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Design of manganese phenol pi-complexes as Shvo-type catalysts for transfer hydrogenation of ketones

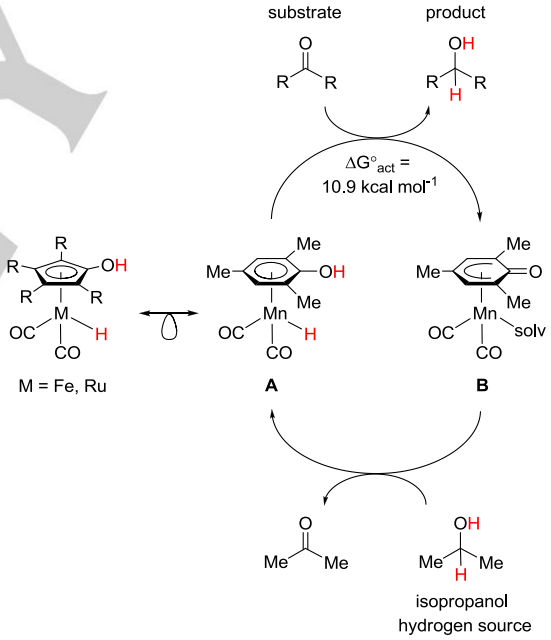
Nikita V. Shvydkiy,[a] Oleksandr Vyhivskyi,[b] Yulia V. Nelyubina,[a] and Dmitry S. Perekalin*[a,c]

Abstract: Catalytic hydrogenation is one of the most important reactions both in academic research and industry. We explored ability of the manganese pi-complexes to act as Shvo-type catalysts for transfer hydrogenation of ketones. DFT calculations suggested that the transfer of hydrogen atoms from the hypothetical intermediate $[(C_6Me_3H_2OH)Mn(CO)_2H]$ to acetone has low activation barrier of 10.9 kcal mol^{-1}. Experimentally a number of ketones with various functional groups (OMe, NH_2, Cl, CF_3, pyridyl) were successfully reduced in isopropanol at 90 °C in the presence of the complex $[(C_6Me_3H_2OH)Mn(CO)_3]BF_4$ (1 mol %) and ^{t}BuOK (75 mol %). However, further investigation revealed that the reduction was mainly promoted by base rather than the manganese complex.

Catalytic hydrogenation is a fundamental transformation, which is widely used in organic synthesis and pharmaceutical industry.[1] One of the current trends of this field is the development of new catalysts based on non-toxic and abundant 3d transition metals.[2] In 2016 the pioneer works of Beller et al. and Milstein et al. have demonstrated high potential of manganese catalysts for hydrogenation processes[3,4] and have led to explosive growth of their application for reduction of aldehydes,[5] ketones,[6,7] esters,[8] and other substrates.[9] The majority of these manganese catalysts are “pincer” complexes; the only exceptions are related compounds, which contain bidentate P,P-, P,N- or N,N-ligands.[10,11] Driven by the interest of our group in arene complexes of transition metals,[12] we decided to explore the ability of manganese phenol π-complexes to act as fundamentally different class of catalysts for hydrogen transfer reactions.

Arene complexes of manganese have been studied in detail[13] and used for stoichiometric organic synthesis,[14] but to the best of our knowledge, they have not been used previously as catalysts. Thanks to Igau et al.[15,16] we noticed that the manganese phenol π-complexes are isolobal to the hydroxy-substituted cyclopentadienyl iron and ruthenium complexes (Shvo-type catalysts), which have shown high catalytic activity in hydrogenation reactions.[17,18] We assumed that the phenol manganese complexes can catalyze hydrogen transfer following the classical mechanism displayed on the Scheme 1.[19] The reduced form of the catalyst **A** can transfer two hydrogen atoms to the ketone substrate and turn into the oxidized form **B**. Then **B** can abstract hydrogen atoms from some source (e.g. isopropanol) to regenerate the hydride form **A** and close up the catalytic cycle.

We investigated the possibility of such catalytic process using DFT calculations at M06L/TZVP level. Activation energy of the key step of hydrogen transfer from **A** to acetone was found to be only 10.9 kcal mol^{-1}, which suggests that it is feasible even at room temperature (see Supporting information for detailed reaction profile and discussion). Noteworthy, the calculated activation energy for the related Knölker catalyst, the hydroxy-cyclopentadienyl iron complex $(C_5R_4OH)Fe(CO)_2H$, is 8.9 kcal mol^{-1}.[20]



Scheme 1. Initially proposed mechanism for the hydrogen transfer by manganese phenol complex.

For experimental verification of catalytic activity we synthesized the manganese complexes **1**–**5** (Scheme 2). Complexes $[(C_6R_5OH)Mn(CO)_3]BF_4$ (**1**–**3**) were obtained in one step from the commercially available $Mn(CO)_5Br$, $AgBF_4$, and corresponding phenols (Scheme 3). The yields of **1** and **2** were ca. 50%, while the more hindered 4-methyl-2,6-di-tert-butylphenol reacted slowly and the corresponding complex **3** was obtained in only 15% yield. The yields of **1** and **2** were improved up to 80−90% by using $MeMn(CO)_5$ and HBF_4 as a starting materials; noteworthy this method allows one to avoid

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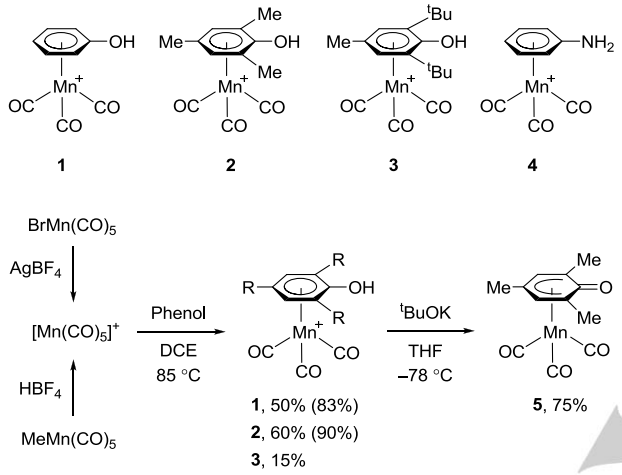
the use of expensive silver salts.[21] The coordinated phenol in complex **2** was easily deprotonated by bases such as KOH or ^{t}BuOK to give the neutral complex **5**, which was also used for further catalytic tests. Attempts to generate the active species **A** or **B** by removal of CO ligand from **2** with Me_3NO in CH_2Cl_2 or isopropanol led to unknown complexes, which were difficult to identify because they slowly decomposed into insoluble paramagnetic products.[22] Compounds **1**–**5** were stable in air both in solid and solution, but were slightly light sensitive. The structures of **2**BF_4 and **5** were confirmed by X-ray diffraction analysis (Figure 1).



Scheme 2. Synthesis of manganese catalysts. Cationic complexes were isolated as salts with BF_4^- counter-ions, which are omitted on the scheme. Yields in parentheses refer to the synthesis from $MeMn(CO)_5$.

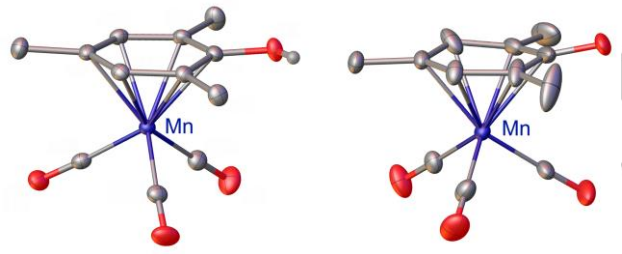
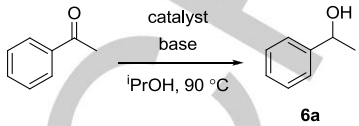


Figure 1. Crystal structures of cation **2** (left) and its deprotonated form **5** (right) in 50% thermal ellipsoids. The second component of the disordered molecule **5** and all hydrogen atoms except OH are omitted for clarity.

As a model catalytic reaction we selected the reduction of ketones by isopropanol via hydrogen transfer mechanism. The conditions were optimized for reduction of acetophenone (Scheme 3, Table 1). While no reaction was observed in the absence of base, in the presence of 75 mol % of ^{t}BuOK complexes **1**–**5** (1 mol %) promoted the reduction of acetophenone into the target 1-phenylethanol product (**6**) with 55–65% yield after 4h at 90 °C (entries 1-5). The extension of reaction time to 24 h allowed to reach quantitative conversion of acetophenone and 92% yield of **6** (entry 6). In accordance with the proposed mechanism, the trimethylphenol complex **2** and its deprotonated form **5** were equally active (entry 2 vs 5). On the contrary, the mesitylene manganese complex, which does not have a hydroxyl group, showed almost no catalytic activity despite the higher loading and prolonged reaction time (entry 7). This fact supported the hypothesis of participation of phenolic ligand in the hydrogen transfer process.



Scheme 3. Model catalytic reaction of hydrogen transfer.

Table 1. Optimization of conditions for reduction of acetophenone. Yields were determined by ^{1}H NMR with 1,4-dioxane as the internal standard.

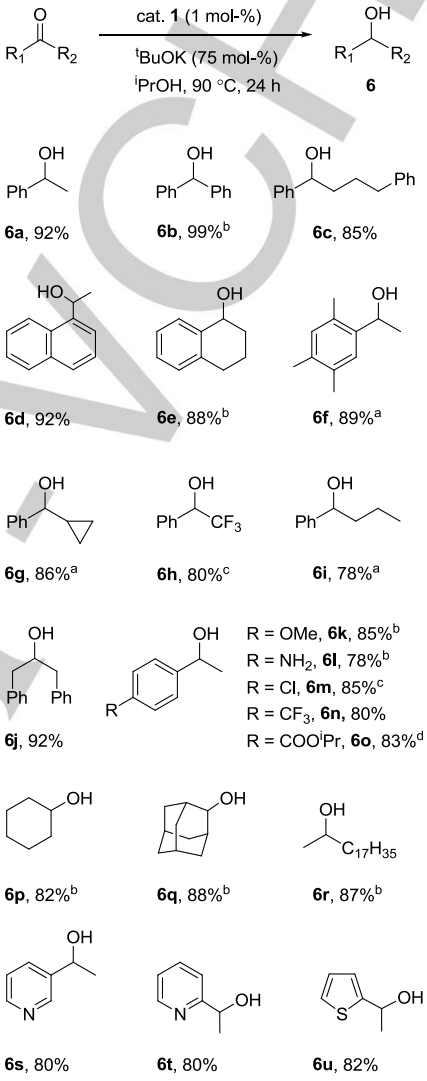
Entry	Catalyst (mol %)	Additive (mol %)	Time	Yield of **6a**
1	**1** (1 mol %)	^{t}BuOK (75 mol %)	4h	58%
2	**2** (1 mol %)	^{t}BuOK (75 mol %)	4h	64%
3	**3** (1 mol %)	^{t}BuOK (75 mol %)	4h	55%
4	**4** (1 mol %)	^{t}BuOK (75 mol %)	4h	53%
5	**5** (1 mol %)	^{t}BuOK (75 mol %)	4h	62%
6	**2** (1 mol %)	^{t}BuOK (75 mol %)	24h	92%
7	$[(C_6H_3Me_3)Mn(CO)_3]$OTf (10 mol %)	^{t}BuOK (75 mol %)	72h	8%
8	**2** (0.1 mol %)	^{t}BuOK (75 mol %)	72h	76%
9	**2** (1 mol %)	^{t}BuOK (30 mol %)	24h	0%
10	**2** (1 mol %)	^{t}BuOK (20 mol %) + KPF_6 (100 mol %)	24h	56%
11	**2** (1 mol %)	^{t}BuOK (20 mol %) + $[NBu_4]PF_6$ (100 mol %)	24h	27%
12	None	^{t}BuOK (75 mol %)	24h	78%

Investigation of the temperature dependence showed that reactions at 90 °C and 110 °C gave essentially the same yield of the alcohol **6a**, while at 70 °C the reduction becomes much

slower. We assumed that high temperature is required for thermal dissociation of CO ligand in the complex **2**, which is necessary for generation of the catalytically active form **B** (Scheme 1). Indeed, DFT calculations suggested that this stage has high activation barrier of 37.7 kcal mol^{-1}. However, the addition of Me_3NO (1 mol %), as a mild CO removal agent, resulted in a notable drop in catalytic activity.

Thus, the optimal reaction conditions were proposed to be 1 mol % of catalyst **2** and 75 mol % of ^{t}BuOK (0.375M) in isopropanol at 90 °C. Under these conditions various aromatic and aliphatic ketones were successfully reduced to give the corresponding alcohols **6a−u** in 78−99% yields. The yields usually did not reach 90% because of the side reactions provoked by the strongly basic conditions (for example, the by-product of aldol condensation was isolated in the case of acetophenone). Benzophenone, which cannot undergo aldol condensation, was reduced to benzhydrol **6b** in almost quantitative yield. The catalytic system tolerated the presence of OMe, NH_2, Cl, CF_3, and cyclopropyl groups in the substrates. As expected, electron-rich and sterically hindered ketones were reduced more slowly than acetophenone, so 2 mol % catalyst loading and longer reaction times were used to obtain the products **6b, 6e**-**g**, **6i,k,l,p-r**. The nitro group was reduced more easily than the keto group and therefore p-nitroacetophenone produced p-aminoacetophenone in 90% yield under standard conditions. The reduction of p-cyanoacetophenone was accompanied by partial hydrolysis and gave 1-(p-carboxamido-phenyl)-ethanol in 70% yield. Importantly, the substrates that contain potentially coordinating heterocycles such as 2-acetylpyridine and 2-acetylthiophene were easily reduced in our conditions to give the corresponding alcohols **6t**,**u**. On the other hand, 2-acetylfuran apparently underwent the opening of heterocyclic ring, so the formation of a mixture of products was observed. Ketones with conjugated double bonds, such as dibenzylideneacetone and isophorone, also produced mixtures of products.

At this point we attempted to improve the selectivity of the reaction by lowering the amount of the base. It was found that at 0.150 M concentration of ^{t}BuOK (corresponds to 30 mol %) the reduction rate dropped to zero (Table 1, entry 9). Recently Pidko et al. have suggested that ^{t}BuOK additive can play two roles.[19b] On one hand, K^+ cation can coordinate with both catalyst and substrate to polarize them and to bring them in proximity. On the other hand, at high concentrations, ^{t}BuOK additive can increase the polarity of reaction medium, which also facilitates the reduction process. In order to verify these hypotheses we performed the reduction of acetophenone in the presence of 100 mol % of KPF_6 electrolyte and found that it indeed proceeded much faster and allowed us to reduce the concentration of ^{t}BuOK to 0.1 M (entry 10). Similar reaction in the presence of 100 mol % of $[NBu]_4PF_6$ electrolyte was about twice less effective (entry 11), indicating the importance of potassium cation. To our surprise, the reduction of acetophenone in the presence of ^{t}BuOK (75 mol %) but without the catalyst **2** also led to formation 1-phenylethanol in a good yield 78% (entry 12). This discovery suggested that the manganese complexes **1−5** had in fact very little influence on the reduction of ketones under such basic conditions.[23] Low conversion of acetophenone in the presence of complex $[(C_6H_3Me_3)Mn(CO)_3]OTf$ (10 mol %; entry 7) can be explained by its decomposition, which consumed large amount of ^{t}BuOK.



Scheme 4. The substrate scope of the manganese catalyzed reduction of ketones. Isolated yields are given. a – 2 mol % of **2**, 48h; b – 2 mol % of **2**, 72h; c – 30 mol % of ^{t}BuOK, 200 mol % of KPF_6; d – p-^{t}BuOOC-acetophenone was used as the starting ketone.

To conclude, we theoretically and experimentally explored ability of the manganese pi-complexes $[(phenol)Mn(CO)_3]^+$ to act as Shvo-type catalysts for transfer hydrogenation of ketones. A number of ketones were successfully reduced in isopropanol at 90 °C in the presence of 1 mol % of the complex **2** and 75 mol % of ^{t}BuOK. However, further investigation revealed that the reduction was mainly promoted by base, while complex **2** has little or no catalytic activity under these conditions. Interestingly, large portion of the base can be substituted by KPF_6 electrolyte.

Experimental Section

General procedure for catalytic reduction of ketones: Under argon atmosphere a ketone (0.5 mmol) was added to a solution of $[(C_6H_2Me_3OH)Mn(CO)_3]BF_4$ (**2**, 1.8 mg, 0.005 mmol) and ^tBuOK (42 mg, 0.375 mmol) in isopropanol (1 ml). The mixture was stirred for 24 h at 90 °C in a closed Schlenk tube. The mixture was then opened to air, quenched by aqueous solution of NH_4Cl (2 ml) and the product was extracted with chloroform (3×5 ml). Combined organic layers were dried over sodium sulfate, the solvent was evaporated and the crude product was purified by column chromatography (eluent hexanes/ethyl acetate).

Acknowledgements

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Keywords: Arene ligands • Base additive • Manganese • Shvo-type catalyst • Transfer hydrogenation

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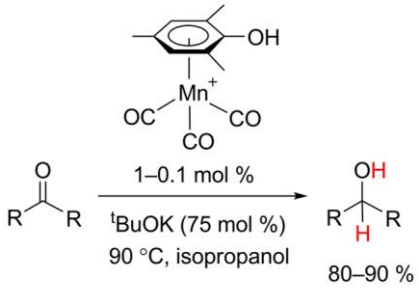
Isolobal analogy: Phenol manganese pi-complexes were proposed as possible Shvo-type catalysts for transfer hydrogenation of ketones. DFT calculations suggested the reaction can proceed via transfer of hydrogen atoms from the intermediate [($C_6Me_3H_2OH$)-$Mn(CO)_2H$] to a ketone. Indeed a number of ketones were reduced in isopropanol at 90 °C in the presence of the complex [($C_6Me_3H_2OH$)-$Mn(CO)_3$]BF_4 (1 mol %) and ^{t}BuOK (75 mol %). However, further investigation revealed that the reduction was mainly promoted by base rather than the manganese complex.



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