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Rhodium(I)-Catalyzed Cycloisomerization of 1,6-Enynes to Bicyclo[4.1.0]heptenes

Sun Young Kim and Young Keun Chung*

Intelligent Textile System Research Center, and Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea

ykchung@snu.ac.kr

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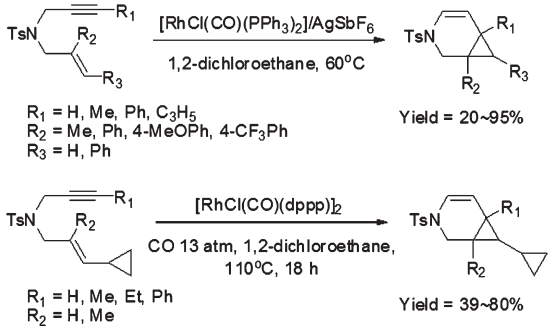

Efficient rhodium(I)-catalyzed cyclopropanation reactions of nitrogen-tethered 1,6-enynes to azabicyclo[4.1.0]heptenes are reported. Moreover, rhodium(I)-catalyzed tandem cycloisomerization and carbonylative [3+3+1] cycloaddition reactions of a cyclopropylenyne have been observed.

The transition metal-catalyzed cycloisomerization of enynes is a powerful method for accessing cyclic structures from acyclic precursors of substantially less molecular complexity.[1] A variety of transition metal compounds have been used as catalysts.[2] Also recently, main group Lewis acids have been used as catalysts.[3] Through the cycloisomerization reaction of enynes, various skeletal frames can be formed. In particular, the selective synthesis of cyclopropane derivatives[4] is attracting a lot of attention, presumably due to their widespread occurrence as a subunit in natural products.[5] In other respects, they can be considered as three-carbon donors in the synthesis of larger rings.[6] Especially, we recently reported[7] on a carbonylative [3+3+1] cycloaddition reaction that uses two cyclopropyl groups in a molecule as two three-carbon donors in the formation of large rings.

Until now, several rhodium-catalyzed cycloisomerization reactions have been disclosed.[7,8] Dechy-Cabaret et al. reported[8e] on the Rh(I)-catalyzed cyclosiomerization of two oxygen-tethered enynes derived from terpenoids. Recently, Chatani reported[8c,9] the $Rh_2(O_2CCF_3)_4$-catalyzed cycloisomerization of enynes to cyclopropanated products. However, reports on the Rh(I)-catalyzed cycloisomerization of enynes to cyclopropanated products, namely bicyclo[4.1.0]heptenes, are still scarce. And the substrate scope is limited and the data are fragmentary. To complement the previous studies, we focused our efforts to find a Rh(I)-catalyzed cycloisomerization of nitrogen-tethered enynes leading to cyclopropanated products. In particular, in relation to the previous research,[7] we also had interest in the Rh(I)-catalyzed tandem cycloisomerization and carbonylative [3+3+1] cycloaddition reactions of cyclopropylenyne (Scheme 1). We herein report on the Rh(I)-catalyzed transformation of N-tethered enynes to 3-azabicyclo[4.1.0]hept-4-enes.

Our initial study used enyne **1a** as a model substrate and $[RhCl(CO)(PPh_3)_2]/AgSbF_6$ as a catalyst. The catalytic system $[RhCl(CO)(PPh_3)_2]/AgSbF_6$ was previously used[10] in

(1) For recent reviews, see: (a) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397. (d) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

(2) For Pt and Au, see: (a) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (b) Barluenga, J.; Dieguez, A.; Fernandez, A.; Rodiriguez, F.; Fananas, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091. (c) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. For Pd, see: (d) Bray, K. L.; Llyod-Jones, G. C.; Muñoz, M. P.; Saltford, P. A.; Tan, E. H. P.; Tyler-Mahon, A. R.; Worthington, P. A. *Chem.—Eur. J.* **2006**, *12*, 8650. For Ru and Rh, see: (e) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. (f) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. (g) Lei, A. W.; Waldkirch, J. P.; He, M. S.; Zhang, X. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. For Co, see: (h) Han, S. D.; Anderson, D. R.; Bond, A. D.; Chu, H. V.; Disch, R. L.; Holmes, J. M.; Schulman, J. M.; Teat, S. J.; Vollhardt, K. P. C.; Whitener, G. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 3227. (i) Genin, E.; Antoniotti, S.; Michelet, V.; Genet, J. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949.

(3) (a) Kim, S. M.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2006**, *8*, 5425. (b) Simmons, E. M.; Sapong, R. *Org. Lett.* **2006**, *8*, 2883. (c) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294. (d) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414.

(4) (a) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jimnez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echvarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1694.

(5) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(6) (a) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446. (b) Zhao, L.; de Meijere, A. *Adv. Synth. Catal.* **2006**, *348*, 2484. (c) Takasu, K.; Nagao, S.; Ihara, M. *Adv. Synth. Catal.* **2006**, *348*, 2376. (d) Kurahashi, T.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881. (e) Kamitani, A.; Chatani, N.; Morimoto, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 9230. (f) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4.

(7) Kim, S. Y.; Lee, S. I.; Choi, S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4914.

(8) (a) Oonishi, Y.; Saito, A.; Mori, M.; Sato, Y. *Synthesis* **2009**, 969. (b) Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6293. (c) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371. (d) Brummond, K. M.; Yan, B. L. *Synlett*. **2008**, 2302. (e) Costes, P.; Weckesser, J.; Dechy-Cabaret, O.; Urrutigoïty, M.; Kalck, P. *Appl. Organomet. Chem.* **2008**, *22*, 211. (f) Liu, F.; Liu, Q.; He, M.; Zhang, X.; Lei, A. *Org. Biomol. Chem.* **2007**, *5*, 3531. (g) DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799. (h) Tanaka, K.; Otake, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 3953. (i) Kim, H.; Lee, C. B. *J. Am. Chem. Soc.* **2006**, *128*, 6336. (j) Kim, H.; Lee, C. B. *J. Am. Chem. Soc.* **2005**, *127*, 10180. (k) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048. (l) Mikami, K.; Yusa, Y.; Hatano, M.; Wakabayashi, K.; Aikawa, K. *Chem. Commun.* **2004**, 98. (m) Tong, X. F.; Zhang, Z. G.; Zhang, X. M. *J. Am. Chem. Soc.* **2003**, *125*, 6370. (n) Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268. (o) Lei, A. W.; Waldkirch, J. P.; He, M. S.; Zhang, X. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526.

(9) Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203.

(10) Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1853.

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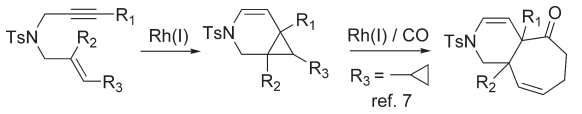
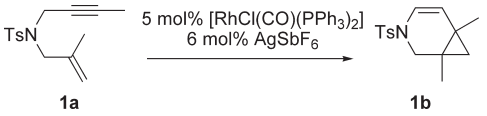
SCHEME 1. Rh(I)-Catalyzed Cycloisomerization and [3+3+1] Cycloaddition Reactions from Cyclopropylenyne



the carbonylative cycloaddition of dienynes. The reaction of **1a** (0.330 mmol) in the presence of a catalytic amount of $[RhCl(CO)(PPh_3)_2]$ (10 mol %)/$AgSbF_6$ (12 mol %) in 1,2-dichloroethane at room temperature for 1.5 h gave the cyclopropanated product **1b** in 77% with a recovery of **1a** in 16% yield (Table 1).

TABLE 1. Optimum Conditions for Cycloisomerization



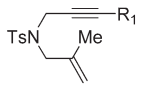
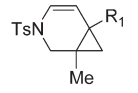
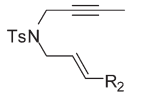
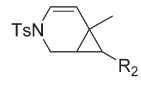
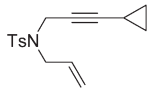
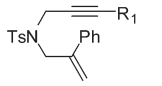
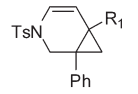
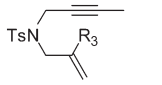
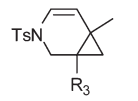
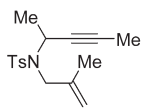
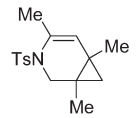
solvent	temp (°C)	time (h)	yield (**1a**/**1b**)[a] (%)
1,2-dichloroethane	rt	1.5	16/77[b]
1,2-dichloroethane	60	1.5	0/95
toluene	60	4	63/37
1,4-dioxane	60	2	65/5
1,2-dichloroethane	60	18	45/48[c]
1,2-dichloroethane	110	18	0/80[c]

[a]Isolated yields. [b]10 mol % of $[RhCl(CO)(PPh_3)_2]$ and 12 mol % of $AgSbF_6$ were used. [c]$[RhCl(CO)_2]_2$ was used under 13 atm of CO.

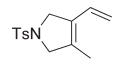
The formation of **1b** was confirmed by ^1H NMR and HR-mass. When the amount of catalyst decreased to 5 mol % and the reaction temperature was increased to 60 °C, the yield of **1b** dramatically improved to 95%. When the reaction medium was changed to toluene or 1,4-dioxane, the yield was quite poor and a considerable amount of **1a** was recovered. We also screened neutral rhodium complexes such as $[RhCl(CO)_2]_2$ and *trans*-$[RhCl(CO)(dppp)]_2$. Both Rh complexes were inactive under most reaction conditions, but they were quite active under 13 atm of CO. Interestingly, the reaction was highly dependent upon the pressure of carbon monoxide. It has been reported[11] that in some transition metal-catalyzed reactions, the presence of carbon monoxide was helpful to the reaction even though the reaction was not related to the carbonylation.

Using $[RhCl(CO)(PPh_3)_2]$/$AgSbF_6$ as a catalyst, the cycloisomerization was studied. The results are summarized in Table 2. Changing a substituent at the alkyne terminus (entries 1, 2, and 3) and at the olefinic carbon (entries 4 and 5) exerted a great influence on the yield. In the case of entry 3, **3b** and methylenecyclohexene **3c** were isolated in 28% and 23% yields, respectively. The formation of **3c** was previously observed[12] in cationic $(PPh_3)Au(I)$-catalyzed cycloisomerization reactions. Enyne with a terminal alkyne **3a** gave relatively poor

TABLE 2. Rhodium(I)-Catalyzed Cyclopropanation of Enynes[a]

Entry	Substrate		Product	Yield (%)[b]
1		**1a** (R_1 = Me)		95 (**1b**)
2		**2a** (R_1 = Ph)		86 (**2b**)
3		**3a** (R_1 = H)		28 (**3b**)[c]
4		**4a** (R_2 = H)		56 (**4b**)[d] (11)[e]
5		**5a** (R_2 = Ph)		75 (**5b**)
6		**6a**		37 (**6b**)[d] (14)[e]
7		**7a** (R_1 = Ph)		81 (**7b**)[d]
8		**8a** (R_1 = Me)		58 (**8b**)
9		**9a** (R_3 = 4-OMePh)		85 (**9b**)
10		**10a** (R_3 = 4-CF_3Ph)		20 (**10b**)[c] (62)[e]
11		**11a**		74 (**11b**)[f]

[a]Reaction conditions: 0.33 mmol of a substrate, $[RhCl(CO)(PPh_3)_2]$ (5 mol %), $AgSbF_6$ (6 mol %), 1,2-dichloroethane (6 mL), 60 °C, 1−2 h. [b]Isolated yields. [c]15 h. **3c** was obtained in 23% yield.



3c (23%)

[d]5−6 h. [e]The parentheses represents the reactant recovered. [f]Reaction conditions: 0.330 mmol of a substrate, $[RhCl(CO)(PPh_3)_2]$ (10 mol %), $AgSbF_6$ (12 mol %), 1,2-dichloroethane (6 mL), 70 °C, 1.5 h.

yields, but enyne with a phenyl-substituted alkyne **2a** produced relatively higher yields (86%). When an enyne with a cyclopropyl-substituted alkyne **6a** was used as a substrate, a relatively poor yield (37%) was observed. Interestingly, an electronic effect was observed when an aryl group was introduced to the 6-position (entries 8−10): the methoxy group enhanced the yield to 85%, but the CF_3 group diminished the yield to 20% with a recovery of the reactant in 62%. When two methyl groups were introduced to the 3 and 6 positions of 1,6-enyne, **11b** was isolated in 74%.

When a 1,7-enyne **12a** was used as a substrate under the same reaction conditions, compound **12d** was obtained as the sole product in 56% yield (eq 1). The formation of **12d** could be deduced by a Rh-catalyzed double-bond migration followed by a Rh-catalyzed Alder-ene reaction[13] and its molecular structure was confirmed by an X-ray diffraction study (Supporting Information).[14] Thus, the chain length has a significant effect on the reactivity of a substrate. Interestingly, **12a** in the presence of $[Rh_2(O_2CCF_3)_4]$ afforded a skeletal

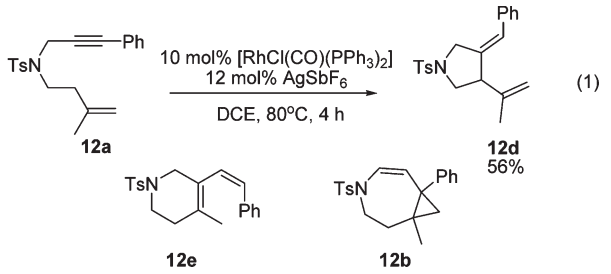
(11) (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Chatani, N.; Morimoto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. (c) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433.

(12) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Lopez, S.; Jimenez-Nunez, E.; Nevado, C.; Herrero-Gomez, E.; Rducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677.

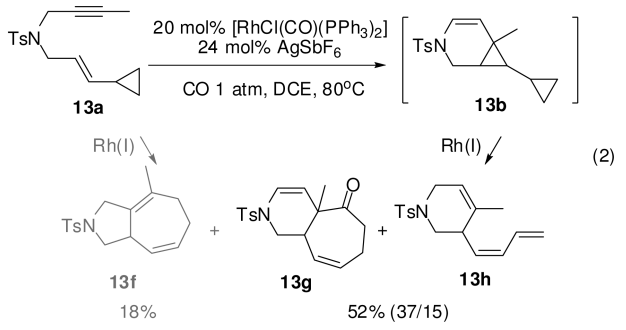
(13) Cao, P.; Wang, B.; Zhang *J. Am. Chem. Soc.* **2000**, *122*, 6490.

(14) The spectroscopic data of the new compound is summarized in the Supporting Information. CCDC-751911 (**12d**) contains 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.

reorganized compound **12e** in 53% yield and in $PtCl_2$ **12b** in 21% yield.[9b]



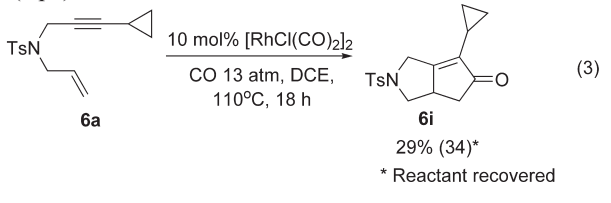
When an 1,6-enyne with a cyclopropyl-substituted olefin **13a** was used as a substrate, a [5+2] cycloadduct **13f** was quantitatively obtained, as we expected. But when the same reaction was carried out under 1 atm of CO at 80 °C, a mixture of three compounds, a [5+2] cycloadduct **13f**, a carbonylative [3+3+1] cycloadduct **13g**, and a cycloisomerized triene **13h**, was obtained, respectively (eq 2). The carbonylative [3+3+1] cycloadduct and the cycloisomerized triene are derived from a bicyclopropyls **13b**.[7] The yield from cyclopropanation might be 52%.



We had to find a catalytic system that would be effective for the cyclopropanation of the enynes with a cyclopropyl-substituted alkene. Gratifyingly, the catalyst *trans*-[RhCl(CO)(dppp)]$_2$ was quite effective under 13 atm of CO (Table 3).

Changing a substituent on the alkyne terminus (entries 1−4) led to the isolation of **b** in reasonable yields (39−80%). As above, an enyne with a terminal alkyne (entry 2) gave the lowest yield (39%). In other cases, a reasonable to high yield was obtained (68−80%).

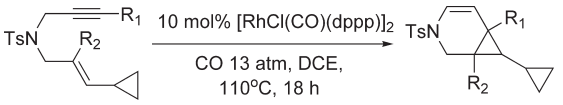
An enyne with a cyclopropyl-substituted alkyne **6a** was subjected to the same reaction conditions except for a catalyst [RhCl(CO)$_2$]$_2$ instead of [RhCl(CO)(dppp)]$_2$. The expected [3+3+1] cycloaddition product was not observed, but a Pauson−Khand-type product was obtained as the sole product in 29% yield (eq 3).



Although little mechanistic information has been obtained, a plausible mechanism is proposed on the basis of the above results and previous studies[15] (Scheme 2). The first step is a metal-based alkyne activation, which is followed by intramolecular cyclopropanation. A metal carbene **I** can be produced, which is expected to undergo a facile [1,2] hydride shift to generate a zwitterion species **II**, followed by elimination of the metal fragment to produce bicyclo[4.1.0]heptene and regeneration of the metal catalyst, which enters the next catalytic cycle.

In summary, we have demonstrated that the judicious choice of a rhodium catalyst system allows the cyclopropanation of nitrogen-tethered enynes. The reaction yield was highly sensitive to the substrate and to the **a** substituent(s) at the alkyne and alkene moieties. Further synthetic applications of these reactions are under investigation.

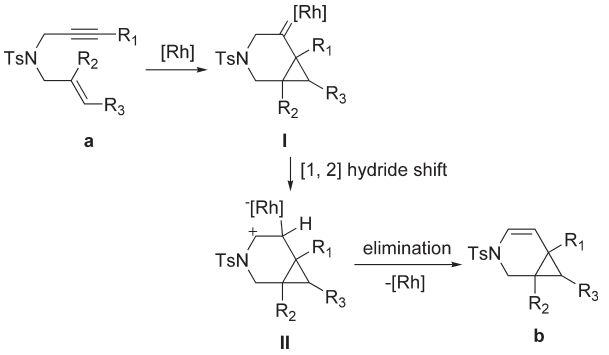
TABLE 3. Rhodium(I)-Catalyzed Cyclopropanation of Cyclopropylenynes[a]



	substrate			
entry	R_1	R_2		yield (%)[a]
1	Me	H	**13a**	78 (**13b**)
2	H	H	**14a**	39 (**14b**)
3	Et	H	**15a**	68 (**15b**)
4	Ph	H	**16a**	80 (**16b**)
5	Me	Me	**17a**	78 (**17b**)

[a]Isolated yields.

SCHEME 2. Proposed Mechanism



Experimental Section

General Procedure for Rh(I)-Catalyzed Cycloisomerization of Enynes (Table 2). Synthesis of 1-Methyl-6-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (2b). [RhCl(CO)(PPh$_3$)$_2$] (12 mg, 0.017 mmol), $AgSbF_6$ (6.9 mg, 0.020 mmol), and 1,2-dichloroethane (2 mL) were added to a Schlenk flask equipped with a stirring bar and capped with a rubber septum. The reaction mixture was stirred at room temperature for 5 min. Then a substrate **2a** (110 mg, 0.33 mmol) and 1,2-dichloroethane (4 mL) were added to the Schlenk flask. The resulting mixture was stirred until the substrate completely disappeared (as checked by TLC) at 60 °C. The reaction mixture was purified by flash chromatography on a silica gel column eluting with *n*-hexane/ethyl acetate (v/v, 10:1). SiO_2 flash chromatography afforded the 1-methyl-6-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene **2b** as a solid (96 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 1.03 (d, J = 4.7 Hz, 1 H), 1.21 (d, J = 4.7 Hz, 1 H), 2.45

(15) For review, see: Zhnag, L.; Sun, J.; Kozman, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

(s, 3 H), 2.78 (d, J = 11.5 Hz, 1 H), 3.94 (d, J = 11.5 Hz, 1 H), 5.34 (d, J = 8.0 Hz, 1 H), 6.40 (d, J = 8.0 Hz, 1 H), 7.13 (d, J = 7.6 Hz, 2 H), 7.19−7.28 (m, 3 H), 7.35 (d, J = 7.9 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 21.5, 23.3, 28.1, 32.5, 46.3, 117.2, 120.4, 126.3, 127.0, 128.0, 128.9, 129.7, 134.9, 141.1, 143.7 ppm. HRMS (EI) calcd for $[C_{20}H_{21}NO_2S]^+$ 339.1293, found 339.1291.

General Procedure for Rh(I)-Catalyzed Cycloisomerization of Cyclopropylenynes to Bicyclopropyls (Table 3). Synthesis of 7-Cyclopropyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene (14b). Reactions were carried out in a 100 mL stainless steel autoclave equipped with a stirring bar. $[RhCl(CO)(dppp)]_2$ (38 mg, 0.0330 mmol), 1,2-dichloroethane (20 mL), and cyclopropylenynes **14a** (95 mg, 0.33 mmol) were added to an autoclave. The reactor was charged with 13 atm of CO and heated at 110 °C for 18 h. After the reactor was cooled to room temperature, the solution was concentrated and a product was isolated by chromatography on a silica gel column, eluting with *n*-hexane/ethyl acetate (v/v, 10:1). SiO_2 flash chromatography afforded the 7-cyclopropyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene **14b** as a solid (37 mg, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.11 to 0.06 (m, 2 H), 0.30−0.33 (m, 2 H), 0.48−0.60 (m, 2 H), 0.90−0.96 (m, 1 H), 1.29−1.32 (m, 1 H), 2.42 (s, 3 H), 2.97 (dd, J = 11.7, 2.9 Hz, 1 H), 3.85 (d, J = 11.7 Hz, 1 H), 5.40 (dd, J = 7.9, 5.5 Hz, 1 H), 6.28 (d, J = 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.1, 3.3, 11.4, 13.1, 21.4, 24.1, 29.5, 40.3, 112.2, 120.6, 126.9, 129.6, 134.6, 143.5 ppm. HRMS (EI) calcd for $[C_{16}H_{19}NO_2S]^+$ 289.1137, found 289.1140.

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Note Added after ASAP Publication. Equation 1 contained an error in the version published ASAP on January 22, 2010; the correct version posted to the web on January 26, 2010.

Supporting Information Available: NMR spectra and HR-mass data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.