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Letter

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Rhodium-Catalyzed Asymmetric [2 + 2 + 2] Cycloaddition of 1,6-Enynes with Cyclopropylideneacetamides

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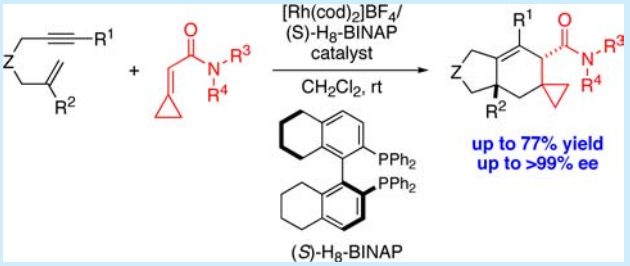
Supporting Information

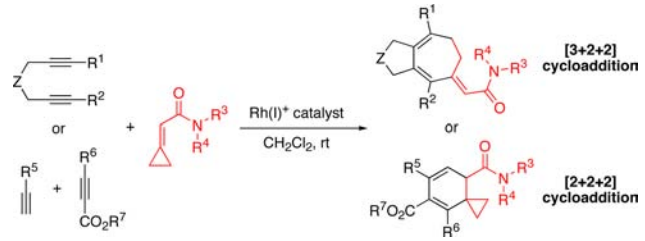
ABSTRACT: It has been established that a cationic rhodium(I)/H_8–BINAP complex catalyzes the asymmetric [2 + 2 + 2] cycloaddition of 1,6-enynes with cyclopropylideneacetamides to produce spirocyclohexenes in excellent enantioselectivity with retaining cyclopropane rings.



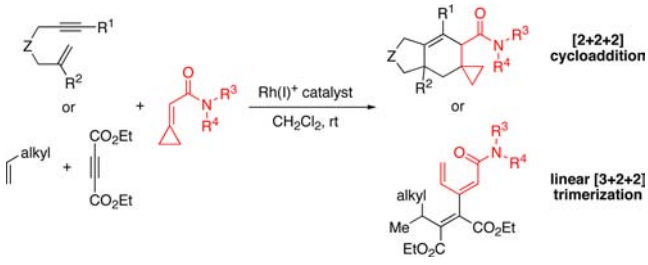
The transition-metal-catalyzed asymmetric [2 + 2 + 2] cycloaddition[1] of 1,6-enynes with unsaturated compounds is a useful and straightforward method for construction of chiral bicyclic scaffolds.[2,3] The Evans[2a] and Shibata[2b] groups independently achieved this transformation by using alkynes as coupling partners and cationic rhodium(I)/axially chiral biaryl bisphosphine complexes as catalysts.[4] These pioneering works enabled the synthesis of chiral bicyclic cyclohexadienes with one stereogenic center with high enantioselectivity. The next challenge is the use of alkenes as coupling partners to produce chiral bicyclic cyclohexenes with two stereogenic centers with high diastero- and enantioselectivity.[5] Recently, our research group achieved this transformation by using acrylamides as alkenes and a cationic rhodium(I)/H_8–BINAP complex as a catalyst.[3,6] Subsequently, our research group reported that the cationic rhodium(I)/H_8–BINAP complex catalyzes the [3 + 2 + 2] cycloaddition of 1,6-diynes with cyclopropylideneacetamides[7] to produce cycloheptadienes through cleavage of cyclopropane rings, on the contrary, a cationic rhodium(I)/BINAP complex catalyzes the asymmetric [2 + 2 + 2] cycloaddition of terminal alkynes, acetylenedicarboxylates, and cyclopropylideneacetamides to produce spirocyclohexadienes[8] with retaining cyclopropane rings (Scheme 1).[9,10]

In this letter, we disclose the rhodium-catalyzed asymmetric [2 + 2 + 2] cycloaddition of 1,6-enynes with cyclopropylideneacetamides leading to spirocyclohexenes with retaining cyclopropane rings. Interestingly, when using an aliphatic alkene and diethyl acetylenedicarboxylate in place of the 1,6-enyne, the rhodium-catalyzed linear [3 + 2 + 2] trimerization proceeded to give a triene through cleavage of the cyclopropane ring (Scheme 2).

Scheme 1



Scheme 2



We first examined the reaction of 1,6-enyne **1a** and *N*-methyl-*N*-phenylcyclopropylideneacetamide (**2a**, 1.1 equiv) at room temperature in the presence of 20 mol % of the cationic rhodium(I)/(*S*)-H_8–BINAP complex (Table 1, entry 1). Pleasingly, [2 + 2 + 2] cycloaddition product **3aa** was obtained with excellent ee value (Table 1, entry 1), while a significant amount of a homo-[2 + 2 + 2] cycloaddition product from **1a** was

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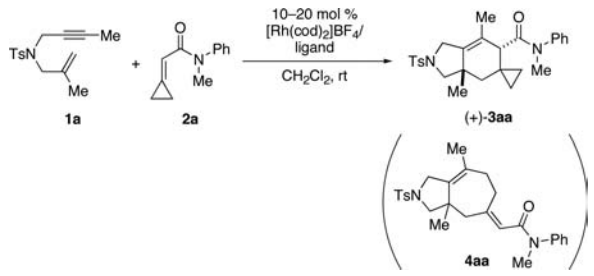
Table 1. Optimization of Reaction Conditions for Rhodium-Catalyzed Asymmetric Cycloaddition of 1a with 2a[a]



entry	ligand	catalyst (mol %)	1a/2a (equiv)	time (h)	3aa (%) yield[b] (% ee)
1	(*S*)-H_8–BINAP	20	1.0/1.1	24	54 (99)
2	(*S*)-H_8–BINAP	20	1.0/2.0	24	45 (99)
3	(*S*)-H_8–BINAP	20	2.0/1.0	24	69 (99)
4	(*S*)-BINAP	20	2.0/1.0	24	59 (97)
5	(*S*)-Segphos	20	2.0/1.0	24	42 (99)
6	(*S,S*)-DIOP	20	2.0/1.0	24	0
7	(*S*)-H_8–BINAP	15	2.0/1.0	72	46 (99)
8	(*S*)-H_8–BINAP	10	2.0/1.0	72	37 (99)

[a]$[Rh(cod)_2]BF_4$ (0.010–0.020 mmol), ligand (0.010–0.020 mmol), **1a** (0.10–0.20 mmol), **2a** (0.10–0.20 mmol), and CH_2Cl_2 (2.0 mL) were used. [b]Isolated yield.

generated as a byproduct. In order to suppress the undesired homo-[2 + 2 + 2] cycloaddition, the amount of **2a** was increased to 2 equiv, but the reaction rate decreased significantly (entry 2).[11] Pleasingly, increasing the amount of **1a** increased the yield of **3aa** with maintaining the reaction rate (entry 3). Screening of bisphosphine ligands (Figure 1) revealed that the use of biaryl

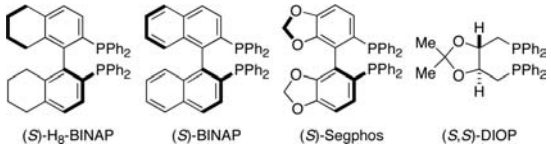
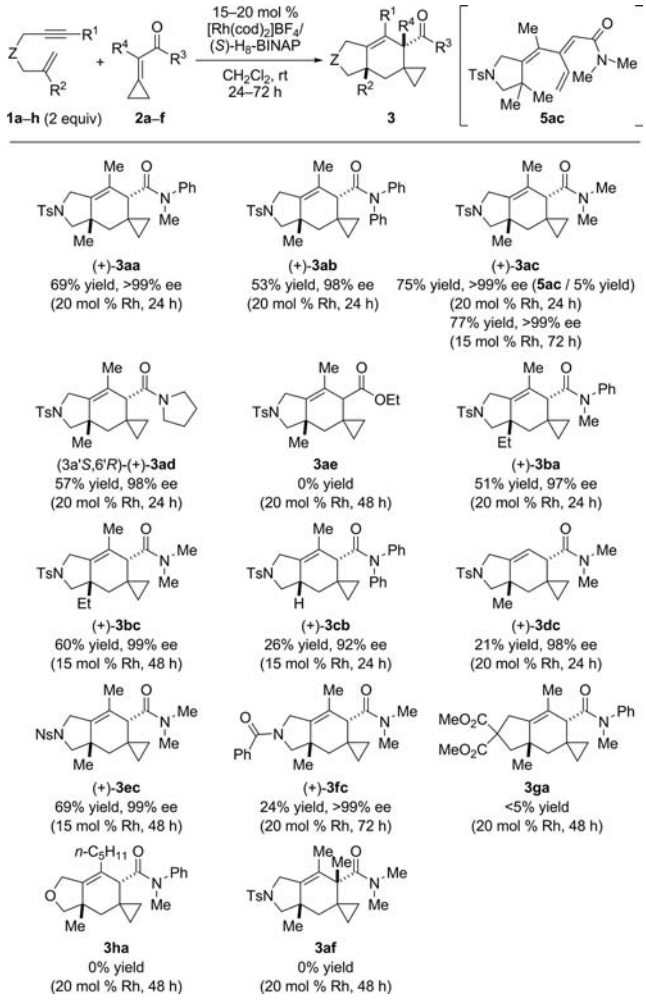


Figure 1. Structures of chiral bisphosphine ligands.

bisphosphine ligands, possessing smaller dihedral angles than H_8–BINAP, decreased the yields of **3aa** (entries 4 and 5), and the use of a nonbiaryl bisphosphine ligand failed to furnish **3aa** (entry 6). Unfortunately, decreasing the catalyst loadings to 15 or 10 mol % decreased the yield of **3aa** (entries 7 and 8). Importantly, in all entries, [3 + 2 + 2] cycloaddition product **4aa** was not detected at all. This feature is in sharp contrast to the reactions of 1,6-diynes with cyclopropylideneacetamides, which furnishes [3 + 2 + 2] cycloaddition products as major products (Scheme 1).[9]

The generality of the reaction with regard to both cycloaddition partners was tested as shown in Scheme 3. Not only *N*-methyl-*N*-phenyl- (**2a**) but also *N*,*N*-diphenyl- (**2b**) and *N*,*N*-dialkyl- (**2c**,**d**) cyclopropylideneacetamides reacted with **1a** to give spirocyclohexenes **3aa**–**3ad** in good yields with excellent ee values. However, cyclopropylideneacetate **2e** failed to react with **1a**. Substituents on cyclopropylideneacetamides **2** affected the product yield and distribution in this process. Increasing the coordination ability of **2** (**2b** < **2a** < **2c**) increased the yields of spirocyclohexenes **3** (**3ab** < **3aa** < **3ac**). Interestingly, the reaction of **1a** with highly coordinative *N*,*N*-dimethylcyclopropylideneacetamide **2c** afforded triene **5ac** as well as spirocyclo-

Scheme 3[a]



[a]$[Rh(cod)_2]BF_4$ (0.0075–0.010 mmol), (*S*)-H_8–BINAP (0.0075–0.010 mmol), **1a**–**h** (0.20 mmol), **2a**–**f** (0.10 mmol), and CH_2Cl_2 (2.0 mL) were used. The cited yields were of isolated products.

hexene **3ac**. Among cyclopropylideneacetamides examined, *N*,*N*-dimethylcyclopropylideneacetamide **2c** showed the highest reactivity, and the catalyst loading could be reduced to 15 mol % without loss of the product yield. With respect to 1,6-enynes, not only methyl (**1a**) but also ethyl (**1b**) substitution at the alkene moiety was tolerable. However, 1,6-enyne **1c**, possessing the monosubstituted alkene moiety, and terminal 1,6-enyne **1d** reacted with **2b** and **2c**, respectively, to give spirocyclohexenes **3cb** and **3dc** in low yields.[12] Not only tosylamide- (**1a**–**e**) but also nosylamide- (**1f**) and benzamide- (**1g**) linked 1,6-enynes could be employed for this reaction, while malonate- and oxygen-linked 1,6-enynes **1g** and **1h**, which are suitable substrates for acrylamides, were failed coupled with **2a**.[12] Finally, construction of two quaternary carbon centers was attempted, while the desired spirocyclohexene **3af** was not obtained at all. Importantly, excellent ee values (92 to >99%) were observed in all products. The relative and absolute configurations of (+)-**3ad** were unambiguously determined by an X-ray crystallographic analysis.

A possible mechanism for the formation of **3** and **5** is shown in Scheme 4. Enyne **1** reacts with rhodium to generate rhodacyclopentene **A**. Regioselective insertion of alkene **2** into **A** generates rhodacycle **B**. Reductive elimination affords

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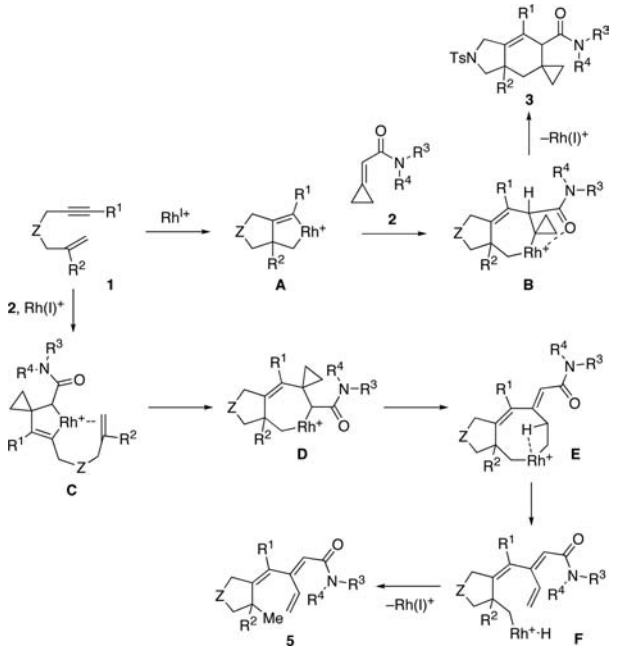
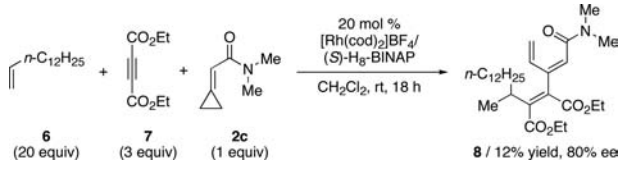
Scheme 4



spirocyclohexene **3**. The amide carbonyl oxygen coordinates to rhodium, and the cyclopropane moiety located at α position with respect to rhodium would suppress β-hydrogen and carbon eliminations, respectively. When using highly coordinative *N*,*N*-dimethylcyclopropylideneacetamide **2c**, the alkyne moiety of **1** reacts with **2** and rhodium to generate rhodacyclopentene **C**.[13] Insertion of the alkene moiety of **1** into **C** generates rhodacycle **D**. β-Carbon elimination affords rhodacycle **E** and subsequent β-hydrogen elimination affords rhodium hydride **F**. Reductive elimination affords triene **5**.

As shown in Scheme 1, the reaction of terminal alkynes, acetylenedicarboxylates, and cyclopropylideneacetamides afforded [2 + 2 + 2] cycloaddition products with retaining cyclopropane rings.[9] Thus, the reaction of 1-tetradecene (**6**), diethyl acetylenedicarboxylate (**7**), and cyclopropylidene-acetamide **2c** was examined (Scheme 5).[13] Interestingly, not the spirocyclohexene but triene **8** was obtained in low yield with good ee value through cleavage of the cyclopropane ring.

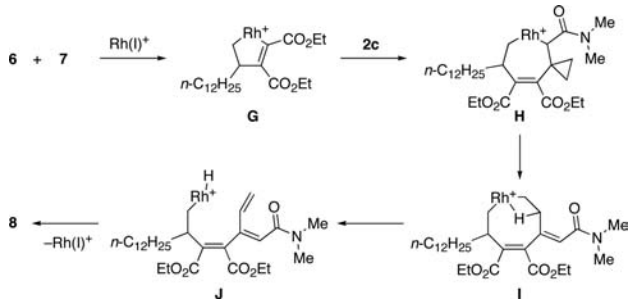
Scheme 5



A possible mechanism for the formation of **8** is shown in Scheme 6. Similar to the proposed mechanism of our previously reported cationic rhodium(I)/(*R*)-BINAP complex-catalyzed asymmetric linear cross-trimerization of alkenes, acetylenedicarboxylates, and acrylamides,[6i] **6** and **7** react with rhodium to generate rhodacyclopentene **G**. Regioselective insertion of **2c** into **G** generates rhodacycle **H**. β-Carbon elimination affords rhodacycle **I** and subsequent β-hydrogen elimination affords rhodium hydride **J**. Reductive elimination affords triene **8**.

In summary, we have established that a cationic rhodium(I)/H_8–BINAP complex catalyzes the asymmetric [2 + 2 + 2] cycloaddition of 1,6-enynes with cyclopropylideneacetamides to produce spirocyclohexenes in excellent enantioselectivity with retaining cyclopropane rings; on the contrary, the reaction of 1-tetradecene, diethyl acetylenedicarboxylate, and the cyclopropylideneacetamide affords a linear [3 + 2 + 2] trimerization product through cleavage of the cyclopropane ring.

Scheme 6



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03387.

X-ray crystallographic file (CIF)
Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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