IRON CATALYSIS IN ORGANIC CHEMISTRY

Dong Lab Literature Talk

Rachel Whittaker

September 2, 2015

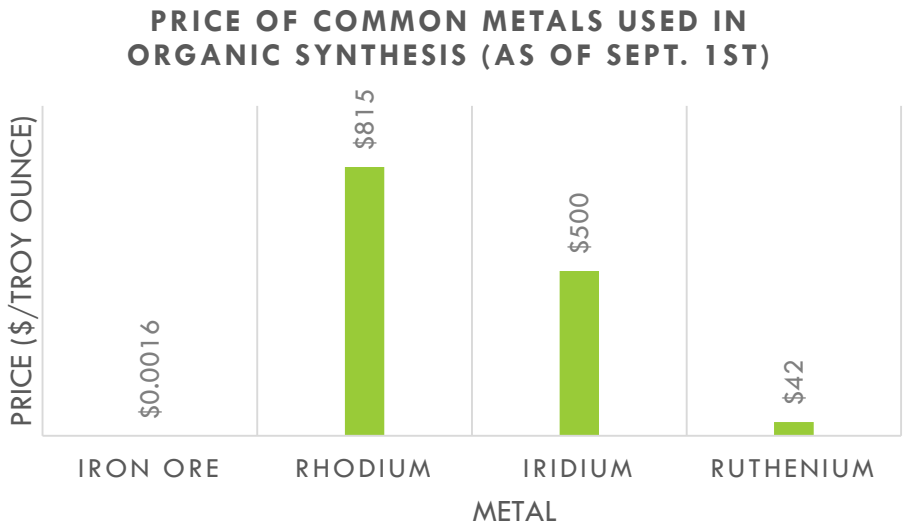
OVERVIEW

- Introduction
- Oxidation Reactions
- Reduction Reactions
- Cycloadditions and Ring Expansion Reactions
- Conclusions

IRON…

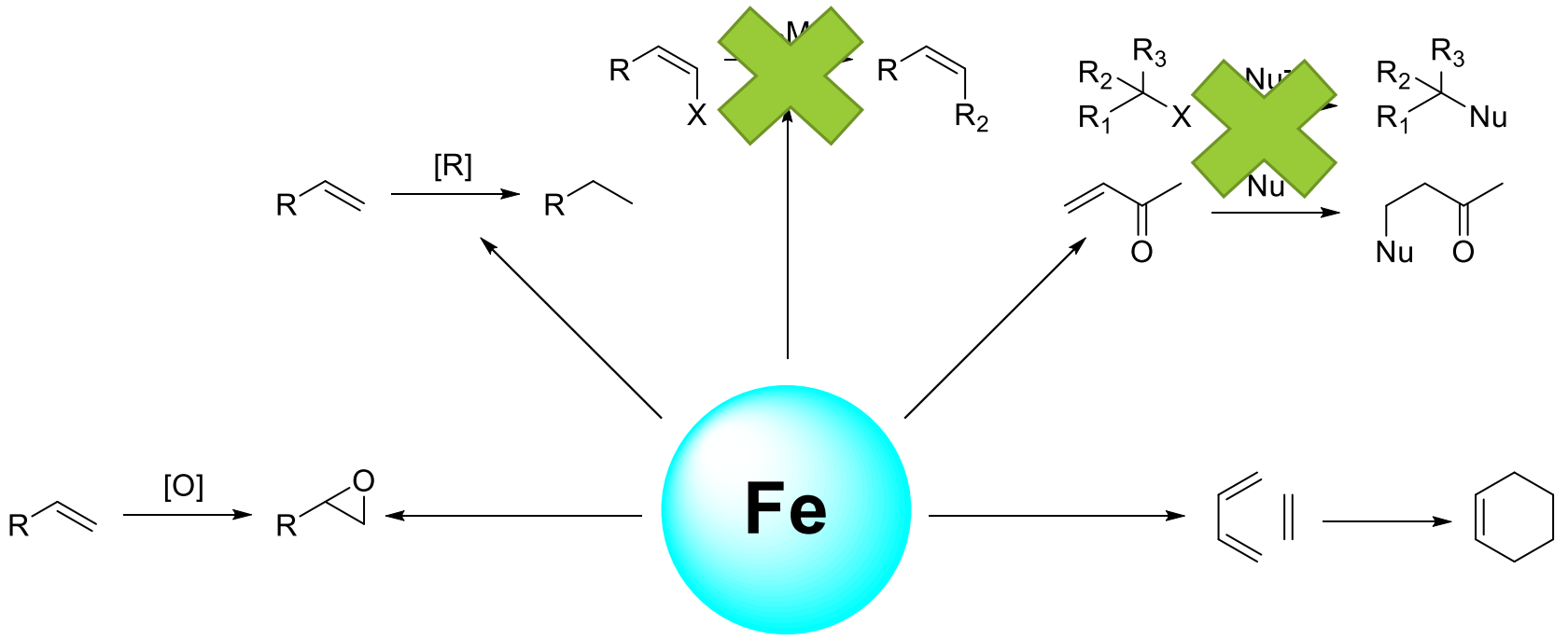
24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.933	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546
42 Mo Molybdenum 95.94	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868
74 W Tungsten 183.85	75 Re Rhenium 168.207	76 Os Osmium 190.23	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.967

- Iron is the most common element on the Earth and thus is relatively cheap.
- 2nd and 3rd row transition metals have a long and developed history of achieving high yields and enantioselectivities for a huge number of reactions.
- Due to price and scarcity, however, finding new options is a challenge for the chemistry community



https://www.quandl.com/collections/markets/rare-metals

IRON CATALYSIS IN ORGANIC CHEMISTRY

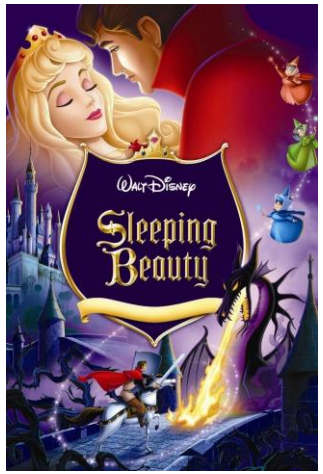


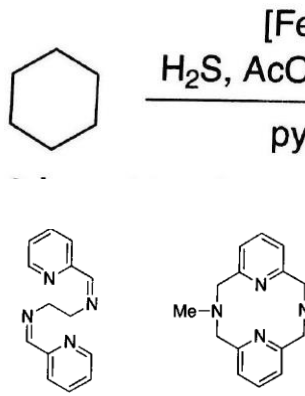
Iron Catalysis in Organic Chemistry; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008.

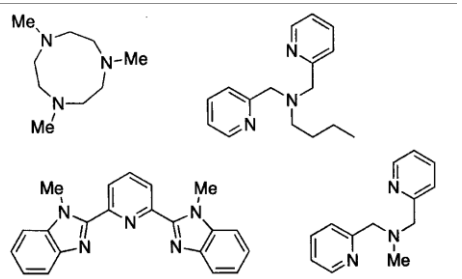
IRON-CATALYZED OXIDATION REACTIONS

1. Oxidations of C-H and C=C Bonds
2. Oxidative Allylic Oxygenation and Amination
3. Recent Advance

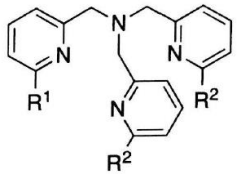
GIF CHEMISTRY



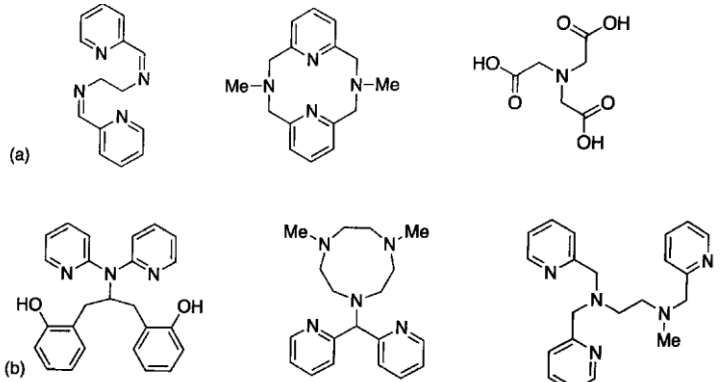




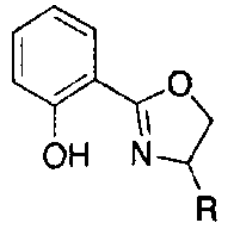
bpmen



α-pyridyl substituted TPA
L1: $R^1 = R^2 = H$
L2: $R^1 = R^2 = Me$
L3: $R^1 = COOMe$, $R^2 = H$

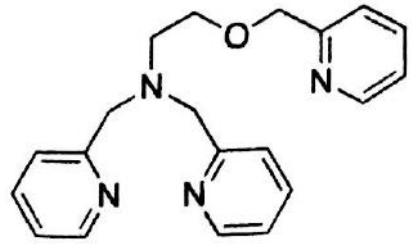


β-pyridyl substituted TPA
L4: $R^1 = R^2 = H$
L5: $R^1 = R^2 = Me$
L6: $R^1 = H$, $R^2 = Me$



R = COOH, *i*Pr

Hphox



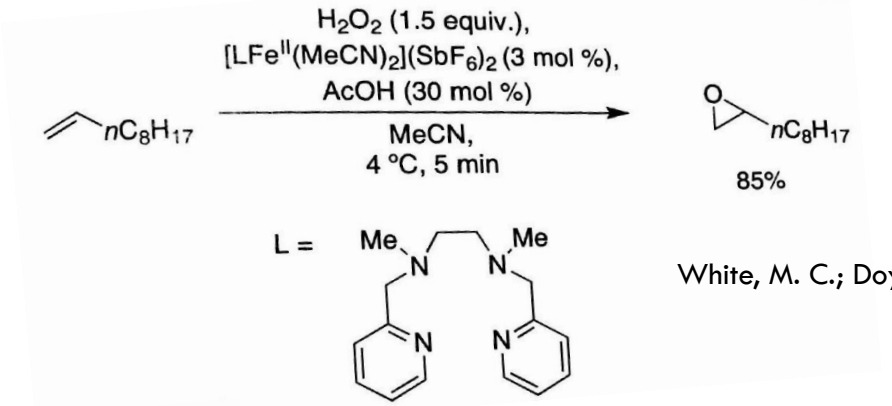
tpoen

- Barton published 46 articles on Gif chemistry and another 60 on Gif-related Chemistry

Mayer, A. C.; Bolm, C. Iron-catalyzed Oxidation Reactions. In *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008; p. 73.

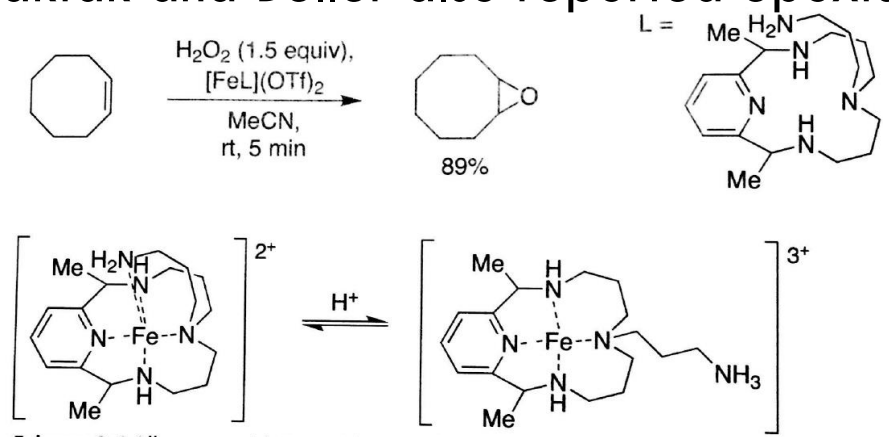
EPOXIDATION

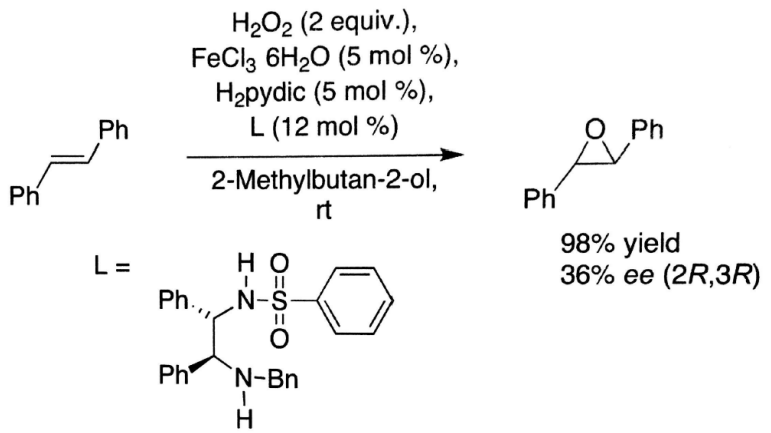
- Jacobsen reported an Fe-catalyzed epoxidation in 2001



White, M. C.; Doyle, A. G.; Jacobsen, E. *JACS*, **2001**, *123*, 7194.

- Taktak and Beller also reported epoxidation reactions



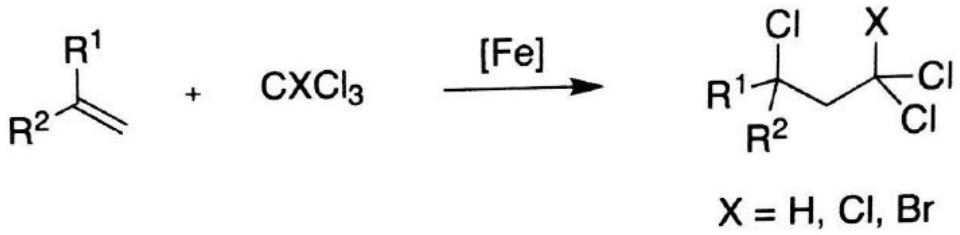


Taktak, S. *et. al. Inorg. Chem.* **2007**, *46*, 2929.

Beller, M. *et. al. ACIE*, **2007**, *46*, 7293.

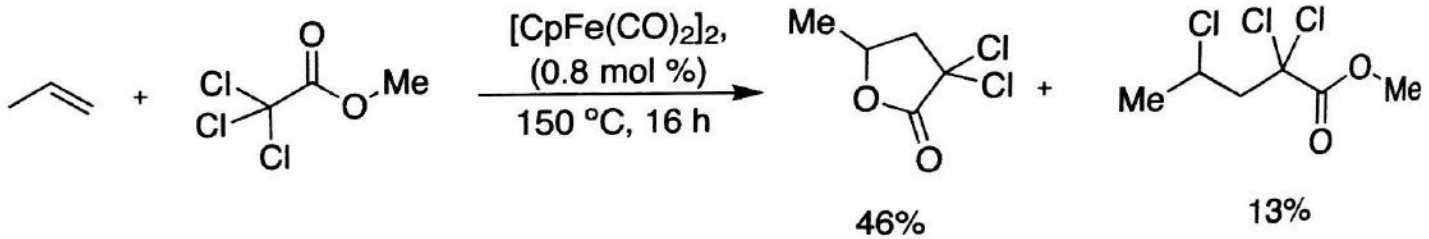
KHARASCH REACTION

- Kharasch first described the addition of halocarbons to alkenes in 1945



Kharasch, E. V. *et. al. Science* **1945**, *102*, 128.

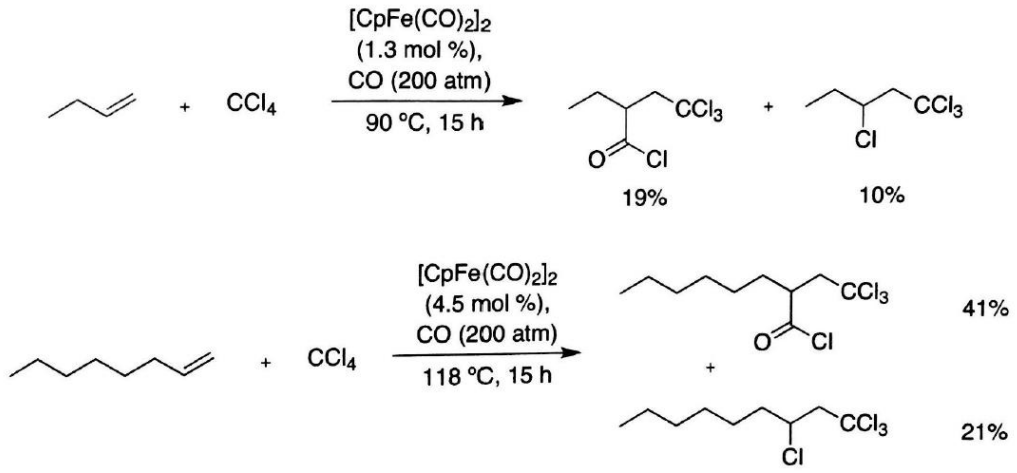
- Mori and Tsuji reported the formation of lactones/esters when methyl trichloroacetate was used



Mori, Y.; Tsuji, J. *Tetrahedron* **1972**, *28*, 29.

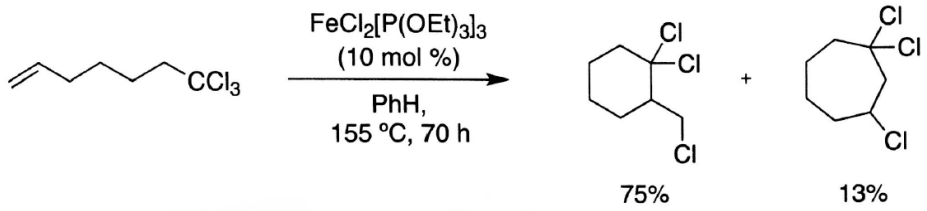
KHARASCH REACTION

- Tsuji also reported the addition of CCl_4 to generate Kharasch products, as well as acyl chlorides



Tsuji, J. *et. al. J. Org. Chem.* **1970**, *35*, 2982.

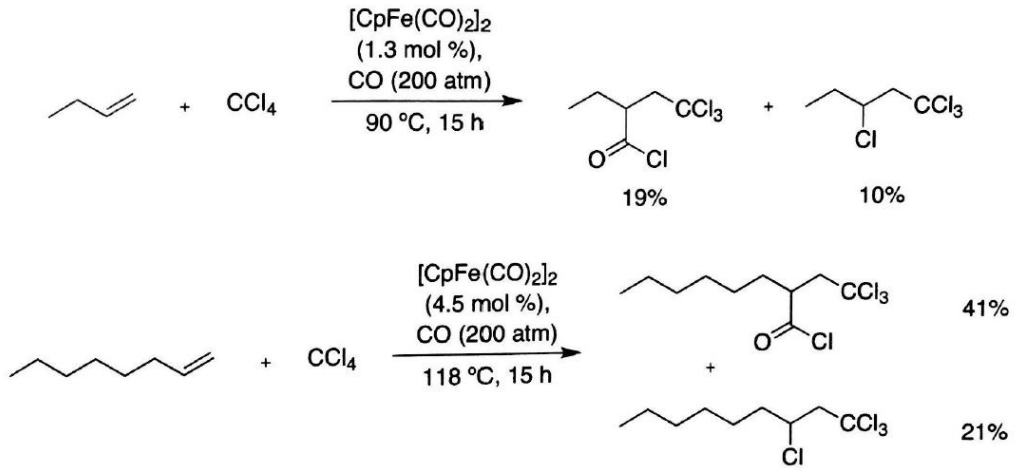
- Weinreb reported an intramolecular variant



Weinreb, S. M. *et. al. J. Org. Chem.* **1990**, *55*, 1281.

KHARASCH REACTION

- Tsuji also reported the addition of CCl_4 to generate Kharasch products, as well as acyl chlorides



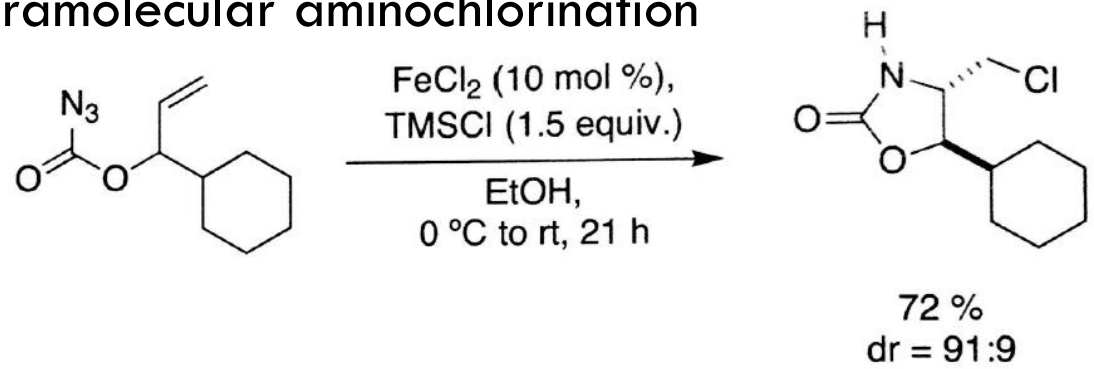
Tsuji, J. *et. al. J. Org. Chem.* **1970,** *35,* 2982.

- Intramolecular lactonization was reported in 1998 by de Campo

de Campo, F. *et. al. Chem. Commun.* **1998,** 2117.

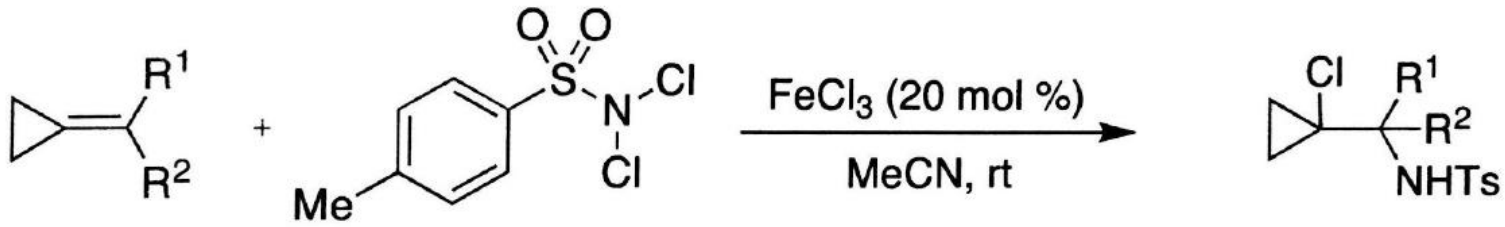
AMINOCHLORINATION

- Bach reported intramolecular aminochlorination



Bach, T. *et. al. Synthesis* **2006**, *551*.

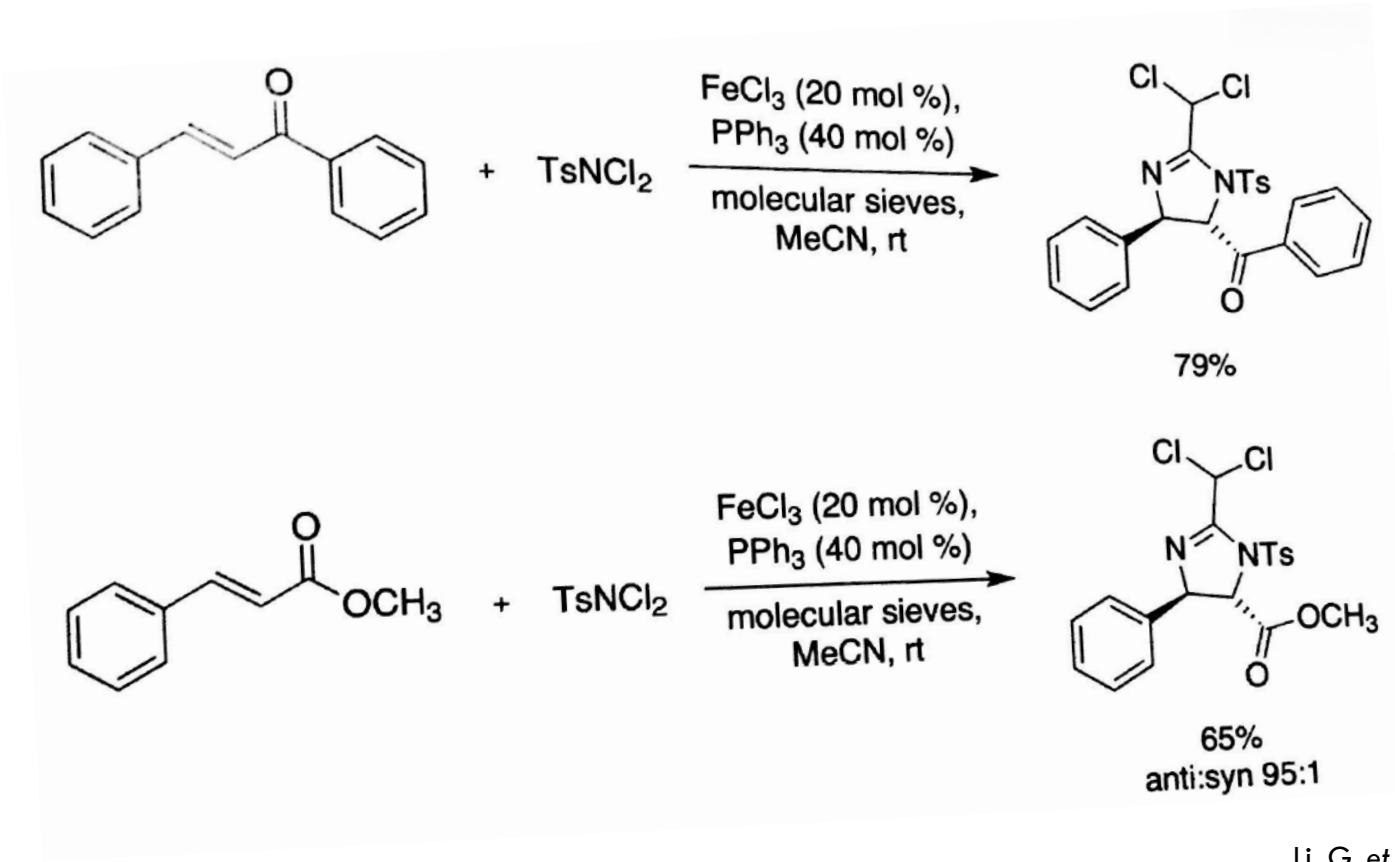
- Li's aminochlorination of cyclopropenes



Li, G. *et. al. Org. Lett.* **2006**, *8*, 625.

DIAMINATION

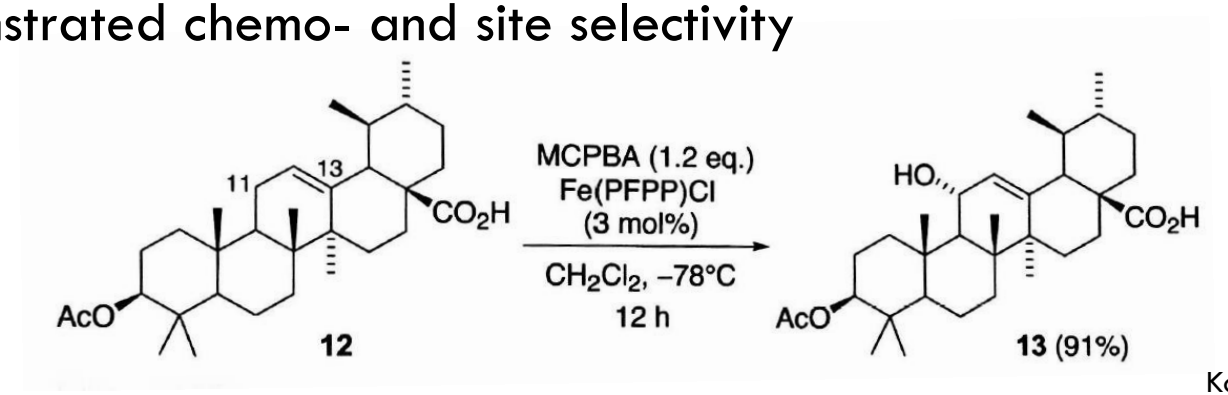
- Li also reported deamination of alkenes



Li, G. *et. al. J. Org. Chem.* **2002,** *67*, 4777.

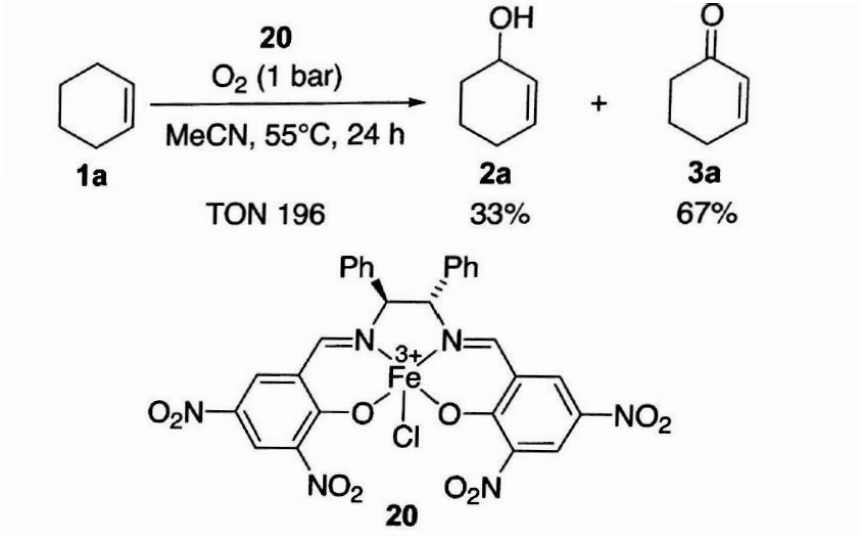
ALLYLIC OXIDATION

- Konoike demonstrated chemo- and site selectivity



Konoike, T. *et. al. Tetrahedron Lett.* **1999**, *40*, 6971.

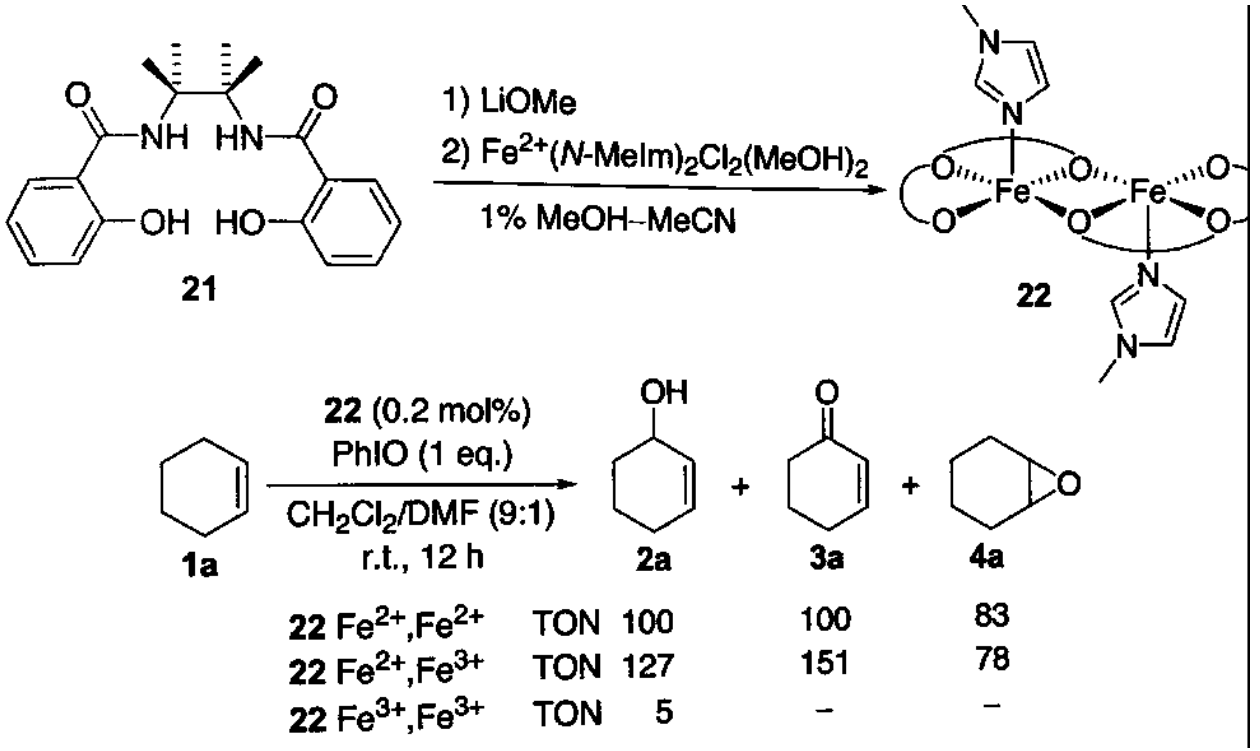
- Böttcher used Fe-salen complexes to oxidize alkenes



Böttcher, A. *et. al. J. Mol. Catal. A* **1996**, *113*, 191.

ALLYLIC OXIDATION

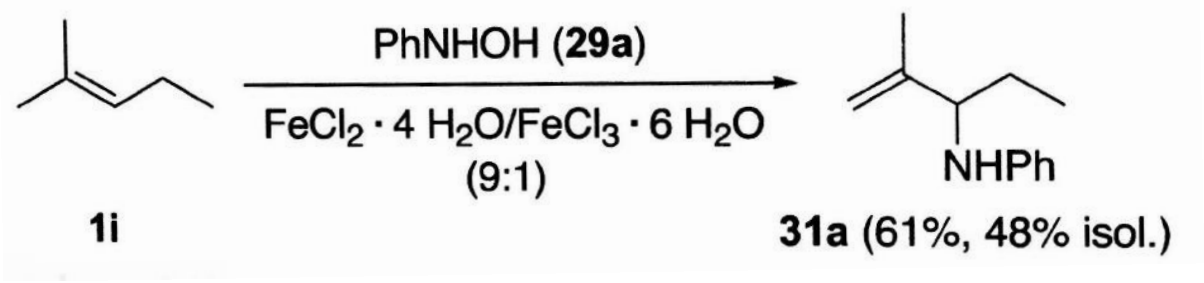
- Mukerjee developed a dinuclear Fe complex that could give high turnover numbers



Mukerjee, S. *et. al. JACS* **1997**, *119*, 8097.

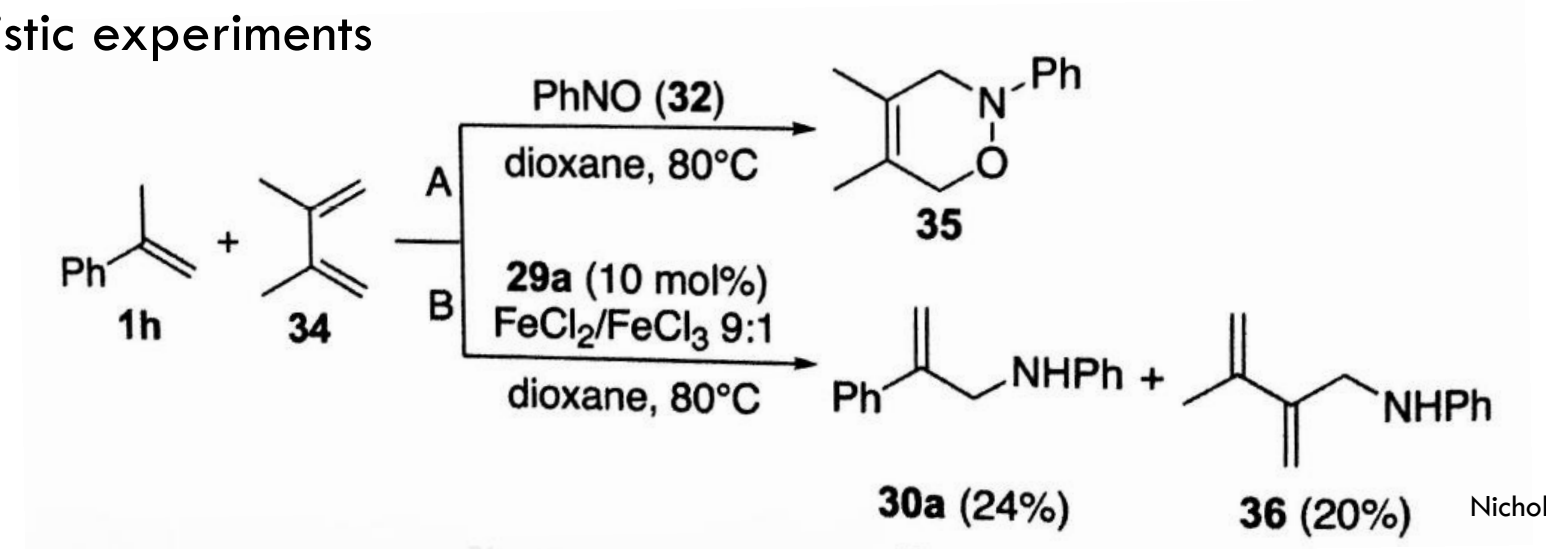
ALLYLIC AMINATION

- Nicholas reported an early catalytic example of allylic amination



Nicholas, K. M. *et. al. Tetrahedron Lett.* **1994**, *35*, 8739.

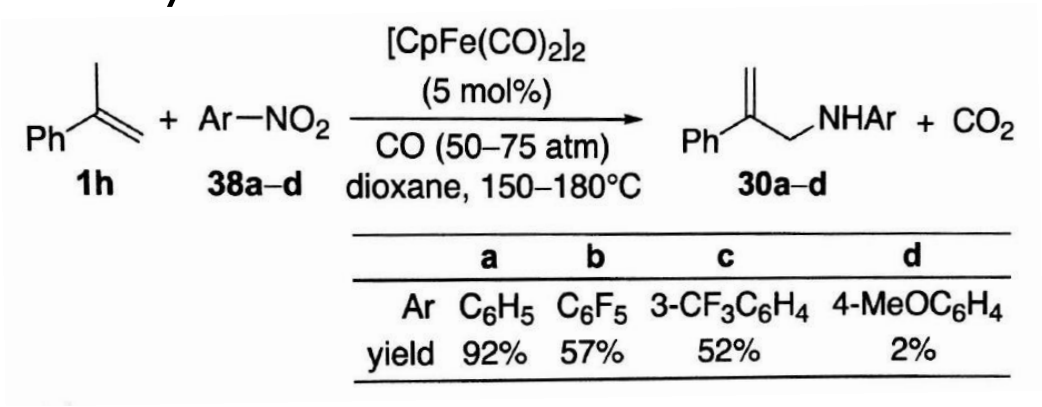
- Mechanistic experiments



Nicholas, K. M. *et. al. JACS* **1997**, *119*, 3302.

ALLYLIC AMINATION

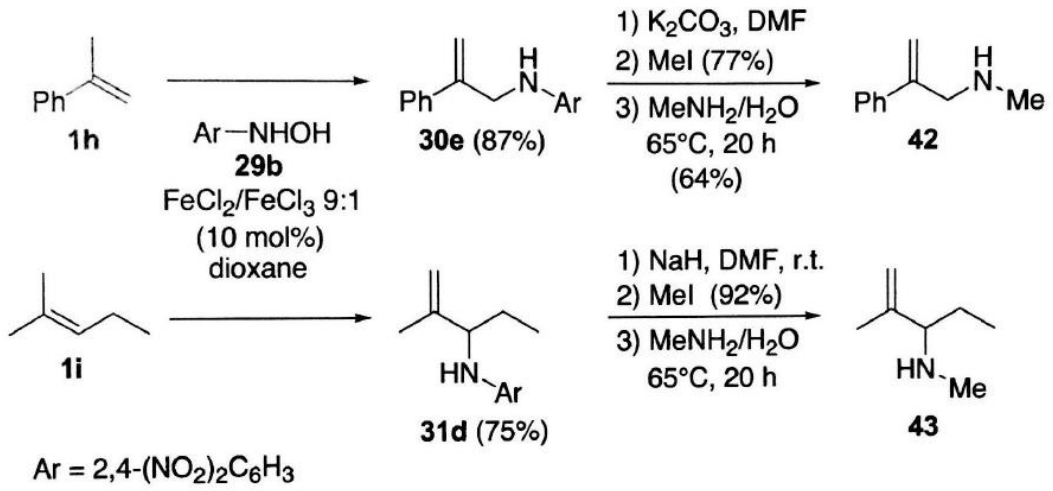
- Nicholas also reported allylic amination with nitroaromatics



	a	b	c	d
Ar	C_6H_5	C_6F_5	3-$CF_3C_6H_4$	4-$MeOC_6H_4$
yield	92%	57%	52%	2%

Nicholas, K. M. *et. al. Chem. Commun.* **1998,** 2705.

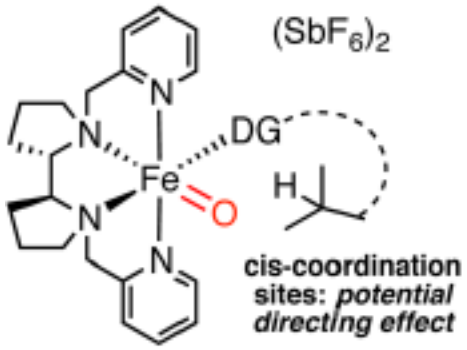
- Additionally, hydroxylamines could be used



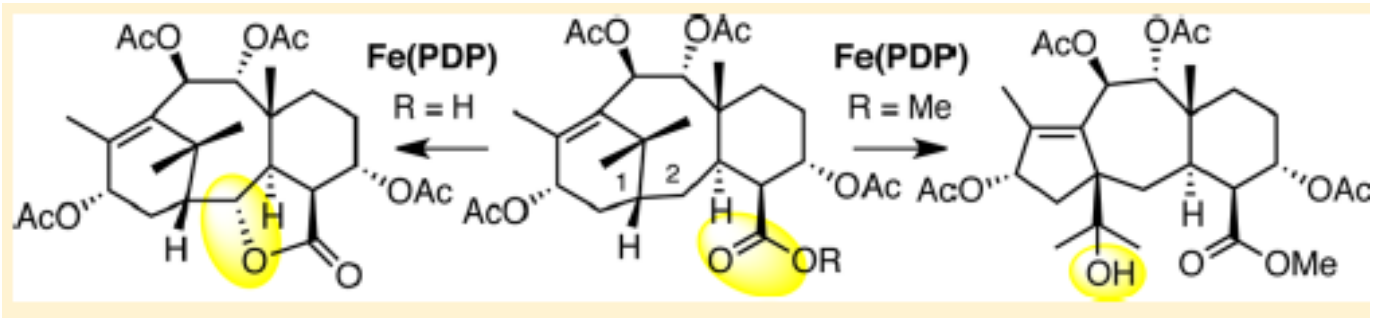
Nicholas, K. M. *et. al. Synth. Commun.* **2001,** *31*, 3087.

RECENT ADVANCE

- White has developed directed metal (oxo) aliphatic C-H hydroxylations



Proposed oxo intermediate for *Fe(S,S-PDP)* ***1***



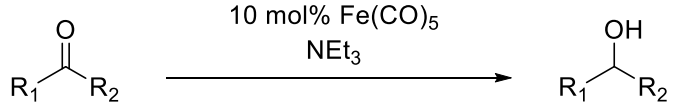
White, M. C. *et. al. JACS* **2012,** *134*, 9721.

HOMOGENEOUS IRON-CATALYZED REDUCTION

1. Hydrogenation of C=O
2. Hydrogenation of C=C
3. Hydrogenation of C=N
4. Recent Advance

C=O REDUCTION

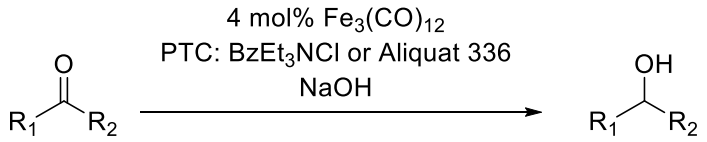
- First catalytic example by Markó in 1983



	Conversion:
R_1 = Me, R_2 = Me	>99%
R_1 = Ph, R_2 = Me	62%
R_1 = *i*-Bu, R_2 = Me	30%
R_1 = Ph, R_2 = H	95%
R_1 = *n*-Pr, R_2 = H	98%
cyclohexanone	>99%

Markó, L. *et. al. Transition Met. Chem.* **1983,** *8,* 207.

- Later, Vancheesan used 2-propanol or 1-phenylethanol

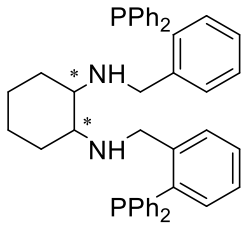


	Yield:
R_1 = Ph, R_2 = Me	36%
R_1 = 4-Cl-C_6H_4, R_2 = Me	42%
R_1 = 4-Me-C_6H_4, R_2 = Me	28%
R_1 = Et, R_2 = Me	20%
cyclohexanone	78%

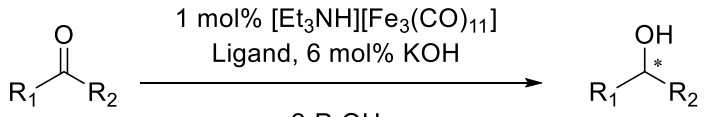
Vancheesan, S. *et. al. J. Mol. Catal.* **1985,** *32,* 11.
Vancheesan, S. *et. al. J. Mol. Catal.* **1989,** *52,* 301.

C=O REDUCTION

- Chen reported asymmetric transfer hydrogenation



Ligand
(*S*,*S*)
(*R*,*R*)

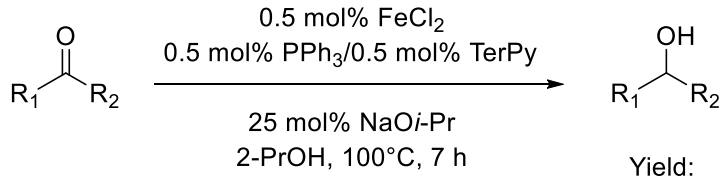


Ligand (*S*,*S*):	*ee*:	Yield:
R_1 = Ph, R_2 = Me	56% (*R*)	92%
R_1 = Ph, R_2 = *t*-Bu	93% (*S*)	19%
R_1 = Bn, R_2 = Me	98% (*S*)	18%
R_1 = Ph, R_2 = Cy	78% (*S*)	73%
Ligand (*R*,*R*):		
R_1 = Ph, R_2 = Et	72% (*S*)	87%
R_1 = Ph, R_2 = *i*-Pr	78% (*S*)	98%

Chen, J.-S. *et. al. Huaxue Xuebao* **2004**, *62*, 1745.

C=O REDUCTION

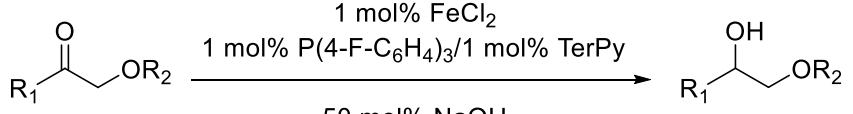
- In 2006, Beller generated an iron catalyst system *in situ*



	Yield:
R_1 = Ph, R_2 = Me	95%
R_1 = 4-Cl-C_6H_4, R_2 = Me	97%
R_1 = 4-Me-C_6H_4, R_2 = Me	83%
R_1 = Ph, R_2 = Et	92%
R_1 = 4-MeO-C_6H_4, R_2 = Me	75%
R_1 = 2-MeO-C_6H_4, R_2 = Me	>99%
R_1 = Ph, R_2 = CH_2Cl	8%
R_1 = Cy, R_2 = Me	93%
R_1 = *t*-Bu, R_2 = Me	>99%

Beller, M. *et. al. Chem. Asian J.* **2006**, *1*, 598.

- Beller also showed reduction of α–substituted ketones

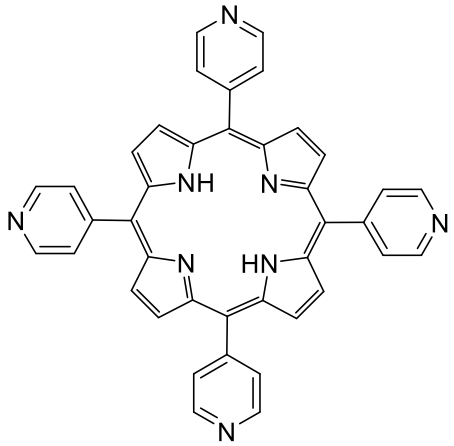


	Yield:
R_1 = Ph, R_2 = Me	92%
R_1 = Ph, R_2 = Ph	94%
R_1 = Ph, R_2 = 4-Cl-C_6H_4	>99%
R_1 = Ph, R_2 = 2,6-(*i*-Pr)$_2$-C_6H_4	45%
R_1 = 4-Me-C_6H_4, R_2 = Ph	99%
R_1 = 4-MeO-C_6H_4, R_2 = Ph	85%
R_1 = *t*-Bu, R_2 = Ph	22%

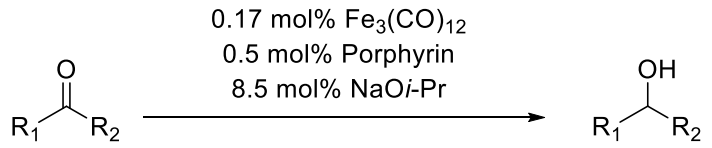
Beller, M. *et. al.* Reduction of Unsaturated Compounds with Homogeneous Iron Catalysts. In *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008; p. 125.

C=O REDUCTION

- Fe porphyrins have also been used as biomimetic catalysts



Porphyrin

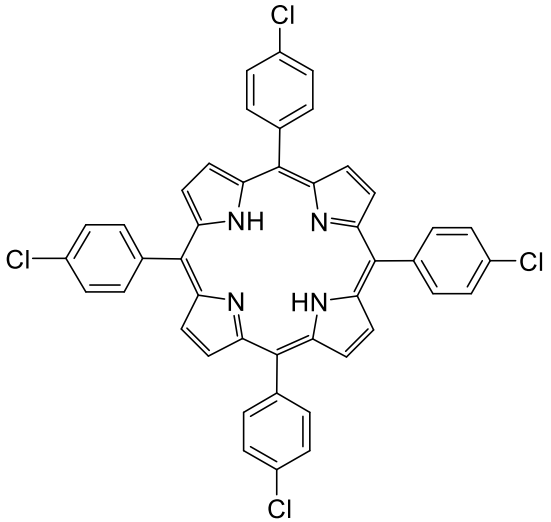


	Yield:
R_1 = 4-Cl-C_6H_4, R_2 = Me	95%
R_1 = Ph, R_2 = Me	94%
R_1 = 4-Me-C_6H_4, R_2 = Me	68%
R_1 = 4-MeO-C_6H_4, R_2 = Me	72%
R_1 = 2-MeO-C_6H_4, R_2 = Me	>99%
R_1 = Ph, R_2 = Et	87%
R_1 = Cy, R_2 = Me	89%
R_1 = *t*-Bu, R_2 = Me	90%

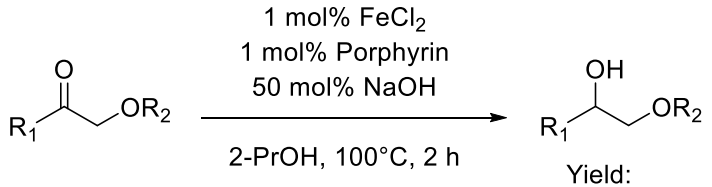
Beller, M. *et. al. Tetrahedron Lett.* **2006,** *47*, 8095.

C=O REDUCTION

- Fe porphyrins have also been used as biomimetic catalysts



Porphyrin

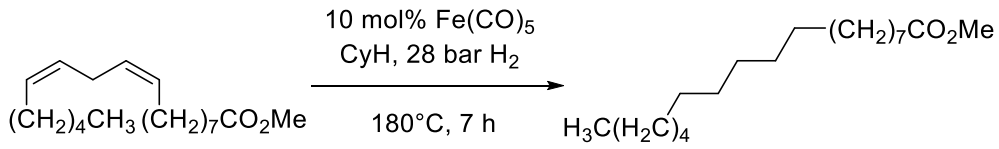


	Yield:
R_1 = Ph, R_2 = Me	>99%
R_1 = Ph, R_2 = Ph	92%
R_1 = Ph, R_2 = 4-Cl-C_6H_4	>99%
R_1 = Ph, R_2 = 2,6-(*i*-Pr)$_2$-C_6H_4	74%
R_1 = 4-Me-C_6H_4, R_2 = Ph	>99%
R_1 = 4-MeO-C_6H_4, R_2 = Ph	83%
R_1 = *t*-Bu, R_2 = Ph	48%

Beller, M. *et. al. Tetrahedron* **2008**, *64*, 3867.

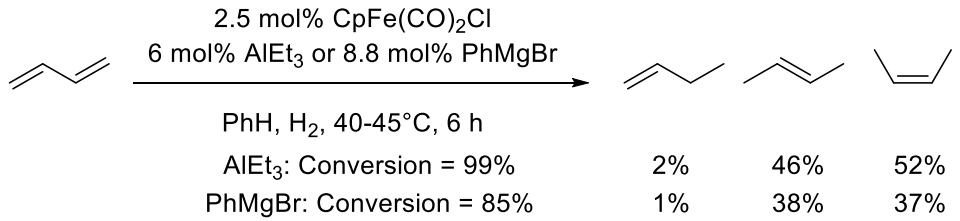
C=C REDUCTION

- Frankel reported reduction of methyl linoleate in the 1960s



Frankel, E. N. *et. al. J. Org. Chem.* **1964**, *29*, 3292.

- Tajima and Kunioka showed reduction of conjugated dialkenes with activated Fe



Tajima, Y.; Kunioka, E. *J. Org. Chem.* **1968**, *33*, 1689.

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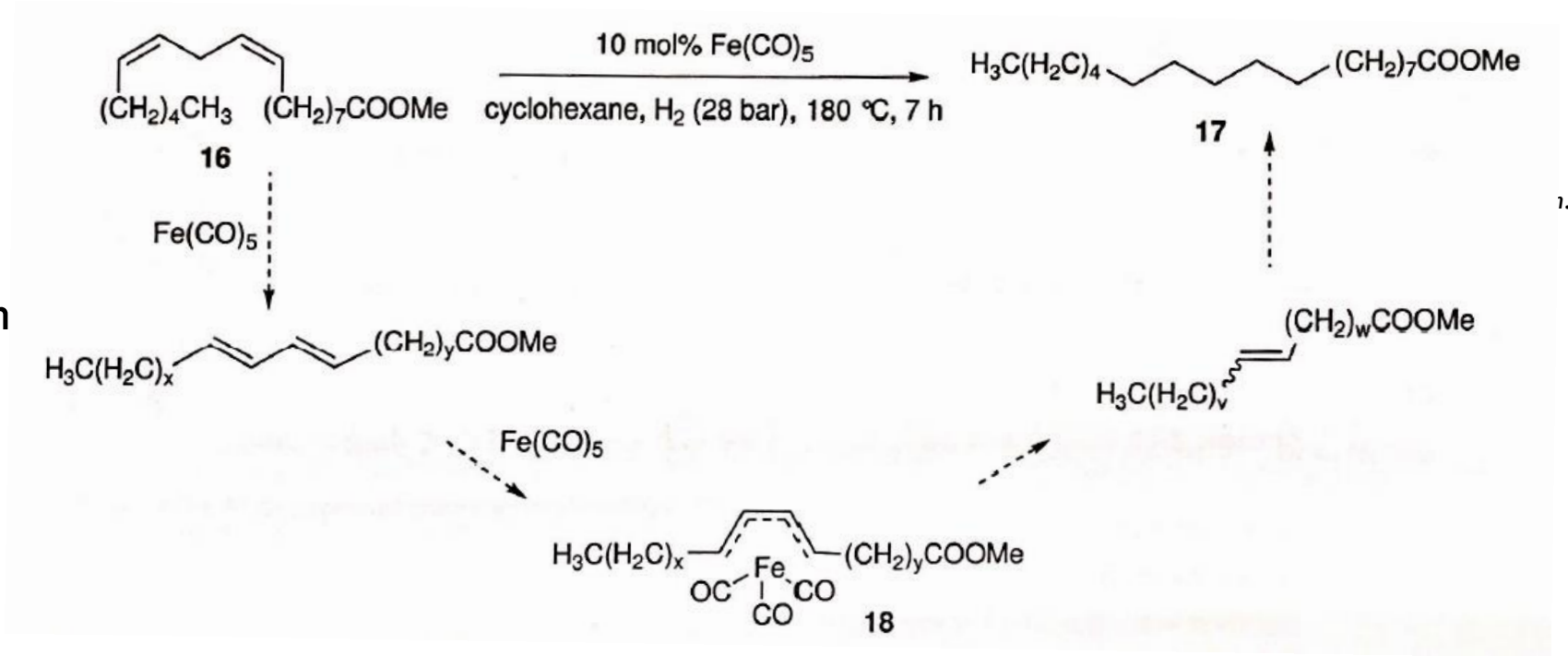

. **1964**, *29*, 3292.

- Tajim Fe

Tajima, Y.; Kunioka, E. *J. Org. Chem.* **1968**, *33*, 1689.

C=C REDUCTION

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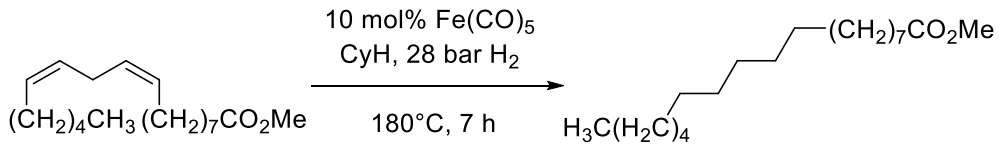

Frankel, E. N. *et. al. J. Org. Chem.* **1964**, *29*, 3292.

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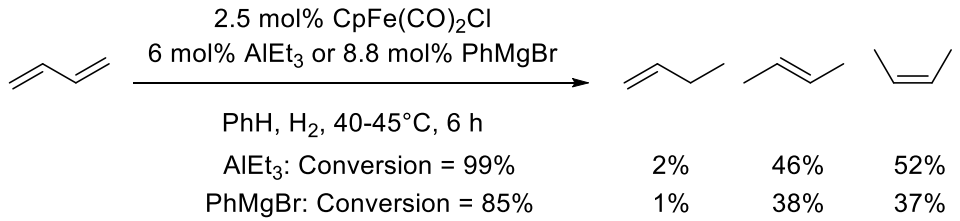
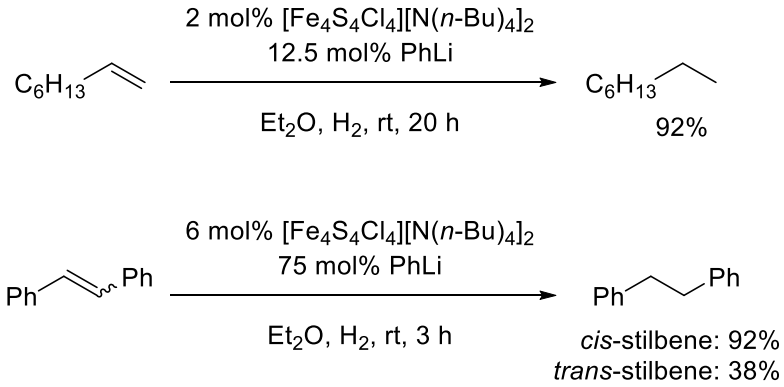
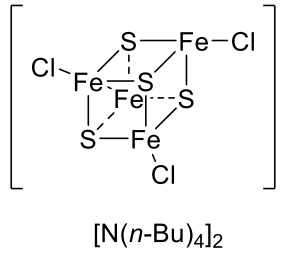


Tajima, Y.; Kunioka, E. *J. Org. Chem.* **1968**, *33*, 1689.

C=C REDUCTION

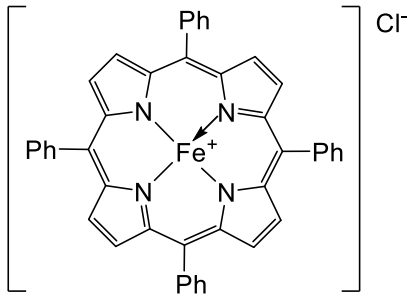
- Inoue showed biomimetic iron-sulfur clusters could also reduce C=C bonds

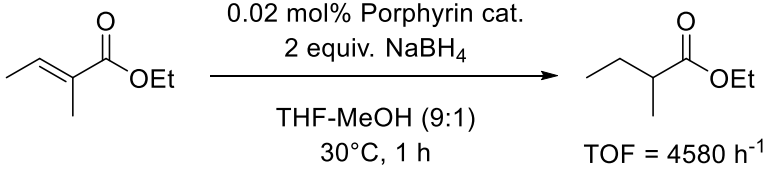




Inoue, H. *et. al. J. Chem. Soc., Chem. Commun.* **1980,** 817.
Inoue, H. *et. al. J. Chem. Soc., Chem. Commun.* **1983,** 983.

- Sakaki utilized porphryins to reduce α,β–unsaturated esters

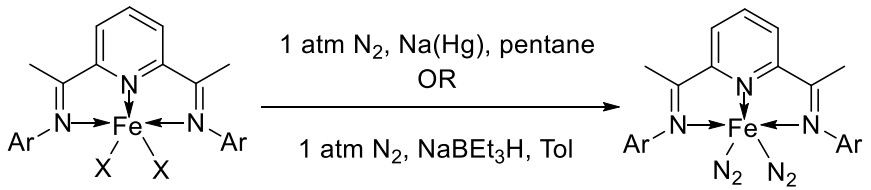


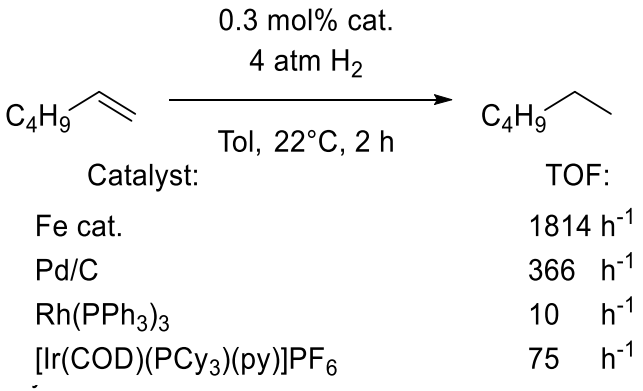


Sakaki, S. *et. al. J. Mol. Catal.* **1992,** *75,* L33.

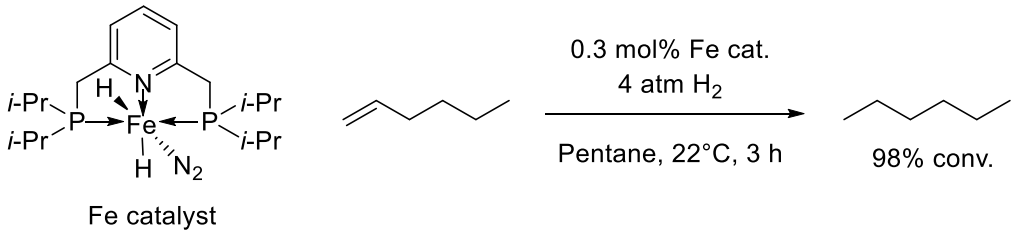
C=C REDUCTION

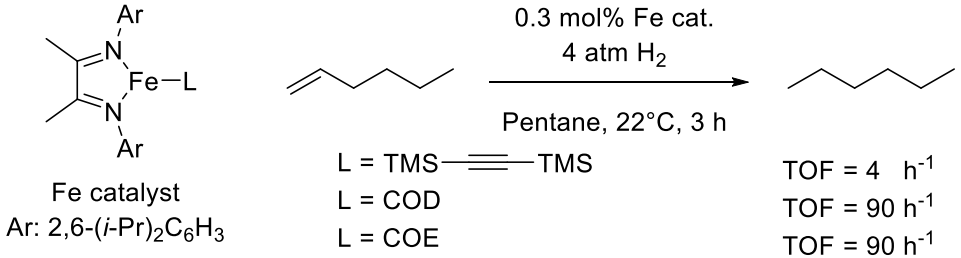
- Chirik has reported several examples of Fe-catalyzed C=C reduction





Chirik, P. J. *et. al. JACS*, **2004**, *126*, 13794.



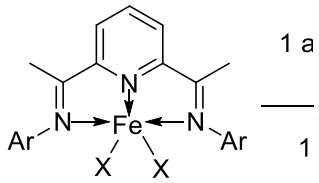


Chirik, P. J. *et. al. Inorg. Chem.* **2006**, *45*, 7252.

Lobkovsky, E. *et. al. Organometallics*, **2005**, *24*, 5518.

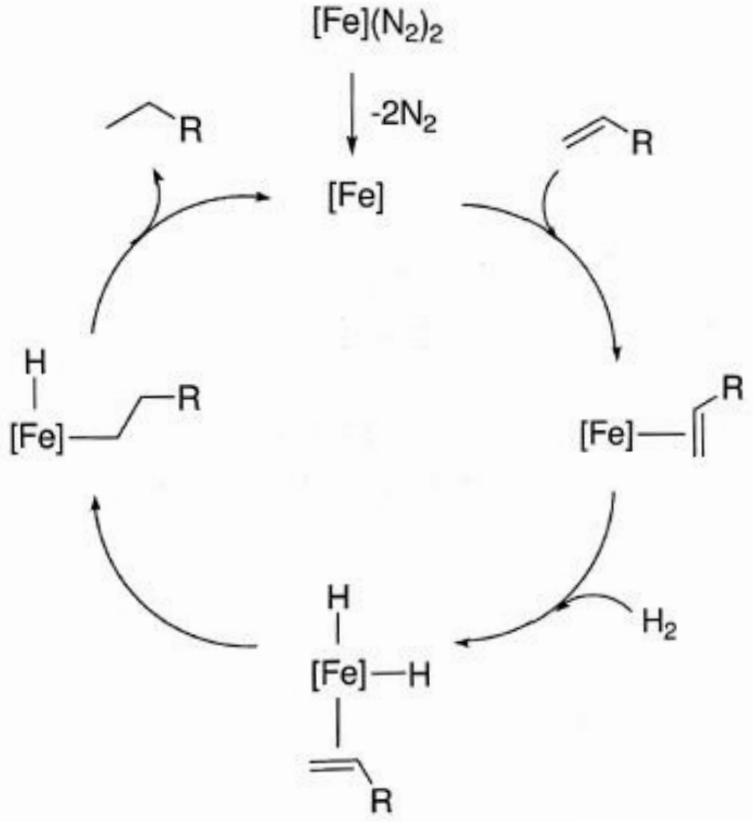
C=C REDUCTION

- Chirik has reported several examples of Fe-catalyzed C=C reduction



1 a

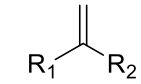
1



Fe cat.

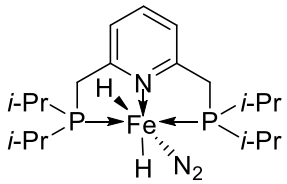
H_2

C, 2 h

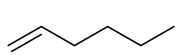


TOF = 1344 h^{-1}
TOF = 104 h^{-1}
TOF = 1814 h^{-1}
: H TOF = 363 h^{-1}
$_2$Me TOF = 3 h^{-1}
TOF = 57 h^{-1}

Chirik, P. J. *et. al. JACS*, **2004**, *126*, 13794.



Fe catalyst



0.3 m

4

Penta

0.3 mol% Fe cat.
4 atm H_2

Pentane, 22°C, 3 h

: TMS—≡—TMS
: COD
: COE

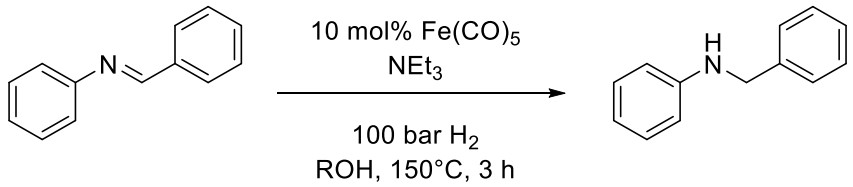
TOF = 4 h^{-1}
TOF = 90 h^{-1}
TOF = 90 h^{-1}

Chirik, P. J. *et. al. Inorg. Chem.* **2006**, *45*, 7252.

Lobkovsky, E. *et. al. Organometallics*, **2005**, *24*, 5518.

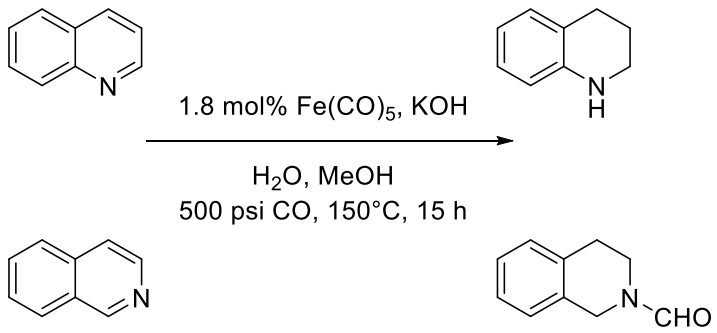
C=N REDUCTION

- Radhi and Markó showed hydrogenation of *N*-benzylideneaniline



- Kaesz reported reduction of nitrogen hetercycles as well

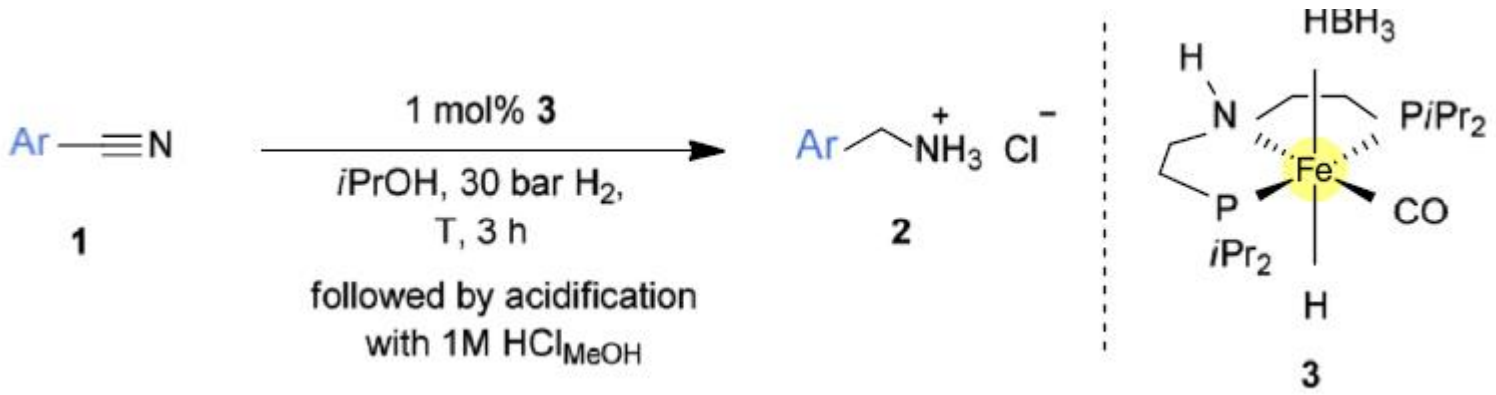
Radhi, M. A.; Markó, L. *J. Organomet. Chem.* **1984**, *262*, 359.



Kaesz, H. D. *J. Org. Chem.* **1984**, *49*, 1266.

RECENT ADVANCES

- Beller has recently described hydrogenation of nitriles



Beller, M. *Nature Comm.* **2014**, *5*, 4111.

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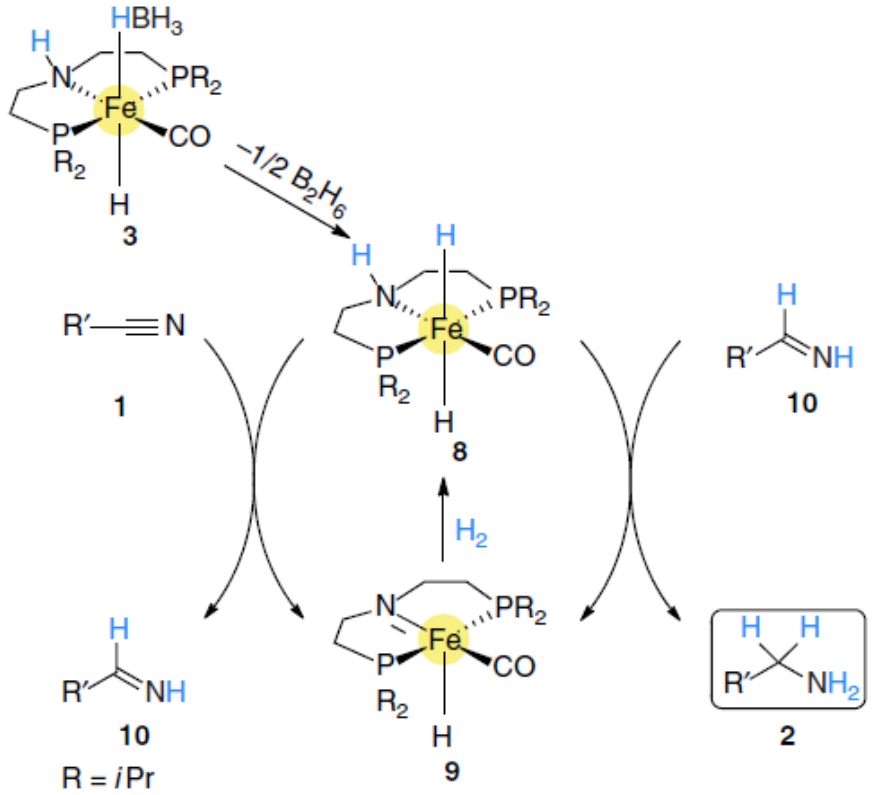


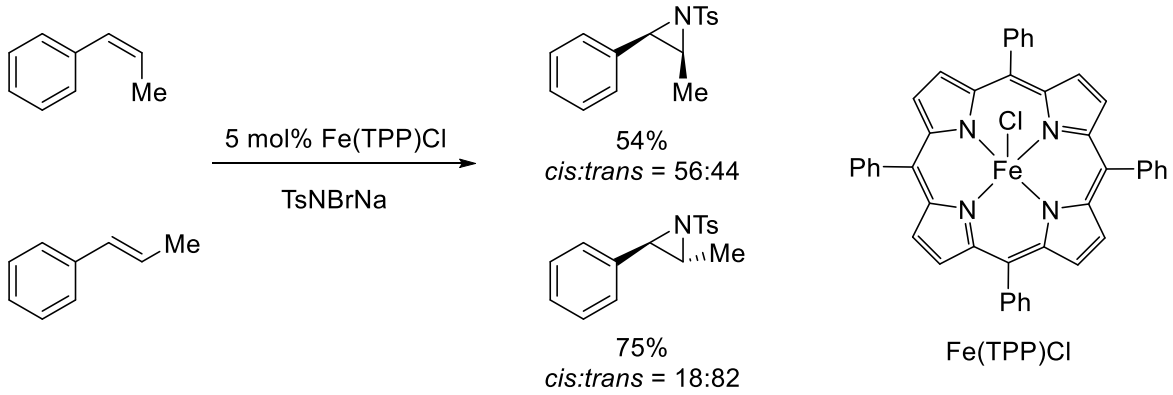
Beller, M. *Nature Comm.* **2014**, *5*, 4111.

IRON-CATALYZED CYCLOADDITIONS AND RING EXPANSION REACTIONS

1. [2+X]-Cycloadditions
2. [3+X]-Cycloadditions
3. Ring Expansions
4. Recent Advance

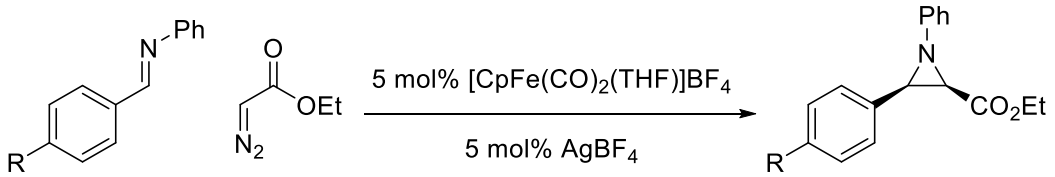
[2+1]-CYCLOADDITIONS: AZIRIDINES

- Zhang used bromamine-T as a nitrene source



Zhang, X. P. *Org. Lett.* **2004**, *6*, 1907.

- Hossain demonstrated iron-catalyzed carbene transfer

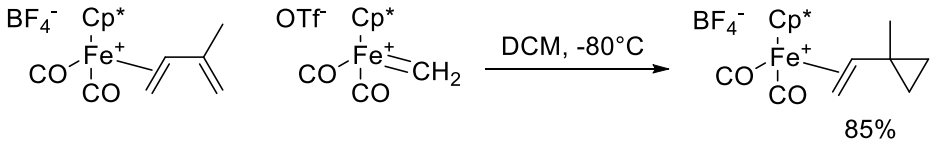


R = OMe	0%
R = H	40% (all *cis*)
R = NO_2	78% (*cis:trans* = 4:1)

Hossain, M. M. *et. al. J. Org. Chem.* **1998**, *63*, 6839.

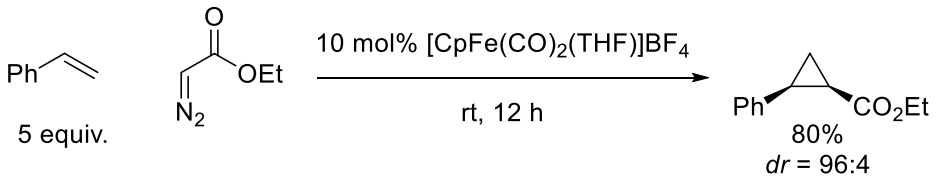
[2+1]-CYCLOADDITIONS: CYCLOPROPANES

- In 1989 Roger and Lapinte reported a stoichiometric example



Roger, C.; Lapinte, C. *Chem. Commun.* **1989**, 1598.

- Hossain used his aziridination catalyst system for cyclopropanes as well



Hossain, M. M. *et. al. Tetrahedron Lett.* **1994**, *35*, 7561.

[2+1]-CYCLOADDITIONS: CYCLOPROPANES

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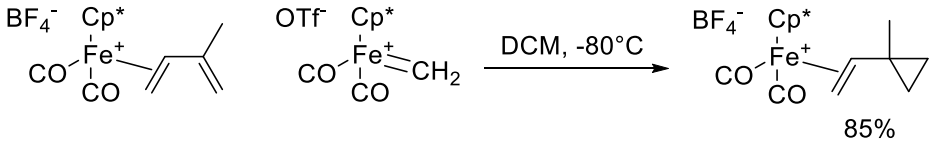
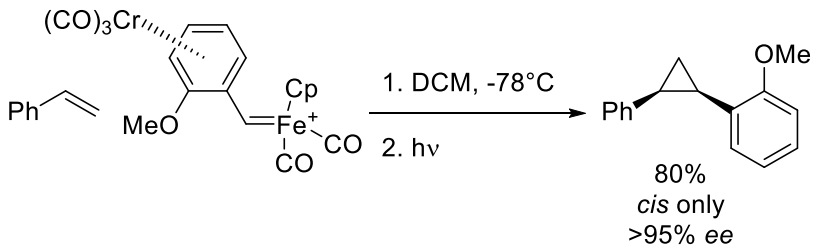


Roger, C.; Lapinte, C. *Chem. Commun.* **1989**, 1598.

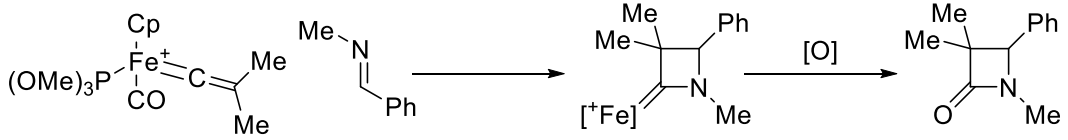
- Hossain also utilized a bimetallic system to achieve high ee's

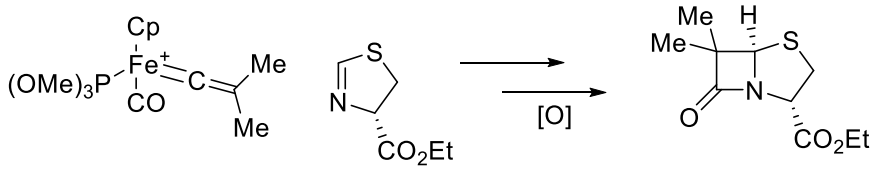


Hossain, M. M. *et. al. J. Organomet. Chem.* **2005**, *690*, 6238.

[2+2]-CYCLOADDITIONS

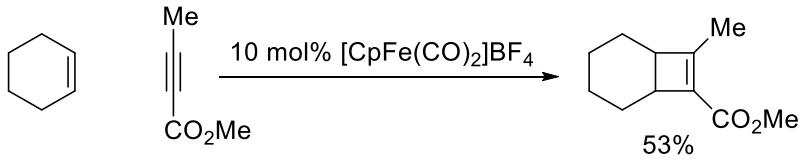
- Barrett reported hetero [2+2] reactions to give β–lactams after oxidation





Barrett, A. G. M. *et. al. Organometallics* **1990**, *9*, 151.

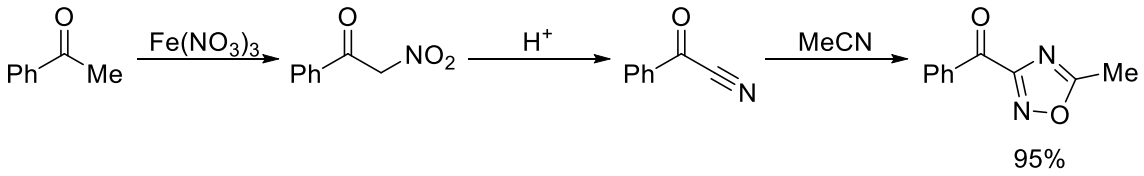
- Rosenblum and Scheck reported a [2+2] between alkenes and alkynes



Rosenblum, M. Scheck, D. *Organometallics* **1982**, *1*, 397.

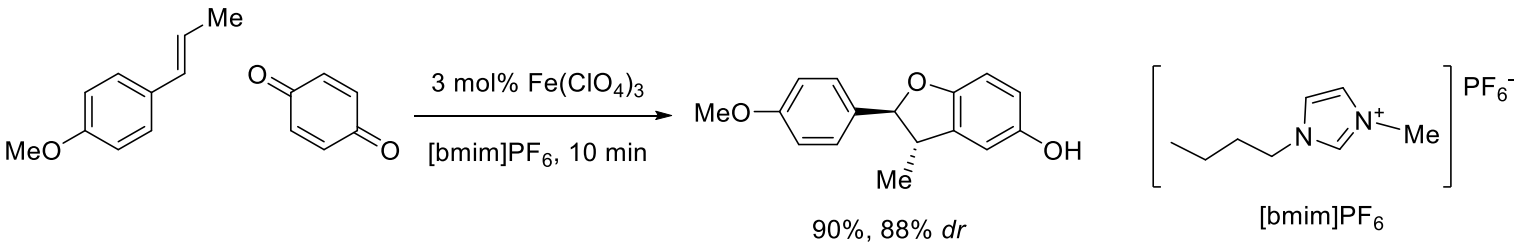
[3+2]-CYCLOADDITIONS

- Itoh reported an iron-initiated Huisgen reaction to form 1,2,4-oxadiazoles



Itoh, K.-i. *et. al. Synthesis* **2005**, 1935.

- Itoh showed a catalytic version with good *dr*



Itoh, T. *et. al. Tetrahedron Lett.* **2002**, *43*, 3041.

[3+2]-CYCLOADDITIONS

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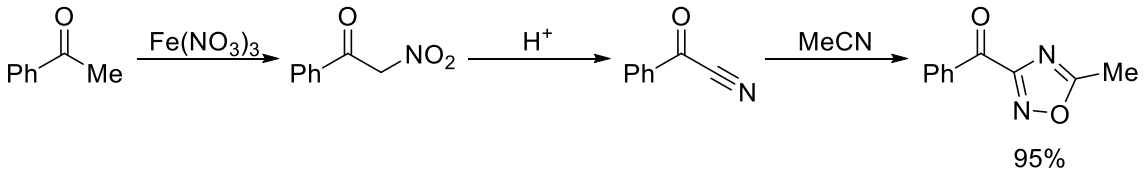
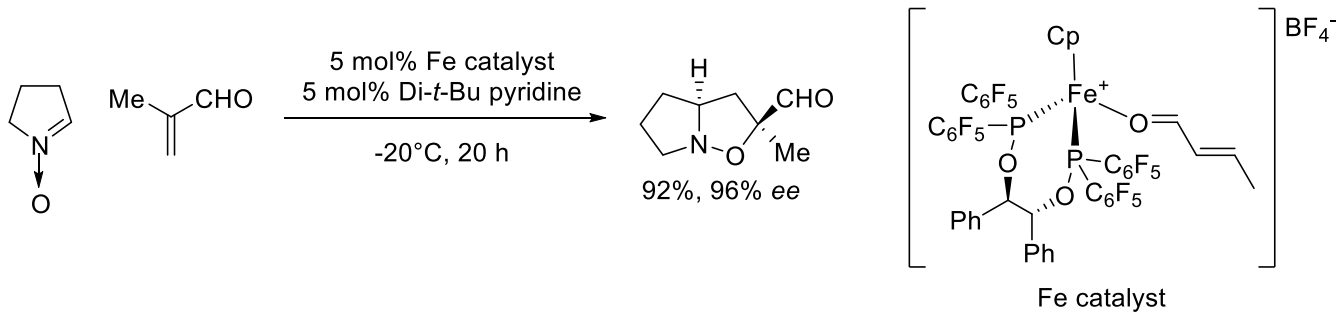


Itoh, K.-i. *et. al. Synthesis* **2005,** 1935.

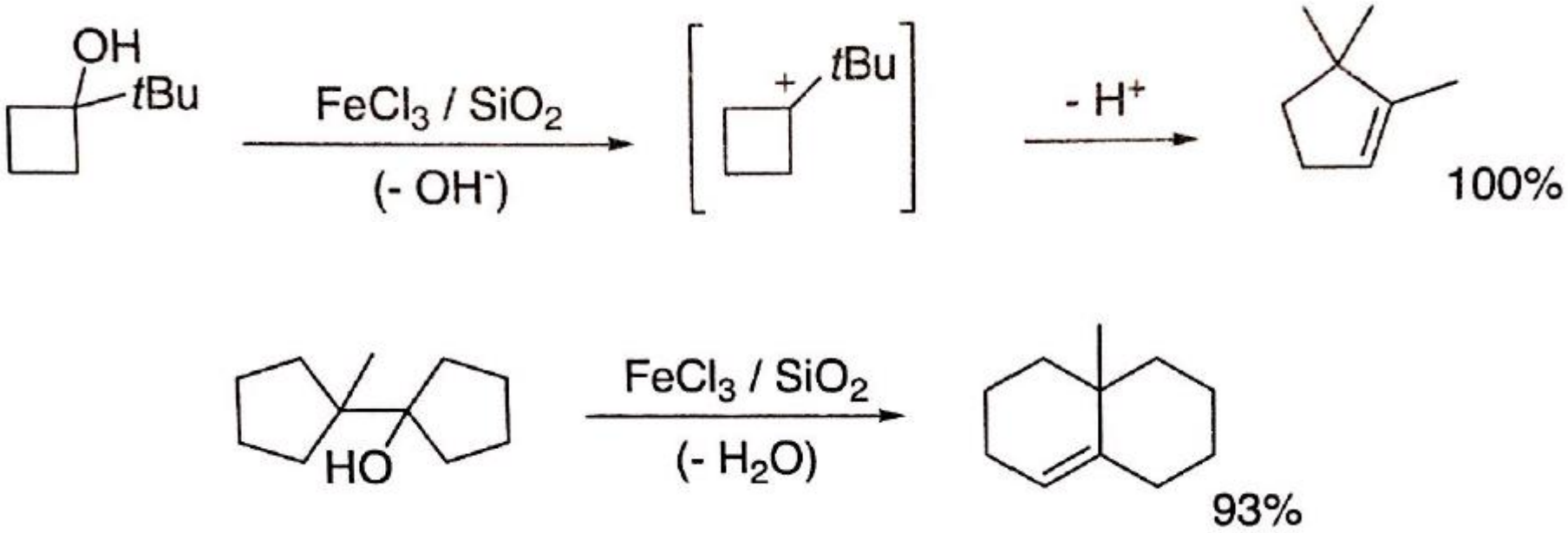
- Kündig showed an asymmetric example with good yields and ees



Kündig, E. P. *et. al. JACS*, **2002,** *124*, 4968.

RING EXPANSIONS

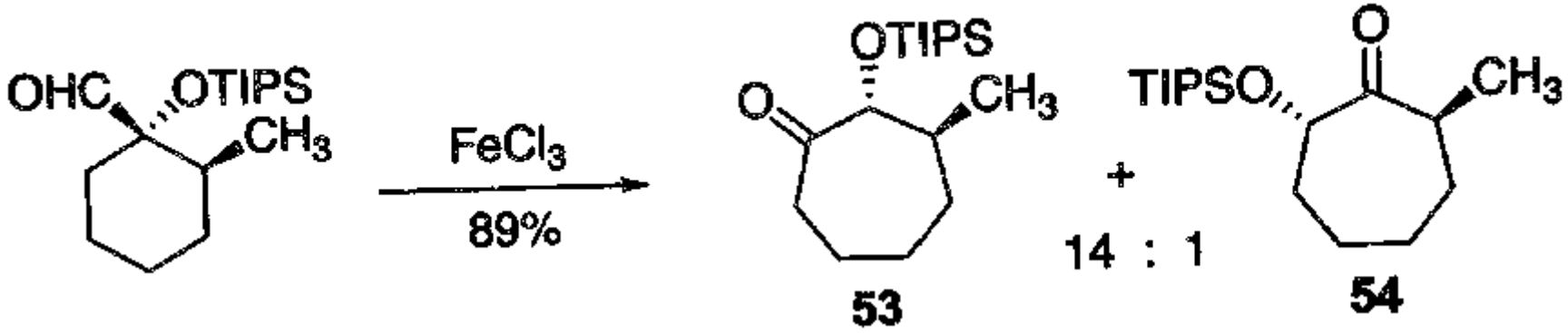
- Fadel and Salaün reported dehydrative ring expansion reactions of cyclic alcohols



Fadel, A.; Salaün, J. *Tetrahedron* **1985**, *41*, 413.
Fadel, A.; Salaün, J. *Tetrahedron* **1985**, *41*, 1267.

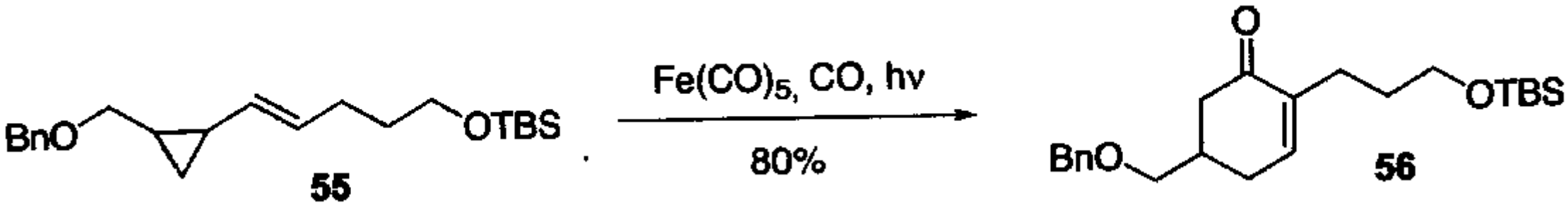
RING EXPANSIONS

- Kuwajima reported ring expansion of cyclohexane carbaldehydes



Kuwajima, I, *et. al. Tetrahedron Lett.* **1989**, *30*, 4267.

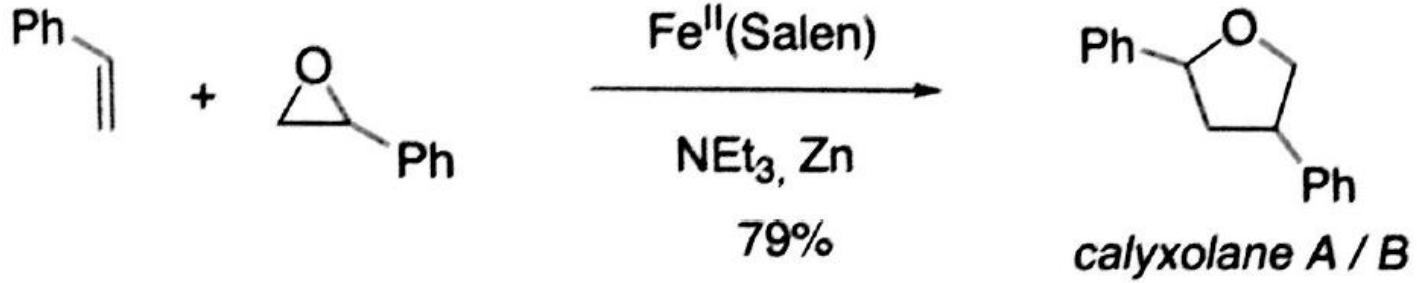
- Taber reported ring expansion of vinyl cyclopropanes



Taber, D. F. *et. al. JACS* **2000**, *122*, 6807.

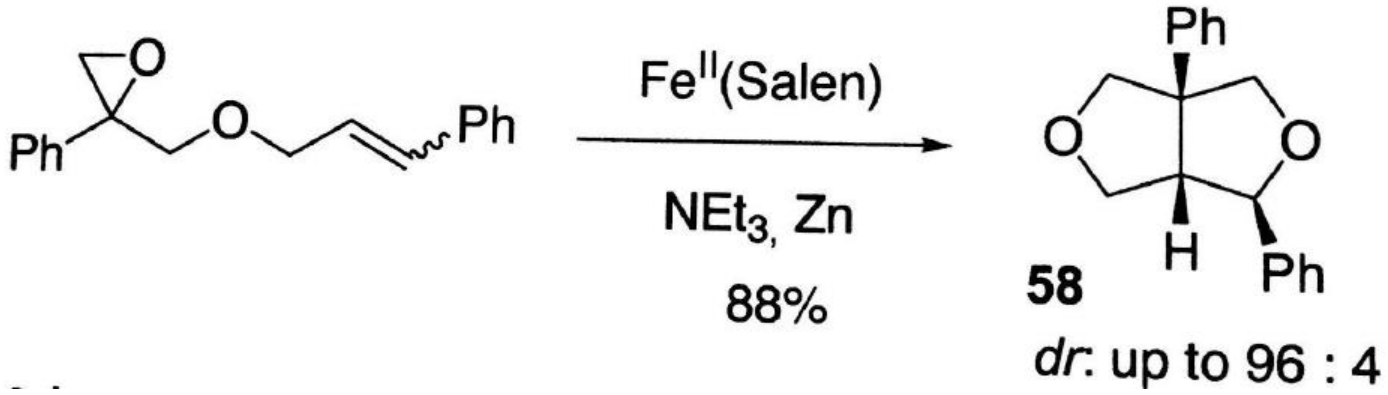
RING EXPANSIONS

- Hilt reported ring expansion of epoxides to THFs



- Hilt also reported an intramolecular variant

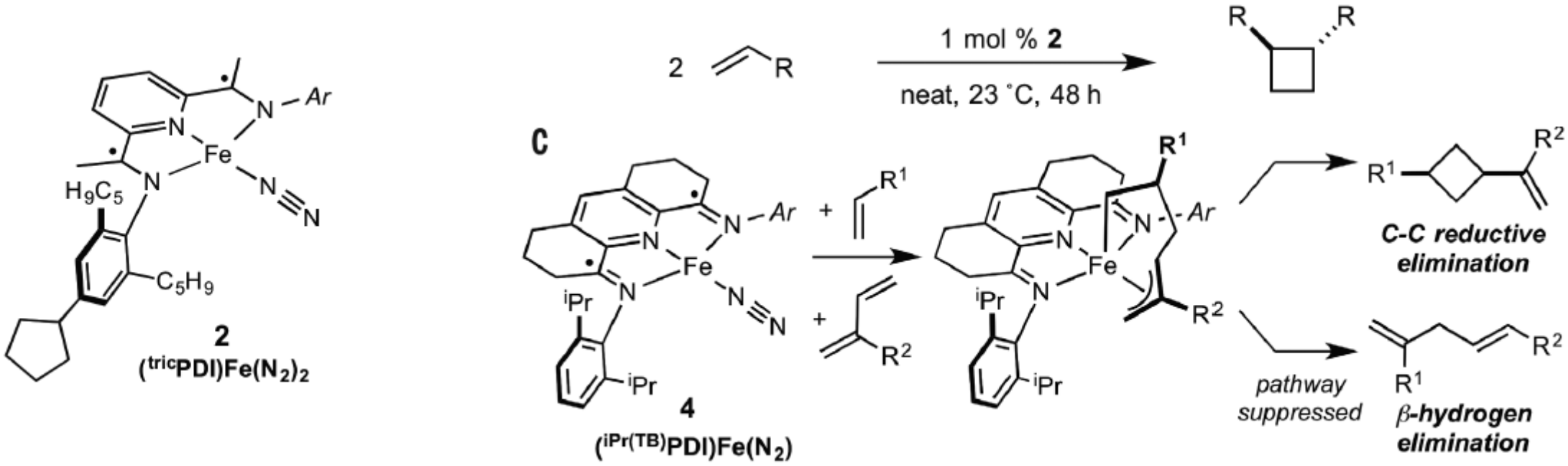
Hilt, G. *et. al. Chem. Commun.* **2005**, 1996.



Hilt, G. *et. al. Adv. Synth. Catal.* **2007**, *349*, 2018..

RECENT ADVANCES

- Chirik reported an iron-catalyzed [2+2]-cycloaddition



Chirik, P. J. *et. al. Science* **2015**, *349*, 960.

SUMMARY

- Iron has had a slower start than 2nd or 3rd row transition metals, but is becoming more popular due to its cost and availability.

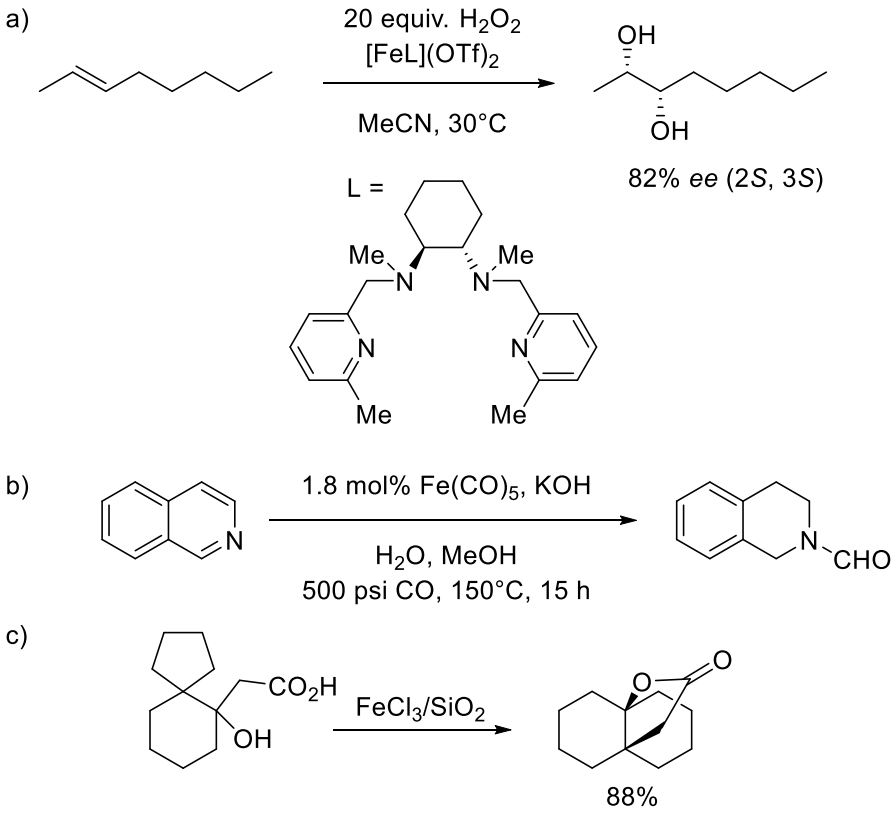
- Iron has great potential to be useful for many organic reactions, such as oxidation, reduction, and cycloadditions, just to name a few.

- The future of iron is very bright (rust-free).

THANKS! QUESTIONS?

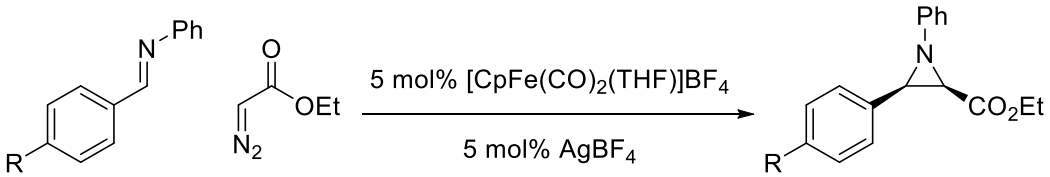
QUESTION 1:

- Please predict the products.

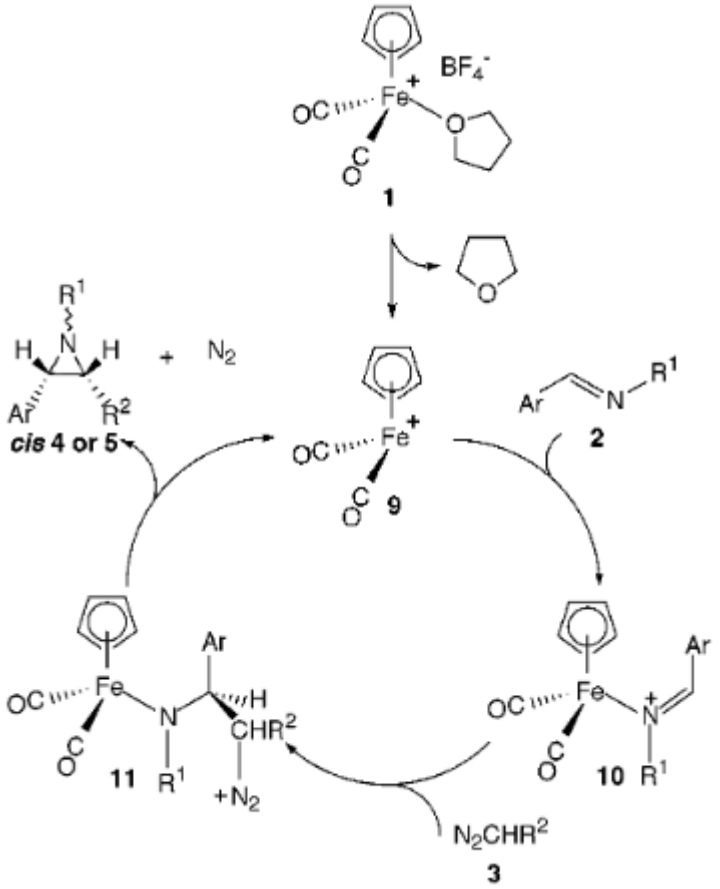


QUESTION 2:

- Please propose a mechanism that explains both the product yields and *cis:trans* ratios.

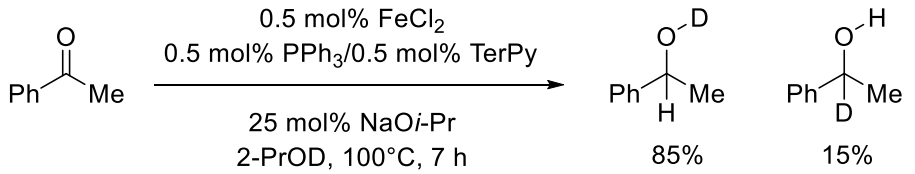


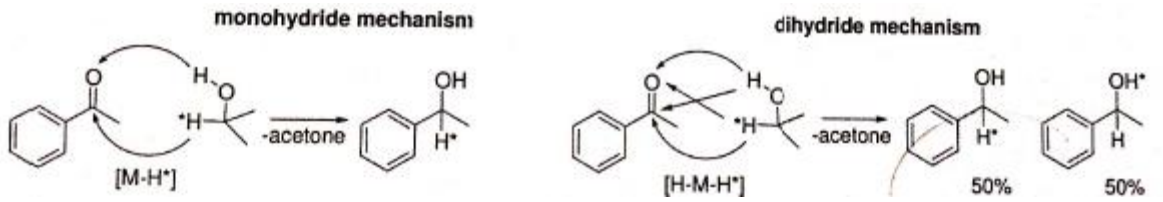
R = OMe	0%
R = H	40% (all *cis*)
R = NO_2	78% (*cis:trans* = 4:1)



QUESTION 3:

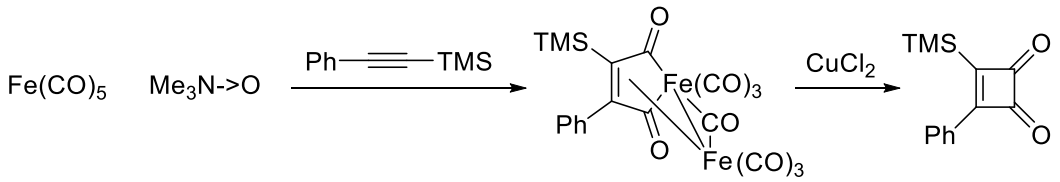
- Based on the deuterium exp shown below, please propose a mechanism for the reduction of acetophenone.



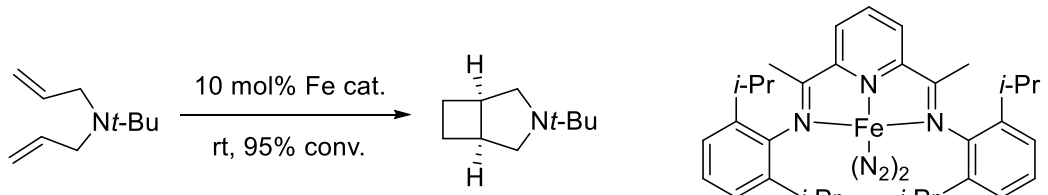


[2+2]-CYCLOADDITIONS

- Raj showed iron-mediated [2+1+1] formation of cyclobutenediones



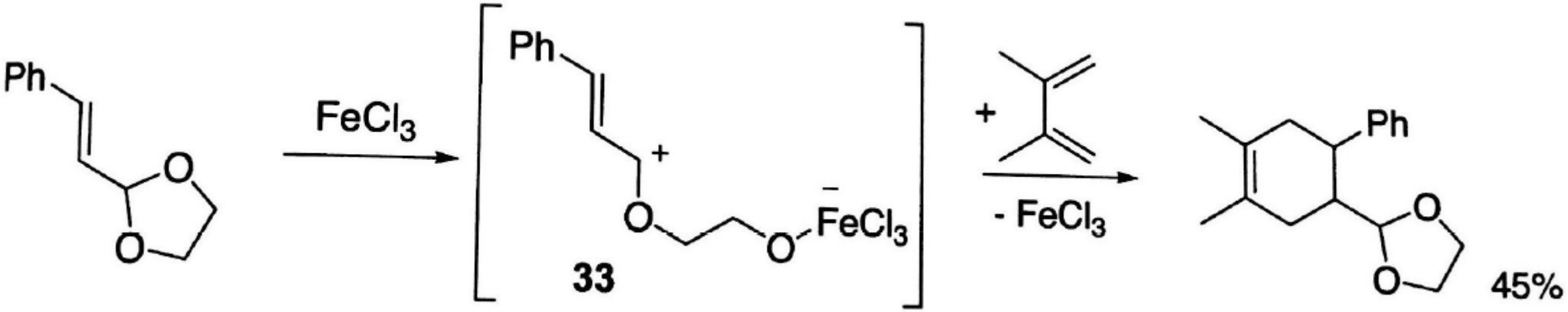
- Chirik demonstrated an intramolecular [2+2] leading to fused ring formation



Fe catalyst

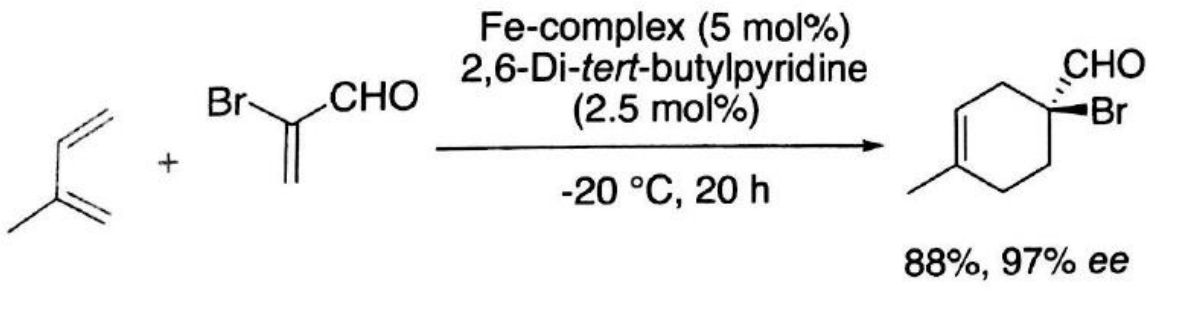
[4+2]-CYCLOADDITIONS

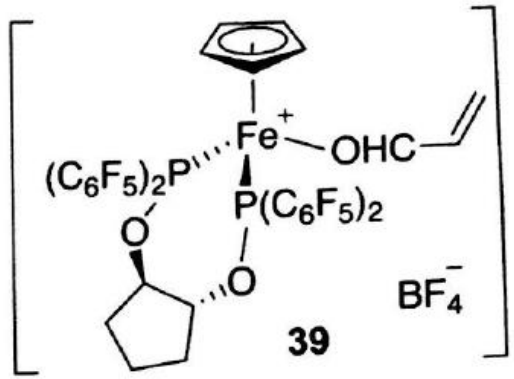
- Normal electron demand

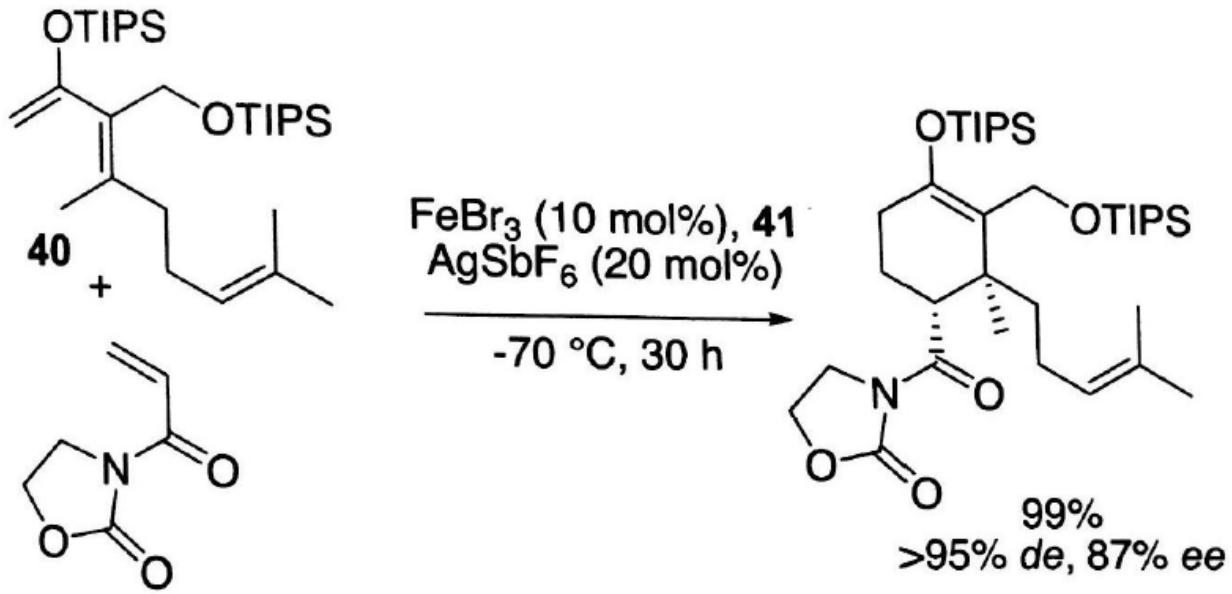


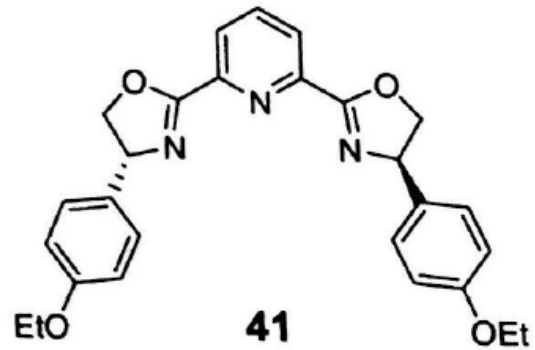
[4+2]-CYCLOADDITIONS

- Normal electron demand



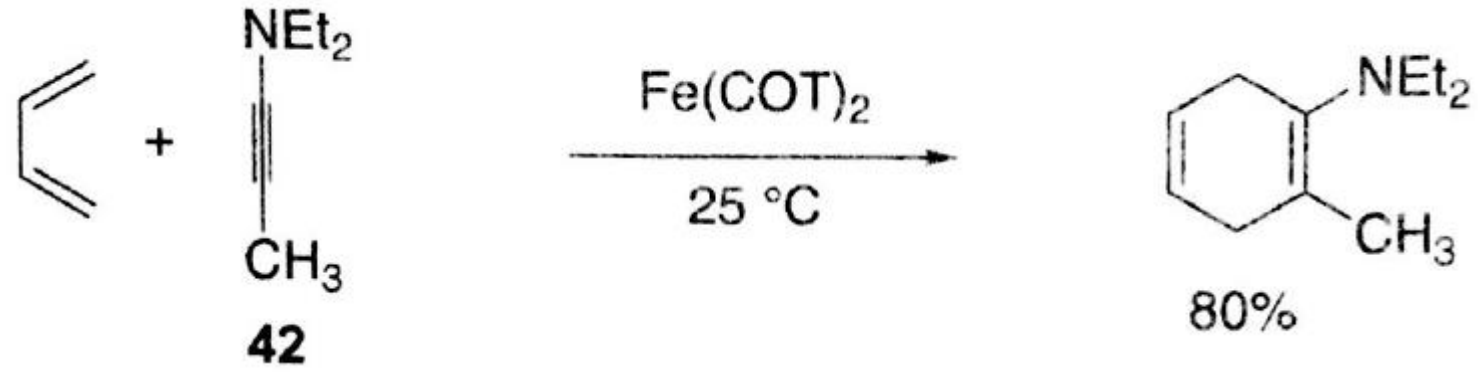






[4+2]-CYCLOADDITIONS

- Neutral electron demand



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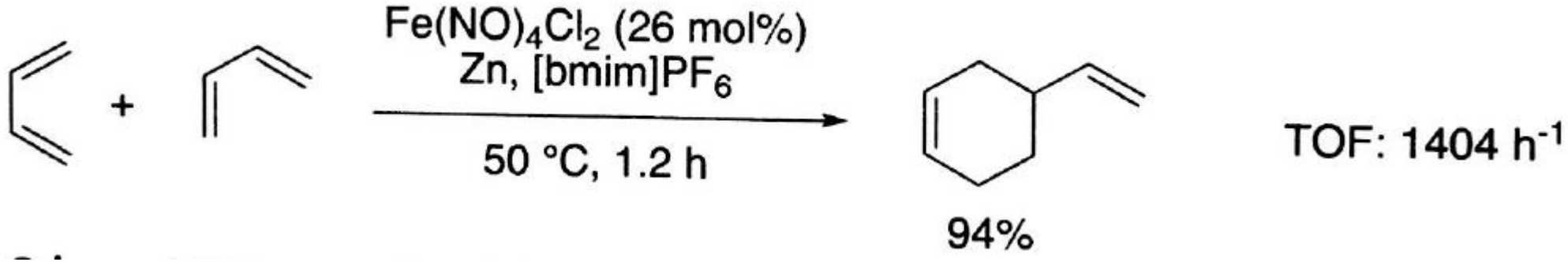

[4+2]-CYCLOADDITIONS

- Inverse electron demand