Title

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Journal

Synlett, 26(11)

ISSN

0936-5214

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Publication Date

2015-07-01

DOI

10.1055/s-0034-1380359

Peer reviewed

Published in final edited form as:

Synlett. 2015 July 1; 26(11): 1533–1536. doi:10.1055/s-0034-1380359.

Rh(I)-Catalyzed Cycloisomerization of 1,6-Enynes

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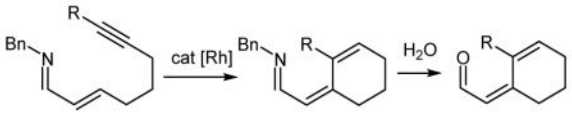
Abstract

A new and unexpected Rh(I)-catalyzed cycloisomerization of 1,6-enynes is reported. Several different alkyne substitution patterns were evaluated under the reaction conditions, including a deuterated derivative that provides some insight into the reaction mechanism.

Graphical Abstract



Keywords

rhodium; homogeneous catalysis; ring closure; isomerization; enones

Previously we have published on Rh(I)-catalyzed C-H alkenylation and electrocyclization cascades for the convergent assembly of 1,2-dihydropyridines **4** from α,β-unsaturated imines **1** and alkynes **2** (Scheme 1).[1,2] The 1,2-dihydropyridine products have further proven to be versatile intermediates for the synthesis of a variety of heterocyclic structures,[1] including pyridines,[1,3,4] piperidines,[5] isoquinuclidines[6] and tropanes.[7]

To access complex, multicyclic heterocycles **6** with high levels of regiocontrol we have explored the intramolecular alkenylation of substrates **5** with the alkyne tethered to the α,β-unsaturated imine via the nitrogen substituent (Scheme 2).[8] Subsequent electrocylization provides **6** with bridgehead double bonds.

In the present study we explored cyclization of 1,6-enyne substrates **7** in which the alkynyl group is tethered to the α,β-unsaturated imine functionality with a different connectivity than that used for **5** (Scheme 3). However, to our surprise, the Rh(I)-catalyzed reaction of 1,6-

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083. Included are the synthesis procedures and analytical data for the cycloisomerization substrates and intermediates in their synthesis. In addition, spectra are provided for intermediates and cycloisomerization substrates **7a-7d** and products **10a-10d** and **11a**.

enynes **7** did not provide any of the expected bicyclic products **8**, but rather resulted in the cycloisomerization products **9**, which upon hydrolysis provided exocyclic enals **10** with good levels of Z-selectivity.

We began our investigations by exploring the Rh(I)-catalyzed transformation of α,β-unsaturated imine **7a** (Scheme 4). Using conditions previously determined to be optimal for α,β-unsaturated imine C-H bond functionalization, which employed $Rh[Cl(coe)_2]_2$ as the precatalyst and the commercially available electron-rich phosphine 4-$Me_2NPhPEt_2$, exocyclic enal **10a** was obtained in 48% yield and predominantly as the less stable Z-isomer. The stereochemistry of **10a** was further rigorously confirmed by complete isomerization to the more stable E isomer **11a** under acidic conditions.

An intriguing aspect of this cycloisomerization reaction is the formal trans C-H bond addition across the alkynyl group. We hypothesized that **7a** might first isomerize to a terminal allene or alkyne prior to cyclization, and therefore evaluated methyl deuterated substrate **7b** (Scheme 5). Product **10b** was isolated in the same yield and stereoisomeric purity as **10a** with the methyl group remaining fully deuterated without any deuterium transfer to other sites in the structure. This result argues against the cycloisomerization first proceeding by π-bond isomerization.

Two additional substrates were evaluated to demonstrate that the reaction is applicable to substitution patterns beyond methyl alkyne derivatives. As shown in Scheme 6, ethyl 1,6-enyne **7c** and benzyl 1,6-enyne **7d** provided cyclic products **10c** and **10d**, respectively, in comparable yields and with very high selectivity for the Z-alkene isomer. We believe that the higher selectivity for these more sterically hindered products is due to reduced isomerization during imine hydrolysis upon filtration through alumina.[10]

Cycloisomerizations of 1,6-enynes to give cyclohexene-based products have previously been reported using Ru- and Mo-metathesis catalysts,[11] cationic Au catalysts,[12] and even Rh(I) catalysts.[13,14] However, almost all of the previous reports, including all of the Rh(I)-catalyzed transformations, employ 1,6-enyne substrates that incorporate a terminal alkyne. Transformations of 1,6-enynes with internal alkynes to give cyclohexenyl products are limited to Ru- and Mo- catalysts proceeding by endo-selective enyne ring-closing metathesis pathways. In fact, the previously reported Rh(I)-catalyzed cycloisomerizations of 1,6-enynes all contained terminal alkynes and monosubstituted alkenes, and for this class of 1,6-enynes, mechanistic studies support a reaction pathway that proceeds via a Rh-vinylidene intermediate. It is notable that Rh-vinylidene intermediates are not accessible for the 1,6-enynes **7** reported here that incorporate internal alkynes.

In conclusion, we have identified a novel Rh(I)-catalyzed cycloisomerization of 1,6-enynes incorporating internal alkyne moieties that gives functionalized 6-membered carbocyclic systems. Further mechanistic inquiry will be necessary to elucidate the reaction mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH Grant No. GM069559 (J.A.E.). R.G.B. was supported by the Director, Office of Science, Office of Basic Energy Sciences, and by the Division of Chemical Sciences, Geosciences, and Biosciences of the U.S. Department of Energy at LBNL under Contract No. DE-AC02-05CH11231. E.M.P. also acknowledges support from an NRSA postdoctoral fellowship (F32GM090661).

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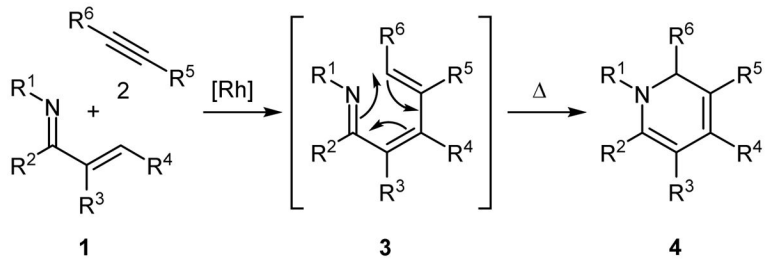
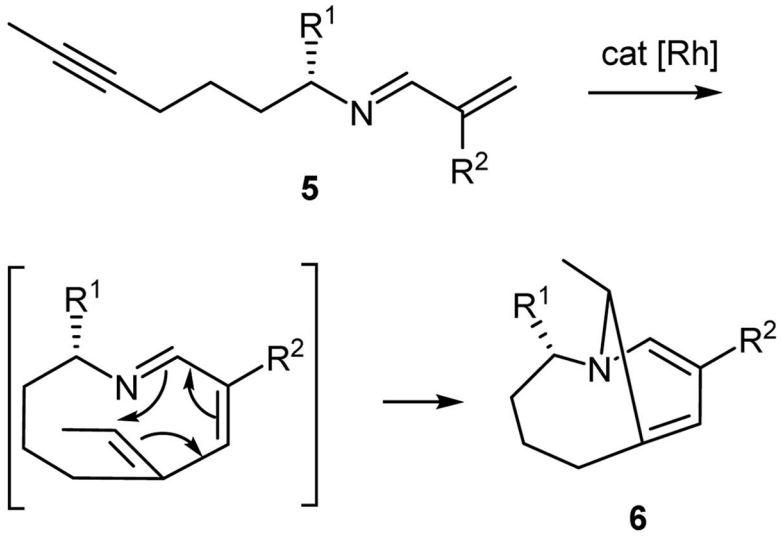
15. **Experimental Procedures for Generation Imines and Rh-Catalyzed Cycloisomerization(*Z*)-2-(2-methylcyclohex-2-en-1-ylidene)acetaldehyde (10a)**In an inert atmosphere box, to the solution

of **7a**(86 mg, 0.63 mmol) in toluene (3 mL) was added benzylamine (68 mg, 0.63 mmol) and molecular sieves (MS) 3Å (800 mg). The flask was removed from the box, and the mixture was stirred at room temperature for 3 hours. The MS 3Å were removed via filtration over celite, which was washed with toluene (8 mL). The filtrate was degassed and brought into an inert atmosphere box. To the solution was added a solution of $[RhCl(coe)_2]_2$ (23 mg, 0.031 mmol) and $Me_2NPhPEt_2$ (13 mg, 0.62 mmol) in toluene (2 mL), and the mixture was stirred at 75 °C for 1 hour. After removal of the solvent, the residual oil was purified by column chromatography on grade III aluminum oxide (100:0 to 99:1, hexanes/EtOAc) to afford **10a (*Z:E* = 6.7:1)**as colorless oil (41 mg, 0.30 mmol, 48% yield). *Rf* = 0.70 (4:1, hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (d, *J* = 8.4 Hz, 1H), 6.11 (ddd, *J* = 5.4, 2.7, 1.3 Hz, 1H), 5.81 (d, *J* = 8.4 Hz, 1H), 2.44 (ddd, *J* = 6.5, 4.3, 1.2 Hz, 2H), 2.30 – 2.20 (m, 2H), 2.17 (dd, *J* = 3.3, 1.8 Hz, 3H), 1.84 – 1.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.28, 156.42, 138.87, 131.95, 127.42, 35.59, 26.55, 26.04, 22.34; IR (thin film): 2927, 2867, 2834, 1653, 1615, 1580, 1448, 1406, 1223, 1178, 1149, 1130, 1101, 1025, 948 cm^{-1}; MS (EI): $[M]^+$ calcd for $C_9H_{12}O^+$: 136.09; found: 136.10.**(*Z*)-2-(2-(methyl-d_3)cyclohex-2-en-1-ylidene)acetaldehyde (10b)** Compound **10b** was synthesized according to the procedure used for compound **10a**. From 80 mg (0.57 mmol) of **7b** was obtained 39 mg (0.28 mmol, 49% yield) of **10b (*Z:E* = 6.7:1)**as colorless oil after purification by column chromatography on grade III aluminum oxide eluting with 100:0 to 99:1, hexanes/EtOAc.; *Rf* = 0.70 (4:1, hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (d, *J* = 8.5 Hz, 1H), 6.11 (td, *J* = 4.2, 1.3 Hz, 1H), 5.81 (d, *J* = 8.5 Hz, 1H), 2.48 – 2.40 (m, 2H), 2.29 – 2.21 (m, 2H), 1.83 – 1.74 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.28, 156.44, 138.87, 131.89, 127.46, 35.60, 26.57, 22.38; IR (thin film): 3009, 2926, 1651, 1611, 1580, 1406, 1230, 1156, 1137, 1096, 1051, 974 cm^{-1}; MS (EI): $[M]^+$ calcd for $C_9H_9D_3O^+$: 139.11; found: 139.15.**(*Z*)-2-(2-ethylcyclohex-2-en-1-ylidene)acetaldehyde (10c)** Compound **10c** was synthesized according to the procedure used for compound **10a**. From 40 mg (0.27 mmol) of **7c** was obtained 18 mg (0.12 mmol, 45% yield) of **10c (*Z: E* = 20:1)** as colorless oil after purification by column chromatography on grade III aluminum oxide eluting with 100:0 to 99:1, hexanes/EtOAc.; *Rf* = 0.70 (4:1, hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (d, *J* = 8.5 Hz, 1H), 6.08 (ddd, *J* = 5.4, 2.8, 1.3 Hz, 1H), 5.76 (d, *J* = 8.5 Hz, 1H), 2.53 – 2.44 (m, 2H), 2.44 – 2.37 (m, 2H), 2.30 – 2.22 (m, 2H), 1.84 – 1.75 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.40, 156.54, 138.12, 135.90, 126.41, 36.28, 30.99, 26.52, 22.88, 13.16; IR (thin film): 2966, 2928, 2876, 1660, 1617, 1583, 1453, 1409, 1222, 1174, 1150, 1127, 1107, 1081cm^{-1}; MS (EI): $[M]^+$ calcd for $C_{10}H_{14}O^+$: 150.10; found: 150.10.**(*Z*)-2-(2-benzylcyclohex-2-en-1-ylidene)acetaldehyde (10d)** Compound **10d** was synthesized according to the procedure used for compound **10a**. From 63 mg (0.30 mmol) of **7d** was obtained 32 mg (0.15 mmol, 51% yield) of **10d (*Z: E* = 15.5:1)** as colorless oil after purification by column chromatography on grade III aluminum oxide eluting with 100:0 to 99:1, hexanes/EtOAc.; *Rf* = 0.70 (4:1, hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.01 (td, *J* = 4.0, 1.0 Hz, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 2H), 2.50 – 2.43 (m, 2H), 2.32 (ddd, *J* = 6.0, 5.1, 2.0 Hz, 2H), 1.90 – 1.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.10, 155.61, 140.14, 138.71, 135.05, 128.58, 128.55, 126.66, 126.41, 44.05, 36.22, 26.72, 22.65; IR (thin film): 3025, 2925, 2862, 1688, 1653, 1616, 1582, 1495, 1453, 1405, 1223, 1147, 1124, 978 cm^{-1}; MS (EI): $[M]^+$ calcd for $C_{15}H_{16}O^+$: 212.12; found: 212.10.**(*E*)-2-(2-methylcyclohex-2-en-1-ylidene)acetaldehyde (11a)** To a solution of **10a** (40 mg, 0.29 mmol) in THF (2 mL) was added a 1M aqueous solution of HCl (1 mL, 1 mmol), and the mixture was stirred at room temperature for 18 hours. After neutralized with Na_2CO_3 aq., the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O and brine, and dried over with $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The residual oil was purified by column chromatography on silica gel (33:1, pentane/ether) to afford **11a** as a colorless oil (36 mg, 0.26 mmol, 89% yield). *Rf* = 0.70 (4:1, hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (d, *J* = 8.1 Hz, 1H), 6.18 (t, *J* = 4.3 Hz, 1H), 5.93 (d, *J* = 8.1 Hz, 1H), 2.95 – 2.86 (m, 2H), 2.26 (dtd, *J* = 7.8, 4.1, 1.9 Hz, 2H), 1.85 (dd, *J* = 3.1, 1.7 Hz, 3H), 1.80 (dt, *J* = 12.5, 6.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.49, 157.28, 138.03, 132.99, 122.62, 26.32, 25.82, 22.26, 19.65; IR (thin film): 2924, 2860, 1663, 1622, 1591, 1455, 1435, 1401, 1386, 1370, 1177, 1145, 1087, 1048 cm^{-1}; MS (EI): $[M]^+$ calcd for $C_9H_{12}O^+$: 136.09; found: 136.00.



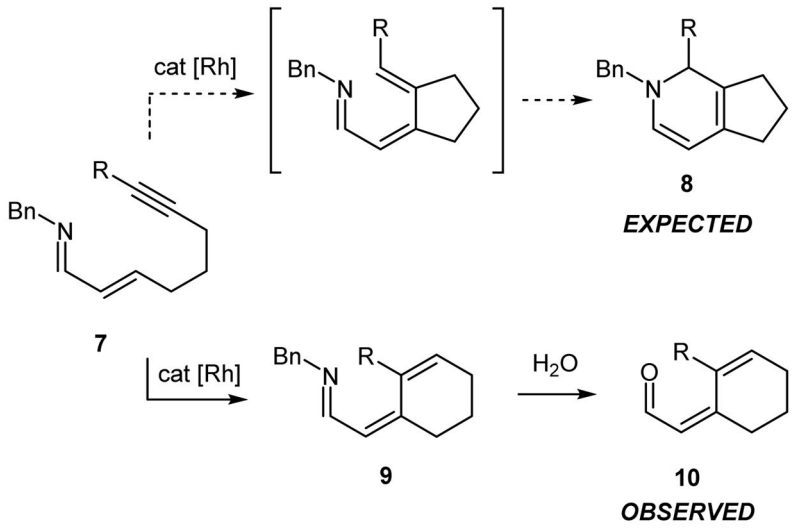
Scheme 1.

C-H alkenylation/electrocyclization cascade to provide 1,2-dihydropyridines.



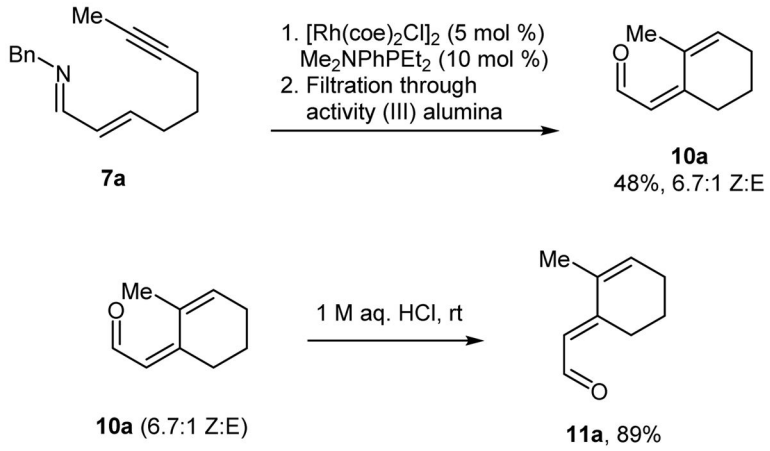
Scheme 2.

Intramolecular C-H alkenylation/electrocyclization cascade of substrates **5** with alkynes tethered to the nitrogen.



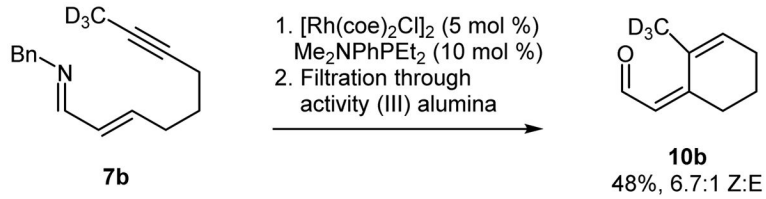
Scheme 3.

Unexpected reaction pathway for substrate **7** with alkynes tethered to the β-carbon of the α,β-unsaturated imine.



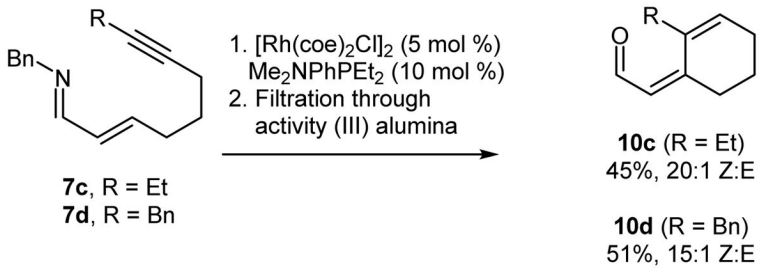
Scheme 4.

Rh-catalyzed cycloisomerization of **7a** and confirmation of stereochemistry of hydrolysis product **10a** by equilibration to **11a**.



Scheme 5.

No deuterium exchange occurs upon Rh-catalyzed cyclisomerization of deuturated substrate **7b**.



Scheme 6.

C-H alkenylation/electrocyclization cascade to provide 1,2-dihydropyridines.