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Base Metal Complexes as Homogeneous Catalysts and Enzyme Mimics

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Abstract: This article is a short overview of some recent research activity in the Laboratory of Inorganic Synthesis and Catalysis (LSCI) at EPFL-ISIC. It summarizes the work on Ni-catalyzed cross-coupling reactions of non-activated alkyl halides. It then describes and discusses the work on the bio-mimetic chemistry of [Fe]-hydrogenase.

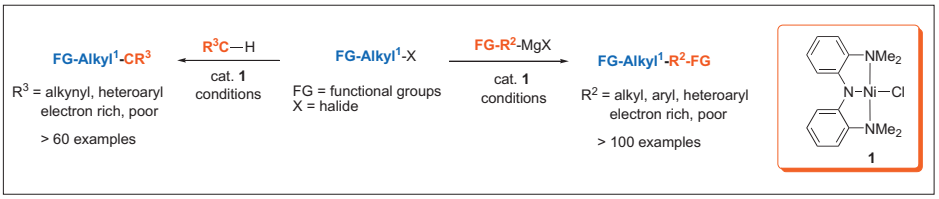
Keywords: Bio-inorganic chemistry · [Fe]-hydrogenase · Homogeneous catalysis · Organometallic chemistry · Nickel

1. Introduction

I joined the Institute of Chemical Sciences and Engineering (ISIC) at EPFL as a tenure-track assistant professor in summer 2007. The mission of my research group is to develop catalysts made of earth-abundant elements for synthesis, energy, and sustainability. Upon my arrival in Lausanne, we started two new projects. The first one is on Ni-catalyzed cross-coupling reactions and the second one is on the model chemistry of [Fe]-hydrogenase. And just recently, we embarked on a project to develop bio-inspired catalysts for hydrogen evolution.

2. Ni-catalysis

Our work on Ni catalysis is part of the program to develop well-defined coordination complexes of late first-row transition metal ions as catalysts for fine chemical synthesis. Our starting point is the pincer-type bis(amino)amide ligand $^{Me}N_2N$ (Scheme 1). Pincer ligands are 'privileged ligands' in homogeneous catalysis.[1] Nitrogen donors are often said to be 'hard',[2] and therefore would match well the 'hard' first-row transition metal fragments. The combination of these two factors might lead to interesting chemistry. Having this in mind, we developed the synthesis of the ligand and its coordination chemistry.[3] We decided to focus on Ni because its complexes were easy to make and characterize (crystalline and diamagnetic).



Scheme 1. The pincer catalyst [($^{Me}N_2N$)NiCl] and the reactions it catalyzes.

When exploring the reactivity of $^{Me}N_2N$-Ni complexes, we found that complex **1**[4] mediated stoichiometric C–C coupling of non-activated alkyl halides.[3,5] Whereas cross coupling of aryl and vinyl electrophiles is now well developed, coupling of non-activated alkyl electrophiles is challenging due to unproductive β-H elimination.[6,7] The activity of **1** prompted us to explore its application in catalytic coupling reactions. Indeed, complex **1** was an excellent catalyst for the coupling of non-activated alkyl halides with alkyl and aryl Grignard reagents. The catalysis displays broad scope and high functional group tolerance. More than 100 examples have been demonstrated (Scheme 1).[8,9] Ester, amide, keto, ether, thioether, acetal, nitrile, various heterocyclic groups, and even aryl halide units are well tolerated. The scope is unusual for coupling reactions using Grignard reagents as nucleophiles, and underscores the high activity of the Ni catalyst.

We have attempted to replace the nucleophiles from reactive Grignard reagents to compounds containing weakly acidic C–H bonds (Scheme 1). Indeed we found methods to couple alkyl halides directly with terminal alkynes and aromatic heterocycles.[10,11] These reactions avoided the use of organometallic reagents. They are straightforward, atom- and step-economic, and have high group tolerance.

We have also started to study the mechanism of catalysis. For example, we found that β-H elimination is kinetically accessible but thermodynamically uphill in Ni-alkyl complexes of $^{Me}N_2N$.[12] This work reveals one of the main factors that contribute to the efficiency of **1** in catalysis.

A large part of our work in Ni catalysis has been summarized in an earlier account in CHIMIA.[13] Interested readers are referred to that account for more details.

3. Bio-mimetic Chemistry of [Fe]-Hydrogenase

A second project of the group is the model chemistry of [Fe]-hydrogenase. Hydrogenases are enzymes that catalyze H_2 production and utilization in nature. The functions of hydrogenases depend on inexpensive and abundant metals such as Fe and Ni.[14,15] The structures of the active sites of hydrogenases and the mechanisms by which they produce and activate H_2 are of great interest, both fundamentally and as biological models for the development of efficient H_2-processing catalysts.

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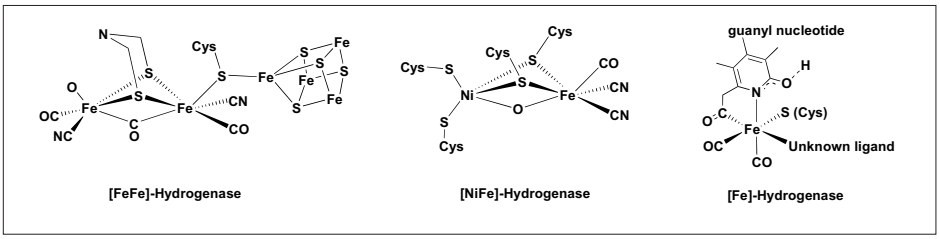


Fig. 1. The active sites of three different hydrogenases.

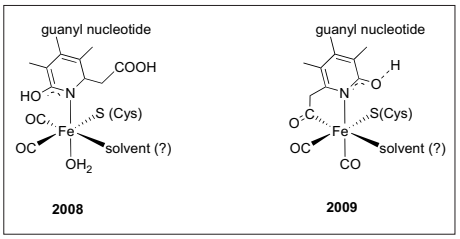
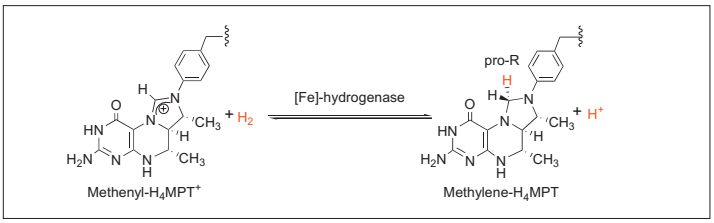


Fig. 2. The proposed active sites of [Fe]-hydrogenases.



Scheme 2. The reaction catalyzed by [Fe]-hydrogenase. In this reaction, a hydride is stereospecifically transferred from H_2 into the pro-R position of methylenetetrahydromethanopterin with a $\Delta G^{o'}$ of -5.5 kJ/mol.

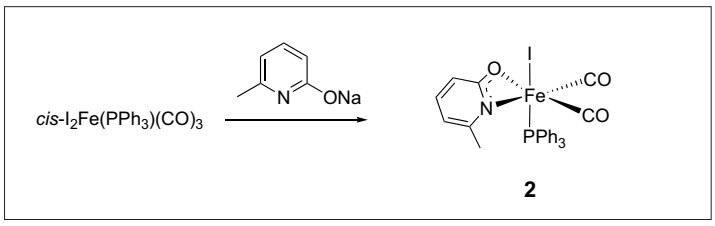
Three types of hydrogenases are known: the [NiFe]-hydrogenase, the [FeFe]-hydrogenase, and the H_2-forming methylenetetrahydromethanopterin dehydrogenase (Hmd) which is now called [Fe]-hydrogenase (Fig. 1).[14,15] The [Fe]-hydrogenase, found only in some methanogenic archaea growing on H_2 and CO_2, catalyzes the reversible reduction of methenyltetrahydromethanopterin (methenyl-H_4MPT^+) with H_2 to form methylenetetrahydromethanopterin (methylene-H_4MPT) and H^+ (Scheme 2). This reaction is an intermediary step in the reduction of CO_2 to methane by methanogens grown under nickel-limiting conditions.[15,16]

[Fe]-hydrogenase is a recent discovery and its crystal structure was first reported in 2008[17] and re-interpreted in 2009.[18] The 2008-proposed active site was shown in Fig. 2, left.[17] The Fe center is 5- or 6-coordinate depending on the state of the enzyme. The most interesting feature is the mono-dentate pyridone ligand with non-coordinating carboxylic acid and pyridone oxygen donors. Shortly after, the structure of C176A mutated [Fe]-hydrogenase crystallized in the presence of dithiothreitol was solved.[18] The result led to a new interpretation of the active site in the wild type [Fe]-hydrogenase. The revised structure (2009) consists of a Fe center coordinated to the pyridone cofactor through both pyridinyl nitrogen and acyl carbon atoms (Fig. 2, right).

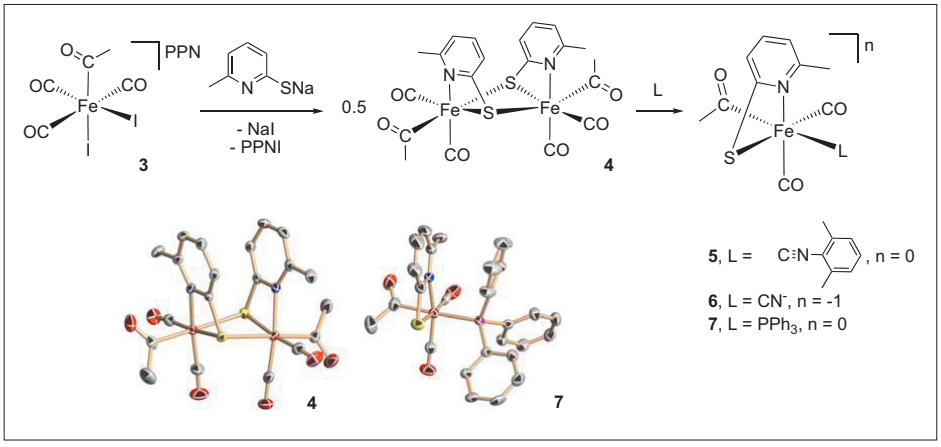
We began to develop model complexes for the active site of [Fe]-hydrogenase following the guide of the 2008 structure. We first focused on the unusual pyridone ligand found in the enzyme. Prior to this work, there were no known complexes in which a pyridone ligand coordinates to a single Fe center. Employing the procedure outlined in Scheme 3, we were able to make the first iron bis(carbonyl)pyridonate complex (**2**).[19] The IR and Mössbauer parameters of this complex are similar to those of the enzyme.

After the 2009 structure of [Fe]-hydrogenase was reported, we turned our attention to model the acyl ligand of the enzyme. An Fe^{II} acyl precursor complex **3** was prepared by reaction of MeLi with $Fe(CO)_5$ and then oxidation with I_2. **3** reacted with sodium 6-methyl-2-mercaptopyridinate to give the diiron dithiolate complex **4**, which reacted rapidly with phosphine, isocyanide, and cyanide to form 6-coordinate and mononuclear Fe^{II} complexes **5**–**7** (Scheme 4).[20] Compared to the active site of [Fe]-hydrogenase (Fig. 2), the Fe ion in complexes **5**–**7** is coordinated to the same set of five donor atoms: one acyl carbon, one sulfur, two *cis*-CO, and one pyridinyl nitrogen. Even the stereochemistry is the same. Complex **6** can also be considered as a mimic for the CN-inhibited form of [Fe]-hydrogenase.

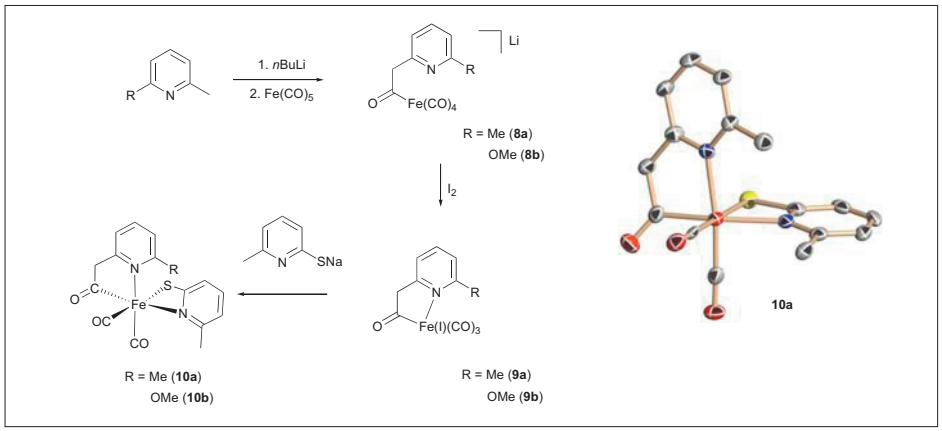
Next, we found a way to mimic the whole pyridinyl methyl acyl unit found in [Fe]-hydrogenase (Scheme 5).[21] Treatment of the *in situ* generated pyridinyl methyl anion with $Fe(CO)_5$, followed by oxidation with I_2, gave [(6-R-$PyCH_2CO$)$Fe(CO)_3I$] (**8a** and **8b**). Further reactions of **8a** and **8b** with sodium 6-methyl-2-mercaptopyridinate produced complexes [(6-R-$PyCH_2CO$)$Fe(CO)_2$(6-Me-PyS)] (**9a** and **9b**, Scheme 5) that were isolated and purified. The molecular structure of **7a** is shown in Scheme 5. The active site of [Fe]-hydrogenase is nicely mimicked. The structure suggests that for Fe^{II} ion, acyl ligand has a stronger *trans*-influence than CO ligand. Thus, the stereochemistry of the coordination sphere of the Fe center in [Fe]-hydrogenase is probably dictated by the electronic properties of the ligands.



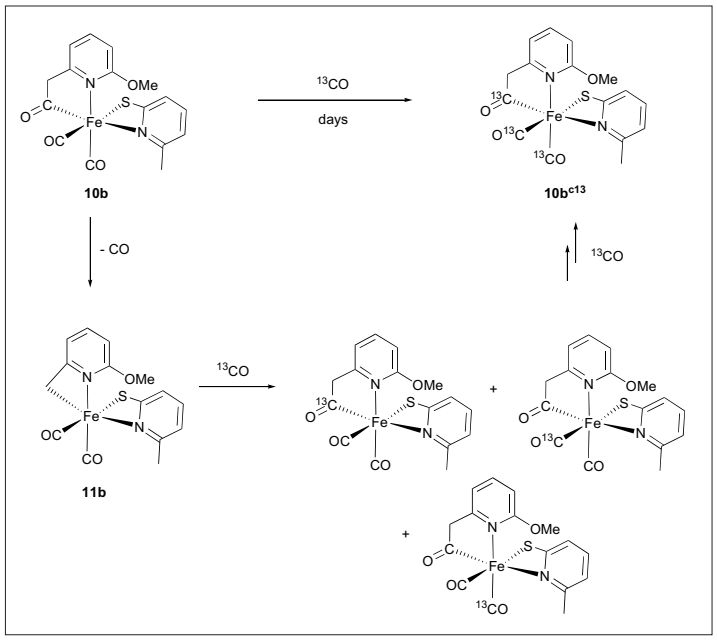
Scheme 3. Synthesis of an iron bis(carbonyl) pyridonate complex.



Scheme 4. Synthesis of iron acyl model complexes **5**-**7**, and structures of **4** and **7**.



Scheme 5. Synthesis of iron pyridinyl methal acyl model complexes **10a** and **10b**, and structure of **10a**.



Scheme 6. CO exchange reaction of mononuclear model complex **10b**.

With a large number of model complexes in hand, we have started to explore their reactivity. We found that complex **4** reacted with CO to form a mononuclear Fe tris(carbonyl) complex, which is a mimic of the CO-inhibited [Fe]-hydrogenase.[21] We also found that complex **9b** undergoes ^{13}CO exchange under one atmosphere of ^{13}CO gas. We propose that one key step is the elimination of CO from the acyl ligand to form a Fe-alkyl species (**11b**), which reacts with ^{13}CO to incorporate the first ^{13}C element (Scheme 6). Repeating the same process two more times would lead to the final product **10b^{c13}**.

Currently we are working on the H_2 activation chemistry using the model compounds.

Acknowledgement

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