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Iron-Catalyzed, Hydrogen-Mediated Reductive Cyclization of 1,6-Enynes and Diynes: Evidence for Bis(imino)pyridine Ligand Participation

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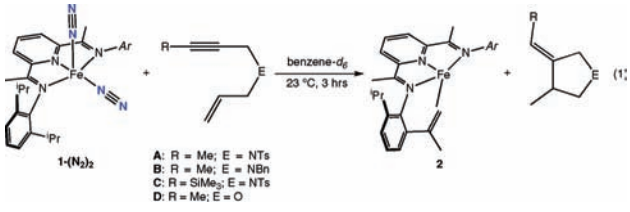
Rhodium-catalyzed, hydrogen-mediated reductive cyclization of 1,6-enynes and diynes has emerged as a powerful method for the construction of five-membered rings,[1] including enantiopure substituted heterocycles.[2] These methods augment previously reported Pd-catalyzed enyne cyclizations using either silanes[3,4] or weak acids as the stoichiometric reductants.[4,5] As interest grows in developing sustainable methods for organic synthesis, there has been a renewed global effort to replace expensive and toxic precious metals with more abundant and benign first-row base metals such as iron.[6−8]

As part of this focus, several iron-catalyzed cycloisomerization reactions have been described. Echavarren and co-workers have reported that simple iron salts such as $FeCl_3$ promote catalytic enyne cycloisomerization, although the substrate scope is limited.[9] Using the well-defined organometallic complex [Li(TMEDA)][(η^5-C_5H_5)Fe(C_2H_4)$_2$],[10] Fürstner et al. have discovered various iron-catalyzed enyne and diyne skeletal rearrangements, including Alder-ene, [4 + 2], [5 + 2], and [2 + 2 + 2] cycloadditions. Our laboratory has reported that the bis(imino)pyridine iron bis(dinitrogen)complex(^{iPr}PDI)Fe(N_2)$_2$[**1-(N_2)$_2$**;^{iPr}PDI=2,6-(2,6-^{i}Pr$_2$$C_6H_3$N=CMe)$_2$$C_5H_3$N] is a functional-group-tolerant precatalyst for the hydrogenation of olefins with activities that rival those of certain precious metal catalysts.[11,12] In addition, **1-(N_2)$_2$** also promotes the catalytic [2 + 2] cycloisomerization of 1,6-dienes to yield four- and five-membered bicycles (bicyclo[0.2.3]heptanes),[13] likely as a consequence of the redox-active chelating ligand that promotes reductive elimination and obviates formation of deleterious Fe(0) species.[12,13] Here we describe a combination of these two processes and report a base metal-catalyzed, functional group tolerant, hydrogen-mediated reductive cyclization of enynes and diynes.

Stirring stoichiometric quantities of 2-butynyl allyl tosylamine (**A**) with **1-(N_2)$_2$** for 3 h at 23 °C resulted in complete consumption of both starting materials. Analysis of the organic product by ^{1}H NMR spectroscopy and GC−MS established clean formation of the 3,4-disubstituted pyrrolidine with only one (*Z*)-alkene substituent, inconsistent with the Alder-ene product, which has two unsaturated ring substituents. Using established hydrolysis procedures for liberation of the free ligand[15] allowed the iron product to be identified as the intramolecular olefin complex **2** arising from net transfer hydrogenation to the enyne (eq 1). Thus, dehydrogenation of an isopropyl aryl substituent promotes iron-mediated reductive enyne cyclization.



The scope of the stoichiometric transfer hydrogenation reaction was examined with the benzylated amine (**B**), the $SiMe_3$-substituted tosyl amine (**C**), and 2-butynyl allyl ether (**D**). In each case, clean and selective reductive cyclization to the (*Z*)-olefin isomer was observed over the course of 3 h at 23 °C (eq 1). The conversion of **D** is noteworthy, as previous studies from our laboratory have demonstrated that **1-(N_2)$_2$** promotes irreversible C−O bond cleavage in allyl-substituted ethers and esters.[16]

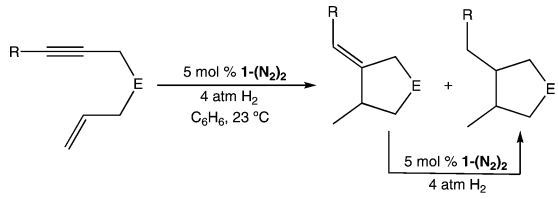
Silanes were also examined as terminal reductants to explore the possibility of iron-catalyzed silylcarbocyclization.[17] Addition of **A** to the bis(imino)pyridine iron bis(silane) complex **1-(PhSiH_3)$_2$**[11] produced in >95% yield (^{1}H NMR) the same pyrrolidine as obtained from transfer dehydrogenation (eq 1). Likewise, replacing the butynyl group with the terminal alkyne (Table 1, entry 2) also resulted in >95% conversion to the corresponding pyrrolidine. The product of dehydrogenative silane coupling, (PhSiH_2)$_2$, was detected in both reactions. Isolated yields ranged between 53 and 77% [see Table S3 in the Supporting Information (SI)].

Observation of a stoichiometric yet iron-promoted carbon−carbon bond-forming transformation prompted exploration of catalytic variants of the reaction. On the basis of precedent with rhodium[2] and the observation that **2** reacts cleanly with H_2 to yield a catalytically active iron dihydrogen complex,[11] H_2 was explored as the stoichiometric terminal reductant. Each hydrogen-mediated catalytic enyne cyclization was conducted with 5 mol % **1-(N_2)$_2$** at 23 °C in benzene solution under 4 atm H_2. The results of these studies are presented in Table 1. Tosyl-, benzyl-, and *tert*-butyl-protected aminoenynes all underwent facile hydrogen-mediated cyclization with turnover frequencies (TOFs) comparable to those of rhodium catalysts.[1] Oxygenated enynes (entries 8 and 9) were also rapidly cyclized, providing a convenient base-metal-catalyzed method for the synthesis of 3,4-disubstituted tetrahydrofurans. An ester-substituted cyclopentane was also assembled using this method, as the diethyl malonate-substituted enyne was also well tolerated by **1-(N_2)$_2$**.

Analysis of the cyclized products by NMR spectroscopy and GC−MS established that substitution on the alkyne influenced the product isolated from iron-catalyzed hydrogen-mediated cyclization. Monitoring of the hydrogen-mediated cyclization of enynes bearing terminal alkynes (entries 1−4 and 8) by ^{1}H NMR spectroscopy established the intermediacy of exo-methylene substituted pyrrolidines, tetrahydrofuran, and cyclopentane. Continued hydrogenation of these intermediates resulted in the formation of the corresponding dimethyl derivatives, which were the isolated products in each case. Analysis of the saturated products by NMR spectroscopy established a preference for the formation of the cis diastereomers over the trans ones. In three cases (entries 1, 3, and 4), the cis product was exclusive. Substrates bearing internal alkynes (entries 5−7 and 9) were also readily cyclized with little erosion in TOF. In these cases, only the unsaturated products were observed because of the reluctance of **1-(N_2)$_2$** to hydrogenate unactivated trisubstituted alkenes.[11,12]

10.1021/ja902478p CCC: $40.75

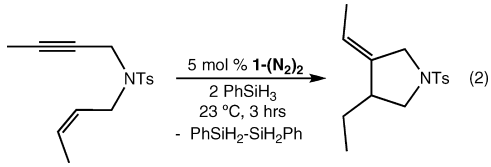
Table 1. Hydrogen-Mediated Enyne Cyclization[a]



entry	E	R	time (min)	yield (%)[b]	TOF (h^{-1})[c]	cis/trans (saturated)
1	N^{t}Bu	H	180	68	6.7	>99:1
2	NTs	H	60	79	20.0	75:25
3	NBn	H	180	71	6.7	>99:1
4	$NCH_2C_6Me_5$	H	180	57[d]	4.9	>99:1
5	NTs	Me	180	79	6.7	–
6	NBn	Me	180	71	6.7	–
7	NTs	$SiMe_3$	540	82	2.2	–
8	O	H	360	95	3.3	61:39[f]
9	O	Me	180	62	6.7	–
10	$(EtCO_2)_2C$	H	180	74[e]	6.7	79:21

[a] Conditions: 4 atm H_2 at 23 °C. [b] Isolated yield. [c] Determined at >95% conversion by ^{1}H NMR spectroscopy and 99% GC−MS. [d] Reduced alkyne compound (16%) was observed. [e] Reduced alkyne complex (26%) was observed. [f] After 24 h, 53% conversion to the 3,4-dimethyltetrahydrofuran was found.

Attempts to cyclize substrates bearing allylic substitution were also made. Catalytic hydrogenation of tosyl-protected butynyl butenyl amine under standard conditions furnished mostly open chain products resulting from conventional hydrogenation, with little evidence for cyclization. Interestingly, repeating the reaction with 2 equiv of $PhSiH_3$ as the stoichiometric reductant furnished the desired pyrollidine in >95% conversion (eq 2).



Following the discovery of a versatile iron-catalyzed hydrogenative carbon−carbon bond-forming reaction with enynes, the cyclization method was extended to diynes. The stoichiometric reaction between **1-$(N_2)_2$** and tosyl-substituted bis(2-butynyl)amine (**E**) cleanly furnished the (*Z*,*Z*)-3,4-diethylene-substituted pyrrolidine in high yield along with the expected dehydrogenated iron complex **2** (Figure 1).

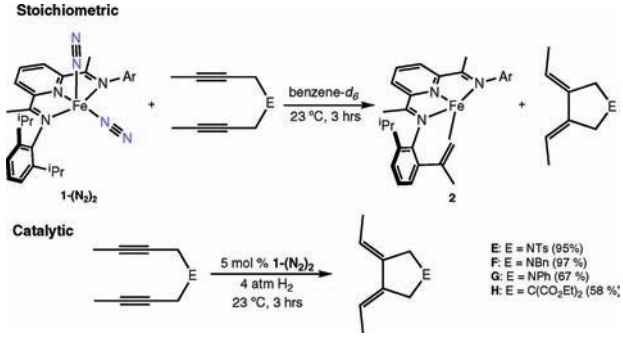


Figure 1. Stoichiometric and catalytic diyne cyclizations with **1-$(N_2)_2$**.

This outcome inspired the exploration of catalytic hydrogen-mediated diyne cyclization with substrates **E**−**H** in the presence of 5 mol % **1-$(N_2)_2$** and 4 atm H_2. Substrates **E**, **F**, and **G** were cleanly converted to the (*Z*,*Z*)-disubstituted pyrrolidines in high yield after 3 h at 23 °C. For the malonate, **H**, the desired cyclopentane was observed in only 58% yield. The remaining material was the open chain alkane derived from traditional homogeneous hydrogenation.

Experiments were also performed with D_2 gas to gain insight into the mechanism of the iron-catalyzed, hydrogen-mediated reductive enyne and diyne cyclizations. Tosylated amino enynes and diynes were used as representative substrates, and the isotopic compositions of all products were determined by a combination of ^{1}H and ^{2}H NMR spectroscopy and GC−MS. Catalytic cyclization of **A** with 5 mol % **1-$(N_2)_2$** and 4 atm D_2 furnished the pyrrolidine-d_2 isotopologue with the isotopic labels exclusively in the methyl group and the vinyl position of the exo alkenyl substituent (Figure 2). Repeating the experiment with the related terminal alkyne substrate furnished the d_4 isotopologue of the expected pyrrolidine with the additional deuterium incorporation arising from deuteration of the exo methylene pyrrolidine intermediate that was observed by ^{1}H and ^{2}H NMR spectroscopy during turnover. Analogous results were obtained with diynes, as catalytic deuteration of **E** furnished the pyrrolidine-d_2 with the two labels in the vinyl positions of the product (Figure 2).

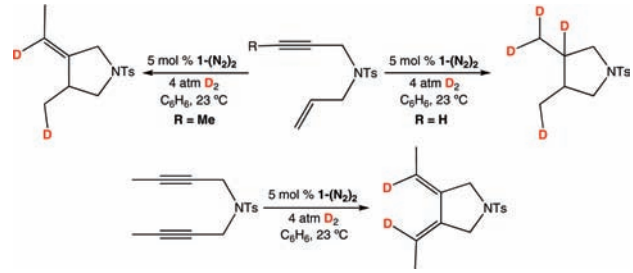


Figure 2. Catalytic reactions with D_2 gas.

Because transfer hydrogenation chemistry was observed in the stoichiometric cyclization reactions, experiments were also performed with the labeled iron dinitrogen complex **1*-$(N_2)_2$**, in which the isopropyl methyl substituents were deuterated.[11] Addition of 1 equiv of enyne **A** resulted in complete and exclusive conversion into two pyrrolidine-d_1 isotopomers (Figure 3), confirming transfer hydrogenation from the isopropyl aryl substituents. Monitoring of the stoichiometric reaction between **1-$(N_2)_2$** and **A** by ^{1}H NMR spectroscopy revealed immediate formation of a red, paramagnetic ($S = 2$) intermediate identified as the iron metallocycle **3**. Repeating the experiment with the isotopically labeled iron compound **1*-$(N_2)_2$** furnished the corresponding deuterated isotopologue **3*** (Figure 3), with no spectroscopic evidence for isotopic scrambling from the isopropyl methyl groups. Degradation studies with **3*** were also performed with NaOH/H_2O and NaOD/D_2O followed by analysis of the organic products by ^{1}H and ^{2}H NMR spectroscopy. This procedure established formation of natural abundance (exclusively) and pyrrolidine-d_2, respectively (Figure 3). Accordingly, treatment of natural abundance **3** with NaOD/D_2O yielded tosylated pyrrolidine-d_2.

Observation of **3** and its deuterated isotopologue **3*** allowed the measurement of the kinetic isotope effect (KIE) for transfer dehydrogenation and liberation of pyrrolidine. Monitoring of the formation of the isotopologues of the pyrrolidines from two separate solutions of **3** and **3*** by ^{1}H NMR spectroscopy at 23 °C yielded a normal primary KIE of 5.8(2) based on the time to reach >95% conversion. First-order rate constants (k_H/k_D) were also determined by monitoring the isotopologues of the pyrrolidine products as a function of time (see the SI). These experiments yielded a

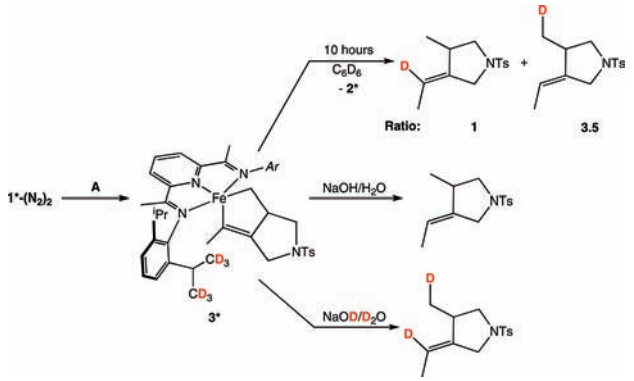


Figure 3. Detection of catalytic intermediates and isotopic-labeling studies.

statistically indistinguishable KIE of 6.0(2) at 23 °C. KIEs of this direction and magnitude are consistent with a C−H bond-breaking event in the turnover-limiting step.

On the basis of these observations, a mechanism for the iron-catalyzed, hydrogen-mediated enyne cyclization is proposed (Figure 4). Cyclization of the substrate upon addition to $\mathbf{1}\text{-}(\mathbf{N_2})_2$ is rapid. On the basis of previous studies from our laboratory with model complexes[14] and the [2 + 2] cycloaddition,[13] we believe that reductive cyclization to form the carbon−carbon bond involves electron transfer and formal oxidation of the bis(imino)pyridine chelate rather than the iron center. Thus, the ferrous oxidation state is preserved throughout the catalytic cycle (Figure 4).

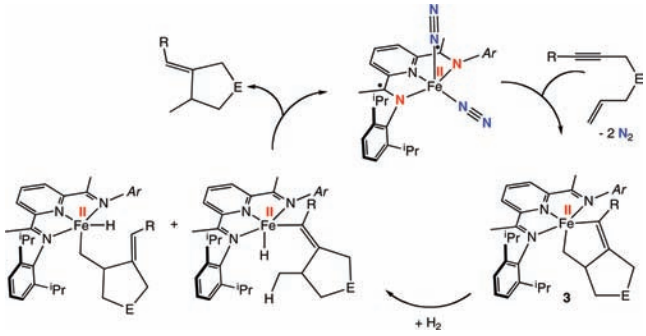


Figure 4. Proposed mechanism for the iron-catalyzed, hydrogen-mediated enyne cyclization.

Observation of **3** under a variety of conditions in conjunction with the KIEs establishes the hydrogenation step as turnover-limiting (Figure 4). Unfortunately, the lack of observables following metallocycle formation limits the amount of available experimental data. Hydrogenation of **3** can occur either at the alkyl or alkenyl position of the metallocycle to form the corresponding iron alkenyl or alkyl hydride intermediate. Deuterium-labeling studies with **3*** (Figure 3) establish that both intermediates are formed. The H_2 addition step and formation of the new C−H and Fe−H bonds can occur either by oxidative addition/reductive elimination or by σ-bond metathesis. Unlike the rhodium-catalyzed variant of this reaction,[1,2b] homolytic rather than heterolytic dihydrogen cleavage is proposed, as exogenous base is not required for turnover. Reductive elimination of a carbon−hydrogen bond from these intermediates forms the observed product and regenerates (in principle) $\mathbf{1}\text{-}(\mathbf{N_2})_2$. The dinitrogen complex is drawn for simplicity, but it is likely that under catalytic conditions the iron dihydrogen or alkyne complex forms following product release.[11]

The lack of deuterium incorporation from the D_2-mediated catalytic cyclization of **A** eliminates a pathway involving β-hydrogen elimination from the iron alkyl hydride to form a bis(alkenyl)-substituted pyrrolidine that is subsequently hydrogenated. A cycle similar to the one presented in Figure 4 is likely operative for catalytic diyne cyclization. The mechanism of the stoichiometric transfer hydrogenation cyclization is also worthy of comment. Following formation of **3**, it is likely that an oxidative addition/reductive elimination or a σ-bond metathesis sequence of a C−H bond from an isopropyl methyl group forms the iron dialkyl or alkenyl alkyl intermediate. Subsequent β-hydrogen elimination from the cyclometalated isopropyl group yields an iron alkenyl (or alkyl) hydride, which undergoes C−H reductive elimination to yield the observed product. It is important to note that because the labeled iron dinitrogen complex $\mathbf{1^*}\text{-}(\mathbf{N_2})_2$ was deuterated only in the methyl position, only pyrrolidine-d_1 isotopologues were formed (Figure 3).

In summary, an iron-catalyzed, hydrogen-mediated method for the reductive cyclization of enynes and diynes has been discovered. The substrate scope and turnover frequencies are comparable to those for established precious metal catalysts, demonstrating that when coaxed into the appropriate coordination environment, iron can indeed perform noble tasks.

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Supporting Information Available: Complete experimental procedures and representative NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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