Diiron Aminocarbyne Complexes as Catalysts for the Synthesis of β-Hydroxynitriles

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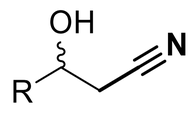
INTRODUCTION & AIM

Nitriles represent versatile building blocks in organic synthesis.[1] For instance, they can act as nucleophiles in aldol-type condensations leading to β-hydroxynitriles



β-Hydroxynitriles are a key intermediates in the pharmaceutical and material industries[2]

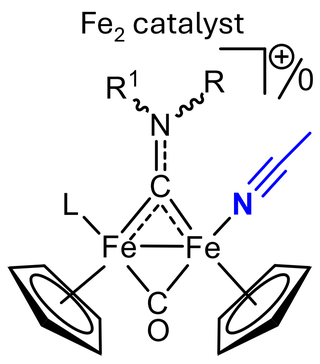
The challenge: Direct activation of simple aliphatic nitriles is constrained by the low acidity of α C–H bonds

Traditional activation[3]
- n-BuLi
- Cryogenic T (-80°C)

Catalytic approach
Nitrile coordination to transition metals enhances α C–H acidity, enabling deprotonation under mild conditions

Current catalysts rely on:
- Noble metals (Rh, Ru)[4]
- Complex structures (Ni with pincer ligands)[5]
- Large amounts of co-catalysts

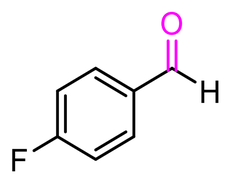
This work



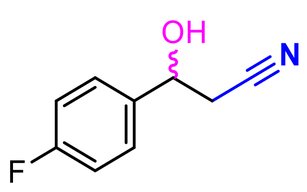
Why diiron complexes:
- Iron is cheap, abundant and sustainable
- Straightforward multigram access from a commercial precursor
- **Cooperative effects** enable uncommon reactivity and stabilization of bridging ligands

CATALYTIC STUDIES- Optimization of conditions: base type, time, and temperature

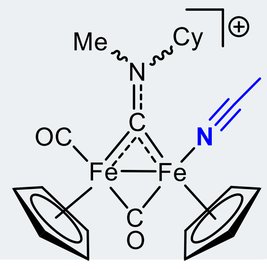
Model reaction



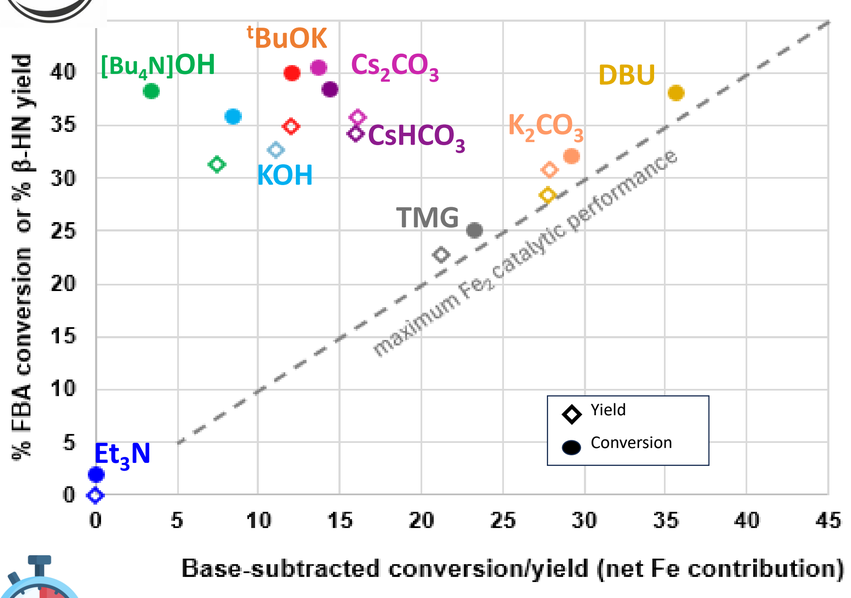
+ CH_3CN $[Fe_2]$ Base



Benchmark catalyst



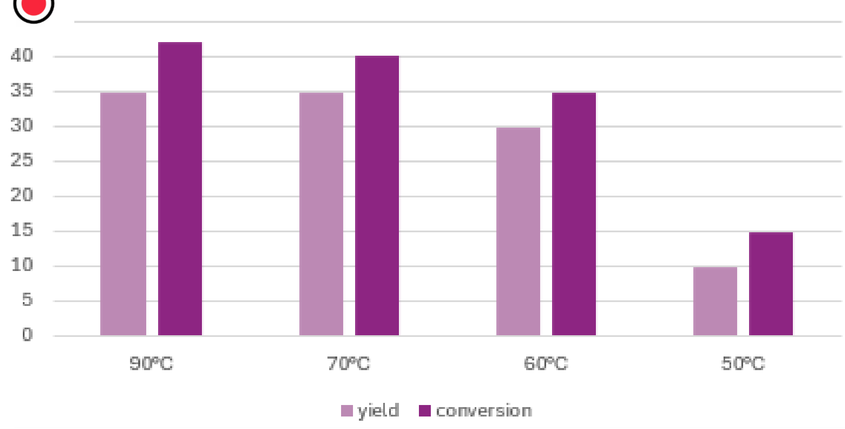
Catalytic performance at reflux temperature



Best compromise among:
-Total conversion
-Selectivity
-Net catalyst contribution

Our choice: Cs_2CO_3

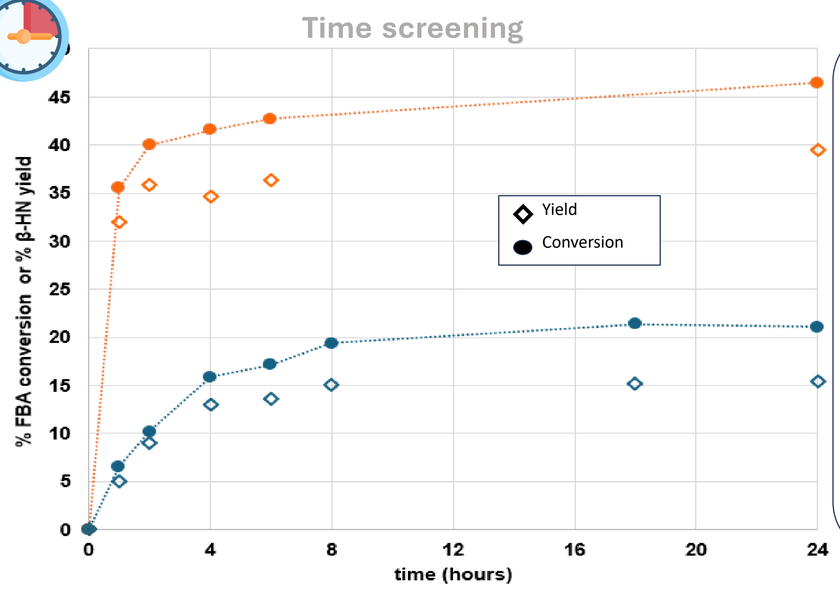
Screening of temperatures



The screening was carried out with Cs_2CO_3 as a co-catalyst

Our choice: 65°C

Time screening



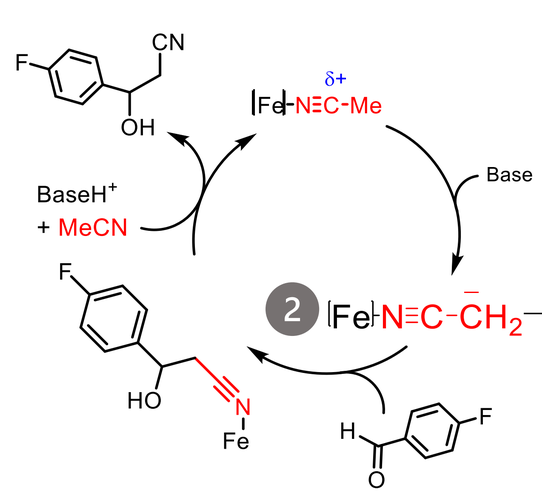
Even after 24 hours the reaction did not reach completion, leading instead to an asymptotic behaviour towards 45% conversion

This is due to the presence of 2 distinct deactivation pathways (v. 1, 2)

DEACTIVATION PATHWAYS

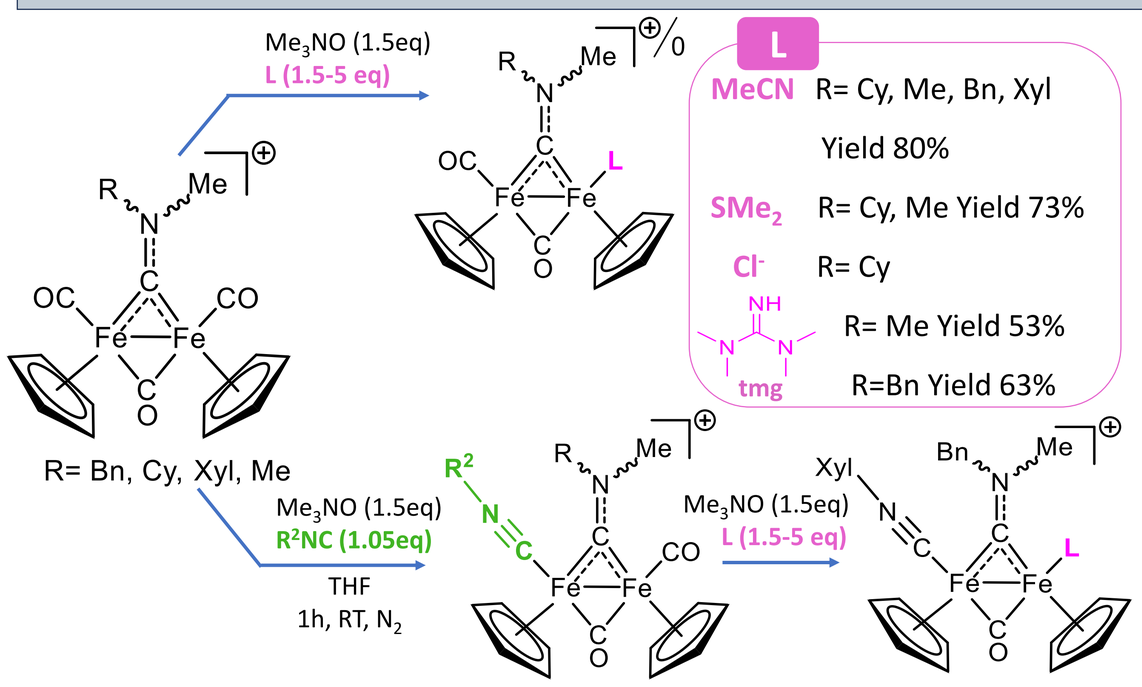
1 $Cs_2CO_3 \xrightarrow{H_2O} CsHCO_3$

1 Reaction of the base with water released from the **dehydration of the hydroxynitrile**



2 - Recoordination of the deprotonated nitrile in an inactive form

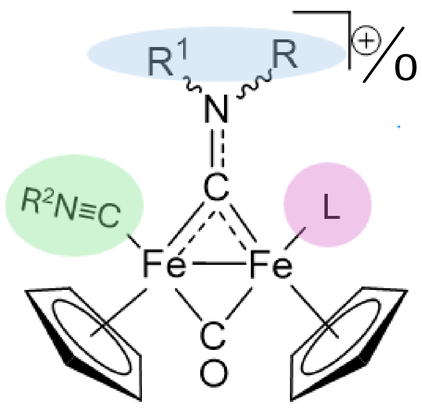
SYNTHETIC RESULTS



L

MeCN	R= Cy, Me, Bn, Xyl Yield 80%
SMe_2	R= Cy, Me Yield 73%
Cl^-	R= Cy
tmg	R= Me Yield 53%
	R=Bn Yield 63%

STRUCTURE-ACTIVITY RELATIONSHIPS



1 Substituents on the aminocarbyne ligand
- Negligible stereoelectronic effects
- R=Me R^1=Cy Conversions ~47%

2 Terminal labile ligands

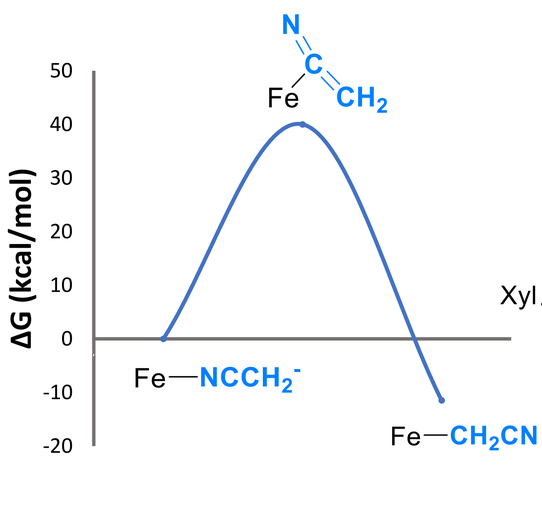
All tested ligands are labile towards MeCN and generate the active species in situ

3 Isocyanide vs. CO

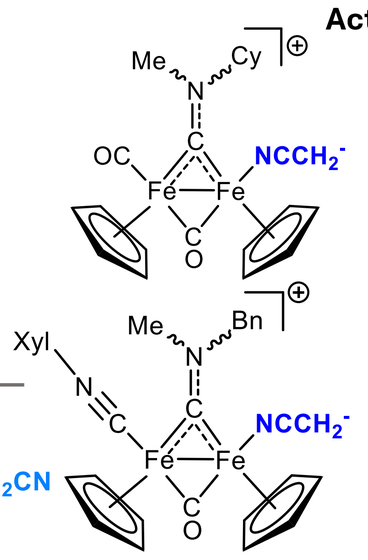
Conversion up to ~55%
Active species still present at the end of the reaction

COMPUTATIONAL ANALYSIS

K-N →K-C Isomerization



Activation energy of isomerization



~40 Kcal/mol

~52 Kcal/mol

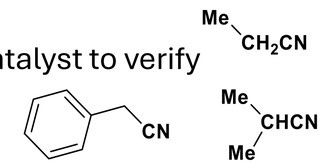
Slightly more stable toward isomerization under catalytic conditions

CONCLUSIONS

1) The catalytic reaction conditions were optimized, reaching 45% conversion
2) Two different deactivation pathways were identified
3) New diiron aminocarbyne complexes with different terminal ligands were synthesized
4) Catalyst stability within the catalytic environment was improved through the introduction of an isocyanide (55% conversion)

FUTURE PERSPECTIVES

1) Testing different substrates, such as substituted nitriles affording β-hydroxynitriles unable to dehydrate
2) Testing scale up reactions for isocyanide substituted catalyst to verify the TON



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