ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: T. Yasui, T. Kikuchi and Y. Yamamoto, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC05429A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/D0CC05429A

COMMUNICATION

Rhodium-catalyzed cycloisomerization of ester-tethered 1,6-diynes with cyclopropanol moiety leading to tetralone/exocyclic diene hybrid molecules

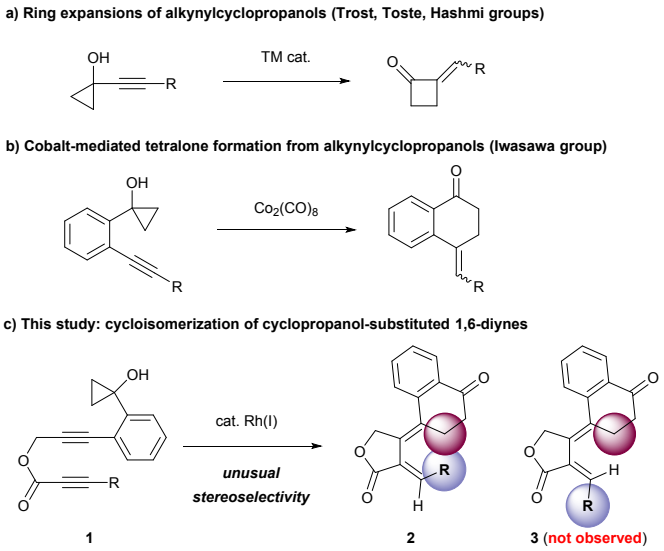
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Takeshi Yasui,* Tomohiro Kikuchi and Yoshihiko Yamamoto*

The rhodium-catalyzed cycloisomerization of ester-tetherd 1,6-diynes bearing a cyclopropanol moiety produced tetralone/exocyclic diene hybrid molecules with thermodynamically unfavorable alkene geometry. The results of control experiments and density functional theory calculations suggest that the ester tether play an important role for the efficiency of *E*/*Z* isomerization process.

Transition-metal-catalyzed transformations of cyclopropanols with the aid of ring-strain relief have been actively investigated since they provide efficient access to diverse molecular entities.[1] Nevertheless, the transition-metal-catalyzed ring expansion of ω-alkynylcyclopropanols has been underdeveloped (Scheme 1a).[2] In particular, only one example of the tetralone formation from (*o*-alkynylphenyl)cyclopropanols using stoichiometric amounts of $Co_2(CO)_8$ was reported by the Iwasawa group (Scheme 1b).[3] This method is significant because tetralones are utilized as bioactive compounds[4] as well as building blocks for natural product synthesis;[5] however, no example of a catalytic variant was reported to date. Thus, the transition-metal-catalyzed reactions of α,ω-diynes bearing a cyclopropanol moiety is fascinating as they should realize a novel cascade reaction involving the cyclopropanol ring expansion and diyne cyclization. Herein, we report our study on the rhodium-catalyzed cycloisomerization of ester-tethered 1,6-diynes **1** bearing a cyclopropanol moiety (Scheme 1c). Intriguingly, this reaction produced tetralone/exocyclic diene hybrid molecules **2**, in which the vinylic substituent (R) orients inside the diene moiety, rather than **3**. The unique reaction mechanism, including the cyclopropanol-ring cleavage via a rhodacyclopentadiene intermediate and *E*/*Z* isomerization via a dienyl-rhodium intermediate, is also proposed based on the results obtained from control experiments and density functional theory (DFT) calculations.



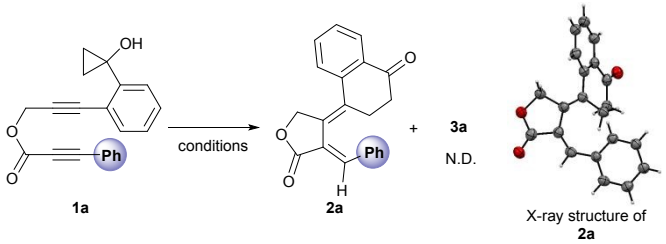
Scheme 1 Transition-metal-catalyzed ring expansions of alkynylcyclopropanols and cyclopropanol-substituted 1,6-diynes.

As an initial study, we screened various reaction conditions using **1a** as a model substrate (Table 1). Transition-metal catalysts used in ring-opening reactions of cyclopropanols or cyclobutanols, such as $Pd(OAc)_2$[6] and $[RhOH(cod)]_2$,[7] were tested (entries 1 and 2); however, exocyclic diene **2a** was not obtained. Next, ruthenium,[8] rhodium,[9] and iridium[10] catalysts, which are widely utilized for diyne cyclization reactions, were employed (entries 3–5). Fortunately, **2a** was obtained in moderate yield with excellent stereoselectivity using a cationic rhodium catalyst prepared from $[Rh(cod)_2]BF_4$ and BINAP, while ruthenium and iridium catalysts were not effective. Notably, the yield of **2a** was improved by diluting the reaction medium, likely as a result of the suppression of intermolecular side reactions (entry 6).[11] Further optimization of reaction conditions, involving the screening of ligands and counterions of the cationic rhodium complex, did not improve the yield of **2a**

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601 (Japan)
E-mail: t-yasui@ps.nagoya-u.ac.jp, yamamoto-yoshi@ps.nagoya-u.ac.jp
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

(Tables S1–S3). The structure of **2a** was unambiguously confirmed by single-crystal X-ray diffraction.[12]

Table 1 Screening of reaction conditions.



entry	conditions	conv. (%)[a]	**2a** (%)[a]
1	10 mol% **Pd(OAc)$_2$** CH_3CN (0.1 M), 50 ºC, 24 h	>99[b]	N.D.
2	1.5 mol% **[RhOH(cod)]$_2$** 3.0 mol% *rac*-BINAP CH_2Cl_2 (0.05 M), 30 ºC, 1 h	<5	N.D.
3	5 mol% **[Cp*RuCl$_2$]$_2$** $ClCH_2CH_2Cl$ (0.1 M), 80 ºC, 17 h	<5	N.D.
4[c]	1.5 mol% **[Ir(cod)Cl]$_2$** 3.0 mol% *rac*-BINAP CH_2Cl_2 (0.1 M), 30 ºC, 1 h	21[b]	N.D.
5[c]	3.0 mol% **[Rh(cod)$_2$]BF$_4$** 3.0 mol% *rac*-BINAP CH_2Cl_2 (0.1 M), 30 ºC, 1 h	>99	47[d]
6[c]	3.0 mol% **[Rh(cod)$_2$]BF$_4$** 3.0 mol% *rac*-BINAP CH_2Cl_2 (**0.05 M**), 30 ºC, 1 h	>99	70[d]

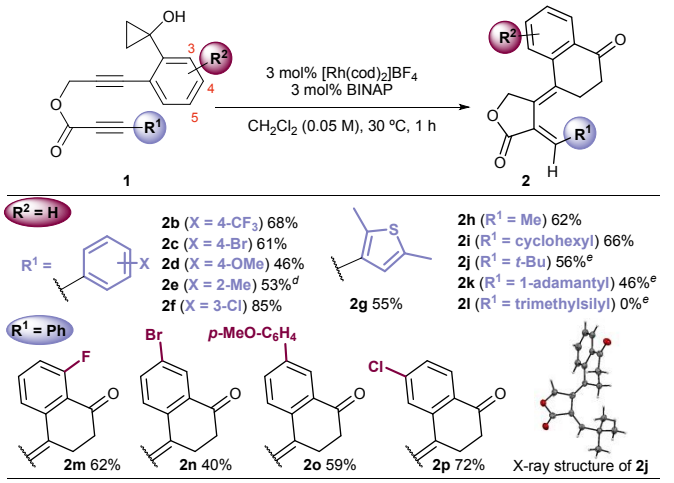
[a]N.D. = Not detected. [b]Complex mixture. [c]Pre-activation of the catalyst was performed under H_2 atmosphere before addition of **1a** to the reaction mixture. [d]Isolated yield.

With the optimized reaction conditions in hand, we investigated the scope of 1,6-diynes **1** (Table 2). Aryl terminal groups with electron-withdrawing substituents at the *para* position, such as trifluoromethyl (**1b**) and bromo (**1c**) groups were tolerated, affording **2b** and **2c** in good yields with complete stereoselectivity. Introduction of a methoxy group at the *para* position (**1d**) resulted in a slightly lower yield of **2d** compared to that of **2b** and **2c**. 2-Methylphenyl (**1e**) and 3-chlorophenyl (**1f**) groups were tolerated and afforded the desired products in good yields (53% and 85%, respectively). Thiophene-based substrate **1g** furnished **2g** in 55% yield. When substrates **1h** and **1i**, bearing alkyl groups such as methyl and cyclohexyl on the alkyne terminus were employed, the corresponding exocyclic dienes **2h** and **2i** were obtained in 62% and 66% yields, respectively. Remarkably, bulky alkyl substituents, such as *tert*-butyl and adamantyl groups (**2j** and **2k**) were oriented inside the diene moiety without erosion of stereoselectivity. However, **1l**, possessing a trimethylsilyl group, did not react. Furthermore, substrates with 3-fluoro (**1m**), 4-bromo (**1n**), 4-(*p*-methoxyphenyl) (**1o**), or 5-chloro (**1p**) groups on the benzene ring adjacent to the cyclopropanol moiety could also be applied to the reaction under the standard conditions, affording **2m–p** in moderate to good yields.

Next, 1,6-diynes **1q–s** bearing various tethers were subjected to the reaction conditions, to elucidate their influence on the stereoselectivity (Scheme 2). The reaction of amide-tethered diyne **1q** gave **2q** in 27% yield, along with stereoisomer **3q** in 19% yield. Notably, when **1r** and **1s** were used as substrates, **2r** and **2s** were not observed, while **3r** and **3s** were obtained in 26% and 30% yields, respectively. These results indicate that the resonance effect of the carbonyl group of the tethers is crucial for the *E*/*Z* selectivity. Additionally, in the reaction of **1s**, phthalan-type product **3s'** was obtained in 30% yield, whereby ring opening of the cyclopropane moiety had not occurred.

To understand the reaction mechanism of the diyne-cyclopropanol cycloisomerization, control experiments and DFT calculations were performed. The cycloisomerization of **1** may be initiated by the ring opening of the cyclopropanol moiety, or via oxidative cyclization of the diyne. First, we performed several control experiments to determine which of the two reaction mechanisms was occurring, as shown in Scheme 3. Under the standard conditions for the cycloisomerization of **1**, the ring-opening reaction of phenylcyclopropanol **4** did not proceed. On the other hand, propiophenone (**5**) was obtained in 80% yield from **4** in the presence of catalytic amounts of $[RhOH(cod)]_2$ and BINAP, while **1a** was largely recovered under the same reaction conditions (Table 1, entry 2). Moreover, cyclopropanol-containing alkyne **6** did not react under standard conditions. In the presence of an excess amount of phenylacetylene, diyne **1h** was converted to [2+2+2] cycloadduct **7** in 90% yield with the cyclopropanol moiety intact. This result indicates that the rhodacyclopentadiene intermediate is likely produced under the standard reaction conditions.[9] According to these observations, it can be assumed that the cycloisomerization of **1** is initiated by the oxidative cyclization of the diyne moiety, rather than by cyclopropanol ring opening.

Table 2 Substrate scope.[a,b,c]



[a]All reactions were performed on a 0.1 mmol scale. [b]Isolated yields are shown. [c]Stereoisomers **3** were not detected. [d]The reaction was performed for 2 h. [e]The reaction was performed with $[Rh(cod)_2]BF_4$ (10 mol%) and BINAP (10 mol%) at 60 ºC in 1,2-dichloroethane.

Based on the results of the control experiments, we then performed DFT calculations with the SMD (CH_2Cl_2) B3LYP(GD3BJ)/6-311G++(d,p)-SDD//B3LYP/6-31G(d)-LanL2DZ

View Article Online
DOI: 10.1039/D0CC05429A

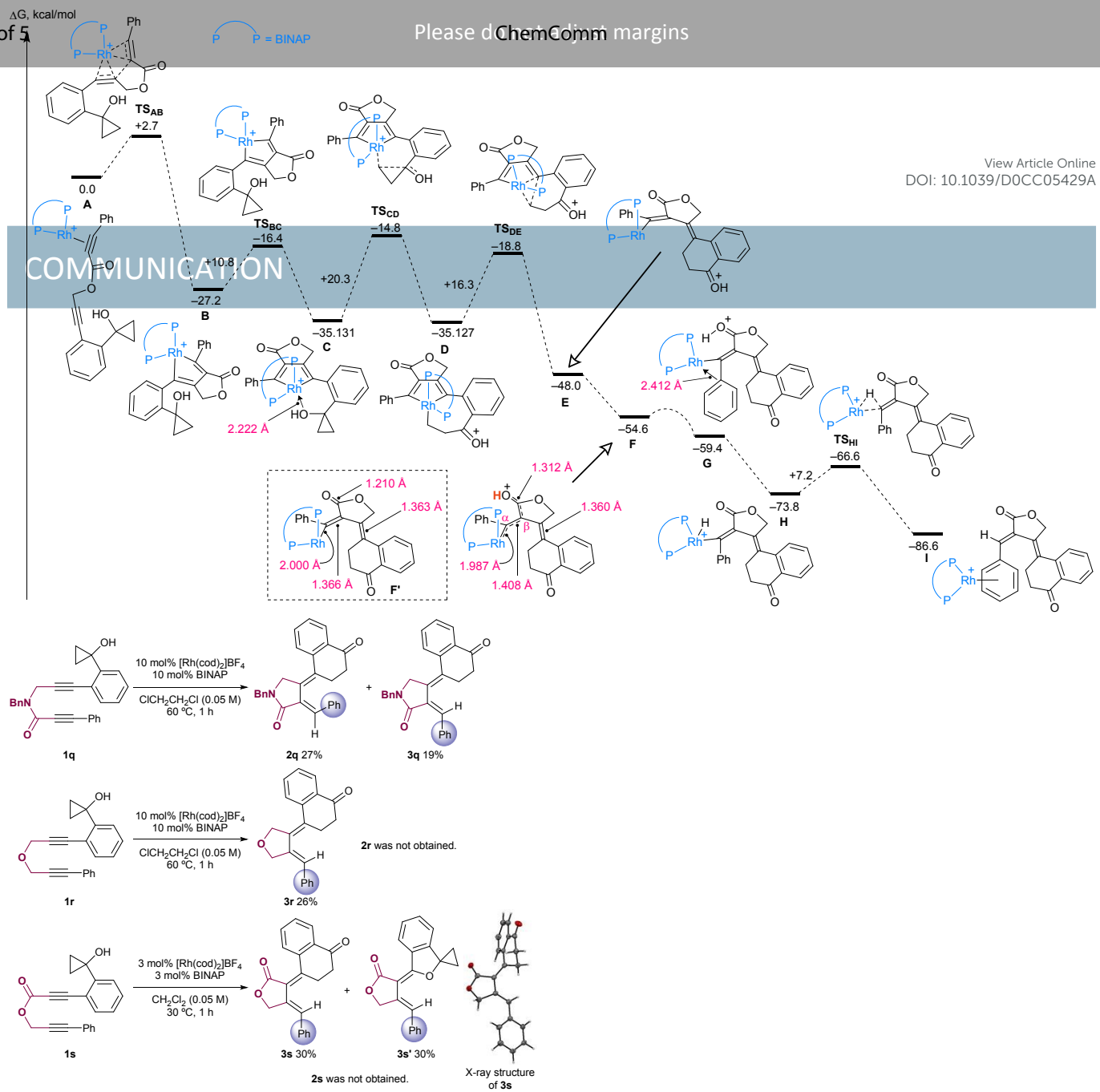


Fig. 1 Gibbs free energy diagram for cycloisomerization reaction of **1a** [SMD (CH_2Cl_2) B3LYP(GD3BJ)/6-311G++(d,p)-SDD//B3LYP/6-31G(d)-LanL2DZ].

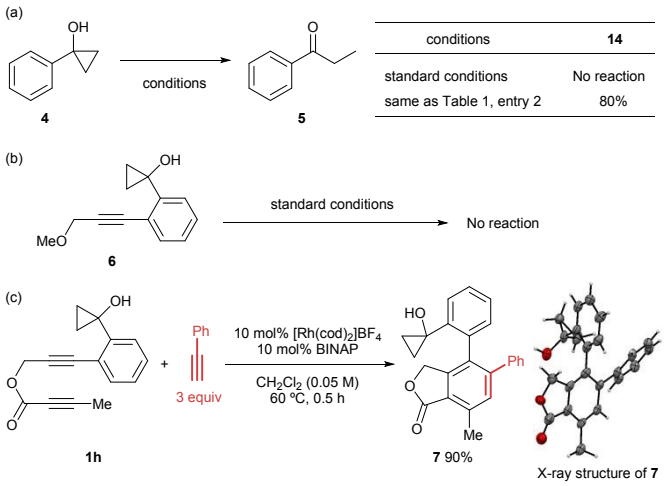
Scheme 2 Effect of tether moiety.

level of theory to gain further insight into the overall reaction mechanism (Fig. 1). The oxidative cyclization of the diyne moiety is initiated by the coordination of **1a** to a cationic Rh(I)-BINAP complex, generating complex **A**. The oxidative cyclization proceeds via $\mathbf{TS_{AB}}$ with a low activation energy of $\Delta G^{\ddagger}$ = +2.7 kcal mol^{-1} to furnish rhodacyclopentadiene **B**, which adopts an envelope conformation. Planar rhodacyclopentadiene **C**, with the hydroxy group occupying the apical position, is readily evolved from **B** through $\mathbf{TS_{BC}}$ with an exergonicity of 7.9 kcal mol^{-1}. Ring opening of the cyclopropanol of **C** occurs via $\mathbf{TS_{CD}}$ with a barrier of 20.3 kcal mol^{-1}, which is the highest activation energy within the overall cycloisomerization process. To the best of our knowledge, this is the first example of cyclopropane ring opening via the formation of rhodacyclopentadiene species. Subsequent reductive elimination in **D** via $\mathbf{TS_{DE}}$ with a barrier of 16.3 kcal mol^{-1} is followed by proton transfer to afford dienyl-rhodium intermediate **F**. The sequence is energetically downhill by 19.5 kcal mol^{-1}. The facile *E*/*Z* isomerization[13,14] of **F** provides **G**, which is 4.8 kcal mol^{-1} lower in energy compared to **F**. The protonation of the lactone carbonyl group is crucial for promoting the bond rotation, as the activation energy of the *E*/*Z* isomerization increases by ca. 10 kcal mol^{-1} without protonation (Figures S9 and S10).[15] The bond length of C_α–C_β in complex **F'** without protonation is 1.366 Å, which becomes longer to 1.408 Å when it binds to proton (complex **F**). This indicates that protonation of the lactone carbonyl group plays an important role in reducing the double-bond character of the C_α–C_β bond in complex **F**, thus enabling facile bond rotation. In addition, the bond length of Rh–C_α in complex **F** is shorter than that in complex **F'**, indicating that the Rh–C_α bond in complex **F** partially has the metal-carbene-bond character. Finally, barrierless proton transfer proceeds from **G** to produce rhodium(III) species **H**, which evolves to complex **I** through C–H bond-forming reductive elimination with a barrier of 7.2 kcal mol^{-1}.

View Article Online
DOI: 10.1039/D0CC05423A

The overall process from complex **A** to **I** is highly exergonic by 86.6 kcal mol^{-1}, indicating that the cycloisomerization of 1,6-diyne **1** is thermodynamically favorable.

In conclusion, we have developed the rhodium-catalyzed cycloisomerization of cyclopropanol-substituted 1,6-diynes, affording tetralone/exocyclic diene hybrid molecules. We proposed a plausible reaction mechanism, including the cyclopropanol-ring opening via a rhodacyclopentadiene intermediate and the *E*/*Z* isomerization triggered by protonation of the lactone carbonyl group, based on the results of control experiments and DFT calculations. These findings would lead to the development of novel synthetic methods for useful helical exocyclic dienes, such as photochromic molecules, ligands, and organocatalysts.[16,17]



Scheme 3 Control experiments.

This research was partially supported by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS) from AMED under Grant Number JP20am0101099) and JSPS KAKENHI (Grant Number JP16KT0051). This work was also supported by the Sasakawa Scientific Research Grant from The Japan Science Society.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selected recent reviews: (*a*) A. Nikolaev and A. Orellana, *Synthesis*, 2016, **48**, 1741; (*b*) G. Fumagalli, S. Stanton, and J. F. Bower, *Chem. Rev*., 2017, **117**, 9404; (*c*) L. R. Mills and S. A. L. Rousseaux, *Eur. J. Org. Chem.*, 2019, 8.

2 (*a*) J. P. Markham, S. T. Staben, and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 9708; (*b*) B. M. Trost, J. Xie, and N. Maulide, *J. Am. Chem. Soc*., 2008, **130**, 17258; (*c*) A. S. K. Hashmi, T. Wang, S. Shi, and M. Rudolph, *J. Org. Chem.*, 2012, **77**, 7761; (d) A. Reding, P. G. Jones, and D. B. Werz, *Org. Lett.*, 2018, **20**, 7266.

3 N. Iwasawa and T. Matsuo, *Chem. Lett.*, 1997, 341.

4 (*a*) A. Evidente, A. Cimmino, and A. Andolfi, *Chirality*, 2013, **25**, 59; (*b*) L. J. Legoabe, A. Petzer, and J. P. Petzer, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2758.

5 P. S. Poon, A. K. Banerijee, W. J. Vera, H. D. Mora, M. S. Laya, L. Bedoya, E. V. Cabrera, and C. E. Melean, *J. Chem. Res.*, 2008, 181.

6 (*a*) H. Okumoto, T. Jinnai, H. Shimizu, Y. Harada, H. Mishima, and A. Suzuki, *Synlett*, 2000, 629; (*b*) S. B. Park and J. K. Cha, *Org. Lett*., 2000, **2**, 147; (*c*) S. Matsumura, Y. Maeda, T. Nishimura, and S. Uemura, *J. Am. Chem. Soc*., 2003, **125**, 8862.

7 (*a*) T. Seiser and N. Cramer, *Angew. Chem. Int. Ed*., 2008, **47**, 9294; (*b*) A. Yada, S. Fujita, and M. Murakami, *J. Am. Chem. Soc*., 2014, **136**, 7217.

8 (*a*) Y. Yamamoto, T. Arakawa, R. Ogawa, and K. Itoh, *J. Am. Chem. Soc*., 2003, **125**, 12143; (*b*) Y. Yamamoto, K. Nishimura, and M. Shibuya, *ACS Catal*., 2017, **7**, 1101; (*c*) Y. Yamamoto, *Tetrahedron Lett*., 2017, **58**, 3787.

9 (*a*) K. Tanaka, *Synlett*, 2007, 1977; (*b*) T. Shibata and K. Tsuchikama, *Org. Biomol. Chem.*, 2008, **6**, 1317; (*c*) Y. Shibata and K. Tanaka, *Synthesis*, 2012, **44**, 323; (*d*) K. Tanaka, *Chem. Asian J.*, 2009, **4**, 508; (*e*) M. Amatore and C. Aubert, *Eur. J. Org. Chem*., 2015, 265.

10 (*a*) T. Hashimoto, A. Okabe, T. Mizuno, M. Izawa, and R. Takeuchi, *Tetrahedron*, 2014, **70**, 8681; (*b*) T. Hashimoto, S. Ishii, R. Yano, H. Miura, K. Sakata, and R. Takeuchi, *Adv. Synth. Catal*., 2015, **357**, 3901.

11 In this reaction, any noticeable side products were not observed by ^{1}H NMR analysis of the crude material. TLC analysis of the reaction showed tailing stains on the bottom of the TLC plate, which suggests that intermolecular side reactions may provide a complex mixture including oligomers.

12 X-ray crystallographic data for compounds **2a**, **2e**, **2j**, **3s**, and **7** have been deposited with the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under codes CCDC2007772, CCDC2007776, CCDC2007773, CCDC2007774, and CCDC2007775 respectively. For details, see ESI.

13 For selected examples involving transition-metal-mediated *E*/*Z* isomerization reactions, see: (*a*) I. Ojima, N. Clos, R. J. Donovan, and P. Ingallina, *Organometallics*, 1990, **9**, 3127; (*b*) R. S. Tanke and R. H. Crabtree, *J. Am. Chem. Soc*., 1990, **112**, 7984; (*c*) S. Xu, K. Chen, H. Chen, J. Yao, and X. Zhu, *Chem. Eur. J.*, 2014, **20**, 16442.

14 We also conducted DFT calculations for the protodemetalation of complex **F** without *E*/*Z* isomerization (Figure S11). For details, see ESI.

15 Energy-scan for the *E*/*Z*-isomerization of an amide-tethered 1,6-diyne substrate suggests that the bond rotation process is energetically unfavorable compared to the process (**F**→**G**) shown in Fig 1 (Figure S12). For details, see ESI.

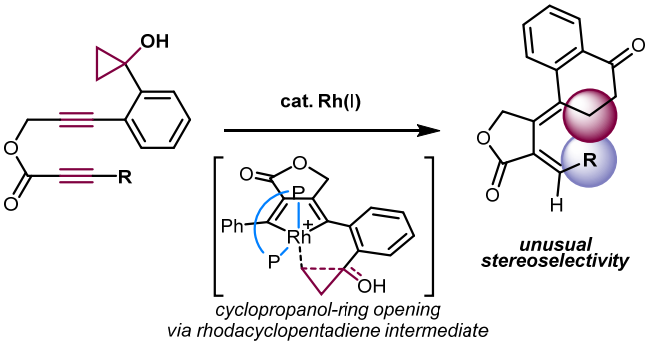
16 For selected examples of applications for helical exocyclic dienes, see: (*a*) Y. Yokoyama, *Chem. Rev*., 2000, **100**, 1717; (*b*) M. Ogasawara, S. Kotani, H. Nakajima, H. Furusho, M. Miyasaka, Y. Shimoda, W. Y. Wu, M. Sugiura, T. Takahashi, and M. Nakajima, *Angew. Chem. Int. Ed*., 2013, **52**, 13798; (*c*) M. Ogasawara, H. Sasa, H. Hu, Y. Amano, H. Nakajima, N. Takenaga, K. Nakajima, Y. Kita, T. Takahashi, and T. Dohi, *Org. Lett.*, 2017, **19**, 4102.

17 Variable-temperature ^{1}H NMR studies on **2j** showed that atropisomerization of **2j** is very fast at 22 ºC while the atropisomers can be distinguished below –60 ºC. For details, see ESI.

View Article Online
DOI: 10.1039/D0CC05429A

Rhodium-catalyzed cycloisomerization of ester-tethered 1,6-diynes with cyclopropanol moiety leading to tetralone/exocyclic diene hybrid molecules

Takeshi Yasui,* Tomohiro Kikuchi and Yoshihiko Yamamoto*



Rhodium-catalyzed cycloisomerization of ester-tethered 1,6-diynes bearing a cyclopropanol moiety affords tetralone/exocyclic diene hybrid molecules with thermodynamically unfavorable alkene geometry.