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Enantioselective Cycloisomerization of 1,6-Enynes to Bicyclo[3.1.0]hexanes Catalyzed by Rhodium and Benzoic Acid

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Supporting Information

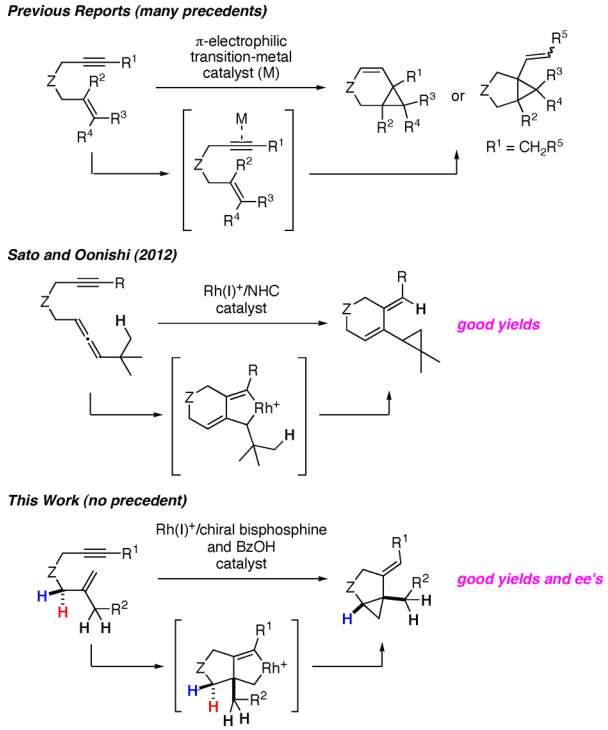
ABSTRACT: It has been established that a cationic Rh(I)/(*S*)-Segphos or (*S*)-DTBM-Segphos complex and benzoic acid catalyze the enantioselective cycloisomerization of 1,6-enynes, possessing carbonyl groups at the enyne linkage, to 2-alkylidenebicyclo[3.1.0]hexanes. The present cycloisomerization may involve site selective γ-hydrogen elimination. The one-pot enantioselective cycloisomerization and lactonization of 1,6-enynes, leading to bicyclic lactones, has also been accomplished.

Transition-metal-catalyzed cycloisomerization reactions are highly efficient methods for the construction of complex cyclic frameworks.[1,2] Among them, the transition-metal-catalyzed cycloisomerization of 1,6-enynes is one of the most actively studied transformations.[2] For example, a number of catalytic cycloisomerization reactions of the 1,6-enynes, leading to bicyclic cyclopropanes (bicyclo[4.1.0]hept-2-enes[3] and 1-vinylbicyclo[3.1.0]hexanes[4]), have been reported to date (Scheme 1, top). These reactions are initiated by activation of alkynes with π-electrophilic transition-metal complexes.[3,4] However, the transition-metal-catalyzed cycloisomerization of 1,6-enynes, leading to the bicyclic cyclopropanes, that proceeds through the formation of metallacycle intermediates has not been reported. Recently, Sato and Oonishi reported the novel cycloisomerization of 1,6-allenynes, leading to none-fused cyclopropanes, via the formation of metallacycles followed by γ-hydrogen elimination by using a cationic Rh(I)/N-heterocyclic carbene (NHC) complex as a catalyst (Scheme 1, middle).[5−8] In this paper, we disclose the unprecedented enantioselective cycloisomerization of 1,6-enynes, leading to bicyclo[3.1.0]-hexanes, catalyzed by a cationic Rh(I)/chiral bisphosphine complex and benzoic acid, which may proceed via the enantioselective formation of metallacycles followed by metallacycle ring-opening and site selective γ-elimination of the methylene hydrogen (Scheme 1, bottom).

Recently, our research group reported the sequential cycloisomerization/hetero Diels−Alder reaction of 1,6-enynes, possessing the monosubstituted alkene moiety, with aldehydes catalyzed by a cationic Rh(I)/BINAP complex and benzoic acid.[9−11] The first step (cycloisomerization of 1,6-enynes to 1,3-dienes) proceeds through the formation of rhodacyclopentene **A** followed by protonation with benzoic acid and β-hydrogen elimination (Scheme 2). In this reaction, the protonation of the bicyclic intermediate **A** with benzoic acid to produce monocyclic intermediate **B** may facilitate the β-hydrogen elimination.[9] Indeed, not the β-hydrogen elimination but the aldehyde insertion to the rhodacyclopentene **A** proceeded in the absence of benzoic acid.[12]

The above result prompted our investigation into the rhodium and benzoic acid-catalyzed reaction of a 1,6-enyne, possessing no β-hydrogen in intermediates **A** and **B**. Thus, the reaction of 1,6-enyne **1a**, possessing the 1,1-disubstituted alkene moiety, in the

Scheme 1



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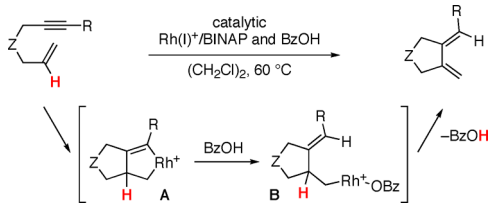
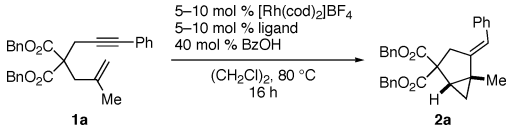
Scheme 2



presence of the cationic Rh(I)/BINAP complex and benzoic acid was attempted. We were pleased to find that 2-alkylidenebicyclo[3.1.0]hexane **2a** was obtained in high yield with high enantioselectivity using 10 mol % of the rhodium catalyst and 40 mol % of benzoic acid at 80 °C (Table 1, entry 1).[13] Importantly, bicyclo[3.1.0]hexane skeletons are found as core structures of natural products.[14] Therefore, the development of a new method for the catalytic enantioselective synthesis of bicyclo[3.1.0]hexane derivatives that would enable facile access to new analogues of this class of compounds in enantiomerically enriched form is an important topic.

Table 1. Optimization of Reaction Conditions for Enantioselective Cycloisomerization of 1,6-Enyne 1a[a]



entry	ligand	Rh/ligand (mol %)	convn (%)[b]	yield (%)[c]	ee (%)
1	(*S*)-BINAP	10	100	89	81 (+)
2	(*S*)-H_8-BINAP	10	83	77	78 (+)
3	(*S*)-Segphos	10	100	96	81 (+)
4	(*S*,*S*)-DIOP	10	83	68	3 (+)
5[d]	(*S*,*S*)-Chiraphos	10	43	28	36 (+)
6[d]	(*R*,*R*)-Me-Duphos	10	0	0	–
7	(*S*)-tol-BINAP	10	77	65	83 (+)
8	(*S*)-xyl-BINAP	10	60	45	82 (+)
9	(*S*)-tol-Segphos	10	64	45	83 (+)
10	(*S*)-xyl-Segphos	10	100	88	81 (+)
11	(*S*)-DTBM-Segphos	10	29	25	95 (+)
12[e]	(*S*)-Segphos	5	100	93	81 (+)

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1a** (0.10 mmol), BzOH (0.040 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used. [b] Determined by recovery of **1a**. [c] Isolated yield. [d] $[Rh(nbd)_2]BF_4$ was used in place of $[Rh(cod)_2]BF_4$. [e] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1a** (0.20 mmol), BzOH (0.080 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used.

The optimization of reaction conditions for the enantioselective cycloisomerization of **1a** to **2a** is shown in Table 1. Screening of chiral bisphosphine ligands (Figure 1, entries 1−6) revealed that biaryl bisphosphine ligands (entries 1−3) showed higher catalytic activity and enantioselectivity than nonbiaryl bisphosphine ligands (entries 4−6). Among biaryl bisphosphine ligands examined, (*S*)-Segphos showed the best result (entry 3). The use of sterically demanding biaryl bisphosphine ligands (entries 7−11) decreased the catalytic activity, although significantly improved enantioselectivity was observed by using (*S*)-DTBM-Segphos as a ligand (entry 11). When using (*S*)-Segphos as a ligand, the catalyst loading could be reduced to 5 mol % without significant decrease of the product yield (entry 12).

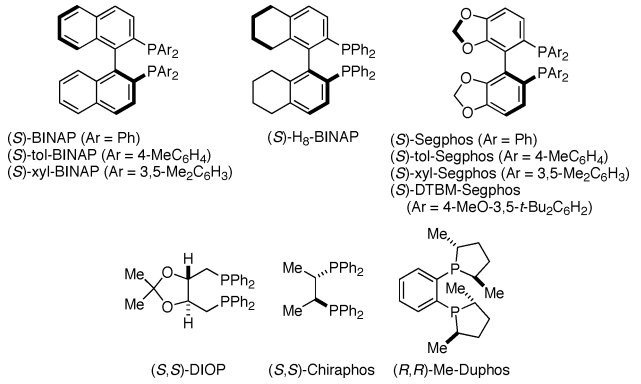


Figure 1. Structures of chiral bisphosphine ligands.

With the optimized reaction conditions in hand, we explored the scope of the cationic Rh(I)/(*S*)-Segphos complex and benzoic acid-catalyzed cycloisomerization of 1,6-enynes **1** to 2-alkylidenebicyclo[3.1.0]hexanes **2** as shown in Table 2. With respect to the substituent at the alkyne terminus (R^1), not only phenyl-substituted enyne **1a** but also 4-methyl-, 4-bromo-, and 4-trifluoromethylphenyl-substituted enynes **1b−d** furnished the desired cycloisomerization products **2b−d** with high yields and ee values. Meta- or ortho-substituted phenyl derivatives **1e−g** were also suitable substrates for this process, although higher reaction temperature (95 °C) was required for 3-trifluoromethylphenyl derivative **1f** in order to complete the reaction. Additionally, the reactions of alkyl-substituted enynes **1h** and **1i** proceeded with high yields and ee values, although higher reaction temperature and catalyst loading (85 °C, 20 mol % Rh) were required for *n*-butyl-substituted enyne **1i**. With respect to the substituent at the alkene moiety (R^2), not only methyl-substituted enyne **1a** but also sterically more demanding ethyl-substituted enyne **1j** afforded the desired product **2j** with high yield and ee value at 95 °C. With respect to the substituent at the quaternary carbon center $[C(C(O)R^3)_2]$, not only dibenzyl malonate-linked enyne **1a** but also dimethyl malonate- and 1,3-diphenylpropane-1,3-dione-linked enynes **1k** and **1l** afforded the desired products **2k** and **2l** with moderate to good yields and ee values at 95 °C. Although the yields were low to moderate, the use of 30 mol % of the cationic Rh(I)/(*S*)-DTBM-Segphos catalyst for phenyl- and methyl-substituted enynes **1a** and **1h** afforded the corresponding cycloisomerization products **2a** and **2h** with excellent ee values. The relative and absolute configurations of (+)-**2c** were unambiguously determined to be 1*S*,5*R* by an X-ray crystallographic analysis.[15]

Interestingly, 1,6-enynes **1m−o** that do not possess carbonyl groups at the enyne linkage did not afford the corresponding 2-alkylidenebicyclo[3.1.0]hexanes **2m−o** at all, although tosylamide-linked 1,6-enyne **1o** afforded the well-known cycloisomerization product **3o**[3c,e] shown in Scheme 1 in low yield (Scheme 3).

A possible mechanism for the present rhodium and benzoic acid-catalyzed cycloisomerization reaction of 1,6-enyne **1a** to 2-alkylidenebicyclo[3.1.0]hexane **2a** is shown in Scheme 4. 1,6-Enyne **1a** reacts with a cationic Rh(I) complex to generate rhodacyclopentene intermediate **C**. Protonation of this rhodacycle **C** with benzoic acid affords rhodium benzoate intermediate **D**.[9] Coordination of the carbonyl group to rhodium forms intermediate **D′**, which forces rhodium to approach γ-hydrogen

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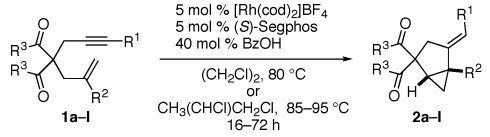
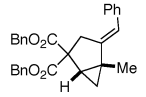
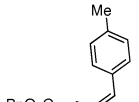
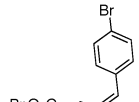
Table 2. Enantioselective Cycloisomerization of 1,6-Enynes 1a–l[a]

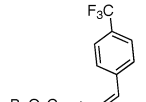


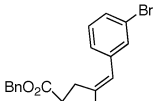
1a–l 2a–l

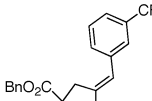

(+)-**2a** / 93%, 81% ee (80 °C, 16 h) 66%, 96% ee [30 mol % $[Rh(cod)_2]BF_4$/(*S*)-DTBM-Segphos, 16 h][b]

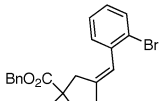

(+)-**2b** / 63%, 80% ee (80 °C, 72 h)

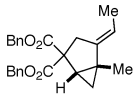

(1*S*,5*R*)-(+)-**2c** / 72%, 81% ee (80 °C, 40 h)

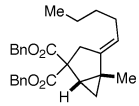

(+)-**2d** / 88%, 82% ee (80 °C, 16 h)

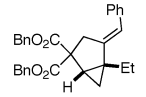

(+)-**2e** / 74%, 78% ee (80 °C, 40 h)

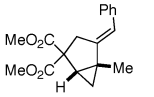

(+)-**2f** / 92%, 76% ee (95 °C, 16 h)[c]

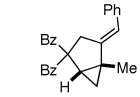

(+)-**2g** / 86%, 77% ee (80 °C, 40 h)


(+)-**2h** / 90%, 88% ee (80 °C, 16 h) 33%, 94% ee [30 mol % $[Rh(cod)_2]BF_4$/(*S*)-DTBM-Segphos, 16 h][b]


(+)-**2i** / 70%, 91% ee (85 °C, 72 h, 20 mol % Rh)[c]


(+)-**2j** / 85%, 74% ee (95 °C, 72 h)


(+)-**2k** / 72%, 73% ee (95 °C, 16 h)


(+)-**2l** / 58%, 54% ee (95 °C, 16 h)

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), (*S*)-Segphos (0.010 mmol), **1** (0.20 mmol), BzOH (0.080 mmol), and $(CH_2Cl)_2$ or $CH_3(CHCl)CH_2Cl$ (1.5 mL) were used. The cited yields are of the isolated products. [b] $[Rh(cod)_2]BF_4$ (0.060 mmol), (*S*)-DTBM-Segphos (0.060 mmol), **1** (0.20 mmol), BzOH (0.080 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used. [c] $[Rh(cod)_2]BF_4$ (0.040 mmol), (*S*)-Segphos (0.040 mmol), **1** (0.20 mmol), BzOH (0.080 mmol), and $CH_3(CHCl)CH_2Cl$ (1.5 mL) were used.

Scheme 3

1m [Z = C(CH2OBn)2]
1n (Z = O)
1o (Z = NTs)

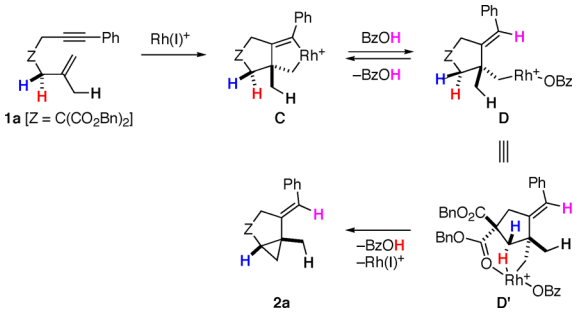
2m / 0% **3m** / 0%
2n / 0% **3n** / 0%
2o / 0% **3o** / 29%, <5% ee

on not the methyl but on the methylene group. Thus, the site selective γ-elimination of the methylene hydrogen proceeds to give **2a** and regenerates the Rh(I) complex and benzoic acid.[16] This proposed mechanism was consistent with the fact that 1,6-enynes **1m–o** without carbonyl groups at the enyne linkage failed to furnish **2m–o** (Scheme 3).

Consistent with the above reaction pathway, the reaction of enyne **1k**-d_2 possessing the dideuterated allylic methylene group furnished monodeuterated product **2k**-*d* (Scheme 5).

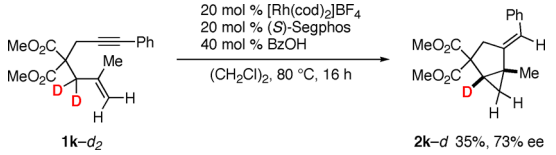
3-Cyclopropylpropionic acids[17] and esters[18] were known for being able to convert to monocyclic lactones with a Brønsted

Scheme 4



1a [Z = C(CO2Bn)2] **C** **D** **2a** **D'**

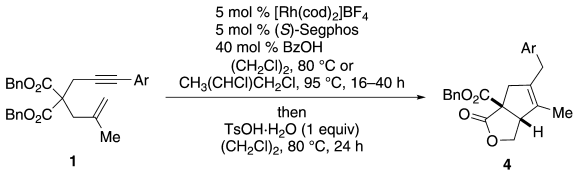
Scheme 5



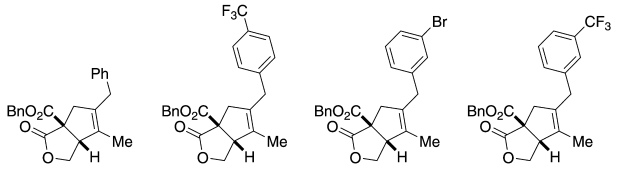
1k-d_2 **2k**-*d* 35%, 73% ee

acid. We were pleased to find that the present cycloisomerization products, bicyclic 3-cyclopropylpropionic esters **2**, could also be converted to the corresponding bicyclic lactones **4**. Conveniently, the one-pot enantioselective cycloisomerization and lactonization of 1,6-enynes **1** were succeeded upon addition of a $(CH_2Cl)_2$ solution of $TsOH{\cdot}H_2O$ to the crude mixture of the cycloisomerization reaction followed by heating at 80 °C. As shown in Table 3, a variety of bicyclic lactones **4** were obtained from 1,6-enynes **1** in one-pot with good yields and ee values.

Table 3. One-Pot Enantioselective Cycloisomerization and Lactonization of 1,6-Enynes 1[a]



1 **4**


(–)-**4a** 62%, 80% ee (–)-**4d** 65%, 78% ee (–)-**4e** 61%, 80% ee (–)-**4f** 69%, 74% ee

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), (*S*)-Segphos (0.010 mmol), **1** (0.20 mmol), BzOH (0.080 mmol), and $(CH_2Cl)_2$ or $CH_3(CHCl)CH_2Cl$, (1.5 mL) were used in the cycloisomerization. Then a $(CH_2Cl)_2$ (0.5 mL) solution of $TsOH{\cdot}H_2O$ (0.20 mmol) was added. The cited yields are of the isolated products.

The present lactonization reaction may proceed through a similar mechanism of the previously reported lactonization of 3-cyclopropylpropionic esters, leading to monocyclic lactones, although the formation of bicyclic lactones has not been reported.[18] As shown in Scheme 6, the ring opening of the cyclopropane moiety of **2a** and elimination of benzyl tosylate may afford bicyclic lactone **4a**.

In conclusion, we have established that a cationic Rh(I)/(*S*)-Segphos or (*S*)-DTBM-Segphos complex and benzoic acid

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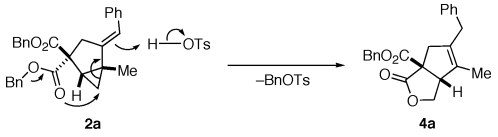
Scheme 6



catalyze the enantioselective cycloisomerization of 1,6-enynes, possessing carbonyl groups at the enyne linkage, to 2-alkylidenebicyclo[3.1.0]hexanes. The present cycloisomerization may involve the site selective γ-hydrogen elimination by coordination of the carbonyl group to rhodium. The one-pot enantioselective cycloisomerization and lactonization of 1,6-enynes to produce bicyclic lactones proceeded in good yields by the addition of $TsOH{\cdot}H_2O$ after the rhodium-catalyzed cycloisomerization.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. 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.

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