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

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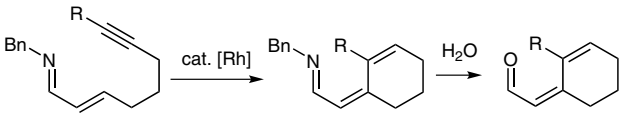
This manuscript is dedicated to Peter Vollhardt, who launched SYNLETT 25 years ago and since that time has continuously served in a number of important editorial capacities.



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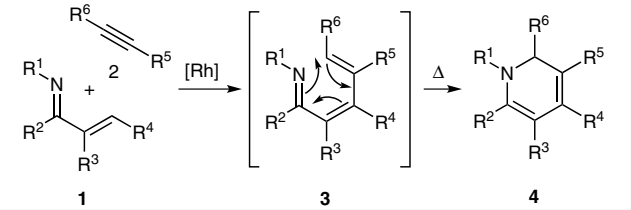
Abstract A new and unexpected rhodium(I)-catalyzed cycloisomerization of 1,6-enynes is reported. Several different alkyne substitution patterns were evaluated under the reaction conditions, including a deuterated derivative that provides some insight into the reaction mechanism.

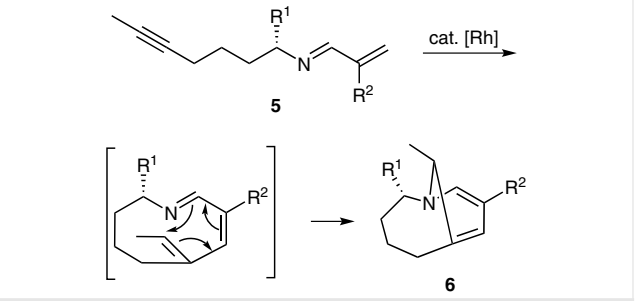
Key words rhodium, homogeneous catalysis, ring closure, isomerization, enones

Previously we have published on rhodium(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]



Scheme 1 C–H alkenylation–electrocyclization cascade to provide 1,2-dihydropyridines

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.



Scheme 2 Intramolecular C–H alkenylation–electrocyclization cascade of substrates **5** with alkynes tethered to the nitrogen

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 rhodium(I)-catalyzed reaction of 1,6-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**[9] with good levels of *Z*-selectivity.

We began our investigations by exploring the rhodium(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 $4\text{-}Me_2NPhPEt_2$, exocyclic enal **10a** was obtained in 48% yield, predominantly as the less stable *Z*-isomer. The stereo-

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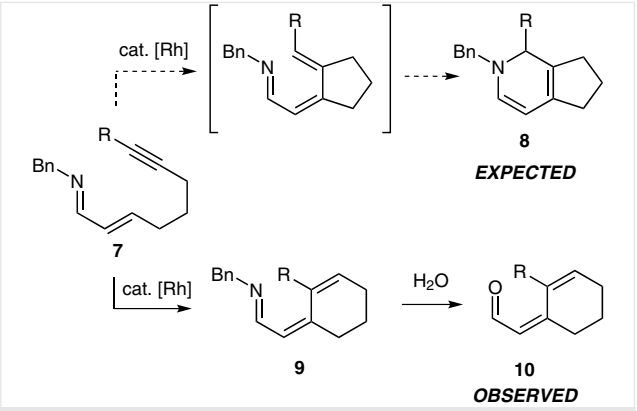
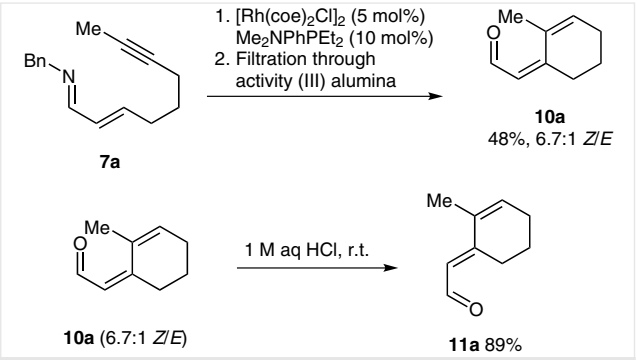


Scheme 3 Unexpected reaction pathway for substrate **7** with alkynes tethered to the β-carbon of the α,β-unsaturated imine

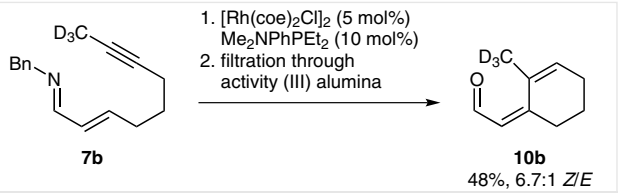
chemistry of **10a** was further rigorously confirmed by complete isomerization to the more stable *E*-isomer **11a**[9] under acidic conditions.



Scheme 4 Rhodium-catalyzed cycloisomerization of **7a** and confirmation of stereochemistry of hydrolysis product **10a** by equilibration to **11a**

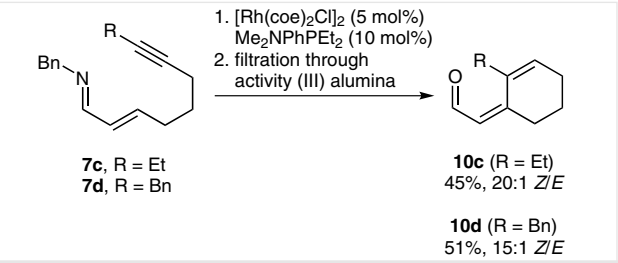
An intriguing aspect of this cycloisomerization reaction is the formal *trans*-C–H bond addition across the alkynyl group.[10] We hypothesized that **7a** might first isomerize to a terminal allene or alkyne prior to cyclization and therefore evaluated methyl-deuterated substrate **7b** (Scheme 5). Product **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



Scheme 5 No deuterium exchange occurs upon rhodium-catalyzed cyclisomerization of deuterated substrate **7b**

more sterically hindered products is due to reduced isomerization during imine hydrolysis upon filtration through alumina.[11]



Scheme 6 C–H alkenylation–electrocyclization cascade to provide 1,2-dihydropyridines

Cycloisomerizations of 1,6-enynes to give cyclohexene-based products have previously been reported using ruthenium and molybdenum metathesis catalysts,[12] cationic gold catalysts,[13] and even rhodium(I) catalysts.[14,15] However, almost all of the previous reports, including all of the rhodium(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 ruthenium and molybdenum catalysts proceeding by *endo*-selective enyne ring-closing metathesis pathways. In fact, the previously reported rhodium(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 rhodium–vinylidene intermediate. It is notable that rhodium–vinylidene intermediates are not accessible for the 1,6-enynes **7** reported here that incorporate internal alkynes.

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

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380359. 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**–**d** and products **10a**–**d** and **11a**.

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(9) **Experimental Procedures for the Generation of Imines and Rhodium-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 3 Å MS (800 mg). The flask was removed from the box, and the mixture was stirred at r.t. for 3 h. The 3 Å MS 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 h. After removal of the solvent, the residual oil was purified by column chromatography on grade III Al_2O_3 (hexanes–EtOAc, 100:0 to 99:1,) to afford **10a** (*Z*/*E* = 6.7:1) as colorless oil (41 mg, 0.30 mmol, 48% yield). R_f = 0.70 (hexanes–EtOAc. 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.23 (d, *J* = 8.4 Hz, 1 H), 6.11 (ddd, *J* = 5.4, 2.7, 1.3 Hz, 1 H), 5.81 (d, *J* = 8.4 Hz, 1 H), 2.44 (ddd, *J* = 6.5, 4.3, 1.2 Hz, 2 H), 2.30–2.20 (m, 2 H), 2.17 (dd, *J* = 3.3, 1.8 Hz, 3 H), 1.84–1.74 (m, 2 H). ^{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*/*z* $[M]^+$ 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 Al_2O_3 eluting with hexanes–EtOAc (100:0 to 99:1). R_f = 0.70 (hexanes–EtOAc. 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (d, *J* = 8.5 Hz, 1 H), 6.11 (td, *J* = 4.2, 1.3 Hz, 1 H), 5.81 (d, *J* = 8.5 Hz, 1 H), 2.48–2.40 (m, 2 H), 2.29–2.21 (m, 2 H), 1.83–1.74 (m, 2 H). ^{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*/*z* $[M]^+$ 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 Al_2O_3 eluting with hexanes–EtOAc (100:0 to 99:1). R_f = 0.70 (hexanes–EtOAc. 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (d, *J* = 8.5 Hz, 1 H), 6.08 (ddd, *J* = 5.4, 2.8, 1.3 Hz, 1 H), 5.76 (d, *J* = 8.5 Hz, 1 H), 2.53–2.44 (m, 2 H), 2.44–2.37 (m, 2 H), 2.30–2.22 (m, 2 H), 1.84–1.75 (m, 2 H), 1.11 (t, *J* = 7.4 Hz, 3 H). ^{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*/*z* $[M]^+$ 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 Al_2O_3 eluting with hexanes–EtOAc (100:0 to 99:1). R_f = 0.70 (hexanes–EtOAc. 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.04 (d, *J* = 8.4 Hz, 1 H), 7.29 (t, *J* = 7.5 Hz, 2 H), 7.21 (t, *J* = 7.4 Hz, 1 H), 7.13 (d, *J* = 7.3 Hz, 2 H), 6.01 (td, *J* = 4.0, 1.0 Hz, 1 H), 5.73 (d, *J* = 8.4 Hz, 1 H), 3.83 (s, 2 H), 2.50–2.43 (m, 2 H), 2.32 (ddd, *J* = 6.0, 5.1, 2.0 Hz, 2 H), 1.90–1.82 (m, 2 H). ^{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*/*z* $[M]^+$ 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 1 M aqueous solution of HCl (1 mL, 1 mmol), and the mixture was stirred at r.t. for 18 h. After being neutralized with aq Na_2CO_3, the aqueous layer was extracted with EtOAc (3 × 5

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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–Et_2O) to afford **11a** as a colorless oil (36 mg, 0.26 mmol, 89% yield). R_f = 0.70 (hexanes–EtOAc. 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.15 (d, *J* = 8.1 Hz, 1 H), 6.18 (t, *J* = 4.3 Hz, 1 H), 5.93 (d, *J* = 8.1 Hz, 1 H), 2.95–2.86 (m, 2 H), 2.26 (dtd, *J* = 7.8, 4.1, 1.9 Hz, 2 H), 1.85 (dd, *J* = 3.1, 1.7 Hz, 3 H), 1.80 (dt, *J* = 12.5, 6.2 Hz, 2 H). ^{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/z* $[M]^+$ calcd for $C_9H_{12}O^+$: 136.09; found: 136.00.

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