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Multiple Rhodium-Catalyzed Cleavages of Single C−C bonds

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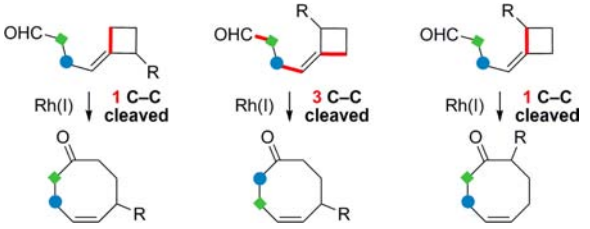
ABSTRACT



The Rh(I)-catalyzed intramolecular hydroacylation of *cis* and *trans* asymmetrically substituted alkylidenecyclobutanes proceeds according to three mechanistic pathways. As shown by deuterium-labeling experiments, the mechanism accounting for the rearrangement of the *cis* isomers includes the cleavage of three carbon−carbon bonds and a remarkable transannular 3-exo-trig carbometalation.

A better mechanistic understanding of the factors controlling the regioselectivity of the transition-metal-catalyzed activation of single carbon−carbon (C−C) bonds is crucial in view of future applications of this strategy in synthesis.[1] While both three- and four-membered cycloalkanes are particularly apt to undergo C−C bond cleavage in the presence of transition metals, the regioselectivity of the β-C elimination of transient cyclobutylcarbinyl metals has rarely been studied.[2] Recently, we reported that treatment of alkylidenecyclobutanes (ACBs) **1** and **2** (R = -$(CH_2)_2$-C_6H_3-3,4-Cl_2) with a rhodium catalyst[3] leads to the formation of eight-membered ring ketone **3** as a single regioisomer (Scheme 1).[4,5] The rearrangement of **1** into **3** could be explained by the following sequential steps: formation of Rh(III)-acyl-hydrido intermediate **A**,[6] *syn* coplanar migratory insertion toward cyclobutylcarbinyl **B**,[7] bond rotation toward **C**, *syn* coplanar β-carbon elimination to give **D**, and finally reductive elimination (Scheme 2). Our assumption that the opening of the cyclobutane ring in **C** is a *syn* coplanar process is based on the numerous examples of *syn* coplanar transition-metal-catalyzed β-C elimination of cyclopropane derivatives.[8] Applying the same rationale to ACB **2** would have led us to predict the formation, not of **3**, but its regioisomer, via β-carbon elimination from **F**, rotamer of **E** (Scheme 2). *Hence, how can we explain the regioconvergent rearrangement of ACBs **1** and **2**?* Importantly, while the conversion of **1** was complete, the conversion of **2** was more

(1) (a) Nečas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835. (d) Murakami, M.; Matsuda, T. *Chem. Commun* **2011**, *47*, 1100. (e) Aïssa, C. *Synthesis* **2011**, 3389. (f) Seiser, T.; Saget, T.; Tran, D. C.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740.

(2) (a) Catellani, M.; Chiusoli, G. P.; Dradi, E.; Salerno, G. *J. Organomet. Chem.* **1979**, *177*, C29. (b) Bunel, E.; Burger, B. J.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 976. (c) Jun, C.-H. *Organometallics* **1996**, *15*, 895. (d) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307. (e) Hustad, P. D.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 11578. (f) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.

(3) The active rhodium catalyst was prepared by hydrogenation of [Rh(nbd)(BINAP)]BF_4 in acetone (nbd = norbornadiene, BINAP = 2,2′-bis(disphenylphosphino-1,1′-binaphthyl)); see: Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946.

(4) Crépin, D.; Dawick, J.; Aïssa, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 620.

(5) For examples of eight-membered ring ketones formed by rhodium-catalyzed intramolecular hydroacylation, see: (a) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610. (b) Bendorf, H. D.; Collela, C. M.; Dixon, E. C.; Marchetti, M.; Matunokis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031. (c) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. (d) Oonishi, Y.; Hosotani, A.; Sato, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1038. (e) Oonishi, Y.; Hosotani, A.; Sato, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 11548.

(6) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 640. (b) Fu, G. C. *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005 p 85. (c) Garralda, M. A. *Dalton Trans.* **2009**, 3635. (d) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

(7) Campbell, R. E., Jr.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824.

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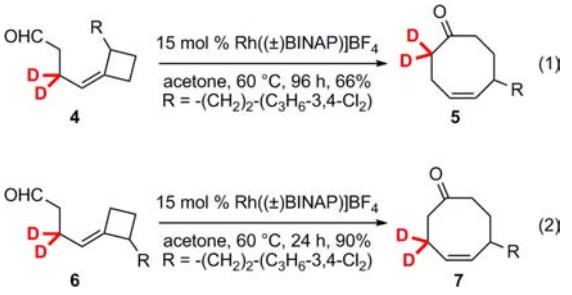
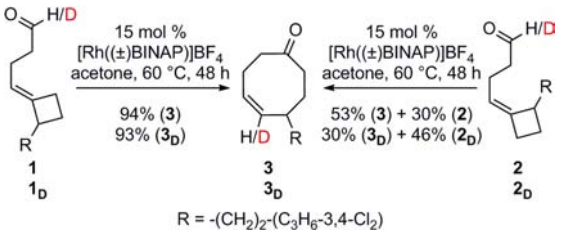
sluggish and this substrate was recovered in 30% yield without isomerization of the *cis* trisubstituted olefin. These results suggested that the observed regioconvergent ring cleavage should be accounted for by a more refined mechanistic rationale.

We initiated our investigations by examining the reactivity of deuterium-labeled substrates displaying the same alkyl side chain on the cyclobutane ring (R = -$(CH_2)_2$-C_6H_3-3,4-Cl_2). We observed a quantitative transfer of the deuterium atom from its initial position in aldehydes $\mathbf{1_D}$ and $\mathbf{2_D}$ (Scheme 1) to the same carbon atom of the olefin in cyclooctenone $\mathbf{3_D}$, although the reaction of $\mathbf{2_D}$ was much slower and led to a mixture of decarbonylation products alongside $\mathbf{3_D}$ and recovered $\mathbf{2_D}$.[9] To our surprise, we also observed that the methylene moieties in α and β positions of the aldehyde group in **4** quantitatively exchanged their positions in the rhodium-catalyzed rearrangement delivering **5** after full conversion (eq 1). Conversely, we verified that the rearrangement of aldehyde **6** into ketone **7** occurred under the same reaction conditions without concomitant migration of the methylene groups (eq 2). The position of the deuterated methylene was ascertained in each case by comparison of the ^{13}C NMR spectra of compounds **3**, **5**, and **7**. These results suggest that *trans* and *cis* ACBs **1** and **2** underwent a regioconvergent intramolecular hydroacylation toward **3** through specific and very distinct mechanistic pathways, in which the less sterically congested C−C bond of the cyclobutane ring was cleaved.

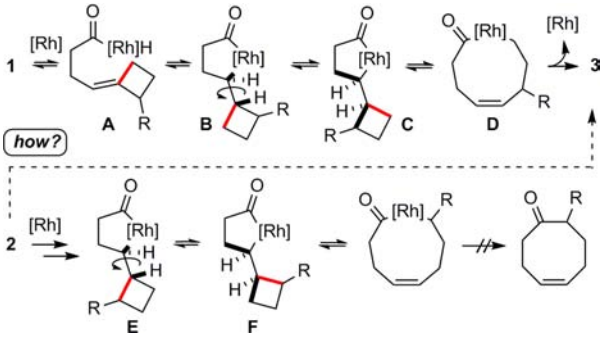


The results obtained with $\mathbf{1_D}$ and **6** can be explained by the sequence of reactions involving intermediates **A**−**D**, already depicted in Scheme 2. In contrast, the outcomes of

Scheme 1. Regioconvergent Ring Opening of ACBs



Scheme 2. β-C Elimination of Cyclobutylcarbinyl Metal Intermediates in the Regioconvergent Ring Opening of ACBs



the deuterium-labeling experiments conducted with $\mathbf{2_D}$ and **4** are in better agreement with the following mechanism (Scheme 3). As discussed previously and depicted in Scheme 2, insertion of the catalyst into the C−H bond of the aldehyde group of *cis* ACB **2** followed by *syn* coplanar hydrometalation would give **E**. Bond rotation toward **G** instead of **F** would align the carbon−rhodium bond and the less sterically hindered C−C bond of the cyclobutane ring for a *syn* coplanar β-C elimination providing *trans* nonarhodacycle **H** (Scheme 3). Then, carbon monoxide extrusion and reinsertion would lead to **I** and then **J**. Examples of such extrusion/reinsertion equilibrium involving smaller rhodacycles are well-known.[10,11] We propose that **J** would then undergo a transannular *syn* coplanar 3-exo-trig carborhodation

(8) Co: (a) Atkins, M.; Golding, B. T.; Bury, A.; Johnson, M. D.; Sellars, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3630. Pd: (b) Owczarzyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. (c) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583. (d) Feutren, S.; McAlonan, H.; Montgomery, D.; Stevenson, P. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1129. (e) Bennasar, M. L.; Zulaica, E.; Solé, D.; Roca, T.; García-Díaz, D.; Alonso, S. *J. Org. Chem.* **2009**, *74*, 8359. Ni: (f) Pinke, P. A.; Stauffer, R. G.; Miller, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4229. (g) Miller, R. G.; Pinke, P. A.; Stauffer, R. D.; Golden, H. J.; Baker, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 4211. (h) Pinke, D. A.; Miller, R. G. J. *J. Am. Chem. Soc.* **1974**, *96*, 4221. Ru: (i) Trost, B. M.; Toste, F. D.; Shen, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 2379. (j) Trost, B. M.; Shen, H. C. *Org. Lett.* **2000**, *2*, 2523. (k) Trost, B. M.; Shen, H. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1313. (l) Trost, B. M.; Shen, H. C.; Horne, D. N.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem.—Eur. J.* **2005**, *11*, 2577. Rh: (m) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442. (n) Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089. (o) Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* **2007**, *129*, 14836.

(9) k_H/k_D = 1.10−1.25 was measured in parallel experiments conducted with **1** and $\mathbf{1_D}$. Attempts of similar measurements with **2** and $\mathbf{2_D}$ led to inconclusive results due to the decomposition of the catalyst by partial decarbonylation of the substrate.

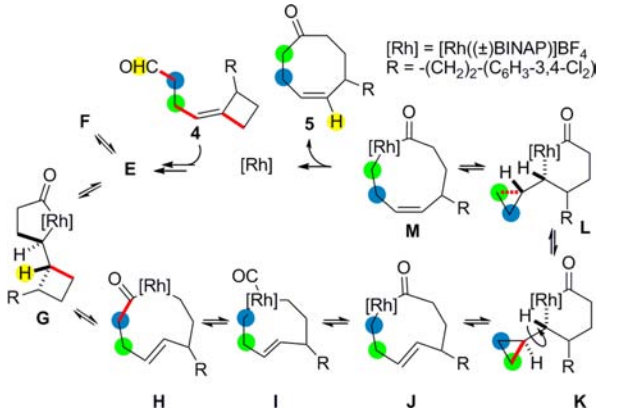
(10) (a) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936. (b) Barnhart, R. W.; Bosnich, B. *Organometallics* **1995**, *14*, 4343. (c) Tanaka, K.; Fu, G. C. *Chem. Commun.* **2002**, 684. (d) Bjørnstad, V.; Undheim, K. *Synthesis* **2008**, 962. (e) Tanaka, K.; Okazaki, E.; Shibata, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10822.

(11) The temporary increase of strain energy during the formation of **I** might be compensated by intramolecular coordination to the olefin; see: Cedeno, D. L.; Sniatynsky, R. *Organometallics* **2005**, *24*, 3882 and pertinent references cited therein.

(12) (a) Zhang, Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (b) Grigg, R.; Dorrity, M. J.; Malone, J. F. *Tetrahedron Lett.* **1990**, *31*, 1343. (c) Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855. (d) Meyer, F. E.; Parsons, P. J.; de Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487. (e) Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623. (f) Oh, C. H.; Kang, J. H.; Rhim, C. Y.; Kim, J. H. *Chem. Lett.* **1998**, 375. (g) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (h) Grigg, R.; Sakee, U.; Sridahran, V.; Sukirthalingam, S.; Thangavelauthum, R. *Tetrahedron* **2006**, *62*, 9523.

toward **K**. Examples of 3-exo-trig carbometalation reactions of transition metal species are abundant in the literature,[8a−h,12] and several involve rhodium species.[13] However, the rearrangement of **J** into **K** is the first example of the transannular variant of a 3-exo-trig carbometalation. Equilibration between rotamers **K** and **L** would explain how, after *syn* coplanar β-C elimination from **L** to *cis* nonarhodacycle **M** and reductive elimination,[14] the methylene groups in α and β positions of the aldehyde group in **4** have exchanged their position in this otherwise regioconvergent rearrangement.

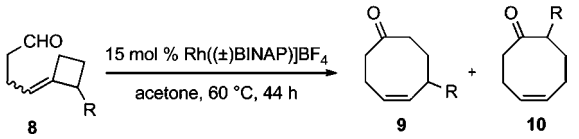
Scheme 3. Mechanistic Rationale Accounting for the Results of the Deuterium-Labeling Experiments with *cis* ACBs



Hence, only one single C−C bond is cleaved in the intramolecular hydroacylation of *trans* ACBs (Scheme 2, **A**−**D**), whereas *three single C−C bonds are cleaved* in the rearrangement of their *cis* isomers (color-coded in red, Scheme 3, **G**−**M**). In both rearrangements, the minimization of steric interactions between the substituent located on the cyclobutane ring and the ligand sphere in intermediates **C** and **G** would dictate the regioselectivity of the β-C elimination step.

Having established a plausible mechanism for the regioconvergent ring opening of substituted ACBs in intramolecular hydroacylation, we examined the generality of this remarkable transformation (Table 1). As it was the case for **1** and **2** (Scheme 1), we observed that the treatment of mixtures of *cis* and *trans* isomers of alkyl-substituted ACBs **8a** and **8b** led to the formation of a single regioisomer **9a** and **9b**, respectively (Table 1, entries 1 and 2). Moreover, all *trans* isomers of aryl-substituted **8c**−**8g** underwent the reaction according to intermediates **A**−**D** (Scheme 2) and afforded **9c**−**9g** in excellent yields, without noticeable influence of the electronic or steric nature of the substituents located on the cyclobutane ring (Table 1, entries 3, 5, 7, 9, and 11). Conversely, *cis* **8c**−**8g** reacted more slowly than their *trans* isomers and the starting material was

Table 1. Regioselectivity of β-C Elimination in the Rh-Catalyzed Hydroacylation of Substituted ACBs



entry	R	**8** (*E*/*Z*)	yield[a]	**9**/**10**[b]
1	nC_7H_{15}	**8a** (1.5:1)	61%	>20:1
2	-$(CH_2)_3$NTs(nPr)	**8b** (1.5:1)	69%	>20:1
3	Ph	**8c** (3:1)	92%	4.2:1
4	Ph	**8c** (<1:20)	51%[c]	1:2.3
5	C_6H_4-2-OBn	**8d** (19:1)	93%	>20:1
6	C_6H_4-2-OBn	**8d** (<1:20)	81%[d]	1:1.3[e]
7	C_6H_4-4-OBn	**8e** (>20:1)	90%	>20:1
8	C_6H_4-4-OBn	**8e** (<1:20)	60%[f]	<1:20
9	C_6H_3-2,4-Cl_2	**8f** (>20:1)	93%	>20:1
10	C_6H_3-2,4-Cl_2	**8f** (<1:20)	24%[g]	12:1
11	C_6H_4-4-CO_2Me	**8g** (1:3.3)	67%[h]	1:1.3[e]

[a] Combined isolated yield of **9** and **10**. [b] Otherwise noted, this ratio was determined by ^{1}H NMR of the crude material. [c] **8c** (*Z* only) was recovered in 13% yield. [d] **8d** (*Z* only) was recovered in 8% yield. [e] Ratio determined from isolated yields of **9** and **10**. [f] Isolated yield of **10e** only; **8e** (*Z* only) was recovered in 21% yield. [g] Isolated yield of **9f** only; **8f** (*Z* only) was recovered in 39% yield. [h] **8g** (*E*/*Z* = 1:6) was recovered in 5% yield after 90 h. Ts = 4-tolylsulfonyl.

recovered without isomerization of the trisubstituted olefin, in up to 39% yield in the case of the least reactive substrate **8f** (entry 10). Moreover, the regioselectivity of the reactions of *cis* **8c**−**8g** depended on the nature of the substituent (entries 4, 6, 8, 10, and 11).

These results enabled us to further refine the mechanistic rationale depicted in Schemes 2 and 3. Hence, the *cis* isomers of aryl-substituted ACBs can undergo the reaction according to two competing catalytic cycles, where the equilibrium between intermediates **E**−**G** is pivotal (Scheme 4). We assume that minimization of steric interactions favors β-C elimination through intermediates **G** and **H**, leading eventually to **9**. However, steric congestion can be compensated, and even overridden, by electronic stabilization of the organorhodium intermediates, which would favor the β-C elimination of intermediate **F** toward secondary nonarhodacycle **N**. From the results listed in Table 1, the degree of electronic influence of substituents R on the formation of regioisomer **10** from *cis* **8c**−**8g** follows the order C_6H_4-4-OBn

(13) (a) Nishihara, Y.; Yoda, C.; Osakada, K. *Organometallics* **2001**, *20*, 2124. (b) Nishihara, Y.; Yoda, C.; Itazaki, M.; Osakada, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1469. (c) Miura, T.; Sasaki, T.; Harumashi, T.; Murakami, M. *J. Am. Chem. Soc.* **2006**, *128*, 2516.

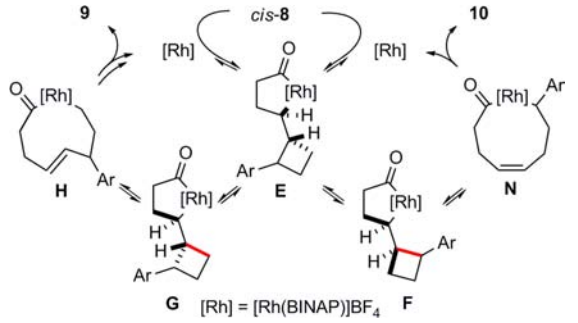
(14) See ref 5a for an example of a similar rearrangement of hexarhodacycle intermediates leading to cyclooctenones.

(15) It was not possible to obtain samples of pure *cis* or *trans* **8g**. However, on the basis of the results obtained with *trans* **8c**−**8f**, it is reasonable to assume that pure *trans* **8g** would give up to 90% of **9g**, which would equate to a 1:4.2 ratio of compounds **9g** and **10g** produced by the *cis* isomer of **8g** in entry 11.

(16) For examples of such stabilization, see: (a) Mak, K. W.; Chan, K. S. *J. Am. Chem. Soc.* **1998**, *120*, 9686. (b) Mak, K. W.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Chem. Soc., Dalton Trans.* **1999**, 3333. (c) Settambolo, R.; Pucci, S.; Bertozzi, S.; Lazzaroni, R. *J. Organomet. Chem.* **1995**, *489*, C50. (d) Settambolo, R.; Caiazzo, A.; Lazzaroni, R. *J. Organomet. Chem.* **1996**, *506*, 337.

(17) In contrast, a phenyl ring is not able to direct in a similar fashion the rhodium-catalyzed ring opening of 4-cyclopropyl-2-cyclobutenones, see: Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 4895.

Scheme 4. Mechanistic Rationale for the Regioselective Ring Opening of *cis* Aryl-Substituted ACBs



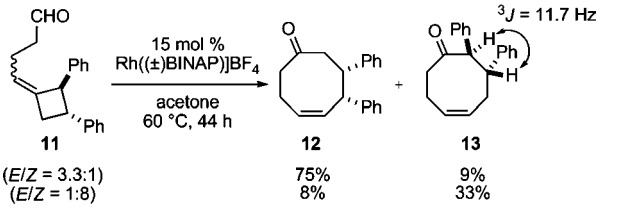
$\gg C_6H_4$-4-CO_2Me > Ph > C_6H_4-2-OBn $\gg C_6H_3$-2,4-Cl_2.[15] It is likely that the polarized carbon−rhodium bond ($C^{\delta-}-Rh^{\delta+}$) of secondary rhodium **N** is better stabilized by an electron-withdrawing substituent such as phenyl than by an alkyl chain.[16,17] This stabilization would be accentuated in the reaction of *cis* **8g**. Although such stabilization is not possible with an electron-rich *para*-benzyloxyphenyl substituent, the reaction of *cis* **8e** gave only **10e**. In this case, we propose that an η^2 interaction between the aryl substituent and the metal would favor the ring enlargement from **F** to **N**. Results of theoretical studies have suggested that a similar interaction favors the cleavage of the most sterically hindered C−C bond in the samarium-promoted ring opening of phenyl-substituted methylenecyclopropane, both kinetically and thermodynamically.[18] A similar explanation has been proposed for the organolanthanide-catalyzed regioselective hydroamination of the same reagent, which also proceeds by cleavage of the most sterically hindered C−C bond.[19] In the case of *cis* **8d** and **8f**, electronic stabilization is less relevant because of the increased steric hindrance.

(18) Tobisch, S. *Chem.—Eur. J.* **2005**, *11*, 3113.

(19) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

(20) ACB **11** was prepared from *anti* 2,3-bisphenylcyclobutanone, itself obtained according to a slight modification of a known procedure reported by Ghosez and coworkers in Falmagne, V. J-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem.* **1981**, *93*, 926. See Supporting Information.

Scheme 5. Retention of Configuration in C−C Cleavage and Reductive Elimination



The rearrangement of a 3.3:1 mixture of *trans* and *cis* isomers of racemic **11**[20] led to the formation of **12** and **13** in 75% and 9% yield, respectively (Scheme 5). Although the rearrangement of a mixture enriched in the *cis* olefin (E/Z = 1:8) was more sluggish, it led predominantly to **13** in 33% yield, accompanied by 8% of **12** and 33% of recovered starting material (E/Z < 1:20) (Scheme 5). Importantly, as inferred from a large pseudodiaxal coupling constant, compound **13** was obtained only as an *anti* diastereomer from *cis* olefin **11**, indicating that β-C elimination of intermediate **F** and subsequent reductive elimination of intermediate **O** (Scheme 4) occurred with retention of configuration.

In conclusion, we have demonstrated that the rhodium-catalyzed intramolecular hydroacylation of *cis* and *trans* asymmetrically substituted ACBs proceeds according to three catalytic pathways. Overall, we anticipate that our results will help in understanding the regioselectivity of other metal-catalyzed C−C bond cleavage processes.

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Supporting Information Available. Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.