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Rhodium-Catalyzed Olefin Isomerization/Allyl Claisen Rearrangement/Intramolecular Hydroacylation Cascade

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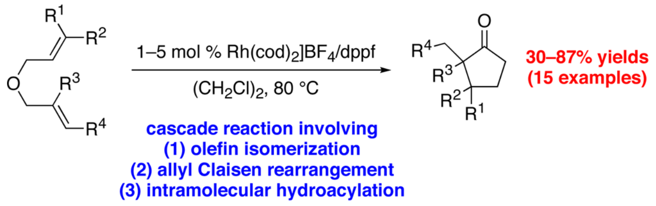
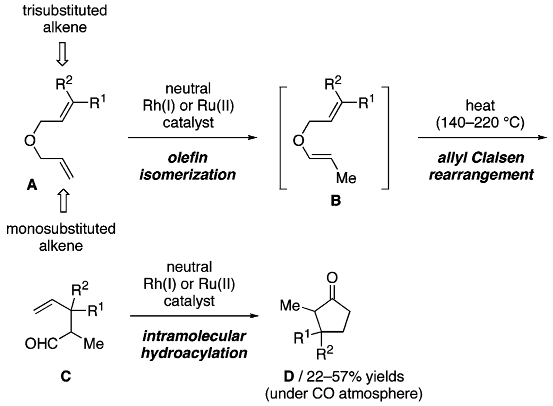
ABSTRACT



It has been established that a cationic Rh(I)/dppf complex catalyzes the olefin isomerization/allyl Claisen rearrangement/intramolecular hydroacylation cascade of di(allyl) ethers to produce substituted cyclopentanones in good yields under mild conditions.

The transition-metal-catalyzed intramolecular hydroacylation of 4-alkenals is a useful method for the synthesis of substituted cyclopentanones.[1−4] However, the synthesis of substituted 4-alkenals is sometimes troublesome. Furthermore, they are unstable under air and gradually oxidized to the corresponding carboxylic acids. Therefore, the use of readily prepared and stable 4-alkenal equivalents is

Scheme 1



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(1) For a review, see: Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

(2) For pioneering work, see: Sakai, K.; Ide, J.; Nakamura, N. *Tetrahedron Lett.* **1972**, 1287.

(3) For examples, see: (a) Hoffman, T. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10670. (b) Vautravers, N. R.; Regent, D. D.; Breit, B. *Chem. Commun.* **2011**, *47*, 6635. (c) Hyatt, I. F. D.; Anderson, H. K.; Morehead, A. T., Jr.; Sargent, A. L. *Organometallics* **2008**, *27*, 135. (d) Oonishi, Y.; Ogura, J.; Sato, Y. *Tetrahedron Lett.* **2007**, *48*, 7505. (e) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042. (f) Morgan, J. P.; Kundu, K.; Doyle, M. P. *Chem. Commun.* **2005**, 3307. (g) Tanaka, M.; Sakai, K.; Suemune, H. *Cur. Org. Chem.* **2003**, *7*, 353. (h) Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X.-M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806. (i) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667. (j) Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Inorg. Chim. Acta* **1997**, *263*, 1. (k) Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821. (l) Sakai, K. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 733. (m) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349. (n) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946. (o) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936. (p) James, B. R.; Young, C. G. *J. Organomet. Chem.* **1985**, *285*, 321. (q) Sakai, K.; Ishiguro, Y.; Funakoshi, K.; Ueno, K.; Suemune, H. *Tetrahedron Lett.* **1984**, 961. (r) James, B. R.; Young, C. G. *J. Chem. Soc., Chem. Commun.* **1983**, 1215. (s) Larock, R. C.; Oertle, K.; Potter, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 190. (t) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281.

(4) For selected recent examples of the Rh(I)-catalyzed alkene hydroacylation, see: (a) von Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, *134*, 15022. (b) Chaplin, A. B.; Hooper, J. F.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 4885. (c) Shibata, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2009**, *131*, 12552. (d) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. (e) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7618 and references therein.

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highly desired. In 1995, Eilbracht and co-workers reported the transition-metal-catalyzed olefin isomerization/allyl Claisen rearrangement/intramolecular hydroacylation cascade of di(allyl) ether **A** to produce substituted cyclopentanone **D** by using a neutral Rh(I)/dppe or Ru(II)/PPh_3 complex (Scheme 1).[5a] In this cascade reaction, the metal-catalyzed chemoselective olefin isomerization of the monosubstituted alkene moiety of **A** proceeds to give alkenyl ether **B**. Subsequent thermal allyl Claisen rearrangement affords 4-alkenal **C**. Metal-catalyzed intramolecular hydroacylation of **C** affords cyclopentanone **D**. However, harsh reaction conditions (140−220 °C under CO atmosphere) were required and the yields of **D** were not satisfactory.

On the other hand, our research group reported the cationic Rh(I)/bisphosphine complex-catalyzed olefin isomerization/propargyl Claisen rearrangement/carbonyl migration cascade of allyl propargyl ethers possessing the 1,1-disubstituted alkene moiety at 80 °C.[6] In this cascade reaction, the olefin isomerization of the 1,1-disubstituted alkene moiety proceeds smoothly. Thus, we designed the following Rh(I)-catalyzed cascade reaction using di(allyl) ether **1** possessing the 1,1- and 1,2-disubstituted alkene moieties (Scheme 2). If the cationic Rh(I)/bisphosphine complex catalyzes the chemoselective isomerization of the 1,1-disubstituted alkene moiety of **1**, the corresponding alkenyl ether **2** would be generated.[7] The subsequent thermal allyl Claisen rearrangement of **2**, which would be accelerated by the Lewis acidic cationic Rh(I) complex, would proceed at a lower temperature to afford 4-alkenal **3**.[8] The Rh(I)-catalyzed intramolecular hydroacylation of **3** would afford cyclopentanone **4**. Herein, we disclose our success of the above-mentioned cascade reaction by using a cationic Rh(I)/dppf catalyst under mild conditions.

Scheme 2

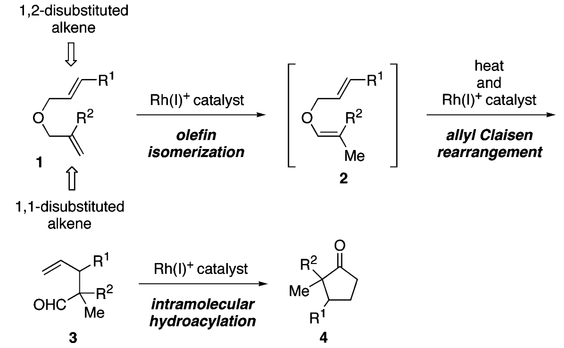
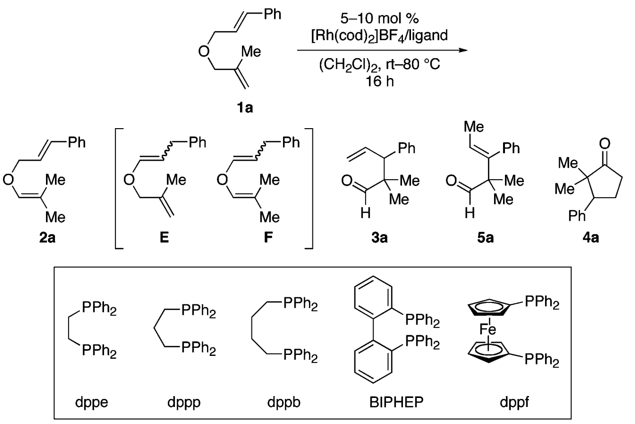


Table 1. Optimization of Reaction Conditions[a]



entry	ligand	temperature	catalyst (mol %)	yield (%)[b]			
				2a	3a	5a	4a
1[c]	dppe	80 °C	10	0	0	14	47
2	dppp	80 °C	10	0	0	3	60
3	dppb	80 °C	10	0	0	5	63
4	BIPHEP	80 °C	10	0	0	31	34
5	dppf	80 °C	10	0	0	<1	79
6	dppf	rt	10	74[d]	8[d]	0	0
7[e]	dppf	80 °C	5	0	0	1	83

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1a** (0.10 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used. [b] Isolated yield. [c] $[Rh(nbd)_2]BF_4$ was used. [d] NMR yield. [e] $[Rh(cod)_2]BF_4$ (0.015 mmol), ligand (0.015 mmol), **1a** (0.30 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used.

We first investigated the reaction of di(allyl) ether **1a** in the presence of a cationic Rh(I)/dppe complex (10 mol %) at 80 °C (Table 1, entry 1). Pleasingly, the desired cyclopentanone **4a** was obtained in moderate yield, while 3-alkenal **5a** was generated as a byproduct. Screening of bisphosphine ligands (entries 1−5) revealed that the use of dppf afforded **4a** in the highest yield without the formation of **5a** (entry 5). At rt, the chemoselective isomerization of the 1,1-disubstituted alkene moiety of **1a** proceeded to give the corresponding alkenyl ether **2a** without forming dienes **E** and **F**, while 4-alkenal **3a** was generated in low yield and cyclopentanone **4a** was not generated at all (entry 6). Finally, the catalyst loading could be reduced to 5 mol % without erosion of the product yield and ee value (entry 7).

With the optimized reaction conditions in hand, the scope of this cascade reaction was examined (Table 2).[9] With respect to substituents at the 1,2-disubstituted alkene moiety (R^1), di(allyl) ethers **1a**−**h** possessing electronically

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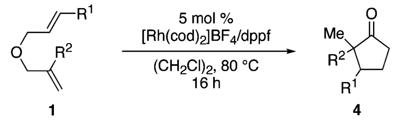
(5) (a) Eilbracht, P.; Gersmeir, A.; Lennartz, D.; Huber, T. *Synthesis* **1995**, 330. For examples of the transition-metal-catalyzed allyl Claisen rearrangement/intramolecular hydroacylation cascade, see: (b) Sattelkau, T.; Eilbracht, P. *Tetrahedron Lett.* **1998**, *39*, 1905. (c) Dygutsch, D. P.; Eilbracht, P. *Tetrahedron* **1996**, *52*, 5461.

(6) Tanaka, K.; Okazaki, E.; Shibata, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10822.

(7) For a recent review of the transition-metal-catalyzed olefin isomerization, see: Tanaka, K. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Ojima, I., Eds.; Elsevier: Oxford, 2007; Vol. 10, p 71.

(8) For recent examples of the sequential olefin isomerization/allyl Claisen rearrangement of di(allyl) ethers, see: (a) McLaughlin, M. G.; Cook, M. J. *J. Org. Chem.* **2012**, *77*, 2058. (b) Geherty, M. E.; Dura, R. D.; Nelson, S. G. *J. Am. Chem. Soc.* **2010**, *132*, 11875. (c) Kerrigan, N. J.; Bungard, C. J.; Nelson, S. G. *Tetrahedron* **2008**, *64*, 6863. (d) Wang, K.; Bungard, C. J.; Nelson, S. G. *Org. Lett.* **2007**, *9*, 2325. (e) Stevens, B. D.; Bungard, C. J.; Nelson, S. G. *J. Org. Chem.* **2006**, *71*, 6397. (f) Trost, B. M.; Zhang, T. *Org. Lett.* **2006**, *8*, 6007. (g) Nelson, S. G.; Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4232. (h) Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, 9735. (i) Schmidt, B. *Synlett* **2004**, 1541. (j) Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000. (k) Le Notre, J.; Brissieux, L.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **2002**, 1772. (l) Ben Ammar, H.; Le Notre, J.; Salem, M.; Kaddachi, M. T.; Dixneuf, P. H. *J. Organomet. Chem.* **2002**, *662*, 63 and references therein.

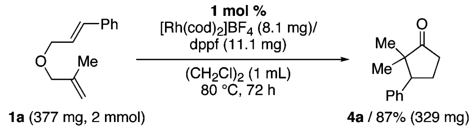
Table 2. Scope of 1,6-Dienes[a]



entry	1	R^1	R^2	time (h)	4	yield (%)[b]	dr
1	**1a**	Ph	Me	16	**4a**	83	–
2	**1b**	4-MeOC$_6$H$_4$	Me	16	**4b**	69	–
3	**1c**	4-F$_3$CC$_6$H$_4$	Me	16	**4c**	70	–
4	**1d**	4-BrC$_6$H$_4$	Me	16	**4d**	60	–
5	**1e**	3-ClC$_6$H$_4$	Me	16	**4e**	78	–
6	**1f**	2-naphthyl	Me	16	**4f**	87	–
7	**1g**	2-MeOC$_6$H$_4$	Me	16	**4g**	60	–
8	**1h**	2-MeC$_6$H$_4$	Me	16	**4h**	65	–
9	**1i**	2-furyl	Me	16	**4i**	58	–
10	**1j**	*n*-Bu	Ph	16	**4j**	30	60:40
11	**1k**	Ph	Ph	40	**4k**	67	66:34
12[c]	**1l**	Ph	H	72	**4l**	37	97:3

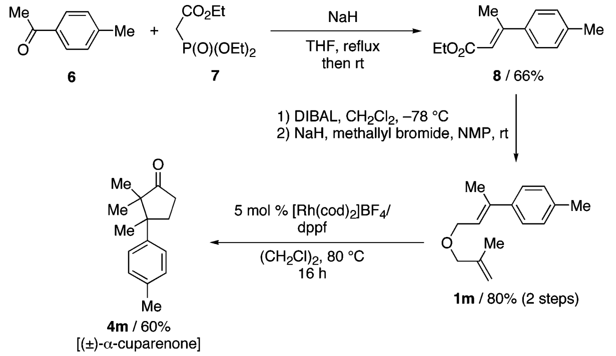
[a] Reactions were conducted using [Rh(cod)$_2$]BF$_4$ (0.015 mmol), dppf (0.015 mmol), **1a**–**l** (0.30 mmol), and (CH$_2$Cl)$_2$ (1.5 mL) at 80 °C for 16 h. [b] Isolated yield. [c] MS4A (100 wt % of **1l**) was used.

Scheme 3

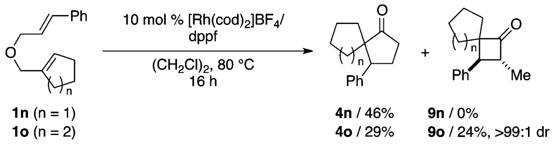


and sterically diverse aryl groups could be employed for this process (entries 1–8). Heteroaryl-substituted di(allyl) ether **1i** could also be employed (entry 9). Unfortunately, the reaction of alkyl-substituted di(allyl) ether **1j** afforded the corresponding cyclopentanone **4j** in low yield due to the formation of a mixture of undesired olefin isomerization products (entry 10). With respect to substituents at the 1,1-disubstituted alkene moiety (R^2), phenyl-substituted di(allyl) ether **1k** afforded the corresponding cyclopentanone **4k** in good yield (entry 11). Unfortunately, the diastereoselectivities of **4j** and **4k** were low (entries 11 and 10). The reaction of monosubstituted 1,6-diene **1l** was examined, but a partial hydrolysis of the allyl ether moiety was observed. The addition of MS4A suppressed the undesired hydrolysis to give the corresponding cyclopentanone **4l** in 37% yield with high diastereoselectivity (entry 12).

Scheme 4



Scheme 5



In general, rhodium-catalyzed hydroacylation reactions require high catalyst loadings due to the formation of catalytically inactive rhodium carbonyl complexes[3o] and the presence of small amounts of carboxylic acid impurities. Especially, sterically demanding α,α-disubstituted 4-alkenals require a higher catalyst loading. Pleasingly, the large-scale reaction of **1a** proceeded in the presence of 1 mol % of the cationic Rh(I)/dppf complex to give **4a** in high yield, presumably as a result of the gradual in situ formation of 4-alkenal **3a** from **1a** under an inert atmosphere (Scheme 3).

Importantly, the present cascade process can also employ di(allyl) ethers possessing the trisubstituted alkene moiety. The reaction of 3-(*p*-tolyl)but-2-en-1-ol derivative **1m**, which was prepared from 1-(*p*-tolyl)ethanone (**6**) and ethyl 2-(diethoxyphosphoryl)acetate (**7**) via ester **8**, also proceeded to give cyclopentanone **4m** [(±)-α-cuparenone[10]] in good yield (Scheme 4).

The reaction of cyclopentadiene derivative **1n** proceeded to give spirocyclic cyclopentanone **4n** in

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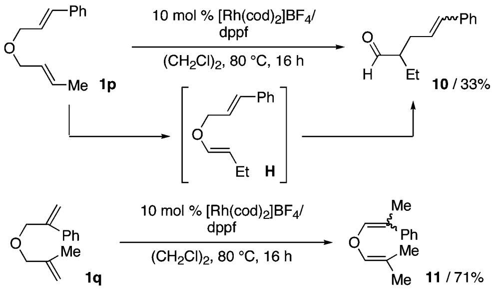
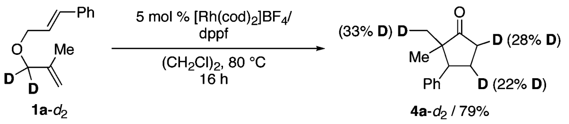
(9) The reaction of di(allyl) ether **1p** possessing two 1,2-disubstituted alkene moieties afforded 4-alkenal **10** presumably through the chemoselective isomerization of the methyl-substituted alkene moiety to form alkenyl ether **H** followed by a 1,3-allylic rearrangement. The reaction of di(allyl) ether **1q** possessing two 1,1-disubstituted alkene moieties afforded di(alkenyl) ether **11**.

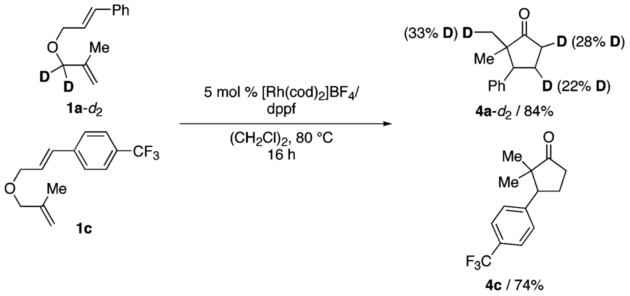


(10) For examples of the synthesis of α-cuparenone, see: (a) Nishii, T.; Miyamae, F.; Yoshizuka, M.; Kaku, H.; Horikawa, M.; Inai, M.; Tsunoda, T. *Tetrahedron: Asymmetry* **2012**, *23*, 739. (b) Gottumukkala, A. L.; Matcha, K.; Lutz, M.; de Vries, J. G.; Minnaard, A. J. *Chem.—Eur. J.* **2012**, *18*, 6907. (c) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716. (d) Shivakumar, I.; Salunke, G. B.; Kumar, S. *Synth. Commun.* **2011**, *41*, 1952 and references therein.

Scheme 6



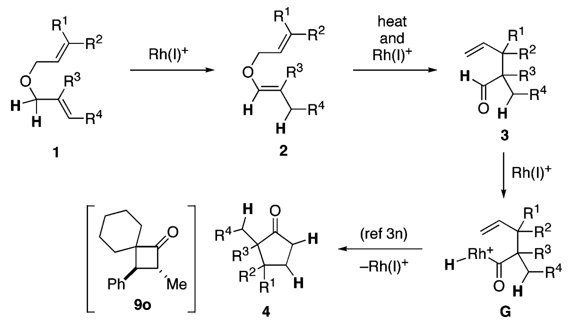
Scheme 7



moderate yield (Scheme 5).[11] Interestingly, that of cyclohexadiene derivative **1o** afforded spirocyclic cyclobutanone **9o** with perfect diastereoselectivity along with spirocyclic cyclopentanone **4o**, although the product yields were low (Scheme 5). It is worthy of note that this is the first example of the cyclobutanone synthesis via the metal-catalyzed intramolecular hydroacylation of the 4-alkenal.[12]

In order to gain mechanistic insight into this reaction, the reaction of a deuterated 1,6-diene in the presence of the cationic Rh(I)/dppf complex was investigated. Deuterium from di(allyl) ether **1a**-d_2 was incorporated into three different positions of cyclopentanone **4a**-d_2 as shown in Scheme 6.

Scheme 8



Furthermore, we have established that the present cascade reaction is an intramolecular process. Treatment of a 1:1 mixture of deuterated di(allyl) ether **1a**-d_2 and nondeuterated di(allyl) ether **1c** with the cationic Rh(I)/dppf complex furnished deuterated **4a**-d_2 and nondeuterated **4c**, and thus no deuterium crossover was observed (Scheme 7).

Scheme 8 depicts a plausible mechanism for the present cascade reaction. The rhodium-catalyzed chemoselective isomerization of the 1,1-disubstituted alkene moiety of di(allyl) ether **1** proceeds to afford alkenyl ether **2** through the intramolecular hydrogen migration.[13] The thermal allyl Claisen rearrangement of **2** affords 4-alkenal **3**.[14,15] An oxidative addition of the aldehyde C−H bond of **3** to rhodium affords rhodium acyl hydride **G**. Endo addition of the rhodium hydride to the alkene followed by reductive elimination furnishes cyclopentanone **4** and regenerates the Rh(I) catalyst. On the other hand, in the reaction of **1o**, exo addition followed by reductive elimination also proceeds to give cyclobutanone **9o**. Deuterium scrambling at the α- and β-positions of cyclopentanone **4a**-d_2 was already explained by a reversible rhodium hydride addition/β-hydride elimination sequence.[3n]

In conclusion, it has been established that a cationic Rh(I)/dppf complex catalyzes the olefin isomerization/allyl Claisen rearrangement/intramolecular hydroacylation cascade of di(allyl) ethers to produce substituted cyclopentanones in good yields under mild conditions. Future work will focus on further utilization of the cationic Rh(I) catalysts for the development of novel cascade reactions.

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Supporting Information Available. Experimental procedures and compound characterization data. 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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[11] For examples of the spirocyclic cyclopentanone synthesis via the transition-metal-catalyzed intramolecular hydroacylation of 4-alkenals, see: (a) Bjoernstad, V.; Undheim, K. *Synthesis* **2008**, 962. (b) Tanaka, M.; Takahashi, M.; Sakamoto, E.; Imai, M.; Matsui, A.; Fujio, M.; Funakoshi, K.; Sakai, K.; Suemune, H. *Tetrahedron* **2001**, *57*, 1197. (c) See also refs 3s, 5a, and 5b.

[12] The cyclobutanone synthesis via the transition-metal-catalyzed intramolecular hydroacylation of 4-alkynals was reported. See: Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078.

[13] A mechanism via π-allyl intermediates has been proposed for the cationic Rh(I)/bisphosphine complex-catalyzed isomerization of allyl ethers. See: (a) Fatig, T.; Soulié, J.; Lallemand, J.-Y.; Mercier, F.; Mathey, F. *Tetrahedron* **2000**, *56*, 101. (b) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287.

[14] For reviews, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

[15] The reaction of **1a** in the presence of a cationic Rh(I)/(*R*)-BINAP complex (10 mol %) at rt afforded **3a** with 14% ee. This result suggests that the cationic Rh(I) complex might partly contribute to the allyl Claisen rearrangement step.