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Biomimetic hydrogenation catalyzed by a manganese model of [Fe]-hydrogenase

Hui-Jie Pan[a] and Xile Hu*[a]

Abstract: *[Fe]-hydrogenase is an efficient biological hydrogenation catalyst. Despite intense research, Fe complexes mimicking the active site of [Fe]-hydrogenase have not achieved turnovers in hydrogenation reactions. Here we describe the design and development of a manganese(I) mimic of [Fe]-hydrogenase. This complex exhibits the highest activity and broadest scope in catalytic hydrogenation among known mimics. Thanks to its biomimetic nature, the complex exhibits unique activity in hydrogenation of compounds analogous to methenyl-H_4MPT^+, the natural substrate of [Fe]-hydrogenase. This activity enables asymmetric relay hydrogenation of benzoxazinones and benzoxazines, involving hydrogenation of a chiral hydride transfer agent using our catalyst coupled to Lewis acid-catalyzed hydride transfer from this agent to the substrates.*

Catalytic hydrogenation is among the most widely used transformations in the chemical industry. The most active and selective hydrogenation catalysts are made of precious metals,[1] although interest in base metal catalysts is rising.[2] Nature provides an example of highly efficient hydrogenation catalyst made of a base metal. [Fe]-hydrogenase[3] catalyzes the hydrogenation of methenyl-H_4MPT^+ to methylene-H_4MPT with a complete stereospecificity and a high turnover frequency of up to 1900 s^{-1} (Fig. 1a).[4] The active site of [Fe]-hydrogenase comprises of a low-spin Fe(II) centre coordinated by one H_2O and two *cis*-CO molecules, a cysteine thiolate, as well as an acyl carbon and a pyridinyl nitrogen from a guanylylpyridinol ligand (Fig. 1b).[4-5] The *2*-OH group of the pyridonol ligand serves as an internal base to facilitate heterolytic H_2 activation upon deprotonation.[6]

Many Fe complexes have been made to model the active site of [Fe]-hydrogenase.[7] Among them, only few complexes could activate H_2.[6, 7g-i] Complex **1** (Fig. 1c), the best structural model, is inactive towards H_2 presumably because the *2*-OH group needs to be first deprotonated. However, **1** is unstable when treated with a base.[7f] This complex became active only when incorporated into the apo-enzyme of [Fe]-hydrogenase.[6] To alleviate the stability problem associated with a *2*-OH group while maintaining a viable internal base, complex **2,** which contains a robust *2*-OMe group and a basic pendant N was prepared (Fig. 1c).[7g] This complex was indeed active for H_2 activation and mediated hydrogenation of an aldehyde. However, the Fe-acyl moiety was prone to decomposition via decarbonylation so that catalysis could not be achieved. Two Fe models supported by an

anthracene-bridged NCS ligand were also active for H_2 activation.[7h, 7i] Notably these two models contained a carbamoyl donor [7c] instead of the acyl donor found in the enzyme. Among them, the neutral derivative **3** (Fig. 1d)[7i] mediated hydrogenation of *2,6*-difluoro(phenyl)-*2*-(*4*-ethyl)imidazolium cation, a model of methenyl-H_4MPT^+.[8] Despite this progress, none of the previous Fe models achieved turnovers in hydrogenation reactions.
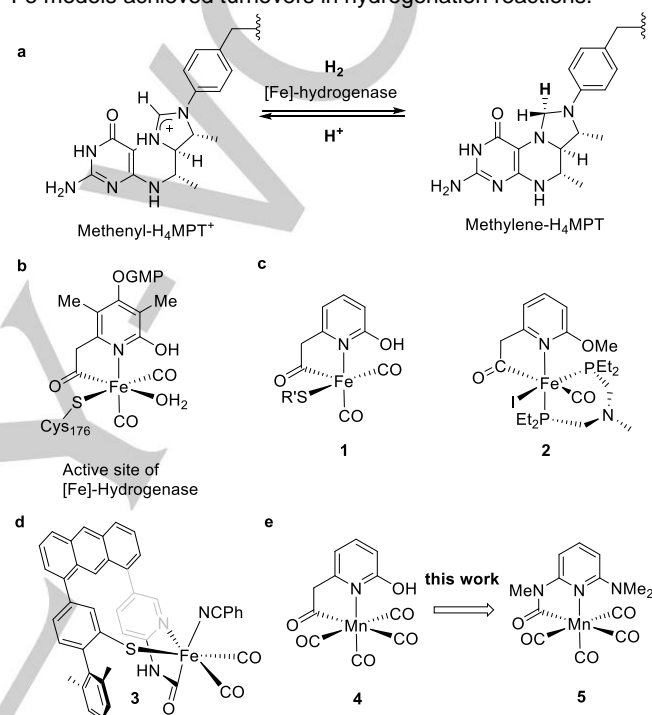
Figure 1. a, Enzymatic hydrogenation catalyzed by [Fe]-hydrogenase; **b**, Active site of [Fe]-hydrogenase; **c**, Selected Fe models with a pyridinylmethylacyl ligand; **d**, A selected Fe model with an anthracene-bridged carbamoyl ligand. **e**, Evolution of Mn models.

Based on the isoelectronic properties of Fe(II) and Mn(I), we recently prepared a Mn(I) model of [Fe]-hydrogenase **4** (Fig. 1e),[9] which was active for both H_2 activation and hydrogenation of organic compounds. The Mn(I) complex was more active and stable than its Fe(II) analogue. However, the catalytic activity and scope remained modest. By incorporating insights learned from the bio-mimetic chemistry of [Fe]-hydrogenase (see above), we designed a new Mn(I) model **5** (Fig. 1e), which featured a carbamoyl donor that was easier to access and more robust than an acyl donor, and a basic *2*-NMe$_2$ moiety that rendered the complex more stable than a *2*-OH group. Complex **5** turned out to be an efficient catalyst for hydrogenation of a wide range of substrates including ketones, aldehydes, imines, as well as enzyme substrate mimics. More importantly, complex **5** enabled a biomimetic enantioselective relay hydrogenation of benzoxazinones and benzoxazines, yielding chiral

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dihydrobenzoxazinones and dihydrobenzoxazines important for the medicinal chemistry.

Complex **5** was prepared, in one-pot, by first deprotonation of *2*-dimethylamino-*6*-methylaminopyridine (**6**) with one equivalent of *n*-BuLi at 0 °C, followed by treatment with Mn(CO)$_5$Br (yield: 71%) (Fig. 2a). The infrared (IR) spectrum of **5** in tetrahydrofuran (THF) exhibits three ν(CO) peaks at 1952, 1975 and 2072 cm^{-1}. ^{1}H NMR sepctrum of **5** in THF-d_8 exhibits two characteristic ^{1}H peaks at 2.74 ppm and 3.15 ppm, corresponding to the *2*-NMe$_2$ proton and the *6*-NMe protons, respectively. Three types of CO carbons were observed in the ^{13}C NMR spectrum at 216.6, 214.9, and 213.6 ppm, and the carbamoyl carbon was observed at 218.3 ppm. These diamagnetic NMR spectra indicate a low-spin configuration for the Mn(I) center. The solid-state molecular structure of **5** was determined by X-ray crystallography (Fig. 2b). The Mn ion of **5** adopts an octahedral coordination geometry, with a bidentate NC and four CO ligands.
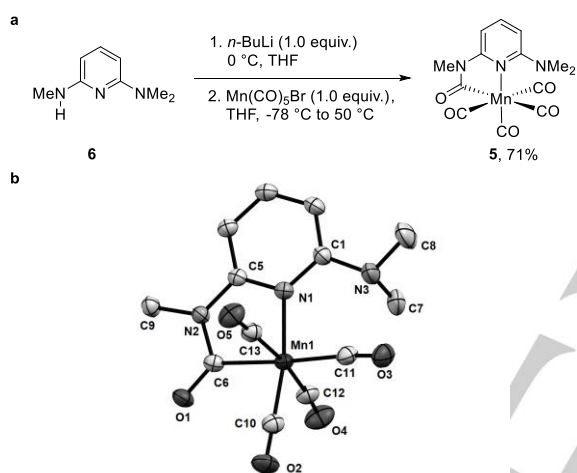
Figure 2. a, Synthesis of complex **5**; b, X-ray structure of complex **5**. The thermal ellipsoids are displayed at 50% probability. All hydrogen atoms are omitted for clarity. Selected bond distances (Å): Mn1-N1 2.0753(12), Mn1-C6 2.0268(14), Mn1-C10 1.7982(17), Mn1-C11 1.8674(17), Mn1-C12 1.8587(16), Mn1-C13 1.8418(16), N2-C5 1.3696(18), N3-C1 1.4104(19), N2-C6 1.4155(18)..

We first tested the activity of **5** in hydrogenation reactions of common organic substrates such as aldehydes, ketones, and imines (Table 1). Addition of *N*-methylpyrrolidine (MP) as base enhanced catalytic activity. Upon optimization (for details see table S1, SI), acetophenone was hydrogenated to *2*-phenylethanol in a yield of 91%. For comparison, hydrogenation using complex **4** as catalyst under the same conditions only had a 45% yield, indicating the higher catalytic activity of **5** over **4**. We further compared the catalytic efficiency of **4** and **5** for other substrates such as **7j**, and **7m** (Table 1). In both cases, significantly higher yields were obtained using **5** as catalyst. We explored the substrate scope using **5** as catalyst. Acetophenone analogues could be hydrogenated, but the reactions depended strongly on the electronic properties of the substrates. Addition of an electron donating OMe group at the *para* position lowered the yield (**8b**) to 57%. An electron withdrawing Cl group at the *para* position slowed down the hydrogenation and two days were

needed to obtain a yield of 98% (**8c**). . An aliphatic ketone could only be hydrogenated in 30% yield (**8d**) after 2 days. These data suggest a modest hydridity of the Mn-H intermediate derived from **5**, which react sluggishly with electron rich ketones. Consistent with this hypothesis, hydrogenation of aldehydes was more efficient. Both aromatic and aliphatic aldehydes were hydrogenated in high yields (> 98%, **8e**-**g**, **8i**). A sterically hindered substrate, 2,4,6-trimethylbenzaldehyde, was hydrogenated in a modest yield of 42% (**8h**). Hydrogenation of C-aryl primary and secondary imines was efficient (**8j**-**8n**). For an unknown reason, a para-Cl substitution significantly inhibited the hydrogenation (**8o**). As expected, an electron-rich C-alkyl secondary imine was a poor substrate (**8p**).

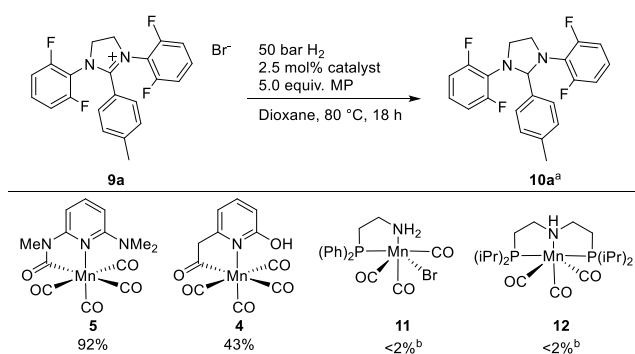^{a} isolated yield; ^{b} 48 h reaction time. MP = *N*-methylpyrrolidine
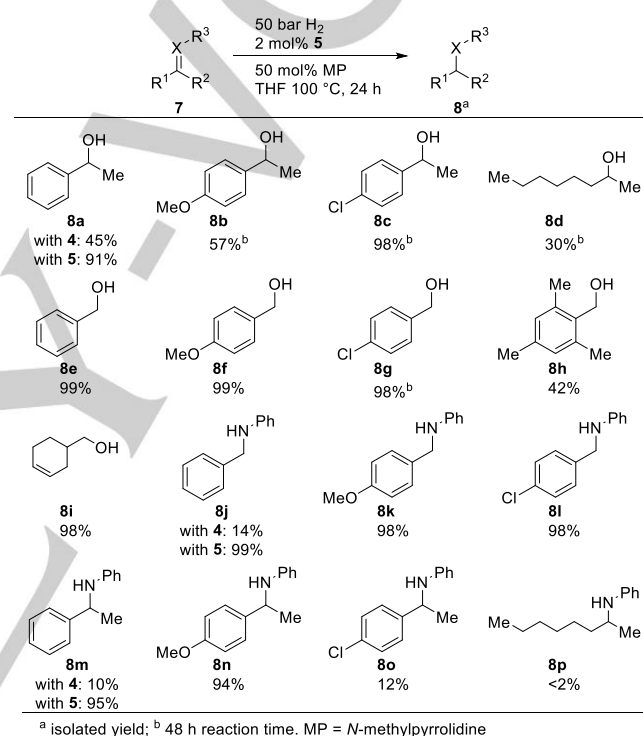
Table 1. Substrate scope of hydrogenation of ketones, aldehydes, and imines catalyzed by complex **5**.

While the activity and scope of **5** in hydrogenation are the best among model complexes of [Fe]-hydrogenase, they are below those of the most active base metal catalysts for common organic substrates.[2a, 2b, 2d-f, 10] We considered that the strength of a biomimetic catalyst like **5** might be its propensity to catalyze biomimetic reactions uncommon to synthetic chemistry. In this context, we examined the hydrogenation of substrates similar to the native substrate of [Fe]-hydrogenase, namely, methenyl-H$_4$MPT$^+$. The hydrogenation of the *1*,*3*-bis(*2*,*6*-difluorophenyl)-*2*-(*4*-tolyl)imidazolinium cation (in its bromide salt **9a**), a previously reported model of methenyl-H$_4$MPT$^+$,[7h, 8] was first tested. After optimizing conditions (see Table S2, SI), we obtained a yield of 92% for the hydrogenation of **9a** to generate **10a** using 2.5 mol% of **5** as catalyst (Scheme 1). For comparison, the previous model **4** afforded only a yield of 43% under the same conditions. We also

tested complexes **11**[11] and **12**[12], which were highly active in hydrogenation of common organic substrates. However, no hydrogenation of **9a** was observed. This result confirms our hypothesis that biomimetic catalysts are better suited for biomimetic reactions. We also probed the scope of hydrogenation of other imidazolinium salts (Table 2). The Cl-substituted analogue of **9a** was hydrogenated in 80% yield (**10b**). The *2,6*-difluoro substituents in **9a** was not essential for a substrate to be hydrogenated. Other imidazolinium salts bearing similar *N*-aryl groups such as **9c-e**[13] were also good substrates of hydrogenation, with yields of over 90%. Both electron withdrawing Cl and electron donating OMe group were tolerated.

Scheme 1. Comparison of the catalytic efficiency of various Mn complexes in the hydrogenation of **9a**, a mimic of methenyl-H4MPT+.
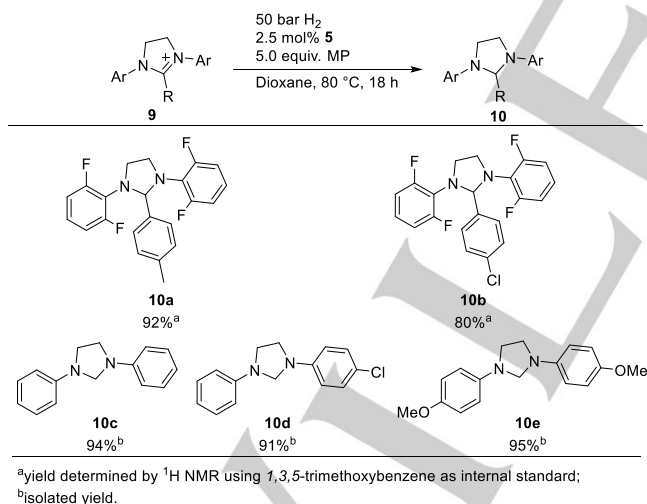

Table 2. Scope of hydrogenation of methenyl-H4MPT+ mimics catalyzed by complex **5**.

Encouraged by the above results, we considered further applications of catalyst **5** in biomimetic hydrogenation. In nature, hydrogenation of methenyl-H4MPT+ gave methylene-H4MPT, which served as a hydride donor for the reduction of F420 (*8*-hydroxy-*5*-deazaflavin) coenzyme to form F420H2, an essential electron carrier for the hydrogenotrophic methanogenesis.[14] The

function of methylene-H4MPT is similar to that of NADH and NADPH in biological hydride transfer reactions.[15] We thought that catalyst **5** might be suitable for hydrogenation of substrates mimicking methenyl-H4MPT+ or NAD+/NADP+, yielding hydride donors that could further utilized for the reduction of another unsaturated molecule. In particular, **5** might catalyze hydrogenation of an enantiomeric pure form of a methenyl-H4MPT+/NAD(P)/NAD(P)H mimic, leading to asymmetric hydrogenation of a second substrate after a hydride transfer relay. Planar-chiral FENAM **13** (a regenerable NAD(P) analogue based on planar-chiral ferrocene) appeared to be a suitable mediator for this relay catalysis (Scheme 2).[16] Hydrogenation of **13** catalyzed by **5** yields **14**, which can serve as a chiral hydride transfer reagent. We chose benzoxazinones and derivatives (**15**) as the terminal substrate for hydrogenation because they are susceptible for hydride transfer reactions [17] and the products dihydrobenzoxazinones are a class of important molecules in medicinal chemistry.[18] The selectivity of a hydrogenation catalyst towards **13** over **15** is key to the success of this relay catalysis. Again due to the biomimetic nature of **13**, we thought catalyst **5** was well suited for this applciation. Analogous relay hydrogenation was previously reported,[16, 19] however, Ru complexes were mostly used for H2 activation.[16, 19a, 19b] A notable exception was reported using an iron catalyst, but the enantioselectivity was sub-optimal.[19c] After screening of different conditions (Table S3, SI), we identified a protocol which reduced benzoxazinone **15a** to dihydrobenzoxazinone **16a** in 63% yield and 96% enantio excess (ee). The optimized conditions involved 10 mol% of **5** as hydrogenation catalyst, 20 mol% **13** as chiral hydride transfer reagent, and 20 mol% La(OTf)3 as Lewis-acid.
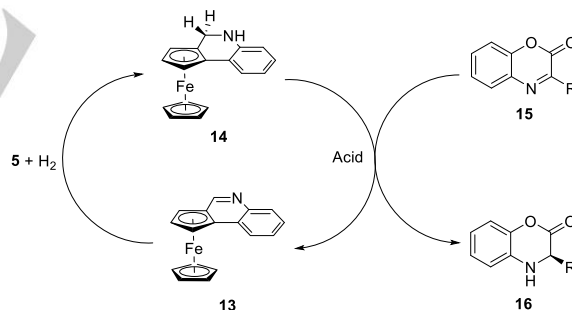

Scheme 2. The strategy for biomimetic asymmetric relay hydrogenation of benzoxazinone (**15**) incorporating **5**-catalyzed hydrogenation of enantiopure NADP analogue **13** as a key step. The chirality of **16** was transfeered from the chirality of **13/14**.

The relay catalysis worked for the enantioselective hydrogenation of a wide range of substrates (Table 3). Benzoxazinones with aromatic substitutes were all reduced with moderate to good yields and high enantioselectivity (**16a-d**). Electronic properties of the aromatic substitutes had limited effect. Benzoxazinones with aliphatic substitutes were hydrogenated in slightly higher yields than their aromatic counterparts (**16e-h**), and again with high enantioselectivity. Comparison of ees of **16e-h** suggested that steric hindrance induced by an alkyl substituent was beneficial for the ees. Benzoxazine substrates were

hydrogenated cleanly and in high yields (**16i-l**). The enantioselectivities of the products, however, dropped compared to **16a-16h**. These data suggest the ester group in benzoxazinones played a role in the enantioselective hydride transfer, probably by coordination to the Lewis acid.
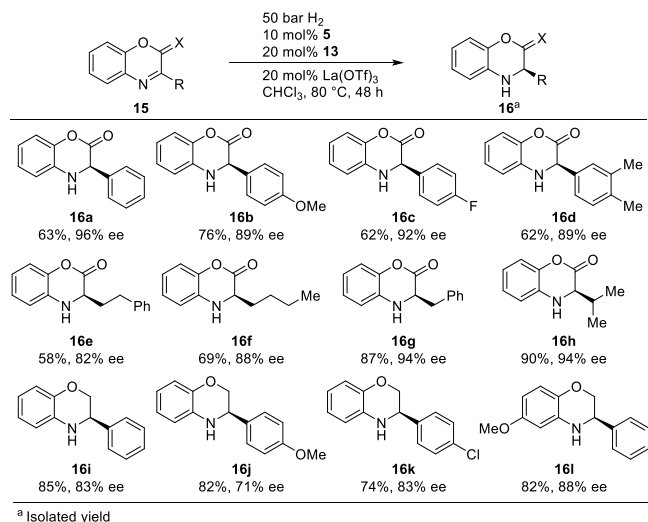
Table 3. Substrate scope of biomimetic asymmetric relay hydrogenation of benzoxazinones and benzoxazines catalyzed by complex **5**. The absolute configuration of products was assigned according to reported HPLC data.[16]

The mechanism of hydrogenation catalyzed by **5** is assumed to be similar to the reaction catalyzed by the analogous catalyst **4** .[9] The detail of the mechanism, however, is subject to future study.

In conclusion, we designed and developed a Mn(I) model of [Fe]-hydrogenase based on insights from biomimetic chemistry of [Fe]-hydrogenase. Key to our design was a chelating pyridine-carbamoyl ligand with a pendant NMe$_2$ base. This ligand was easy to assemble and conferred improved efficiency and scope in catalytic hydrogenation. Compared to other synthetic Mn catalysts, our biomimetic catalyst exhibits unique activity for hydrogenation of bio-mimetic substrates. This activity enabled an enantioselective relay catalysis of benzoxazinones and benzoxazines, via Mn-catalyzed hydrogtenation of an enantiomeric pure hydride acceptor, followed by Lewis-acid catalyzed asymmetric hydride transfer. This work demostrates the potenital utility of biomimetic catalysts in hydrogenation reactions.

Acknowledgements

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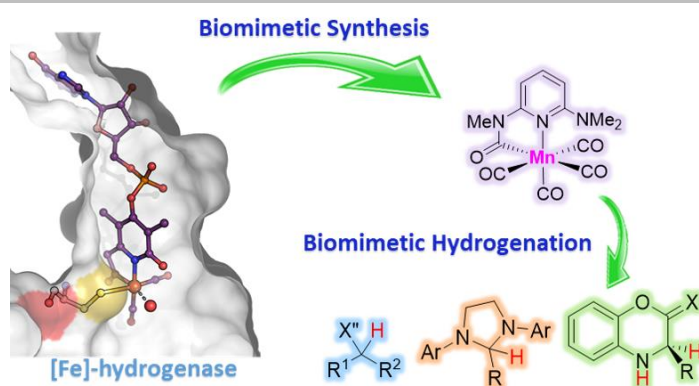
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