization reactionab

Entry	Rh (mol%)/ Ag (mol%)	Solvent	Temp (°C)	Yield 3 a ^b (%)
1	(2.5)/(10)	3:2 Dioxane/H ₂ O	50	92
2	(2.5)/(10)	3:2 Dioxane/H ₂ O	30	67
3	(2.5)/(10)	DCE	50	58
4	(2.5)/(10)	Dioxane	50	35
5	(2.5)/(10)	95: 5 Dioxane/H ₂ O	50	61
6	(2.5)/(10)	Acetic acid	50	99
7	(2.5)/(0)	Acetic acid	50	57
8	(0)/(10)	Acetic acid	50	0
9	None	Acetic acid	50	0

^a Conditions: 1a (2.0 equiv.), 2a (1.0 equiv.) using [Cp*RhCl₂]₂ and AgSbF₆ for 20 h (0.2 M). b Determined by NMR analysis relative to 1,3,5-trimethoxybenzene as an external standard.

the solvent proved to be optimal, 7a,12a giving a near quantitative yield of the desired β -hydroxy ketone 3a (entry 6). Additionally, 3a was obtained in 57% yield when employing only the rhodium dimer [Cp*RhCl₂]₂ in the absence of a silver halide abstractor demonstrating that a pre-formed cationic Rh catalyst is not required for this transformation (entry 7). However, when rhodium was excluded, the desired product 3a was not obtained (entries 8 and 9).

After identifying optimal conditions for the formation of βhydroxy ketone 3a, we next explored the scope of the tethered electrophile substrate (Table 2). Pure 3a was isolated in near quantitative yield from the parent substrate 2a. Substrates with electron-donating and withdrawing substituents on the phenyl ring also afforded β -hydroxy ketones 3b, 3c, and 3d in high yield. X-ray structural analysis of 3b provided rigorous confirmation of product stereochemistry. An alkyl enone, which is a weaker acceptor than the corresponding aryl enone substrates, proved to be effective giving 3e with only a modest reduction in yield. Introduction of oxygen and nitrogen heteroatoms into the tether were also acceptable substitutions, and provided the substituted tetrahydropyran 3f and piperidine 3g, respectively. Additionally, the use of an aromatic tether was well-tolerated and gave indane 3h in good yield. However, for this substrate, 3:2 dioxane/H2O as solvent, a higher catalyst loading, and a lower reaction temperature were employed to minimize β-hydroxyl group elimination, which is particularly facile for β -hydroxy ketone 3h.

We next examined the scope for different C-H bond coupling partners (Table 3). Derivatives of 2-phenylpyridine with electron-donating and withdrawing substituents also provided high yields of the corresponding β-hydroxy ketones 3i, 3j, and 3k. Notably, the applicability of alkenyl C(sp²-H) functionalization to this transformation was demonstrated with 2-cyclohexenylpyridine, which gave 31 in good yield. Deviations from the pyridyl directing group are also noteworthy. The pyrazole and pyrimidine heterocycles were quite efficient in forming products 3m and 3n. N-Pyrimidylindole provided 3o, highlighting C-H functionalization on a heteroaryl ring. In addition, the N-methoxybenzamide and O-methyl oxime directing groups provided access to the products 3p and 3q in moderate yields. For these substrates, higher yields were obtained with 3:2 dioxane/H2O rather than acetic acid as solvent.

A mechanism for the Rh-catalyzed cascade C-H bond addition/aldol reaction is depicted in Scheme 1. The first step of this process proceeds via concerted metalation/deprotonation of 1 to generate rhodacycle 4, which has previously been proposed as an intermediate in other Rh-catalyzed C-H functionalization reactions.^{3,13} Coordination of the enone π -bond provides 5, which undergoes conjugate addition to give rhodium enolate 6. The rhodium enolate 6 can then undergo an intramolecular aldol reaction with the tethered aldehyde to form rhodium alkoxide 7.14 Coordination of another equivalent of 1 to the Rhalkoxide complex then provides 8, which undergoes concerted metalation/deprotonation to release the alcohol product 3 and regenerate the active rhodium species 4.15

Scope for tethered electrophile partner ab Table 2

Conditions: 1a (2.0 equiv.), 2 (1.0 equiv.), at 0.2 M. ^b Isolated yield after silica gel chromatography. c Reaction conducted at 40 °C. d Reaction conducted in 95 : 5 AcOH/H₂O (0.2 M). ^e Reaction conducted using 10 mol% $[RhCp*Cl_2]_2$ and 20 mol% $AgSbF_6$ in 3 : 2 dioxane/ H_2O (0.2 M).

Table 3 Scope for C–H bond partner^{ab}

 a Conditions: 1 (2.0 equiv.), 2a (1.0 equiv.) at 0.2 M. b Isolated yield after silica gel chromatography. c Reaction conducted in 3 : 2 dioxane/H₂O (0.5 M). d Reaction conducted in 3 : 2 dioxane/H₂O (0.2 M).

To ascertain whether or not cyclization upon the aldehyde carbonyl after enone addition proceeds via the proposed Rhenolate intermediate 6 (Scheme 1), the independently prepared acyclic enone addition product 9a was subjected to the reaction conditions with and without the cationic rhodium catalyst (Table 4). With dioxane/H₂O as the solvent (entries 1 and 2), a low yield of β-hydroxy ketone 3a was obtained even in the presence of the Rh precatalyst and AgSbF₆ (entry 1). In addition, whether or not Rh was added, complete consumption of 9a was observed, presumably as a result of selective formation of enolates or enols from the more acidic aldehyde functionality followed by unproductive side-reactions. These results are consistent with aldol cyclization proceeding via the Rh-enolate generated upon enone addition. When acetic acid was used as the solvent, a moderate yield of 3a was obtained suggesting that acetic acid can mediate this cyclization step, although once again decomposition pathways competed with the desired cyclization pathway (entries 3 and 4).

C-H bond addition to generate a rhodium-enolate intermediate was rigorously established using the simplified enone substrate phenyl vinyl ketone (Fig. 2). To facilitate crystallization of the Rh-enolate, tetrakis(pentafluorophenyl)borate was employed as the counterion with DCE as the solvent, which for the cascade reaction is only slightly less effective than acetic acid or dioxane/water as solvent, *vide infra* (see 3r in Table 5).

Scheme 1 Proposed mechanism for transformation.

After only 30 min at rt, rhodacycle **10** was isolated in very high yield. The X-ray structure of **10** shows a coordinatively saturated Rh($\rm III$) complex with interatomic distances consistent with an η^3 -bound enolate. Although rhodium enolates have been proposed as intermediates for a number of transformations, ¹⁶ very few X-ray structures have been reported. ¹⁷ To our knowledge, the only published example of a Cp*Rh($\rm III$) enolate is for a neutral complex with an η^1 C-bound enolate. ¹⁷ α

The potential for performing an intermolecular threecomponent C–H activation/addition/aldol reaction cascade was also evaluated (Table 5). Several different directing groups provided three-component cascade addition products using enone **2r** along with either an activated aldehyde or imine. Coupling 2-phenylpyridine and *N*-phenyl pyrazole with enone **2r**

Table 4 Control studies on reaction intermediate 9a^a

Entry	Rh (mol%)/ Ag (mol%)	Solvent	Yield 3a ^a (%)	Remaining 9a ^a (%)
1	(2.5)/(10)	3:2 Dioxane/H ₂ O	11	1
2	None	3:2 Dioxane/H ₂ O	12	1
3	(2.5)/(10)	Acetic acid	44	1
4	None	Acetic acid	45	<1

^a Yield determined by NMR analysis relative to 1,3,5-trimethoxybenzene as an external standard.

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Fig. 2 Preparation, isolation and X-ray structural characterization of a cationic Rh(III)-enolate. The $B(C_6F_5)_4$ ion has been omitted from the X-ray structure for clarity.

and ethyl glyoxylate gave products 3**r** and 3**s** in good yields, respectively. Moreover, the synthetically more versatile secondary and tertiary amide directing groups provided products 3**t** and 3**u** in moderate to good yields. In addition, three-component coupling with the *N*-tosyl imine derived from ethyl glyoxylate efficiently provided amine 3**v**, though the use of DCE as solvent was necessary to minimize the competitive imine hydrolysis that occurred in acetic acid.

The complete selectivity for initial C–H bond addition to the enone rather than the aldehyde is an interesting feature of this reaction. This outcome might result from kinetic control with C–H bond addition to the enone occurring much faster than to

 Table 5
 Three-component coupling reaction^{ab}

the aldehyde. Alternatively, thermodynamic control might be operative because C(sp²)-H bond addition to aldehydes is known to be reversible, ¹⁸ although C-H bond addition products are favored for destabilized aldehydes such as ethyl glyoxylate. ⁶

Conclusions

In summary, a Rh(III)-catalyzed C-H bond addition/aldol cyclization cascade has been developed and represents the first C-H bond addition across an alkene π -bond and a carbonyl. This robust transformation can be carried out under mild conditions and for tethered substrates generates three contiguous stereocenters with high diastereoselectivity. An intermolecular threecomponent C-H bond addition/aldol reaction cascade has also been demonstrated. Preliminary mechanistic studies also provide the first X-ray structural characterization of a cationic Cp*Rh(III) enolate. In continuing efforts we are broadening the scope of this class of cascade reactions to include different tethered electrophilic species. We are also actively investigating stereoselective intermolecular three-component reactions with carbon-carbon π -bonds and carbonyl/imine electrophiles.

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