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Enantioselective Synthesis of Branched Allylic Esters via Rhodium-Catalyzed Coupling of Allenes with Carboxylic Acids

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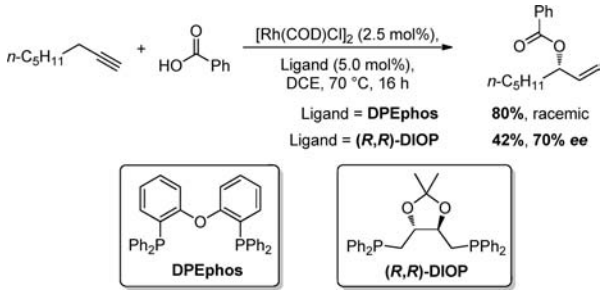
Supporting Information

ABSTRACT: We report on the first intermolecular asymmetric catalytic regio- and enantioselective addition of carboxylic acids to terminal allenes to form valuable branched allylic esters, employing a rhodium(I)/(*R*,*R*)-DIOP catalyst system.

The selective synthesis of enantiopure allylic alcohols and their derivatives as versatile intermediates for the construction of complex molecules[1] has been intensively studied, and many different methods for their preparation are known.[2] In the past decade, access to these compounds via transition-metal-catalyzed allylic substitution[3−6] and allylic oxidation[7,8] has drawn considerable interest. Both approaches require a stoichiometric amount of a leaving group and an oxidant, respectively, making them less attractive in terms of atom economy,[9] whereas methods for allylic oxidation additionally suffer from limited scope and/or low *ee*.

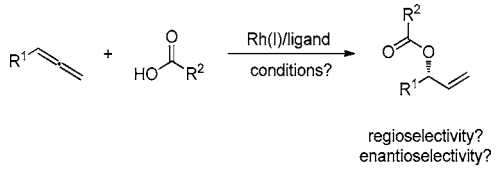
A different and, in terms of utility, more advanced approach for the synthesis of allylic esters has recently been developed in our working group.[10] It offers a truly atom-economic and redox-neutral process by rhodium-catalyzed CH oxidation of terminal alkynes with the alkyne serving as the formal oxidant for the internal redox reaction. Although this method focuses on the use of the achiral DPEphos ligand, giving racemic products, initial experiments employing a rhodium(I)/(*R*,*R*)-DIOP catalyst system led to the branched allylic esters with a promising enantioselectivity of 70% *ee* (Scheme 1).

Scheme 1. Previous Results for Racemic and Enantioselective Coupling of Terminal Alkynes with Carboxylic Acids



We proposed that this transformation proceeds via an intermediate allene formation, evidence for which was obtained by starting directly from this substrate, leading to the same product in comparable yields with perfect regioselectivity for the branched allylic ester. Although several methods for transition-metal-catalyzed intra- and intermolecular addition of C-, N-, O-, and S-nucleophiles to allenes are known,[11−13] only two examples, reported by Yamamoto[14] and Krische,[15] describe the addition of carboxylic acids leading to allylic esters. But because palladium is used as a catalyst for Yamamoto's report, and the scope is restricted to 1,1-dimethyl allene for Krische's report, only linear esters and reverse prenylated esters, respectively, can be formed, which limits both methods to the synthesis of achiral products thus far. Since allenes are an easily accessible and remarkably stable substrate class,[16] we wondered if by starting directly from allenes, our rhodium catalyzed methodology could be used to develop the first general atom-economic and enantioselective synthesis of branched allylic esters by intermolecular addition of carboxylic acids to terminal allenes (Scheme 2).

Scheme 2. General Reaction Scheme for Enantioselective Coupling of Terminal Allenes with Carboxylic Acids



We started our investigations on looking at the addition of benzoic acid to cyclohexyl allene and screening different reaction conditions and chiral bidentate phosphine ligands varying widely in terms of natural bite angle and electronic properties (Table 1). Whereas most tested ligands led to disappointingly low conversions, (*R*,*R*)-DIOP appeared to be the best ligand with complete conversion and promising enantiomeric excess of 86% *ee* at 60 °C. This can be explained by the very similar bite angle and flexibility range of (*R*,*R*)-DIOP and DPEphos,[17] which had been found as the optimal ligand for our racemic alkyne methodology. Since starting from the highly reactive allene makes the initial isomerization step, which is needed for our alkyne methodology, redundant, milder reaction conditions could be achieved. Although a reaction temperature of −3 °C resulted in a very high enantioselectivity of 95% *ee*, the drop in reactivity led to incomplete conversion. We were pleased to find that the addition of a catalytic amount of Cs_2CO_3 accelerated the

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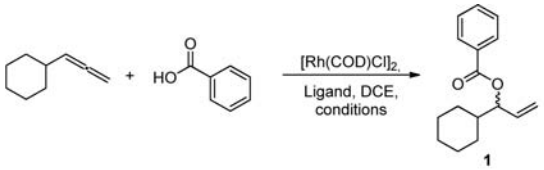
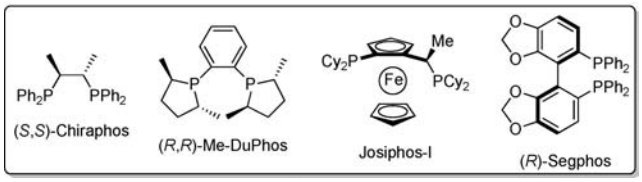
Table 1. Screening of Chiral Phosphine Ligands and Reaction Conditions[a]





#	ligand	T/°C	t/h	additive	conversion/%[b]	ee/%[c]
1	(*S*,*S*)-chiraphos	60	16		0	
2	(*R*,*R*)-Me-DuPhos	60	16		0	
3	josiphos-I	60	16		14	80 (*S*)
4	(*R*)-segphos	60	16		26	59 (*S*)
5	(*R*,*R*)-DIOP	60	16		100	86 (*R*)
6	(*R*,*R*)-DIOP	25	16[d]		100	88 (*R*)
7	(*R*,*R*)-DIOP	0	48		90	91 (*R*)
8	(*R*,*R*)-DIOP	−3	48		63	95 (*R*)
9	(*R*,*R*)-DIOP	−3	48	Cs_2CO_3[e]	100	95 (*R*)

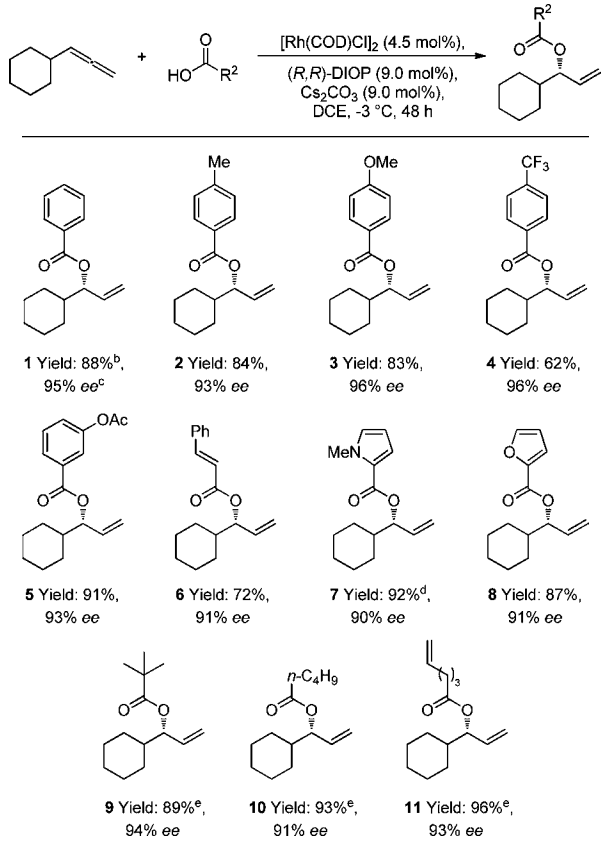
[a]A screw-cap flask was charged with 0.020 mmol of $[Rh(COD)Cl]_2$, 0.040 mmol of the ligand, and 0.44 mmol of acid in 4.4 mL of 1,2-dichloroethane and set to the according reaction temperature. Allene (0.53 mmol) was added, and the reaction was stirred for the according reaction time. [b]Determined by integration of the aromatic signals in the crude ^1H NMR spectrum. [c]Determined by chiral HPLC. [d]Complete conversion after 5 h. [e]Cs_2CO_3 (0.040 mmol) was added.

reaction significantly, with complete conversion being observed after 48 h (Table 1, entry 9).

Utilizing the optimized conditions (entry 9, Table 1), we investigated the scope of the process with respect to the carboxylic acid substrates (Table 2). We were pleased to find that the reaction worked efficiently for all acids tested, with the desired products being obtained in good to almost quantitative yields and very high enantioselectivities (>90% *ee*). In all cases, the branched allylic ester was the only product observed. Besides the unsubstituted benzoic acid (**1**), both electron-rich and electron-poor aromatic carboxylic acids were suitable reaction partners (**2**−**5**). Also, cinnamic acid as a vinylogous benzoic acid presented a suitable substrate for the reaction (**6**). *N*- and *O*-heteroaromatic carboxylic acids turned out to serve well as substrates for our methodology, although the increased steric hindrance of the *N*-methylated compound required a higher reaction temperature (15 °C) in order to obtain complete conversion (**7** and **8**). Furthermore, aliphatic carboxylic acids (linear and branched) worked well, leading to the desired allylic esters (**9**−**11**) in excellent yields and high enantioselectivities. However, an elevated reaction temperature (25 °C) was necessary for complete conversion. A terminal alkene functionality in the molecule is also tolerated, leading to an interesting ester product bearing two terminal alkene functional groups, offering the possibility to access enantiopure lactones via RCM.[18]

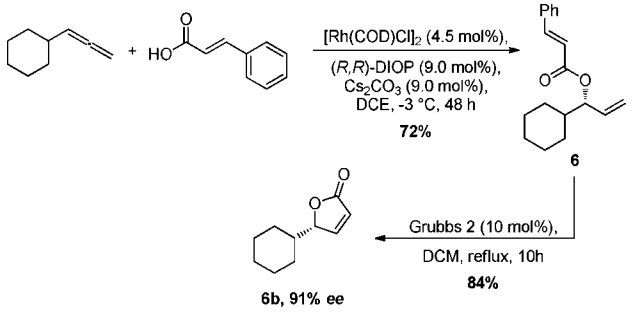
The successful enantioselective addition of α,β-unsaturated acids opens up the possibility for a quick access to γ-butyrolactones as an important structural motif in an array of natural products.[19] This was demonstrated by performing a RCM on the cinnamic

Table 2. Enantioselective Rhodium-Catalyzed Synthesis of Branched Allylic Esters: Scope of Carboxylic Acids[a]



[a]A screw-cap flask was charged with 0.020 mmol $[Rh(COD)Cl]_2$, 0.040 mmol (*R*,*R*)-DIOP, 0.040 mmol Cs_2CO_3, and 0.44 mmol of acid in 4.4 mL of 1,2-dichloroethane and cooled to −3 °C. Allene (0.53 mmol) was added, and the reaction was stirred for 48 h. [b]Isolated yields. [c]Determined by chiral HPLC. [d]Reaction performed at 15 °C. [e]Reaction performed at 25 °C.

Scheme 3. Enantioselective Two-Step Synthesis of the γ-Butyrolactone 6b



ester product (**6**), which led to the corresponding γ-butyrolactone **6b** in very good yield without loss of chirality (Scheme 3). The product was isolated with an overall yield of 60% over two steps and an enantiomeric purity of 91% *ee*.

Furthermore, the scope of the allene coupling partner was investigated (Table 3). The terminal allenes used were either commercially available or easily prepared by one or two steps (see the Supporting Information).[16] Besides cyclohexyl allene with its branched saturated side chain, linear aliphatic substituents on the allene functionality worked with very high yields, albeit reduced enantioselectivity was noted (**12**).

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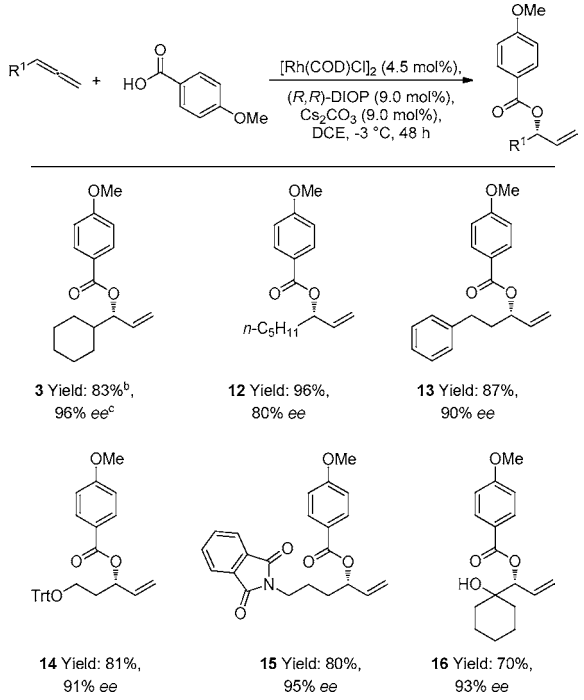
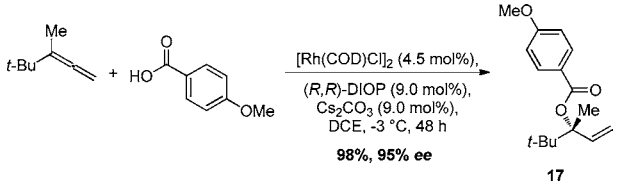
Table 3. Enantioselective Rhodium-Catalyzed Synthesis of Branched Allylic Esters: Scope of Allenes[a]



[a]A screw-cap flask was charged with 0.020 mmol $[Rh(COD)Cl]_2$, 0.040 mmol (*R*,*R*)-DIOP, 0.040 mmol Cs_2CO_3, and 0.44 mmol of acid in 4.4 mL of 1,2-dichloroethane and cooled to −3 °C. Allene (0.53 mmol) was added, and the reaction was stirred for 48 h. [b]Isolated yields. [c]Determined by chiral HPLC.

However, an allene equipped with a related phenethyl substituent performed with significantly improved enantioselectivity (**13**).[20] Comparable results were obtained with heteroatom-containing allenes (**14** and **15**). Even an unprotected alcohol at the α-position of the new chiral center formed was very well tolerated (**16**), formally giving access to 1,2- and 1,3-dihydroxylated structures and showing the potential of this methodology for the preparation of heteroatom-containing target structures.

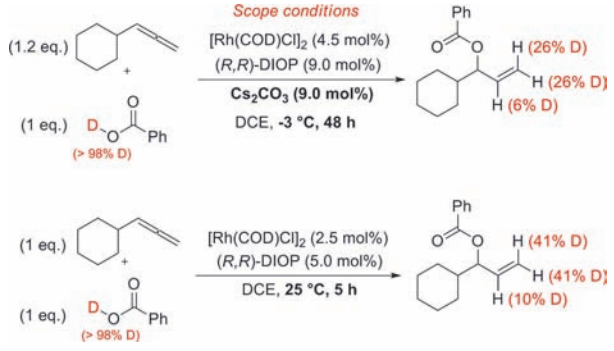
Scheme 4. Enantioselective Rh-Catalyzed Synthesis of a Branched Allylic Ester with a Quaternary Center



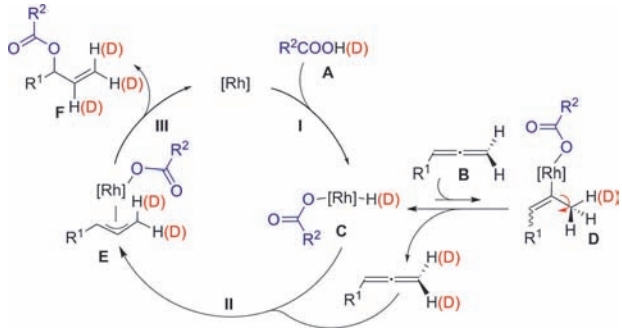
Furthermore a 1,1-unsymmetrically disubstituted allene was probed as a substrate (Scheme 4). We were pleased to see that the corresponding tertiary alcohol derivative was obtained in high yield and excellent enantioselectivity for the formation of a quaternary stereocenter (**17**).

Taking into account the results of labeling experiments using deuterated benzoic acid (Scheme 5), the following mechanistic rationale can be proposed (see Scheme 6). The catalytic cycle may start by oxidative addition of the carboxylic acid **A**, leading to the Rh(III) complex **C** (step **I**). A fast hydrometalation of the less substituted allene double bond furnishing σ-vinyl-Rh

Scheme 5. Isotopic Labeling Experiments with Deuterated Benzoic Acid



Scheme 6. Proposed Mechanism for the Enantioselective Rhodium-Catalyzed Coupling of Terminal Allenes with Carboxylic Acids



species **D** followed by β-hydrogen elimination could explain the incorporation of the deuterium at the terminal position. A slower hydrometalation of the more substituted allene double bond generates the Rh-π-allyl complex **E** (step **II**), which after reductive elimination (or external carboxylate attack) would furnish the allylic ester product **F** (step **III**). The observed regioselectivity for the final step has previously been described in the literature and is typical for Rh-π-allyl complexes.[21]

In summary, we have documented the first intermolecular addition of carboxylic acids to terminal allenes to form highly useful branched allylic esters with perfect regioselectivity and excellent enantioselectivities employing a simple and commercially available rhodium(I)/DIOP catalyst. The reaction is completely atom economic and displays a broad scope. Even 1,1-disubstituted allenes could be employed, leading to the formation of allylic esters with a quaternary chiral center. Further studies will focus on mechanistic investigations as well as on the extension toward other nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

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

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