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# Rhodium-Catalyzed One-Pot Intermolecular [2 + 2 + 2] Trimerization/ Asymmetric Intramolecular [4 + 2] Cycloaddition of Two Aryl Ethynyl Ethers and 5-Alkynals

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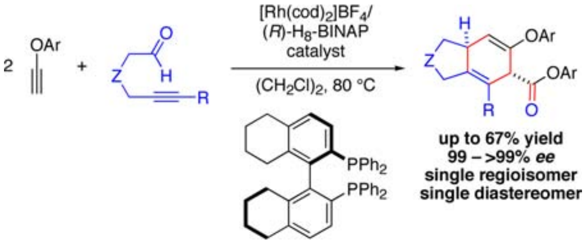
## ABSTRACT



**It has been established that a cationic Rh(I)/($R$)-H$_8$-BINAP complex catalyzes the one-pot intermolecular [2 + 2 + 2] trimerization/asymmetric intramolecular [4 + 2] cycloaddition of two aryl ethynyl ethers and 5-alkynals to produce annulated 1,4-cyclohexadienes possessing two stereogenic centers.**

One-pot catalyses, which allow the preparation of complex organic molecules from simple starting materials, are highly attractive methods in modern organic synthesis.[1] If such one-pot reactions proceed by using a single catalyst, it is obviously more advantageous than the use of binary catalysts. Our research group has reported that cationic Rh(I) complexes are highly effective catalysts for a wide variety of [2 + 2 + 2] cycloaddition reactions[2] via metallacycle intermediates.[3] As a recent example, we developed the cationic Rh(I) complex-catalyzed chemo-, regio-, and

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(1) For selected recent reviews, see: (a) Albrecht, Ł.; Jiang, H.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (b) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 443. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (d) Arns, S.; Barriault, L. *Chem. Commun.* **2007**, 2211. (e) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484. (f) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.

(2) For selected recent reviews, see: (a) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525. (b) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430. (c) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (d) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. (e) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830. (f) Tanaka, K. *Chem.—Asian J.* **2009**, *4*, 508. (g) Varela, J. A.; Saá, C. *Synlett* **2008**, 2571. (h) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, 1317. (i) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085.

(3) For reviews of the Rh-catalyzed [2 + 2 + 2] cycloaddition, see: (a) Shibata, Y.; Tanaka, K. *Synthesis* **2012**, *44*, 323. (b) Tanaka, K. *Heterocycles* **2012**, *85*, 1017. (c) Tanaka, K. *Synlett* **2007**, 1977. (d) Fujiwara, M.; Ojima, I. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 129.

(4) Miyauchi, Y.; Kobayashi, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 10922.

(5) For other examples of the Rh-catalyzed [2 + 2 + 2] cycloaddition of alkynes with carbonyl compounds, see: (a) Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc.* **2005**, *127*, 17756. (b) Tanaka, K.; Otake, Y.; Wada, A.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 2203. (c) Tsuchikama, K.; Yoshinami, Y.; Shibata, T. *Synlett* **2007**, 1395. (d) Tanaka, K.; Otake, Y.; Sagae, H.; Noguchi, K.; Hirano, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1312. (e) Tanaka, K.; Tanaka, R.; Nishida, G.; Hirano, M. *Synlett* **2008**, 2017. (f) Otake, Y.; Tanaka, R.; Tanaka, K. *Eur. J. Org. Chem.* **2009**, 2737. (g) Suda, T.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 4475. For the Rh-catalyzed reductive coupling of acetylene gas and aldehydes, see: (h) Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16040.

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stereoselective intermolecular [2 + 2 + 2] trimerization of two aryl ethynyl ethers with carbonyl compounds leading to aryloxy-substituted dienyl esters.[4−8] Based on this result, we designed the following Rh(I) complex-catalyzed one-pot reaction (Scheme 1).[9] If the chiral cationic Rh(I) complex-catalyzed intermolecular [2 + 2 + 2] trimerization of two aryl ethynyl ethers **1** with the formyl group of 5-alkynal **2** rather than the alkyne moiety proceeds chemo-, regio-, and stereoselectively, the corresponding dienyne **3** would be generated. Subsequently, if the same chiral cationic Rh(I) complex is able to catalyze the asymmetric intramolecular [4 + 2] cycloaddition of the dienyne **3**,[10−12] the corresponding annulated 1,4-cyclohexadiene **4**, possessing two stereogenic centers, would be generated. However, the transition-metal-catalyzed asymmetric intramolecular [4 + 2] cycloaddition of a dienyne, possessing the trisubstituted diene moiety, has not been reported.[13] Therefore, the reactivity and enantioselectivity of densely functionalized dienynes in the latter asymmetric transformation is interesting. However, we were successful with the above-mentioned asymmetric one-pot reaction by using a cationic Rh(I)/(*R*)-H$_8$-BINAP catalyst.

**Scheme 1**

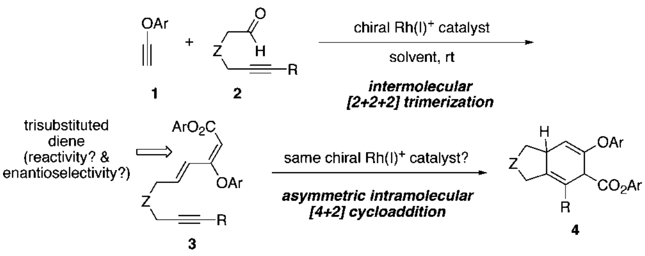
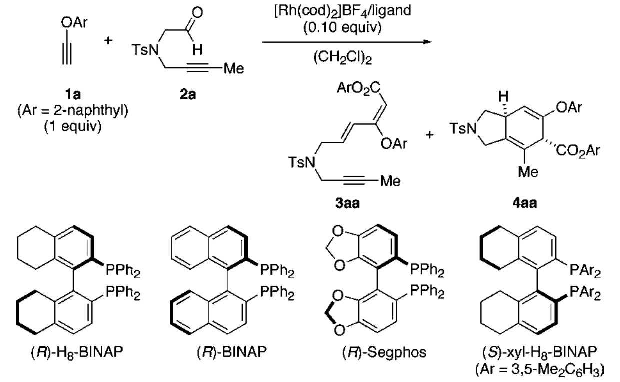


**Table 1.** Optimization of Reaction Conditions for One-Pot Transformation of **1a** and **2a** Leading to **4aa**[a]



| entry | ligand | **2a** (equiv) | conditions | **3aa** % yield[b] | **4aa** % yield,[b] dr, % ee |
|---|---|---|---|---|---|
| 1 | (*R*)-H$_8$-BINAP | 1 | rt, 1 h | 43 | 0 |
| 2 | (*R*)-H$_8$-BINAP | 1 | 80 °C, 24 h | 0 | 46, >99:1, >99 (−) |
| 3 | (*R*)-BINAP | 1 | 80 °C, 24 h | 0 | 38, >99:1, 97 (−) |
| 4 | (*R*)-Segphos | 1 | 80 °C, 24 h | 0 | <5 |
| 5 | (*S*)-xyl-H$_8$-BINAP | 1 | 80 °C, 24 h | 0 | 48, >99:1, 98 (+) |
| 6 | (*R*)-H$_8$-BINAP | 2 | 80 °C, 24 h | 0 | 67, >99:1, >99 (−) |

[a] [Rh(cod)$_2$]BF$_4$/ligand (0.010 mmol), **1a** (0.10 mmol), **2a** (0.10 mmol), and (CH$_2$Cl)$_2$ (2.0 mL) were used. [b] Isolated yield from **1a**.

We first investigated the reaction of ethynyl 2-naphthyl ether (**1a**) and tosylamide-linked 5-alkynal **2a** in the presence of a cationic Rh(I)/(*R*)-H$_8$-BINAP complex at rt (Table 1, entry 1). Although the desired intermolecular

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(6) For examples of the [2 + 2 + 2] cycloaddition of alkynes with carbonyl compounds catalyzed by other transition metals, see: (a) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570. (b) Yamamoto, Y.; Takagishi, H.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 6844. (c) Tekevac, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037. (d) Tekevac, T. N.; Louie, J. *J. Org. Chem.* **2008**, *73*, 2641.

(7) For other examples of the Rh-catalyzed [2 + 2 + 2] cycloaddition involving alkynyl ethers, see: (a) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 6605. (b) Clayden, J.; Moran, W. J. *Org. Biomol. Chem.* **2007**, *5*, 1028. (c) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464. (d) Komine, Y.; Kamisawa, A.; Tanaka, K. *Org. Lett.* **2009**, *11*, 2361. (e) Oberg, K. M.; Lee, E. E.; Rovis, T. *Tetrahedron* **2009**, *65*, 5056. (f) Komine, Y.; Tanaka, K. *Org. Lett.* **2010**, *12*, 1312. (g) Komine, Y.; Miyauchi, Y.; Kobayashi, M.; Tanaka, K. *Synlett* **2010**, 3092.

(8) For examples of the [2 + 2 + 2] cycloaddition involving alkynyl ethers catalyzed by other transition metals, see: (a) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215. (b) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253. (c) Hillard, R. L., III; Parnell, C. A.; Vollhardt, K. P. C. *Tetrahedron* **1983**, *39*, 905. (d) Semmelhack, M. F.; Park, J. *Organometallics* **1986**, *5*, 2550. (e) Tsuda, T.; Kunisada, K.; Nagahama, N.; Morikawa, S.; Saegusa, T. *Synth. Commun.* **1989**, *19*, 1575.

(9) For our previous reports of the cationic Rh(I) complex-catalyzed one-pot reactions, see: (a) Okazaki, E.; Okamoto, R.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 6722. (b) Okamoto, R.; Okazaki, E.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2011**, *13*, 4894. (c) Kobayashi, M.; Suda, T.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1664. (d) Tanaka, K.; Okazaki, E.; Shibata, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10822.

(10) For examples of the transition-metal-catalyzed asymmetric intramolecular [4 + 2] cycloaddition of dienynes, see: Rh: (a) Shintani, R.; Sannohe, Y.; Tsuji, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7277. (b) Aikawa, K.; Akutagawa, S.; Mikami, K. *J. Am. Chem. Soc.* **2006**, *128*, 12648. (c) Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077. Ir: (d) Shibata, T.; Takasaku, K.; Takesue, Y.; Hirata, N.; Takagi, K. *Synlett* **2002**, 1681. The Rh-catalyzed asymmetric intermolecular [4 + 2] cycloaddition of 1,3-dienes with an electron-deficient alkyne was also reported. See: (e) Shibata, T.; Fujiwara, D.; Endo, K. *Org. Biomol. Chem.* **2008**, *6*, 464. See also ref 10a.

(11) For examples of the transition-metal-catalyzed nonasymmetric intramolecular [4 + 2] cycloaddition of dienynes, see: Rh: (a) Jolly, R. S.; Leudtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (b) Gilbertson, S. R.; Hoge, G. S. *Tetrahedron. Lett.* **1998**, *39*, 2075. (c) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045. (d) Wang, B.; Cao, P.; Zhang, X. *Tetrahedron. Lett.* **2000**, *41*, 8041. (e) Motoda, D.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1860. (f) Yoo, W.-J.; Allen, A.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 5853. (g) Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 91. (h) Saito, A.; Ono, T.; Hanzawa, Y. *J. Org. Chem.* **2006**, *71*, 6437. (i) Gomez, F. J.; Kamber, N. E.; Deschamps, N. M.; Cole, A. P.; Wender, P. A.; Waymouth, R. M. *Organometallics* **2007**, *26*, 4541. Ni: (j) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (k) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824. Au: (l) Furstner, A.; Stimson, C. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8845. (m) Kim, S. M.; Park, J. H.; Chung, Y. K. *Chem. Commun.* **2011**, *47*, 6719. Pd: (n) Kumar, K.; Jolly, R. S. *Tetrahedron. Lett.* **1998**, *39*, 3047. Fe: (o) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

(12) For a review of the Rh-catalyzed [4 + 2] carbocyclization, see: Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 241.

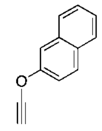
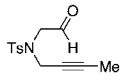
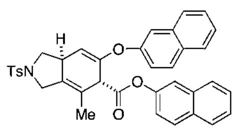
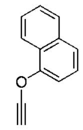
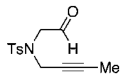
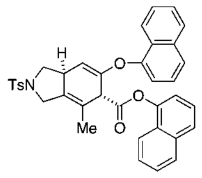
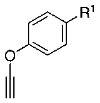
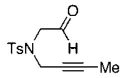
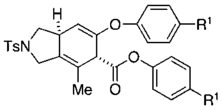
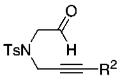
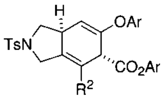
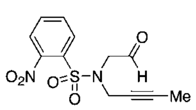
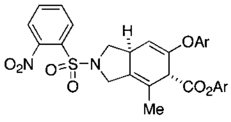
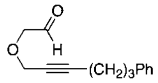
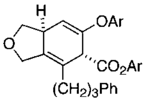
(13) Only one example of the transition-metal-catalyzed nonasymmetric intramolecular [4 + 2] cycloaddition of a dienyne, possessing the trisubstituted diene moiety, has been reported by using a cationic Rh(I)/*N*-heterocyclic carbene complex as a catalyst. See: Reference 11g.

[2 + 2 + 2] trimerization between two alkynes **1a** and the formyl group of **2a** proceeded to give dienyne **3aa** in moderate yield[14] with complete regio- and stereoselectivity, the subsequent asymmetric intramolecular [4 + 2] cycloaddition did not proceed. Pleasingly, when the same reaction was carried out at 80 °C for 24 h, the expected [4 + 2] cycloaddition product **4aa** was obtained in moderate yield with complete diastereo- and enantioselectivity (entry 2). Other biaryl bisphosphine ligands were also tested (entries 3−5), which were less effective than $H_8$-BINAP. Finally, increasing the amount of **2a** further improved the product yield (entry 6).

With the optimized reaction conditions in hand, the scope of this asymmetric one-pot reaction was examined (Table 2). With respect to aryl ethynyl ethers, electronically and sterically different aryl ethynyl ethers **1a**−**d** could be employed (entries 1−4).[15] With respect to 5-alkynals, various tosylamide-linked 5-alkynals **2b**−**d** could be employed (entries 5−7).[16] Nosylamide- and oxygen-linked 5-alkynals **2e** and **2f** also reacted with **1a** to give cyclohexadienes **4ae** and **4af** (entries 8 and 9). Importantly, all the reactions proceeded with almost complete regio-, diastereo-, and enantioselectivity. The relative and absolute configurations of (−)-**4ac** were determined to be 5*R*,7a*S* by X-ray crystallographic analysis.[17]

The reaction of **1a** and 5-alkynone **2g** was also examined (Scheme 2). The expected dienyne **3ag**, generated through the trimerization step, possesses a tetrasubstituted diene moiety; however, the transition-metal-catalyzed [4 + 2] cycloaddition of such a sterically demanding dienyne has not been reported. Pleasingly, the desired one-pot reaction proceeded to give the corresponding cyclohexadienes **4ag** and **4ag′** with high yields and ee values, although diastereoselectivity was moderate.[18]

**Table 2.** Rh-Catalyzed Asymmetric One-Pot Reactions of Alkynes **1** and Alkynals **2** Leading to Cyclohexadienes **4**[a]

| entry | 1 | 2 | 4 / yield,[b] dr, ee |
|---|---|---|---|
| 1 | <br>**1a** | <br>**2a** | <br>(−)-**4aa** / 64% yield, >99:1 dr, >99% ee |
| 2 | <br>**1b** | <br>**2a** | <br>(−)-**4ba** / 48% yield, >99:1 dr, >99% ee |
| 3 | <br>**1c** ($R^1$ = $CF_3$) | <br>**2a** | <br>(−)-**4ca** / 67% yield, >99:1 dr, 99% ee |
| 4 | **1d** ($R^1$ = OMe) | **2a** | (−)-**4da** / 27% yield, >99:1 dr, 99% ee |
| 5 | <br>**1a** (Ar = 2-naphthyl) | <br>**2b** ($R^2$ = Et) | <br>(−)-**4ab** / 38% yield, >99:1 dr, >99% ee |
| 6 | **1a** (Ar = 2-naphthyl) | **2c** ($R^2$ = *n*-Bu) | (5*R*,7a*S*)-(−)-**4ac**<br>42% yield, >99:1 dr, >99% ee |
| 7 | **1a** (Ar = 2-naphthyl) | **2d** ($R^2$ = *n*-$C_{10}H_{21}$) | (−)-**4ad** / 31% yield, >99:1 dr, 99% ee |
| 8 | <br>**1a** (Ar = 2-naphthyl) | <br>**2e** | <br>(−)-**4ae** / 64% yield, >99:1 dr, >99% ee |
| 9 | <br>**1a** (Ar = 2-naphthyl) | <br>**2f** | <br>(−)-**4af** / 35% yield, >99:1 dr, >99% ee |

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$/(R)-$H_8$-BINAP (0.020 mmol), **1** (0.20 mmol), and **2** (0.40 mmol) in $(CH_2Cl)_2$ (2.0 mL) at 80 °C for 16 h. [b] Isolated yield from **1**.

Transformations of the present asymmetric one-pot reaction product **4aa** were examined briefly (Scheme 3). Aryl ester **4aa** could be converted to the corresponding methyl ester **5** by treatment with NaOMe in MeOH. Oxidation of **4aa** with *m*-CPBA afforded the corresponding epoxide **6** with complete diastereoselectivity.

Scheme 4 depicts a plausible mechanism for this rhodium-catalyzed one-pot transformation. Two aryl ethynyl ethers **1** react with rhodium to generate rhodacyclopentadiene **A**. Insertion of the formyl group of 5-alkynal **2** into **A** generates rhodacycle **B**.[19] Reductive elimination of rhodium affords pyrane **C**. Subsequent electrocyclic ring opening affords dienyne **3**, which reacts with rhodium

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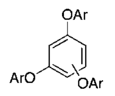
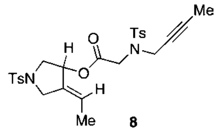
[14] In the reactions of Table 1, the homo-[2 + 2 + 2] cycloaddition of **1a** leading to benzene **7** and the homodimerization of **2a** leading to ester **8** were observed as side reactions. For the formation of **8**, see: Tanaka, R.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1238.



**7**



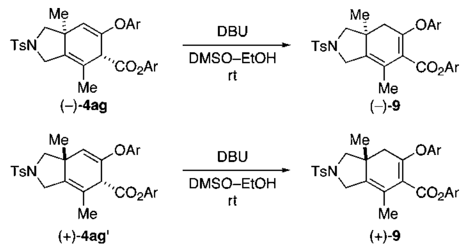
**8**

[15] Alkyl ethynyl ethers could not be employed in the presence of the Lewis acidic cationic Rh(I) complex due to their instability.

[16] Although the reaction of **1a** and a terminal 5-alkynal was examined, the corresponding cyclohexadiene was generated in low yield and could not be isolated in a pure form due to the formation of a complex mixture of byproducts.

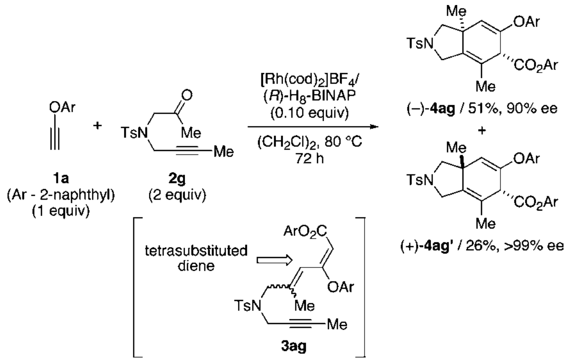
[17] See the Supporting Information.

[18] The opposite stereochemistry at the bridged carbon atoms of (−)-**4ag** and (+)-**4ag′** was confirmed by treatment of these 1,4-cyclohexadienes with DBU leading to an enantiomeric pair of 1,3-cyclohexadienes, (−)-**9** and (+)-**9**.

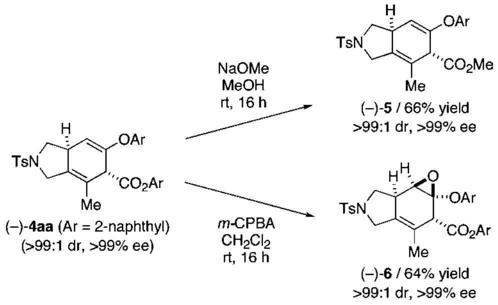


[19] For a discussion about the facile insertion of the carbonyl group to the rhodacycle **A**, see: Reference 4.

**Scheme 2**



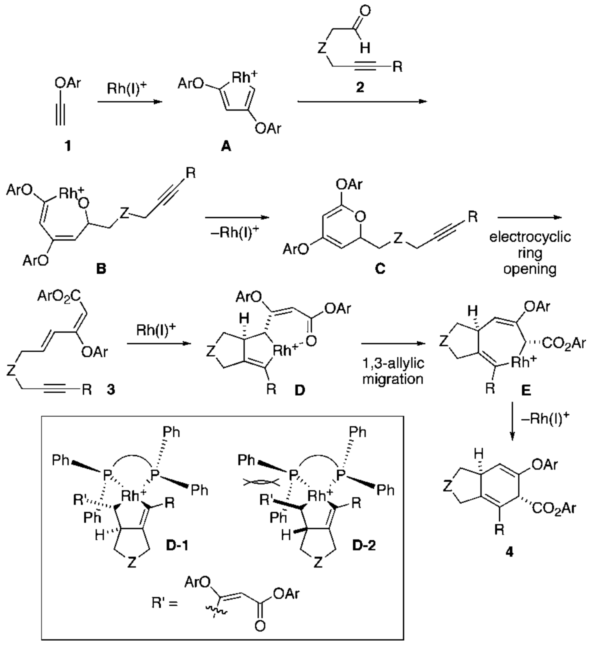
**Scheme 3**



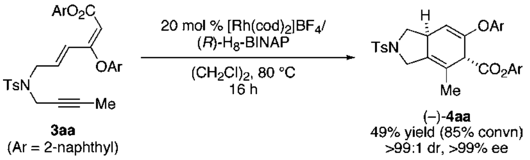
again to generate rhodacyclopentene **D**. Of the two possible intermediates **D-1** and **D-2**, **D-1** would be more favorable due to the absence of the steric interaction between the equatorial phenyl group of (*R*)-$H_8$-BINAP and the alkenyl group (R′). This mechanism is consistent with the formation of (5*R*,7a*S*)-(−)-**4ac**. 1,3-Allylic migration affords rhodacycle **E**. Reductive elimination of rhodium affords cyclohexadiene **4**.[20,21]

The intermediacy of dienyne **3** in this one-pot reaction is confirmed by the reaction of the isolated dienyne **3aa** (Scheme 5). Treatment of **3aa** with the cationic Rh(I)/(*R*)-$H_8$-BINAP catalyst at 80 °C indeed afforded the cyclohexadiene **4aa**.

**Scheme 4**



**Scheme 5**



In conclusion, it has been established that a cationic Rh(I)/$H_8$-BINAP complex catalyzes the one-pot intermolecular [2 + 2 + 2] trimerization/asymmetric intramolecular [4 + 2] cycloaddition of two aryl ethynyl ethers and 5-alkynals to produce annulated 1,4-cyclohexadienes. Future work will focus on further utilization of the cationic Rh(I) catalysts for the development of novel one-pot reactions.

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**Supporting Information Available.** Experimental procedures, compound characterization data, and an X-ray crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(20) For a mechanistic proposal of the Rh-catalyzed intramolecular [4 + 2] cycloaddition of dienynes, see: References 10a−10c.

(21) A possible explanation for the formation of two diastereomers **4ag** and **4ag′** is as follows. At rt, the reaction of **1a** and **2g** affords *E*-dienyne **3ag** as a predominant stereoisomer. At 80 °C, equilibration between *E*-dienyne **3ag** and *Z*-dienyne **3ag′** occurs in the presence of the cationic Rh(I) catalyst. (For the cationic Rh(I) complex-catalyzed *E*/*Z* isomerization of enones, see: Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 2687.) Although *E*-dienyne **3ag** may be thermodynamically more stable, the cyclization of **3ag** may be slow as a result of the steric interaction between the methyl and aryloxyvinyl groups in intermediate **F**. In contrast, the cyclization of thermodynamically less stable *Z*-dienyne **3ag′** may be fast as a result of the formation of less sterically demanding intermediate **F′**. The formation of **4ag** and **4ag′** through different rhodacycles **F** and **F′**, respectively, is consistent with their different ee values.