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Rhodium(III) vs. cobalt(III): a mechanistically distinct three-component C–H bond addition cascade using a Cp*Rh^{III} catalyst[†]

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Three-component C–H bond additions across two different coupling partners remain underdeveloped. Herein, we report the first threecomponent Rh^{III}-catalyzed C–H bond additions to a wide range of dienes and aldehydes. Our method constitutes a complementary access with Ellman's Co^{III}-catalytic system to homoallylic alcohols.

Transition metal-catalyzed directed C–H bond functionalization with unsaturated π -bonds has become an attractive alternative to assemble keystone building blocks.¹ Of the many transition-metal catalysts that facilitate this process, Cp*Rh^{III} catalysts have been demonstrated to be among the most useful.² Very recently, some studies demonstrated that the Cp*Co^{III} catalyst could promote the reactions already established with Cp*Rh^{III} catalysts to access identical products.^{3,4} More interestingly, further research proved that the Cp*Co^{III} catalyst and Cp*Rh^{III} catalyst would also show different reactivities and substrate scopes, which provide the opportunity to build up complementary access to important organic transformation.⁵

Sequential multicomponent reactions have long been recognized as a powerful tool to enable the rapid generation of complex molecular scaffolds.⁶ However, despite the growing number of publications describing transition metal-catalyzed directed C-H bond addition,^{1,7} three-component C-H bond additions across two different coupling partners remain underdeveloped. In 2016, Ellman described the first three-component C-H addition cascade by Rh^{III}-catalysis.⁸ Later on, Ellman proved that the three-component C-H addition cascade can be significantly improved by employment of a Cp*Co^{III}-catalytic system.⁹ However, at that stage, both Rh^{III} and Co^{III}-systems were only efficient with α , β -unsaturated ketones. Inspired by Ellman's work, we rationalized that a switch of the α , β -unsaturated ketone to a simple diene in three-component C-H bond addition would generate a nucleophilic allyl-M species, which may further undergo an addition to an aldehyde. During the preparation of this manuscript, Ellman *et al.* reported three-component Co^{III}-catalyzed C-H bond addition to dienes and aldehydes (Fig. 1a).¹⁰ However, their method still suffers from limitations: (1) the use of 1-aryl-1,3butadienes did not provide the three-component coupling product and (2) the unconjugated dienes have never been investigated. Herein, we report the first three-component Rh^{III}-catalyzed C-H bond additions to dienes (Fig. 1b). Our further study indicates that the Rh^{III}-catalytic system in this reaction involved a different ratedetermining step and catalytic cycle from Ellman's Co^{III}-catalytic system with a different scope of substrates.

We sought to identify the reactivity with the reaction between 2-phenyl pyridine, 1-phenyl-1,3-butadiene and ethyl glyoxylate. After an extensive survey, the optimized conditions were identified to be: $[RhCp^*(CH_3CN)_3](SbF_6)_2$ as the catalyst (10 mol%) and a mixture of acetonitrile and hexafluoroisopropanol (HFIP) as the solvent (4:1; 0.5 mL), wherein product **4a** was afforded in 68%



Fig. 1 Rhodium(\mathfrak{m}) vs. cobalt(\mathfrak{m}) in three-component C–H bond addition to dienes and aldehydes.

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Table 1 Control experiments for the screening of reaction conditions^a

	$ \frac{V_{Py}}{a} + \frac{V_{Py}}{2a} + \frac{V_{Py}}{3a} $	Et M ^{III} catalyst solvent (0.5 mL) 100 °C,24h	Py OH (±)-4a
Entry	M ^{III} -catalyst	Solvent	$\mathrm{Yield}^{b}\left[\%\right]\left(\mathrm{d.r.}\right)$
1	[RhCp*(CH ₃ CN) ₃](SbF ₆) ₂	CH ₃ CN/HFIP	68 (90:10)
2	[Cp*RhCl ₂] ₂ /AgSbF ₆	CH ₃ CN/HFIP	55 (94:6)
3	$[Cp*Co(CO)I_2]/AgSbF_6$	CH ₃ CN/HFIP	N.R.
4	Cp*Co(CO)I ₂ /AgNTf ₂	CH ₃ CN/HFIP	N.R.
5	[RhCp*(CH ₃ CN) ₃](SbF ₆) ₂	CH ₃ CN	65 (85:15)
6	[RhCp*(CH ₃ CN) ₃](SbF ₆) ₂	HFIP	N.R.
7 ^c	[RhCp*(CH ₃ CN) ₃](SbF ₆) ₂	CH ₃ CN/HFIP	64(86:14)
8		CH ₃ CN/HFIP	N.R.

^{*a*} Reactions were carried out using M^{III} catalyst (10 mol%), **1a** (0.2 mmol), **2a** (0.4 mmol), and **3a** (0.24 mmol) in a CH₃CN/HFIP mixture (0.5 mL, 0.4 mL:0.1 mL) for 24 h at 100 °C under an N₂ atmosphere. ^{*b*} Isolated yields; the diastereoselectivities were checked by ¹H NMR. ^{*c*} Reaction time: 48 h.

yield with 90:10 diastereoselectivity at 100 °C (Table 1, entry 1). Control experiments were subsequently conducted to understand the role of each component. Switching of $[RhCp^*(CH_3CN)_3](SbF_6)_2$ to the precatalyst $[Cp^*RhCl_2]_2$ with AgSbF₆ led to a decrease in the yield (Table 1, entry 2). Changing the Rh^{III} catalyst to Co^{III} species dramatically reduced the yield of this three component C-H addition cascade (Table 1, entries 3 and 4).¹⁰ The effect of each component of the mixed solvents was also investigated (entries 5 and 6). It has been proved that both the solvents are important for achieving both high reactivity and good diastereoselectivity. Extending the reaction time is not advantageous (Table 1, entry 7). Finally, we proved that the Rh^{III} catalyst is essential for this three component C-H addition cascade (Table 1, entry 8).

Having optimized the reaction conditions, we first investigated the substrate scope of dienes using 1a as the C-H bond substrate and 3a as the aldehyde (Fig. 2). The terminal conjugated dienes bearing an aryl group at the α-position (Fig. 2, 2b-l), which are incompatible with Ellman's Co^{III}-catalytic system, were first tested under the optimized conditions. In general, with electronneutral, electron-withdrawing or electron-rich substituents at the ortho, meta-, or para-position of the phenyl ring, the reaction proceeded smoothly, with comparable yields and diastereoselectivities (Fig. 2, 4b-l). Additionally, 1-heteroaryl substituted 1,3-butadiene 2m was also a capable substrate. Furthermore, we proved that the α -alkyl substituted 1,3-butadienes 2n-r also underwent the reaction smoothly and the yields and diastereoselectivities were comparable to those of the 1-aryl substituted 1,3-butadiene 2b-l (Fig. 2, 4n-r). The sterically congested α, α -disubstituted 1,3-butadienes 2s and t are also reactive (Fig. 2, 4s and t). Furthermore, some of the 2-substituted 1,3-butadienes could also be converted into the corresponding products with decreased yields (Fig. 2, 4u and v). In addition, the skipped dienes 2w and x and isolated diene 2y were also explored to expand the range of diene substrates. Interestingly, all of the skipped dienes and isolated diene gave identical products with their corresponding conjugated 1,3-dienes





Fig. 2 The substrate scope of dienes. If we didn't point out the diastereoselectivity, it means only a single diastereoisomer was observed for this substrate in the reaction.

(Fig. 2, **2w** to **4n**; **2x** and **2y** to **4q**), which indicated an iterative protodemetalation/allylic activation process of the C=C bond during this reaction for these substrates.

Subsequently, we examined the scope of C-H bond substrates in this three-component C-H activation/chain walking/ addition cascade. As shown in Fig. 3, a series of three-component coupling products bearing substituents at the 4-, 5-, and/or 6-positions of the phenyl ring were synthesized in good yields and high diastereoselectivities (Fig. 3, 5a-t). It is important to stress that the reactions were preferred at the more sterically accessible position when a meta-substituent was attached to the phenyl ring of the C-H bond compounds (Fig. 3, 5n-r). This method was remarkably compatible with important functional groups such as halogens and OTf, ester, ketone, vinyl, hydroxy, and trifluoromethoxy groups, which could be subjected to further synthetic transformations. Our method is suitable for not only diverse 2-aryl pyridines, but also the other C-H substrates bearing different directing groups such as pyrimidines and pyrazoles (Fig. 3, 5u and 5v).

Furthermore, we wondered if aryl aldehydes are also suitable as the coupling substrates. The reaction between **1a**, **2a** and benzaldehyde was examined. Unfortunately, only trace amounts of the desired product were obtained. After an extensive screening,



Fig. 3 The scope of C–H bond substrates. If we didn't point out the diastereoselectivity, it means only a single diastereoisomer was observed for this substrate in the reaction.

we found that the reaction occurred smoothly with good yields with the assistance of stoichiometric amounts of $Zn(OAc)_2$ and pentafluorobenzoic acid A1 under neat conditions upon switching the benzaldehyde to aryl aldehyde bearing an electron-withdrawing group at the *para-* or *meta-*position (Fig. 4, **6a–e**). This result clearly highlights the difference and the complementarity between Co^{III} and Rh^{III} catalysis for this three-component C–H bond addition cascade.

The structures and the relative stereochemistry for all the products were assigned from analogy to the crystal structures **4s** and **5d** (Fig. S1, ESI⁺).¹¹ Then, a series of mechanistically insightful reactions were conducted. First, the value of $k_{\rm H}/k_{\rm D} = 1.0$ as well as the value of KIE = 1.3 indicated that the C–H bond cleavage process is not rate-determining (Fig. 5a).¹² Additionally, we proved that by using 10 mol% Rh^{III} catalyst 7 in CH₃CN/HFIP (4:1), the reaction between **1s**, **2a** and **3a** works efficiently (Fig. 5b), suggesting the plausible intermediacy of cyclometalated complex 7 in the catalytic cycle. Furthermore, a series of control experiments were carried out. First, we separately subjected diene **2a** and aldehyde **3a** to the standard conditions with **1a** (Fig. 5c and d). Diene **2a** resulted in only a 10% yield of diene **8**. Attempted coupling of **1a** with aldehyde **3a** only resulted in a trace amount of **9** with more than 95% recovery of **1a**. Furthermore, we conducted the reaction



Fig. 4 The scope of aldehyde substrates. Only single diastereoisomers were detected for these substrates in the reaction.



Fig. 5 A series of mechanistically insightful reactions

between 2-phenyl pyridine derived-diene 8 and 3a as well as the reaction between 1s, diene 8 and 3a (Fig. 5e and f). Both of the reactions only gave around 10% yield of product 4a. In addition, it was observed that the reaction between 2-phenyl pyridine derivedalkene 10 and 3a is incapable of forming the desired product 4a (Fig. 5g). These observations imply that (1) the synergistic reactivity of the diene and aldehyde might be crucial; (2) a stepwise pathway involving free intermediates such as 8 or 10 is rather unlikely; and (3) the internal hydride transfer involving Rh^{III}-H species is unlikely. Instead, a pathway in which the hydroarylated product between 2-phenyl pyridine 1a and diene 2a stays coordinated to the rhodium center until the addition to aldehyde 3a step is complete seems more likely. When the reaction was performed with 4,4-di-deuterated diene, H/D scrambling in the product has never been observed and mono-deuterated product 4a' is exclusively formed in 60% yield (Fig. 5h). It reveals that the intramolecular H-migration during the reaction seems not to occur and the irreversible allylic C-H bond activation is more likely to be involved, which is different from Ellman's Co^{III}-catalytic system. Additionally, when the reaction was performed in CH₃CN/MeOD, deuterium incorporation was observed at the 4-position of 4a (Fig. 5i), implying that protodemetalation of C-Rh species might occur.

On the basis of our mechanistic experiments, we propose a directed C–H bond cleavage to form intermediate 7 as the first



Fig. 6 Proposed catalytic cycle for the Rh^{III}-catalyzed C-H addition cascade.

step in the presence of Rh^{III} catalyst, which is followed by alkene coordination and insertion, thus affording the η^{1} - or η^{3} -Rh^{III}-allyl species **11** (Fig. 6). The formation of resulting Rh^{III}-allyl species **11** presumably involves protodemetalation with the H-source (ROH) to form intermediate **12**, which might further undergo allylic C-H bond activation to afford Rh^{III}-allyl species **13** with the assistance of the directing group. The nucleophilic addition of an aldehyde **3** with the Rh^{III}-allyl species **13** and subsequent protonolysis would provide the desired homoallylic alcohols **4–6** and regenerate the Rh^{III} catalyst. For nonconjugated dienes, the reaction would involve a sequential elimination/reinsertion process of the double bond to access the thermodynamically favored Rh^{III}-allyl species **11**.

In conclusion, we have developed the first Rh^{III}-catalyzed directing group-assisted three-component C–H addition cascade across dienes and aldehydes. Our method is suitable for a wide range of conjugated and nonconjugated dienes, and constitutes a complementary access with Ellman's Co(III) catalytic system. Mechanistic experiments indicated a directed aryl C–H bond activation/directed allylic C–H bond activation/addition cascade, which is different from Ellman's proposal in the Co^{III} catalytic system.

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Conflicts of interest

There are no conflicts to declare.

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