

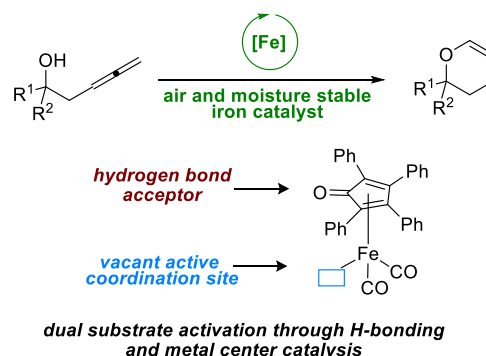
Experimental and computational study of an unexpected iron catalyzed carboetherification by cooperative metal and ligand substrate interaction and proton shuttle

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Abstract: A new iron catalyzed carboetherification of allenols to deoxygenated pyranose glycals has been developed. Combined experimental and computational studies show that the iron complex exhibits a dual catalysis role in that the non-innocent cyclopentadienone ligand acts as proton shuttle by initial hydrogen abstraction of the alcohol and by facilitating protonation and deprotonation events in the isomerization and demetalation steps. Molecular orbital analysis provides insight into the unexpected and selective formation of the 3,4-dihydro-2H-pyran.

The development of new atom-economical transformations is one of the most important challenges in modern synthetic chemistry.^[1] Key for the sustainable future of industrial chemistry is the replacement of precious metal catalysts by the first-row, earth-abundant catalysts.^[2] In this regard the use of iron salts and complexes has become an important field.^[3] More recently iron tricarbonyl complexes have attracted considerable interest due to their redox activity, robust nature and ready accessibility. However, so far the application of the iron tricarbonyl complexes is mainly restricted to the reduction of polar bonds and hydrogen borrowing transformations.^[4–6]

During our recent investigations on the use of iron tricarbonyl complexes as Fe-hydrogenase mimics we observed an unexpected carboetherification of allenic alcohols (Scheme 1). Herein, we report our preliminary results on the experimental and computational exploration of this first iron tricarbonyl catalyzed carboetherification of the allenic alcohols which gives access to valuable 3,4-dihydro-2H-pyrans, a heterocycle which is ubiquitous in natural products and is frequently used as a precursor of the synthesis of bioactive molecules, including glycals, polyethers and deoxynucleosides antibiotics.^[8] Previously the cyclization of β -hydroxyallenes using gold(I) catalysts has been established. However, these reactions afford the regioisomer 3,6-dihydro-2H-pyran, indicating a mechanistically distinct pathway.^[9,10]



Scheme 1. Iron catalyzed carboetherification of allenols

In preliminary experiments, the carboetherification of the allenol **10a** was investigated using the iron complexes **Fe1–Fe9** (Figure 1) in toluene at 70 °C. The air and moisture stable pre-catalysts were activated *in situ* by oxidative decarbonylation using trimethylamine *N*-oxide. Application of **Fe1** gave only 17% yield of the desired enol ether **11a**, while **Fe2** afforded the same product in 25% yield (Table 1, entries 1–2). The iron complexes **Fe3**, **Fe4** or **Fe5**^[11] did not show any catalytic activity (Table 1, entries 3–5). A slightly better result was obtained when **Fe6** was used (Table 1, entry 6). In hydrogen transfer processes the iron hydride is the reactive iron species and the hydrogen transfer occurs *via* an outer sphere pathway. Therefore, a bulky substituent on the dienone ligand is crucial for the complex stability and catalytic activity. However, in the carbocyclization under investigation the iron complex bearing a non-innocent ligand may exhibit a dual role.^[12] Activation of the allene may occur *via* a metal π -interaction while simultaneously the nucleophile is activated by a hydrogen bond abstraction through the dienone moiety of the ligand. Thus, the use of an iron catalyst, which is bearing smaller substituents should lead to improved results. To our delight, full conversion and good yield (84%) was observed if **Fe7** was employed (Table 1, entry 7). In order to investigate the effect of the electron density on the cyclopentadienone moiety, the electron rich iron complex **Fe8** and the comparably more electron deficient catalyst **Fe9** were tested. However, no change in yield was observed indicating that the electron density does not change the catalyst activity (Table 1, entries 8–9). The addition of catalytic amounts of DBU had a detrimental effect on the reactivity and only 35% yield was obtained (Table 1, entry 10). Importantly, increasing the reaction concentration did not influence the yield (Table 1, entry 11). Finally, when the iron trichloride was used as a catalyst no product formation was observed (Table 1, entry 12).

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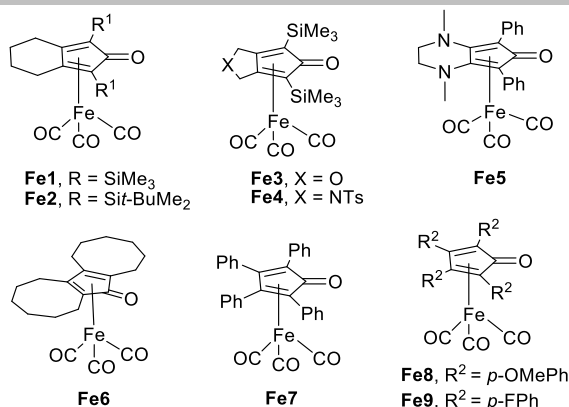


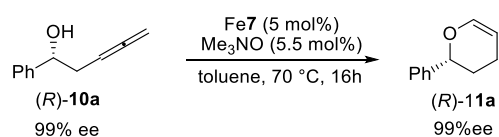
Figure 1. Selection of iron cyclopentadienone complexes applied in the carbocyclization.^[4]

Table 1. Optimization of the reaction conditions.^[a]

Entry	Cat. (mol%)	Additive (mol%)	Yield (%) ^[b]
1	Fe1 (5)	Me ₃ NO (5.5)	17
2	Fe2 (5)	Me ₃ NO (5.5)	25
3	Fe3 (5)	Me ₃ NO (5.5)	0
4	Fe4 (5)	Me ₃ NO (5.5)	0
5	Fe5 (5)	Me ₃ NO (5.5)	0
6	Fe6 (5)	Me ₃ NO (5.5)	38
7	Fe7 (5)	Me ₃ NO (5.5)	85
8	Fe8 (5)	Me ₃ NO (5.5)	85
9	Fe9 (5)	Me ₃ NO (5.5)	85
10	Fe7 (5)	Me ₃ NO (5.5) / DBU (20)	35
11^[c]	Fe7 (5)	Me₃NO (5.5)	85
12	FeCl ₃ (10)	-	0

[a] The reactions were performed on 0.2 mmol scale with an iron complex and additive in 1 mL of toluene-*d*₈ at 70 °C in a Schlenk tube under an inert atmosphere for 16h. [b] Yields were determined by the ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] The reaction was performed in 1 mmole scale in 1 mL of toluene.

We then decided to investigate the carboetherification of the enantiomerically pure (*R*)-**10a** under the optimized reaction conditions. Pleasingly, the reaction proceeded with complete retention of configuration and provided the optically pure enol ether (*R*)-**11a** in 81% yield and 99% ee (Scheme 2). This result indicates that the cyclization reaction is much faster than the alcohol racemization pathway previously established.^[5]



Scheme 2. Retention of chirality in the intramolecular carboetherification.

To demonstrate the potential and applicability of this methodology, an array of allenic alcohols was cyclized (Table 2). In general, aryl substituted allenols with both electron donating as well as electron withdrawing groups could be successfully applied and the corresponding pyrans (**11b-h**) were isolated in good yields (entries 2-8).

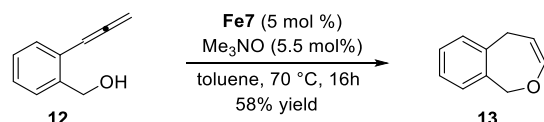
Table 2. Iron-catalyzed 6-endo hetrocyclization of β-allenols.^[a]

Entry	Product	Entry	Product
1	11a , 81% yield	8	11h , 63% yield
2	11b , 84% yield	9	11i , 74% yield
3	11c , 81% yield	10	11j , 82% yield
4	11d , 90% yield	11	11k , 64% yield
5	11e , 75% yield	12	11l , 82% yield
6	11f , 69% yield	13	11m , 76% yield
7	11g , 71% yield	14	11n , 67% yield

[a] Reaction conditions: **10** (1 mmol) and catalyst **Fe7** (5 mol%) and Me₃NO (5.5 mol%) in toluene (1 mL) were stirred at 70 °C for 16h in a Schlenk tube under an inert atmosphere. Yields after column chromatography.

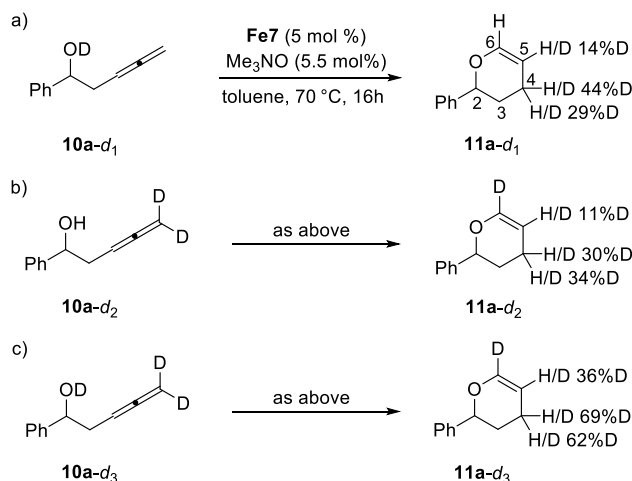
Furthermore, the cyclic and acyclic aliphatic derivatives **10i** and **10j** were cycloisomerized to the unsaturated pyrans **11i** and **11j** in 74% and 82% yields respectively (entries 9-10). Importantly, the pyrane **11k** was produced in good yield (entry 11). This deoxy sugar is of relevance as it can be used in the synthesis of the six membered analogues of several clinically relevant antibiotics such as AZT, d4T and Puromycin.^[13] The method was

also found to be applicable to heteroarenes as shown by derivative **10i** (entry 12). Moreover, the carboetherification of the tertiary alcohol **10m** gave the pyrane **11m** with a quaternary carbon atom (entry 13). Finally, product **11n** was obtained in 67% yield demonstrating a new and efficient method for the construction of spirocyclic ethers (entry 14). Following the successful demonstration of the variability and applicability of the newly developed iron catalyzed carboetherification we decided to examine the cyclization of the more challenging aromatic allenol **12**. To our delight, the iron complex catalyzed the regioselective 7-*endo* heterocyclization and afforded the interesting 2-benzoxepine **13** (Scheme 3).



Scheme 3. Iron catalyzed 7-*endo* heterocyclization.

In order to gain more insight into the nature of the catalytic active iron species, we conducted a series of deuterium labeling experiments using the iron catalyst **Fe7** (Scheme 4). When the heterocyclization reaction was performed with allenic alcohol **10a-d₁**, the unsaturated pyrane **11a-d₁** was formed with 14% deuterium incorporation at vinylic position C5 and 44% and 29% in the allylic hydrogen atoms on C4. In the case of allenol **10a-d₂**, complete deuterium incorporation was detected at C6 position and deuterium incorporation was detected on both C4 and C5. The carboetherification of **10a-d₃** afforded the cyclic product with complete deuterium incorporation at C6 position and double deuterium incorporation was found on both C4 and C5.



Scheme 4. Deuterium labelled experiment.

With this experimental background in mind we performed DFT calculations to rationalize the possible reaction mechanism (Figure 2,3) as well as the selective 3,4-dihydro-2*H*-pyran formation. As shown in Figure 2 and 3, the catalytically active species **A** is initially produced by the partial decarbonylation of the iron tricarbonyl pre-catalyst **Fe7**. This 16e iron species exhibits a dual catalysis behavior as it can coordinate to the

terminal double bond of the allene and at the time forms a H-bond between the alcohol moiety of the allene and the C=O group of the cyclopentadienone (intermediate **B**; see additional details in the Supporting Information). Hence, the ligand plays a crucial role in the activation of the substrate and as such belongs to the group of cooperative or non-innocent type ligands.^[12] The activated O atom of **B** can undergo a 6-*endo*-dig attack with transfer of the alcoholic H atom to the cyclopentadienone ligand, leading to the formation of the iron vinylidene intermediate **C**, via transition state (TS **B** → **C**, Figure 3) and a Gibbs free energy barrier (ΔG_{act}) of 18.6 kcal mol⁻¹ at 70 °C. The next step along the preferred reaction pathway is the isomerization of the iron vinylidene intermediate **C** into the more stable (by 2.6 kcal mol⁻¹) iron vinylidene intermediate **E** via the iron carbene intermediate **D**, see Figure 2 and 3. This isomerization consists of two consecutive H-transfers. The first is from the cyclopentadienone ligand to the C4 atom of the substrate, the second from the C6 atom of the substrate to the cyclopentadienone ligand, with the low ΔG_{act} of 14.2 (**C** → **D**) and 3.2 (**D** → **E**) kcal mol⁻¹. The observed deuterium distribution confirms the equilibrium between intermediates **C** and **D**. The catalytic cycle is completed by protodemetalation of the iron vinylidene intermediate **E** to the product coordinated intermediate **F** (ΔG_{act} = 15.0 kcal mol⁻¹). Product dissociation costs 11.3 kcal mol⁻¹ and regenerates the activated catalyst **A**.

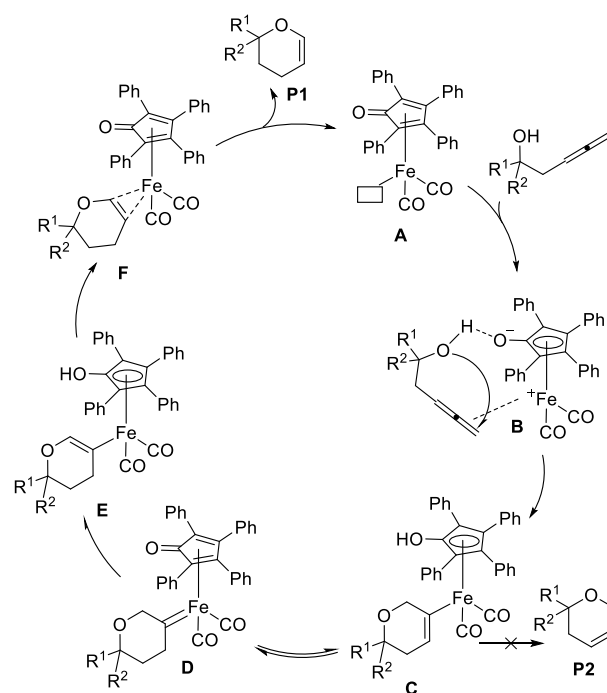


Figure 2. Proposed catalytic cycle.

Consistently with experiments, the competitive formation of the 3,6-dihydro-2*H*-pyran, **P2**, via protodemetalation of intermediate **C** (ΔG_{act} = 26.8 kcal mol⁻¹) is disfavored over protodemetalation of intermediate **E** which gives the 3,4-dihydro-2*H*-pyran, **P1** (ΔG_{act} = 15.0 kcal mol⁻¹). The different propensity of intermediates **C** and **E** to undergo protodemetalation is rationalized by comparison of the electronic properties of the C5 carbon of **C** and **E**.

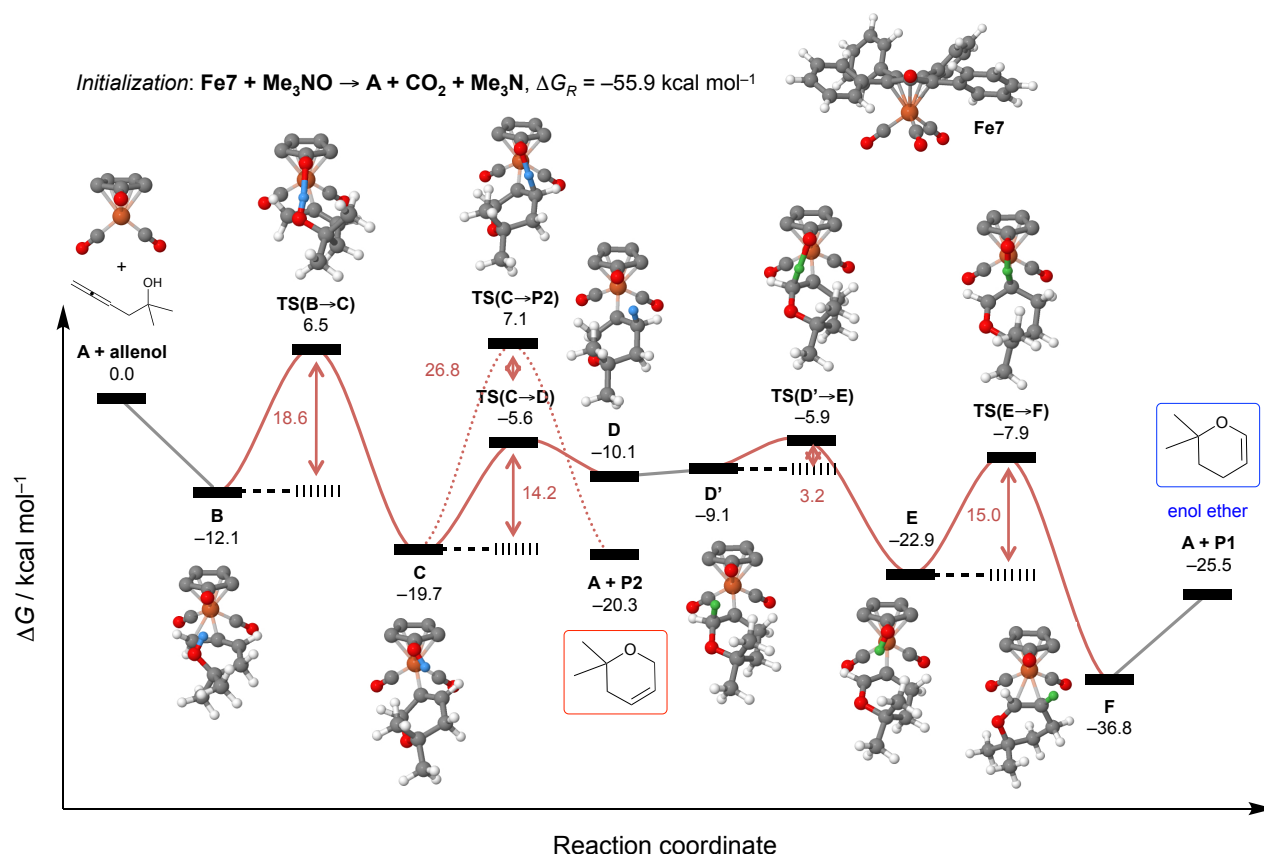


Figure 3. Proposed reaction mechanism. Gibbs free energies (70 °C), in kcal mol^{-1} . Results at the M06/TZVP level including solvent effects (toluene) through the PCM approach.^{[14],[15]} Reactive H atoms are highlighted in blue and green colors. **D** and **D'** structures are conformational minima. For clarity, phenyl groups from the cyclopentadienone moiety have been omitted. (See full computational details and full structures in the Supporting Information).

The former has a higher natural population charge, q_{NBO} , and Fukui nucleophilicity index (f^-), consistent with the higher reactivity (lower ΔG_{act}) of **E** (see Figure 4). Molecular orbital (MO) analysis of **C** and **E** (Figure 4) indicates that the saturated C6 of **C** prevents mixing of the O p -orbital with the π -orbital of the C4=C5 double bond. Conversely, the p -orbital on the O-atom can mix with the π -orbital of the C5=C6 double bond in **E**, resulting in a bonding interaction (explaining the higher thermodynamic stability of **P1** relative to **P2**), and in an antibonding interaction that reduces the energy gap with the empty MO corresponding to the $-\text{OH}$ bond from 3.58 to 2.94 eV, explaining the higher reactivity of **E**.

In conclusion, we here report a new iron catalyzed carboetherification of allenols. The reaction represents not only the first example in which an iron cyclopentadienone complex is used for carbon-heteroatom formation but, more importantly, readily available allenic alcohols can be easily transformed into deoxygenated pyranose glycals which are important building blocks for the synthesis of bioactive molecules and natural products. Mild reaction conditions, good functional group tolerance as well low catalyst loadings of an air stable inexpensive iron complex are characteristics of this new transformation. Computational studies support a reaction mechanism in which the iron cyclopentadienone complex plays a dual role. While the catalytically active 16e iron species is coordinating to the allene, the non-innocent cyclopentadienone ligand acts as proton shuttle by initial hydrogen abstraction of the alcohol and by facilitating protonation and deprotonation events in the isomerization and demetalation steps. Furthermore, the unexpected formation of the 3,4-dihydro-2H-pyran as compared to the previously observed 3,6-dihydro-2H-pyran can be explained through molecular orbital analysis of the iron vinylidene intermediate which demonstrates that formation of the enol product is more favorable. Thus, the results of this combined computational and experimental study will guide explorations in the design of further new reactions using iron cyclopentadienone tricarbonyl complexes in metal-ligand cooperative catalysis.

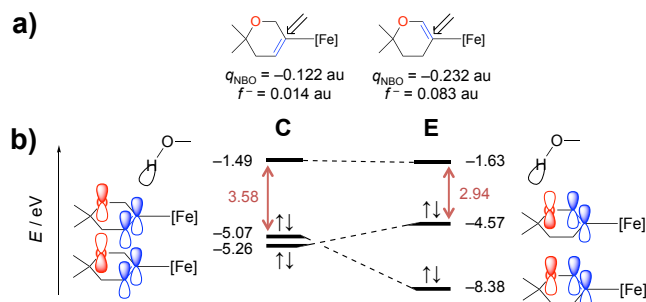


Figure 4. a) Natural population charge, q_{NBO} , and nucleophilic Fukui function, f^- ; and b) MO analysis for the **C** and **E** iron vinylidene intermediates.

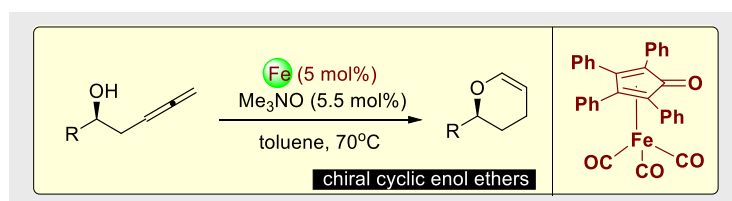
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Keywords: synthetic methods • iron catalysis • carboetherification • enol ethers • heterocycles

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COMMUNICATION



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