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Iron-Catalyzed Reductive Cyclization of 1,6-Enynes

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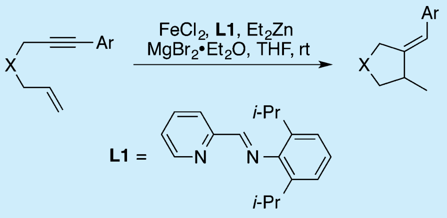
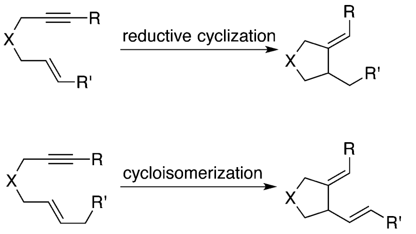
Ⓢ *Supporting Information*

ABSTRACT: A precatalyst of $FeCl_2$ and iminopyridine was activated in situ by a combination of diethylzinc and magnesium bromide etherate; it catalyzed the reductive cyclization of 1,6-enynes to give pyrrolidine and tetrahydrofuran derivatives from *N*- and *O*-tethered 1,6-enynes. The scope of the transformation was explored.



Iron catalysis for organic synthesis has experienced significant growth in recent decades.[1] Compared with other late transition metals, iron stands out because it is one of the most abundant elements in the Earth's crust, and most of iron salts are nontoxic. Thus, development of iron-based catalysis is desirable because of its relevance to "green" chemical processes and to a more sustainable chemical industry. Further, iron catalysis frequently shows reactivities and selectivities complementary to other transition metal catalysis: facets that can be exploited synthetically. The reductive cyclization and cycloisomerization of 1,6-enynes are powerful approaches for the synthesis of five-membered carbo- and heterocycles from acyclic substrates (Scheme 1).[2] Whereas a number of transition metal catalysts have been developed for these transformations, very few examples of iron catalysis exist.[3] Specifically, Fürstner described the Alder-ene cycloisomerization of 1,6-enynes using a well-defined low-valent organoiron complex $[Li(TMEDA)][(\eta^5\text{-}C_5H_5)Fe(C_2H_4)_2]$ as the catalyst,[4] and the reductive cyclization of 1,6-enynes with the bis(imino)pyridine iron bis(dinitrogen) complex $[(^{i\text{-}Pr}PDI)Fe(N_2)_2]$ was reported by Chirik.[5,6] Both of these transformations make use of air-sensitive organoiron complexes that have to be separately prepared, and the latter also has to be carried out under an atmosphere of H_2 under pressure. As part of our efforts to develop practical and sustainable iron-catalyzed transformations, herein we report an operationally simple approach for iron-catalyzed reductive cyclization of unactivated 1,6-enynes to give pyrrolidine and tetrahydrofuran derivatives. This transformation was enabled by the discovery of Et_2Zn and $MgBr_2$·Et_2O as a unique combination for activating a precatalyst consisting of $FeCl_2$ and a bidentate iminopyridine ligand.

Scheme 1. Reductive Cyclization and Cycloisomerization of 1,6-Enynes



At the outset of our research, we envisioned that a catalytically competent low-valent iron species might be formed by the reaction of $FeCl_2$ and the Grignard reagents.[7] Thus, we commenced with the reductive enyne cyclization of the *N*-tethered 1,6-enyne **1a** by treatment with $FeCl_2$ and cyclopentylmagnesium bromide in THF (Table 1, entry 1). The initial results were promising as the desired cyclization product **2a** was obtained in 20% yield as a single (*Z*)-isomer. Similar yields were obtained when ethylmagnesium bromide (entry 2) or isopropylmagnesium bromide (entry 3) were used. In an effort to improve reaction efficiency, we also tested diethylzinc as a reducing agent for generating the catalytic iron species. Whereas diethylzinc alone gave **2a** in 26% yield at room temperature over 12 h or in 43% yield at 60 °C over 6 h (entries 4 and 5), addition of $MgBr_2$·Et_2O and ligand **L1** led to a dramatic improvement of the reaction,[8] which was complete in 6 h at room temperature to give **2a** in 78% yield (entry 8). The same product was obtained with a comparable yield when $FeCl_2$ of 99.99% purity was employed (entry 9), indicating that the transformation was indeed under iron catalysis.[9] Interestingly, low conversion of the reaction was observed when **L1** was used as the sole additive (entry 6), and rapid degradation of the starting material occurred when $MgBr_2$·Et_2O was used by itself (entry 7). Reduction of the amount of either Et_2Zn or $FeCl_2$ led to decreased yield (entries 10 and 11). Further screening of the reaction conditions, which included testing various ligands (**L2**−**L7**, entries 10−15), iron precatalysts (Table S1, Supporting Information), and solvents (Table S1, Supporting Information), led us to choose the conditions shown in entry 8 for all subsequent reactions.[10]

The scope of the reaction was evaluated using various substrates, and the results are shown in Figure 1. *N*-Tethered 1,6-enynes with a methoxy group at either the *para*- or *meta*-position of the aryl group were found to be compatible with the

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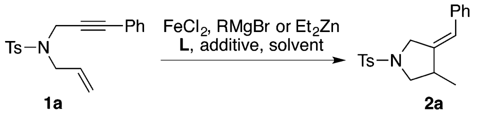
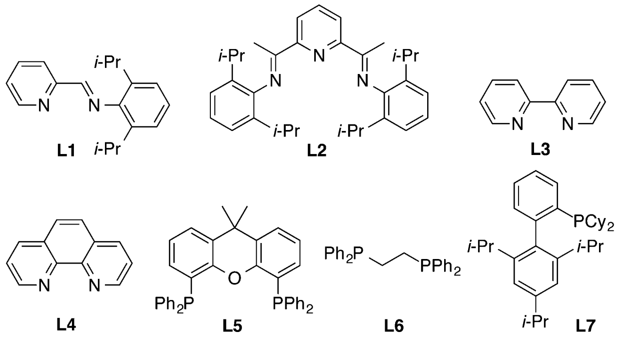
Table 1. Screening of Reaction Conditions[a]





entry	L	RM	additive	time (h)	yield[b] **2a** (%)
1[c]	–	C_5H_5MgBr	–	6	20
2[c]	–	EtMgBr	–	6	17
3[c]	–	*i*-PrMgBr	–	6	22
4	–	Et_2Zn	–	12	26
5[d]	–	Et_2Zn	–	6	43
6	**L1**	Et_2Zn	–	16	<10
7	–	Et_2Zn	$MgBr_2{\cdot}Et_2O$	16	trace
8	**L1**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	78
9[e]	**L1**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	75
10[f]	**L1**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	56
11[g]	**L1**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	43
12	**L2**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	41
13	**L3**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	29
14	**L4**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	33
15	**L5**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	18
16	**L6**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	30
17	**L7**	Et_2Zn	$MgBr_2{\cdot}Et_2O$	6	22

[a] Reactions typically carried out with 0.2 mmol of **1a**, 20 mol % of $FeCl_2$, 20 mol % of the ligand, 3.0 equiv of Et_2Zn, and 1.0 equiv of $MgBr_2{\cdot}Et_2O$ in 3.0 mL of THF at room temperature. [b] Isolated yield. [c] 1.5 equiv of RMgBr was used. [d] The reaction was carried out at 60 °C. [e] $FeCl_2$ of 99.99% purity was used. [f] 2.0 equiv of Et_2Zn was used. [g] 10 mol % of $FeCl_2$ was used.

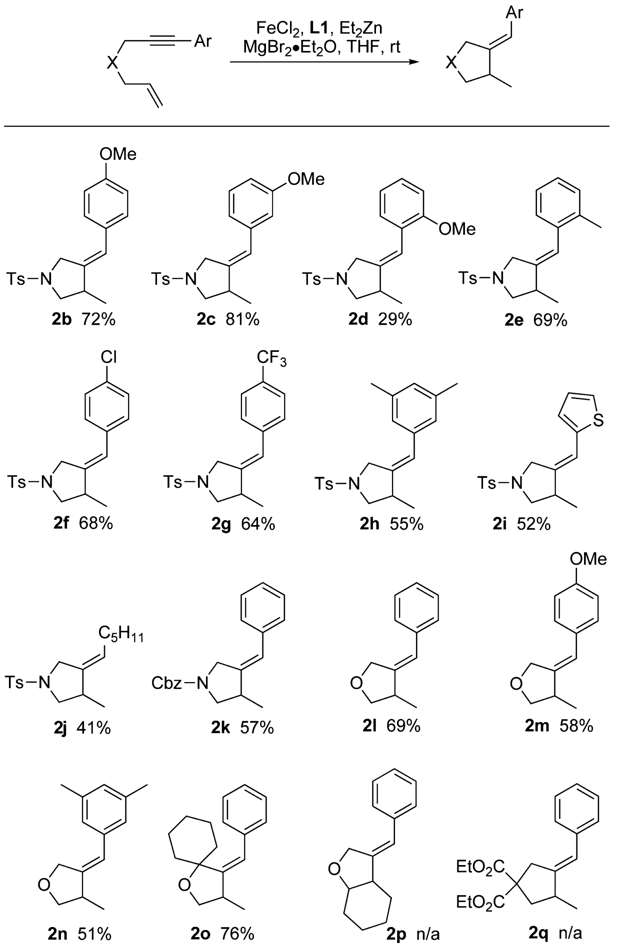
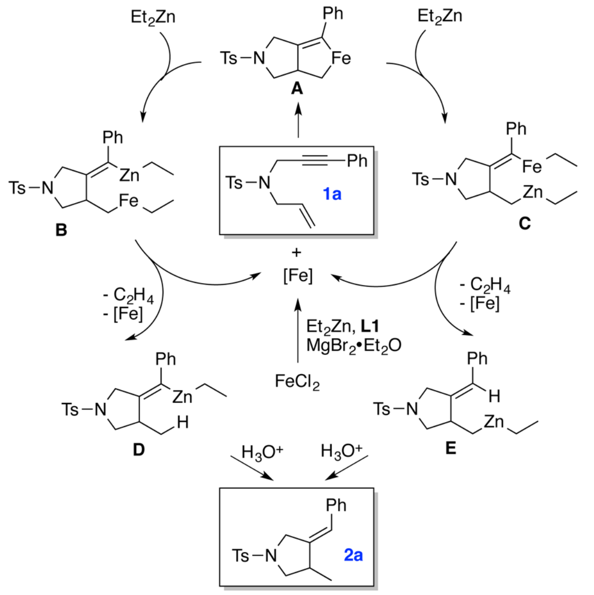


Figure 1. Substrate scope. Reactions were carried out with 20 mol % of $FeCl_2$, 20 mol % of **L1**, 3.0 equiv of Et_2Zn, and 1.0 equiv of $MgBr_2{\cdot}Et_2O$ in THF at room temperature.

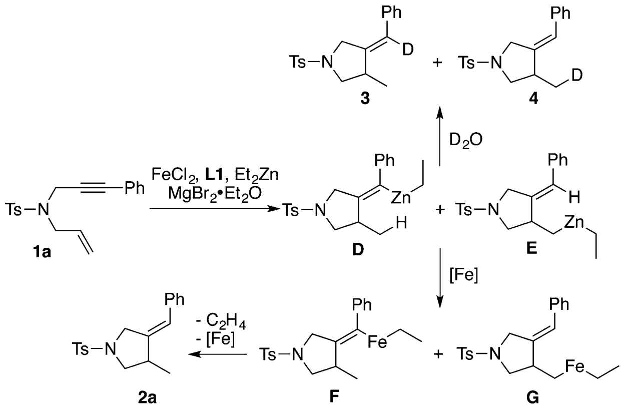
reaction, and the reductive cyclization products were obtained in good yields (72% yield for **2b** and 81% yield for **2c**). However, the same substituent at the *ortho*- position of the aryl led to formation of **2d** with significantly reduced efficiency (29%). This was attributed to unfavorable interactions of the lone pair of the methoxy group and the catalytic center. Indeed, the corresponding *ortho*-methyl substrate gave the product (**2e**) in 69% yield.[11] Electron-withdrawing chloro- or trifluoromethyl groups at the *para*- position of the aryl led to products in 68% (for **2f**) and 64% (for **2g**) yield, respectively, and the chloride substituent remained intact under the reaction conditions. Disubstitution at the 3′- and 5′-positions of the aryl with two methyl groups caused a somewhat reduced yield (**2h**, 55%). The reaction also proceeded smoothly with a thiophene-containing 1,6-enyne substrate to give **2i** in 52% yield. An alkyl-substituted enyne substrate was found to give the desired product **2j** in 41% yield. The *N*-tosyl of the *N*-tethered enyne substrate could be replaced with the *N*-Cbz, and the reductive cyclization product **2k** was obtained in 57% yield. We further tested this transformation using *O*-tethered 1,6-enynes. Despite the potential competing reductive elimination pathway with these substrates, methylene tetrahydrofurans **2l**−**2n** were obtained in good to moderate yields under the reaction conditions. The Thorpe−Ingold effect likely contributed to the higher efficiency for formation of **2o**.[12] Our experiments also revealed a limitation of the reaction. Despite our efforts, the enyne substrate with an internal alkene failed to deliver the desired product **2p** under the current reaction conditions. A diethyl malonate-tether substrate also failed to deliver the expected product **2q**.

Although the exact nature of the iron catalyst is unknown, we speculate that the reductive cyclization of **1a** proceeds as shown in Scheme 2. It starts with formation of metallacycle **A** by oxidative cyclization of **1a** with a low-valent iron species, which was generated from $FeCl_2$ and $MgBr_2{\cdot}Et_2O$ with Et_2Zn in the presence of **L1**. Transmetalation of **A** with Et_2Zn cleaves the metallacycle and gives intermediates **B** and **C**, which can convert to **D** and **E** through rapid *β*-hydride elimination followed by reductive elimination of the iron hydride intermediates. The catalytic iron species is also regenerated. Protonolysis of **D** and **E** gave **2a.**[13] This proposed mechanistic pathway is consistent with the following experimental observation: The monodeuterated products **3** and **4** and the undeuterated **2a** were obtained in 49:31:19 ratio from **1a** upon quenching the reaction with D_2O (Scheme 3). Whereas deuterolysis of **D** and **E** led to **3** and **4**, formation of a small

Scheme 2. Proposed Reaction Mechanism



Scheme 3. Deuteration Study



amount of the undeuterated **2a** likely proceeded by transmetalation of **D** and **E** with an iron species to give **F** and **G**. Compound **2a** was formed upon β-hydride and reductive eliminations of **F** and **G**. For reasons yet to understand, our attempts of trapping the organometallic intermediates with common electrophiles have been unsuccessful.[14]

In summary, we have developed an operationally simple iron-catalyzed reductive cyclization of 1,6-enynes. This transformation was enabled by the unique combination of diethylzinc and $MgBr_2 \cdot Et_2O$ for converting the precatalyst $FeCl_2$ and the α-iminopyridine ligand into the catalytically competent species in situ. Functionalized pyrrolidine and tetrahydrofuran derivatives were obtained from *N*- and *O*-tethered 1,6-enynes in good-to-moderate yields. We elucidated the scope of the reaction and revealed its limitations. Further exploration of the utility of this iron-based catalytic system and elucidation of its exact mechanism of action will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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