Summer 2015

Synthesis of Pyridone Ligands and Iron Precursors for the Development of Iron-based Hydrogenation Catalysts

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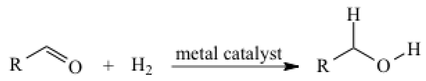
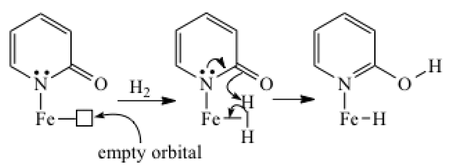
Department of Chemistry, University of Puget Sound, Summer 2015

Background

- **Hydrogenation** is a key reaction in many multi-step chemical syntheses.
  - Requires the addition of a metal catalyst.



  - Largely adopted by the pharmaceutical industry as a cost-effective and green approach to a wide range of compounds.
- Known efficient catalysts are based on the expensive and toxic transition metals Ir, Ru, Rh.
- **Proposed iron-based hydrogenation catalysts**: inexpensive and nontoxic
  - Several iron-based hydrogenation catalysts are known but there is ample room for improvement.[1]
  - A key step for hydrogenation is the formation of a Fe-H bond through ligand-assisted heterolytic cleavage of H_2.
  - We propose to use a pyridone ligand attached to the metal center to act as base in the activation of H_2:

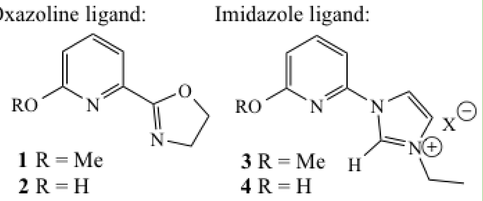


  - This mechanism, which has proven to be effective for known non-iron catalysts, is not documented for iron.[2]

Objectives of the Research

- Synthesize pyridone-based ligands

Oxazoline ligand: Imidazole ligand:



1 R = Me
2 R = H

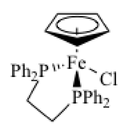
3 R = Me
4 R = H

- Synthesize iron complex precursors

A:

5 L = P(O*i*-Pr)$_3$
6 L = P(OMe)$_3$
7 L = P(OEt)$_3$
8 L = PPh$_3$
9 L = AsPh$_3$
10 L = SbPh$_3$

B:



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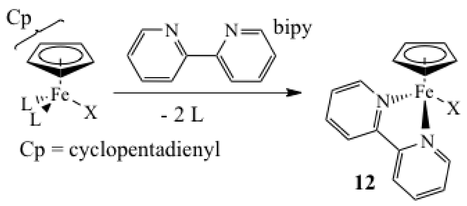
- Test iron precursors by attempting to attach model ligand 2,2'-bipyridine (bipy).



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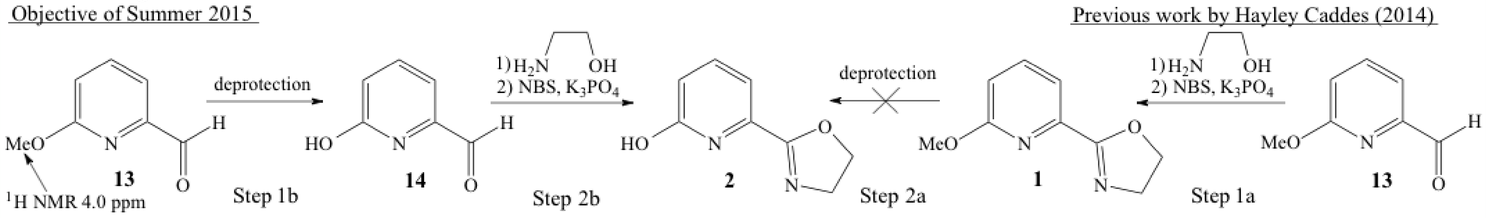
Synthesis of Ligands

Oxazoline Ligand:

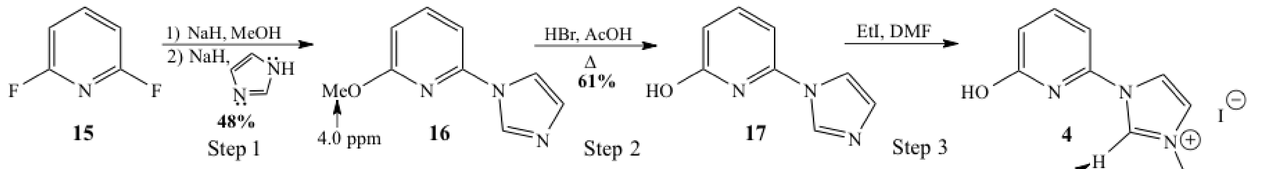
Objective of Summer 2015



Previous work by Hayley Caddes (2014)

- Step 1b: seven deprotection attempts were made, but more work is necessary.
  - Acidic conditions (HBr, HCl, AcOH, BBr_3) were too harsh, forming black sludge along with low yields of the product.
  - Nucleophilic conditions (LiCl, TMSCl and NaI) were too mild, presence of the starting material confirmed by ^{1}H NMR.

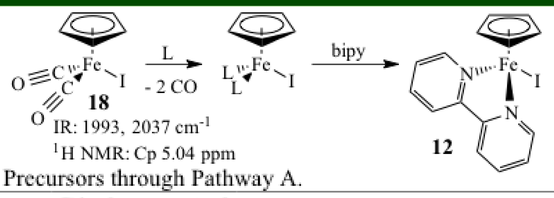
Imidazole Ligand:



- Step 1: following the procedure optimized by Hayley Caddes (2014); formation of the product confirmed by ^{1}H NMR analysis.
- Step 2: successful deprotection under acidic conditions and heat.
  - Formation of the product confirmed by ^{1}H NMR spectroscopy, including the absence of a methyl peak at 4.0 ppm.
- Step 3: successful attachment of ethyl group in DMF.
  - Presence of a quartet at 4.6 ppm and a triplet at 1.6 ppm in the ^{1}H NMR spectrum are consistent with values reported in the literature, as well as the hydrogen on the imidazole ring shifting up to 10.5 ppm.[5]
  - Excess EtI reacts at other locations forming an unknown side-product seen by ^{1}H NMR spectroscopy.
  - Using DMF at room temperature yielded the best outcome with a 1:1 product/side-product ratio.
  - No reaction occurred with any other solvent (THF, CH_3CN, EtOAc, toluene, acetone); the starting material was insoluble in most of them.

Formation of Iron Complexes

Pathway A:

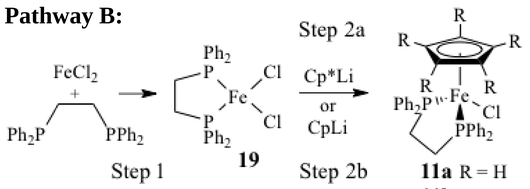


5 L = P(O*i*-Pr)$_3$ **8** L = PPh$_3$
6 L = P(OMe)$_3$ **9** L = AsPh$_3$
7 L = P(OEt)$_3$ **10** L = SbPh$_3$

Table 1. Synthesis of Iron Precursors through Pathway A.

Iron Precursor	L	Displacement of CO groups	Notes	Attachment of bipy	Notes
5	P(O*i*-Pr)$_3$	Single	Confirmed by a CO signal at 1953 cm^{-1} on IR.[5]	Unsuccessful	Cp ring signal disappeared on ^{1}H NMR.
6	P(OMe)$_3$ (^{1}H NMR: 3.5 ppm)	Double	Confirmed by ^{1}H NMR with a doublet at 3.33 ppm for the attached P(OMe)$_3$ and a singlet at 4.32 ppm for the Cp ring.[5]	Unsuccessful	Cp ring signal disappeared on ^{1}H NMR.
7	P(OEt)$_3$ (^{31}P NMR: 139 ppm)	Double	Confirmed by ^{31}P NMR with a strong peak at 182.20 ppm for the P(OEt)$_3$ on the product.[5]	NA	NA
8	PPh$_3$	Single	Confirmed by a CO signal at 1943 cm^{-1} on IR.[6]	Unsuccessful	Cp ring signal disappeared on ^{1}H NMR.
9	AsPh$_3$	Single	Confirmed by a CO signal at 1945 cm^{-1} on IR.[6]	NA	NA
10	SbPh$_3$	Mixture of single and displacement of iodine	Ratio of products with signals at 1942, 1987, and 2033 cm^{-1} followed by IR.[6]	NA	NA

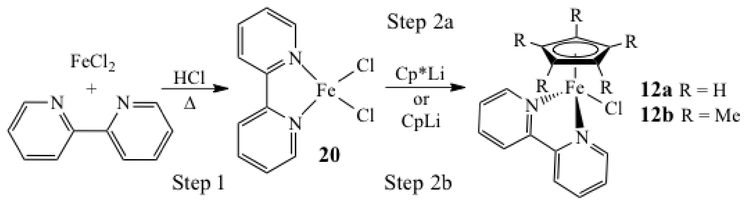
Pathway B:



- Step 1: yellow-white powdery solid synthesized following procedure developed by Liz Meucci (2014).
  - **11a** and **11b** are paramagnetic so ^{1}H NMR spectra are unhelpful.
- Step 2a: black solid formed that is consistent with descriptions in the literature but insoluble in all solvents tried; unable to analyze by ^{1}H NMR spectroscopy .6
- Step 2b: unsuccessful attachment of Cp ring confirmed by ^{1}H NMR signals inconsistent with those in the literature.[6]

Pathway C:

- Step 1: previously performed successfully by Liz Meucci (2014).
- Step 2a: unsuccessful attachment of Cp* ring confirmed by the absence of a signal for the methyl groups on the Cp*ring in ^{1}H NMR.
- Step 2b: unsuccessful attachment of Cp ring confirmed by an ^{1}H NMR spectrum that was identical to that of step 2a.

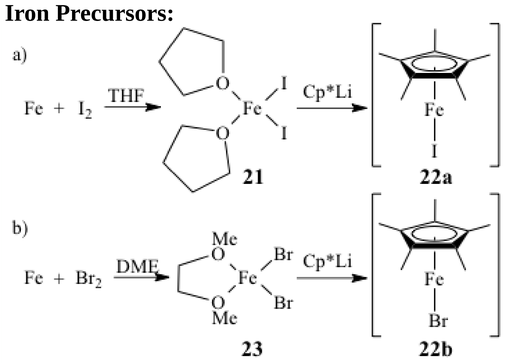


Conclusions

- Ligands **1** and **3** were both synthesized.
- In the formation of ligand **2**, acidic conditions were too harsh and the nucleophilic conditions tested were too mild.
- Ligand **4** was synthesized, but a side-product formed in the conditions tested.
- Six iron precursors synthesized through Pathway A.
- Pathway C attempts to form iron precursors were unsuccessful.

Future Work

Iron Precursors:



- The reported formation of iron complexes **22a** and **22b** will be investigated as they could serve as highly reactive iron precursors.[7,8]
- More trials of pathways A, B, and C will be conducted.
- More attempts of the attachment of bipyridine will be conducted and analyzed with IR spectroscopy.[5]
- Further analysis will be done on pathway B.

Synthesis of Ligands:

- Further attempts of Step 2b of oxazoline ligand synthesis will be done under nucleophilic conditions.
- More trials of Step 4 in the synthesis of the imidazole ligand will be conducted, as well as further investigation of the solubility of the product.

References

Green chemistry graphic from: https://kimiaundip09.wordpress.com/2012/07/09/green-chemistry

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