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Rhodium-Catalyzed Asymmetric [2+2+2] Cyclization of 1,6-Enynes and Aldehydes

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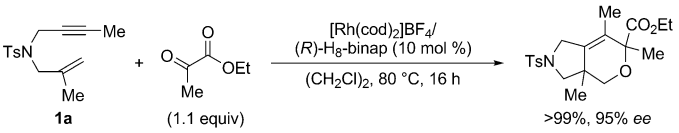
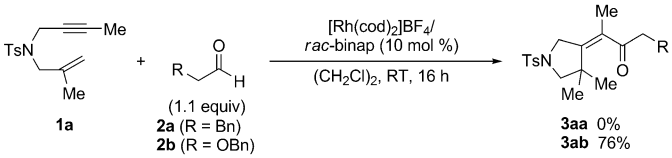
The transition-metal-catalyzed [2+2+2] cyclization of 1,6-enynes and alkynes is a valuable method to construct complex cyclic frameworks in a single reaction step.[1,2] Asymmetric variants of this reaction have been developed by using cationic rhodium(I)/chiral bisphosphine complexes as catalysts.[3] However, the successful transition-metal-catalyzed [2+2+2] cyclizations of 1,6-enynes and unsaturated compounds excluding alkynes are relatively rare.[4–7] In 2008, two research groups, including ours, independently discovered the transition-metal-catalyzed [2+2+2] cyclization of 1,6-enynes and carbonyl compounds.[4–6,8] Our research group developed the cationic rhodium(I)/H_8-binap complex catalyzed asymmetric [2+2+2] cyclization of 1,6-enynes and electron-deficient ketones, which produced bicyclic heterocycles in high yields with high enantiomeric excess (*ee*; Scheme 1).[4]



Scheme 1. Rhodium-catalyzed asymmetric [2+2+2] cyclization of 1,6-enyne **1a** and α-ketoester.

The Louie group developed the nickel-catalyzed [2+2+2] cyclization of 1,6-enynes and electron-rich carbonyl compounds.[6] In this reaction, not only ketones, but also aldehydes are able to react with 1,6-enynes. We also examined the reaction of 1,6-enyne **1a** and aldehyde **2a** in the presence of a cationic rhodium(I)/*rac*-binap complex. However, homo-reaction products of **1a**, not the desired cross-reaction product between **1a** and **2a**, were generated (Scheme 2). On the other hand, we have recently reported the asymmetric cyclization of γ-alkynylaldehydes with aldehydes.[9] In this reaction, chelating alkoxylacetaldehydes are suitable reaction partners, whereas unfunctionalized aldehydes failed to react with γ-alkynylaldehydes. Therefore, the reaction of **1a** and commercially available benzyloxylacetaldehyde (**2b**) was examined, which revealed that the desired achiral cross-reaction product **3ab** was obtained in good yield at room temperature (Scheme 2).



Scheme 2. Rhodium-catalyzed reactions of 1,6-enyne **1a** and aldehydes **2a** and **2b**; Bn = benzyl.

To develop an asymmetric variant of this [2+2+2] cyclization, the reaction of 1,6-enyne **1b**, possessing the monosubstituted alkene moiety, and **2b** was investigated in the presence of a cationic rhodium(I)/(*R*)-binap complex (10 mol%). After 16 h at room temperature, the desired ketone **3bb** was obtained in 88% yield with 95% *ee* (Table 1, entry 1). The effect of chiral bisphosphine ligands (Scheme 3) was then examined (Table 1, entries 1–8), which revealed that biaryl bisphosphines are suitable ligands (entries 1–5), and the use of (*R*)-binap gives both high product yield and *ee* value (entry 1). The catalyst loading could be reduced to 5 mol% without erosion of the product *ee* value, although the product yield decreased within acceptable levels (Table 1, entry 9).

Thus, the scope of the asymmetric [2+2+2] cyclization of 1,6-enynes with aldehydes was explored by using 5 mol% of the cationic rhodium(I)/(*R*)-binap complex at room temperature (Scheme 4). Not only enyne **1b** possessing the methyl group at the alkyne terminus, but also 1,6-enynes **1c** and **1d** possessing the aryl group at the alkyne terminus reacted with **2b** in good yields with high *ee* values, although an excess of **2b** was used. The absolute configuration of ketone (+)-**3db** was unambiguously determined to be *R* by the anomalous dispersion method (Figure 1).[10] Not only tertiary stereocenters but also a quaternary stereocenter could

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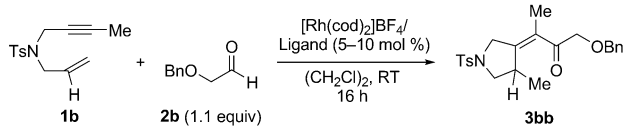
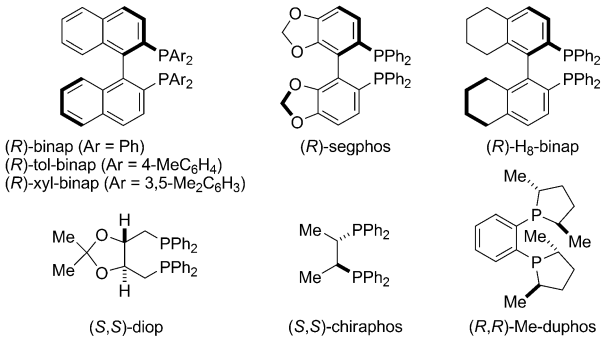
Table 1. Screening of reaction conditions for rhodium-catalyzed asymmetric [2+2+2] cyclization of 1,6-enyne **1b** and aldehyde **2b**.[a]



Entry	Ligand	Catalyst [mol%]	Yield [%][b]	*ee* [%]
1	(*R*)-binap	10	88	95 (+)
2	(*R*)-segphos	10	89	91 (+)
3	(*R*)-H_8-binap	10	72	89 (+)
4	(*R*)-tol-binap	10	75	95 (+)
5	(*R*)-xyl-binap	10	77	96 (+)
6	(*S,S*)-diop	10	55	8 (−)
7[c]	(*R,R*)-Me-duphos	10	7	9 (+)
8[c]	(*R,R*)-chiraphos	10	11	21 (−)
9[d]	(*R*)-binap	5	72	95 (+)

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol; cod = 1,5-cyclooctadiene), ligand (0.010 mmol), **1b** (0.10 mmol), **2b** (0.11 mmol), and $(CH_2Cl)_2$ (2.0 mL) were used. [b] Yield of the isolated product. [c] $[Rh(nbd)_2]BF_4$ was used. [d] **1b** (0.20 mmol) and **2b** (0.22 mmol) were used.



Scheme 3. Structures of chiral bisphosphine ligands.

be constructed, and ketone **3eb** was obtained with an excellent *ee* value. The present asymmetric [2+2+2] cyclization is not limited to the nitrogen-linked 1,6-enynes. Oxygen- and carbon-linked 1,6-enynes **1f–i** were also suitable substrates for this process. Next, we examined the scope of aldehydes. Unfortunately, 3-(benzyloxy)propionaldehyde (**2c**) failed to react with nitrogen- and oxygen-linked 1,6-enynes **1b** and **1f**. However, interestingly, carbon-linked 1,6-enyne **1g**

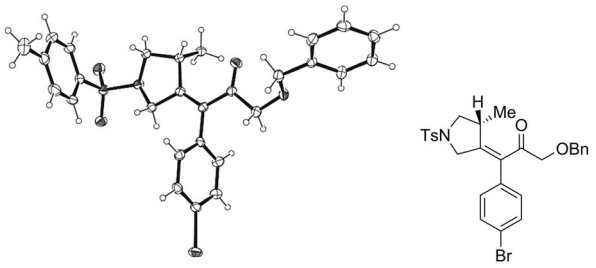
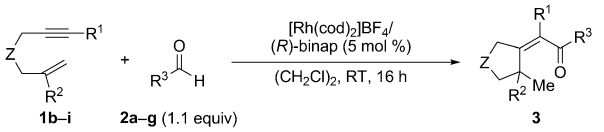
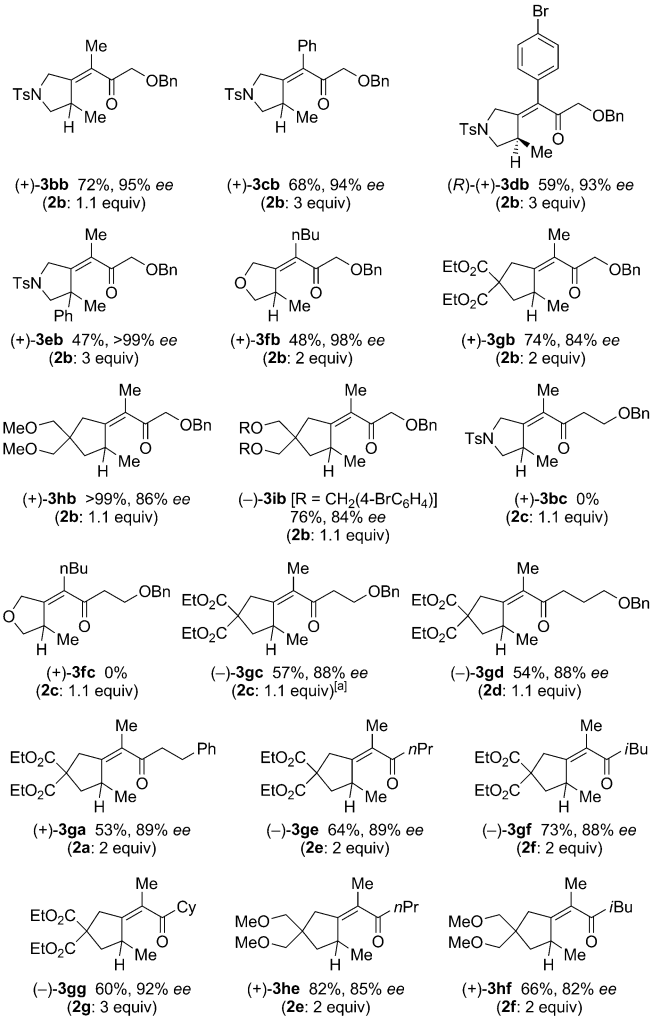


Figure 1. ORTEP diagram of (*R*)-(+)-**3db** with ellipsoids at 30% probability.



1b (Z = NTs, R^1 = Me, R^2 = H)
1c (Z = NTs, R^1 = Ph, R^2 = H)
1d (Z = NTs, R^1 = 4-BrC_6H_4, R^2 = H)
1e (Z = NTs, R^1 = Me, R^2 = Ph)
1f (Z = O, R^1 = *n*Bu, R^2 = H)
1g (Z = $C(CO_2Et)_2$, R^1 = Me, R^2 = H)
1h (Z = $C(CH_2OMe)_2$, R^1 = Me, R^2 = H)
1i (Z = $C(CH_2OR)_2$, R^1 = Me, R^2 = H)
(R = CH_2(4-BrC_6H_4))

2a (R^3 = CH_2CH_2Ph)
2b (R^3 = CH_2OBn)
2c (R^3 = CH_2CH_2OBn)
2d (R^3 = $CH_2CH_2CH_2OBn$)
2e (R^3 = *n*Pr)
2f (R^3 = *i*Bu)
2g (R^3 = Cy)

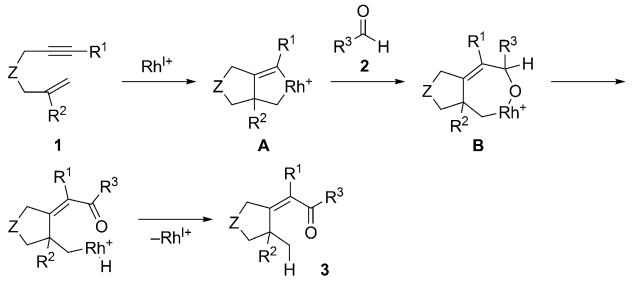


Scheme 4. Rhodium-catalyzed asymmetric [2+2+2] cyclization of 1,6-enynes **1b–i** and aldehydes **2a–g**. $[Rh(cod)_2]BF_4$ (0.010 mmol), (*R*)-binap (0.010 mmol), **1b–i** (0.20 mmol), **2a–g** (0.22–0.60 mmol), and $(CH_2Cl)_2$ (2.0 mL) were used. Cited yields are of isolated products. [a] $[Rh(cod)_2]BF_4$ (0.020 mmol), (*R*)-binap (0.020 mmol), **1g** (0.40 mmol), and **2c** (0.44 mmol) were used.

smoothly reacted with 4-(benzyloxy)butylaldehyde (**2d**) as well as with **2c**. Furthermore, unfunctionalized aldehydes **2a** and **2e–g** could equally be employed.[11] Another carbon-linked 1,6-enyne **1h** also reacted with unfunctionalized alde-

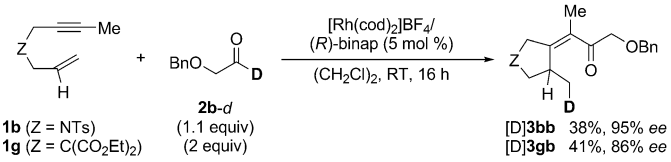
hydes **2e** and **2f** to give the corresponding [2+2+2] cyclization products with good yields and *ee* values.

Scheme 5 depicts our proposed reaction mechanism for this [2+2+2] cyclization. 1,6-Enyne **1** reacts with rhodium to generate the rhodacyclopentene intermediate **A**. Insertion of aldehyde **2** into intermediate **A** generates intermediate **B**.[12] β-Hydride elimination followed by reductive elimination of rhodium gives dienone **3**.



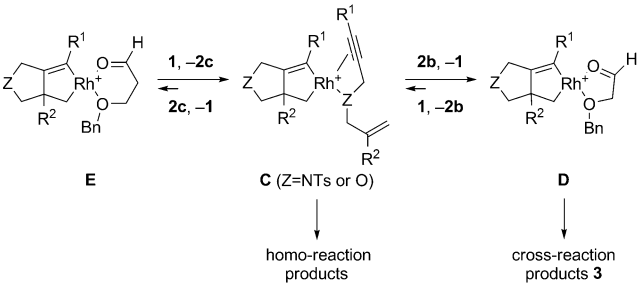
Scheme 5. Proposed reaction mechanism.

Consistent with the above pathway, the reactions of both nitrogen- and carbon-linked 1,6-enynes **1b** and **1g** with deuterium-labeled aldehyde [D]**2b** led to selective and quantitative incorporation of deuterium in the methyl group attached to the chiral center of the products [D]**3bb** and [D]**3gb** (Scheme 6).



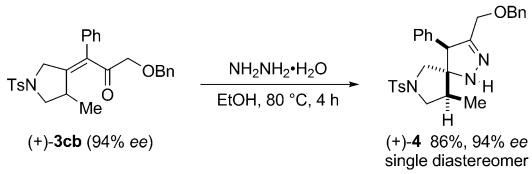
Scheme 6. Deuterium labeling studies.

A possible explanation for the significant difference of reactivity between **2b** and **2c** in the reactions with heteroatom-linked 1,6-enynes **1b** and **1f** is shown in Scheme 7. 1,6-Enyne **1** reacts with rhodium in the presence of **2b** to generate an equilibrium mixture of intermediates **C** and **D** through the bidentate coordination of **1** and **2b** to rhodium.[13] Intermediate **D**, which would give cross-reaction products **3**, might be predominantly generated as a result of the stable five-membered chelation of **2b** to rhodium. In contrast, 1,6-enyne **1** reacts with rhodium in the presence of **2c** to generate intermediate **C**, which would give homo-reaction products, not intermediate **E** exclusively, presumably due to the labile six-membered chelation of **2c** to rhodium. In the case of weakly coordinating carbon-linked 1,6-enynes **1g–i**, the aldehyde coordination to rhodium followed by insertion to the rhodacyclopentene may not be hampered.



Scheme 7. Equilibration between intermediates **C**–**E**.

The cyclic compound, obtained from this asymmetric cyclization reaction, may serve as a useful chiral building block (Scheme 8). Treatment of **3cb** with hydrazine afforded spiro compound **4**, with three consecutive stereogenic centers, in high yield as a single diastereomer.[14]



Scheme 8. Transformation of reaction product **3cb**.

In conclusion, the first asymmetric [2+2+2] cyclization of 1,6-enynes and aldehydes was achieved by using a cationic rhodium(I)/(*R*)-binap complex as a catalyst, although this ring closure generally cannot be applied to the reaction of heteroatom-linked 1,6-enynes with aldehydes without an oxygen functionality. Coordination of the substrate heteroatom to the cationic rhodium plays an important role in this cyclization reaction. Further exploitation of the rhodium-catalyzed enyne cyclization reactions is underway in our laboratory.

Experimental Section

Representative procedure (Scheme 4, (+)-3bb): Under an argon atmosphere, (*R*)-binap (6.2 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were dissolved in CH_2Cl_2 (2.0 mL) and the mixture was stirred at RT for 5 min. H_2 was introduced to the resulting solution in a Schlenk tube. After stirring at RT for 30 min, the resulting mixture was evaporated to dryness. A solution of **1b** (52.6 mg, 0.200 mmol) and **2b** (33.0 mg, 0.220 mmol) in $(CH_2Cl)_2$ (2.0 mL) was added to the residue at RT. The mixture was stirred at RT for 16 h. The resulting solution was concentrated and purified by a preparative TLC (hexane/EtOAc/CH_2Cl_2 = 3:1:1), which gave **(+)-3bb** as a colorless oil (59.5 mg, 0.144 mmol, 72% yield, 95% *ee*).

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Keywords: aldehydes · asymmetric catalysis · cyclization · enynes · rhodium

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[10] CCDC-831429 [(*R*)-(+)-**3db**] contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] Nitrogen- and oxygen-linked 1,6-enynes **1b** and **1f** failed to react with unfunctionalized aldehydes **2e**–**g**, and instead a homo-[2+2+2]cycloaddition of **1b** and **1f** proceeded as a major side reaction.

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