Enantioselective Construction of 5–6–5 Tricyclic Lactone Framework Bearing a Quaternary Bridgehead Carbon via Rh-Catalyzed Asymmetric [2+2+2] Cycloaddition of Enediynes

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Abstract. Herein, we report a Rh-catalyzed asymmetric [2+2+2] cycloaddition of ene-yne-yne enediynes to generate enantio-enriched tricyclic cyclohexadienes bearing a quaternary bridgehead carbon. We found that the Rh-Phanephos complex is an appropriate catalyst for the cycloaddition of enediynes bearing an unsubstituted propiolate terminus, whereas Rh-biaryl bisphosphine catalysts, which have been widely used for asymmetric cycloadditions of alkynes and alkenes, are not applicable for the reaction of such enediynes. Several control experiments suggest that the reaction using the Rh-Phanephos complex exclusively proceeds via a rhodacyclopentadiene intermediate, unlike when using a Rh-biaryl bisphosphine complex that can form a rhodacyclopentadiene intermediate as well as a rhodacyclopentene intermediate in a substrate-dependent manner.

Keywords: Cycloaddition; Rhodium; Asymmetric synthesis; Lactones; Reaction mechanisms

The catalytic enantioselective construction of quaternary stereocenters has been an important topic in organic synthesis.[1] In particular, the enantiocontrol of those at the bridgehead carbon has been a formidable challenge in the synthesis of biologically active natural products.[2] We have been involved in the development of the efficient method of the construction of a 5–6–5 tricyclic lactone framework bearing quaternary bridgehead carbons since this motif is found in complex natural products exhibiting significant biological activities, such as pleurotin, perforanoid A, and *seco*-prezizaane-type sesquiterpenes (Figure 1).[3] In particular, the last natural product family consists of diversely oxygenated congeners, some of which have attracted considerable attention because of their potent neurotrophic activities, such as jiadifenolide, jiadifenin, and jiadifenoxolane A.[4] In addition to these natural products, Danishefsky et al. and Theodorakis et al. reported that simplified analogues

display higher potency in terms of their neurite outgrowth activity when compared to their parent natural products.[5] Accordingly, a diverse structural exploration of these molecules may lead to the discovery of drug candidates for managing neurodegenerative diseases, such as Parkinson's and Alzheimer's disease.
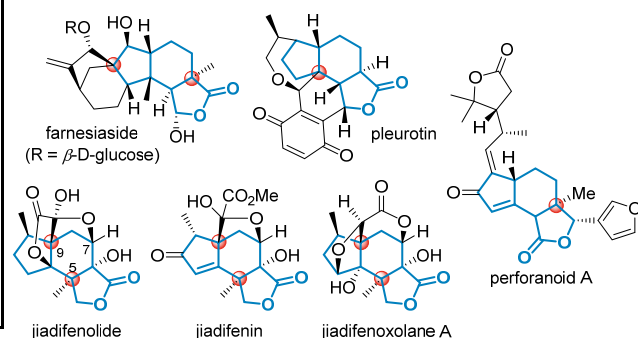

Figure 1. Representative natural products containing a 5–6–5 tricyclic lactone framework with quaternary bridgehead carbons.

The transition metal-catalyzed intramolecular [2+2+2] cycloaddition of alkynes and alkenes is a practical method used to construct polycyclic frameworks from simple acyclic precursors.[6] We previously reported a Ru-catalyzed [2+2+2] cycloaddition of enediynes to generate racemic lactone-fused cyclohexadienes bearing a quaternary bridgehead carbon at the C9 position (Scheme 1a).[7] Tricyclic cyclohexadienes have great potential as versatile platforms for the synthesis of diverse analogues of the aforementioned natural products using diastereoselective transformations based on the stereochemistry of the C9 stereocenter. In fact, we demonstrated the diastereoselective transformations of the cyclohexadiene platform toward the construction of diverse scaffolds bearing oxygen-containing

functional groups. Very recently, we also achieved the introduction of a methyl group at the C5 position in a highly diastereoselective manner, leading to the construction of a tricyclic lactone scaffold with two quaternary bridgehead carbons.[8] Therefore, controlling the stereochemistry of the C9 bridgehead stereocenter in the cyclohexadiene platform is crucial for the enantioselective synthesis of various functionalized tricyclic lactones using this synthetic strategy.
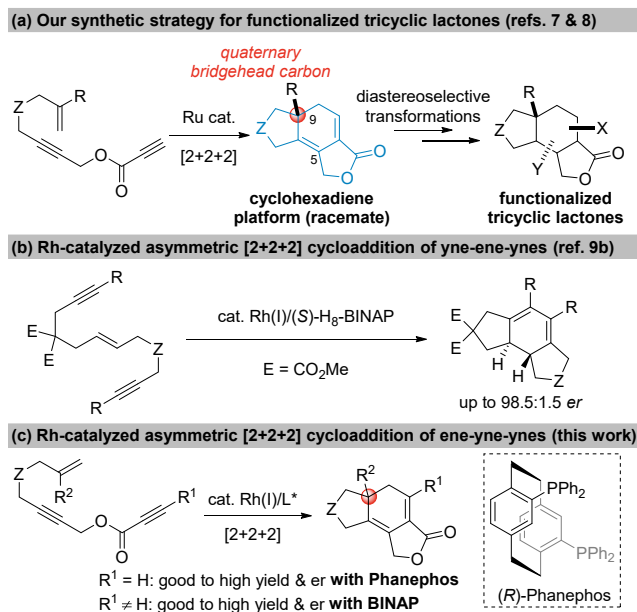
**Scheme 1.** Synthetic strategy for functionalized tricyclic lactones.

The asymmetric [2+2+2] cycloaddition of enediynes can be facilitated using a chiral phosphine-Rh complex.[9,10] For example, Shibata and co-workers reported a Rh-catalyzed asymmetric [2+2+2] cycloaddition of yne-ene-yne enediynes to provide enantio-enriched tricyclic cyclohexadienes. However, the products were limited to tricyclic cyclohexadienes without a quaternary stereocenter (Scheme 1b).[9b] On the other hand, a transition metal-catalyzed asymmetric [2+2+2] cycloaddition of ene-yne-yne enediynes has not been reported to date.[11] Herein, we report a Rh-catalyzed asymmetric [2+2+2] cycloaddition of ene-yne-yne enediynes to prepare enantio-enriched tricyclic cyclohexadienes bearing a quaternary bridgehead carbon (Scheme 1c). In this reaction, the Rh-Phanephos complex can facilitate the reaction of enediynes bearing an unsubstituted propiolate terminus, while the Rh-BINAP complex is an efficient catalyst for the reaction of enediynes possessing a substituted propiolate terminus. Interestingly, several control experiments suggest that the Rh-Phanephos complex-catalyzed reaction exclusively proceeds via a rhodacyclopentadiene intermediate, unlike the Rh-BINAP complex-catalyzed reaction that can proceed via a rhodacyclopentadiene intermediate as well as a

rhodacyclopentene intermediate in a substrate-dependent manner.[12]
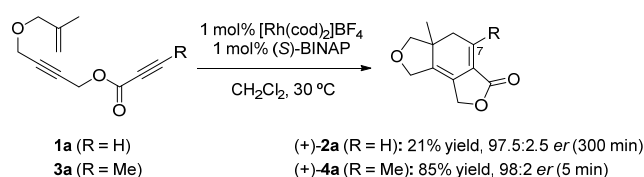
Scheme 2. Rh-catalyzed asymmetric [2+2+2] cycloaddition of **1a** and **3a**.
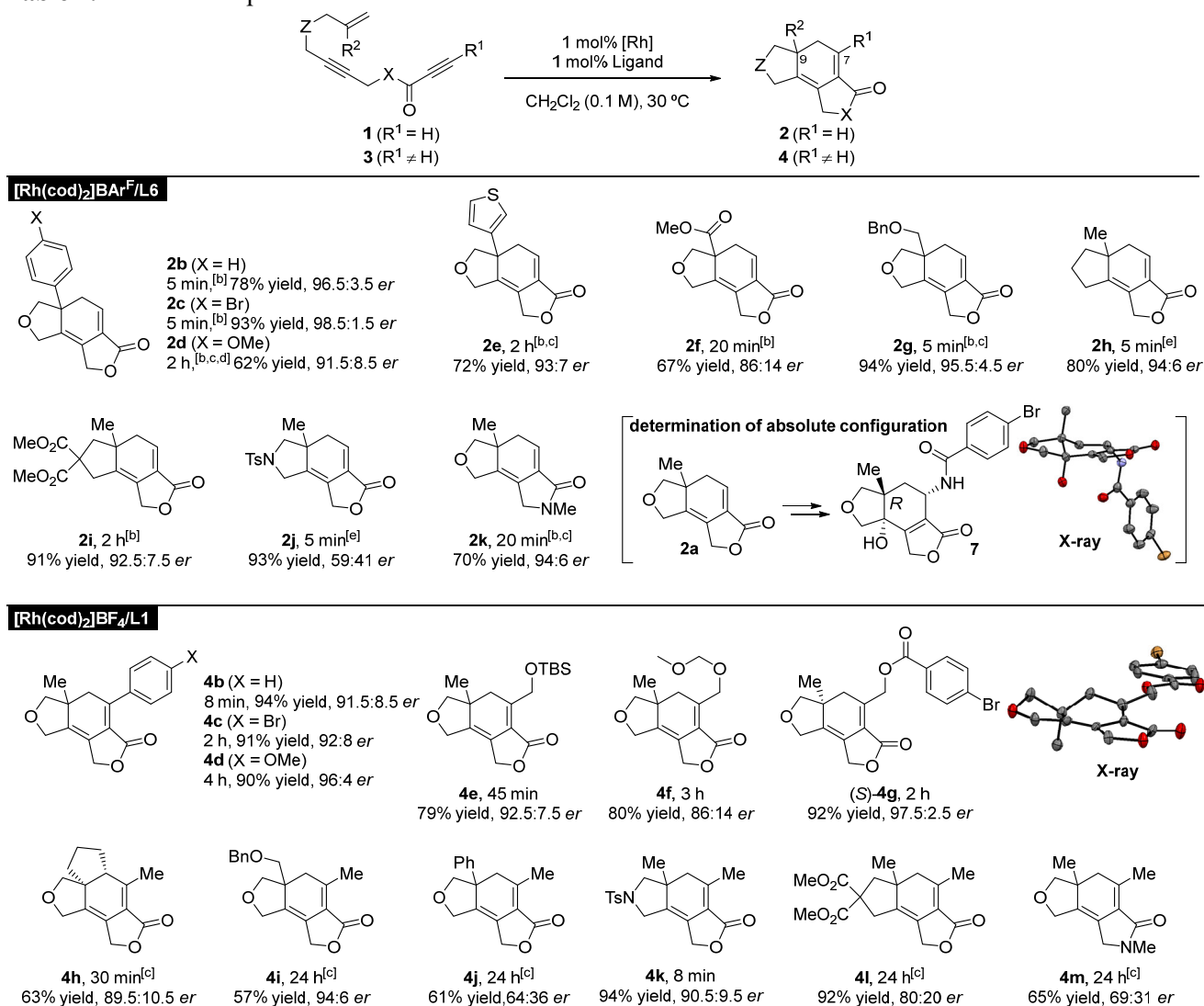
Table 1. Optimization of reaction conditions.[a]
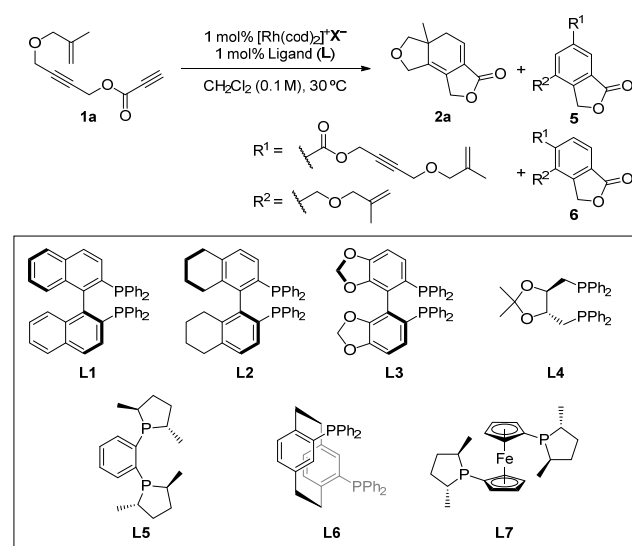
Entry	X	L	Time (min)	2a (%)[b]	5 (%)[c]	6 (%)[c]	Er of 2a[d] (+):(−)
1	BF$_4$	**L1**	300	21	<1	<1	97.5:2.5
2	BF$_4$	**L2**	300	30	<1	<1	96:4
3	BF$_4$	**L3**	120	20	<1	<1	94.5:5.5
4	BF$_4$	**L4**	120	28	34	26	36.5:63.5
5	BF$_4$	**L5**	30	25	31	32	44:56
6	BF$_4$	**L6**	60	69	4	12	3.5:96.5
7	BF$_4$	**L7**	300	6	<3	<8	8:92
8[e]	BF$_4$	**L6**	8	92	ND	2	3.5:96.5
9[e]	SbF$_6$	**L6**	13	76	ND	6	4.5:95.5
10[e]	BAr^F	**L6**	8	85	ND	2	2:98

[a] Pre-activation of the rhodium catalyst was performed under H$_2$ atmosphere before addition of **1a** to the reaction mixture. [b] Isolated yield. [c] NMR yield. [d] Er values were determined by HPLC analysis. [e] **1a** was added drop-wise over 3 min.

We initiated our study using the reaction of **1a** (R = H) bearing an unsubstituted propiolate terminus because it can lead to the straightforward synthesis of neurotrophic natural product analogs bearing a hydrogen atom at the C7 position. However, the reaction of **1a** catalyzed by a cationic Rh(I)-(S)-BINAP complex, which is one of the most widely used catalysts for the asymmetric [2+2+2] cycloaddition
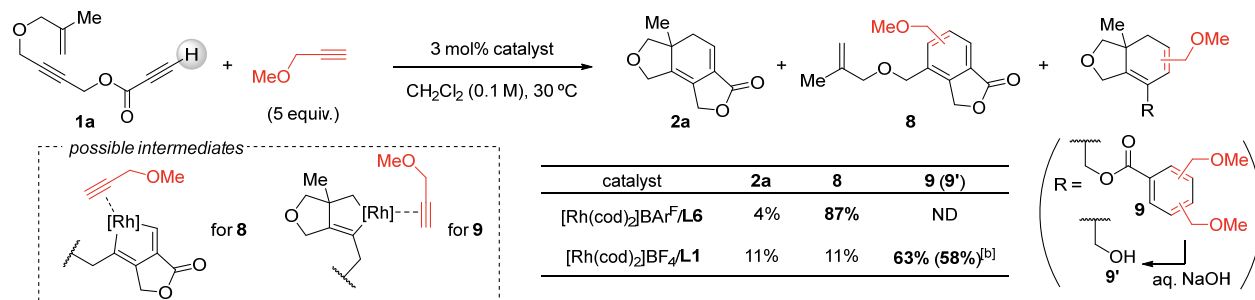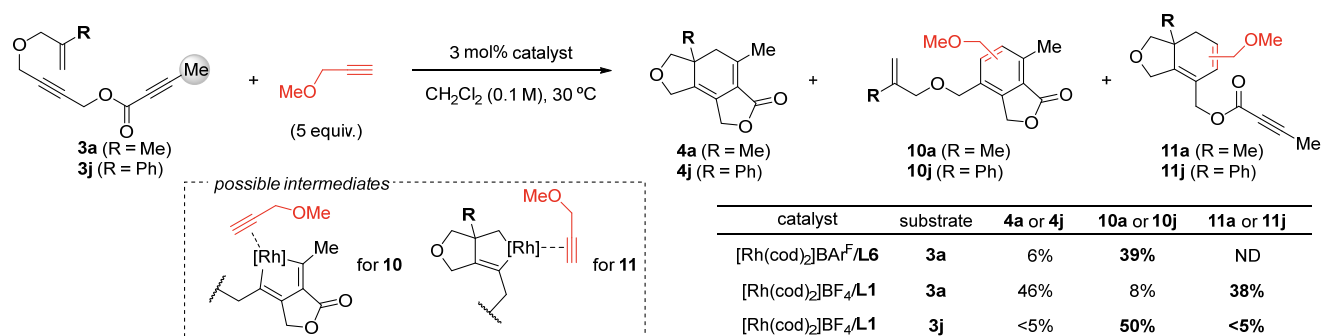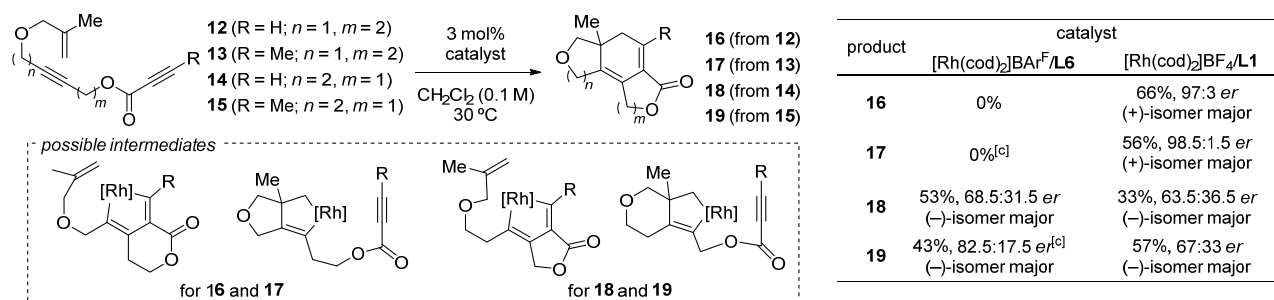
2

Table 2. Substrate scope.[a]

1 (R^1 = H)
3 (R$^1 \neq$ H)

2 (R^1 = H)
4 (R$^1 \neq$ H)

1 mol% [Rh]
1 mol% Ligand
CH$_2$Cl$_2$ (0.1 M), 30 °C

[Rh(cod)$_2$]BAr^F/L6

2b (X = H)
5 min,[b] 78% yield, 96.5:3.5 er
2c (X = Br)
5 min,[b] 93% yield, 98.5:1.5 er
2d (X = OMe)
2 h,[b,c,d] 62% yield, 91.5:8.5 er

2e, 2 h[b,c]
72% yield, 93:7 er

2f, 20 min[b]
67% yield, 86:14 er

2g, 5 min[b,c]
94% yield, 95.5:4.5 er

2h, 5 min[e]
80% yield, 94:6 er

2i, 2 h[b]
91% yield, 92.5:7.5 er

2j, 5 min[e]
93% yield, 59:41 er

2k, 20 min[b,c]
70% yield, 94:6 er

determination of absolute configuration

2a → 7

X-ray

[Rh(cod)$_2$]BF$_4$/L1

4b (X = H)
8 min, 94% yield, 91.5:8.5 er
4c (X = Br)
2 h, 91% yield, 92:8 er
4d (X = OMe)
4 h, 90% yield, 96:4 er

4e, 45 min
79% yield, 92.5:7.5 er

4f, 3 h
80% yield, 86:14 er

(S)-**4g**, 2 h
92% yield, 97.5:2.5 er

X-ray

4h, 30 min[c]
63% yield, 89.5:10.5 er

4i, 24 h[c]
57% yield, 94:6 er

4j, 24 h[c]
61% yield, 64:36 er

4k, 8 min
94% yield, 90.5:9.5 er

4l, 24 h[c]
92% yield, 80:20 er

4m, 24 h[c]
65% yield, 69:31 er

[a] Pre-activation of the rhodium catalyst was performed under H$_2$ atmosphere before addition of enediynes to the reaction mixture. Er values were determined by HPLC analysis. [b] Enediyne **1** was slowly added over 20 min. [c] 5 mol% of the catalyst was used. [d] The reaction was performed at 50 °C. [e] Enediyne **1** was slowly added over 3 min.

reactions of alkynes and alkenes,[13] gave a complex mixture of products and the yield of the desired lactone (**2a**) was very low, albeit with high enantioselectivity (Scheme 2). On the other hand, the introduction of a methyl group at the propiolate terminus (**3a**) afforded lactone **4a** in 85% yield with high enantioselectivity. These results suggest that the propiolate moiety in **1a** interrupts the desired cyclization under the reaction conditions when using the Rh-BINAP catalyst, which may be attributed to the high reactivity of the unsubstituted propiolate moiety.[14]

To address this issue, we examined the effects of various chiral phosphine ligands (Table 1). Biaryl bisphosphine ligands such as (S)-H$_8$-BINAP (**L2**) and
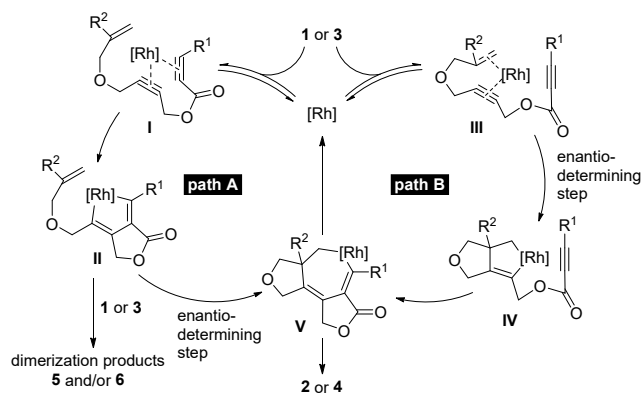
Scheme 3. Plausible reaction mechanism.

3

(a) [2+2+2] Cycloaddition of 1a in the presence of an excess amount of alkyne[a]

possible intermediates — for **8** — for **9**

catalyst	2a	8	9 (9')
[Rh(cod)₂]BArᶠ/**L6**	4%	87%	ND
[Rh(cod)₂]BF₄/**L1**	11%	11%	63% (58%)[b]

R = **9** → 9' aq. NaOH

(b) [2+2+2] Cycloaddition of 3a and 3j in the presence of an excess amount of alkyne[a]

3a (R = Me)
3j (R = Ph)

4a (R = Me) / **4j** (R = Ph)
10a (R = Me) / **10j** (R = Ph)
11a (R = Me) / **11j** (R = Ph)

possible intermediates — for **10** — for **11**

catalyst	substrate	4a or 4j	10a or 10j	11a or 11j
[Rh(cod)₂]BArᶠ/**L6**	3a	6%	39%	ND
[Rh(cod)₂]BF₄/**L1**	3a	46%	8%	38%
[Rh(cod)₂]BF₄/**L1**	3j	<5%	50%	<5%

(c) [2+2+2] Cycloaddition of endiynes 12–15

12 (R = H; n = 1, m = 2)
13 (R = Me; n = 1, m = 2)
14 (R = H; n = 2, m = 1)
15 (R = Me; n = 2, m = 1)

16 (from **12**)
17 (from **13**)
18 (from **14**)
19 (from **15**)

possible intermediates — for 16 and 17 — for 18 and 19

product	catalyst	
	[Rh(cod)₂]BArᶠ/**L6**	[Rh(cod)₂]BF₄/**L1**
16	0%	66%, 97:3 er (+)-isomer major
17	0%[c]	56%, 98.5:1.5 er (+)-isomer major
18	53%, 68.5:31.5 er (−)-isomer major	33%, 63.5:36.5 er (−)-isomer major
19	43%, 82.5:17.5 er[c] (−)-isomer major	57%, 67:33 er (−)-isomer major

Scheme 4. Control experiments. [a] NMR yields are shown. [b] Isolated yield. [c] 10 mol% of the catalyst was used.

(S)-Segphos (**L3**) gave similar results to those obtained when using (S)-BINAP (**L1**) (entries 1–3). In sharp contrast, the use of (R,R)-DIOP (**L4**) and (S,S)-Me-DuPhos (**L5**) afforded tricyclic lactone **2a** in 25–28% yields with low enantioselectivities, along with dimerization products **5** and **6** in 31–34% and 26–32% yields, respectively (entries 4 and 5). Remarkably, good yields and high enantioselectivities were achieved when using (R)-Phanephos (**L6**),[15] although **5** and **6** were obtained in 4% and 12% yields, respectively (entry 6). In terms of the absolute configuration, the (−)-isomer of **2a** was formed as the major isomer during the reaction using **L6**, although the (+)-isomer was predominant when using **L1**. (R,R)-Me-Ferrocelane (**L7**) was also investigated in the reaction. However, it resulted in a low conversion and **2a** was obtained in a low yield (entry 7). From these results, it was elucidated that **L6** was the most effective among the ligands screened in this reaction. Notably, the slow addition of **1a** over 3 min improved the yield of **2a** (92% yield), which can be attributed to the reduction in the formation of dimerization products **5** and **6** due to the low concentration of **1a** present in

the reaction mixture (entry 8). Finally, we investigated the effect of the counter anion. Although replacing BF₄ with SbF₆ slightly reduced the enantioselectivity (entry 9), a bulkier anion, BArᶠ, produced the highest enantioselectivity (entry 10). Intriguingly, the cycloaddition of **3a** using **L6** generated product **4a** in a very low yield, unlike that observed when using **L1**. This result suggests that **L6** is an efficient ligand for the cycloaddition of enediynes **1** bearing an unsubstituted propiolate terminus, while **L1** is appropriate for the cycloaddition of enediynes **3** bearing a substituted propiolate terminus.

The scope of enediynes **1** was then investigated using a catalytic amount of [Rh(cod)₂]BArᶠ and **L6**. The results are summarized in Table 2. The reaction of enediynes bearing phenyl (**1b**) and 4-bromophenyl (**1c**) groups on the alkene moiety produced products **2b** and **2c** in high yields with high enantioselectivities. The reaction of enediyne **1d** bearing a 4-methoxyphenyl group required a higher catalyst loading and heat to proceed with product **2d** obtained in 62% yield with 91.5:8.5 *er*. The introduction of 3-thienyl (**1e**), methoxycarbonyl (**1f**), and

4

benzyloxymethyl (**1g**) groups on the alkene moiety produced **2e–g** with good to high enantioselectivities. With respect to the tether moieties, methylene-tethered enediyne **1h** and malonate-tethered enediyne **1i** were efficiently transformed into their corresponding products (**2h** and **2i**) in high yields with high enantioselectivities. In contrast, the introduction of tosylamide as a tether of the enyne moiety (**1j**) caused a significant decrease in the enantioselectivity. Lactam **2k** was successfully obtained from amide-tethered enediyne **1k** in a good yield with high enantioselectivity. The absolute configuration of **2a** was determined to be *R* using X-ray crystallographic analysis of **7**, which was derived from **2a** over four steps (Scheme S2).[16] Next, we also investigated the scope of enediynes **3** using a catalytic amount of [Rh(cod)$_2$]BF$_4$ and **L1**. Cyclohexadiene products bearing aryl groups at the C7 position, such as phenyl (**4b**), 4-bromophenyl (**4c**), and 4-methoxyphenyl (**4d**), were obtained in 90–94% yields with high enantioselectivities. Enediynes bearing *tert*-butyldimethylsilyl ether (**3e**), methoxymethyl ether (**3f**), and 4-bromobenzoate (**3g**) moieties were tolerated under the reaction conditions and their corresponding cyclohexadienes (**4e–g**) were obtained in high yields with good to high enantioselectivities. The major enantiomer of **4g** was determined to be the (*S*)-isomer based on X-ray crystallographic analysis.[16] Cyclopentane-fused tetracyclic cyclohexadiene **4h** was obtained in 63% yield with good enantioselectivity. The reaction of enediynes possessing benzyloxymethyl (**3i**) and phenyl (**3j**) groups at the alkene moiety required higher catalyst loading and prolonged reaction times because of their relatively low reactivity, providing desired products **4i** and **4j** in moderate yields. Tosylamide was applicable as a tether in the enyne moiety, affording product **4k** in 94% yield with good enantioselectivity. However, the use of malonate-tethered enediyne **3l** resulted in product **4l** with a decreased enantioselectivity. The introduction of an amide as a tether in the diyne moiety (**3m**) reduced the reactivity and enantioselectivity.

There are two possible pathways for the Rh-catalyzed enantioselective cycloaddition of enediynes, which occurs via a rhodacyclopentadiene or rhodacyclopentene intermediate. A plausible reaction mechanism is illustrated in Scheme 3. In path A, complex **I** is initially formed via coordination of the Rh catalyst to the diyne moiety in the enediyne, followed by the yne-yne oxidative coupling to generate rhodacyclopentadiene intermediate **II**. Alkene insertion into the Rh–C*sp^2* bond generates intermediate **V**, which is the enantio-determining step in this pathway. Finally, cyclohexadiene products were obtained through reductive elimination. In path B, the ene-yne oxidative coupling initially occurs to form rhodacyclopentene intermediate **IV** via complex **III**, which is the enantio-determining step. Subsequently, alkyne insertion into the Rh–C*sp^2* bond of intermediate **IV** generates intermediate **V**. Finally, reductive elimination produces the tricyclic product and the Rh catalyst is regenerated. The substrate scope

of the cycloaddition of enediynes was sometimes limited because of the difference in the enantio-determining step in paths A and B. The groups of Shibata and Tanaka reported that enantioselectivity is highly dependent on the substrate used in intramolecular or intermolecular cycloadditions of two alkynes and one alkene because Rh-biaryl bisphosphine complexes can proceed via either a rhodacyclopentadiene intermediate or a rhodacyclopentene intermediate in a substrate-dependent manner.[9b,13e,13f] In fact, several control experiments using ene-yne-yne enediynes indicate that the Rh-**L1** complex can facilitate the yne-yne coupling as well as the ene-yne coupling in a substrate-dependent manner (*vide infra*). With respect to the dimerization reaction, **5** and **6** can be obtained from intermediate **II** upon reaction with another substrate molecule. Considering that **5** and **6** were obtained when using non-biaryl bisphosphine ligands, such as **L4–L6** (Table 1, entries 4–6), these ligands would contribute predominantly to path A.
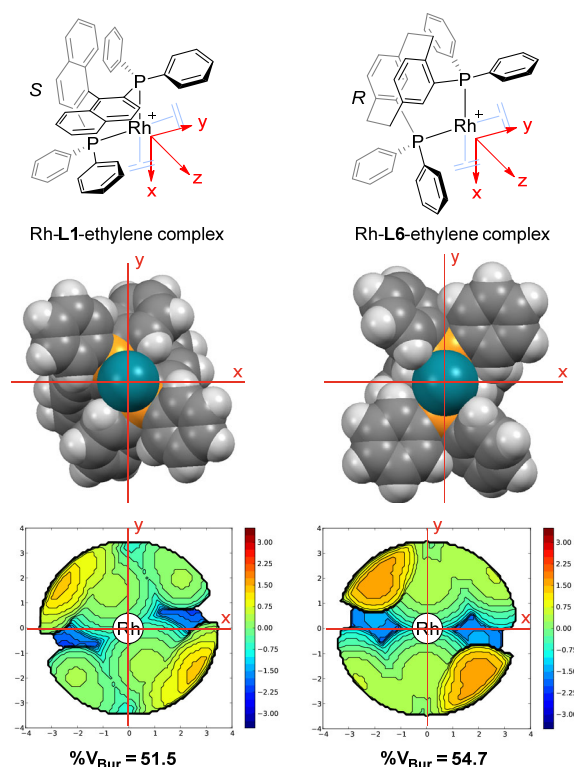

Figure 2. Topographic steric maps of Rh-**L1**-ethylene and Rh-**L6**-ethylene complexes based on the DFT-optimized structures (ethylene ligands are omitted).

To gain insight into the reaction mechanism of the cycloaddition of enediynes, several control experiments were performed (Scheme 4). The cycloaddition of **1a** in the presence of an excess amount of methyl propargyl ether afforded product **2a** in 4% yield along with phthalide **8** (87% yield), which was derived from intermediate **II** and methyl propargyl ether (Scheme 4a).[17] Remarkably, bicyclic ether products, which can be obtained from

5

intermediate **IV** and methyl propargyl ether, were not detected. In contrast, the same reaction using a catalytic amount of [Rh(cod)$_2$]BF$_4$ and **L1** produced **8** in 11% yield along with **2a** (11% yield). Notably, ^{1}H NMR analysis of the crude product mixture showed that two major signals corresponding to the vinylic protons, which were derived from bicyclic ether **9**, are observed at δ 6.0 and 5.7 ppm (Figure S3). However, identification of the other signals was difficult because of the complexity of the signals, which can be ascribed to several regioisomers possessing benzoyl moieties formed via alkyne trimerization of the propiolate moiety with two methyl propargyl ether molecules. Therefore, hydrolysis of the crude product mixture was performed to remove the benzoyl group, which gave the corresponding alcohol (**9'**) in 58% yield. This result indicates that the reaction using the Rh-**L1** complex tends to proceed via path B, even though the unsubstituted propiolate moiety in **1a** has relatively high reactivity. However, it cannot be ruled out that the generation of **9** results from the cycloaddition of the enyne moiety and methyl propargyl ether after the formation of the benzoyl moiety. The cycloaddition of **3a** was then carried out in the same manner as used for **1a** (Scheme 4b). Phthalide **10a** was obtained as the major product when using the Rh-**L6** complex, while bicyclic ether **11a** was obtained in 38% yield when using the Rh-**L1** complex. Notably, phthalide **10j** was obtained from **3j** as the major product when using the Rh-**L1** complex, which can be assumed that the bulkiness of the phenyl group at the alkene moiety suppressed the ene-yne coupling to allow the yne-yne coupling. Furthermore, we performed the cycloaddition of enediynes **12**–**15** leading to 5–6–6 or 6–6–5 tricyclic lactones **16**–**19** (Scheme 4c). Regarding the cycloaddition of enediynes **12** and **13**, which tends to proceed via the oxidative cyclization of the 1,6-enyne moiety rather than that of the 1,7-diyne moiety, the reaction using the Rh-**L6** complex did not proceed, while **16** and **17** were obtained in 66% and 56% yields, respectively, when using the Rh-**L1** complex. In contrast, the reaction of enediynes **14** and **15** proceeded in both methods. The reactions using the Rh-**L6** complex afforded **18** and **19** in 53% and 43% yields, respectively. When the Rh-**L1** complex was applied, **18** and **19** were obtained in 33% and 57% yields, respectively. Remarkably, in terms of the enantioselectivities of **18** and **19**, the same configuration of their enantiomers was observed in both cases when using **L1** and **L6**, unlike that observed when using **1a** as the substrate (Table 1, entry 1 vs. 10). This was attributed to the yne-yne coupling of **14** and **15** being more favorable over the ene-yne coupling even when using **L1**. Therefore, in these cases, the asymmetric induction via path A becomes predominant, which leads to the formation of the (−)-isomers of **18** and **19**. These results indicate that the reaction using the Rh-**L6** complex exclusively proceeds via intermediate **II**, unlike when using the Rh-**L1** complex.

To evaluate the steric environment of the catalytic pockets of the Rh-**L1** and Rh-**L6** complexes, we analyzed topographic steric maps based on the density functional theory (DFT)-optimized structures of their ethylene complexes. The maps show the elevation from the metal center with a coloring scheme from blue to red, similar to classical physical maps used for geographical features, which indicate the amount of space occupied by the ligands.[18] These maps suggest that the catalytic pocket of the Rh-**L6** complex is sterically more hindered than that of the Rh-**L1** complex (buried %V$_{Bur}$ was 51.5% for **L1** and 54.7% for **L6**; Figure 2). Considering the steric hindrance and conformational rigidity of **L6**, the reactivity of the Rh-**L6** complex can be easily affected by the bulkiness of the substrates, leading to selective recognition of a diyne moiety, including an unsubstituted propiolate terminus. On the other hand, the Rh-**L1** complex has a relatively large cavity and is conformationally more flexible when compared to the Rh-**L6** complex, which would allow it to react with an enyne moiety as well as a diyne moiety.

Finally, we demonstrated the diastereoselective synthesis of **2l**, which can be transformed into tricyclic lactone **20** over several steps (Scheme 5).[8] The [2+2+2] cycloaddition of (*S*)-**1l** using [Rh(cod)$_2$]BAr^F and (*R*)-Phanephos provided (4*S*,5a*S*)-**2l** with good diastereoselectivity (86:14 *dr*), although the Ru-catalyzed cycloaddition of (*S*)-**1l** resulted in very low diastereoselectivity (45:55 *dr*). On the other hand, the use of (*S*)-Phanephos instead of (*R*)-Phanephos afforded (4*S*,5a*R*)-**2l** in 76% yield with 11:89 *dr*, indicating that the diastereoselectivity of this reaction was controlled by the catalyst rather than the substrate.
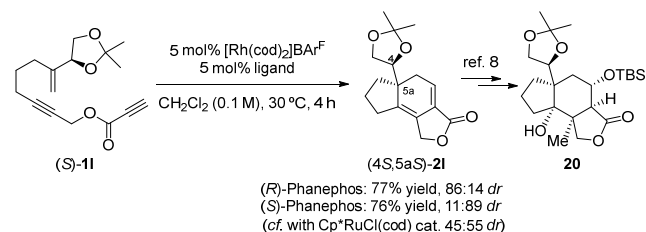
Scheme 5. Diastereoselective synthesis of **2l** via the [2+2+2] cycloaddition of (*S*)-**1l** with the Rh-Phanephos catalysis.

In summary, we developed a Rh-catalyzed asymmetric [2+2+2] cycloaddition of ene-yne-yne enediynes to prepare enantio-enriched tricyclic cyclohexadienes bearing a quaternary bridgehead carbon. We found that the Rh-Phanephos complex is an appropriate catalyst for the reaction of enediynes bearing an unsubstituted propiolate terminus, while the Rh-BINAP complex is suitable for the cycloaddition of enediynes possessing a substituted propiolate terminus. Several control experiments revealed that the Rh-Phanephos catalyst has unique properties that differ from Rh-biaryl bisphosphine catalysts in the [2+2+2] cycloaddition of enediynes. Unlike when using the Rh-BINAP complex that can form a rhodacyclopentadiene intermediate as well as a rhodacyclopentene intermediate in a substrate-

dependent manner, the Rh-Phanephos complex-catalyzed reaction exclusively proceeds via a rhodacyclopentadiene intermediate, which may be ascribed to the relatively narrow cavity of the Rh-Phanephos complex compared to that of the Rh-BINAP complex. We believe that these findings will lead to development of related asymmetric cycloisomerization reactions based on the selective recognition of multiple bonds of unsaturated substrates, such as 1,6-diynes bearing an unsubstituted propiolate terminus in this case.

Experimental Section

Representative procedure for the [2+2+2] cycloaddition of enediyne 1a: (*R*)-Phanephos (**L6**, 1.7 mg, 0.0030 mmol) and [Rh(cod)$_2$]BAr^F (3.5 mg, 0.0030 mmol) were dissolved in dry degassed CH$_2$Cl$_2$ (1.0 mL) and the mixture was stirred at 30 ºC for 10 min under Ar atmosphere. The reaction tube was evacuated and refilled with H$_2$ using a balloon, which was repeated 3 times. After stirring at 30 ºC for 1 h under H$_2$ atmosphere, the reaction tube was evacuated and refilled with Ar using a balloon, which was repeated 3 times. To the resulting mixture was added a solution of enediyne **1a** (61 mg, 0.30 mmol) in dry degassed CH$_2$Cl$_2$ (2.0 mL) dropwise over 3 min by using a syringe pump. The solution was stirred at 30 ºC for 5 min. The resulting solution was concentrated and purified by column chromatography on silica gel (hexane/EtOAc = 3:1) to give **2a** (49 mg, 85% yield, 98:2 *er*) as a white solid.

Acknowledgements

References

[1] a) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181–191; b) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, *Chem. Rev.* **2016**, *116*, 7330–7396; c) P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou, J. Zhou, *ACS Catal.* **2019**, *9*, 1820–1882.

[2] a) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740–751; b) R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep.* **2015**, *32*, 1584–1601; c) M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156–4186; d) C. Li, S. S. Ragab, G. Liu, W. Tang, *Nat. Prod. Rep.* **2020**, *37*, 276–292.

[3] a) N. P. Sahu, K. Koike, S. Banerjee, B. Achari, Z. Jia, T. Nikaido, *Tetrahedron Lett.* **1997**, *38*, 8405–8408; b) W. J. Robbins, F. Kavanagh, A. Herver, *Proc. Natl. Acad. Sci. U. S. A.* **1947**, *33*, 171–176; c) J. Grandjean, R. Huls, *Tetrahedron Lett.* **1974**, 1893–1895; d) C. Lv, X. Yan, Q. Tu, Y. Di, C. Yuan, X. Fang, Y. Ben-David, L. Xia, J. Gong, Y. Shen, Z. Yang, X. Hao, *Angew. Chem. Int. Ed.* **2016**, *55*, 7539–7543; *Angew. Chem.* **2016**, *128*, 7665–7669.

[4] a) M. Kubo, C. Okada, J.-M. Huang, K. Harada, H. Hioki, Y. Fukuyama, *Org. Lett.* **2009**, *11*, 5190–5193; b) R. A. Shenvi, *Nat. Prod. Rep.* **2016**, *33*, 535–539; c) J. M. Witkin, R. A. Shenvi, X. Li, S. D. Gleason, J. Weiss, D. Morrow, J. T. Catow, M. Wakulchik, M. Ohtawa, H. H. Lu, M. D. Martinez, J. M. Schkeryantz, T. S. Carpenter, F. C. Lightstone, R. Cerne, *Biochem. Pharmacol.* **2018**, *155*, 61–70; d) M. Shoji, M. Ueda, M. Nishioka, H. Minato, M. Seki, K. Harada, M. Kubo, Y. Fukuyama, Y. Suzuki, E. Aoyama, M. Takigawa, T. Kuzuhara, *Biochem. Biophy. Res. Commun.* **2019**, *519*, 309–315; e) Y. Fukuyama, M. Kubo, K. Harada, *J. Nat. Med.* **2020**, *74*, 648–671.

[5] a) Y. S. Cho, D. A. Carcache, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 14358–14359; b) D. A. Carcache, Y. S. Cho, Z. Hua, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 1016–1022; c) L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobley, E. A. Theodorakis, *Chem. Eur. J.* **2013**, *19*, 6398–6408.

[6] For recent reviews involving transition-metal-catalyzed [2+2+2] cycloaddition reactions, see: a) K. Tanaka, *Synlett* **2007**, 1977–1993; b) T. Shibata, K. Tsuchikama, *Org. Biomol. Chem.* **2008**, *6*, 1317–1323; c) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; *Angew. Chem.* **2008**, *120*, 4338–4386; d) Y. Shibata, K. Tanaka, *Synthesis* **2012**, *44*, 323–350; e) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508–518; e) M. Amatore and C. Aubert, *Eur. J. Org. Chem.* **2015**, 265–286; f) G. Domínguez, J. Pérez-Castells, *Chem. Eur. J.* **2016**, *22*, 6720–6739; g) Y. Yamamoto, *Tetrahedron Lett.* **2017**, *58*, 3787–3794; h) A. Pla-Quintana, A. Roglans, *Asian J. Org. Chem.* **2018**, *7*, 1706–1718; i) A. Roglans, A. Pla-Quintana, M. Solà, *Chem. Rev.* **2021**, *121*, 1894–1979.

[7] M. Shibuya, T. Sudoh, T. Kawamura, Y. Yamamoto, *Org. Biomol. Chem.* **2015**, *13*, 5862–5866.

[8] T. Kawamura, H. Moriya, M. Shibuya, Y. Yamamoto, *J. Org. Chem.* **2019**, *84*, 12508–12519.

[9] a) K. Tanaka, G. Nishida, H. Sagae, M. Hirano, *Synlett* **2007**, 1426–1430; b) T. Shibata, H. Kurokawa, K. Kanda, *J. Org. Chem.* **2007**, *72*, 6521–6525; c) T. León, M. Parera, A. Roglans, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2012**, *51*, 6951–6955; *Angew. Chem.* **2012**, *124*, 7057–7061.

[10] For selected examples of asymmetric [2+2+2] cycloadditions to construct a quaternary bridgehead stereocenter, see: a) T. Shibata, Y. Arai, Y. Tahara, *Org. Lett.* **2005**, *7*, 4955–4957; b) T. Shibata, Y. Tahara, *J. Am. Chem. Soc.* **2006**, *128*, 11766–11767; c) H. Sagae, K. Noguchi, M. Hirano, K. Tanaka, *Chem. Commun.* **2008**, 3804–3806; d) K. Tanaka, Y. Otake, K. Noguchi, M. Hirano, *Angew. Chem. Int. Ed.* **2008**, *47*, 1312–1316; *Angew. Chem.* **2008**, *120*, 1332–1336; e) T. Suda, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2011**, *50*, 4475–4479; *Angew. Chem.* **2011**, *123*, 4567–4571; f) A. T. Brusoe, E. J. Alexanian, *Angew. Chem. Int. Ed.* **2011**, *50*, 6596–6600; *Angew. Chem.* **2011**, *123*, 6726–6730;

g) S. Suzuki, Y. Shibata, K. Tanaka, *Chem. Eur. J.* **2020**, *26*, 3698-3702.

[11] For selected examples of the synthesis of racemic tricyclic cyclohexadienes via transition-metal-catalyzed [2+2+2] cycloadditions, see: a) R. L. Halterman, K. P. C. Vollhardt, *Organometallics* **1988**, *7*, 883–892; b) Y. Yamamoto, S. Kuwabara, Y. Ando, H. Nagata, H. Nishiyama, K. Itoh, *J. Org. Chem.* **2004**, *69*, 6697–6705; c) A. Torrent, I. González, A. Pla-Quintana, A. Roglans, *J. Org. Chem.* **2005**, *70*, 2033–2041; d) S. Brun, L. Garcia, I. González, A. Torrent, A. Dachs, A. Pla-Quintana, T. Parella, A. Roglans, *Chem. Commun.* **2008**, 4339–4341; e) A. L. Jones, J. K. Snyder, *J. Org. Chem.* **2009**, *74*, 2907–2910; f) A. Geny, S. Gaudrel, F. Slowinski, M. Amatore, G. Chouraqui, M. Malacria, C. Aubert, V. Gandon, *Adv. Synth. Catal.* **2009**, *351*, 271–275; g) A. L. Jones, J. K. Snyder, *Org. Lett.* **2010**, *12*, 1592–1595; h) A. Dachs, A. Pla-Quintana, T. Parella, M. Solà, A. Roglans, *Chem. Eur. J.* **2011**, *17*, 14493–14507; i) S. Ventre, C. Simon, F. Rekhroukh, M. Malacria, M. Amatore, C. Aubert, M. Petit, *Chem. Eur. J.* **2013**, *19*, 5830–5835.

[12] A mechanistic study for the RhCl(PPh$_3$)$_3$-catalyzed [2+2+2] cycloaddition of enediynes has been reported, see: A. Dachs, A. Roglans, M. Solà, *Organometallics* **2011**, *30*, 3151–3159.

[13] For selected examples involving the synthesis of chiral cyclohexadienes via the Rh-catalyzed enantioselective intermolecular [2+2+2] cycloadditions, see: a) P. A. Evans, K. W. Lai, J. R. Sawyer, *J. Am. Chem. Soc.* **2005**, *127*, 12466–12467; b) K. Tsuchikama, Y. Kuwata, T. Shibata, *J. Am. Chem. Soc.* **2006**, *128*, 13686–13687; c) P. A. Evans, J. R. Sawyer, P. A. Inglesby, *Angew. Chem. Int. Ed.* **2010**, *49*, 5746–5749; d) J. Hara, M. Ishida, M. Kobayashi, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2014**, *53*, 2956–2959; *Angew. Chem.* **2014**, *126*, 3000–3003; e) Y. Aida, H. Sugiyama, H. Uekusa, Y. Shibata, K. Tanaka, *Org. Lett.* **2016**, *18*, 2672−2675; f) Y. Aida, Y. Shibata, K. Tanaka, *J. Org. Chem.* **2018**, *83*, 2617−2626; g) Q. Teng, W. Mao, D. Chen, Z. Wang, C.-H. Tung, Z. Xu, *Angew. Chem. Int. Ed.* **2020**, *59*, 2220–2224; *Angew. Chem.* **2020**, *132*, 2240–2244.

[14] a) Y. Kishimoto, P. Eckerle, T. Miyake, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1994**, *116*, 12131–12132; b) K. Maeda, H. Goto, E. Yashima, *Macromolecules* **2001**, *34*, 1160–1164.

[15] a) P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, *119*, 6207−6208; b) H.-Y. Jang, F. W. Hughes, H. Gong, J. Zhang, J. S. Brodbelt, M. J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 6174−6175; c) L. A. Schwartz, M. Holmes, G. A. Brito, T. P. Gonçalves, J. Richardson, J. C. Ruble, K.-W. Huang, M. J. Krische, *J. Am. Chem. Soc.* **2019**, *141*, 2087−2096.

[16] CCDC-2063018 ((*S*)-**4g**) and 2063019 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] a) T. Yasui, T. Kikuchi, Y. Yamamoto, *Chem. Commun.* **2020**, *56*, 12865–12868; b) J. Nogami, Y. Tanaka, H. Sugiyama, H. Uekusa, A. Muranaka, M. Uchiyama, K. Tanaka, *J. Am. Chem. Soc.* **2020**, *142*, 9834−9842.

[18] a) L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, L Cavallo, *Organometallics* **2016**, *35*, 2286–2293; b) L. Falivene, Z. Cao, A. Petta, L. Serra, A. Poater, R. Oliva, V. Scarano, L. Cavallo, *Nat. Chem.* **2019**, *11*, 872–879.

Enantioselective Construction of 5–6–5 Tricyclic Lactone Framework Bearing a Quaternary Bridgehead Carbon via Rh-Catalyzed Asymmetric [2+2+2] Cycloaddition of Enediynes

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