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 silanes3-5 or weak acids as the stoichiometric reductants.4,6 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 FeCl3 promote catalytic enyne cyclizations, although the substrate scope is limited.9 Using the well-defined organometallic complex [Li(TMEDA)][(η5-C3H2Fe(C5H3)N)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 (Ph3Si)2(C5H4)2Fe(N2)2[1-(N2)2]11 produced in >95% yield (1H 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 pyrroline. The product of dehydorgenative silane coupling, (PhSiH2)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 rhodium2 and the observation that 2 reacts cleanly with H2 to yield a catalytically active iron dihydrogen complex,11 H2 was explored as the stoichiometric terminal reductant. Each hydrogen-mediated catalytic enyne cyclization was conducted with 5 mol % 1-(N2)2 at 23 °C in benzene solution under 4 atm H2. The results of these studies are presented in Table 1. Tosyl-, benzyl-, and tert-butyll-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 eser-substituted cyclopentanel was also assembled using this method, as the diethyl malonate-substituted enyne was also well tolerated by 1-(N2)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 1H NMR spectroscopy established the intermediacy of exo-methylene substituted pyrrolidines, tetrahydrofurans, and cyclopentanes. 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-(N2)2 to hydrogenate unactivated trisubstituted alkenes.11,12

The scope of the stoichiometric transfer hydrogenation reaction was examined with the benzylated amine (B), the SiMe3-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-(N2)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-(Ph-SiH2)2 produced in >95% yield (1H 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 pyrroline. The product of dehydorgenative silane coupling, (PhSiH2)2, was detected in both reactions. Isolated yields ranged between 53 and 77% [see Table S3 in the Supporting Information (SI)].
Table 1. Hydrogen-Mediated Enyne Cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>E</th>
<th>R</th>
<th>time (min)</th>
<th>yield (%)</th>
<th>cis/trans (%)</th>
<th>TOF (h⁻¹)</th>
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<tr>
<td>1</td>
<td>N'Bu</td>
<td>H</td>
<td>180</td>
<td>68</td>
<td>6.7</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>NTs</td>
<td>H</td>
<td>60</td>
<td>79</td>
<td>20.0</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>NBn</td>
<td>H</td>
<td>180</td>
<td>71</td>
<td>6.7</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>NCH₂₂₅Me₅</td>
<td>H</td>
<td>180</td>
<td>57</td>
<td>4.9</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>NTs</td>
<td>Me</td>
<td>180</td>
<td>79</td>
<td>6.7</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>NBn</td>
<td>Me</td>
<td>180</td>
<td>71</td>
<td>6.7</td>
<td>99:1</td>
</tr>
<tr>
<td>7</td>
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<td>SiMe₅</td>
<td>540</td>
<td>95</td>
<td>3.3</td>
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<tr>
<td>8</td>
<td>O</td>
<td>H</td>
<td>360</td>
<td>95</td>
<td>6.7</td>
<td>99:1</td>
</tr>
<tr>
<td>9</td>
<td>O</td>
<td>Me</td>
<td>180</td>
<td>62</td>
<td>6.7</td>
<td>99:1</td>
</tr>
<tr>
<td>10</td>
<td>(EtCO₂)₂C</td>
<td>H</td>
<td>180</td>
<td>74</td>
<td>6.7</td>
<td>79:21</td>
</tr>
</tbody>
</table>

*a* Conditions: 4 atm H₂ at 23 °C. *b* Isolated yield. *c* Determined at >95% conversion by 1H 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 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 PhSiH₃ as the stoichiometric reductant furnished the desired pyrrolidine in >95% conversion (eq 2).

Following the discovery of a versatile iron-catalyzed hydrogenative carbon–carbon bond-forming reaction with enynes with enynes, the cyclization method was extended to diynes. The stoichiometric reaction between 1-(N₂)₂ and tosyl-substituted bis(2-butynyl)amine (E) cleanly furnished the (Z,Z)-3,4-diyne-substituted pyrrolidine in high yield along with the expected dehydrogenated iron complex 2 (Figure 1).

However, the reaction with E furnished the corresponding deuterated isotopologue 3 (Figure 2), in which the isopropyl aryl substituents were deuterated. Addition of 1 equiv of enyne A resulted in complete and exclusive conversion into two pyrrolidine-d₁ isomers (Figure 3), confirming transfer hydrogenation from the isopropyl aryl substituents. Monitoring of the stoichiometric reaction between 1-(N₂)₂ and A by 1H 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 complex 1*-(N₂)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/H₂O and NaOD/D₂O following by analysis of the organic products by 1H and 2H NMR spectroscopy. This procedure established formation of natural abundance (exclusively) and pyrrolidine-d₂, respectively (Figure 3). Accordingly, treatment of natural abundance 3 with NaOD/D₂O yielded tosylated pyrrolidine-d₂.

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 1H 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_D/k_H) were also determined by monitoring the isotopologues of the pyrrolidine products as a function of time (see the SI). These experiments yielded a
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 1-(N2)2 is rapid. On the basis of previous studies from our laboratory with model complexes and the [2 + 2] cycloaddition, 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 3. Detection of catalytic intermediates and isotopic-labeling studies.

The lack of deuterium incorporation from the D2-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 dinyne 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 an α-bond metathesis sequence of a C–H bond from an isopropyl methyl group forms the iron dialkyl or alkyl alkyl intermediate. Subsequent β-hydrogen elimination from the cyclometalated isopropyl group yields an iron alkylen (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 1-(N2)2 was deuterated only in the methyl position, only pyrrolidine-d1 isotopologues were formed (Figure 3).

In summary, an iron-catalyzed, hydrogen-mediated method for the reductive cyclization of enynes and dienes 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.

References