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Rhodium(I)-Catalyzed Ene-Allene Carbocyclization Strategy for the Formation of Azepines and Oxepines

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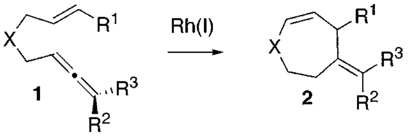
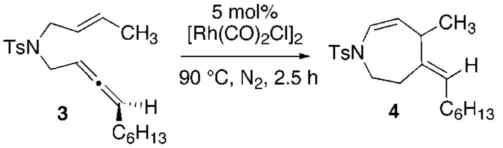
ABSTRACT



A novel strategy for the preparation of seven-membered heterocyclic compounds has been realized. Treatment of ene-allene 1 with a catalytic quantity of rhodium biscarbonyl chloride dimer affords the cyclization product 2 in moderate to high yields. The scope and limitations of this new method are currently under investigation, and the results obtained to date are discussed within.

Our laboratory has been extensively active in exploring allenes and transition metal catalyzed carbocyclization reactions.[1] During our studies involving the Pauson−Khand reaction, we discovered a Rh(I)/Ir(I)-catalyzed allenic Alder-ene reaction that affords convenient formation of cyclized cross-conjugated trienes.[2] Given that these trienes are typically formed in minutes and in high yields, we were very interested in testing the extreme limits of this reaction. One of these extreme cases involved the replacement of the alkyne with an alkene group. Treatment of ene-allene **3** to 5 mol % $[Rh(CO)_2Cl]_2$ in toluene at 90 °C for 2.5 h resulted in the complete consumption of starting material. To our surprise, the only isolable product from this reaction was the tetrahydroazepine **4**, obtained as a single stereoisomer in 42% yield.[3] Although the yield of this reaction was somewhat low, the fortuitous formation of azepine **4** provides another example of a novel carbon−carbon bond forming process involving allenes.[4] In addition, azepine formation in this manner should be useful in the preparation of natural products and natural product-like compounds.[5] For these reasons, further investigations into the scope and synthetic utility of this reaction were enticing.



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[1] Brummond, K. M.; Sill, P. C.; Chen, H. *Org. Lett.* **2004**, *6*, 149. Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491. Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002**, *4*, 1931. Brummond, K. M.; Sill, P. C.; Rickards, B.; Geib, S. J. *Tetrahedron Lett.* **2002**, *43*, 3735. Brummond, K. M.; Lu, J.; Petersen, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 4915. Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087. Brummond, K. M. An Allenic [2 + 2 + 1] Cycloaddition. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press Inc.: Stamford, CT, 1999; Vol. 6, p 211. Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535. Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, *39*, 931. Kent, J. L.; Wan, H.; Brummond, K. M. *Tetrahedron Lett.* **1995**, *36*, 2407.

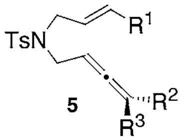
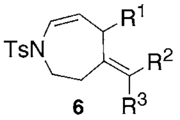
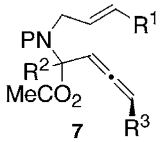
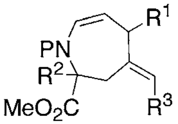
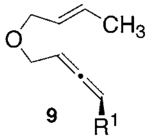
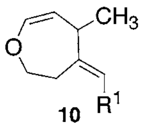
[2] Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186. Shibata subsequently reported a similar finding: Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268.

[3] For ruthenium-catalyzed cycloisomerization of 1,6-enynes to form seven-membered carbocycles initiated by C−H activation, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728. The initial disclosure of this finding was published in the abstracts for the 226th ACS National Meeting, New York, September 7, 2003. After this submission, Itoh reported a similar result involving the formation of a seven-membered carbocycle: Makino, T.; Itoh, K. *Tetrahedron Lett.* **2003**, *44*, 6335. In a full account a single azepine was assembled using this carbocyclization method: Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395.

[4] For a palladium-catalyzed carbocyclization to form five-membered rings involving ene-allenes initiated by C−H activation, see: Franzen, J.; Backvall, J.-E. *J. Am. Chem. Soc.* **2003**, 6056. For a review on palladium-catalyzed reactions of allenes, see: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. For a carbocyclization involving an allene and a π-allyl palladium intermediate generated from an allylic acetate, see: Doi, T.; Yangisawa, A.; Nakanishi, S.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 2602.

10.1021/ol049390a CCC: $27.50

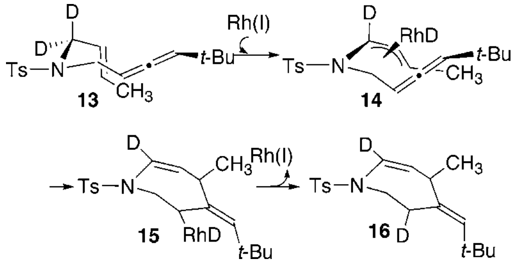
Table 1. Scope of Cyclization Strategy to Form Heterocycles

Entry	Ene-allene	Heterocycle	time (h)	yield (%)
	 **5**	 **6**		
1	$R^1 = CH_3$, $R^2 = C_6H_{13}$, $R^3 = H$		2.5	50
2	$R^1 = CH_3$, $R^2 = CH_3$, $R^3 = CH_3$		2	72[a]
3	$R^1 = CH_3$, $R^2 = t$-Bu, $R^3 = H$		1.5	95
4	$R^1 = R^2 = R^3 = H$		<1	trace
5	$R^1 = C_3H_7$, $R^2 = C_6H_{13}$, $R^3 = H$		2.5	28
6	$R^1 = Ph$, $R^2 = C_6H_{13}$, $R^3 = H$		2	trace
7	$R^1 = H$, $R^2 = C_6H_{13}$, $R^3 = H$		4	62[b]
8	$R^1 = H$, $R^2 = CH_3$, $R^3 = CH_3$		6	68
9	$R^1 = SiMe_2Bn$, $R^2 = t$-Bu, $R^3 = H$		1	97
10	$R^1 = SiMe_3$, $R^2 = t$-Bu, $R^3 = H$		1	82
	 **7**	 **8**		
11	P = Bz, $R^1 = CH_3$, $R^2 = Bn$, $R^3 = CH_3$		4	95
12	P = Bz, $R^1 = H$, $R^2 = Bn$, $R^3 = CH_3$		4	66[c]
13	P = Bz, $R^1 = CH_3$, $R^2 = CH_2OTBS$, $R^3 = CH_3$		4	72[d]
14	P = CBz, $R^1 = R^2 = R^3 = Me$		4	63[e]
15	P = CBz, $R^1 = R^2 = CH_3$, $R^3 = i$-Pr		4	51[e]
	 **9**	 **10**		
16	$R^1 = C_6H_{13}$		2.5	40 (53%)[f]
17	$R^1 = t$-Bu		1	55

[a] Toluene was used as the solvent; DCE was used for all other entries. [b] Diastereomeric ratio = 1.3:1. [c] Diastereomeric ratio = 2.5:1. [d] Diastereomeric ratio = 4.5:1. [e] Difficult to purify by flash chromatography. [f] Yield in parentheses was determined by ^1H NMR.

The results obtained to date, with regard to the scope of this azepine-forming process, are summarized below and in Table 1. In an effort to increase the yield of this transformation, the catalyst loading was increased from 5 to 10 mol % of $Rh(CO)_2Cl]_2$. This led to a marginal increase in the overall yield as is evidenced by comparing eq 1 to entry 1, Table 1. An additional alkyl group on the terminus of the allene **5** gives a much higher yield of the azepine **6** (entry 2, Table 1). Continuing along this line of reasoning, placement of a *tert*-butyl group on the terminus of the allene gives one of the highest yielding conversions observed when using only 5 mol % of the catalyst (entry 3). On the basis of these results it was not too surprising that substitution of the terminus of the allene with two hydrogens gave rapid decomposition of the starting material, which showed only broadened peaks and a trace amount of the azepine by ^1H NMR (entry 4). Replacement of the (*E*)-alkene in entries 1 and 2 with a (*Z*)-alkene gave none of the azepine product. We attribute this to steric congestion in the initial oxidative addition step. We were surprised to find that simply increasing the length of the alkyl chain on the alkene from a methyl to a propyl group resulted in a substantial decrease in the yield of azepine **6** (28%, entry 5). Likewise, a phenyl group on the terminus of the alkene also gave only a trace of the azepine (entry 6). An unsubstituted allyl group gave good yields of the azepines for both di- and trisubstituted allenes (entries 7 and 8, Table 1). In the case of entry 7 a 1.3:1 mixture of *E*:*Z* isomers was observed. A silicon group on the terminus of the alkene gave excellent yields of the azepines (entries 9 and 10). It should be noted that for both entries 9 and 10, there is a *tert*-butyl group on the terminus of the allene. An allene and alkene tethered together by the ester of an amino acid also gave good yields of the azepines as is demonstrated by entries 11−15. A benzamide (Bz) and carboxybenzyl (CBz) group on the nitrogen proved to be compatible with the reaction conditions. Although the CBz-protected amines showed evidence of decomposition during flash chromatography even when the silica gel was pretreated with triethylamine.

Scheme 1. Deuterium Labeling Study



Next, bis allyl ethers **9** were subjected to the same reaction conditions (entries 16 and 17). The corresponding oxepines **10** were obtained in a somewhat low but promising yield. It would appear that these conditions are not optimal for the ether substrates since an NMR study revealed the formation of multiple byproducts. Finally, attempts to use an all carbon tether resulted in either decomposition or the isolation of minor amounts of unidentifiable products. Thus, it would appear that a heteroatom in the tether is necessary for the carbocyclization process under these reaction conditions.

A working mechanism for this reaction has been postulated on the basis of the results shown in Table 1 and a deuterium labeling study that was performed, which is shown in Scheme 1. Initially, oxidative addition of the rhodium(I) catalyst into the allyl fragment proximal to the heteroatom of **13** gives a π-allyl rhodium deuteride species **14**. The conformation necessary for the oxidative addition most likely prohibits reaction of the *Z*-alkene isomer and the terminally disubstituted alkene. Next, carbocyclization of the rhodium deuteride species onto the proximal double bond of the allene gives azepine **15**. Finally, reductive elimination affords the product

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(5) For a Rh(I)-catalyzed [5 + 2] cycloaddition strategy to form dihydroazepines, see: Wender, P. A.; Pedersen, T. M.; Scanio, M. J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15154. For azepine-containing natural products, see: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131; O'Hagan, D. *Nat. Prod. Rep.* **1997**, 637.

16 and the Rh(I) catalyst. The conversion of **13** to **16** occurs in 1 h and gives an 89% yield when using 10 mol % of rhodium biscarbonyl chloride dimer. Moreover, ^{1}H NMR data showed that complete incorporation of one deuterium at each C-2 and C-6 position of the azepine ring had occurred.

In conclusion, treatment of ene-allenes with a rhodium(I) catalyst results in the formation of tetrahydroazepines and oxepines.[6] Depending upon the substitution pattern of the substrates the yields can vary from excellent to complete decomposition of the substrates. We are continuing our investigations into the scope and limitations of this new ring-closing process to form seven-membered heterocycles.

Acknowledgment. We gratefully acknowledge the financial support provided by the National Science Foundation and Johnson & Johnson.

Supporting Information Available: Complete experimental details and full data for all ene-allene precursors and cycloisomerization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) **Representative Experimental Procedure.** To a flame-dried test tube equipped with a magnetic stirring bar were added *N*-[(*E*)-2-butenyl]-*N*-5,5-dimethyl-2,3-hexadienyl-4-methylbenzenesulfonamde (**5**, entry 3, Table 1, 29.9 mg, 0.009 mmol) and dichloroethane (DCE, 0.5 mL). The test tube was evacuated and charged with argon three times, and then $[Rh(CO)_2Cl]_2$ (1.7 mg, 0.0045 mmol) was added in DCE. The mixture was heated at 90 °C for 1.5 h and monitored by GC until the starting material was consumed. The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO_2, hexanes/ethyl acetate = 9:1) to afford **6,** entry 3, Table 1, as a colorless oil (28.3 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.68 (m, 2H), 7.32−7.29 (m, 2H), 6.35 (dd, J = 1.5 and 9.3 Hz, 1H), 5.21 (d, J = 1.0 Hz, 1H), 4.83 (dd, J = 5.5 and 9.3 Hz, 1H), 3.62 (ddd, J = 3.8, 7.7, 13.5 Hz, 1H), 3.52 (ddd, J = 3.8, 7.7, 13.5 Hz, 1H), 2.98 (dtq, J = 1.1, 7.0, 7.0, 1H), 2.73 (dddd, J = 1.1, 3.8, 7.7, 15.5, 1H), 2.55 (dddd, J = 1.1, 3.8, 7.7, 15.5, 1H), 2.42 (s, 3H), 1.07 (d, J = 7.2 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.8, 136.4, 135.3, 129.7, 126.9, 125.7, 119.1, 47.8, 41.0, 31.9, 31.2, 29.3, 21.5, 21.1; IR (neat) ν 2958, 1647, 1350, 1164 cm^{-1}; EI-HRMS calcd for $C_{19}H_{27}NO_2S$ $[M^+]$ *m*/*z* 333.1763, found 333.1777. The stereochemistry of the double bond was confirmed by NOE.