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Cooperative Metal−Ligand Catalyzed Intramolecular Hydroamination and Hydroalkoxylation of Allenes Using a Stable Iron Catalyst

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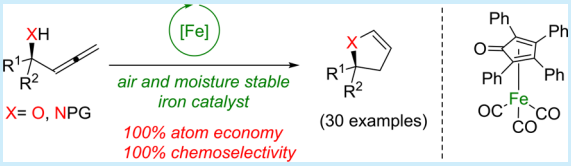
Supporting Information

ABSTRACT: A new iron-catalyzed chemoselective intramolecular hydroamination and hydroalkoxylation of the readily available α-allenic amines and alcohols to valuable unsaturated 5-membered heterocycles, 2,3-dihydropyrrole and 2,3-dihydrofuran, is reported. Effective selectivity control is achieved by a metal−ligand cooperative activation of the substrates. The mild reaction conditions and the use of low amounts of an air and moisture stable iron catalyst allow for the hydrofunctionalization of a wide range of allenes bearing different functional groups in good yields in the absence of base or any sensitive additives.



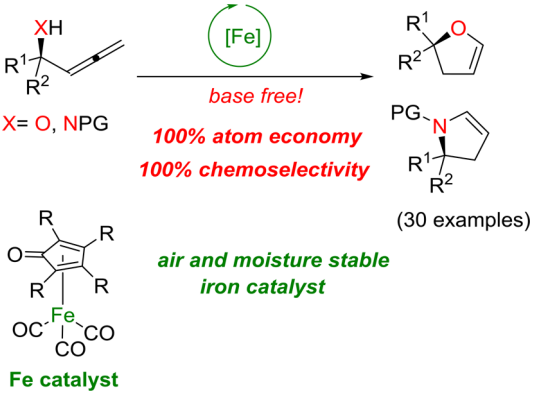
Nitrogen- and oxygen-containing heterocycles are present in most naturally occurring and biologically relevant compounds.[1] Therefore, the development of efficient atom-economical methods for the synthesis of heterocyclic compounds is of importance. One elegant approach for the synthesis of heterocycles is the transition-metal-catalyzed intramolecular hydrofunctionalization of allenes with heteroatom nucleophiles.[2] Recently, we reported that air- and moisture-stable iron cyclopentadienone complexes can be applied for carboetherifications and the synthesis of deoxygenated 6-membered oxygen-based heterocycles.[3] This unusual transformation was observed during our investigation of iron cyclopentadienone complexes as hydrogen autotransfer catalysts in dynamic kinetic resolutions.[4,5]

Regarding the intramolecular hydroalkoxylation of α-allenic alcohols to 2,5-dihydrofuran a procedure using 5−10 mol % of $AuCl_3$ was reported by Krause et al.[6] More recently, Bäckvall and co-workers applied 4 mol % of a ruthenium-based catalyst to achieve the intramolecular addition reaction.[7] In addition to these preliminary studies, the intramolecular hydrofunctionalization of allenes with *N*-nucleophiles has been explored. This transformation leads to valuable dihydropyrroles, a ring system which is ubiquitous in natural products and is frequently used as a precursor in the synthesis of natural products and bioactive molecules, such as serotonin reuptake inhibitor from Eli Lilly.[8] So far, the *endo*-cyclization of allene amines was achieved using silver[9] and gold(III)[10] catalysts. In analogy to the hydroalkoxylations, these reactions afford the 2,5-dihydropyrrole regioisomer.

To the best of our knowledge, a catalytic intramolecular hydroamination of allenic amines to cyclic enamines has not been reported, although the products would be valuable intermediates which could be easily modified. Therefore, we decided to examine whether the readily available and stable iron cyclopentadienone catalysts could be applied as general catalysts for the intramolecular hydro-functionalization of allenes.

Herein, we report a general and efficient *endo*-hydrofunctionalization of allenes with nitrogen and oxygen nucleophiles to afford useful 2,3-dihydropyrroles and 2,3-dihydrofurans (Scheme 1).

Scheme 1. Iron-Catalyzed Hydroamination and Hydroalkoxylation of Allenes



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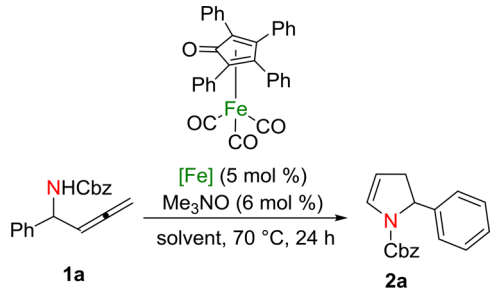
Our studies began with the examination of different cyclopentadienone iron catalysts for the intramolecular hydroamination of allenes. From the outset, we focused on readily removable amine protecting groups, such as the Cbz-protected amine **1a**.

The best results were achieved with the tetraphenyl-substituted cyclopentadienone iron tricarbonyl catalyst [**Fe**]. This air- and moisture-stable complex can be easily synthesized by reaction of two commercially available inexpensive substrates, tetraphenylcyclopentadienone and iron pentacarbonyl.[11] [**Fe**] can be activated in situ by oxidative decarbonylation using trimethylamine *N*-oxide. The hydroamination of the Cbz-allenic amine **1a** was subsequently examined using 5 mol % of [**Fe**] at 70 °C in different solvents (Table 1). When the reaction was performed in toluene, the desired enamine **2a** was obtained in 72% yield (Table 1, entry 1). The application of hexane as a solvent led to only 40% yield (Table 1, entry 2).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

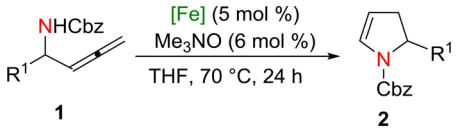
entry	solvent	yield (%)
1	toluene	72
2	hexane	40
3	DCE	39
4	THF	90
5	dioxane	89
6	CPME	76
7	acetonitrile	32
8[b]	**THF**	87

[a]Reaction conditions: **1** (0.1 mmol), [Fe] (5 mol %), and Me_3NO (6 mol %) in solvent (0.5 mL) were stirred at 70 °C for 24 h in a Schlenk tube under an inert atmosphere. Yields determined by ^1H NMR using mesitylene as internal standard. [b]**1** (0.5 mmol) in 1 mL of THF. Yield of product after chromatography. CPME = cyclopropyl methyl ether

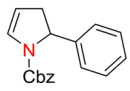
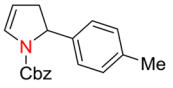
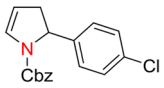
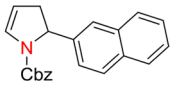
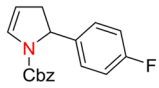
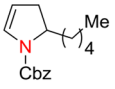
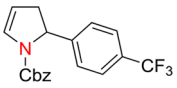
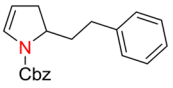
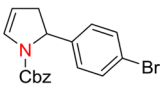
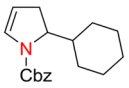
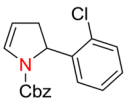
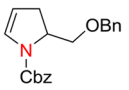
Furthermore, the halogenated solvent dichloroethane gave the same product in low yield (Table 1, entry 3). Further screening of solvents showed that ethers are superior to nonpolar solvents (Table 1, entries 4–6). The best results were obtained when the reaction was performed in tetrahydrofuran, and the desired product was isolated in 87% yield (Table 1, entries 4 and 8). Use of acetonitrile gave only 32% yield, which can be explained by the strong coordination of the acetonitrile with the active iron species (Table 1, entry 7).

In order to demonstrate the broad practicability of our newly developed method, we applied the optimized cyclization protocol to various allenic amines (Table 2) bearing different functionalities. Thus, various 2,3-dihydropyrroles can be effectively obtained in good yields. Next to 2,3-dihydropyrrole **2a**, which was isolated in 87% yield (Table 2, entry 1), dihydropyrroles **2b–e** bearing electron-withdrawing substituents in the para position of the arene were also obtained in very good yields (Table 2, entries 2–5). Allenic amine **1f** with an electron-withdrawing substituent in the ortho position gave the corresponding pyrrole in 74% yield (Table 2, entry 6), while **1g** with an electron-donating methyl group was cyclized in a good yield of 69% (Table 2, entry 7). Furthermore, the 2-naphthyl-substituted 2,3-dihydropyrrol **2h** was isolated in 81% yield (Table 2, entry 8). Our method could also be applied to the aliphatic allenic amines **1i–l**, leading to the corresponding heterocycles **2i–l** in moderate to good yields (Table 2, entries 9–12). This cyclic enamine **2l** is of relevance as it can be used for the synthesis of the pyrrole analogues of several antibiotics.[12]

Table 2. Iron-Catalyzed Hydroamination of α-Allenic Amines[a]



1 **2**

entry	heterocycle	entry	heterocycle
1	 **2a** (82%)	7	 **2g** (69%)
2	 **2b** (78%)	8	 **2h** (81%)
3	 **2c** (86%)	9	 **2i**[b] (57%)
4	 **2d** (81%)	10	 **2j** (82%)
5	 **2e** (60%)	11	 **2k** (67%)
6	 **2f** (74%)	12	 **2l** (60%)

[a]Reaction conditions: 1 (0.5 mmol), [Fe] (5 mol %) and Me_3NO (6 mol %) in THF (1 mL) were stirred at 70 °C for 24 h in a Schlenk tube under inert atmosphere. Isolated yields are given. [b][Fe] (10 mol %) and Me_3NO (12 mol %).

Following the successful development of the intramolecular hydroamination of allenes to provide 2,3-dihydropyrroles, we became interested in the generalization of this new protocol by applying α-allenic alcohols.

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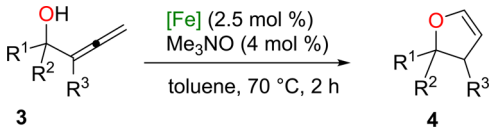
This hydroalkoxylation would result in valuable 2,3-dihydrofurans. To our delight, α-allenic alcohols could also successfully be applied. Indeed, if compared to α-allenic amines the reaction proceeded faster, and thus, a reduction to 2.5 mol % of the [**Fe**] catalyst was feasible to provide the product in 2 h. It is noteworthy that the required catalyst loading for the previously reported Ru protocol was 4 mol %, which further highlights the advantage of the current base-metal alternative. We then investigated the scope of iron-catalyzed intramolecular hydroalkoxylation of allenic alcohols (Table 3). Various aryl-substituted allenic alcohols could be applied, showing the generality of our method. All investigated substrates bearing electron-withdrawing groups and electron-donating groups **3a**–**g** reacted smoothly, providing the corresponding 2,3-dihydrofurans in high yields (Table 3, entries 1–7). Furthermore, the carboetherification of the naphthyl-substituted allenic alcohol **3h** proceeds well to afford the corresponding furan in 95% yield (Table 3, entry 8). Moreover, several cyclic and acyclic aliphatic derivatives **3i**–**l** were cyclized to the unsaturated furans **4i**–**l** in good yields (Table 3, entries 9–12). Importantly, deoxysugar **4l** is of high relevance as it is industrially used in the synthesis of clinically relevant antibiotics such as AZT, d4T, and puromycin.[12] Interestingly, the unsaturated furan bearing conjugated double bond **4m** was also obtained in good yield (Table 3, entry 13). The new protocol was also found to be applicable to heteroarenes as demonstrated for the derivatives **4n** and **4o** (Table 3, entries 14 and 15). Importantly, our catalytic system has been useful for the construction of the spirocyclic ethers such as **4p** (Table 3, entry 16). Moreover, the hydroalkoxylation of the tertiary alcohol **3q** gave the furan **4q** bearing a quaternary carbon atom (Table 3, entry 17). Following the successful demonstration of the applicability of the newly developed iron catalyzed hydroalkoxylation of 1-substituted allenols, we turned our attention to the use of 1,2-disubstituted α-allenols, which should provide two different diastereomers. Applying the same protocol, we could convert the disubstituted allenic alcohol **3r** to the corresponding disubstituted dihydrofuran in 68% yield and 4:1 diastereomeric ratio, demonstrating a new and efficient method for the construction of cyclic ethers with two chiral centers (Table 3, entry 18).

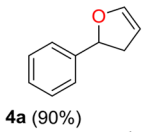
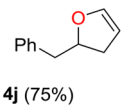
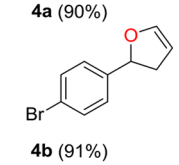
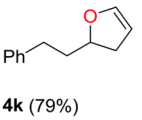
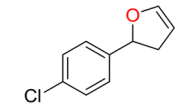
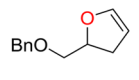
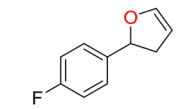
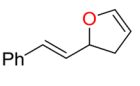
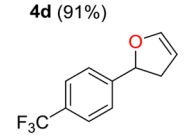
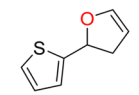
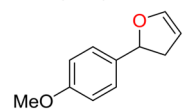
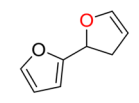
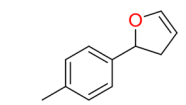
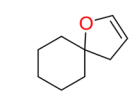
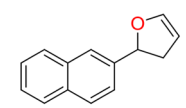
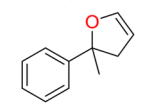
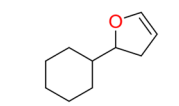
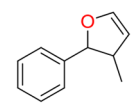
Based on the results and our previous work,[3] we propose that the reaction is catalyzed by the in situ generated 16e iron species **A**, which is obtained by decarbonylation of the iron tricarbonyl precatalyst [**Fe**]. The bifunctional catalytic species **A** bearing a noninnocent ligand[13] exhibits a dual catalytic task. While the C═O group of the ligand activates the nucleophile through hydrogen bonding the iron metal center activates the terminal double bond of allene by coordination. The activated O- or N-nucleophile of **B** can undergo intramolecular attack with transfer of a hydrogen atom to the cyclopentadienone ligand, producing the iron vinylidene intermediate **C**. The next steps involve two consecutive hydrogen transfers, leading to the isomerization of the iron vinylidene intermediate **C** into the more stable iron vinylidene intermediate **E** via the iron carbene intermediate **D**. Finally, the desired product is selectively formed via protodemetalation of the intermediate **E** (Scheme 2).

In conclusion, we report the first example of an intramolecular hydroamination of allenic amines to enamines as well as an efficient base metal catalyzed hydroalkoxylation of α-allenic alcohols to valuable cyclic enol ethers.[7b] The general applicability of this protocol is highlighted by the synthesis of 30 unsaturated heterocycles with good yields and excellent chemoselectivity. The key to achieve this unusual selectivity is the use of an iron-based metal–ligand catalyst which can activate the substrate in a dual catalytic fashion. The absence of any sensitive chemicals as well as base additives is an additional

Table 3. Iron-Catalyzed Hydroalkoxylation of Allenic Alcohols[a]



3 **4**

entry	heterocycle	entry	heterocycle
1	 **4a** (90%)	10	 **4j** (75%)
2	 **4b** (91%)	11	 **4k** (79%)
3	 **4c** (86%)	12	 **4l** (74%)
4	 **4d** (91%)	13	 **4m** (62%)
5	 **4e** (75%)	14	 **4n** (62%)
6	 **4f** (92%)	15	 **4o** (86%)
7	 **4g** (82%)	16	 **4p** (76%)
8	 **4h** (95%)	17	 **4q** (92%)
9	 **4i** (70%)	18	 **4r** (68%, dr = 4:1)

[a]Reaction conditions: **3** (1 mmol), [Fe] (2.5 mol %), and Me_3NO (4 mol %) in toluene (1 mL) were stirred at 70 °C for 2 h in a Schlenk tube under an inert atmosphere. Isolated yields are shown.

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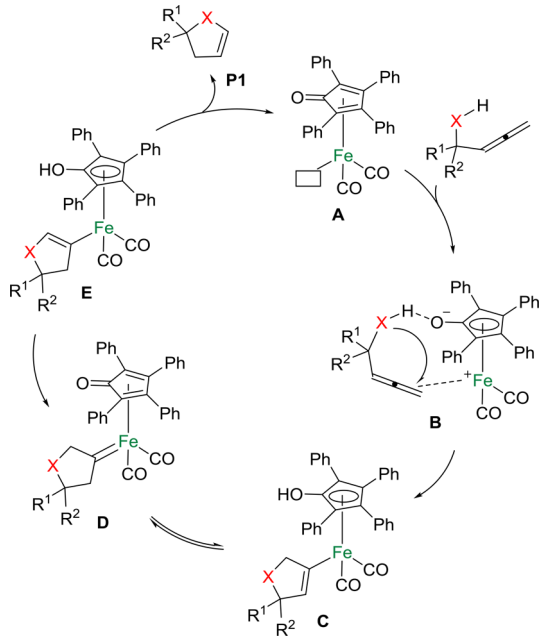
Scheme 2. Proposed Reaction Mechanism



advantage of the reported protocol. We believe that this strategy will find practical application in the synthesis of bioactive molecules and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03828.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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