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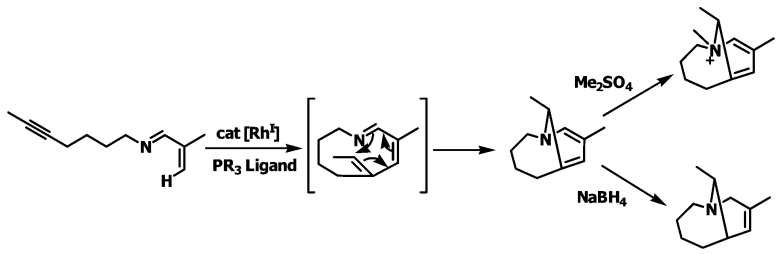

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The Stereoselective Formation of Bicyclic Enamines with Bridgehead Unsaturation via Tandem C−H Bond Activation/Alkenylation/Electrocyclization

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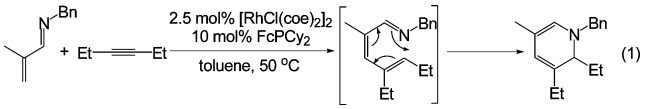
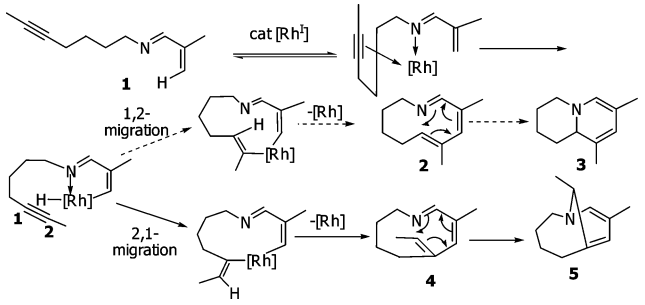
Rhodium-catalyzed intermolecular C−H activation of α,β-unsaturated imines in the presence of alkynes leads to a tandem process in which coupling to the alkyne occurs at the β-C−H bond of the imine, followed by electrocyclization of the resulting aza-triene intermediates to give dihydropyridines (eq 1).[1,2]



(1)

Consideration of the intramolecular version of this overall transformation (Scheme 1) raises interesting regiochemical issues. For example in a compound such as **1**, where the nitrogen and alkyne are connected by a 4-carbon tether, the presumed first-formed hydrido(vinyl)rhodium intermediate can add to the triple bond in a 1,2-fashion, producing complex **2** with a new endocyclic

Scheme 1. Proposed Mechanism for the Formation of **5**

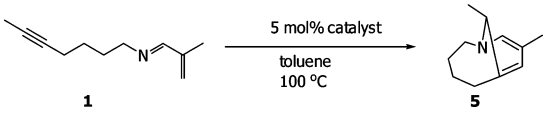


double bond. Alternatively, addition might occur in a 2,1-fashion, leading to product **4** with an exocyclic double bond.

We now wish to report that this intramolecular cyclization occurs smoothly at 100 °C, and the exocyclic double bond route is exclusively followed. Remarkably, products such as **4** do not resist further cyclization. Even though both the transition state for this process and the resulting product are presumably strained, the overall transformation leads to good yields of unusual bridgehead doubly bonded enamines such as **5**.[3] The unique chemistry of conjugated enamine **5** is consistent with the increased strain of this molecule as well as with inhibited conjugation between the nitrogen lone pair and the adjacent double bond (vida infra).

We began our investigation into the C−H activation/cyclization of alkyne-tethered imine **1** by extensive screening of transition metal catalysts for this process.[4] Rhodium-based catalysts were found to be the most efficient (Table 1), leading exclusively to the bridgehead dienamine; none of the catalysts that were employed in the screening led to quinolizidine **3** or to the product of intramolecular Diels−Alder reaction.

Table 1. Optimization of Reaction Conditions

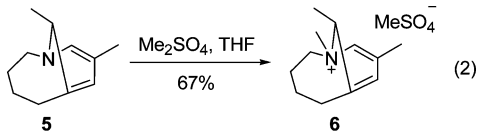


1 **5**

entry	catalyst	added ligand[a]	time (h)	% yield[b]
1	$Ru(H_2)CO(PPh_3)_3$		4	45
2	$Rh(PPh_3)_3Cl$		4	59
3	$[Rh(coe)_2Cl]_2$	PPh_3	2	41
4	$[Rh(coe)_2Cl]_2$	PCy_3	8	72
5	$[Rh(coe)_2Cl]_2$	$FcPCy_2$	4	52
6	**$[Rh(coe)_2Cl]_2$**	**(*p*-NMe_2)$PhPEt_2$**	**4**	**75 (54)[c]**
7	$[Rh(coe)_2Cl]_2$	(*p*-NMe_2)$PhPCy_2$	4	72

[a] Reaction run using 5 mol % ligand (1:1 ratio to the catalyst). [b] All yields were determined by NMR integration relative to 2,6-dimethoxytoluene as an internal standard. [c] Isolated yield.

The optimized reaction conditions employ the electron-rich monophosphine ligand (*p*-NMe_2)$PhPEt_2$ in 1:1 ratio relative to the metal (entry 6).[1b] Other phosphine ligands also provided product **5**, but lower yields were observed. Of particular note, the commercially available phosphine, PCy_3, gave yields that were nearly identical to those obtained using the optimized conditions (entry 4). Monitoring the progress of the reaction by NMR showed that the nine-membered ring aza-triene intermediate **4** was observed to form initially, as is proposed in Scheme 1. This intermediate undergoes spontaneous electrocyclization to form **5**.[5] In the Rh−H addition step, the geometry of the alkyne-tethered imine substrate presumably guides H-transfer to the less hindered site of the tethered alkyne.



5 **6** (2)

We also investigated the chemistry of **5** because of its novel structure. Upon treatment with Me_2SO_4, **5** was converted exclusively to *N*-methylated product **6** (eq 2), a regioselectivity that is opposite to that observed with acyclic and monocyclic enamines, which usually give *C*-alkylation.[6,7] Crystals of **6** suitable for X-ray analysis were obtained, and the resulting crystal structure (Figure 1) confirmed the structure for **5** proposed above. The bridgehead double bond of **6** is found to be significantly nonplanar (twist).[8] The deviation from the optimal planar geometry caused by the bicyclic structure in **5** presumably also results in poor delocalization of the nitrogen lone pair electrons into the adjacent diene orbitals, which would account for the observation of *N*-alkylation.[9]

10.1021/ja710981b CCC: $40.75

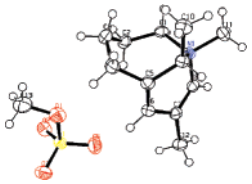
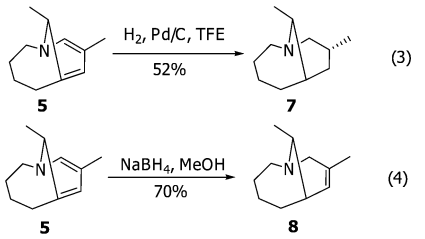


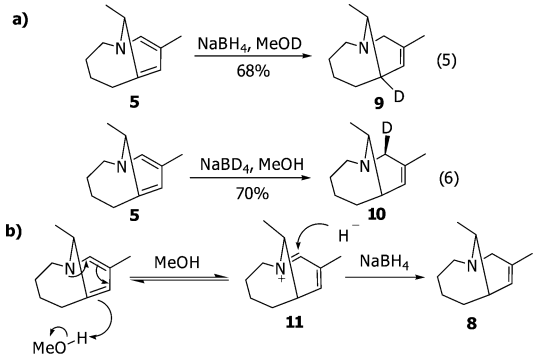
Figure 1. ORTEP diagram with 50% thermal ellipsoids illustrating the results of the X-ray crystal structure determination of **6**.

Hydrogenation of **5** under standard conditions gives the fully reduced tertiary amine product **7** as a single diastereomer (eq 3). Ring strain is also alleviated by reduction of **5** with $NaBH_4$ in methanol, which provides **8** as the only product (eq 4). This result contrasts with the reduction of 1,2-dihydropyridines under the same conditions, which proceeds to give a different double bond isomer.[10]



To investigate the mechanism of the borohydride reduction, two isotope labeling studies were conducted. Reduction of **5** with $NaBH_4$ in MeOD-d_4 results in the placement of a deuterium at the bridgehead (eq 5), while treatment of **5** with $NaBD_4$ in MeOH results in product that is deuterated at the position α to nitrogen (eq 6). On the basis of these observations, we propose that the overall reaction involves initial reversible protonation by MeOH to give iminium intermediate **11**, followed by hydride attack on the strained iminium double bond (Scheme 2b).

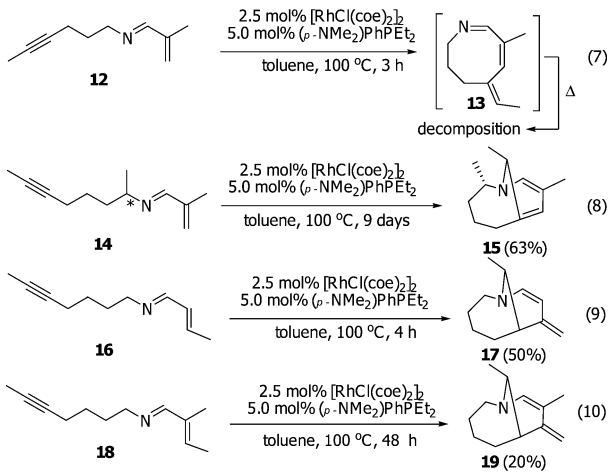
Scheme 2. (a) Isotope Labeling Experiments of $NaBH_4$ Reduction; (b) the Proposed Mechanism of $NaBH_4$ Reduction



Other α,β-unsaturated aldimine substrates with tethered alkynyl groups were also examined (Scheme 3). Imine **12** with a tether shorter than **1** undergoes C−H functionalization to form a smaller eight-membered ring aza-triene intermediate **13** (detectable by NMR). However, this unstable species decomposes over time and the bicyclic product analogous to **5** was not detected (eq 7). It is likely that the optimum geometry required for cyclization in the eight-membered ring cannot be achieved.

Imine **14** with a methyl group α to the nitrogen provides bridgehead nine-membered ring **15** as a single diastereomer (eq 8). The prolonged reaction time was necessary because of a slow electrocyclization step. We also investigated the reaction of substrate **16**, but the expected bridgehead product was not obtained. Instead, bicyclic amine **17** with an exocyclic double bond was formed (eq 9). This product is likely formed by isomerization to relieve ring strain. However, a lower yield was obtained in the case of the more highly substituted imine **18**.

Scheme 3. C−H Functionalization of Other Imine Substrates[11]



In summary, we have demonstrated the Rh-catalyzed C−H activation of alkyne-tethered α,β-unsaturated imines, followed by reaction of the activated intermediate with alkynes. This leads to an intermediate that undergoes further spontaneous, presumably thermal, electrocyclization to form strained bicyclic enamines with bridgehead unsaturation. The unique chemistry of these products in alkylation and reduction is a consequence of the strain in the bicyclic system.

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Supporting Information Available: Complete experimental details and spectral data for all compounds described (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) See Supporting Information for experimental procedures for the preparation and cyclization of alkyne-tethered imine substrates.
(5) Attempted isolation of the aza-triene intermediate resulted either in decomposition or spontaneous cyclization to give bridgehead product. Therefore, we are unable to determine whether electrocyclization is thermal rather than catalyzed by Rh, proton, or Lewis acid.
(6) Other methylating agents such as MeI also give *N*-methylation.
(7) Cook, A. G. In *Enamines: Synthesis, Structure and Reaction*; Marcel Dekker Inc.: New York-London, 1988; pp 181-204.
(8) Torsional angle = 146.2° (see CIF file in Supporting Information for more detail).
(9) A similar *N*-methylation of a twisted bridgehead enamine has been reported in ref 3a.
(10) For the reduction of 1,2-dihydropyridines with $NaBH_4$ in MeOH, see: (a) Casini, A.; Di Rienzo, B.; Micheletti Moracci, F.; Tortorella, S.; Liberatore, F. *Tetrahedron Lett.* **1978**, *24*, 2139. (b) Jacobson, A. E.; May, E. L. *J. Med. Chem.* **1964**, *7*, 409. (c) Jacobson, A. E.; May, E. J. *J. Med. Chem.* **1965**, *8*, 563. (d) Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Suzuki, Y.; Baba, Y.; Morita, T.; Fujiyama, H.; Nozaki, M.; Niwa, M. *J. Med. Chem.* **1985**, *28*, 1656.
(11) Yields were calculated by NMR integration relative to internal standard (see Supporting Information for isolated yields).

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