Asymmetric Catalysis

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Rhodium-Catalyzed Regio-, Diastereo-, and Enantioselective [2+2+2] Cycloaddition of 1,6-Enynes with Acrylamides**

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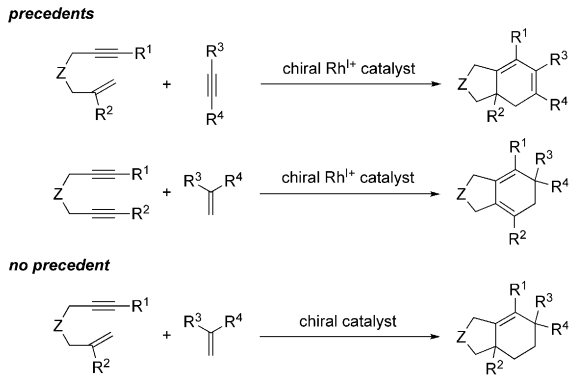
Transition-metal-catalyzed intermolecular [2+2+2] cycloadditions of α,ω-diynes or enynes with unsaturated compounds are valuable methods for the synthesis of complex bicyclic molecules in a single step.[1] For example, the transition-metal-catalyzed [2+2+2] cycloaddition of 1,6-enynes with alkynes enables the facile preparation of densely substituted annulated cyclohexadienes.[2] In 2005, the groups of Evans and Shibata developed asymmetric variants of this reaction that furnish annulated cyclohexadienes with one stereogenic center by using cationic rhodium(I)/chiral bisphosphine complexes as catalysts (Scheme 1).[3,4] Additionally, it has been reported that the cationic rhodium(I)/chiral bisphosphine complexes catalyze the asymmetric [2+2+2] cycloaddition of 1,6-diynes with electron-deficient alkenes, to also afford annulated cyclohexadienes with one stereogenic center (Scheme 1).[5] However, the transition-metal-catalyzed [2+2+2] cycloadditions involving two alkene units have been largely limited to the intramolecular reactions of dienynes.[6] Only two examples of the transition-metal-catalyzed intermolecular [2+2+2] cycloaddition involving two alkene units have been reported to date.[7,8] In 1999, Montgomery and co-workers reported the nickel-catalyzed [2+2+2] cycloaddition of 1,6-enynes with enones.[7] In 2010, Ogoshi et al. reported the nickel-catalyzed [2+2+2] cycloaddition of two enones with alkynes.[8] However, these reactions are limited to enone derivatives and their asymmetric variants have not been realized (Scheme 1). On the other hand, our research group has demonstrated that acrylamide derivatives are highly reactive substrates in cationic rhodium(I)/bisphosphine-catalyzed carbon–carbon bond-forming reactions.[9] Herein, we have achieved the unprecedented catalytic asymmetric [2+2+2] cycloaddition of 1,6-enynes with alkenes by using acrylamides as alkenes and a cationic rhodium(I)/(*R*)-H_8-binap complex as the catalyst.



Scheme 1. Transition-metal-catalyzed asymmetric [2+2+2] cycloadditions involving alkene units.

We first examined the reaction of 1,6-enyne **1a**, possessing a disubstituted alkene moiety, and *N*,*N*-dimethylacrylamide (**2a**) at room temperature in the presence of the cationic rhodium(I)/chiral bisphosphine catalysts (Table 1, entries 1–6). Pleasingly, the use of biaryl bisphosphine ligands furnished the desired annulated cyclohexene **3aa** with complete regio- and diastereoselectivity and high enantioselectivity together with diene **4aa** as a minor product (Table 1, entries 1–3). However, the use of nonbiaryl bisphosphine ligands failed to furnish both **3aa** and **4aa** (Table 1, entries 4–6). H_8-binap, possessing the largest dihedral angle of the tested ligands, showed the highest yield of **3aa** as well as the highest enantioselectivity (Table 1, entry 3). Sterically more-demanding xyl-H_8-binap was also tested, and the yield of **3aa** decreased significantly (Table 1, entry 7). As the catalytic activity of the rhodium/H_8-binap catalyst was very high, the reaction could even be carried out in the presence of 5 or 3 mol% of the catalyst without erosion of the product yield and *ee* value (Table 1, entries 8 and 9).

We tested the generality of the reaction with regard to both cycloaddition partners by using the cationic rhodium(I)/(*R*)-H_8-binap catalyst at room temperature (Scheme 2). *N*,*N*-Dialkyl- (**2a–c**), *N*-methyl-*N*-phenyl- (**2d**), and *N*,*N*-diphenyl- (**2e**) acrylamides and Weinreb amide **2f** reacted with 1,6-enyne **1a** to give the corresponding annulated cyclohexenes in high yields with high *ee* values,[10] although sterically demanding amide **2c** and Weinreb amide **2f** required high catalyst loadings. With respect to 1,6-enynes, not only tosylamide- (**1a**) but also malonate- (**1b**) and oxygen- (**1c**) linked 1,6-enynes, possessing the disubstituted alkene moiety, reacted with **2d** to give the corresponding

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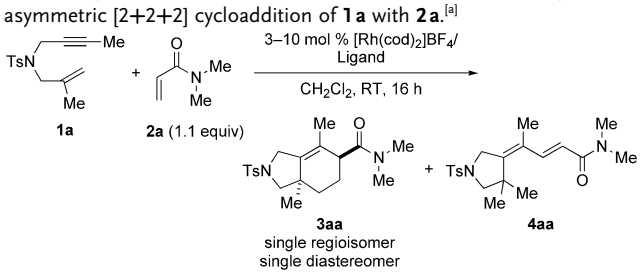
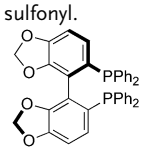
Table 1: Optimization of reaction conditions for rhodium-catalyzed asymmetric [2+2+2] cycloaddition of **1a** with **2a**.[a]

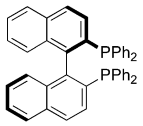


Entry	Ligand	Catalyst (mol%)	**3aa**/Yield [%] (% *ee*)[b]	Yield of **4aa** [%] [b]
1	(*R*)-segphos	10	(−)-**3aa**/63 (>99)	5
2	(*R*)-binap	10	(−)-**3aa**/82 (98)	14
3	(*R*)-H_8-binap	10	(−)-**3aa**/85 (>99)	8
4	(*S*,*S*)-diop	10	0	0
5[c]	(*S*,*S*)-chiraphos	10	0	0
6[c]	(*R*,*R*)-Me-duphos	10	0	0
7	(*S*)-xyl-H_8-binap	10	(+)-**3aa**/33 (>99)	3
8[d]	(*R*)-H_8-binap	5	(−)-**3aa**/86 (>99)	9
9[e]	(*R*)-H_8-binap	3	(−)-**3aa**/85 (>99)	11

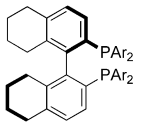
[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1a** (0.10 mmol), **2a** (0.11 mmol), and CH_2Cl_2 (1.5 mL) were used. [b] Yield of the isolated product. [c] $[Rh(nbd)_2]BF_4$ was used. [d] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1a** (0.20 mmol), **2a** (0.22 mmol), and CH_2Cl_2 (1.5 mL) were used. [e] $[Rh(cod)_2]BF_4$ (0.0060 mmol), ligand (0.0060 mmol), **1a** (0.20 mmol), **2a** (0.22 mmol), and CH_2Cl_2 (1.5 mL) were used. cod = cyclooctadiene, nbd = norbornadiene, Ts = *p*-toluenesulfonyl.



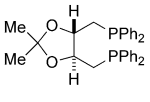
(*R*)-segphos



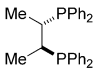
(*R*)-binap



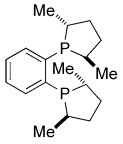
(*R*)-H_8-binap (Ar = Ph)
(*R*)-xyl-H_8-binap (Ar = 3,5-$Me_2C_6H_3$)



(*S*,*S*)-diop



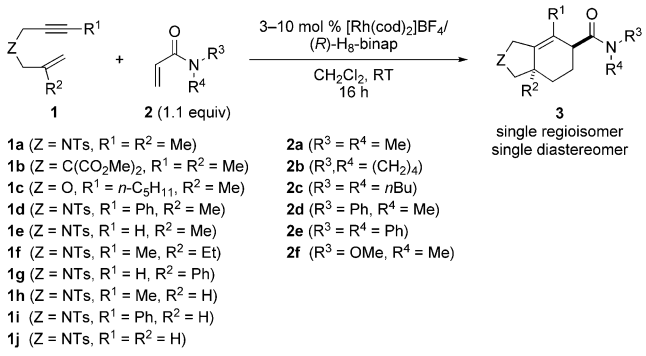
(*S*,*S*)-chiraphos



(*R*,*R*)-Me-duphos

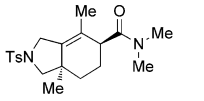
annulated cyclohexenes in good yields with high *ee* values, although elevated temperature and/or high catalyst loading were required. Various substituents, such as methyl (**1a**,**b**), pentyl (**1c**), phenyl (**1d**), and hydrogen (**1e**) could be incorporated at the alkyne terminus. Not only methyl (**1a**–**e**) but also ethyl (**1f**) and phenyl (**1g**) substitutions at the alkene moiety were tolerated. Furthermore, 1,6-enynes **1h**–**j**, possessing the monosubstituted alkene moiety, reacted with **2a** and **2d**–**f** to give the corresponding cyclohexenes in good yields with high *ee* values.

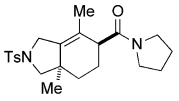
As shown in Table 2, interesting substituent effects on the yields and *ee* values of cyclohexenes **3** and dienes **4** were

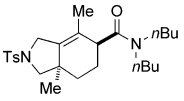


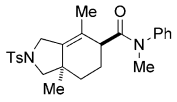
1a (Z = NTs, R^1 = R^2 = Me)
1b (Z = $C(CO_2Me)_2$, R^1 = R^2 = Me)
1c (Z = O, R^1 = *n*-C_5H_{11}, R^2 = Me)
1d (Z = NTs, R^1 = Ph, R^2 = Me)
1e (Z = NTs, R^1 = H, R^2 = Me)
1f (Z = NTs, R^1 = Me, R^2 = Et)
1g (Z = NTs, R^1 = H, R^2 = Ph)
1h (Z = NTs, R^1 = Me, R^2 = H)
1i (Z = NTs, R^1 = Ph, R^2 = H)
1j (Z = NTs, R^1 = R^2 = H)

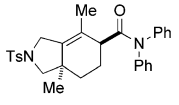
2a (R^3 = R^4 = Me)
2b (R^3,R^4 = $(CH_2)_4$)
2c (R^3 = R^4 = *n*Bu)
2d (R^3 = Ph, R^4 = Me)
2e (R^3 = R^4 = Ph)
2f (R^3 = OMe, R^4 = Me)

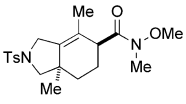

(5*S*,7a*R*)-(−)-**3aa**
85% yield, >99% *ee*
(3 mol % Rh)

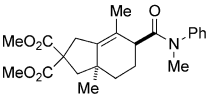

(−)-**3ab**
>99% yield, >99% *ee*
(5 mol % Rh)

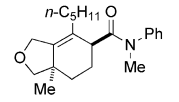

(−)-**3ac**
91% yield, >99% *ee*
(10 mol % Rh)

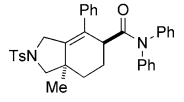

(−)-**3ad**
>99% yield, >99% *ee*
(3 mol % Rh)

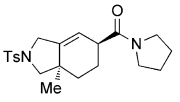

(−)-**3ae**
97% yield, >99% *ee*
(3 mol % Rh)

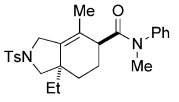

(−)-**3af**
92% yield, >99% *ee*
(10 mol % Rh)

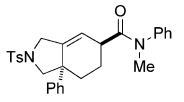

(−)-**3bd**
72% yield, >99% *ee*
(10 mol % Rh)

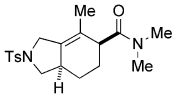

(−)-**3cd**
59% yield, 93% *ee*
(10 mol % Rh, 40 °C)

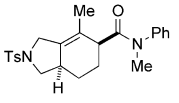

(−)-**3de**
90% yield, 95% *ee*
(10 mol % Rh, 40 °C)

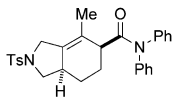

(5*S*,7a*R*)-(−)-**3eb**
79% yield, >99% *ee*
(5 mol % Rh, **2b**: 3 equiv)

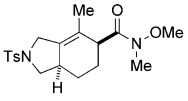

(−)-**3fd**
86% yield, >99% *ee*
(5 mol % Rh)

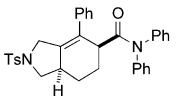

(−)-**3gd**
47% yield, 94% *ee*
(10 mol % Rh)

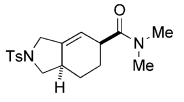

(−)-**3ha**
51% yield, 97% *ee*
(5 mol % Rh)


(−)-**3hd**
62% yield, 91% *ee*
(5 mol % Rh)


(−)-**3he**
77% yield, 95% *ee*
(5 mol % Rh)


(−)-**3hf**
71% yield, 97% *ee*
(5 mol % Rh)

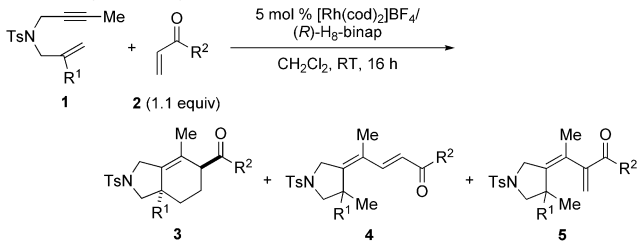

(−)-**3ie**
88% yield, 87% *ee*
(5 mol % Rh)


(−)-**3ja**
57% yield, 96% *ee*
(5 mol % Rh, **2a**: 3 equiv)

Scheme 2. Rhodium-catalyzed asymmetric [2+2+2] cycloaddition of 1,6-enynes **1a–j** with acrylamides **2a-f**. Reaction conditions: $[Rh(cod)_2]BF_4$ (0.0060–0.020 mmol), (*R*)-H_8-binap (0.0060–0.020 mmol), **1** (0.20 mmol), **2** (0.22–0.60 mmol), and CH_2Cl_2 (1.5 mL) were used. Cited yields are of isolated products.

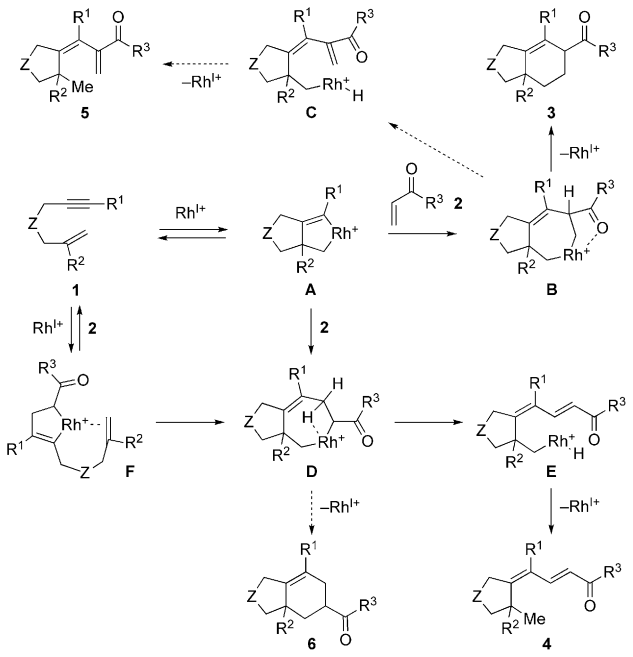
observed. In the reaction of 1,6-enyne **1a**, possessing the disubstituted alkene moiety, with sterically less-demanding and more-coordinative *N*,*N*-dimethylacrylamide (**2a**), cyclohexene **3aa** was obtained in high yield and diene **4aa** was obtained in low yield (Table 2, entry 1). In the reaction of **1a**

Table 2: Effects of substituents on the yields and *ee* values of cyclohexenes **3**, dienes **4**, and dienes **5**.[a]



Entry	**1** (R^1)	**2** (R^2)	**3**/Yield [%][b] (% *ee*)	**4**/Yield [%][b] (% *ee*)	**5**/Yield [%][b]
1	**1a** (Me)	**2a** (NMe_2)	(−)-**3aa**/86 (>99)	**4aa**/9	**5aa**/0
2	**1a** (Me)	**2e** (NPh_2)	(−)-**3ae**/97 (>99)	**4ae**/0	**5ae**/0
3	**1h** (H)	**2a** (NMe_2)	(−)-**3ha**/51 (97)	(+)-**4ha**/41 (68)	**5ha**/0
4	**1h** (H)	**2e** (NPh_2)	(−)-**3he**/77 (95)	**4he**/0	**5he**/0
5	**1a** (Me)	**2g** (OMe)	(−)-**3ag**/11 (99)[c]	**4ag**/10[c,d]	**5ag**/16[c]

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), (*R*)-H_8-binap (0.010 mmol), **1** (0.20 mmol), **2** (0.22 mmol), and CH_2Cl_2 (1.5 mL) were used. [b] Yield of the isolated product. [c] Isolated as a mixture of **3ag**/(*E*)-**4ag** or (*Z*)-**4ag**/**5ag**. Yields were determined by ^1H NMR spectroscopy and analytically pure compounds were isolated by GPC. [d] *E*/*Z* = 32:68.



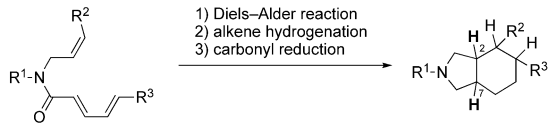
Scheme 3. A possible mechanism for the reaction of enyne **1** with alkene **2**.

and sterically more-demanding and less-coordinative *N*,*N*-diphenylacrylamide (**2e**), cyclohexene **3ae** was obtained in higher yield than **3aa** and diene **4ae** was not obtained at all (Table 2, entry 2). On the other hand, in the reactions of 1,6-enyne **1h**, possessing the monosubstituted alkene moiety, with **2a** and **2e** (Table 2, entries 3 and 4), cyclohexenes **3ha** and **3he** were obtained in lower yields than **3aa** and **3ae**, and diene **4ha** was obtained in significantly higher yield than **4aa**. Interestingly, the *ee* value of **4ha** was markedly lower than **3ha** (Table 2, entry 3). Importantly, regioisomeric diene **5ag** was generated, along with cyclohexene **3ag**, in the reaction of 1,6-enyne **1a** and acrylate **2g** (Table 2, entry 5).

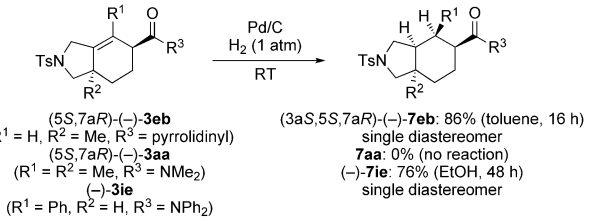
A possible mechanism for the formation of **3**, **4**, and **5** is shown in Scheme 3. Enyne **1** reacts with rhodium to generate rhodacyclopentene **A**. Regioselective insertion of alkene **2** into **A** generates rhodacycle **B**. Reductive elimination affords cyclohexene **3**. Chelation of the amide carbonyl oxygen to rhodium would suppress β-hydride elimination, thus resulting in formation of diene **5** via rhodium hydride **C**. However, diene **5ag** was generated in the reaction of **1a** and acrylate **2g** presumably owing to weak chelation of the ester carbonyl oxygen to rhodium. On the other hand, insertion of alkene **2** into **A** could also occur with opposite regioselectivity to generate rhodacycle **D**. β-Hydride elimination to generate rhodium hydride **E** is more favorable than reductive elimination to generate cyclohexene **6** and then subsequent reductive elimination affords diene **4**. Alternatively, the alkyne moiety of enyne **1** reacts with alkene **2** and rhodium to generate rhodacyclopentene **F**.[11] Insertion of the alkene moiety of **1** into **F** generates **D**. However, as the enantio-determining step in the former pathway (**1**→**A**→**D**→**E**→**4**) is the formation of **A**, the *ee* value of **4** should be as high as that of **3**.[12] The observed markedly lower *ee* value of **4ha** than of **3ha** might suggest that the less-enantioselective latter pathway (**1**→**F**→**D**→**E**→**4**) may be involved, at least in part, in the formation of diene **4**.[13] The observed substituent effects on the yields of **3** and **4** (Table 2) might be explained as follows. With respect to acrylamides, the formation of **D** from **A** would be more difficult with sterically more-demanding amide **2e** than sterically less-demanding amide **2a** as a result of the steric interaction between the carbamoyl group and the ligand. The formation of **D** from **F** would be more likely with more-coordinative amide **2a** than less-coordinative amide **2e**. These explanations are consistent with the formation of dienes **4** from **2a** but not from **2e**. With respect to 1,6-enynes, insertion of the sterically less-demanding monosubstituted alkene moiety of **1h** into **F** leading to **D** would be more facile than that of the sterically more-demanding disubstituted alkene moiety of **1a**. This explanation is consistent with the markedly higher yield of **4ha** than of **4aa**.

N,3,4-trisubstituted octahydroisoindoles show pharmaceutical activity.[14] These compounds were prepared through the Diels–Alder reaction with subsequent alkene hydrogenation and carbonyl reduction (Scheme 4).[14] As the Diels–Alder reaction was employed as a key step, 2- and 7-positions were limited to trisubstituted carbons.

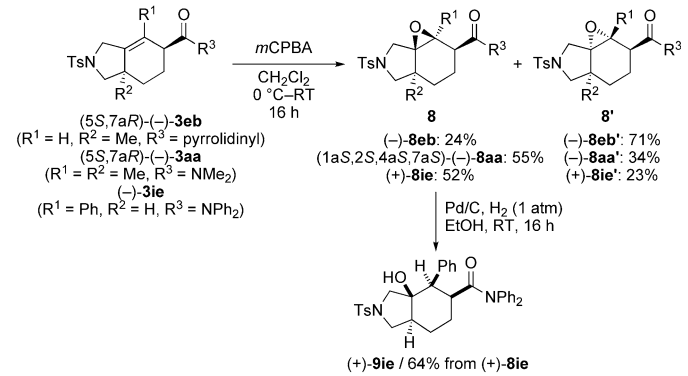
Reductive and oxidative transformations of the present [2+2+2] cycloaddition products enable the asymmetric synthesis of novel chiral octahydroisoindole derivatives, including those possessing a tetrasubstituted carbon at the 2- or 7-position (Scheme 5 and 6). Hydrogenation of **3eb**, possessing a trisubstituted alkene moiety, afforded N,4,7-trisubstituted octahydroisoindole **7eb**, possessing a tetrasubstituted carbon at the 7-position, in high yield with perfect diastereoselectivity. Hydrogenation of **3ie**, possessing the tetrasubstituted



Scheme 4. Synthesis of pharmaceutically active N,3,4-trisubstituted octahydroisoindoles.



Scheme 5. Reductive transformations of chiral annulated cyclohexenes **3**.



Scheme 6. Oxidative transformations of chiral annulated cyclohexenes **3**.

alkene moiety, also proceeded to give N,3,4-trisubstituted octahydroisoindole **7ie**, but the hydrogenation of **3aa** did not proceed at all. The oxidation of **3eb**, **3aa**, and **3ie** with *m*CPBA (*m*-chloroperoxybenzoic acid) proceeded smoothly to give the corresponding epoxides **8** and **8′** in high yields with moderate diastereoselectivities. The epoxide **8ie** could be reduced to the corresponding alcohol **9ie**, possessing a tetrasubstituted carbon at the 2-position, in moderate yield. The relative and absolute configurations of octahydroisoindoles (−)-**7eb** and (−)-**8aa** were unambiguously determined to be (3a*S*,5*S*,7a*R*) and (1a*S*,2*S*,4a*S*,7a*S*), respectively, by the anomalous dispersion methods.[15]

In conclusion, the unprecedented regio-, diastereo-, and enantioselective [2+2+2] cycloaddition of 1,6-enynes with alkenes to give annulated cyclohexenes was achieved by using acrylamides as alkenes and a cationic rhodium(I)/(*R*)-H_8-binap complex as a catalyst. In the present rhodium catalysis, regioselective insertion of the acrylamide into a rhodacyclopentene intermediate and the coordination of the carbonyl group of the acrylamide to the cationic rhodium would suppress the undesired β-hydride elimination. Further exploitation of the rhodium-catalyzed asymmetric intermolecular [2+2+2] cycloaddition reactions involving two alkene units is underway in our laboratory.

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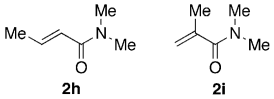
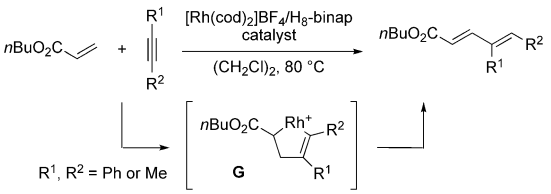
[10] The reactions of 1,6-enynes **1a** and **1h** with crotonamide **2h** and methacrylamide **2i** were also examined, and the desired [2+2+2] cycloaddition products were not obtained at all instead the corresponding homo-[2+2+2] cycloaddition products of **1a** and **1h** were generated.



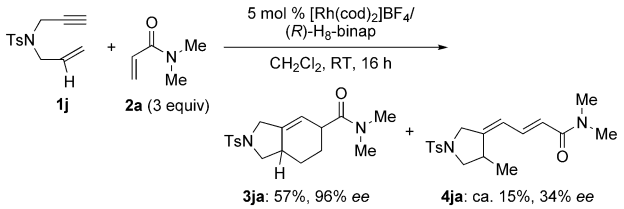
2h **2i**

[11] A similar regioselective formation of rhodacyclopentene **G**, possessing the alkoxycarbonyl group at the sp^3- hybridized carbon atom adjacent to rhodium, was proposed in the cationic rhodium(I)/(*R*)-H_8-binap-catalyzed dimerization of acrylates with internal alkynes, see: Y. Shibata, M. Hirano, K. Tanaka, *Org. Lett.* **2008**, *10*, 2829.



[12] In general, the cycloaddition reactions of 1,6-enynes via rhodacyclopentene **A** are highly enantioselective. For representative examples of the asymmetric [2+2+1] cycloadditions (Pauson–Khand reactions), see: a) N. Jeong, B. K. Sung, Y. K. Choi, *J. Am. Chem. Soc.* **2000**, *122*, 6771; b) T. Shibata, K. Takagi, *J. Am. Chem. Soc.* **2000**, *122*, 9852; for examples of the asymmetric [2+2+2] cycloadditions, see: references [3] and [9b–d].

[13] Similarly, the reaction of **1j** and **2a** furnished the corresponding cyclohexene **3ja** with a high *ee* value and the corresponding diene **4ja** with a low *ee* value, although **4ja** could not been isolated in a pure form by silica gel chromatography.



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[15] CCDC 894213 ((−)-**7eb**) and 894214 ((−)-**8aa**) 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.

