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Rhodium-Catalyzed Chemo- and Regioselective Decarboxylative Addition of *β*-Ketoacids to Allenes: Efficient Construction of Tertiary and Quaternary Carbon Centers

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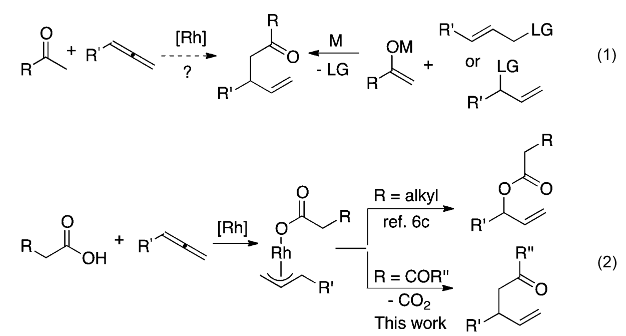
Supporting Information

ABSTRACT: A rhodium-catalyzed chemo- and regioselective intermolecular decarboxylative addition of *β*-ketoacids to terminal allenes is reported. Using a Rh(I)/DPPF system, tertiary and quaternary carbon centers were formed with exclusively branched selectivity under mild conditions. Preliminary mechanism studies support that the carbon−carbon bond formation precedes the decarboxylation and the reaction occurs in an outer-sphere mechanism.

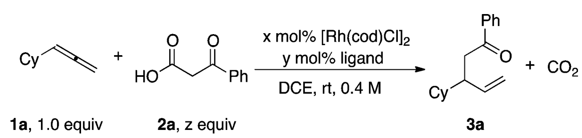
Transition-metal-catalyzed allylic alkylation represents one of the most powerful methods to construct C−C bonds in organic synthesis.[1] Under certain conditions, transition metal catalysts can regioselectively produce the branched allylic compounds, which provides an opportunity to obtain chiral molecules (Scheme 1, eq 1, right).[2−5] Recently, we developed a rhodium-catalyzed regioselective addition of carboxylic acids and anilines to alkynes or allenes to furnish branched allylic esters and amines in an atom-economic manner,[6] which avoids the installation of leaving groups on the substrates and generation of waste.[7] Unfortunately, many efforts to extend the reactions to ketones (carbon nucleophiles) have failed (eq 1, left). The possible reasons are the relatively weak acidities (or the ability of oxidative addition with rhodium complexes) and the difficulty to form the nucleophilic enolate under nonbasic conditions. Inspired by the decarboxylative enolate formation during the biosynthesis of polyketides and fatty acids,[8] we thought that the installation of a carboxylic group[6b−d] to the *α*-position of the ketone may address the problem: (a) the carboxylic acid may initiate the reaction through the formation of the allyl rhodium intermediate; (b) the nucleophilicity of *α*-carbon would be enhanced; (c) CO_2 can be eliminated spontaneously as a traceless directing group[9] (eq 2). Herein, we present a rhodium-catalyzed regioselective decarboxylative[10] addition of *β*-ketoacids[11] to allenes[12] as an efficient method to construct tertiary and quaternary[13] carbon centers under mild and neutral reaction conditions, of which can be regarded as an alternative to enolate allylation under basic conditions.[14]

Scheme 1. Proposed Rhodium Catalyzed Decarboxylative Addition of *β*-Ketoacids to Terminal Allenes



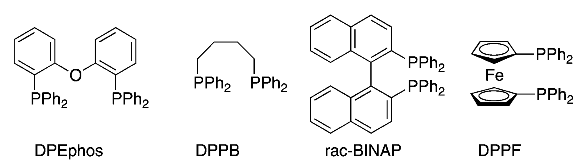
We commenced our studies employing cyclohexylallene **1a** (1.0 equiv) and benzoylacetic acid **2a** (1.2 equiv) as model substrates (Table 1). In the presence of 2.5 mol % of $[Rh(cod)Cl]_2$ and 5.0 mol % DPEphos ligand,[6c,d] the reaction proceeded smoothly at room temperature in DCE to give 46 mol % of the branched *γ*,*δ*-unsaturated ketone **3a** as the only regiomer, along with acetophenone as a byproduct (entry 1).[15] Next, different bidentate ligands were tested (entries 2−4)

Table 1. Optimization of Reaction Conditions



entry	ligand	*x*/*y*	*z* equiv	time (h)	yield[a] (%)
1	DPEphos	2.5/5.0	1.2	16	46[b]
2	DPPB	2.5/5.0	1.2	16	39[b]
3	*rac*-BINAP	2.5/5.0	1.2	3	24[b]
4	DPPF	2.5/5.0	1.2	1	88
5	DPPF	2.5/−	1.2	48	0
6	DPPF	−/5.0	1.2	24	0
7	DPPF	1.0/2.0	1.2	2	84
8	DPPF	1.0/2.0	1.5	2	87

[a]Isolated yield. [b]Some allene **1a** was recovered, and benzoylacetic acid **2a** was all consumed.



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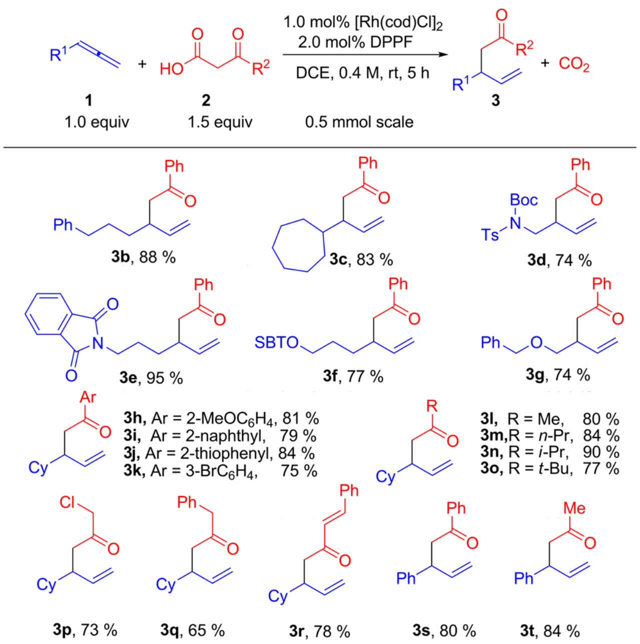
among which the DPPF derived catalyst showed the highest reactivity, consuming the allene substrate **1a** in 1 h at room temperature to give 88% isolated yield of **3a**, without any trace of allyl benzoylacetate (entry 4, see eq 2) detected. Control experiments showed that both the rhodium catalyst and the ligand are mandatory for the reaction (entries 5 and 6). By reducing the catalyst loading to 1 mol %, the reaction was still efficient to give a similar yield within 2 h (entry 7). When 1.5 equiv of benzoylacetic acid **2a** was used in the reaction, the product yield increased (entry 8).

With the optimized conditions in hand, we investigated the scope of the decarboxylative addition reaction (Table 2). The

Table 2. Scope of Rhodium-Catalyzed Regioselective Synthesis of Tertiary Carbon Centers

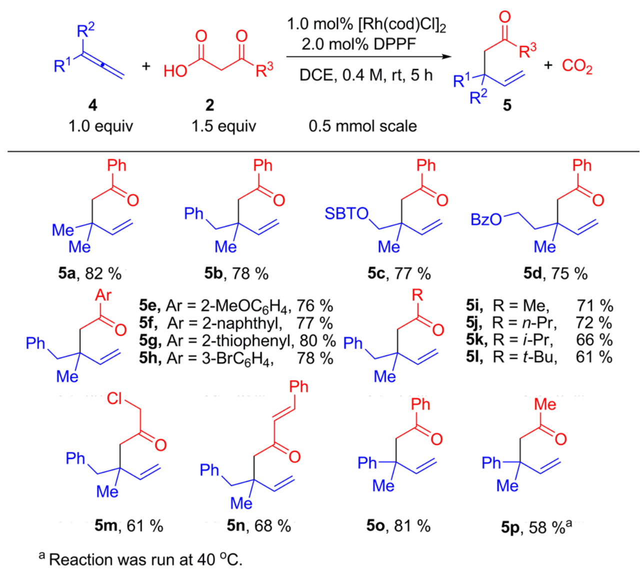


terminal allenic substrates used were readily prepared in one or two steps from commercially available starting materials.[16] A linear alkyl-substituted allene (**3b**) and an α-branched alkyl-substituted allene (**3c**) were both suitable substrates for the addition reaction. Protected amines (**3d** and **3e**) and alcohols (**3f** and **3g**) were tolerated and furnished the desired products smoothly, allowing for further functional group manipulations.

Additionally, a variety of β-ketoacids were tested with cyclohexylallene **1a** as the model substrate. Electron-donating (**3h**) and halogenated (**3k**) aromatic rings, naphthyl (**3i**), and heterocycles such as a thiophene (**3j**) were compatible with the reaction conditions. Replacing the aromatic groups with alkyl groups bearing potentially acidic α-hydrogens showed little to no complication. Primary (**3l** and **3m**), secondary (**3n**), and tertiary (**3o**) alkyl groups can all be introduced. In particular **3m** is an interesting case, because the differentiation of a methylpropylketone in enolate chemistry toward methyl allylation is extremely difficult. Furthermore, β-ketoacids with chloride (**3p**) and alkenic functions (**3r**) gave the coupling products in satisfactory to good yields. Reactions with phenylallene also gave high yields (**3s** and **3t**). In all cases, only branched products were observed.

We then tested the more challenging 1,1-disubstituted allenes as substrates for quaternary carbon construction (Table 3). Commercially available 3-methyl-1,2-butadiene (**4a**) did react with benzoylacetic acid (**2a**) under the standard

Table 3. Scope of Rhodium-Catalyzed Regioselective Synthesis of Quaternary Carbon Centers



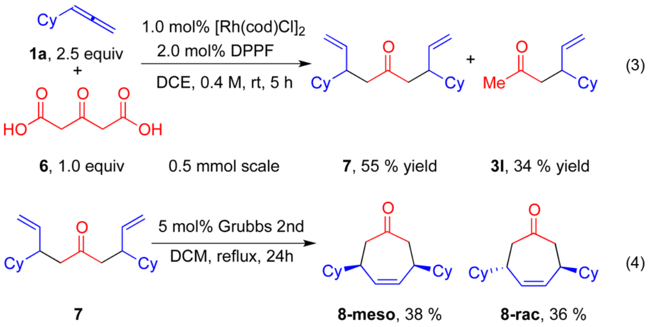
[a]Reaction was run at 40 °C.

conditions to furnish **5a** in 82% yield with concomitant formation of a quaternary carbon center. The allene with a benzyl substituent (**4b**) also gave the desired product **5b** in 78% yield, even though this substrate is potentially vulnerable to undergo isomerization to the corresponding 1,3-diene via β-hydride elimination.[17] Allenes with silyl ether and ester protecting groups gave the quaternary carbon centers (**5c** and **5d**) smoothly as well. With the allene **4b** as the model substrate, different β-ketoacids were examined in aromatic systems with an electron-donating group (**5e**), a halogen (**5h**), a naphthyl (**5f**), and a thiophene heterocycle (**5g**) that reacted smoothly. Methyl, *n*-propyl, isopropyl, and *tert*-butyl groups can all be tolerated in the decarboxlative addition reactions (**5i** to **5l**), which is difficult in the allylic substitution reactions with unsymmetrical ketone enolates under basic conditions. Aryl-substituted quaternary carbon centers can also be formed (**5o** and **5p**). Furthermore, for the preparation of quaternary carbon stereocenters, the allylic substitution reaction requires isomerically pure trisubstituted alkenes as substrates, which can be synthetically challenging.[13e] Conversely, 1,1-disubstitued allenes are prepared in one or two steps from commercially available starting materials.[16]

Furthermore, the commercially available acetone-1,3-dicarboxylic acid **6** reacted with 2.5 equivalents of cyclohexylallene **1a** under the rhodium(I)/DPPF condition to give 55% symmetrical diallylic product **7**, along with 34% monoallylic product **3l** (Scheme 2, eq 3). A subsequent ring closing metathesis with Grubbs' second generation catalyst furnished the 3,6-dicyclohexylcyclohept-4-enone **8** as a separable mixture (**8**-meso and **8**-rac) (eq 4). This two-step sequence allows the ready preparation of a cyclohept-4-enone from commercially available **1a** and **6**.

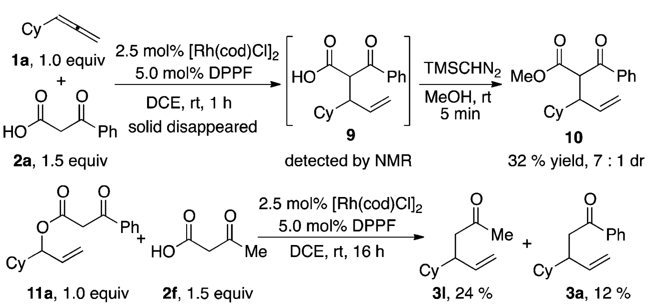
There are two fundamental questions in the mechanism of this rhodium-catalyzed decarboxylative allylation reaction: (a) decarboxylation and allylation, and which of these steps precedes the other; (b) inner-sphere or outer-sphere

Scheme 2. Rhodium Catalyzed Decarboxylative Diallylation of Acetone-1,3-dicarboxylic Acid and RCM to Cyclohept-4-enone



mechanism regarding the nucleophilic attack.[10] To address the first question, because the benzoylacetic acid **2a** is not soluble in DCE, the reaction of **1a** and **2a** in the presence of the $[Rh(cod)Cl]_2$/DPPF catalyst system was stopped immediately when the solid **2a** disappeared after approximately 1 h. The NMR of the crude reaction mixture showed both the α-allyl-β-ketoacid intermediate **9** and the product **3a** after decarboxylation. Intermediate **9** can decompose slowly to product **3a** within 24 h.[16] Furthermore, when solid **2a** disappeared, trimethylsilyldiazomethane was added to methylate the intermediate **9**. The β-ketoester **10** can be isolated in 32% yield with a 7:1 dr, along with 35% of **3a** (scheme 3). These

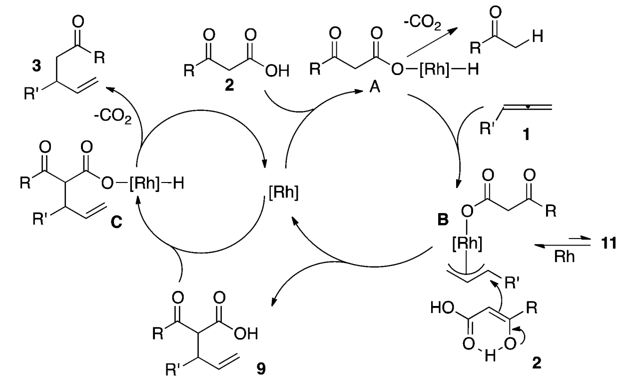
Scheme 3. Detection, Capture of Reaction Intermediate, and Crossover Experiment



results suggest that allylation precedes decarboxylation in this rhodium-catalyzed reaction. With regard to the second question, a crossover reaction was conducted. While benzoylacetate **11a** was found to be completely unreactive under standard catalysis conditions, when acetoacetic acid **2f** was added, the crossover product **3l** could be observed and isolated in 24% yield. Another 12% of **3a** was formed most likely from the released benzoylacetic acid **2a**. 36% of the benzoylacetate **11a** was recovered.[18] These experiments suggest the following conclusions: first, a π-allyl rhodium intermediate[19] (vide infra), generated through ionization of **11a**, seems to be involved; second, the π-allyl rhodium intermediate reacts with another β-ketoacid; and third, the reaction proceeds more likely via an outer-sphere mechanism,[20] although other mechanistic alternatives cannot be ruled out at this point.

Based on the experiments above, we propose the following reaction mechanism (Scheme 4). Carboxylic acid **2** reacts with the rhodium catalyst to give intermediate **A**. Two pathways are possible from **A**. One is to release carbon dioxide and give the byproduct methyl ketone.[15] The other one is to insert into

Scheme 4. Proposed Catalytic Cycle



allene **1** and generate the π-allyl-rhodium intermediate **B**.[19] Another molecule of β-ketoacid **2** attacks the allylic carbon in **B** through its enol form followed by the release of β-ketoacid **9** and **2**. A second allylation of α-allyl-β-keto-acid **9** is for steric reasons certainly significantly slower.[21] Instead, we propose that **9** enters a second catalytic cycle involving a rhodium-catalyzed decarboxylation via intermediate **C** generating the final product **3**.[22]

In conclusion, we have developed a highly regioselective decarboxylative addition of β-ketoacids to terminal allenes to produce γ,δ-unsaturated ketones. Branched tertiary and quaternary carbon centers were constructed under very mild reaction conditions with commercially available $[Rh(cod)Cl]_2$ and DPPF. This reaction releases CO_2 as the only byproduct, which shows high atom economy and provides a mild alternative to existing enolate allylation under basic conditions. Preliminary mechanistic studies suggest that the carbon—carbon bond formation precedes the decarboxylation and the reaction occurs in an outer-sphere mechanism. Further investigation on the asymmetric version of this reaction and the attempt to extend the substrates from allenes to alkynes are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytic data for synthesized compounds, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(15) Benzoylacetic acid **2a** was consumed within 3 h in the presence of the Rh(I)/dppf catalyst, while benzoylacetic acid **2a** decomposes in 48 h without the rhodium complex.

(16) For the details, see Supporting Information

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(19) For alternative ($\sigma+\pi$) rhodium intermediate, see ref 3g.

(20) Coupling of carboxylic acid and allene with $[Rh(cod)Cl]_2$ and (−)-DIOP gave above 90% *ee*, while the same ligand lead to 0% *ee* in this decarboxylative C−C bond formation reaction, which suggests the reactions may occur by different mechanisms.

(21) The reaction of 1-oxocyclohexane-2-carboxylic acid and cyclohexylallene **1a** gave only a trace amount of the desired product under the standard conditions.

(22) A linear selective addition of β-ketoacid to the allene followed by a Carroll rearrangement can be ruled out. For details, see Supporting Information.