

Ruthenium-Catalyzed Enantioselective Addition of Carboxylic Acids to Allenes

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ABSTRACT: A ruthenium-catalyzed synthetic method for branched allylic esters via addition of carboxylic acids to allenes is reported. Ligands were designed and prepared based on the Josiphos skeleton, with which the reaction achieved up to 95% yield and up to >99% enantiomeric excess. A deuterium labeling experiment was performed and a plausible mechanism was proposed. Enantiopure lactones of five- and six-membered ring were synthesized via a RCM reaction of the branched allylic ester product. **KEYWORDS:** *Ruthenium catalyzed, Enantioselective, Allylic addition, Carboxylic acids, Allenes, Josiphos, Lactones*

As a Group VIII transition metal, ruthenium has a variety of unique characteristics.¹ Thanks to its ability to assume different oxidation states and its cost advantage,² ruthenium stands out among the transition metals in organic synthesis.³ In recent years, a large number of novel, useful rutheniumcatalyzed reactions, such as hydrogenation⁴ and transfer hydrogenation,⁵ oxidation,⁶ olefin metathesis,⁷ C–H bond activation,⁸ carbonylation,⁹ and miscellaneous nucleophilic,¹⁰ as well as electrophilic,¹¹ reactions, to name a few, have been developed.

Chiral allylic esters are important building blocks in organic synthesis and are very versatile structural motifs in many natural products.¹² Traditionally, they have been synthesized via acylation of the corresponding allylic alcohols.¹³ In recent years, much progress in their synthesis has been achieved by transition-metal-catalyzed asymmetric reactions. Such as allylic substitution, which is quite demanding on the substrate's Z/E configuration and requires a leaving group that is not atomeconomic (Scheme 1a)¹⁴ and allylic C–H oxidation, which requires stoichiometric amounts of oxidant and has a limited substrate scope or low enantiometric excess (ee) (Scheme 1b).¹⁵

Asymmetric allylic addition of carboxylic acids to allenes offers an atom-economic alternative that overcomes those drawbacks. Our group has been pioneering in allylic addition reaction of different pronucleophiles to allenes or alkynes. But unfortunately, until now, only the rare and, thus, very expensive rhodium catalyst has been applied successfully, which limits its further applications.¹⁶ Development of complementary catalytic platform involving inexpensive transition-metal catalysts is of utmost importance. We envisioned that ruthenium catalysts would be a perfect choice for the search of other novel catalysts in the redox-neutral addition of carboxylic acids to allenes, which might resolve the drawbacks of the existing methods in the synthesis of branched allylic esters. Herein, we report our initial results on this ruthenium-catalyzed reaction (Scheme 1c).

We started our study by applying the racemic ruthenium complex $[rac-BINAP-Ru(p-cymene)Cl]Cl^{17}$ as catalyst to the reaction of carboxylic acids with terminal allenes. We were pleased to find that the reaction worked efficiently to obtain branched allylic ester as the single product. The reaction has a general scope both in allenes and carboxylic acids (see Table 1). We observed high yields (up to 98%) and functional groups

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Scheme 1. Transition-Metal-Catalyzed Synthesis of Chiral Esters



such as esters (3i-1), protected alcohols (3f-1, 3g-1) and amines (3h-1) were well-tolerated in this reaction.

Inspired by the results from the racemic reaction, we began to investigate and optimize the conditions for the asymmetric

Table 1	. Racemi	c Scope of	Rutheni	ium-Cata	alyzed	Reaction
of Carb	oxylic Ao	cids with T	erminal	Allenes	L I	



^aReaction conditions: 1 (1.2 mmol, 3 equiv), 2 (0.4 mmol), [*rac*-BINAP-Ru(*p*-cymene)Cl]Cl (0.02 mmol, 5 mol %), KOt-Bu (0.04 mmol, 10 mol %) and 3 Å molecular sieve (100 mg) in 2.0 mL *m*-xylene at 90 °C for 24 h; yield is presented as of isolated product.

version of the ruthenium-catalyzed reaction. We tried to use the [(S)-BINAP-Ru-(p-cymene)Cl]Cl complex as a catalyst, which only showed an ee of 4%. After an extensive screening of different ruthenium-complex-bearing chiral BINAP-type ligands, the best result we obtained was only 33% yield and 57% ee (see the Supporting Information (SI)). We then focused on applying *in-situ*-formed ruthenium catalysts with different chiral ligands to the reaction of penta-3,4-dien-1-ylbenzene (1a) and benzoic acid (2–1) (see the SI). By using Josiphos SL-J001-1 as the ligand in *m*-xylene, the branched allylic product 3a-1 was formed exclusively in 73% yield and 55% ee (Table 2, entry 1) at 90 °C. We modified and synthesized ligands by changing the dicyclohexylphosphine group of Josiphos SL-J001-1 to dicycloheptylphosphine (L1) and



\bigcirc	◆ + PhCO ₂ H -	[Ru(<i>p</i> -cymene)Cl ₂] ₂ (2.5 mol %) L (6 mol %) KOt-Bu (10 mol%), <i>m</i> -xylene	Ph O*O	
		3 Å MS, 90 °C, 0.2 M, 24 h		
1a	2-1		3a-1	
	R ¹ ₂ P Fe PR ² ₂	R ² 2P Me ¹ y H		
	R ¹ = Ph, R ² = Cy: SL-J001-1	$R^1 = Ph, R^2 = Cycloheptyl: L1$		
	R ¹ = Ph, R ² =3,5-Me ₂ C ₆ H ₃ : SL-J005	05-1 R ¹ = PMP, R ² = Cy: L3		
	R ¹ = 2-MeOC ₆ H ₄ , R ² = Cy: L4 R ¹ = 3,5-(CF ₃) ₃ C ₆ H ₂ , R ² = Cy: SL-J R ¹ = DTBM, R ² = Cy: L5	R' = PMP, R ^z = Cycloheptyl: I 006-1 R ¹ = 6-MeO-2-Naphthyl, R ² = C	-6 Cyclohepty: L7	
	R ¹ = Cy, R ² = Cy: SL-J003-1			
Entry	Ligand	Yield ^[b] (%)	ee ^[c] (%)	
1	SL-J001-1	73	55 (S)	
2 ^[d]	11	90	66 (R)	

1	SL-J001-1	73	55 (S)
2 ^[d]	L1	90	66 (R)
3 ^[d]	L2	37	65 (R)
4	SL-J002-1	n.r	-
5	SL-J005-1	n.r	-
6	SL-J006-1	37	4 (S)
7	SL-J003-1	47	45 (S)
8 ^[d]	L4	n.r	-
9 ^[d]	L5	n.r	-
10 ^[d]	L3	51	60 (R)
11 ^[e]	L1	59	76 (R)
12 ^[e]	L6	47	73 (R)
13 ^[e]	L7	71	78 (R)
14 ^[e,f]	L7	83	88 (R)

^{*a*}Reaction conditions: **1** (1.2 mmol, 3 equiv), **2** (0.4 mmol), $[\text{Ru}(p-cymene)Cl_2]_2$ (0.01 mmol, 2.5 mol%), ligand (0.024 mmol, 6 mol%), KOt-Bu (0.04 mmol, 10 mol%), and 3 Å molecular sieve (100 mg) in 2.0 mL *m*-xylene at 90 °C for 24 h. ^{*b*}Isolated yield. ^cDetermined by chiral HPLC, absolute configuration assigned by referring with the literature (see the Supporting Information (SI)). ^{*d*}0.2 mmol reaction scale. ^{*e*}0.2 mmol reaction scale in a mixed solvent *m*-xylene/DCE (1/1). ^{*f*}Isobutyric acid (2–19) was used instead of benzoic acid (2–1).

dicyclopentylphosphine (L2) groups. Indeed, we were pleased to find a higher ee for both L1 and L2, the yield increased to 90% for L1 while it rapidly decreased to 37% for L2 (Table 2, entries 2 and 3). SL-J002-1 and SL-J005-1 with a bulkyl phosphine resulted in no reaction (Table 2, entries 4 and 5). We then studied the effect of the phosphine substituent attached to the ferrocene backbone. Ligand SL-J006-1 bearing electron-withdrawing groups leads to a decrease both in ee and yield (Table 2, entry 6). With an alkylphosphine, the ee decreased slightly (Table 2, entry 7). Bulky phosphine substituents resulted in no reaction (Table 2, entries 8 and 9). Among the other trials (see the SI for more detail), L3 with an electron-rich phosphine had a slight increase of ee compared to Josiphos SL-J001-1 (Table 2, entry 10). By using a 1/1 solvent mixture of *m*-xylene and DCE, the ee further improved to 76% with a slight decrease in the yield (Table 2, entry 11).

Based on this result, we synthesized some more ligands bearing diarylphosphine on the ferrocene backbone and a dicycloheptylphosphine at the α -position. To our delight, when we were using L6 and L7, a slight increase both in ee and yield with L7 was detected (Table 2, entry 13). Finally, we switched from benzoic acid (2–1) to isobutyric acid (2–19) and obtained the optimized conditions with an ee of 88% (3a-19; see Table 2, entry 14).

With the optimized asymmetric reaction condition in hand, the scope of allenes was examined using 2-19 as the acid substrate. Allenes (1a-1c) with different chain length worked well in this reaction. The reactions of o-, m-, and p-substituted benzyl allenes (1j-1q) gave products in good yields with excellent ee values. Similarly, 1-naphthylmethyl allene 1r also gave product 3r-19 in 79% yield with 94% ee. It is noteworthy that alkoxy (1s) or alkyl (1t) allenes are also suitable for the present reaction. We were pleased to find that the reaction worked efficiently for all acids tested when using 2-methyl benzylallene (11) for the scope of carboxylic acids, with the desired products being obtained in good to excellent yields and very high enantioselectivities. Among those, different saturated and unsaturated (2-14, 2-42 to 2-46) aliphatic carboxylic acids, heteroarylcarboxylic acids (2-33 and 2-34) and aromatic acids (2-1) were excellent reaction partners, among which some were even obtained enantiospecifically in good yields (see Table 3).

When running labeling experiments with deuterated benzoic acid, we found deuterium incorporation at the terminal alkene positions to 24% each as well as 23% incorporation of deuterium in the 2-position (see Scheme 2). For the remaining allene excess, we observed a deuterium incorporation at the terminal position of 9%.

Based on the results, we propose a plausible mechanism in Scheme 3. First, a Ru(IV) complex was formed by oxidative addition of the carboxylic acid to a Ru(II) complex (step I). The observed deuteration at the terminal position can be explained by a fast reversible hydrometalation of the lesssubstituted allene double bond, followed by β -hydrogen elimination. The Ru- π -allyl complex was generated by hydrometalation of the more substituted allene double bond (step II), which furnish the allylic ester product by reductive elimination (step III) and release the initial Ru(II) complex to complete the catalytic cycle.

As can be seen from the reaction scope, several examples of the products bearing two double bonds have ee values of >99%. Enantiopure lactones,¹⁸ which represent a very common

Table 3. Scope of Allenes and Carboxylic Acids^a



^aReaction conditions: 1 (0.6 mmol, 3 equiv), 2 (0.2 mmol), $[Ru(p-cymene)Cl_2]_2$ (0.005 mmol, 2.5 mol %), L7 (0.012 mmol, 6 mol %), KOt-Bu (0.02 mmol, 10 mol %) and 3 Å molecular sieve (50 mg) in a mixed solvent *m*-xylene/DCE (1/1, 1 mL) at 90 °C for 24 h with isolated yield and ee was determined by chiral HPLC.



^aThe extent of deuterium incorporation was determined using ¹H NMR spectroscopy.

and important motif both in natural products and organic synthesis, could be easily obtained by a RCM from them. Indeed, with a 5 mol % loading of Grubbs' second-generation catalyst, lactones 4l-14 and 4l-44 could be synthesized in yields of 95% and 90%, respectively, with retention of enantiopurity (Scheme 4). We envision that, by choosing a carboxylic acid with unsaturated C==C bonds at different positions of the chain, different branched vinyl esters could be obtained enantioselectively using the method described here, which will further furnish chiral lactones with different ring sizes by RCM reaction.

Scheme 3. Proposed Mechanism for the Ruthenium-Catalyzed Coupling of Terminal Allenes with Carboxylic Acids



Scheme 4. RCM Reaction of the Allylic Esters To Form Chiral Lactones



In summary, we have developed a ruthenium-catalyzed redox-neutral atom economic intermolecular addition of carboxylic acids to terminal allenes. With careful design and modification of the Josiphos ligands, branched allylic esters were formed in high yields with perfect regioselectivities and excellent enantioselectivities. The reaction has a broad scope and a good tolerance of functional groups both on the allene and carboxylic acid coupling partner. The allylic products with the double bond and the newly formed chiral center are attractive for subsequent chemical transformations such as RCM to form chiral lactones with different ring sizes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c03306.

General procedures, optimization studies, ligand synthesis, analytical data (NMR, HR-MS, HPLC) (PDF)

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Author Contributions

All experiments were performed by J.-L.H. All authors made contributions in writing the manuscript. All authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(2) According to the German precious and special metals technology group Heraeus, the average bid price in June 2021 is 13.44 \notin /g for Ru; 28.09 \notin /g for Pt; 48.06 \notin /g for Au; 67.72 \notin /g for Pd; 122.81 \notin /g for Ir; and 485.63 \notin /g for Rh. Available via the Internet at: https://www.heraeus.com/en/hpm/pm_prices/prices/prices.html.

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