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Rhodium-Catalyzed Ring-Opening Hydroacylation of Alkylidenecyclopropanes with Chelating Aldehydes for the Synthesis of γ,δ-Unsaturated Ketones

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01751 Read Online

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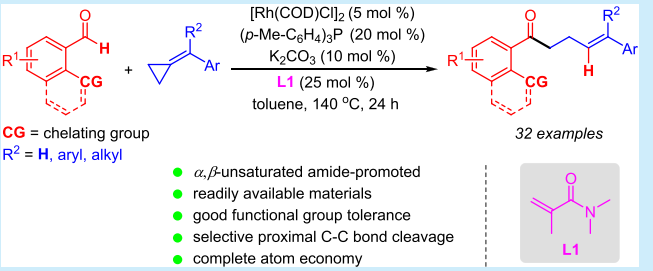
ABSTRACT: The first intermolecular ring-opening hydroacylation of alkylidenecyclopropanes with chelating aldehydes through a rhodium-catalyzed acrylamide-promoted protocol is reported. This highly efficient catalytic system enables the direct synthesis of a diverse range of linear γ,δ-unsaturated ketones. Good functional group compatibility is demonstrated for the completely atom-economical and remarkably selective proximal C−C bond cleavage process. Mechanistic studies reveal that the bidentate coordination of *N*,*N*-dimethylmethacrylamide (**L1**) to the acylrhodium intermediates might facilitate the cyclopropane ring fragmentation and isomerization.



The past two decades have witnessed a portfolio of chemical transformations of alkylidenecyclopropanes (ACPs) in the presence of transition-metal catalysts for the rapid elaboration of structural complexity.[1] With respect to the ring opening, the reaction pathways affected by the substitution patterns on the cyclopropyl ring or the terminal of the double bond of ACPs would be complicated and versatile,[1c] since the unleashing of cyclopropyl ring strain facilitates the distal C−C bond or proximal C−C bond cleavage. Consequently, the evolution of transition-metal-catalyzed selective cleavage of the C−C bond of readily accessible ACPs[2] is highly challenging and desirable for accessing diversified functionalized molecules.

γ,δ-Unsaturated ketone (homoallylic ketone), a moiety ubiquitously found in marketed drugs (Figure 1),[3] can serve as an intriguing building block for the preparation of naturally occurring products and therapeutically useful heterocyclic or polycyclic compounds.[4] Traditional methods for the synthesis of γ,δ-unsaturated ketones usually required a multistep reaction sequence.[5] Accordingly, chemists turn their attention to the transition-metal-catalyzed hydroacylation[6] of alkene-containing components. Shair and co-workers were among the first to develop a rhodium(I)-catalyzed ring-opening hydroacylation of vinylcyclopropanes for the synthesis of cyclooctenones in an intramolecular fashion (Scheme 1a).[7] A similar hydroacylation of ACPs with the intramolecular aldehyde moieties was subsequently accomplished by Fürstner et al. using a rhodium catalyst (Scheme 1b).[8] Surprisingly, there are few intermolecular hydroacylation methods that effectively target the homoallylic ketones. In 2009, Ohmura, Suginome, and co-workers reported a selective synthesis of γ,δ-unsaturated ketones through a nickel(0)-catalyzed ring-expanding hydroacylation reaction of methylenecyclopropanes (MCPs) with simple aldehydes (Scheme 1c).[9] However, this method was not suitable for the hydroacylation of ACPs.

Intrigued by these impressive precedents, we wondered about the feasibility of the hydroacylation reactions between ACPs and chelating aldehydes to deliver linear γ,δ-unsaturated ketones (Scheme 1d). Such a transformation faces the following fundamental challenges: (1) a stable acylrhodium intermediate is indispensable for establishing the hydroacylation of ACPs; (2) the ring-opening hydroacylation process must outcompete the conventional direct hydroacylation of the alkene moiety of ACPs, which means that the

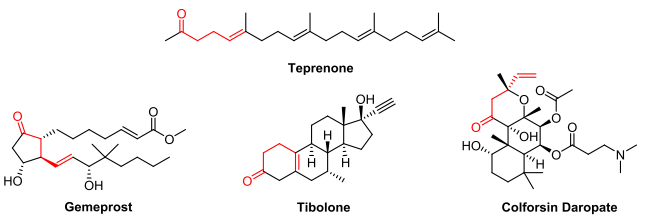


Figure 1. Selected marketed drugs containing γ,δ-unsaturated ketone scaffold.

Received: May 24, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01751
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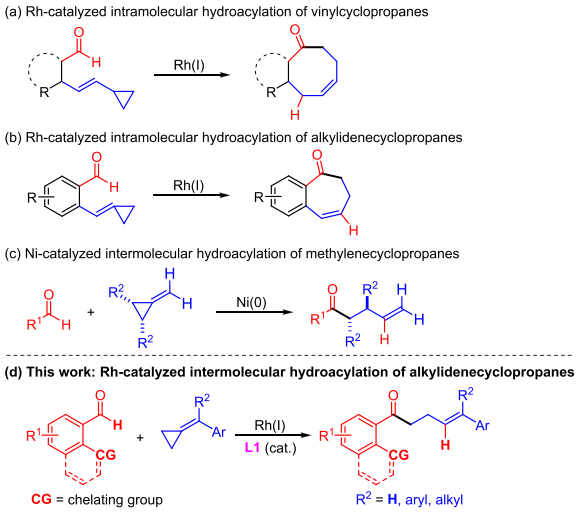
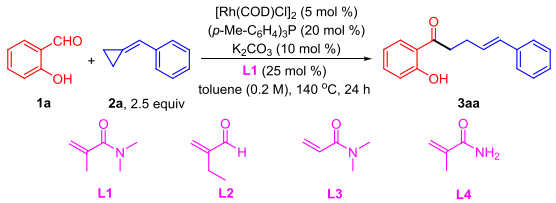
Scheme 1. Transition-Metal-Catalyzed Ring-Opening Hydroacylation for the Synthesis of γ,δ-Unsaturated Ketones



cyclopropane ring fragmentation and isomerization is predominant over reductive elimination;[7] and (3) control of the selectivity would be a difficult task in order to obtain high yields of the desired linear γ,δ-unsaturated ketones. In continuation of our research on rhodium(I)-catalyzed regioselective C−C bond formation reactions,[10] herein we describe the development of a new strategy that highlights the chelation assistance of a catalytic amount of *N*,*N*-dimethylmethacrylamide (**L1**), enabling the first example of the intermolecular hydroacylation of ACPs by the proximal C−C bond cleavage.

Initially, we investigated the possibility of such a conversion by examining the model reaction between salicylaldehyde **1a** and *freshly prepared* benzylidenecyclopropane **2a** under rhodium(I) catalysis (Table 1). In light of the bidentate coordination of α,β-unsaturated compounds to the rhodium(I) intermediates,[10b,11] we added a commercially available material to the mixture to promote the reaction. To our delight, the $[Rh(COD)Cl]_2/(p\text{-Me-}C_6H_4)_3P/K_2CO_3$ catalytic system in combination with 25 mol % of *N*,*N*-dimethylmethacrylamide (**L1**) delivered 73% yield of the linear *trans*-γ,δ-unsaturated ketone **3aa** (entry 1). The absence of **L1** proved very detrimental to the yield of the desired ring-opening hydroacylation product (entry 2). It is noteworthy that 2-ethylacrolein (**L2**) that could promote the hydroacylation of 1,3-dienes with salicylaldehydes[10b] was much less efficient (entry 3), demonstrating the importance of acrylamides in promoting the transformation. Switching **L1** to other homologues such as *N*,*N*-dimethylacrylamide (**L3**) and methacrylamide (**L4**) gave slightly lower yields of the product (entries 4 and 5). The influences of the loading of **L1** on the ring-opening hydroacylation were also examined, and all led to low conversions (entries 6−8). In addition, decreasing the loading of benzylidenecyclopropane **2a** to 1.5 equiv lowered the yield to 59% (entry 9). Replacing $(p\text{-Me-}C_6H_4)_3P$ with PPh_3 still afforded the homoallylic ketone in 64% yield (entry 10). An experiment carried out without the base showed a poorer yield for **3aa** (entry 11). The hydroacylation performed in *p*-xylene produced a yield comparable to that achieved in toluene (entry 12). However, running the reaction at a lower concentration resulted in inferior yield of **3aa** (entry 13).

Table 1. Optimization Studies for the Rhodium-Catalyzed Synthesis of γ,δ-Unsaturated Ketone 3aa[a]



entry	variation from the standard conditions	yield[b] (%)
1	none	73
2	without **L1**	33
3	**L2** instead of **L1**	25
4	**L3** instead of **L1**	64
5	**L4** instead of **L1**	62
6	100 mol % of **L1** instead of 25 mol % of **L1**	45
7	50 mol % of **L1** instead of 25 mol % of **L1**	53
8	10 mol % of **L1** instead of 25 mol % of **L1**	48
9	1.5 equiv of **2a** instead of 2.5 equiv of **2a**	59
10	PPh_3 instead of $(p\text{-Me-}C_6H_4)_3P$	64
11	without K_2CO_3	55
12	*p*-xylene instead of toluene	70
13	0.1 M instead of 0.2 M	60
14	120 °C instead of 140 °C	58

[a]Unless otherwise noted, each reaction was run with **1a** (0.2 mmol, 1 equiv) and **2a** (2.5 equiv) in 1 mL of toluene at 140 °C for 24 h. [b]Isolated yield. COD = 1,5-cyclooctadiene.

Finally, the ring-opening hydroacylation proved to be less efficient when it was performed at a lower temperature (entry 14).

The generality of the rhodium-catalyzed intermolecular ring-expanding hydroacylation with regard to the alkylidenecyclopropane partner was subsequently investigated utilizing the optimized conditions (Scheme 2). The methyl-, *tert*-butyl-, and methoxy-substituted benzylidenecyclopropanes all reacted smoothly with salicylaldehyde **1a** under rhodium(I) catalysis to provide isolated 61−78% yields of γ,δ-unsaturated ketones (**3ab**−**3ae**). Significantly, a variety of alkylidenecyclopropane derivatives bearing electron-neutral or electron-deficient groups expressed moderate to good reactivity to produce the desired ketones (**3af**−**3ak**). Of note, 2-furyl-, 3-benzofuryl-, and 2-pyridinyl-substituted components (**3al**−**3an**) were also compatible with the reaction conditions for the hydroacylation, highlighting the robustness of the protocol. It was found that the symmetrical diphenylmethylenecyclopropane underwent the coupling reaction smoothly to afford the anticipated compound **3ao** in 54% yield. Unfortunately, the substrate bearing a long-chain alkyl group (**2p**) was not allowed for this transformation. Moreover, the substrate substituted with methyl and phenyl groups on the double bond was also evaluated in the coupling reaction, but the product was isolated in low yield (**3aq**).

Our attention was then turned to the coupling reactions of chelating aldehydes with ACPs, and the results are illustrated in Scheme 3. Good functional group compatibility for the synthesis of linear γ,δ-unsaturated ketones was again observed, with methyl (**3ba**), benzyloxy (**3ca**), chloro (**3da**), trifluoromethyl (**3ea**), nitro (**3fa**), and ester (**3ga**) groups all being well-tolerated. Electron-donating salicylaldehydes reacted with halo-substituted partners smoothly to furnish the corresponding products **3hh** and **3ii** in 69% and 67% yield, respectively.

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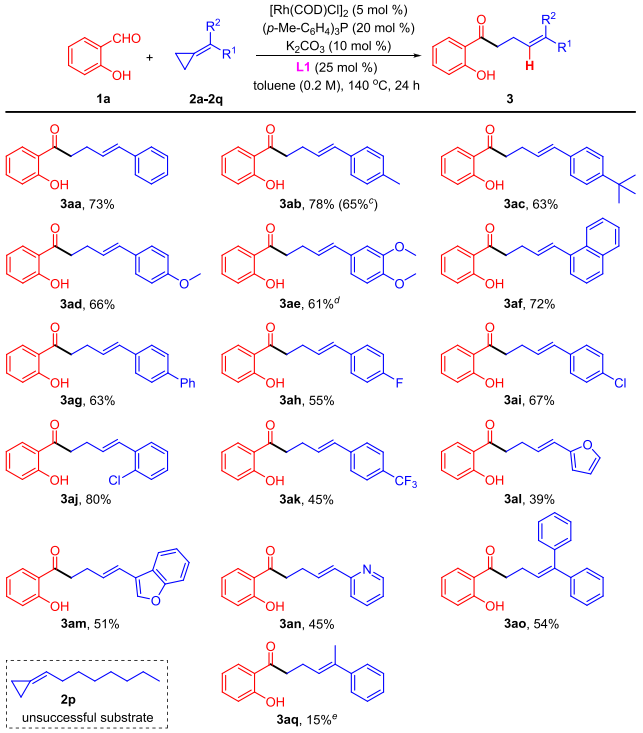
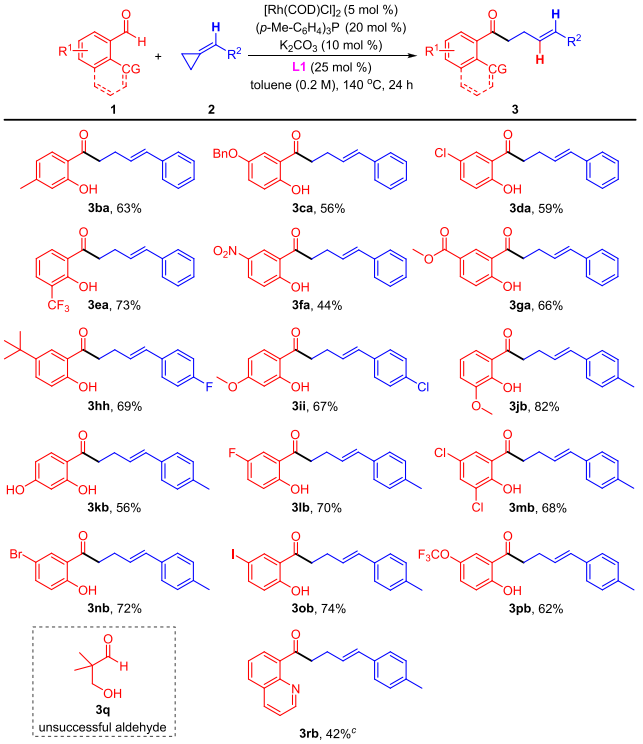
Scheme 2. Substrate Scope with Respect to Alkylidenecyclopropanes[a,b]



[a]Unless otherwise noted, all reactions were carried out with salicylaldehyde **1a** (0.2 mmol), alkylidenecyclopropane **2** (0.5 mmol), $[Rh(COD)Cl]_2$ (5 mol %), $(p\text{-Me-}C_6H_4)_3P$ (20 mol %), K_2CO_3 (10 mol %), and **L1** (25 mol %) in 1 mL of toluene at 140 °C for 24 h. [b]Isolated yield. [c]Reaction was carried out on a 1 mmol scale. [d]2 mL of toluene was used. [e]Only the *E*-isomer was observed by ^1H NMR analysis of the crude mixture.

Scheme 3. Substrate Scope with Respect to Chelating Aldehydes and Alkylidenecyclopropanes[a,b]



[a]Unless otherwise noted, all reactions were carried out with chelating aldehyde **1** (0.2 mmol), alkylidenecyclopropane **2** (0.5 mmol), $[Rh(COD)Cl]_2$ (5 mol %), $(p\text{-Me-}C_6H_4)_3P$ (20 mol %), K_2CO_3 (10 mol %), and **L1** (25 mol %) in 1 mL of toluene at 140 °C for 24 h. [b]Isolated yield. [c]1.5 mL of toluene was used.

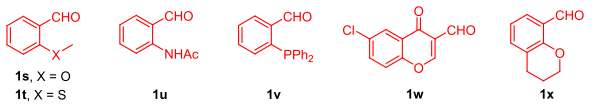


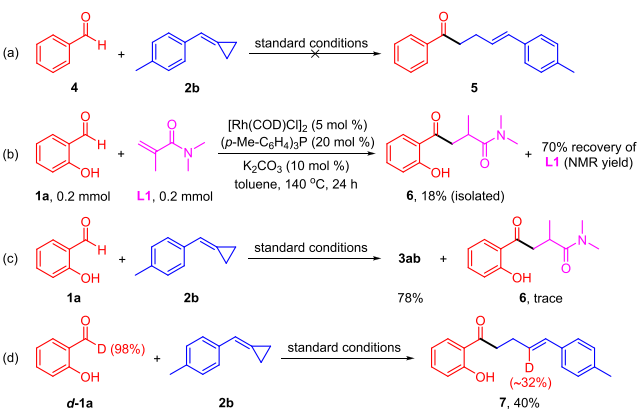
Figure 2. Substrates which failed to afford the desired products.

Furthermore, introducing a methoxy group at the *ortho* position of the hydroxyl group on the substrate did not influence the ring-opening hydroacylation, since a good yield of **3jb** was provided. Remarkably, exposure of the aldehyde possessing a free phenolic hydroxyl group to the catalytic system afforded the anticipated compound **3kb** in moderate yield. The substrates containing various medicinally relevant and chemical biologically useful groups, including fluoro (**3lb**), chloro (**3mb**), bromo (**3nb**), iodo (**3ob**), and trifluoromethoxy (**3pb**), were well-tolerated. However, the aliphatic aldehyde possessing a hydroxyl group located at the proper position such as 3-hydroxy-2,2-dimethylpropanal (**3q**) was not suitable for the coupling reaction. To our delight, this protocol can be extended to quinoline-8-carbaldehyde,[6e,12] from which a 42% yield of **3rb** was obtained.

The formation of chelation-stabilized intermediates is essential to the success of this rhodium(I)-catalyzed ring-opening hydroacylation process, which could be deduced from the substrate scope studies. As shown in Figure 2, the substituent at the *ortho* position of the aldehyde group has a profound influence on the reactivity of the substrate. The incapability of conversion of the substrates (**1s**−**1v**)[6e] might be attributed to the steric hindrance that impedes the coordination of **L1** to the rhodium intermediates (vide infra, proposed catalytic mechanism). Additionally, the weak coordination performance of the fixed chelating moieties, such as carbonyl and alkoxy groups, might account for the unfruitful coupling reactions of the substrates (**1w** and **1x**).

Further evidence for the role of α,β-unsaturated amide and the catalytic mechanism was demonstrated by control experiments (Scheme 4). Initially, benzaldehyde **4** was not observed to deliver the linear γ,δ-unsaturated ketone **5** upon

Scheme 4. Key Mechanistic Experiments



https://dx.doi.org/10.1021/acs.orglett.0c01751
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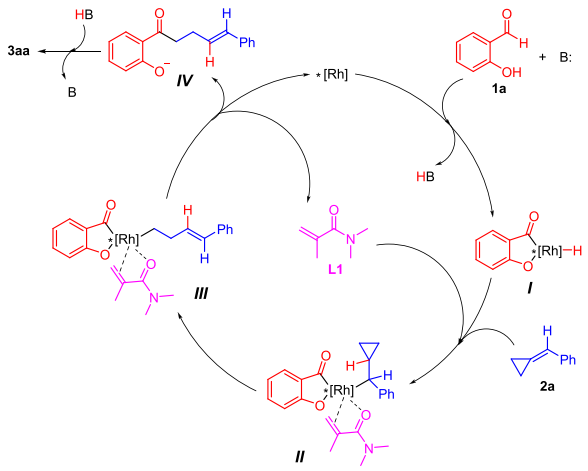
reaction of the alkylidenecyclopropane **2b** instead of **2a** under the standard conditions (Scheme 4a), suggesting that the ring-expanding hydroacylation did not occur in the absence of a chelating group. Although the intermolecular hydroacylation of *N,N*-dialkylacrylamides[11] or enamides[13] with simple aldehydes has been investigated, the coupling of **L1** with salicylaldehyde **1a** without the alkylidenecyclopropane in this $[Rh(COD)Cl]_2$/$(p\text{-Me-}C_6H_4)_3P/K_2CO_3$ catalytic system only delivered 18% yield of the product **6** with 70% NMR yield of the material observed (Scheme 4b). Meanwhile, only a trace amount of **6** was detected with a negligible loss of **L1** by NMR analysis while performing the coupling of **1a** with **2b** (Scheme 4c). The results unambiguously indicate that **L1** participated in the hydroacylation reactions sluggishly and that strong bidentate chelation of the acrylamide to the cationic rhodium played a pivotal role in promoting the reaction. Furthermore, a deuterium-labeling experiment using *d*-**1a** as the substrate under the standard reaction conditions afforded deuterium incorporation at the γ-C (32% D) position of the carbonyl group of the product **7** (Scheme 4d).

On the basis of preliminary mechanistic investigations in combination with previous reports on the hydroacylation of ACPs and their analogues,[7−9] a tentative mechanism for the synthesis of γ,δ-unsaturated was proposed (Scheme 5). The

Scheme 5. Proposed Catalytic Mechanism



oxidative insertion of the rhodium(I) catalyst into the aldehyde C−H bond of **1a** in the presence of potassium carbonate readily delivers a Rh(III) chelate **I**,[14] which couples with **2a** through intermolecular hydrorhodation to give the stabilized intermediate **II** by the bidentate chelation assistance of *N,N*-dimethylmethacrylamide (**L1**).[11] Note that selective cleavage of the proximal C−C bond and isomerization initiated by Rh(III), consistent with the reported literature,[7,8] is more favorable than the direct reductive elimination, thus leading to the intermediate **III**. Subsequent reductive elimination and protonation liberates the linear hydroacylation product and reproduces the rhodium(I) catalyst.

In summary, a rhodium-catalyzed chelation-assisted intermolecular ring-expanding hydroacylation of ACPs with O- and N-chelating aldehydes is reported. The reactions delivered the linear *trans*-γ,δ-unsaturated ketones through selective proximal C−C bond cleavage when monosubstituted ACPs were used as the substrates. *N,N*-Dimethylmethacrylamide (**L1**) might stabilize acylrhodium intermediates by bidentate coordination. This method provides a complementary alternative to the nickel-catalyzed transformation of MCPs within the hydroacylation arena.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01751.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of Shandong Province (ZR2019MB003), the Key Research and Development Program of Shandong Province (2018GGX109010), Academic Promotion Programme of Shandong First Medical University (2019LJ003), the National Natural Science Foundation of China (21602256), the CAMS Innovation Fund for Medical Sciences (CIFMS, 2017-I2M-2-004), and the High-Level Project Cultivation Program of TSMC (2018GCC16).

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